# ADDITION OF 1,3-DICARBONYL COMPOUNDS TO THE CYCLOHEPTATRIENE DERIVATIVES

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

BY

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

DECEMBER 2009

Approval of the thesis:

**ADDITION OF 1,3-DICARBONYL COMPOUNDS TO THE CYCLOHEPTATRIENE DERIVATIVES**

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## ABSTRACT

### ADDITION OF 1,3-DICARBONYL COMPOUNDS TO THE CYCLOHEPTATRIENE DERIVATIVES

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December 2009, 177 pages

The one electron oxidant $Mn(OAc)_3$ has been used for years for the oxidative addition of 1,3-dicarbonyls to alkenes to give dihydrofuranes. Since cycloheptatriene is in equilibrium with its valance isomer norcaradiene, it will be interesting to study the reaction of CHT derivatives with $Mn(OAc)_3$ in the presence of 1,3-dicarbonyls. In our research, we have observed that unsubstituted cycloheptatriene gave CHT based products. However, when electron withdrawing –CN group was attached to C-7 position of CHT we obtained norcaradiene based products. We have also observed that there exist an equilibrium between [3+2] addition products through 1,5-hydride shift. In addition, we obtained dihydrofurane derivatives in the presence of $Mn(OAc)_3$ from compounds which have "already formed C-C bond" between 1,3-dicarbonyl and alkene. Formation of dihydrofurane derivatives from these compounds brought up two questions; whether reaction is going over oxygen atom or not and whether reaction involves a cyclopropane intermediate or not. Despite all efforts, we could not manage to synthesize the required material for the investigation of these questions.



Keywords: Cycloheptatriene, norcaradiene, manganese (III) acetate, radicalic cyclization reactions.

# ÖZ

## 1,3-DİKARBONİL BİLEŞİKLERİNİN SİKLOHEPTATRİEN TÜREVLERİNE KATILMASI

Südemen, M. Burak
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Aralık 2009, 177 sayfa

Tek elektron oksidantı olan $Mn(OAc)_3$, yıllardır 1,3-dikarbonil bileşiklerinin oksidatif olarak alkenlere katılarak dihidrofuran oluşumunda kullanılmaktadır. Sikloheptatrien valans izomeri norkaradiene ile dengede olduğundan, CHT türevlerinin 1,3-dikarbonillerle, $Mn(OAc)_3$ eşliğinde yapılan reaksiyonlarının ilginç sonuçları olacaktır. Araştırmamızda sübsütüentsiz CHT'nin CHT bazlı ürünler verdiğini gördük. Fakat CHT'nin C-7 pozisyonuna electron çekici –CN grubu bağladığımızda ise NOR bazlı ürünler elde ettik. Araştırmamızda gördüğümüz bir diğer önemli nokta ise [3+2] eklenme ürünleri arasında 1,5-Hidrat kaymasından dolayı bir denge olduğudur. Bunlara ek olarak, 1,3-dikarbonil ile alken arasında önceden oluşturulmuş C-C bağı bulunan sistemlerin, $Mn(OAc)_3$ eşliğindeki reaksiyonlarından dihidrofuran türevleri elde ettik. Bu reaksiyonlar sonucunda dihidrofuran türevlerini elde etmemiz aklımıza iki yeni soru getirdi. Siklizasyon oksijen atomu üzerinden gidebilirmi? ve siklizasyon bir siklopropan ara ürünü içeriyor olabilirmi?. Tüm çabalarımıza rağmen, bu soruları cevaplamak için gerekli materyali elde edemedik.

Anahtar Kelimeler: Sikloheptatrien, norkaradien, mangan(III) asetat, radikal halkalaşma reaksiyonları.

**To my parents and my fiancé**

## ACKNOWLEDGEMENT

I would like to present my feelings of gratitude to my supervisor Prof. Dr. Metin Balcı for his invaluable guidance, endless patience and support. It was an honor for me to serve, to learn and to take this degree from him .

I would like to thank to NMR specialists Seda Karayılan and Zehra Uzunoglu for the NMR experiments. I am pleased towards their patience, understanding and kindness.

I wish to express my thanks to my fiancé for being supportive, encouraging, and inspiring throughout my master studies.

I would like to express my special thanks to all the members of SYNTHOR Research Group, for being kind and friendly at all times.

The last but not the least, I would like to present my sincere appreciation to my parents for their support and I would like to specially thank to my room mates Osman Aydın and Mert Bilir for their understanding, help and support in the preparation of this very thesis.

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## LIST OF ABBREVIATIONS

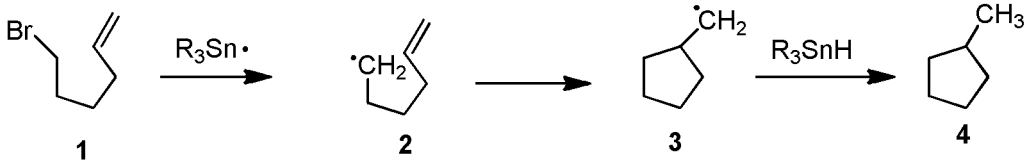
| | |
|---|---|
| CAN | : Cerium Ammonium Nitrate |
| CHT | : Cycloheptatriene |
| NOR | : Norcaradiene |
| AcAc | : Acetylacetone |
| DMF | : Dimethylformamide |
| DMSO | : Dimethyl sulfoxide |
| NMR | : Nuclear Magnetic Resonance |
| J | : Coupling Constant |
| mg | : miligram |
| mmol | : milimol |

# CHAPTER I

# INTRODUCTION

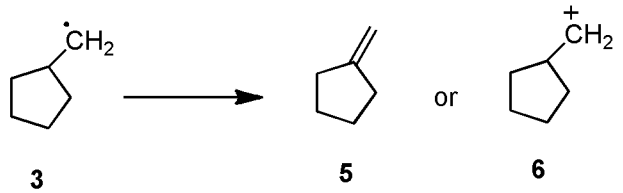
## 1.1 Oxidative Free Radicalic Cyclization Reactions

Free radicalic cyclization method is one of the most popular method for creating cyclic molecules from alkenes. In this method compounds containing halogen or another proper functional group are turned into radicals with the use of $R_3SnH$ and this radicals undergoes addition reactions with olefins in order to create hydrocarbons [1]. Eventhough this method gives high yields of products, inapplicability of the method to compounds with no functional groups is the major limitation of it.




Scheme 1

If the radical **3** formed after cyclization somehow undergoes oxidation and become a carbocation, this would add a synthetic utility to the compound in which cyclic compounds with functional groups on it can be synthesized.



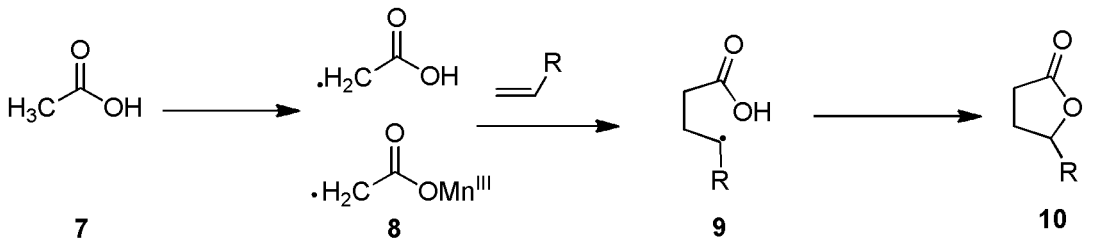

Scheme 2

## 1.2 Free Radical Reactions In The Presence of Manganese (III) Acetate

Use of metal oxidants for the formation of a new C-C bond through oxidative radical reactions has been taking attention for the last 40 years. These reactions are initiated with the abstraction of hydrogen radical from the acidic methylenic proton by metal oxidants such as $Mn(OAc)_3$; giving a methylenic radical. This step is followed by the formation of an intramolecular or intermolecular new C-C bond between the active radicalic methylene and electron rich alkene/alkyne. Heiba, Dessau [2a-b], Bush and Finkbeiner [2c] have discovered the oxidative free radicallic cyclization reactions and leaded its development.

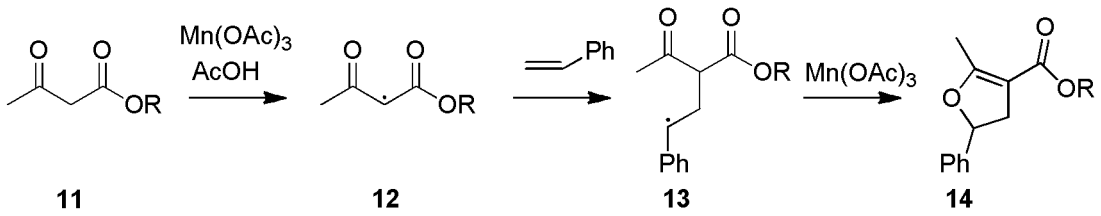
Oxidation mechanism of monocarbonyl compounds with $Mn(OAc)_3$ have been investigated thoroughly and the rate determining step has been found out as the oxidation of acetic acid [3a]. This oxo-centered metal oxidant, Mn(III), is triangular shaped and covered with acetate bridges.

Heiba, Dessau, Bush and Finkbeiner accomplished the oxidative addition of acetic acid to alkenes in 1968 and this study provides the basis for a general approach to oxidative free-radical cyclization [2b-c]. The reaction proceeds as in Scheme 3 which is the initial formation of a carboxymethyl radical followed by addition of this radical to the alkene to create a new C-C bond. Subsequent oxidation of the radical with another mole of $Mn(OAc)_3$ followed by cyclization produces γ-lactones.



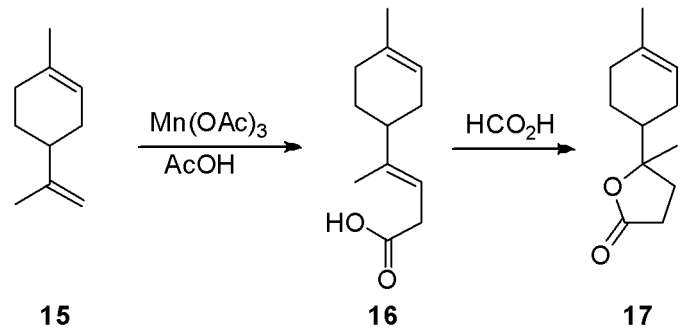

Scheme 3

Heiba and Dessau [4] carried out another type of reaction with $Mn(OAc)_3$ which is the oxidation of β-keto esters in the presence of olefins. They created a radical on β-keto ester compound and observed a dihydrofurane derivative formed by the addition of the radical to an alkene. In their reaction they used ethyl acetoacetate **11** as β-keto ester and styrene as alkene. After the completion of the reaction they observed dihydrofuran **14**. The only problem was the uncertainity of the course of the reaction. It wasn't clear whether cyclization is radicalic or cationic. Corey and co-workers [5] have also carried out research on $Mn(OAc)_3$ oxidation where they have also used β-keto esters and β-keto acids. Eventhough they mostly used Mn(III) or Mn(III)/Cu(II) couple, they mainly focused on the one-electron oxidants such as Ce(IV), Fe(III) ve Cu(II).



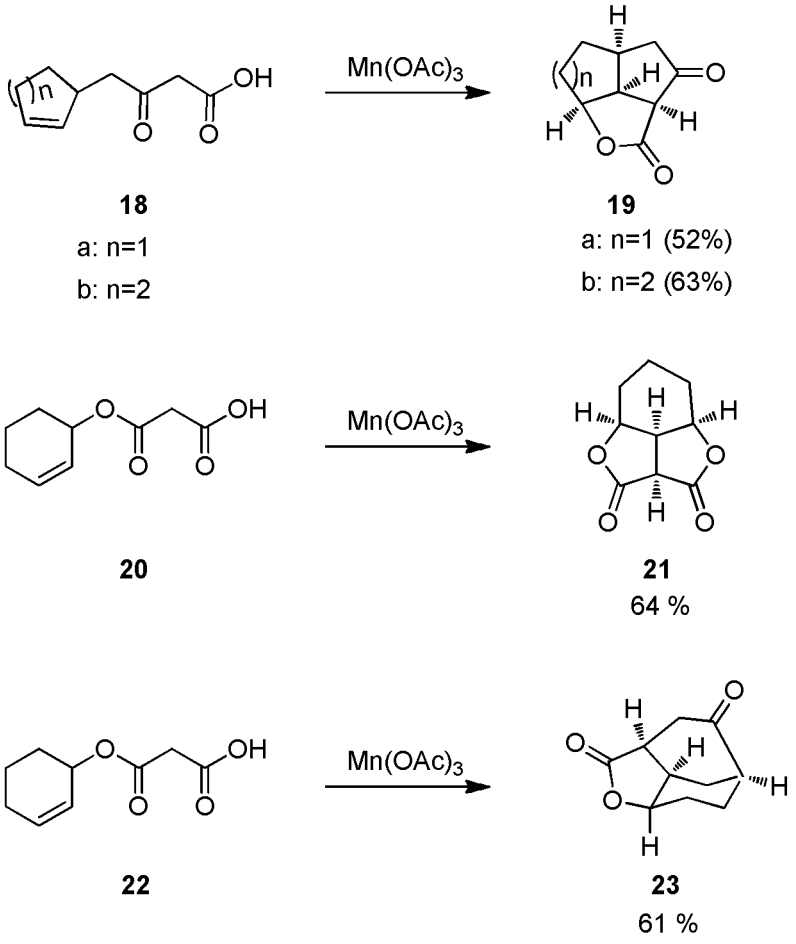

Scheme 4

Reactions of $Mn(OAc)_3$ have been used for the synthesis of natural compounds. For example, Gardrat [6] obtained lactone norbisalid **17** from limonene **15** through intermolecular processes as given on Scheme 5.




Scheme 5

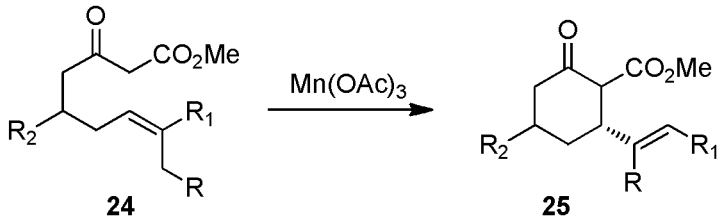
Development of the synthesis of the compounds, containing lots of functional groups, from simple molecules with intramolecular cyclization reactions in the presence of $Mn(OAc)_3$ have been an important synthetic route in the recent years. Corey and Kang [5a] developed the novel synthesis of polycyclic γ-lactones such as **19**, **21** and **23**, using maloic acid monoester in the presence of $Mn(OAc)_3$. They also obtained tricyclic lactones using malonate mono ester, di-γ-lactones and ketoacids.




Scheme 6

Snider and co-workers [7a-c] carried out a research in which they synthesized carboxylic products via free radicalic cyclization of unsaturated β-ketoesters in the presence of $Mn(OAc)_3$ as shown in Scheme 7. By this research a novel method for the synthesis of bicyclic and spiro products have been developed. Application of this

new methodology in natural product synthesis such as aloesapanol III **30a** [7b], and okicenone [7b] **30b** as a key step as, shown in Scheme 8, proved $Mn(OAc)_3$ to have a wide range of synthetic utility.



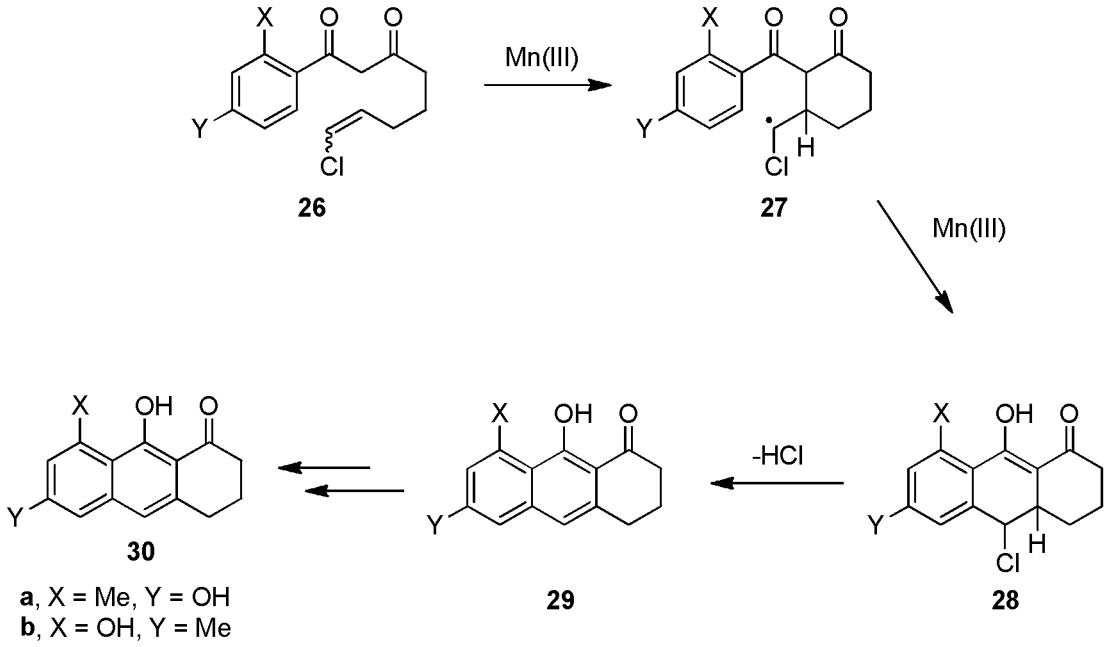

**24** **25**

a: $R_1 = R_2 = H$, $R = C_3H_7$ 75 %

b: $R_1 = H$, $R_2 = OH$, $R = Me$ 41 %

c: $R_1 = Me$, $R_2 = H$, $R = H$ 41 %

Scheme 7



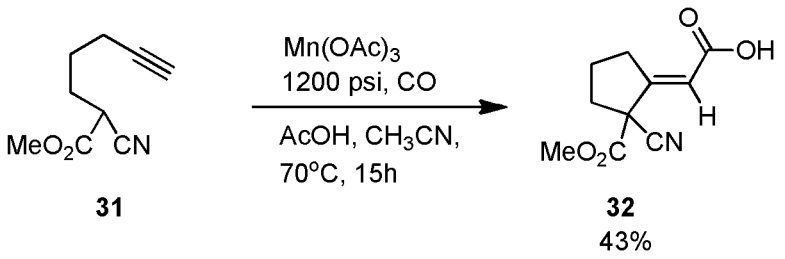

**26** **27** **28** **29** **30**

**a**, X = Me, Y = OH

**b**, X = OH, Y = Me

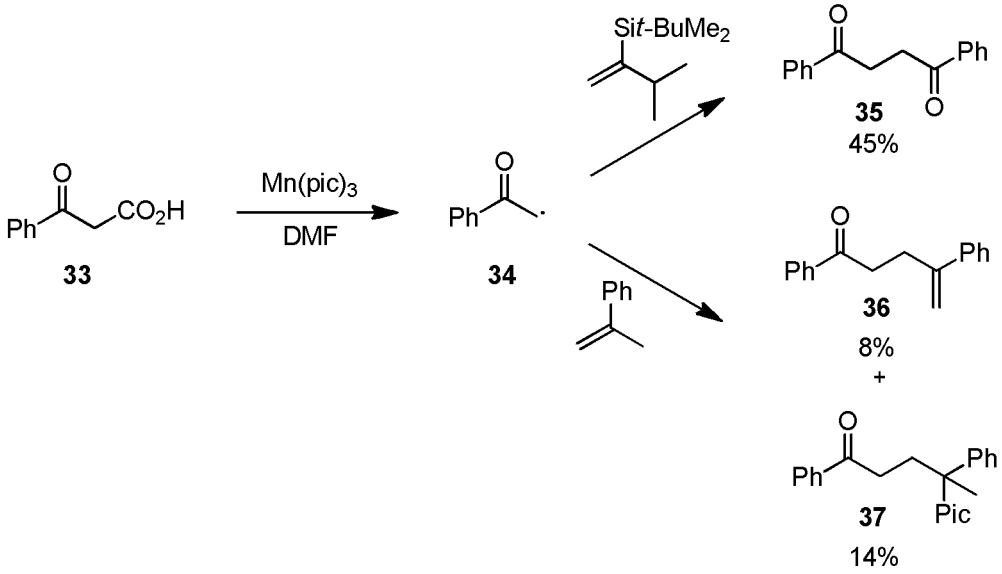
Scheme 8

Mn(III) based reactions are also used for the addition of CO and $O_2$ to the olefins as in Scheme 9. Alper et al. [9c] achieved the addition of CO to alkenyl malonates and alkynyl cyanoesters in the presence of $Mn(OAc)_3$.

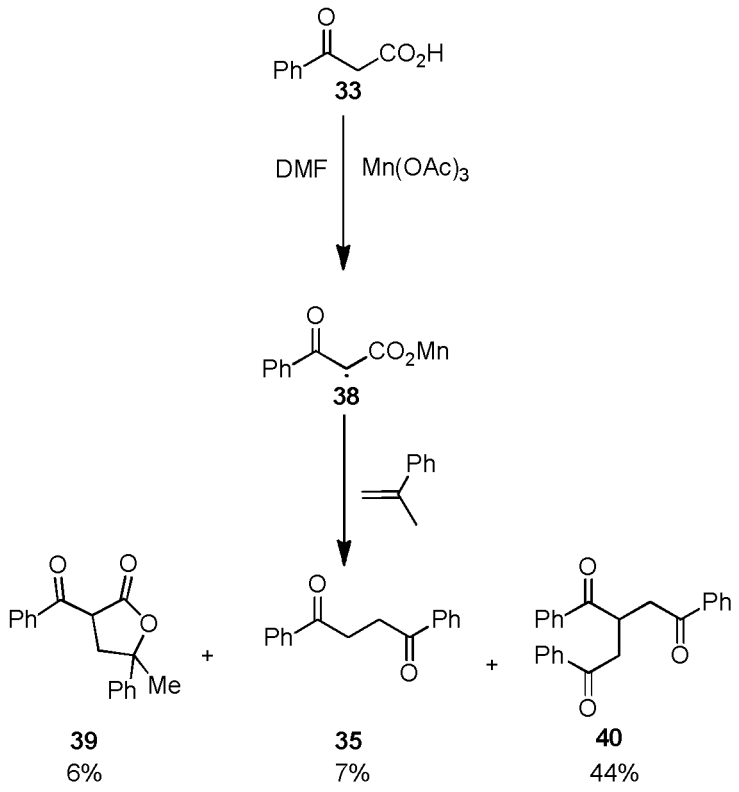



Scheme 9

The radicalic cyclization reactions of β-keto esters with another type of manganese (III) reactive, manganese (III) picolate ($Mn(pic)_3$), has been investigated by Iwasava [10]. It was observed that the reactions of β-keto acids **33** in the presence of $Mn(pic)_3$ and $Mn(OAc)_3$ separately in DMF gave different products as shown in Scheme 10 and 11.

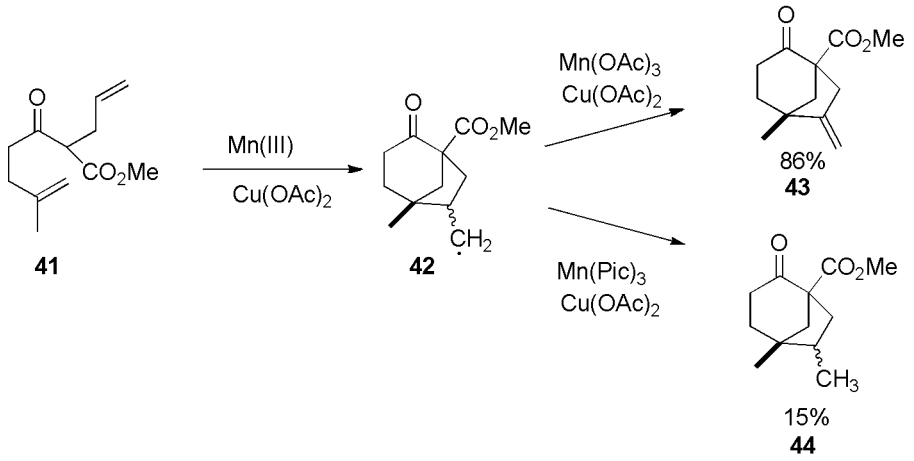



Scheme 10



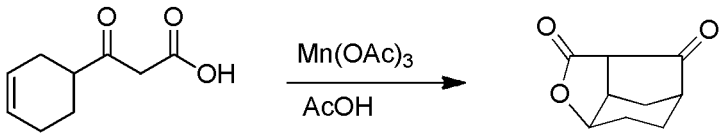

Scheme 11

In 1993, Snider [1] carried out a research about radicalic cyclization reactions using Mn(III) reactives and $Cu(OAc)_2$. In this research, different products were observed at the end of the reactions as shown in Scheme 12. This difference arises from the faster reaction rate of $Mn(pic)_3$ compared to $Mn(OAc)_3$.




Scheme 12

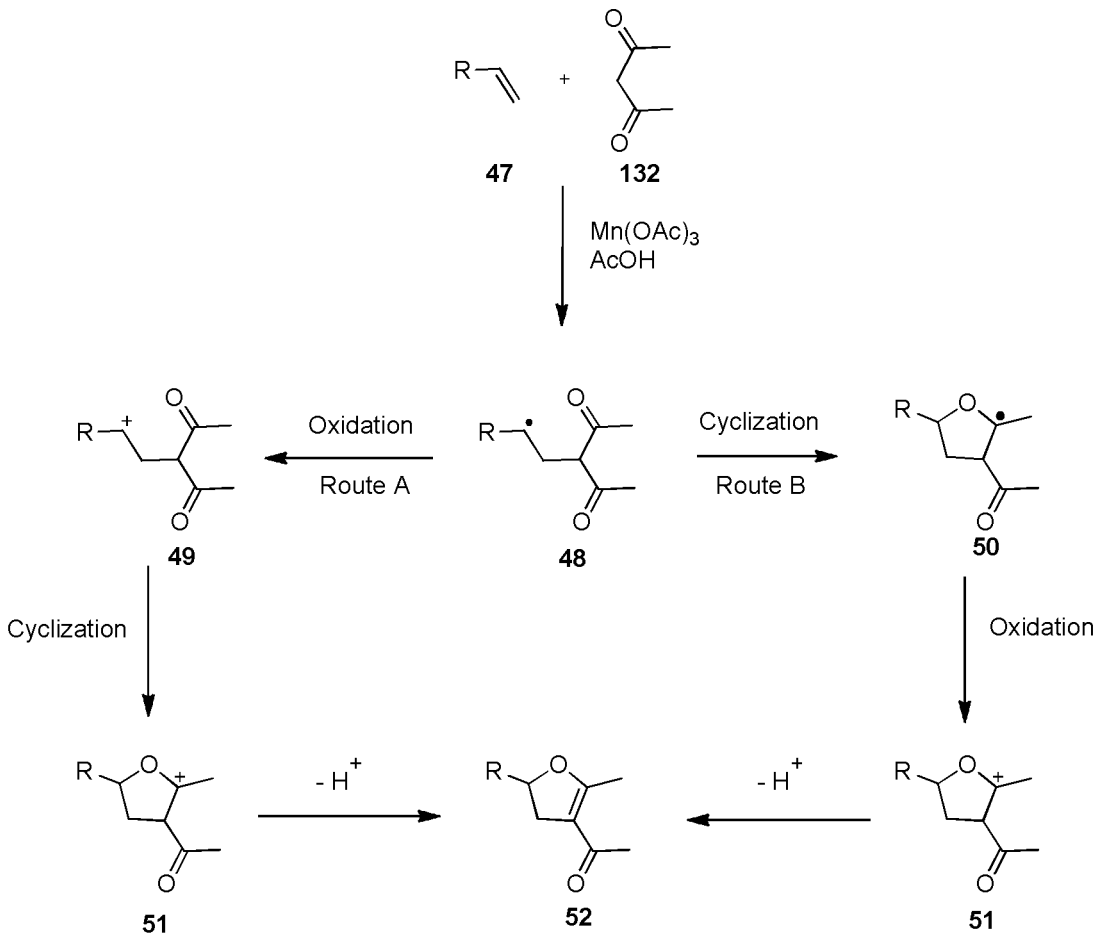
The application of Mn(III) acetate oxidation to β-keto acids was firstly found by Corey, Fristad, and Snider. Corey and Kang reported the oxidative cyclization of unsaturated β-keto acids in 1984 and Corey accomplished the synthesis of γ-lactone derivatives which was named with his name 'Corey Lactones'. By the oxidative cyclization of β-keto acid **45**, lactone **46** was obtained in 63% yield as shown in Scheme 13 [5a].




**45** **46**

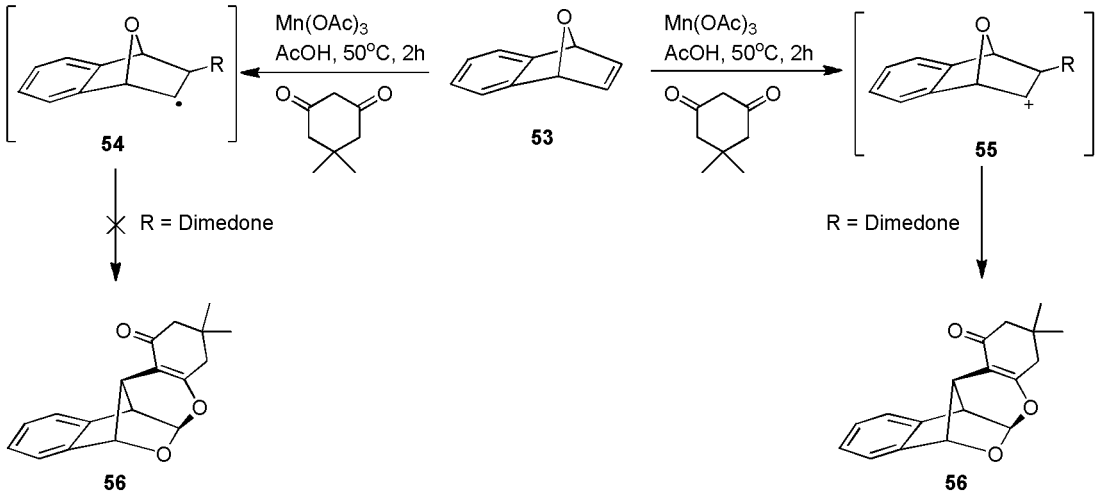
Scheme 13

In regard to the cyclization mechanism, some questions have to be answered. Heiba and Dessau proposed oxidation of the radical **48** to the cation **49** followed by cyclization to the tetrahydrofuran derivative **51** and then loss of a proton to give **52** as in route A in Scheme 13 [2a-b]. On the other hand, Fristad et al. [3a-b] have proposed an alternative route B, where the formed radical **48** undergoes first a cyclization reaction followed by oxidation as shown in Scheme 14.




Scheme 14

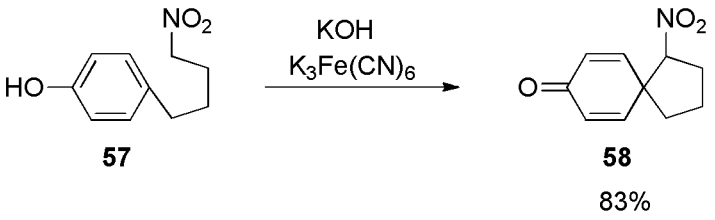
In order to clarify the question, at which stage the second oxidation takes place, Balcı and his co-workers designed a reaction in which possible intermediates such as **48** and **49,** which undergo cyclization, were incorporated in a bicyclic system as shown in Scheme 15. Carbocation intermediates generated on benzonorbornadiene system such as **55** are able to rearrange through a non-classical carbocation and can form new carbon-carbon bond. On the other hand, it is known that radicalic intermediate such as **54**, does not have any tendency for rearrangement. The aim of the research was to see whether any rearranged cyclic products will be observed or not. As the formation of compound **56** was observed, route A was proposed as the mechanism of reaction of alkene and diketone in the presence of $Mn(OAc)_3$ [11].




Scheme 15

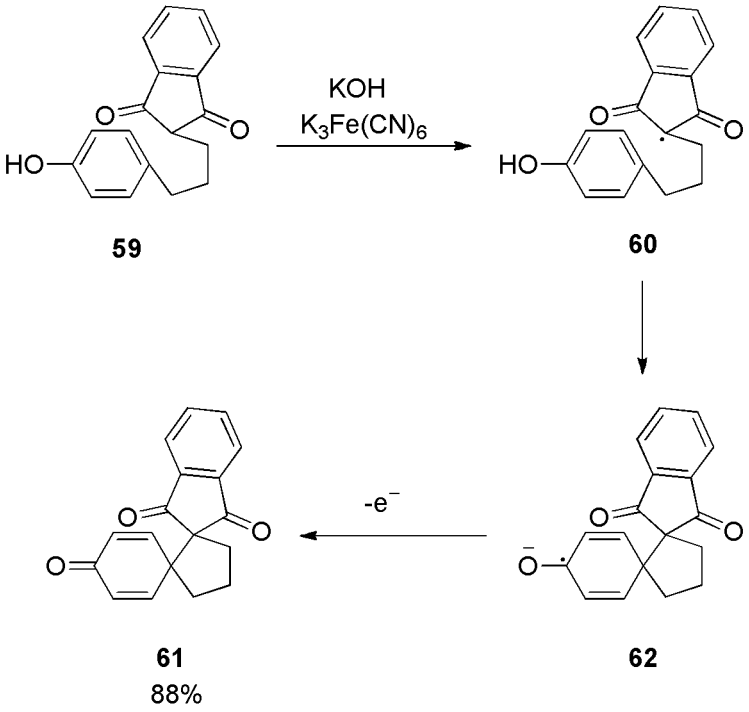
## 1.3 Oxidative Reactions Using Ce(IV), Fe(III), V(V) Metals

Different types of one electron oxidants are also used for free radical formation. It has been found a wide range of application of one electron oxidants such as Ce(IV), Fe(III) etc. to phenolic compounds [12]. Kende [13] used potassium ferrocyanide to oxidize phenols and showed that the nitro group on the side chain of **57** in Scheme 16 acts like an enolizable carbonyl group. He explained the possible course of the reaction as through radicalic and anionic reactive intermediates.



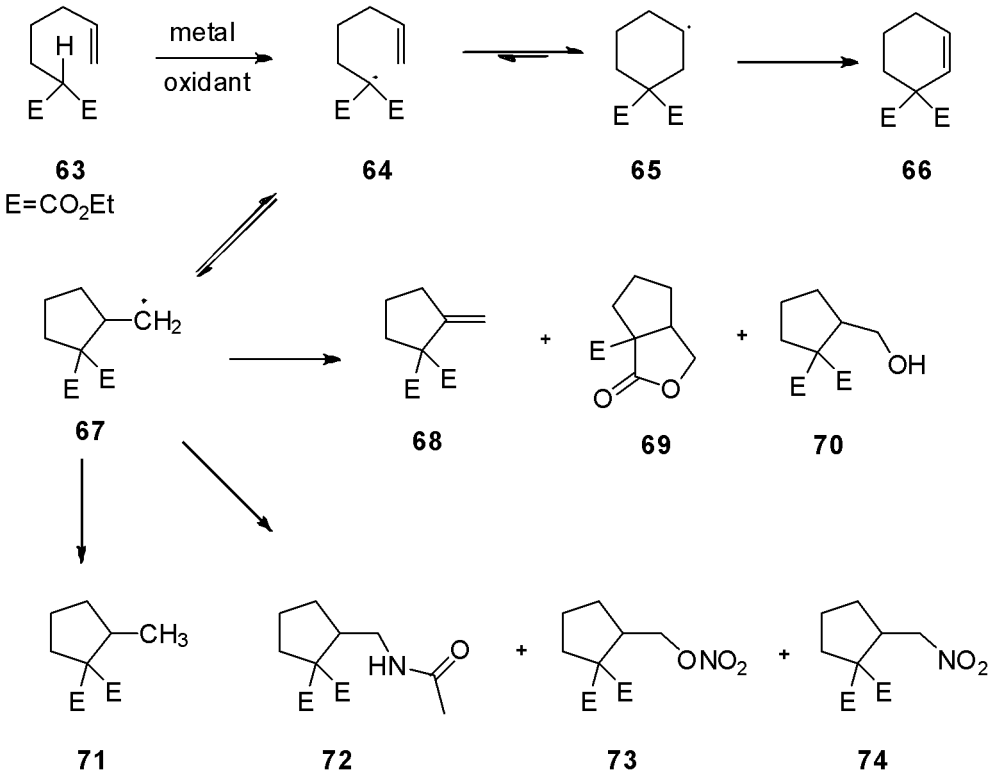

Scheme 16

Furthermore, it has been demonstrated that 1,3-dicarbonyl compound **59** undergoes similar reaction with $K_3[Fe(CN)_6]$ and forms spiro compound **61** in 88% yield as shown in Scheme 17 [13].




Scheme 17

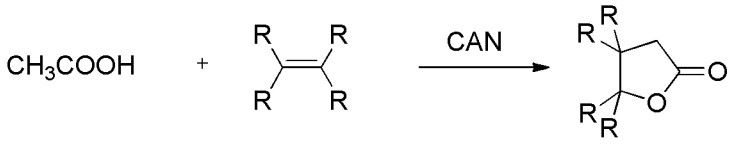
In some cases, using different oxidants gave completely different results [7c]. For example, reaction of **63** with $Mn(OAc)_3$ gave 48% of **69**, 20% of **68** and 7% **67**. However, reaction of **63** with $Fe(ClO_4)_3.9H_2O$ gave 7% of **66**, 4% of **68**, 44% of **69**, 7% of reduction product **71**, 10% of alcohol **70** and 6% of amide **72** as shown in Scheme 17. The last 3 products were not observed when the reaction was carried out using Mn(III) metal. Moreover, when CAN is used, products **73** and **74** are formed too. When $Cu(BF_4)_2$ is used along with CAN, lactone **69** also forms in 86% yield. The difference of the results from the reactions of different oxidation metals arises from the stage at which the oxidation ends. All the oxidants create compound **64** and the formation ratio of compounds **64** to **67** is 9 to 1. The stage at which oxidation ends, depends on the metal, ligand and the solvent.




Scheme 18

Cerium ammonium nitrate (CAN) is a chemical reactive discovered by Smith group in 1936 [14]. CAN, which can easily be obtained in pure form, has cerium atom in the center and contains 6 nitrate groups around it. CAN is used as an oxidant in the redox reactions. CAN is similar to $Mn(OAc)_3$ since it is a one electron oxidant and it has a large oxidation potential (+1,61 V). On the other hand, CAN is superior to $Mn(OAc)_3$ since it is highly soluble in water and poorly soluble in organic solvents which provides better handling in work-up and purification processes.

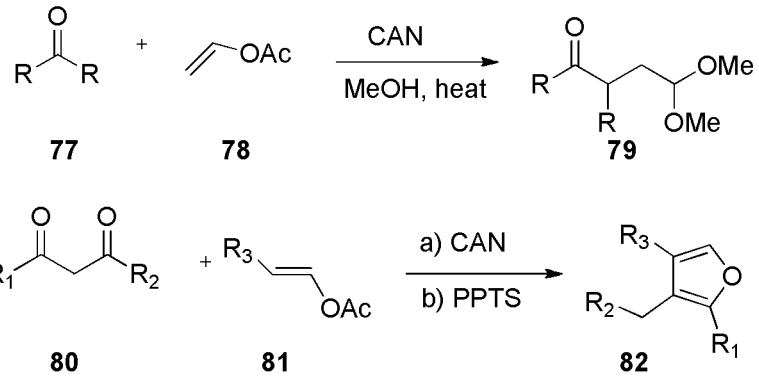
In the reaction of carboxylic acids and alkenes with CAN, lactones are obtained as product [2a].




**7** **75** **76**

Scheme 19

Reactive alkenes such as enol ethers and enol acetates can easily undergo oxidative addition reactions in the presence of CAN [15].

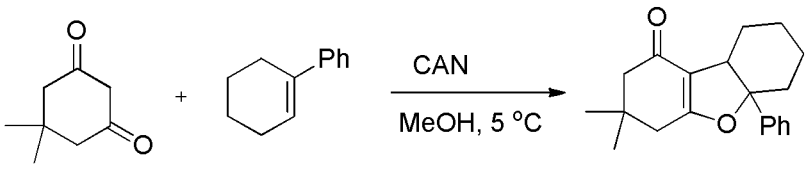



**77** **78** **79**

**80** **81** **82**

Scheme 20

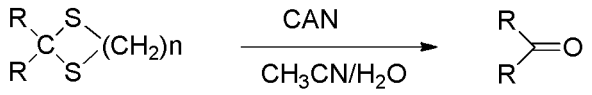
As shown in Scheme 21, addition of β-diketones to cyclic or acyclic alkenes in the presence of CAN gives furan derivatives in high yields [16].




**83** **84** **85**

Scheme 21

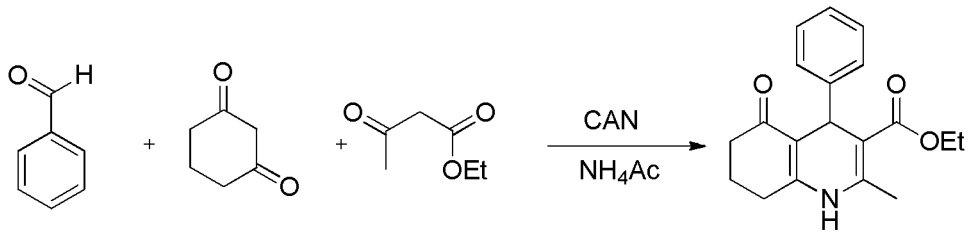
CAN can be used in the deprotection reactions as oxidizing agent as in Scheme 22 [17].




**86** **87**

Scheme 22

Dihydropyridine derivatives, which are pharmaceutical raw chemicals, can also be obtained from the reaction of CAN with diketones as in Scheme 23 [18].




**88** **89** **90** **91**

Scheme 23

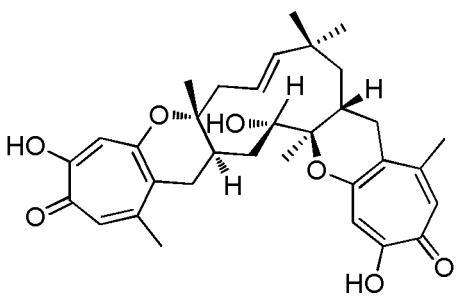
With the use of different oxidative reagents, it is possible to oxidize β-dicarbonyl compounds and create a radical. However, it is important to use up all the oxidative reagents in the reaction medium. Moreover, the metal being used should have the desired oxidative potential and should have a good solubility for the reaction to proceed smoothly.

## 1.4 1,3,5-Cycloheptatriene (Tropylidene)

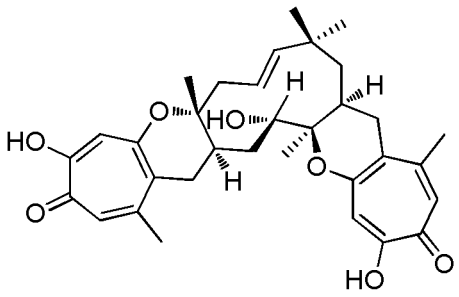
Cycloheptatriene was first synthesized by Richard Willstätter in 1901 [19]. The synthesis was started from cycloheptanone and the seven membered ring structure of the compound was proved.

Cycloheptatriene was considered as an aromatic compound since it has 6 π-electrons and obeys 4+2 rule [20]. Later on, since one of the seven carbon atoms has $sp^3$ hybridization, it was determined with IR spectroscopy [21], electron diffraction, microwave spectroscopy [22] and x-ray crystallography [23] that cycloheptatriene does not have a planar structure and thus is not an aromatic compound.

Cycloheptatriene structure is rarely observed in nature and can be found in the structures of different natural products such as pycnidone and epolone B [24]. It is important to state that antibacterial activity of cycloheptatriene was investigated on different types of bacterias and found that it has considerable effects on the bacterias [25].

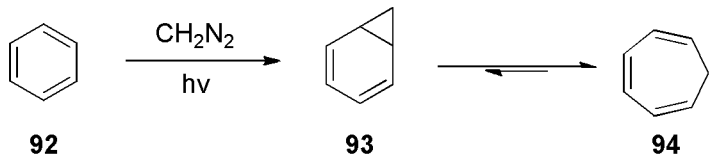



Pycnidone




Epolone B

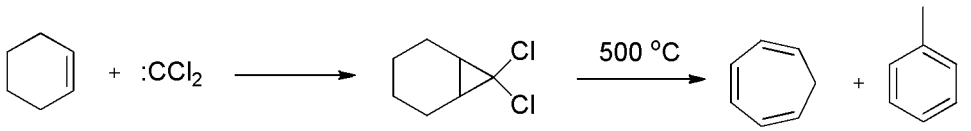
Doering and Knox showed that cycloheptatriene can be synthesized easily by the reaction of benzene with diazomethane through a ring enlargement reaction using ultraviolet light as shown in Scheme 24 [26].




**92** **93** **94**

Scheme 24

Another method for the synthesis of cycloheptatriene is the addition of dichlorocarbene to cyclohexene as in Scheme 25. Further heating of the formed substance at 500°C provides cycloheptatriene along with toluene [26].

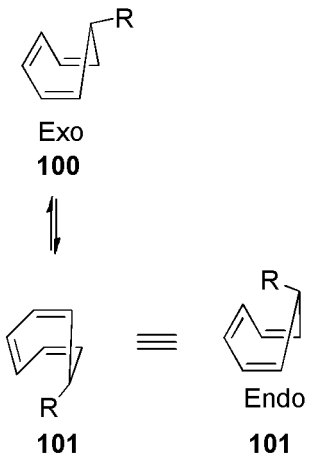



**95** **96** **94** **97**

Scheme 25

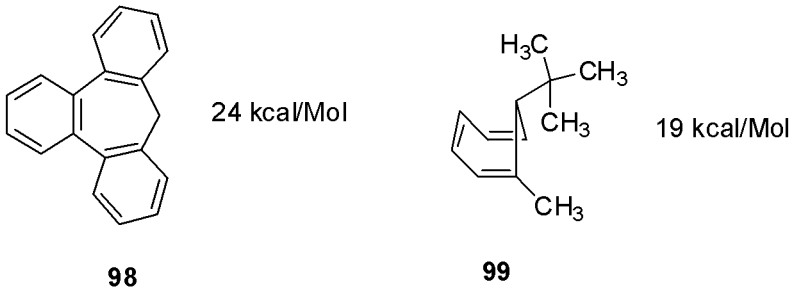
It was later proven by Woods that cycloheptatriene can be quantitatively converted to toluene at 478 °C [27].

Due to its comformation, cycloheptatriene can undergo ring inversion as shown in Scheme 26. The required activation energy for ring inversion is $\Delta G$ = 6 kcal/mol and this amount changes depending on the size of the substituents on carbon C-7. The activation energies, for instance, for tribenzocycloheptatriene **98** is 24 kcal/mol and for 1-methyl-7-tert-butyl-cycloheptatriene **99** is 19 kcal/mol as shown in Scheme 27 [28].




Scheme 26

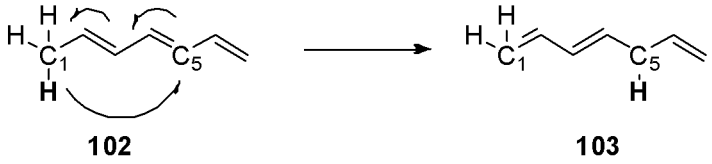
There are two states through ring inversion of cycloheptatriene depending on the position of –R group attached to carbon C-7. Among these states, exo state is more stable because in endo state there is repulsion between R group and π-orbitals of the double bond.




Scheme 27

## 1.5 1,5-Hydride Shift

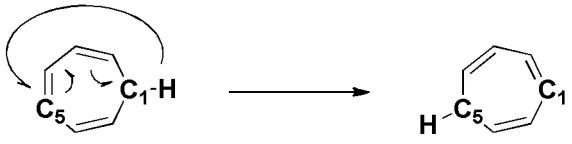
1,5-Hydride shift is the transfer of a proton from C-1 carbon atom to the C-5 carbon atom as demonstrated in Scheme 28.




102 103

Scheme 28

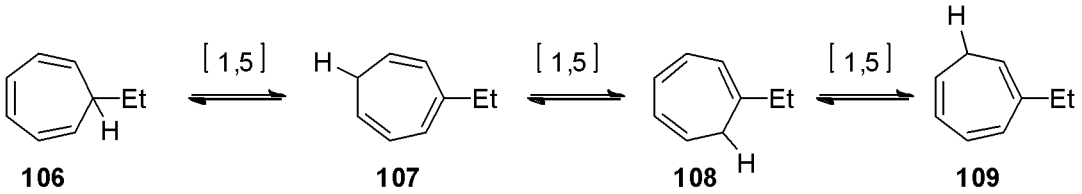
This type of hydride shift is thermally allowed and observed in cycloheptatriene derivatives and the required temperature for this process is 110 °C for unsubstituted cyclohepta-1,3,5-triene as in Scheme 29 [29].




104 105

Scheme 29

The pyrolysis of 7-ethylcycloheptatriene at 400 °C results in the formation of four different isomers [30]. 1,5-Hydride shift is responsible for the formation of these isomers.

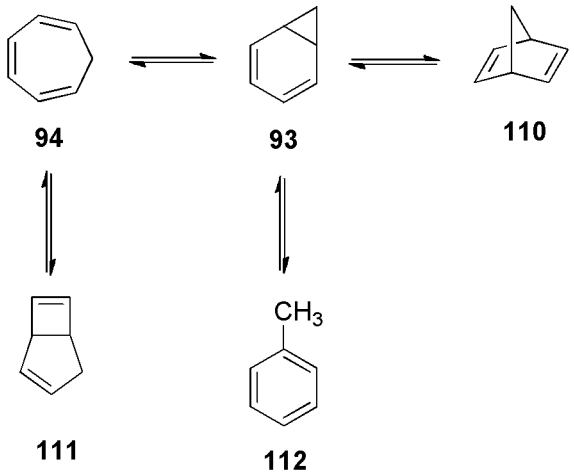



106 107 108 109

Scheme 30

## 1.6 Rearrangements of Cycloheptatriene

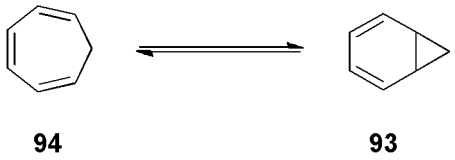
Cycloheptatriene can rearrange to norbornadiene (**110**) [31a-b], bicyclo[3.2.0]heptadiene (**111**) [32], toluene (**112**) [31] and norcaradiene (**93**) [33] through thermal processes [34].




Scheme 31

Among all of these rearrangements, equilibrium between cycloheptatriene and its valance isomer norcaradiene is the most important one.

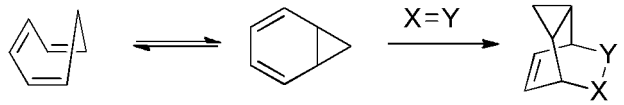
Experimental and theoretical calculations have shown that transformation of cycloheptatriene to norcaradiene structure through [3,3] Cope rearrangement, via disrotatory ring closure according to Woodward-Hoffmann rules, requires 10 kcal/mole.




Scheme 32

Spectroscopic applications could not determine the presence of norcaradiene structure in the case of unsubstituted CHT. Chemical reactions such as Diels-Alder cyclo-addition proved that there exists an equilibrium between cycloheptatriene and norcaradiene. Since cycloheptatriene does not have a planar diene unit, activation energy ($E_a$) is high for a Diels-Alder type reaction. On the other hand, norcaradiene

has a planar diene unit. Therefore, it can undergo easily Diels-Alder reaction due to the lowered activation barrier as in Scheme 33.



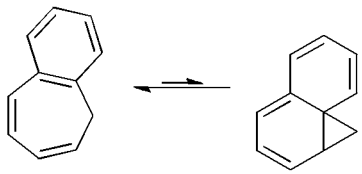

**94** **93** **113**

Scheme 33

Cycloheptatriene – norcaradiene equilibrium can be controlled if desired. There are many factors which can influence the equilibrium.

**a)** If one of the double bonds in CHT or NOR is incorporated in a benzene ring, CHT-NOR equilibrium can be shifted to the side of CHT or NOR as shown below.

**114** **115**



**116** **117**

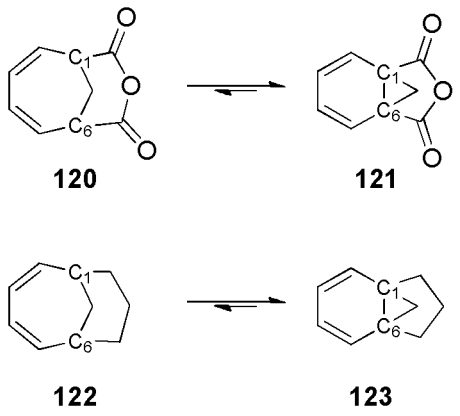
Scheme 34 Cycloheptatriene favored molecules.

**118** **119**

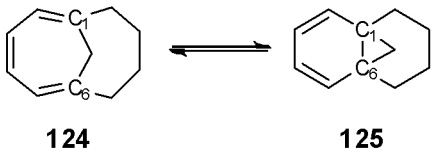
Scheme 35 Norcaradiene favored molecule.

**b)** Since a new bond is being formed between C-1 and C-6 of norcaradiene, any factor that will bring these atoms closer will favor the equilibrium to NCD form. According to this statement a bridge which combines C-1 and C-6 of CHT will shift the equilibrium to NCD form since opening of C-1 - C-6 bond will be prevented by the bridge [35].

However, this shift depends on the number of atoms building the bridge. It has been shown by spectroscopic measurements that while three membered bridge shifts the equilibrium to the side of norcaradiene form as in Scheme 36, whereas five membered bridge shifts the equilibrium to the side of cycloheptatriene as in Scheme 38. On the other hand, four membered bridges have proven to rebuild the equilibrium as shown in Scheme 37.




Scheme 36 Three membered bridges favor NOR form.




Scheme 37 Four membered bridges rebuild the equilibrium.


**126** **127**

Scheme 38 Five membered bridges shift the equilibrium to the CHT form.

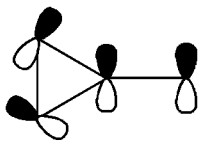
**c)** Electronic structures of substituents on C-7 also affect the equilibrium between cycloheptatriene and norcaradiene. The effects of these groups are separated into 2 main parts.

1- σ-interaction : Interaction of the substituent orbitals with exocyclic orbital of the carbon C-7 [35a].

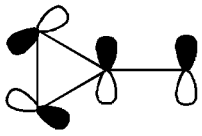
In this type of interaction σ – electron donating groups, such as -Li or $-BH_2$, favors norcaradiene form while σ – electron withdrawing groups, such as $-CF_3$, favors cycloheptatriene form.

2- π-interaction : Interaction with the Walsh orbitals of cyclopropane [35a].

This interaction arises from the electron transfer from the HOMO of cyclopropane to the LUMO of the substituent.



$\Psi_3$ HOMO +(2p)



$\Psi_4$ LUMO +(2p)

Figure 1 HOMO and LUMO Walsh orbitals of cyclopropane and the substituent

If the substituent on C-7;

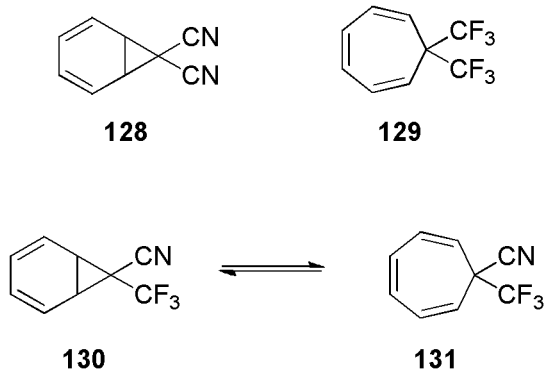
1- is a good π-acceptor
2- has empty 2p molecular orbitals in low energy levels such as –CHO, -CN, -COOR, $-CH_2^+$, this empty orbitals will interact with the HOMO of cyclopropane. With this interaction, electron transfer occurs from HOMO of cyclopropane to the vacant 2p orbitals of the substituent.

Since HOMO of cyclopropane is the main connector between C-1 and C-6, electron transfer from this orbitals to another makes the bond between C-1 and C-6 stronger, since this bond has an antibonding character. This consequently makes the cyclopropane more stable and pushes the equilibrum to the side of norcaradiene form.

If the substituent on C-7;

1- is a good π-donor
2- has completely occupied 2p orbital such as –OR, $-NR_2$, this occupied orbital transfers electron to the LUMO of cyclopropane. Since LUMO of cyclopropane is the anti connector between C-1 and C-6, having this orbital occupied will increase the anti connecting property of LUMO and makes the bond between C-1 and C-6 open up more easily, making norcaradiene unstable and favors the cycloheptatriene form.

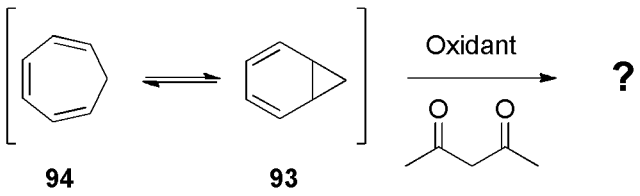
For example, dicyano compound **128** does not equilibrate and it has a norcaradiene structure, whereas, trifluoromethyl substituted compound **129** has CHT structure. On the other hand, compound having trifluoromethyl and cyano groups is in equilibrium with norcaradiene structure.




Scheme 39 π-acceptor and π-donor substituent will rebuild the equilibrium.

## 1.7 Aim of the Study

The aim of the work consists of two parts. In the first part, we had intention to study the reaction of cycloheptatriene with some metal oxidants in the presence of 1,3-diketones.




Scheme 40

Furthermore, we were interested in addressing the question whether CHT or NOR isomer will be involved in the oxidation reaction. Additionally, C-7 substituted CHT derivatives will also be studied during this work to see the effect of the substituent on the course of the reaction.

In the second part, we searched the mechanism for the addition of 1,3-dicarbonyl compounds to double bonds. Mainly, we were interested in answering the question whether cyclization is going over oxygen radical or cyclopropane intermediate.

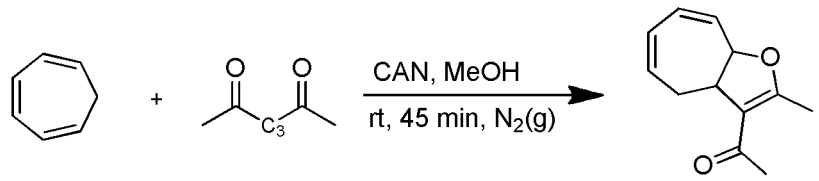
# CHAPTER 2

## RESULTS AND DISCUSSION

### 2.1 Reactions of Cycloheptatriene and Acetylacetone in the presence of Oxidative Reagents Cerium Ammonium Nitrate and Manganase(III) Acetate

In the first part, reactions of CHT and AcAc were carried out under different reaction conditions where different metal oxidants were used.

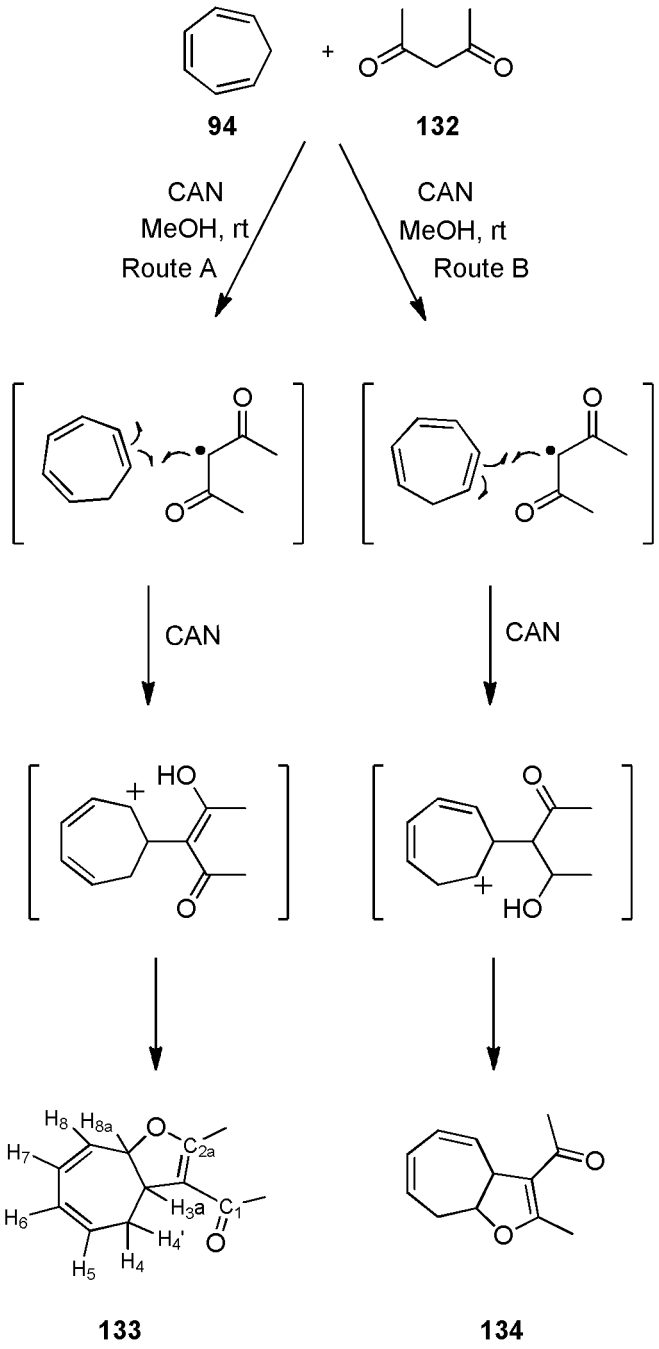
The reaction of cycloheptatriene with acetylacetone in the presence of cerium ammonium nitrate at room temperature provided compound **133**. The reaction was completed in 45 minutes. The formation of any isolable side product was not detected.




**94** **132** **133**

Scheme 41

The reaction proceeds regiospecifically since there are two possible expected products in this reaction. The radical forming on C-3 of acetylacetone by CAN can be added both as in route A and route B as shown in Scheme **42**.




Scheme 42

However, since the allylic radical and its carbocation forming in route A is more stable than the radical and carbocation forming in route B, we do not observe compound **134** in this reaction.

In $^{1}H$ NMR of compound **133**, there are ten different protons. The olefinic protons resonate very close to each other between 5.8 and 6.1 ppm. Olefinic proton H-5 couples with methylenic proton H-4 and olefinic proton H-6 giving a doublet of doublets. Since proton resonances do not show any correlation between protons H-4′ and H-5, we can assume that the dihedral angle between protons H-5 and H-4′ is close to 90°. Proton H-6 resonates as "doublet of doublets of doublets" and these couplings come from two olefinic protons H-5, H-7 and an allylic proton H-4. However, we can not observe an allylic coupling between the proton H-7 and proton H-8a, which brings up the same result as in the case of proton H-4′ and H-5 which is dihedral angle is close to 90°. The coupling constants of the olefinic protons are in the usual range.

As for proton H-8a, it resonates at 4.92 ppm due to the oxygen atom and the double bond in the α-position.

Proton H-3a resonates as "broad triplet" at 3.18 since it has an α-double bond and β-oxygen. The triplet splitting is probably arising from the coupling with the protons H-8a and H-4. Line broadening is probably due to the coupling with H4′(dihedral angle is probably close to 90°) and long range coupling with methyl protons.

Methyl group attached to the double bond resonates as doublet at 2.16 ppm due to the long range coupling, whereas the other methyl group resonates as singlet at 2.18 ppm.

Even though structure was expected and confirmed by $^{1}H$ and $^{13}C$ NMR spectra, it has further been proved with 2D NMR spectra such as COSY, HMBC and HSQC. Our key point for the structural assignment of compound **133** is the correlation of protons H-8a and H-8 in COSY spectrum. Correlation between these protons can easily be observed as in Figure 2 below.

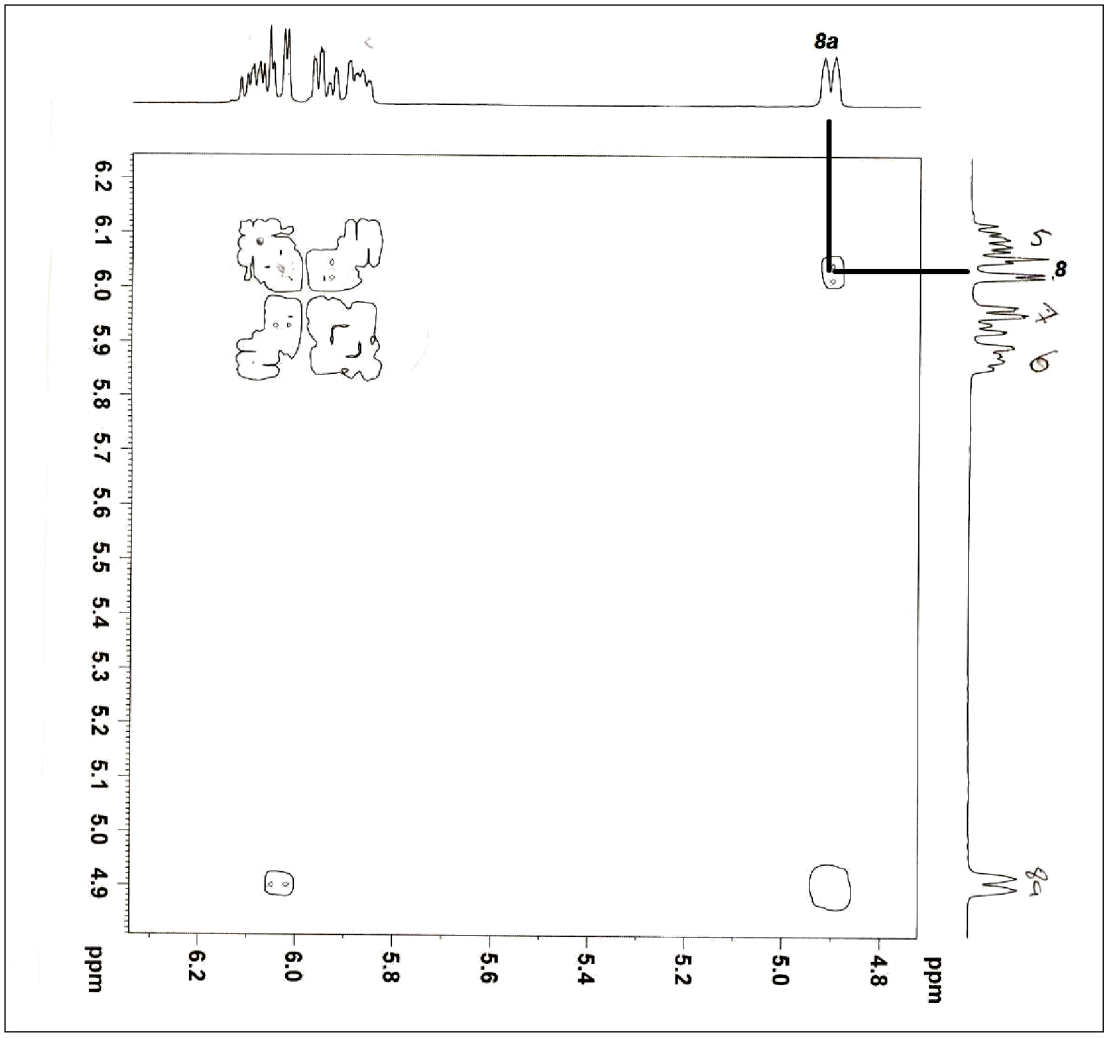


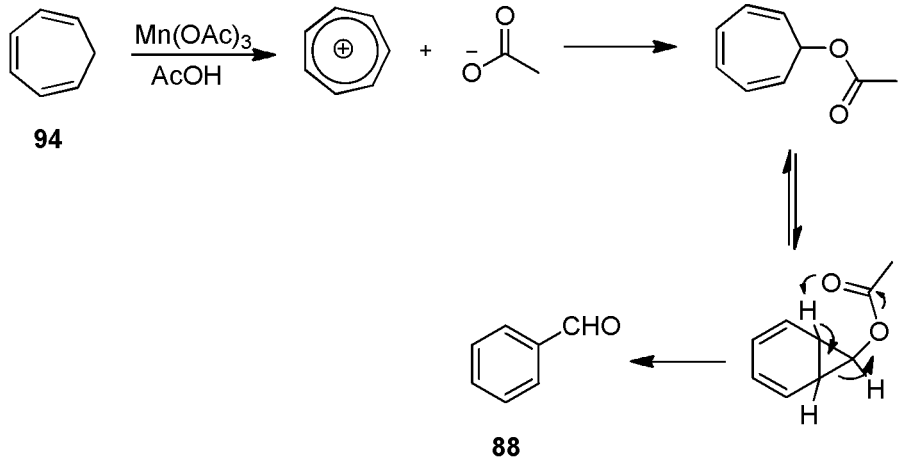

**Figure 2** A part of COSY spectrum of compound **133**

Carbon NMR is in good agreement with the structure proposed. Peaks at 193.1 and 166.9, which are C-1 and C-2a, proves the existence of an α,β-unsaturated carbonyl group indicating the formation of a dihydrofuran ring . Apart from C-2a there are 5 more alkene carbon peaks that belong to carbons C-5, C-6, C-7, C-8 and C-3.

The obtained product proves us that the mechanism of the reaction is in agreement with the pathway that Balcı et al. have proven before [11].

In the second reaction, cycloheptatriene was reacted with acetylacetone in the presence of $Mn(OAc)_3/Cu(OAc)_2$ in acetic acid at 80 °C. Use of AcOH as solvent is crucial because it can easily dissolve $Mn(OAc)_3$ compared to any other organic solvent.

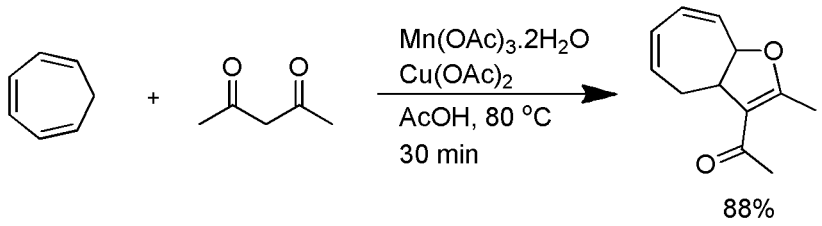
The reaction of CHT with $Mn(OAc)_3$ when there is no 1,3-dicarbonyl compounds results in the formation of benzaldehyde in high yield [6]. The formation mechanism of the reaction is given below. The first step involves the abstraction of hydrogen radical ($H^{\cdot}$) from the methylenic protons followed by oxidation. The formed tropylium cation can be transferred into benzaldehyde as shown on Scheme 43.




Scheme 43

It was interesting to note that the formation of benzaldehyde was not detected during our reaction. This can be explained by the fact that $Mn(OAc)_3$ removes hydrogen radical from the methylenic protons of 1,3-diketone compound since they are more acidic than the methylenic protons of CHT.

Formed radical on AcAc adds to the double bond of CHT. Oxidation of the radical on CHT followed by ring closure results in the formation of the same product **133** with 88% yield that we obtained before shown in Scheme 44.

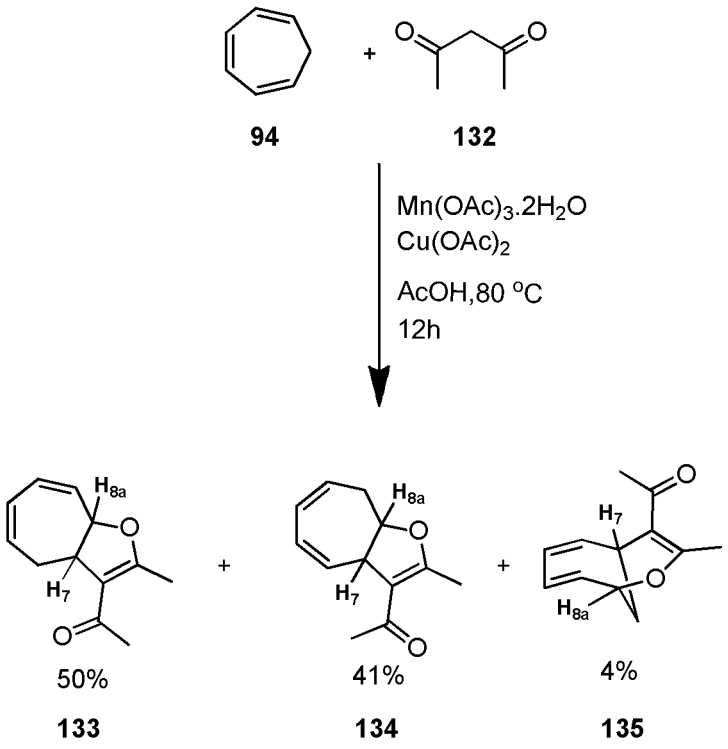



**94** **132** **133**

Scheme 44

In this reaction, 2.7 equivalence of $Mn(OAc)_3$ and 0.3 equivalence of $Cu(OAc)_2$ were used. Generally, using of $Cu(OAc)_2$ with $Mn(OAc)_3$ increases the rate of the oxidation reaction of the initially formed radical.

In the next step, the reaction time was changed. CHT was reacted under the same reaction conditions with $Mn(OAc)_3/Cu(OAc)_2$ at 80 °C for 12 hours. Inspection of the reaction mixture showed the formation of two new additional products **134** and **135** in 41% and 4% yields at the cost of **133,** respectively as shown in Scheme 45.




**133** **134** **135**

Scheme 45

The resemblance of the $^{1}H$ and $^{13}C$ NMR spectra of compound **134** with that of compound **133** indicated the presence of an isomeric mixture. However, olefinic proton resonances were collapsed. The analysis of the signals was not possible. Taking the NMR spectrum in benzene-$d_6$ resolved the resonance signals and made it possible to analyze NMR spectrum as shown in Figure 3 and Figure 4.

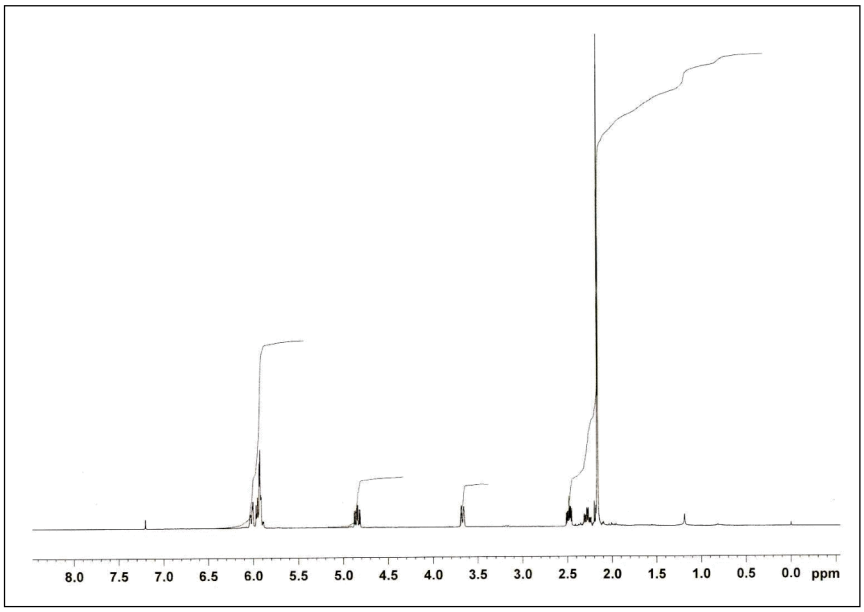



**Figure 3** $^{1}H$ NMR spectrum of **134** in d-$CHCl_3$

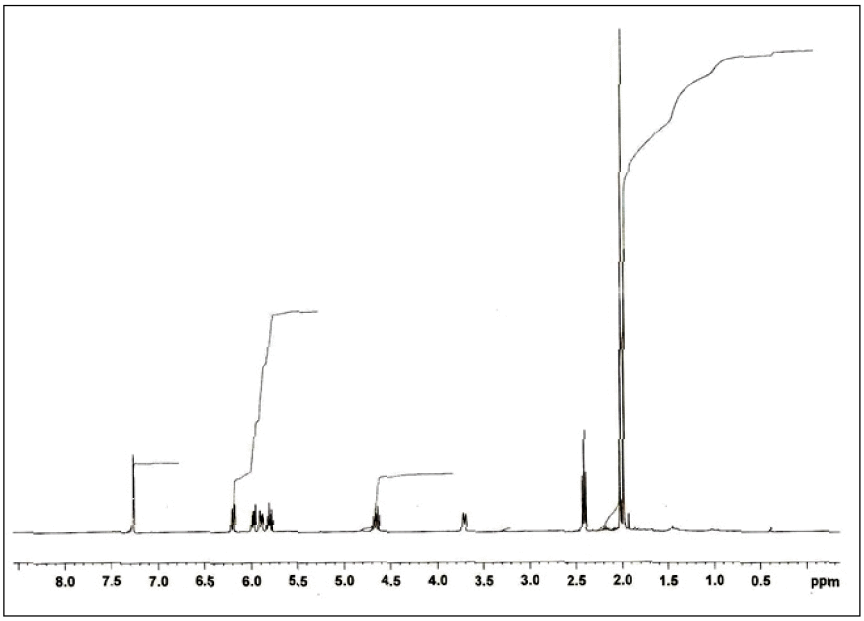



**Figure 4** $^{1}H$ NMR spectrum of **134** in d-$C_6H_6$

As in the case of compound **133,** there are four olefinic protons resonating between 5.7 and 6.2 ppm. The main difference between the two molecules is the position of double bonds as shown in **133** and **134**. H-7 proton resonates at lower field due to the presence of an additional double bond in the α-position. On the other hand H-8a proton resonates at higher field. The remaining proton resonances of **134** are quite similar to those of **133**.

It can easily be observed from the COSY spectrum of **134** that the proton H-8a does not have any correlation to any of the olefinic protons as seen in Figure 5. On the other hand, proton H-3a has strong correlation to an olefinic proton in the α-position. This information is the key point for the constitutional determination of compound **134**.

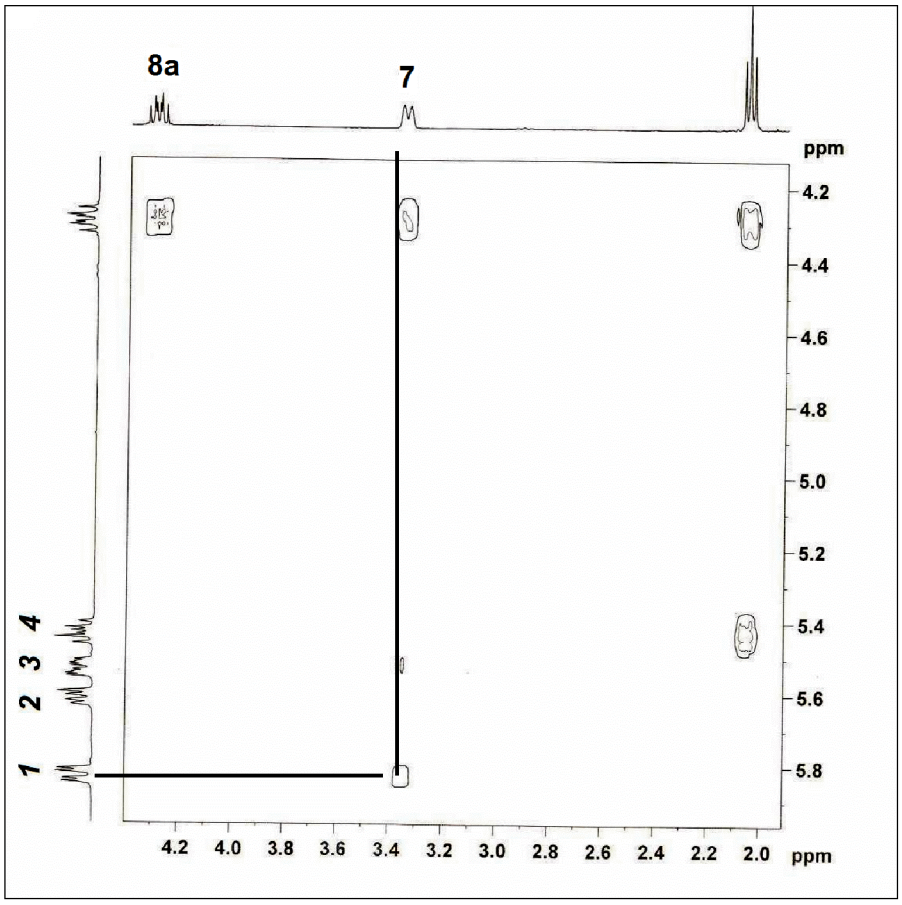
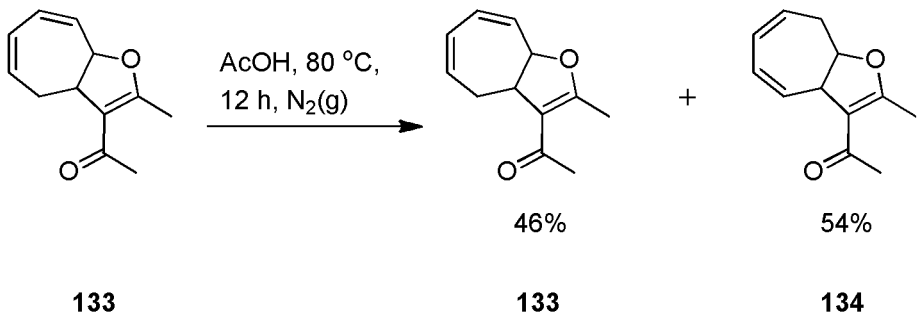



**Figure 5** A part of the COSY spectrum of compound **134**

When we look at the $^{13}C$ NMR spectrum, we again see the peaks of an α,β-unsaturated carbonyl group at 192.2 and 167.3. Also there are five additional alkene carbons observed as in compound **133**.

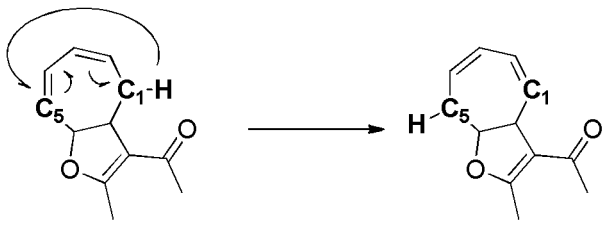
The formation of isomer **134** needs an explanation. Considering the formation mechanisms of the products we can say that while compound **135** is a primary product, compound **134** can only be a secondary product

Still, in order to prove that compound **134** is a secondary product we heated **133** in AcOH at 80 °C for 12 hours as shown in Scheme 46.




Scheme 46

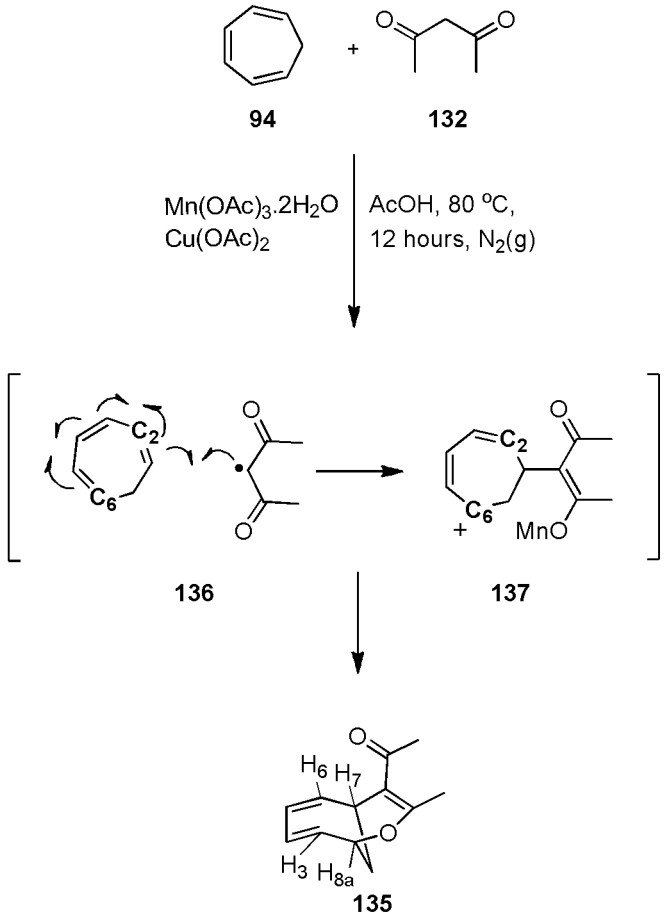
We noticed that approximately the half of the starting material **133** was converted into **134**. After being sure that compound **134** is a secondary product, the formation mechanism was quite easy to comprehend. Only possible phenomena for the formation of compound **134** would be [1,5] thermal hydride shift. This type of shift of hydrogen is thermally allowed in CHT molecule and the required temperature is 110 °C for unsubstituted CHT. Obviously the required temperature is around 80 °C for compound **133** due to the attached dihydrofuran ring, which bring the compound in a suitable conformation and decrease the activation barrier required by [1,5] hydrogen shift.




**133** **134**

Scheme 47 [1,5] thermal hydride shift on compound **133**

The third compound **135** is probably formed via [6+3] addition of AcAc to CHT which is a common addition process for CHT. The formation mechanism is similar to the formation of **133**. Initially formed radical undergoes an oxidation to give **137** which can be stabilized by delocalization of the positive charge. Ring closure at C-6 can provide the compound **135** as in Scheme 48.




Scheme 48 The formation mechanism of compound **135**

For the characterization of compound **135** we mainly used COSY spectrum along with HSQC. The protons H-7 and H-8a both have correlation with the olefinic protons while in compounds **133** and **134** only one proton had the correlation with olefinic protons. Also, unlike compounds **133** and **134**, there were no correlations between protons H-7 and H-8a. This fact can only be explained by 1,6-bridging in **135**. Other spectral data is in good agreement with the proposed structure.

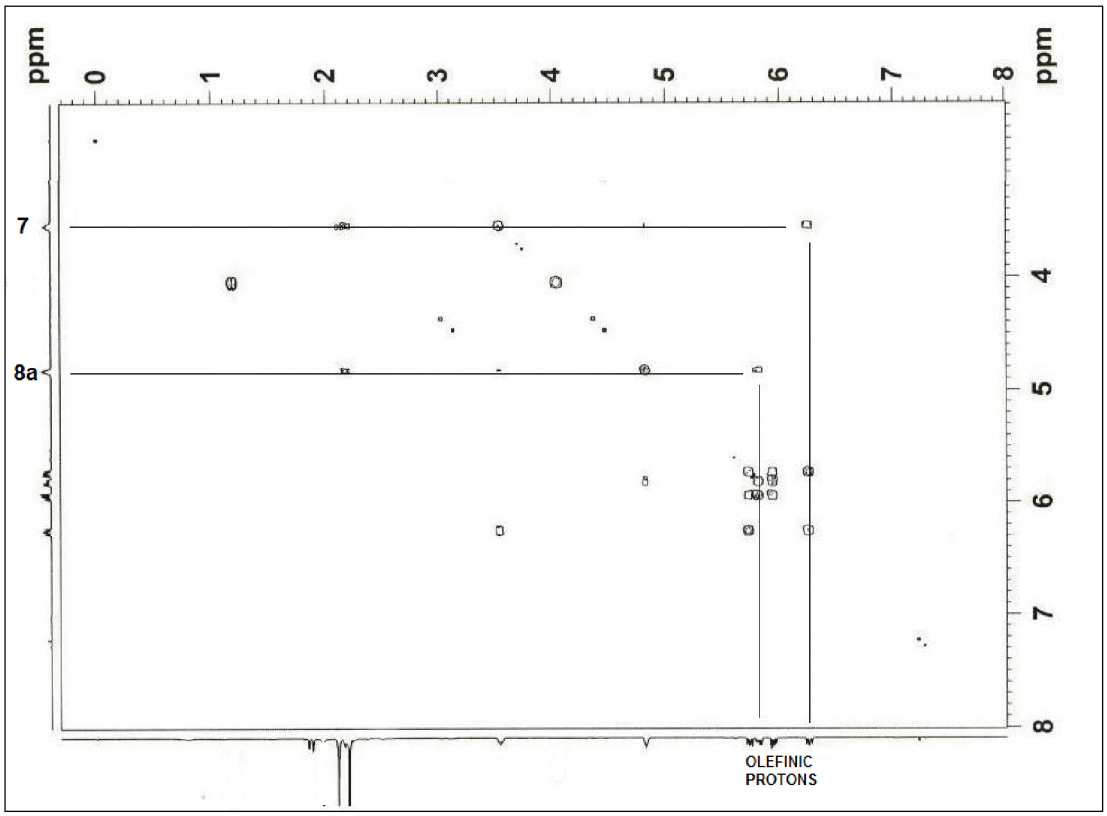
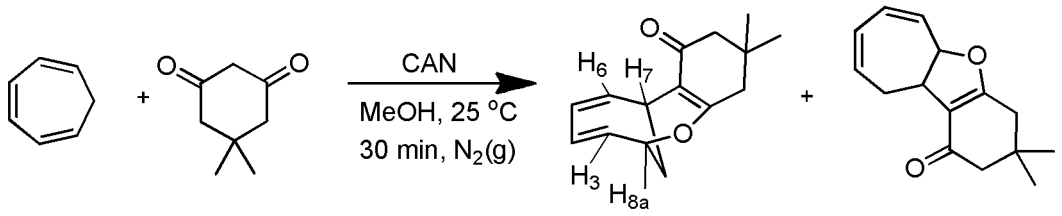



**Figure 6** A part of COSY spectrum of compound **135**

## 2.2 Reactions of Cycloheptatriene and Dimedone in the presence of CAN Or $Mn(OAc)_3$

We continued the first part of our work with the reaction of CHT and dimedone, a better enolizable 1,3-diketone, and discussed our results.

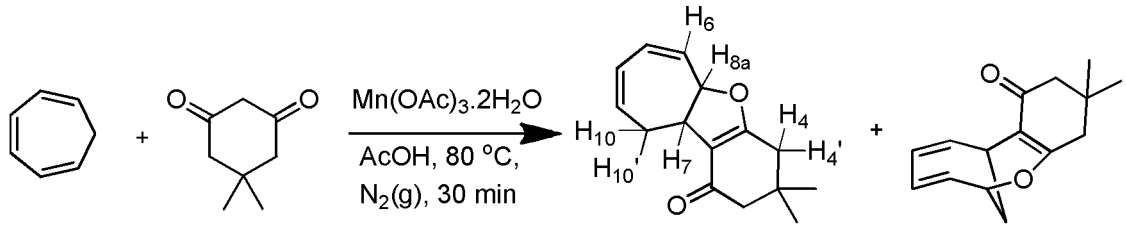
First, we have searched the reaction of dimedone with CHT in the presence of CAN. This time we observed [6+3] addition compound **138** as the major product beside the [3+2] addition product **139** which is the minor product as shown in Scheme 49.




Scheme 49

Compound **138** has similarities with compound **135** such as resonation of olefinic protons, and the position of H-8a and H-7. This resemblance brings up a [6+3] addition of dimedone to CHT which was then proved by using 2D NMR spectra like COSY, HSQC and HMBC. Again the key point was the correlation of protons H-8a and H-7 with olefinic protons H-3 and H-6 respectively. Since they both have correlation, unlike their [3+2] addition product counterparts, [6+3] addition skeleton was the only possible structure. We can also easily observe that the methyl groups of dimedone are resonating at 1.02 and 1.05 ppm.

Reaction of CHT with dimedone in the presence of $Mn(OAc)_3$ gave the same products, observed by the reaction with CAN, however, totally in reversed yields. The major product was [3+2] addition product while [6+3] addition product was formed as the minor product as shown in Scheme 50.



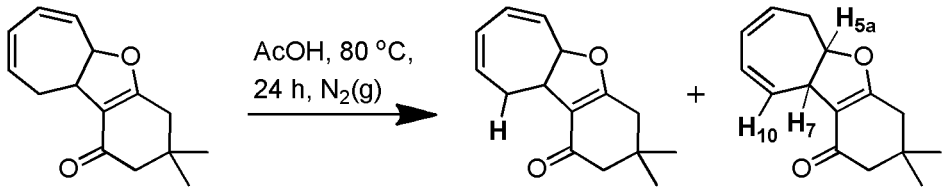

**94** **83** **139** **138**

Scheme 50

Compound **139** has similarities with compound **133**. The key point for the structural assignment was the correlation of proton H-8a with olefinic proton H-6. The existence of dihydrofurane ring also proves that there is a cyclization of dimedone unit present. In this molecule we can not observe a measurable coupling between methylenic protons H-10, H-10' and proton H-7. The reason is due to line broadening of the coupling between protons H-7 and H8a. This large coupling constant prevents the observation of small coupling constants between protons H-10, H-10' and proton H-8a. And the reason of this small coupling constants, even though any measurements were not made, may arise from the dihedral angle between methylenic protons H-10, H-10' and proton H-7. Another reason for the broadness of the peak that belongs to proton H-7 is due to small, long range coupling constant coming from the methylenic protons H-4 and H-4'.

In order to see whether this adduct **139** can also undergo a similar 1,5-hydrogen shift or not, **139** has been dissolved in AcOH and heated for 24 hours. Analysis of the reaction mixture indicated the formation of an isomeric mixture consisting of **139** and **140** approximately in a ratio of 1:1 as shown in Scheme 51. The isomer **140** has similarities with compound **134** as compounds **139** and **138** have with their AcAc counterparts. The key point for structural assignment was the observation of the correlation of proton H-7 with olefinic proton H-10 which requires the use of a COSY spectrum. The absence of correlation between the proton H-5a and an olefinic

proton again proves that a [1,5] thermal rearrangement has taken place. With the existence of dihydrofurane ring the structure was proved.




48% 52%

**139** **139** **140**

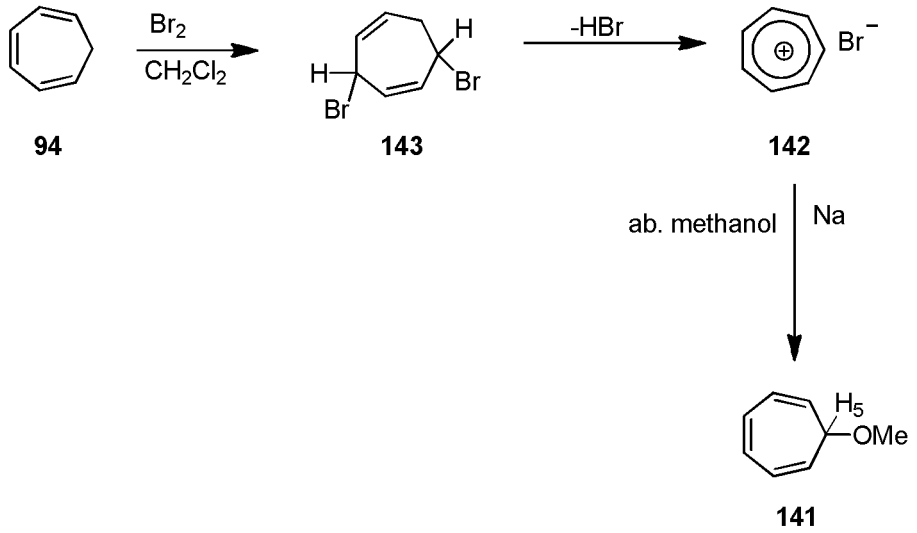
Scheme 51

## 2.3 Synthesis of Substituted Cycloheptatriene Derivatives

During oxidation reactions of CHT with different metals and different 1,3-dicarbonyl compounds, we did not observe any trace of products derived from the valance isomer norcaradiene. Therefore, we decided to carry out similar reactions with at C-7 substituted CHT derivatives. The substituents were chosen as –OMe and –CN groups which are electron releasing and electron withdrawing groups respectively.

### 2.3.1 Reactions of 7-Methoxycyclohepta-1,3,5-triene (141)

In order to obtain compound **141**, we synthesized tropylium cation **142** according to the procedure by Doering and Knox [36] by the bromination of CHT followed by HBr elimination under reduced pressure as in Scheme 52. Once we have tropylium cation **142** we added freshly prepared $NaOCH_3$ solution prepared by the addition of metallic sodium to absolute methanol and obtained compound **141** in 2 hours.

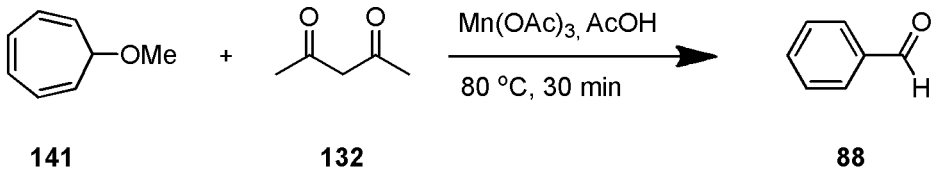



Scheme 52

Compound **141** supposed to have five different protons which are three different olefinic protons, one methoxy proton and proton H-5, that we should observe in the $^1$H NMR spectrum. However, even though we can observe the three olefinic protons we can not observe the other two protons separately.

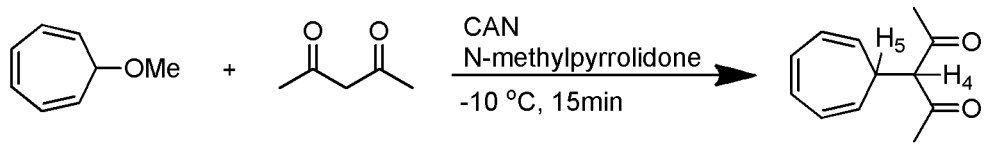
The reaction of compound **141** with AcAc in the presence of $Mn(OAc)_3$ in AcOH, gave benzaldehyde as the only product. Careful examination of the reaction mixture did not reveal the formatin of any addition product as we have observed in the reaction of unsubstituted CHT.

Formation of benzaldehyde was expected since it is commonly observed with cycloheptatriene molecules having electron releasing groups on C-7 position as in Scheme 53.




Scheme 53

When we change our solvent and metal oxidant with N-methylpyrrolidone and CAN respectively, we obtained compound **144** as shown in Scheme 54.



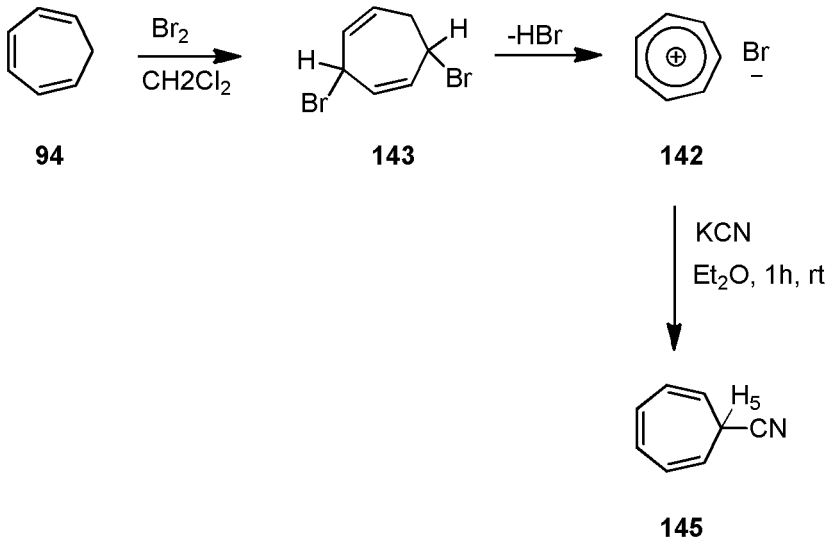

**141** **132** **144**

Scheme 54

Compound **144** has similar olefinic proton resonances as **141**. The $^{1}H$ NMR spectrum shows the presence of two equal methyl protons and two different CH protons resonating separately. There are also three different olefinic protons in the alkene range. Moreover, since the doublet with 11.4 Hz coupling at 4.0 ppm is a typical peak for proton H-4 we can conclude that the doublet of triplets at 2.92 ppm belongs to proton H-5. $^{13}C$ NMR is also in agreement with the structure, giving 7 different peaks at plausible points.

### 2.3.2 Reactions of 7-Cyanocycloheptatriene (145)

For the synthesis of 7-cyanocycloheptatriene **145**, tropylium cation was dissolved in water and treated with KCN salt. After a proper extraction with $Et_2O$, compound **145** was obtained.

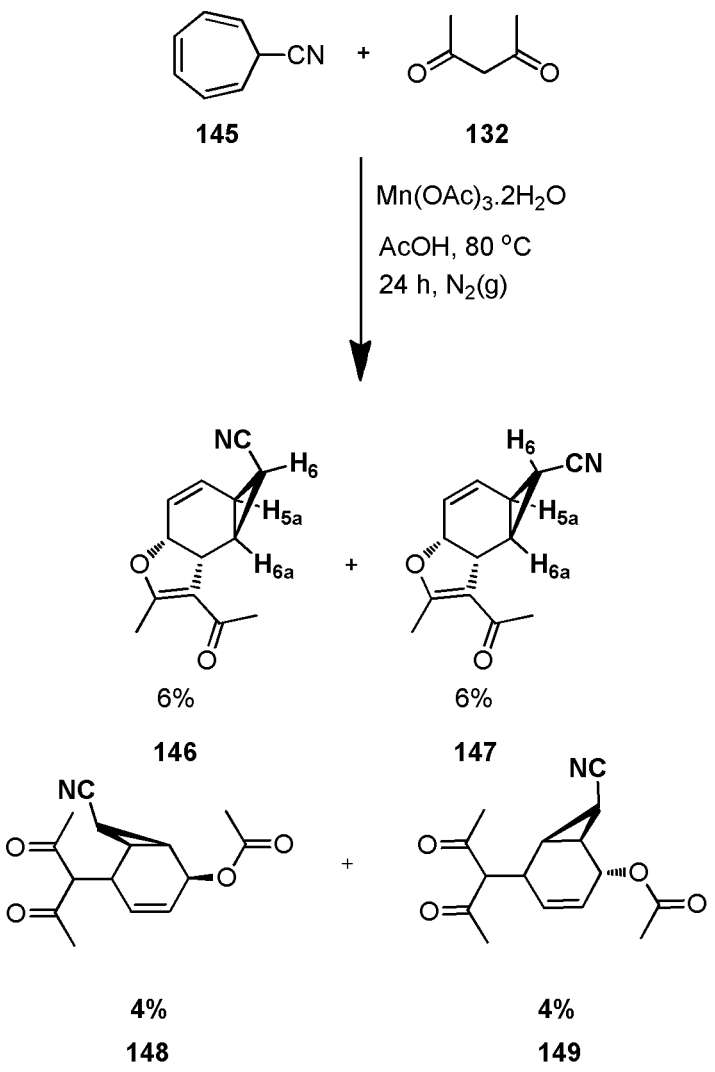



**94** **143** **142** **145**

Scheme 55

$^{1}$H NMR spectrum of compound **145** resembles that of compound **144**'s. The expected peaks in $^{1}$H NMR spectrum are well separated. Three olefinic protons resonate at 5.4, 6.3 and 6.7 ppm. The remaining proton resonates at 3.0 ppm and the integral ratio of the protons is 2:2:2:1. Also in $^{13}$C NMR, the presence of three resonances in olefinic ranges, one peak for the carbon bearing H-5 and the specific peak for –CN group at 121 ppm is in good agreement with the structure.

Since it is known that electron withdrawing groups such as –CN, shifts the CHT-NOR equilibrium to the NOR side, we expected products derived from norcaradiene upon reaction of 7-cyanocycloheptatriene with oxidants in the presence of dicarbonyl compounds. The reaction of **145** with AcAc in the presence of $Mn(OAc)_3$ in AcOH formed four different products of two different types with very low yields as shown in the Scheme 55 below. The forming products were all NOR type products as expected.




Scheme 55

Unfortunately we could only separated compound **146** and compound **147**. The other two isomers could not be separated. In the characterization of compound **146** and **147**, the key point was the cyclopropane ring resonances in the $^1$H NMR spectrum. A typical trans coupling is usually higher than cis coupling. However, in the case of cyclopropane, cis coupling is always higher than trans coupling. Since the coupling constant between proton H-6 and protons H-5a and H-6a in compound **146** (J=8.3 Hz) is larger than that of compound **147** (J=5.4 Hz), the compound **146** was assigned as the endo isomer. The existence of a cyclopropane ring means that reactions proceeded through NOR form due to electron withdrawing group on C-7 position. It

can easily be seen from the $^{13}C$ NMR spectrum that dihydrofuran ring also exists proving the structure we proposed.

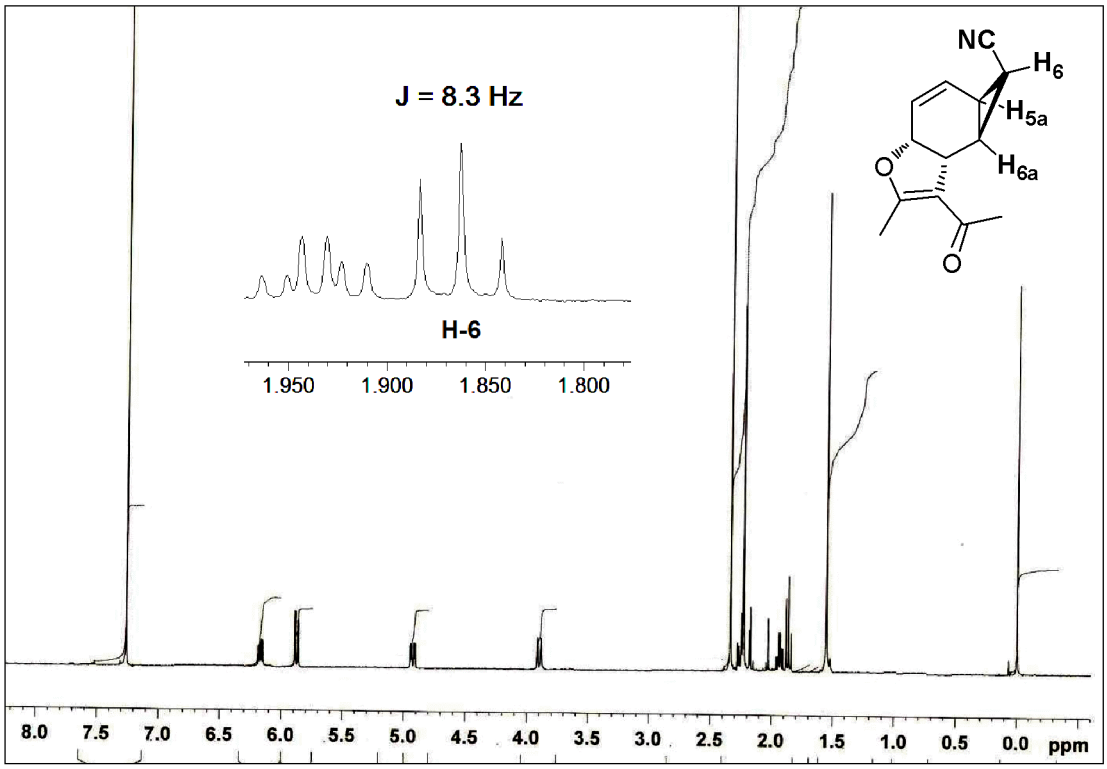



**Figure 7** $^{1}H$ NMR spectrum of compound **146**

The $^{1}H$ NMR spectrum of isomer **147** is almost identical to that of compound **146**. Only main difference is in the high field by cyclopropane ring's protons. As mentioned earlier this difference arises from the endo and exo positions of CN group on cyclopropane. Since the coupling constant between the cyclopropane protons in **147** is smaller than that of compound **146**, this molecule has the exo structure. $^{13}C$ NMR spectra are also quite similar, proving the existence of a dihydrofurane ring.

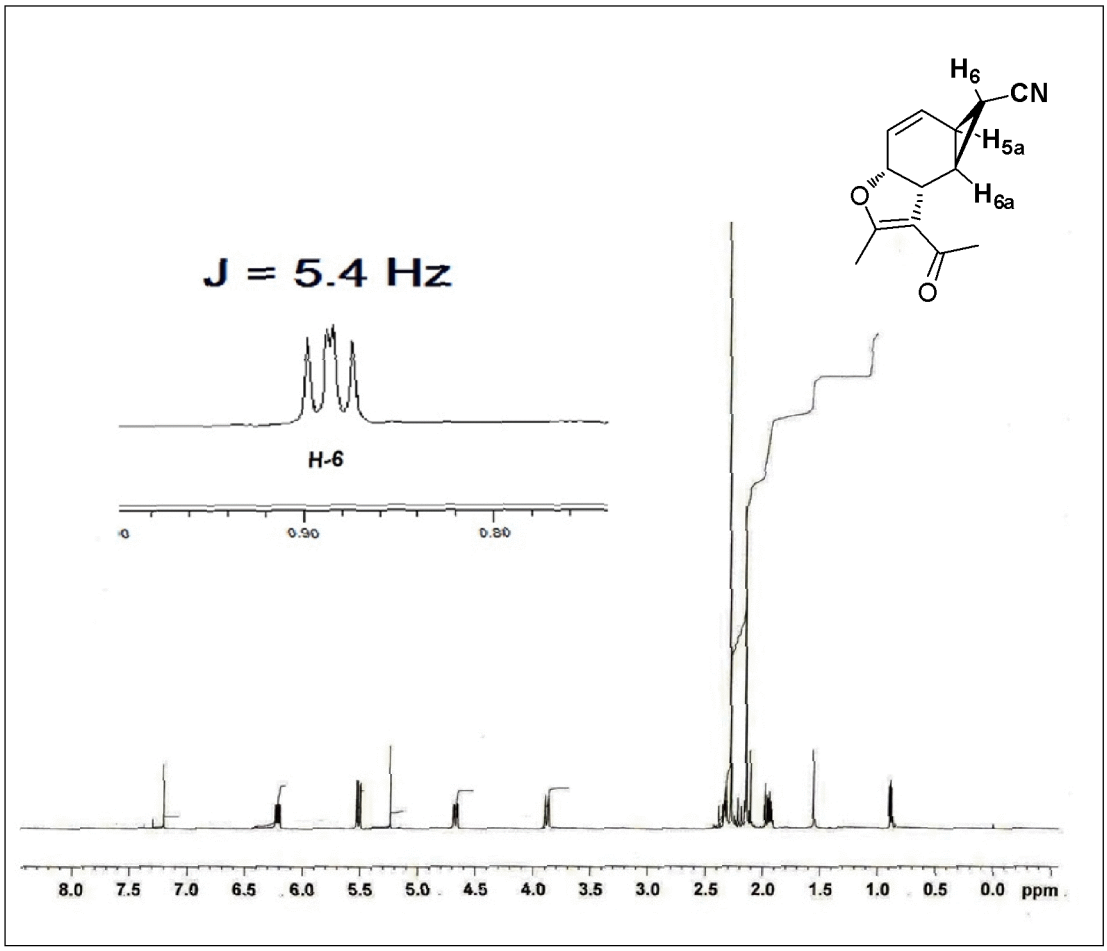
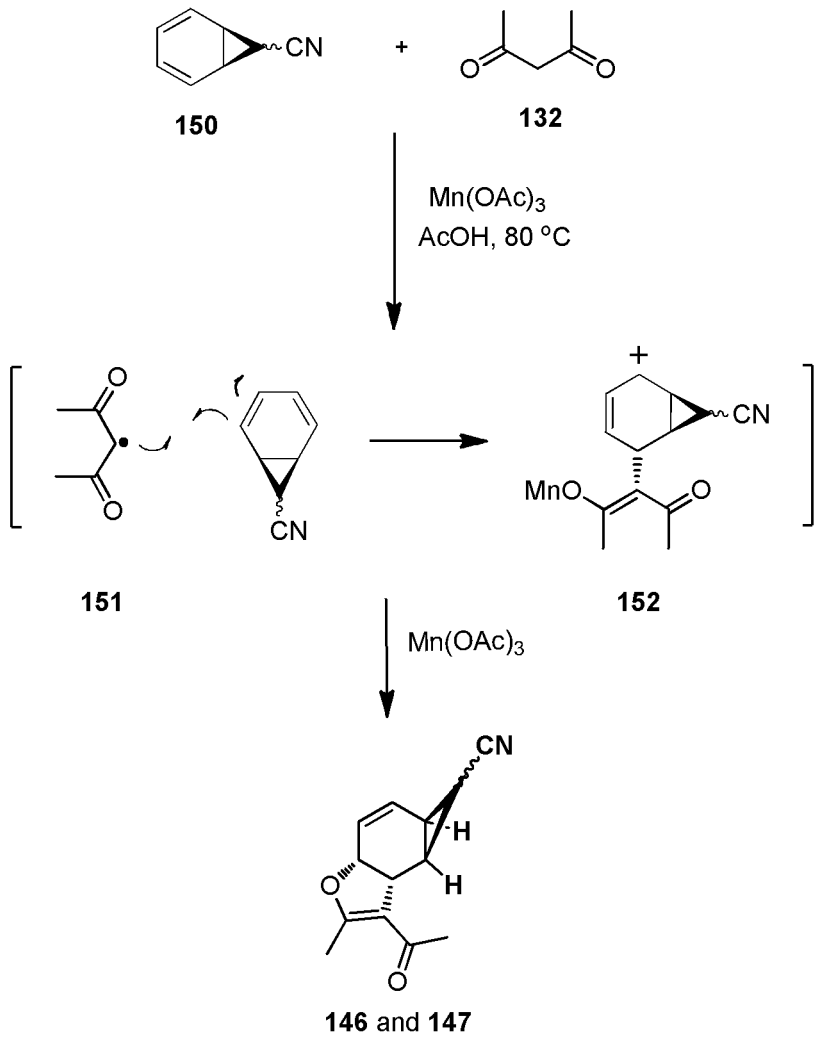



**Figure 8** $^{1}$H NMR spectrum of compound **147**

The other isomers, compounds **148** and **149**, which could not be separated, were characterized by using 2D NMR spectra such as COSY, HMBC and HSQC. The analysis of the $^{1}$H NMR spectrum of the mixture showed the trans configuration of the cyano group. So the isomerization is not due to the position of –CN group. Instead, it is due to a chiral point which is probably the attachment of acetate group coming from the solvent.

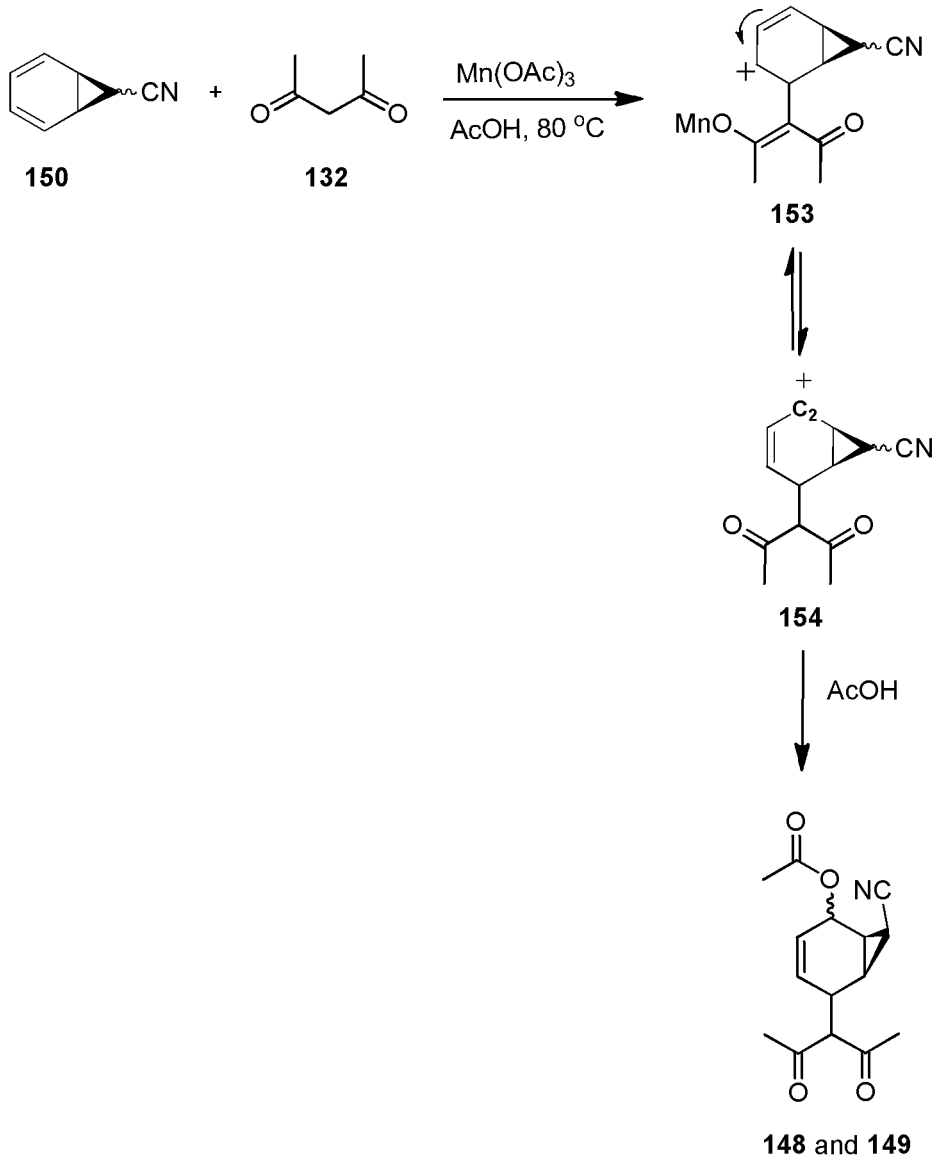
For the formation of **146** and **147** we suggest the following mechanism as shown in Scheme 56. The radical **151** adds to the norcaradiene structure and the formed radical

will be oxidizes to form **152**. Carbocation **152** can undergo cyclization to form the isomeric mixture **146** and **147**.




Scheme 56 Formation mechanism of compounds **146** and **147**

Formation of compounds **148** and **149** were not expected but it is not a surprise to be formed. Once the new C-C bond is formed between AcAc and **150**, formed radical oxidizes to create a carbocation as is the case for the other reactions. As the formed carbocation delocalizes on C-2 as shown in **154**, a cyclization with one of the carbonyl groups can not take place due to the geometrical reasons. However, this cation **154** can be captured by solvent molecule to give **148** and **149** as in Scheme 57.



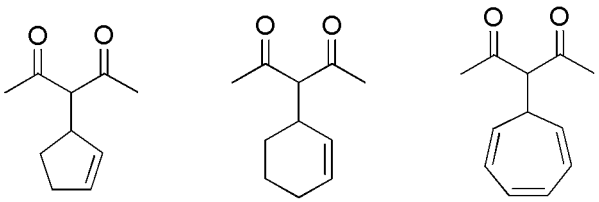

Scheme 57 Formation mechanism of compounds **148** and **149**

## 2.4 Cyclization Reactions of Acetylacetone Substituted Cyclopentene, Cyclohexene and Cycloheptatriene

In the second part of our research, we were interested in answering the question whether cyclization is going over oxygen radical or not. Normally, our cyclization reactions in the presence of $Mn(OAc)_3/Cu(OAc)_2$ couple proceeds with an initial abstraction of hydrogen radical from the methylenic protons of 1,3-diketone followed

by forming of a new C-C bond with alkene. Since we will provide starting materials with already formed C-C bond between 1,3-diketone and alkene, the results would provide better understanding about the cyclization mechanism.

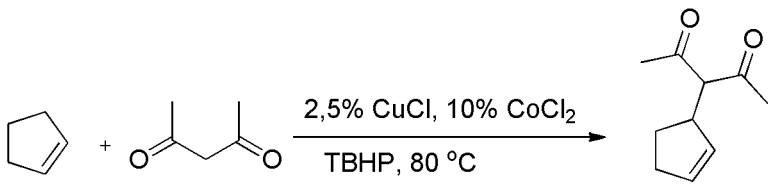
To address the question concerning cyclization mechanism we synthesized starting materials **144**, **155** and **156** containing AcAc functional groups attached at the allylic positions. The three starting materials are synthesized as described in the literature [8].



**155** **156** **144**

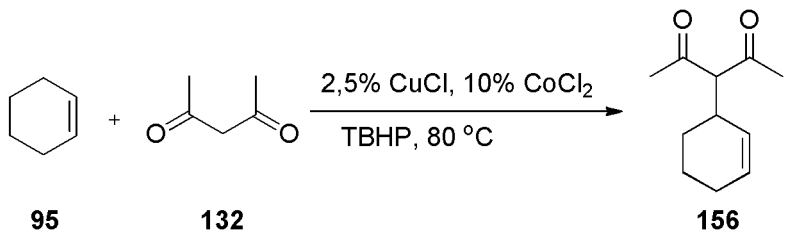
**Figure 9** Selected starting materials

The synthesis of compounds **155** and **156** were carried out by the reaction of appropriate alkene with acetylacetone in the presence of 2.5% CuCl, 10% of $CoCl_2$, 2 equivalence of 30% tertbutylhydroperoxide at 80 °C as shown in Scheme 58. They were characterized easily by comparing their data with those reported in the literature.



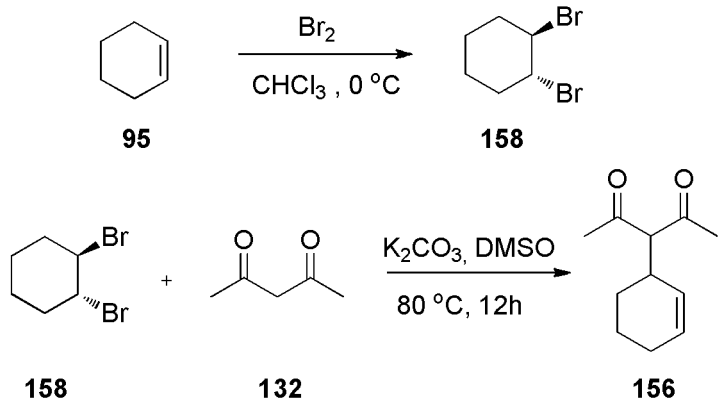

**157** **132** **155**

Scheme 58



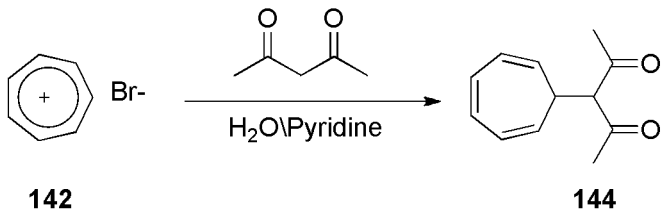

Scheme 58 (Continuing)

Another route to synthesize compound **156** with higher yield is through bromination of cyclohexene **95** followed by dropwise addition of formed 1,2-dibromocyclohexane **158** along with AcAc into a DMSO solution of $K_2CO_3$ at 80 °C as in Scheme 59.




Scheme 59

Moreover, a better synthetic way towards compound **144** is through tropylium cation **142** as shown in Scheme 60. After the formation of tropylium cation, acetylacetone was added dropwise and slowly to the solution of tropylium cation in water/pyridine mixture.

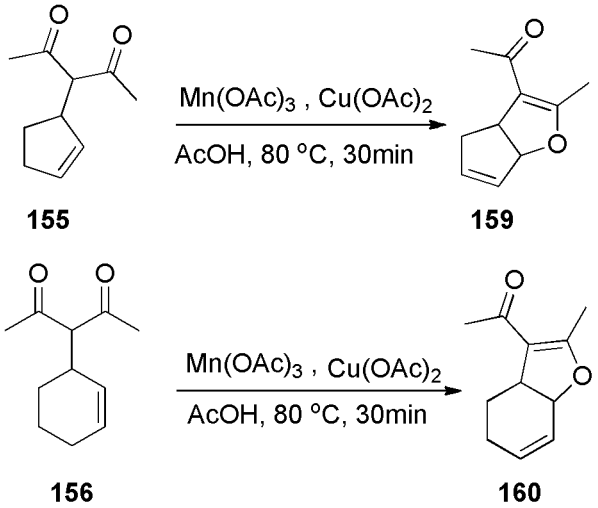



142 144

Scheme 60

### 2.4.1 Reactions Of Compounds 144, 155 and 156 in the Presence of $Mn(OAc)_3$ and $Cu(OAc)_2$

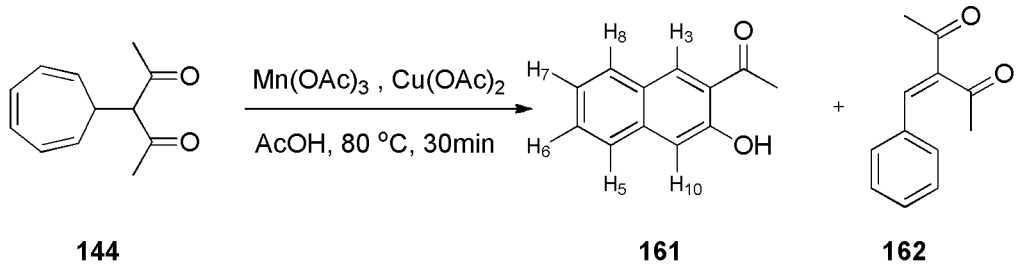
After obtaining our starting materials they were exposed to $Mn(OAc)_3/Cu(OAc)_2$ couple oxidation reaction. Characterization of the formed products were done by comparing their NMR data with already published data for cyclization compounds in the literature [40a,b]. We have noticed that cyclization has taken place as we expected in the case of compounds **155** and **156** and gave us compounds **159** and **160**, while compound **144** provided two different oxidation products **161** and **162** as shown in Scheme 61.




155 159

156 160

Scheme 61

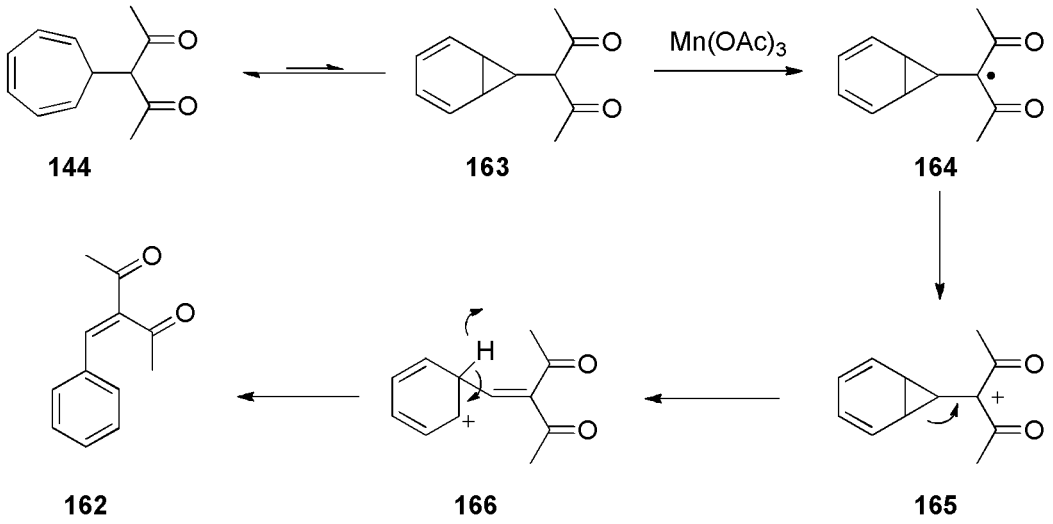



**144** **161** **162**

Scheme 61 (Continuing)

$^{1}$H NMR of compound **162** shows simply four singlets. Fortunately, integral values give us the necessary information about the molecule. The singlets are at 2.25 ppm 2.45 ppm, 7.40 ppm and 7.50 ppm. Their integral values are 3:3:5:1 respectively. By looking at the ratios we can easily conclude that the singlets with 3:3 ratio are two separate methyl groups. Moreover, broadness of the singlet at 7.4 pm with an integral ratio of 5 means that we have mono substituted benzene ring. Considering the proposed structure in hand, we can conclude that the singlet at 7.5 ppm is a part of α,β-unsaturated carbonyl group system. $^{13}$C NMR also backs up the data we have obtained from $^{1}$H NMR by showing two peaks at the hydrocarbon range and two peaks for two different carbonyls. Also two quaternary carbon peaks in addition to two regular peaks helps us understand that the two different benzene carbon atoms coincides with each other at 139.7 and 129.0 ppm.

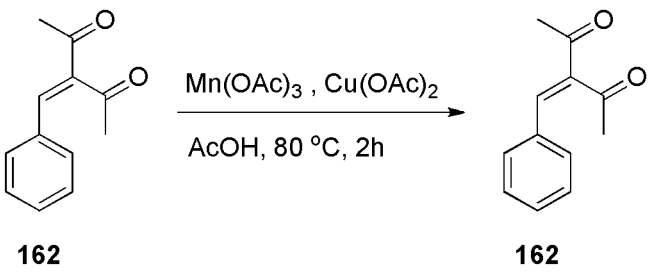
The proposed formation mechanism of compound **162** is going over norcaradiene structure. The initial radical forms between two carbonyl groups due to its acidity. Then oxidation takes place and electrolytic cyclopropane ring opening takes place moving the carbocation on cyclohexadiene unit. After elimination of the proton, benzene ring forms giving us compound **162**.




Scheme 62 Formation mechanism of compound **162**

$^{1}$H NMR spectrum of compound **161** shows peaks mainly on the aromatic range. There are two separate protons resonating as "doublet of doublet of doublets" which belong to H-6 and H-7. Coupling constants of these protons show that they have two ortho coupling in addition to a meta coupling. There are also two broad doublets which are H-5 and H-8. Their broadness is due to the small meta couplings. We can easily observe –OH peak at 11.5 ppm. Also the singlet, almost in the lowest possible aromatic range, belongs to H-3 since its electron density is reduced by carbonyl group in the β-position. $^{13}$C NMR shows peaks in the same pattern. We observed only one carbonyl group as expected along with its α,β-unsaturated system counterparts at 157.4 ppm and 127.2 ppm. Apart from these peaks, we observed eight more peaks in the aromatic region.

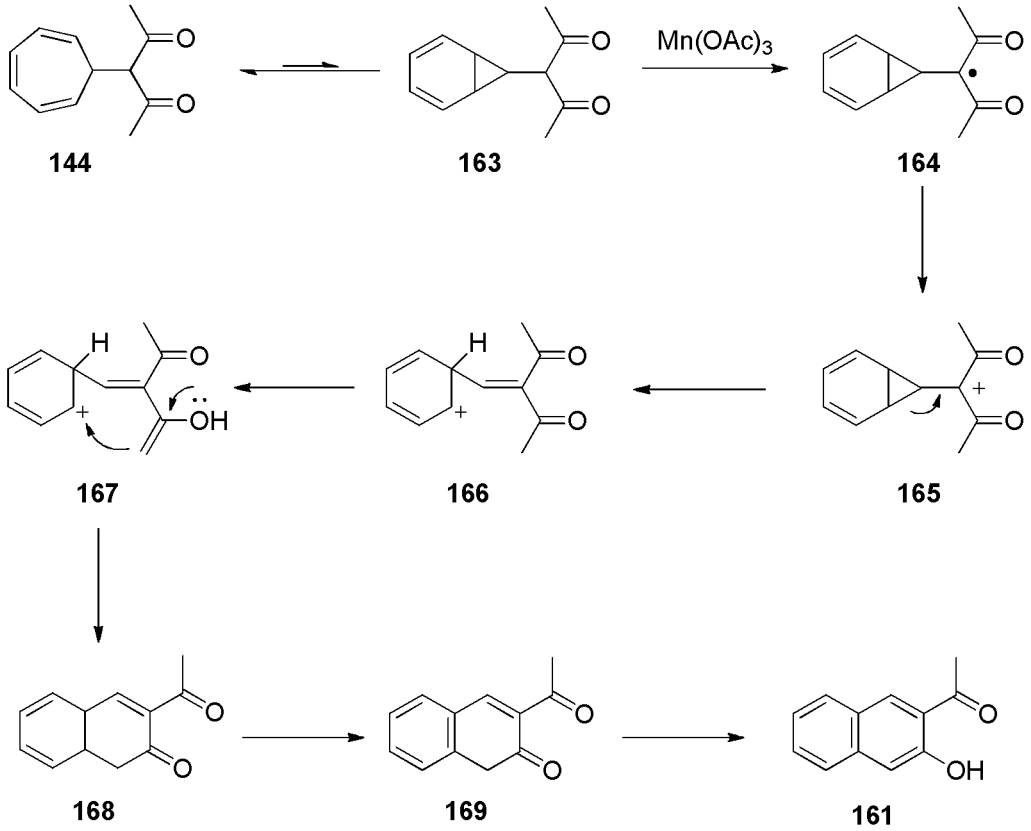
We first assumed that **161** is a secondary product and derived from **162**. In order to check the validity of our assumption we subjected compound **162** to the same reaction conditions which compound **161** was formed as in Scheme 63. However, we couldn't observe compound **161** at the end of the reaction which means that compound **161** is a primary product as compound **162** is.




**162** **162**

Scheme 63

For the formation of compound **161**, we suggested the following mechanism. The mechanism goes the same with compound **162** until the formation of **166**. At this step instead of elimination, one of the carbonyl groups take enol form and the formed double bond attacks the carbocation along with re-formation of carbonyl group creating **168**. Further oxidation creates benzene derivative **169** and after enolization of the carbonyl group we get compound **161**.

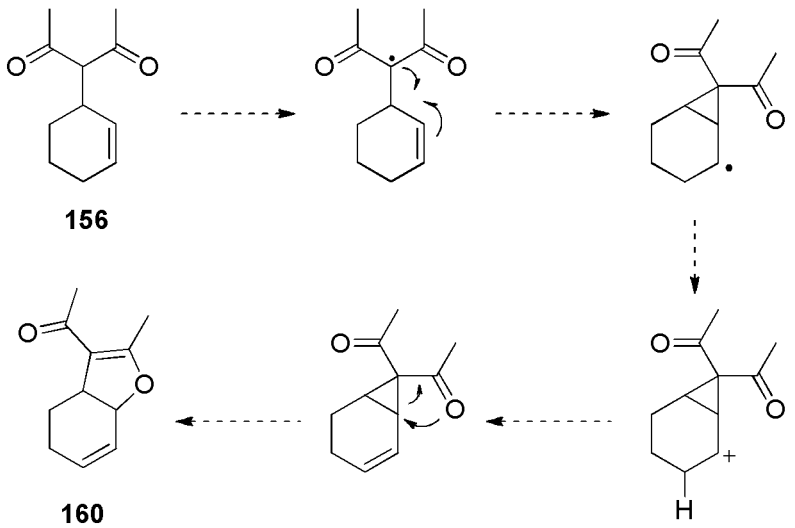



**144** **163** **164** **165** **166** **167** **168** **169** **161**

Scheme 64 Formation mechanism of compound **161**

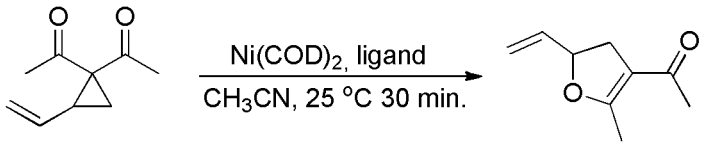
## 2.5 Investigation of Cyclopropane Intermediated Cyclization in $Mn(OAc)_3$ Type Reactions

Formation of cyclization products from the reactions of compound **155** and **156** brings up another question along with our first hypothesis which was whether cyclization reaction can occur over oxygen atom or not. Our new question was "Can cyclization take place over a cyclopropane intermediate". Balcı et al. [37] reported cyclopropane derivative product in the reaction of oxabenzonorbornadiene and dimedone in the presence of $Mn(OAc)_3$ and $Cu(OAc)_2$. This product or its analog of our compounds could have been the key to the mechanism in question.




Scheme 65 Proposed mechanism over cyclopropane

There are reports in the literature, stating that they have transformed 1,3-diketone cyclopropane derivatives to dihydrofuranes. For example, the reaction of compound **171** in the presence of $Ni(COD)_2$ catalyst and bipyridine ligand, dihydrofurane **172** forms with high yield as shown in Scheme 66 [38].

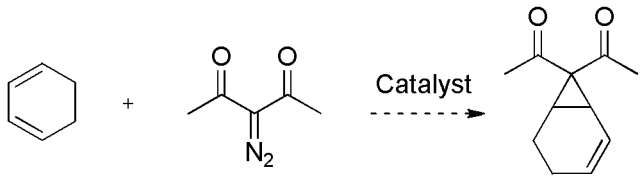



**171** **172**

Scheme 66

### 2.5.1 Attempts to Synthesize 1,1'-(Bicyclo[4.1.0]hept-2-ene-7,7-diyl)diethanone (173)

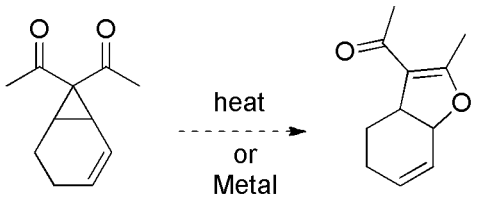
So we changed our scope to synthesize 1,3-diketonecyclopropane derivative such as compound **173**. In order to synthesize compound **173**, we designed a pathway as in Scheme 67.




**174** **175** **173**

Scheme 67 Proposed route for the synthesis of compound **173**

Observation of compound **160** when **173** is heated or treated with a metal oxidant, as shown in Scheme 68, would elucidate the mechanism of oxidative free radicalic cyclization reactions.

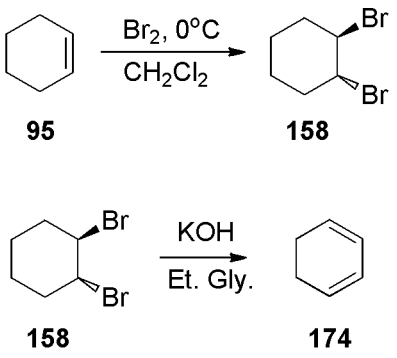



**173** **160**

Scheme 68

### 2.5.1.1 Synthesis of Cyclohexadiene (174)

In our synthetic strategy, cyclohexadiene, **174**, was synthesized by bromination of cyclohexene **95** in $CHCl_3$ followed by elimination with KOH in ethylene glycol at high temperature while being distilled at the same time as shown in Scheme 69. Forming clear solution of 1,3-cyclohexadiene should be kept at cold since it is highly volatile.

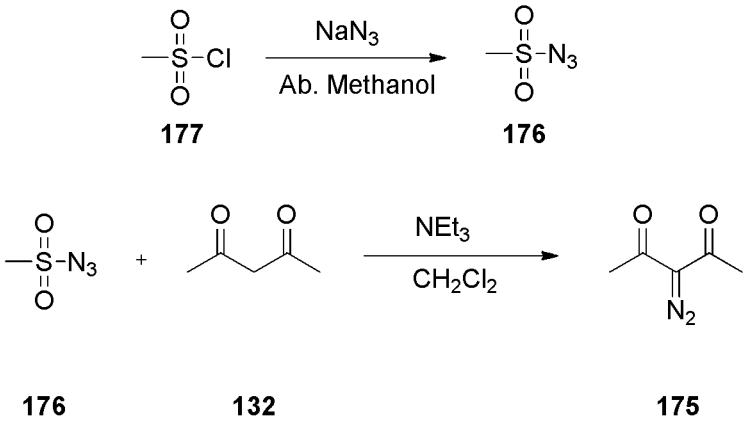



Scheme 69

### 2.5.1.2 Synthesis of Diazoacetylacetone (175)

In order to create 1,3-diketone cylopropane we chosed diazo analog of AcAc. In our diazo transfer reaction we used mesyl azide **176**. Mesyl azide can be easily synthesized by the addition of $NaN_3$ into an absolute methanol solution of methanesulfonylchloride **177** over one and a half hour. Formation of mesyl azide can be proved by IR spectroscopy with the azide peak around 2100 $cm^{-1}$.

Diazoacetylacetone **175** was synthesized by the addition of mesyl azide **176** dropwise over 15 minutes into a mixture of AcAc and 1,2 equivalence of $Et_3N$ in freshly distilled $CH_2Cl_2$ as in Scheme 70. Then the mixture is left for stirring for 5 hours. As the solution stirs, formation of white solid mesyl amine can be observed during the reaction.

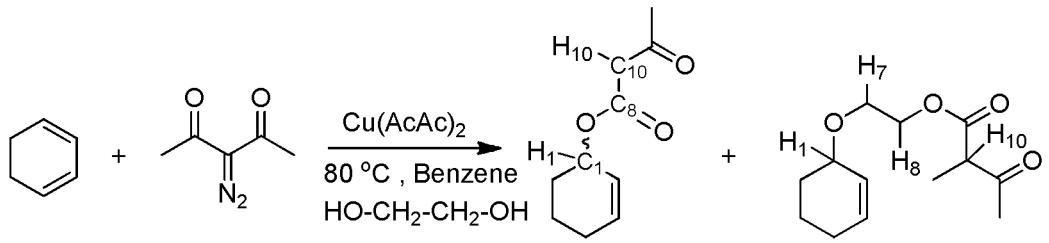



Scheme 70

Diazoacetylacetone is a yellow liquid which has only one peak at 2.41 ppm in $^{1}H$ NMR and three peaks at 28.6, 84.7, and 188.4 in $^{13}C$ NMR.

### 2.5.1.3 Addition Reaction of Diazoacetylacetone with Different Metal Catalysts

We then started our trials of diazo addition reactions to cyclohexadiene in the presence of different metal catalysts such as $Pd(OAc)_2$, $Rh_2(OAc)_4$, Cu metal powder and $Cu(AcAc)_2$. We carried out the reactions at room temperature since high temperature would be critical for the transformation of cyclopropane into dihydrofuran. Unfortunately neither cyclopropane nor dihydrofuran derivatives were observed. So we increased the reaction temperature to 80 $^{o}C$ in a hope to observe dihydrofuran products. Yet, we could not observe any dihydrofuran derivatives this time either. However, in the reaction of cyclohexadiene with diazoacetylacetone in the presence of $Cu(AcAc)_2$ at 80$^{o}C$ in benzene we observed two different products which are compounds **178** and **179** as shown in Scheme 71.




**174** **175** **178** **179**

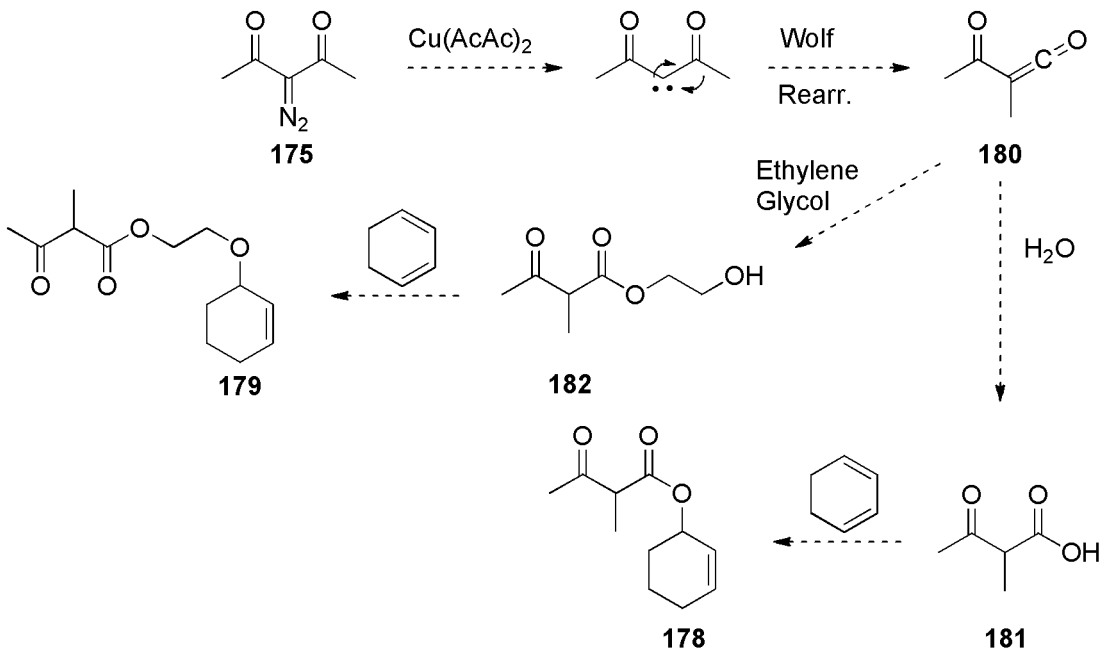
Scheme 71

Their characterizations were made by using mainly 2D NMR spectra such as COSY, HMBC and HSQC. Compound **178** shows two separate olefinic proton peaks and a proton resonance at 5.3 ppm which belongs to H-1. Correlation studies further showed that the methyl resonance at 1.3 ppm appears as doublet due to the coupling with H-10. This methyl group is migrated from C-8. In addition to the methy migration, oxygen atom between cyclohexene and 1,3-diketone in compound **178** might be due to $H_2O$ in the reaction media. $^{13}C$ NMR spectrum shows that there exists a diastereomer mixture of **178** due to the asymmetric centers C-1 and C-10. We can easily see that there is two pair of peaks of almost all the carbon atoms on the structure.

Formation of compound **179** is due to the ethylene glycol left in 1,3-cyclohexadiene **174** during the distillation. We can easily see the methylenic protons H-8, H-7 along with protons H-1 and H-10 have an integral ratio of 2:2:1:1 in $^1H$ NMR spectrum. The doublet splitting of the methyl group at 1.3 ppm can also be seen in this spectrum. $^{13}C$ NMR provides peaks for a ketone carbonyl group, an acetate carbonyl group, two different double bond carbons and for the rest of the molecule.

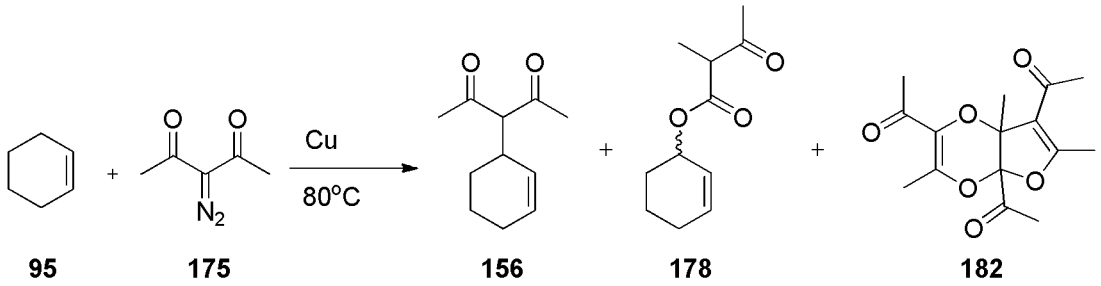
For the formation of these compounds we suggested the following mechanism: Copper-catalyzed removal of nitrogen from the diazo compound **175** first generates a carbene which undergoes Wolf-rearrangement to give the corresponding ketene **180**

which is then trapped by $H_2O$ or ethylene glycol existing in the reaction media. The formed acid and ester derivatives add to the double bond as shown in Scheme 72.




Scheme 72

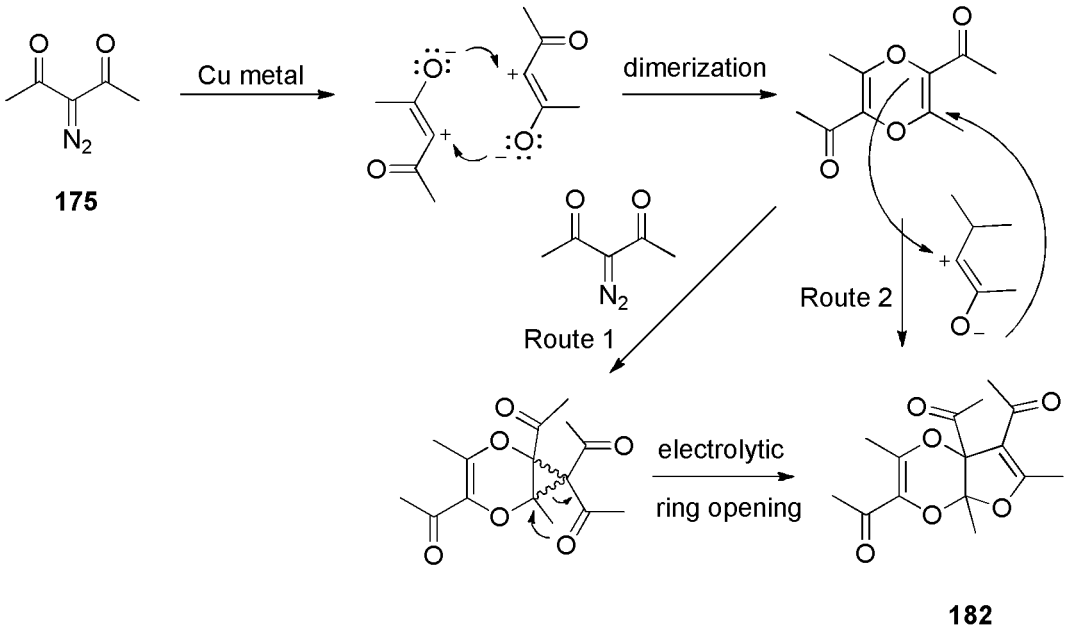
When the same type of reaction was carried out without a solvent with cyclohexene and Cu metal instead of 1,3 cyclohexadiene and Cu(AcAc)2 respectively, we again observed **178** along with allylic addition product **156** and an acetylacetone trimer **182** as shown in Scheme 73.




Scheme 73

Observing **178** at the end of the reaction of cyclohexene and diazoacetylacetone with Cu metal supports the idea that oxygen atom on the allylic position is not due to ethylene glycol and comes from water present in the reaction medium as shown in Scheme 72.

As for the compound **182**, we proposed two routes of mechanism for the formation of it which are shown in Scheme 74 below.




**175** **182**

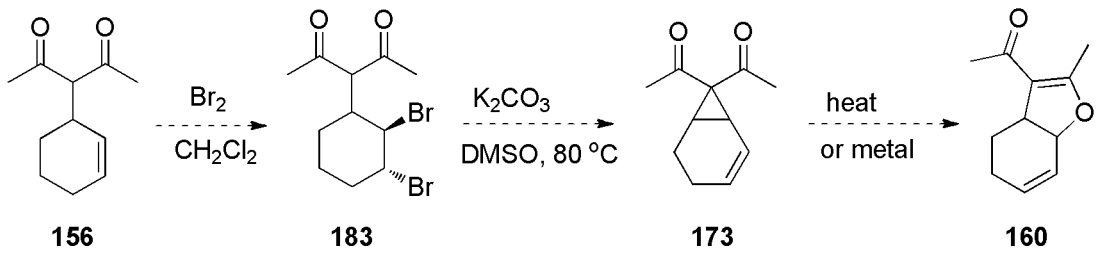
Scheme 74 Two routes of proposed mechanism for the formation of compound **182**

The $^{1}H$ and $^{13}C$ NMR spectra of compound **182** are interesting. While the $^{1}H$ NMR spectrum shows only six separate singlets, $^{13}C$ spectrum shows 15 different peaks. $^{1}H$ NMR spectrum, even though it shows six singlets as our proposed structure should have, is not a real proof of the entire structure. On the other hand, $^{13}C$ NMR spectrum shows significant data for certifying the structure. By these data we can observe three carbonyl peaks at 199.8, 196,3 and 195.1 ppm, two of which are the part of an α,β-unsaturated carbonyl system with peaks at 163.5-121.8 and, 149.8-110.8. Moreover, there are six peaks between 17 ppm and 28 ppm which belongs to the methyl groups.

The fact that we could not obtain any cyclopropane or dihydrofurane derivatives could be due to the nature of AcAc since there are very few examples of diazoacetylacetone addition to an alkene in the literature except for those giving dihydrofuran products with 6% yield in 6 days and another dihydrofuran product by the addition of diazo-compound to an electron-rich allene [39a,b].

### 2.5.1.4 Attempts to Synthesize Compound 173 without Diazo Addition

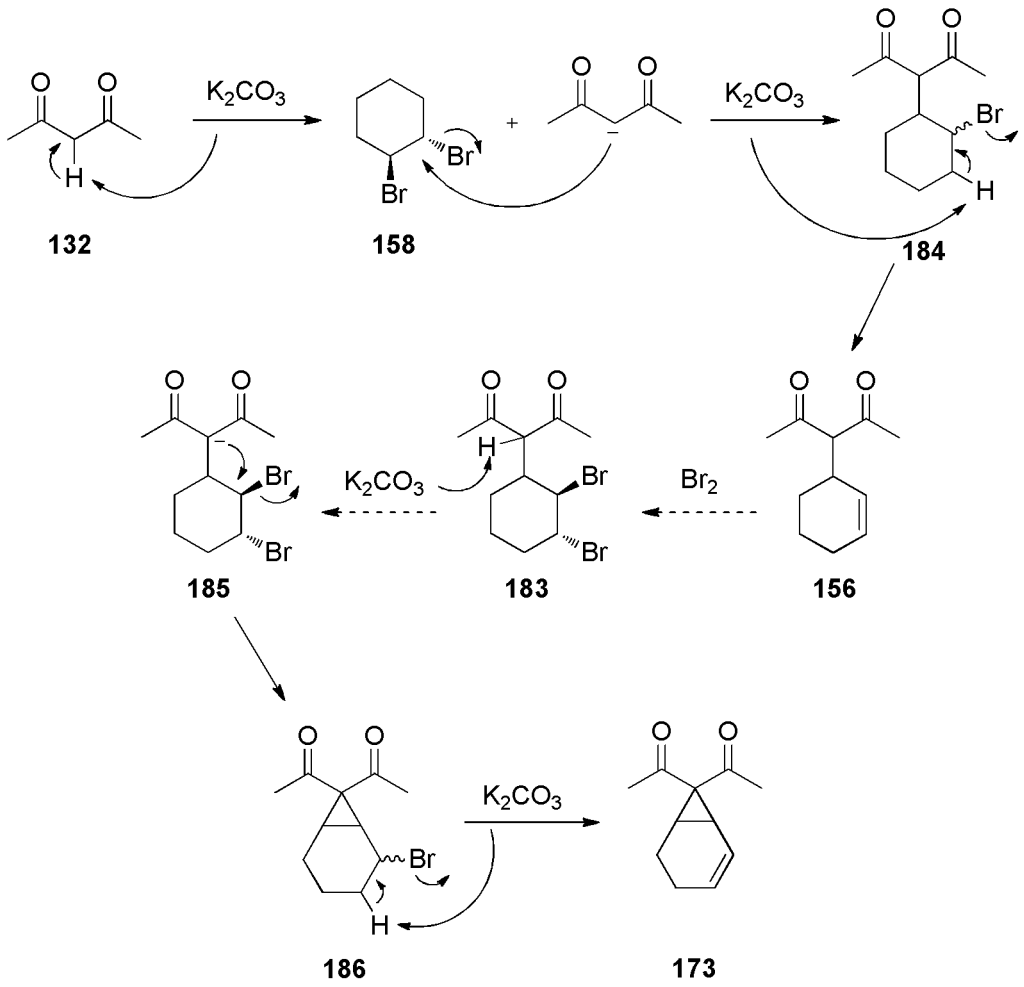
Since we could not obtain the desired product **173** in diazoacetylacetone based reactions we changed our strategy towards the synthesis of cyclopropane derivatives as in Scheme 75.




**156** **183** **173** **160**

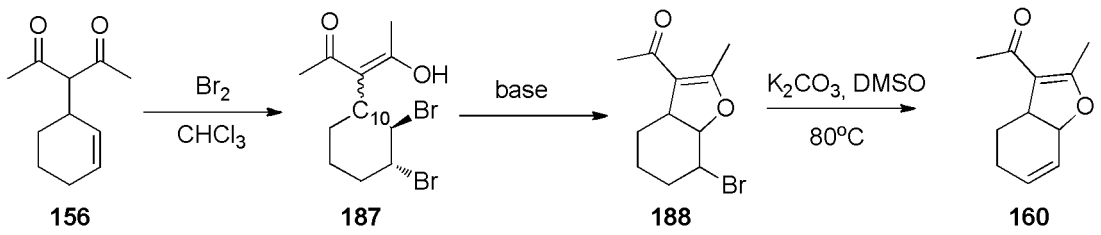
Scheme 75 Proposed synthetic route towards compound **160**

We have obtained compound **156** via bromination of cyclohexene and further addition of AcAc in DMSO at 80 °C in the presence of $K_2CO_3$ as discussed earlier. Considering the route of the mechanism, a second bromination of compound **156** and further elimination with the same mechanism described above would give us the desired cyclopropane product **173** as described in Scheme 76 below.




Scheme 76 Proposed formation mechanism of compound **173**

Bromination of compound **156** and further treatment with $K_2CO_3$ in DMSO at 80 °C gave us the dihydrofurane derivative **160**. While the formation of dihydrofurane derivative through the mechanism discussed above would be thought as a proof for cyclopropane intermediate, this was not the case. Purification of the brominated product revealed that one of the carbonyl group takes enol form giving us compound **187** and this product has a high tendency to undergo cyclization in treatment with any base, no matter how weak it is, giving us compound **188**. Further treatment with $K_2CO_3$ of the compound **188** will naturally eliminate HBr and will give us dihydrofurane derivative **160** as shown in Scheme 77.




Scheme 77

In the characterization of compound **187** $^{1}H$ and $^{13}C$ NMR spectrums gave important data. $^{1}H$ NMR spectrum provided evidence of a broad –OH peak at 11.5 ppm along with two protons in the α-position of Br atoms. On the other hand, $^{13}C$ NMR shows two peaks of each carbon atom on the structure such as two separate α,β-unsaturated carbonyl systems and two peaks of each C-Br carbons. These peaks arise from the other diastereomer due to the chiral centers at C-10. In the addition of $Br_2$ molecule, considering the mechanism, Br atom and AcAc in the α-position could be either cis or trans which will eventually bring up two diastereomers.

For compound **188**, $^{1}H$ NMR spectrum resembles that of compound **187**. The two main difference is that the -OH peak and the proton in the α-position of Br atom at 4.9 ppm in the $^{1}$NMR spectrum of compound **187** was gone and a new peak at 4.6 ppm came up. Also $^{13}C$ NMR shows the specific systems of a dihydrofurane ring which are α,β-unsaturated carbonyl group and a γ-O atom system at 194.2, 167,3 and 120.5 ppm respectively.

# CHAPTER 3

# EXPERIMENTAL

## 3.1 General Considerations

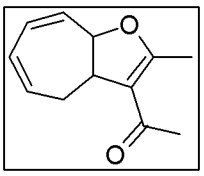
Nuclear Magnetic Resonance ($^{1}H$, $^{13}C$ and 2D) spectra were recorded on a Bruker Instruments Avance Series-Spectrocpin DPX, Ultra Sield (400 MHz), High Performance digital FT-NMR spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane (TMS) reference and deuterochloroform ($CDCl_3$) as the solvent. 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 doublets, ddd: doublet of doublet of doublets, dtd: doublet of doublet of triplets, br. d: broad doublet. Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm-1).

Column chromatographic separations were performed by using Fluka Silicagel 60 with 0.063-0.170 mm particle size. The relative proportions of solvents refer to volume:volume ratio.

All the solvent purifications were done as stated in the literature [41].

### 3.2 Synthesis of 1-(2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-yl) ethanone (133) in the presence of CAN

0.92 g (10 mmol) Cycloheptatriene **94** and 1.0 g (10 mmol) acetylacetone **132** was dissolved in 50 mL of MeOH and cooled down to 0 °C. To this mixture was added a solution of 10.96 g (20 mmol) CAN in 100 mL of MeOH dropwise in 30 minutes and was stirred for 45 minutes. After the completion of the reaction, MeOH was evaporated and dissolved in $CH_2Cl_2$ then extracted with water. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $CaCl_2$. Removal of the solvent gave 1.75 g compound **133** with a yield of 92 %, which chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1).



**$^1$H NMR** (400 MHz, $CDCl_3$) δ:6.09 (dd, J= 9.8 and 5.4 Hz, 1H), 6.05 (dd, J=11.9 and 2.9 Hz, 1H), 5.95 (dd, J=11.9 and 5.3 Hz, 1H), 5.88 (ddd, J=9.8, 1.2 and 5.3 Hz, 1H), 4.92 (br d, 1H), 3.18 (br t, 1H), 2.21 (m, 1H), 2.18 (s, 3H), 2.16 (d, J=0.9 Hz, 3H), 1.92 (tdd, J=5.4 and 1.2 Hz , 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 193.1, 166.9, 134.5, 129.9, 127.1, 126.9, 118.1, 84.5, 51.8, 30.0, 29.0, 15.3.

**IR** (KBr, $cm^{-1}$) 3027.7, 1699.6, 1662.5, 1608.3, 1387.0, 1299.6, 1266.48, 1226.4, 1202.7, 944.9, 710.8, 678.6

### 3.3 Synthesis of 1-(2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-yl) ethanone (133) in the presence of $Mn(OAc)_3/Cu(OAc)_2$

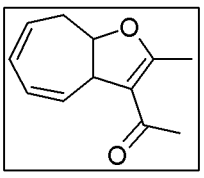
7.24 g (27 mmol) of $Mn(OAc)_3.2H_2O$ and 0.546 g (3 mmol) of $Cu(OAc)_2$ were dissolved in 100 mL of acetic acid. A mixture of 0.92 g (10 mmol) cycloheptatriene

**94** and 1.0 g (10 mmol) acetylacetone **132** was prepared in 50 mL of acetic acid and added to the metal oxidant solution dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80 °C for additional 30 minutes. After the completion of the reaction, the mixture was extracted with $CH_2Cl_2$ and water then organic phase was washed with saturated $Na_2CO_3$. After the organic extracts are dried over $CaCl_2$ the solvent was removed to give 1.71 g of compound **133** crude product which then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1) to give 1.55 g of **133** with a yield of 81 %.

### 3.4 Synthesis of 1-(2-methyl-8,8a-dihydro-3aH-cyclohepta[b]furan-3-yl) ethanone (134) and 1-(8-methyl-7-oxabicyclo[4.3.1]deca-2,4,8-trien-9-yl)ethanone (135)

7.24 g (27 mmol) of $Mn(OAc)_3.2H_2O$ and 0.546 g (3 mmol) of $Cu(OAc)_2$ were dissolved in 100 mL of acetic acid and to this solution was added a mixture of cycloheptatriene **94** (0.92 g, 10 mmol) and acetylacetone **132** (1.0 g, 10 mmol) in 50 mL of acetic acid dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80 °C for 12 hours. After the completion of the reaction the mixture was extracted with $CH_2Cl_2$ and water. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic phase was washed with saturated $Na_2CO_3$ and dried over $CaCl_2$. The solvent was removed giving compounds **133**, **134** and **135** with product ratios of 55:41:4 respectively which then chromatographed on silica gel (100 g) eluting with n-hexane/EtOAc (9:1) to give 0.8 g of **133,** 0.4 g of **134** and 0.05 g of **135** with yields of 42 %, 20 % and 2.5 % respectively.

#### 1-(2-Methyl-8,8a-dihydro-3aH-cyclohepta[b]furan-3-yl)ethanone (134)



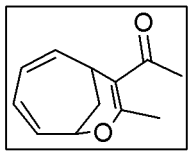
**$^1$H-NMR** (400 MHz, $CDCl_3$) δ: 6.19 (dd, J=11.2 and 3.5 Hz, 1H), 5.98 (dd, J= 10.2 and 4.4 Hz, 1H), 5.90 (ddd, J=11.2, 4.4 and 2.5 Hz, 1H), 5.82 (dt, J=10.2 and 6.8 Hz, 1H), 4.66 (dt, J=10.5 and 7.8

Hz, 1H), 3.71 (br d, J=10.5 Hz, 1H), 2.42 (t, J= 7.8 Hz, 1H) 2.04 (s, 3H), 2.00 (d, J=1.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 192.2, 167.3, 136.9, 131.0, 127.6, 127.3, 117.0, 92.9, 46.1, 31.6, 29.1, 14.8.

**IR** (KBr, $cm^{-1}$) 2352, 2271, 1690, 1640, 1412, 1337, 965, 623, 500.

**1-(8-Methyl-7-oxabicyclo[4.3.1]deca-2,4,8-trien-9-yl)ethanone (135)**



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 6.25 (dd, J=10.8 and 8.6 Hz, 1H), 5.73 (dd, J=7.1 and 10.8 Hz, 1H), 5.94 (ddd, J=6.9, 11.8 and 0.5 Hz, 1H), 5.81 (dd, J=11.8 and 6.1 Hz, 1H), 4.81 (tdd, J=6.1, 1.7 and 0.5 Hz, 1H), 3.54 (br t, 1H), 2,20 (s, 3H), 2,11 (br d, J=9.5 Hz, 1H), 2.11 (d, J=1.3 Hz,3H), 1,86 (ddd, J=1.7, 13,9 and 1,3 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 198.7, 163.0, 138.2, 130.0, 128.9, 124.3, 114.6, 71.3, 32.5, 31.4, 27.7, 21.0;

**IR** (KBr, $cm^{-1}$) 2940, 2920, 1710, 1680, 1600, 1557, 1330, 1306, 1240, 1211, 1166, 1070, 1047, 912, 705.

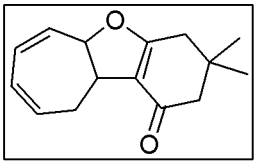
### 3.5 Synthesis of 3,3-dimethyl-2,3,4,5a,10,10a-hexahydro-1H-benzo[d]-cyclohepta[b]furan-1-one (139) and 10,10-dimethyl-7,9,10,11-tetrahydro-2,7-methanobenzo[b]oxonin-8(2H)-one (138) in the presence of $Mn(OAc)_3$

7.24 g (27 mmol) $Mn(OAc)_3.2H_2O$ and 0.126 g (3 mmol) LiCl were dissolved in 100 mL of acetic acid and to this solution was added a mixture of 0.92 g (10 mmol) cycloheptatriene **94** and 1.4 g dimedone **83** (10 mmol) in 50 mL of acetic acid dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80 °C

for 30 minutes. After the completion of the reaction the mixture was extracted with $CH_2Cl_2$ and water. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic phase was washed with saturated $Na_2CO_3$ and dried over $CaCl_2$. The solvent was removed giving the crude products **138** and **139** with 4.4 % and 82 % yields respectively which then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1).

**3,3-Dimethyl-2,3,4,5a,10,10a-hexahydro-1H-benzo[d]cyclohepta[b]furan-1-one (139)**

White solid, m.p. 66.5 – 67.0 °C from ethyl acetate/hexane.



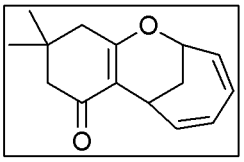
**$^1$H-NMR** (400 MHz, $CDCl_3$) δ: 6.13 (td, J=10.3 and 5.3 Hz, 1H), 6.10 (dd, J=12.0 and 2.7 Hz, 1H) 5.99 (ddd, J=5.4, 12.0 and 1.8 Hz, 1H), 5.91 (ddd, J=5.4, 10.3 Hz, and 1.3 Hz, 1H), 5.13 (br d, J=9.2 Hz, 1H), 3.38 (br t, J=9.2 Hz, 1H) 2.45 (ddd, J=8.3, 2.0 Hz, and 13.4 Hz, 1H), 2.24 (d, J=0.8 Hz, 2H), 2.16 (s, 1H), 2.14 (s, 1H), 1.89 (dddd, J=1.9, 13.4 and 5.3 Hz, 1H), 1.05 (s, 3H), 1.02 (s, 3H)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 194.6, 175.0, 134.8, 130.1, 127.7, 127.2, 115.7, 87.5, 51.2, 50.2, 37.7, 34.1, 29.4, 29.2, 27.0;

**IR** (KBr, $cm^{-1}$) 2970.5, 1614.0, 1399.3, 1366.9, 1223.6, 1166.6, 1133.4, 1036.9, 959.3, 912.9, 887.3, 839.2, 716.8, 687.0

**10,10-Dimethyl-7,9,10,11-tetrahydro-2,7-methanobenzo[b]oxonin-8(2H)-one (138)**

White solid, m.p. 84.0 – 84.5 °C from ethyl acetate/hexane.



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ: 6.35 (br t, J=11.0 Hz, 1H), 5.92 (dd, J=7.3 and 11.8 Hz, 1H), 5.79 (dd, J=11.8 and 6.2 Hz, 1H), 5.67 (dd, J=11.0 and 7.3 Hz, 1H), 4.89 (m, 1H), 3.39 (br t, 1H), 2,16 (m, J=14 Hz, 1H), 2.15 (s, 2H), 2.09 (d, 2H), 1.85 (br d, J=14 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H).

**$^{13}$C-NMR** (100 MHz, CDCl3) δ 194.7, 166.1, 137.1, 127.6, 126.1, 121.3, 111.2, 70.4, 48.6, 40.3, 30.1, 27.1, 26.1, 25.7, 25.6.

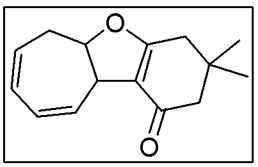
**IR** (KBr, $cm^{-1}$) 3030.6, 1642.6, 1376.1, 1340.3, 1216.1, 1134.8, 1082.8, 1029.9, 966.9, 731.3, 691.4.

### 3.6 Synthesis of 3,3-dimethyl-2,3,4,5a,10,10a-hexahydro-1H-benzo[d] cyclohepta [b]furan-1-one (139) and 10,10-dimethyl-7,9,10,11-tetrahydro-2,7-methano benzo[b]oxonin-8(2H)-one (138) in the presence of CAN

0.92 g Cycloheptatriene **94** (10 mmol) and 1.4 g dimedone **83** (10 mmol) was dissolved in 50 mL of MeOH. To this mixture was added dropwise a solution of 10.96 g CAN (20 mmol) in 100 mL of MeOH in 30 minutes and was stirred for 45 minutes. After the completion of the reaction the mixture was evaporated and dissolved in $CH_2Cl_2$ then extracted with water. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $CaCl_2$. Removal of the solvent gave the crude products which then chromatographed on silica gel (50 g) eluting with n-hexane/$CH_2Cl_2$ (9:1) to get 1.5 g of compound **138** and 0.28 g of compound **139** with yields of 80 % and 15 % respectively.

### 3.7 Synthesis of 3,3-dimethyl-2,3,4,5a,6,10a-hexahydro-1H-cyclohepta[b] benzofuran-1-one (140)

0.46 g (2 mmol) of compound **139** was heated at 80 °C in AcOH for 24 hours. After the completion of the reaction, the mixture was extracted with $CH_2Cl_2$ and water then organic phase was washed with saturated $Na_2CO_3$. After the organic extracts are dried over $CaCl_2$, the solvent was removed giving the crude products in a ratio of 48:52 of compound **139** to compound **140** which then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1) to give 0.15 g of both compounds with yields of 32 %.



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 6.22 (dd, J=11.4 and 3.4 Hz, 1H), 6.02 (dd, J=10.1 and 4.8 Hz, 1H), 5.87 (m, 2H), 4.98 (dt, J=10.4 and 3.5 Hz, 1H), 3.80 (br. d, J=10.4 Hz, 1H) 2.51 (ddd, J=3.6, 7.7 and 12.4 Hz, 1H), 2.15-2.39 (m, 1H), 2.21 (d, J=1.1 Hz, 1H), 2.18 (d, J=2.0 Hz, 1H), 2.17 (s, 2H), 1.12 (s, 3H), 1.11 (s, 3H).

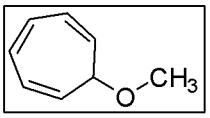
**$^{13}$C-NMR** (100 MHz, CDCl3) 194.5, 175.8, 134.0, 131.0, 126.7, 126.5, 114.5, 94.2, 51.3, 43.0, 37.8, 34.0, 31.7, 28.8, 28.4.

**IR** (KBr, $cm^{-1}$) 3030.6, 1712.6, 1345.6, 1216.1, 976.9, 651.4.

### 3.8 Synthesis of 7-methoxycyclohepta-1,3,5-triene (141)

3.0 g (33 mmol) of CHT was dissolved in $CHCl_3$ and to this solution was added dropwise 5.28 g (33 mmol) of bromine in $CHCl_3$ over 3 hours. After the completion of the reaction, solvent was evaporated and the residue was exposed to a low pressure heating at 90 °C for 6 hours. 5.0 g (29 mmol) of tropylium bromide **142** was then dissolved in 20 mL absolute methanol and was added into a solution of 3.7 g of metallic sodium in 20 mL methanol with small portions. After 2 hours of stirring, the mixture was filtered to remove precipitated sodium bromide. Removal of the solvent

afforded yellow oil which was washed with water and extracted with diethylether (3 × 10 mL). After drying with $CaCl_2$, solvent was evaporated and 3.0 g (25 mmol) of compound **141** was obtained with a yield of 80% [42].



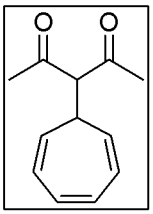
**$^1$H-NMR** (400 MHz, $CDCl_3$) δ: 3.41 (s, 3 H), 3.41 (t, 1 H), 5.51 (m, 2H), 6.18 (m, 2 H), 6.67 (m, 2 H).

**$^{13}$C-NMR** (100 MHz, CDCl3) δ: 56.5, 77.9, 123.2, 125.4, 131.1.

### 3.9 Synthesis of 3-(cyclohepta-2,4,6-trienyl)pentane-2,4-dione (144)

1.22 g (10 mmol) of compound **141** and 1.0 g (10 mmol) of acetylacetone **132** was dissolved in 50 mL of N-methylpyrrolidone and cooled down to -10 °C. To this mixture was added dropwise a solution of 10.96 g (20 mmol) CAN in 100 mL of N-methylpyrrolidone in 30 minutes and was stirred for 15 minutes. After the completion of the reaction diethylether was added along with water. The organic phase was separated and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic extracts were dried over $CaCl_2$. Removal of the solvent gave the crude product, which chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1) to give 1,5 g of **144** with 80% yield.

White solid, mp 118-120 °C. from ethyl acetate/hexane.



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ: 6.71 (t, J=3.2 Hz, 2H), 6.26 (dt, J=3.2 and 9.2 Hz, 2H), 5.18 (dd, J=6.6 and 9.2 Hz, 2H), 4.05 (d, J=11.4 Hz, 1H), 2,92 (dt, J=11.4 and 6.6 Hz, 2H), 2,19 (s, 6H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 203.1, 131.1, 126.4, 121.9, 69.9, 38.1, 29.5.

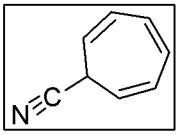
**IR** (KBr, $cm^{-1}$) 2359.8, 2341.9, 1723.6, 1691.4, 1417.6, 1356.9, 1275.2, 1248.4, 1201.4, 1165.9, 1143.2, 951.6, 742.1, 728.0, 700.1.

### 3.10 Synthesis of 3-(cyclohepta-2,4,6-trienyl)pentane-2,4-dione (144)

1.71 g (10 mmol) of tropylium bromide **142** in 10 mL of distilled water was clarified by stirring with activated charcoal and filtered through filter paper. The resulting yellow solution was treated with 2.0 g (20 mmol) of acetylacetone **132**. A white precipitate started to form. 1 mL. of Pyridine was added dropwise with stirring. The yellow color disappeared as more white precipitate formed. The solid was collected and air-dried to give **144** (1.8 g, 95%). [43].

### 3.11 Synthesis of cyclohepta-2,4,6-trienecarbonitrile (145)

30 g (0.33 mol) of CHT was dissolved in $CHCl_3$ and to this solution was added drop wise 52.8 g (0.33 mol) of bromine in $CHCl_3$ over 3 hours. After the completion of the reaction, solvent was evaporated and the residue was exposed to a low pressure heating at 90 $^{o}C$ for 6 hours. 50 g (0.29 mol) of tropylium bromide **142** was then dissolved in 200 mL water and to the resulting solution was added 20.2 g of KCN in 50 mL of water with stirring. After 2 hours of stirring, the mixture was extracted with diethylether. After drying the organic phase with $CaCl_2$ solvent was evaporated and 26 g (0.22 mol, 75 %) of compound **145** was obtained [36].



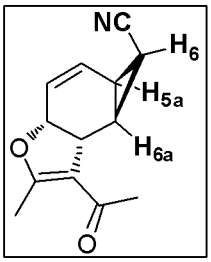

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ 6.74 (t, J=3.3 Hz, 2H), 6.34 (dtd, J=8.9, 2.7 and 0.7 Hz, 2H), 5.40 (dd, J=8.9 and 6.1 Hz, 2H), 3.00 (t, 6.1 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 131.5, 129.3, 120.5, 118.9, 30.7

### 3.12 Synthesis of (3aR,5aR,6R,6aS,6bR)-1-acetyl-2-methyl-5a,6,6a,6b-tetrahydro-3aH-cyclopropa[e]benzofuran-6-carbonitrile (146) (147) and (1S,2S,6S,7R)-7-cyano-5-(2,4-dioxopentan-3-yl)bicyclo[4.1.0]hept-3-en-2-yl acetate (148) (149) derivatives.

20.6 g (30 mmol) $Mn(OAc)_3.2H_2O$ was dissolved in 200 mL of acetic acid and to this solution was added a mixture of 3.0 g (25.6 mmol) of compound **145** and 2.56 g (25.6 mmol) of acetylacetone **132** (25.6 mmol) in 50 mL of acetic acid dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80 °C for 24 hours. After the completion of the reaction the mixture was extracted with $CH_2Cl_2$ and water. The aqueous phase was extracted with $CH_2Cl_2$ again (3 x 50 mL). The combined organic phase was washed with saturated $Na_2CO_3$ and dried over $CaCl_2$. The solvent was removed, giving 4.3 g of crude product of compounds **146, 147, 148** and **149** with 6 %, 6 %, 4 % and 4 % ratios respectively which then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc(9:1) to give 0.25 g **146**, 0.25 g **147** and 0.3 g of **148** – **149** mixture.

**(3aR,5aR,6R,6aS,6bR)-1-acetyl-2-methyl-5a,6,6a,6b-tetrahydro-3aH-cyclopropa[e]benzofuran-6-carbonitrile (146)**

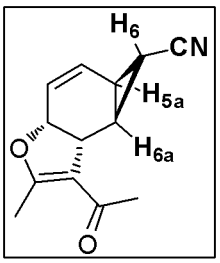



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 6.09 (dd, J=10.1 and 5.1 Hz, 1H), 5.81 (dd, J=10.1 and 3.7 Hz, 1H), 4.87 (ddd, J=11.4, 3.7 and 0.9 Hz, 1H), 3.85 (br. d, J= 11.4 Hz, 1H), 2.27 (s, 3H), 2.19 (m, 1H), 2.16 (d, J=1.3 Hz, 3H), 1.87 (dt, J=8.3 and 5.1 Hz, 1H), 1.80 (t, J=8.3 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, CDCl3) δ 193.7, 167.5, 125.1, 124.5, 118.2, 116.2, 74.5, 36.6, 29.7, 17.2, 17.0, 16.0, 13.6

**IR** (KBr, $cm^{-1}$) 2930.6, 2204.7 1662.6, 1340.3, 1234.8, 831.3, 621.4.

**(3aR,5aR,6R,6aS,6bR)-1-acetyl-2-methyl-5a,6,6a,6b-tetrahydro-3aH-cyclopropa[e]benzofuran-6-carbonitrile (147)**

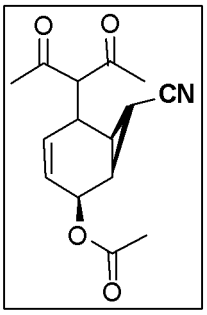



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ 6.21(dd, J=10.2 and 5.0 Hz, 1H), 5.51 (dd, J=10.2 and 3.6 Hz, 1H), 4.68 (ddd, J=11.0, 3.6 and 1.1 Hz, 1H), 3.88 (br. d, J=11.0 Hz, 1H), 2.33 (m, 1H), 2.23 (s, 3H), 2.14 (d, J=1.4 Hz, 3H), 1.94 (m, 1H), 0.88 (dd, J=5.4 and 4.1 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, CDCl3) δ 193.9, 167.3, 128.5, 122.7, 119.8, 116.8, 72.9, 39.1, 29.7, 19.9, 19.7, 15.1, 14.6

**IR** (KBr, $cm^{-1}$) 3010.6, 2213.4, 1682.6, 1376.1, 1216.1, 1092.8, 1049.9, 831.3, 631.4.

**(1S,2S,6S,7R)-7-cyano-5-(2,4-dioxopentan-3-yl)bicyclo[4.1.0]hept-3-en-2-yl acetate (148)**

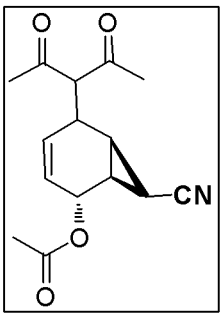



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ 5.81 (dd, J=10.1 and 5.5 Hz, 1H), 5.74 (ddd, J=10.1, 5.5 and 1.5 Hz, 1H), 5.47-5.51 (m, 1H), 3.86 (d, J=9.3 Hz, 1H), 3.45-3.50 (m, 1H), 2.29 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.94-1.99 (m, 1H), 1.65-1.70 (m, 1H), 1.58 (t, J=4.8 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, CDCl3) δ 201.7, 201.6, 170.4, 130.4, 123.9, 120.1, 74.1, 63.9, 31.3, 28.9, 28.7, 28.2, 20.8, 19.1, 3.8.

**IR** (KBr, $cm^{-1}$) 3449.1, 2239.6, 1733.6, 1701.3, 1421.7, 1364.6, 1237.5, 1153.5, 1020.8, 958.0, 913.4, 744.7.

**(1S,2S,6S,7R)-7-cyano-5-(2,4-dioxopentan-3-yl)bicyclo[4.1.0]hept-3-en-2-yl acetate (149)**



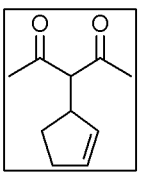

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 5.58-5.60 (m, 1H), 5.51-5.53 (m, 1H), 5.54-5.58 (m, 1H), 3.64 (d, J=9.0 Hz, 1H), 3.41 (m, 1H), 2.26 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.21 (overlap 1H), 1.72 (ddt, 1H), 1.38 (t, J=4.7 Hz, 1H)

**$^{13}$C-NMR** (100 MHz, CDCl3) δ 201.5, 201.4, 170.1, 126.5, 126.3, 119.7, 72.7, 64.8, 32.8, 30.1, 23.7, 22.1, 21.1, 21.0, 3.6.

**IR** (KBr, $cm^{-1}$) 3449.1, 2239.6, 1733.6, 1701.3, 1421.7, 1364.6, 1237.5, 1153.5, 1020.8, 958.0, 913.4, 744.7.

### 3.13 Synthesis of 3-(cyclopent-2-en-1-yl)pentane-2,4-dione (155)

To a mixture of 0.025 g (0.25 mmol) CuCl, 0.13 g (1 mmol) $CoCl_2$, 3.4 g (50 mmol) cyclopentene and 1.0 g (10 mmol) acetyacetone, 0.18 g (20 mmol, ~5.5 M in decane) tert-butyl hydroperoxide was added under $N_2$ at room temperature. The reaction temperature was raised to 50 °C and left for reflux for overnight. The resulting mixture was purified by column chromotography on silica gel (hexane/ethyl acetate= 9/1), to give 0.85 g of the desired product **155** with 50 % yield [44].




**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 5.82 (ddd, J=5.6, 4.4 and 2.0 Hz, 1H), 5.52 (ddd, J=6.0, 4.0 and 2.0 Hz, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.50-3.43 (m, 1H), 2.39-2.30 (m, 2H), 2.19 (s, 6H), 2.12-2.03 (m, 1H), 1.42-

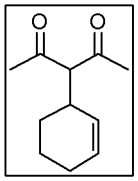
1.34 (m, 1H)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) 203.3, 203.2, 132.9, 130.7, 74.9, 45.3, 31.6, 30.0, 29.3, 27.7

**IR** (KBr, $cm^{-1}$) 3400, 2936, 1709, 1698, 1593, 1358, 1253, 1045, 947, 733

### 3.14 Synthesis of 3-(cyclohex-2-en-1-yl)pentane-2,4-dione (156)

To a mixture of 0.025 g (0.25 mmol) CuCl, 0.13 g (1 mmol) $CoCl_2$, 4.1 g (50 mmol) cyclohexene and 1.0 g (10 mmol) acetyacetone, 0.18 g (20 mmol, ~5.5 M in decane) of tert-butyl hydroperoxide was added under $N_2$ at room temperature. The reaction temperature was raised to 80 °C and left for reflux for overnight. The resulting mixture was purified by column chromotography on silica gel (hexane/ethyl acetate 9/1), to give 1.17 g of the desired product **156** with 65 % yield [44].



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) 5.76 (ddd, J = 10.0, 6.0 and 3.6 Hz, 1H), 5.37 (ddd, J = 10.0, 4.4 and 2.4 Hz, 1H), 3.62 (d, J = 10.8 Hz, 1H), 3.06-2.97 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.02-1.96 (m, 2H), 1.76-1.66 (m, 2H), 1.61-1.52 (m, 1H), 1.27-1.17 (m, 1H)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 203.6, 203.3, 129.7, 126.8, 74.6, 35.6, 30.1, 29.6, 26.57, 24.9, 20.6

**IR** (KBr, $cm^{-1}$) 2932, 1695, 1358, 1266, 1156, 701.

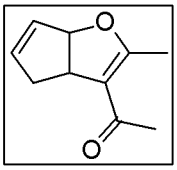
### 3.15 Synthesis of 3-(cyclohex-2-en-1-yl)pentane-2,4-dione (156)

To a mixture of 1.0 g (10 mmol) acetylacetone **132** and 3.45 g (25 mmol) of $K_2CO_3$ in DMSO was added 2.42 g (10 mmol) of 1,2-dibromocyclohexane **158** dropwise in an hour. The reaction was left for overnight at 80 °C. After the completion of the

reaction, the mixture was poured into water and added $Et_2O$ for the extraction. The combined organic phase was dried over $CaCl_2$ and the solvent was removed, giving 1.35 g of crude product compound **156** with 75 % yield [45].

### 3.16 Synthesis of 1-(2-methyl-4,6a-dihydro-3aH-cyclopenta[b]furan-3-yl)ethanone (159)

7.24 g (30 mmol) $Mn(OAc)_3.2H_2O$ and 0.5 g (3 mmol) of $Cu(OAc)_2$ were dissolved in 100 mL of acetic acid and to this solution was added a mixture of 1.66 g (10 mmol) of compound **155** in 25 mL of acetic acid dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80° C for 30 minutes. After the completion of the reaction, the mixture was extracted with $CH_2Cl_2$ and water. The aqueous phase was extracted with $CH_2Cl_2$ again (3 x 50 mL). The combined organic phase was washed with saturated $Na_2CO_3$ and dried over $CaCl_2$. The solvent was removed, giving 1.0 g of the crude product, compound **159** with 62 % yield which then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1).



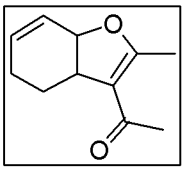
**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 6.08-6.07(m, 1H), 5.82-5.81(m, 1H), 5.63(d, J = 8.5 Hz, 1H), 3.89 (t, J = 8.0 Hz, 1H), 2.81 (dd, *J* = 17.6 and 8.0 Hz, 1H), 2.42 (ddd, *J* = 17.6, 2.0 and 2.0 Hz, 1H), 2.24 (s, 3H), 2.20 (d, *J* = 1.5 Hz, 3H)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) 194.6, 167.3, 136.9, 128.1, 117.4, 88.6, 47.1, 40.5, 29.1, 15.3

**IR** (KBr, $cm^{-1}$) 2390, 1709, 1594, 1356, 1265, 1237, 1212, 1006, 702.

### 3.17 Synthesis of 1-(2-methyl-3a,4,5,7a-tetrahydrobenzofuran-3-yl)ethanone (160)

7.24 g (30 mmol) $Mn(OAc)_3.2H_2O$ and 0.5 g (3 mmol) of $Cu(OAc)_2$ were dissolved in 100 mL of acetic acid and to this solution was added a mixture of 1.8 g (10 mmol) of compound **156** in 25 mL of acetic acid dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80 °C for 30 minutes. After the completion of the reaction, the mixture was extracted with $CH_2Cl_2$ and water. The aqueous phase was extracted with $CH_2Cl_2$ again (3 x 50 mL). The combined organic phase was washed with saturated $Na_2CO_3$ and dried over $CaCl_2$. The solvent was removed, giving 1,38 g of the crude product, compound **160** with 78 % yield which then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1).



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 6.20 (ddt, 1H), 5.95 (dtd, J = 9.9 and 3.1, 1H), 4.7 (ddt, J = 8.4 and 1.8 Hz, 1H), 3.05 (ddd, J = 8.4, 4.5 and 11.9 Hz, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 1.85-2.10 (m, 2H), 1.15-1.27 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) 194.3, 168.2, 134.6, 122.9, 118.9, 78.1, 40.6, 29.2, 25.0, 23.3, 15.6

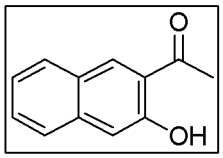
**IR** (KBr, $cm^{-1}$) 2391, 1716, 1584, 1384, 1220, 1186, 1096, 991, 945, 909, 723, 701.

### 3.18 Synthesis of 1-(3-hydroxynaphthalen-2-yl)ethanone (161) and 3-benzylidenepentane-2,4-dione (162)

7.24 g (30 mmol) $Mn(OAc)_3.2H_2O$ and 0.5 g (3 mmol) of $Cu(OAc)_2$ were dissolved in 100 mL of acetic acid and to this solution was added a mixture of 1.9 g (10 mmol) of compound **144** in 25 mL of acetic acid dropwise under nitrogen atmosphere in 30 minutes. The reaction was stirred at 80 °C for 30 minutes. After the completion of the

reaction, the mixture was extracted with $CH_2Cl_2$ and water. The aqueous phase was extracted with $CH_2Cl_2$ again (3 x 50 mL). The combined organic phase was washed with saturated $Na_2CO_3$ and dried over $CaCl_2$. The solvent was removed, giving the crude products, compound **161** and compound **162** with 10 % and 60 % yield respectively. The mixture was then chromatographed on silica gel (50 g) eluting with n-hexane/EtOAc (9:1).

**1-(3-Hydroxynaphthalen-2-yl)ethanone (161)**

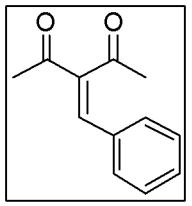



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 11.58 (bs, 1H), 8.38 (bs, 1H), 7.83 (bd, J=8.3 Hz, 1H), 7.68 (bd, J=8.4 Hz, 1H), 7.53 (ddd, J=6.8, 8.4 and 1.2 Hz, 1H), 7.34 (ddd, J=8.3, 6.8 and 1.1 Hz, 1H), 7.28 (bs, 1H), 2.8 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 205.0, 157.4, 138.5, 133.8, 129.9, 129.6, 127.2, 126.6, 124.3, 121.7, 112.6, 27.2.

**IR** (KBr, $cm^{-1}$) 2983, 1736, 1655, 1447, 1372, 1220, 1044, 916, 732, 700.

**3-Benzylidenepentane-2,4-dione (162)**



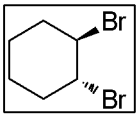

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40 (br. s, 5H), 2.42 (s, 3H), 2.25 (s, 3H)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 205.6, 196.5, 142.9, 139.8, 132.9, 130.6, 129.7, 129.0, 31.6, 26.5

**IR** (KBr, $cm^{-1}$) 3057, 1709, 1657, 1615, 1574, 1494, 1385, 1352, 1309, 1246, 1175, 760, 692.

### 3.19 Synthesis of trans-1,2-dibromocyclohexane (158)

20.5 g of cyclohexene **95** (0.25 mole) is dissolved in 30 mL of chloroform and cooled to 0 °C in an ice bath. Equimolar amount of bromine (0.25 mole, 40 g) is dissolved in 80 mL of chloroform and is added dropwise. When dropping is completed, the solvent is evaporated and 63 g of product **158** is obtained with a yield of 92 % [46].




**$^1$H NMR** (400 MHz, CDCl3) δ 4.45 (s, 2H), 2.51-2.45 (m, 2H), 1.93-1.88 (m, 2H), 1.85- 1.78 (m, 2H), 1.54-1.50 (m, 2H).

**$^{13}$C NMR** (100 MHz, CDCl3) δ 55.1, 31.9, 22.4.

### 3.20 Synthesis of 1,3-cyclohexadiene (174)

63 g of trans-1,2-dibromocyclohexane (**158**), 72 g potassium hydroxide and 177 mL ethylene glycol is heated up to 150 - 170 °C in an oil bath. The mixture is continuously stirred mechanically throughout the reaction. The product is collected via distillation through a condenser. 5.5 g of product is obtained with a yield of 30 % [46].

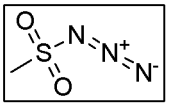
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.89-5.87 (m, A-part of AB-system, 2H) 5.80-5.77 (m, B-part of AB-system, 2H), 2.14 (s, 4H).

**$^{13}$C NMR** (100 MHz, CDCl3) δ126.3, 124.4, 22.2.

### 3.21 Synthesis of mesyl azide (176)

To a well stirred solution of 11.4 g. (0.10 mole) of methanesulfonylchloride **177** in 40 mL. of absolute methanol was added, over a period of one hour, in half gram portions of 8.5 g. (0.13 mole) of sodium azide. The solution was stirred for further 30

minutes, filtered, and methanol is evaporated. 6.6 g (55 %) Mesyl azide which is a colorless liquid at room temperature was obtained [47].

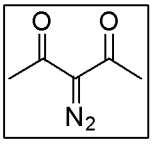


**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 3.29 (s, 3H).

**IR** (KBr, $cm^{-1}$) 3034, 2937, 2378, 2142 ($N_3$), 1733, 1359, 1329, 1199, 1167, 967, 781, 729, 573, 509

### 3.22 Synthesis of diazoacetylacetone (175)

To a cooled (0-3 °C) solution of 10.0 – 10.5 g (0.100 - 0.105 mol) of acetylacetone **132** in 100 mL of anhydrous methylene chloride was added, with strongly stirring, 13 g (0.13 mol) of triethylamine. 5 minutes later a solution of 12.1 g (0.01 mol) of mesyl azide (**176**) in 50 mL of methylene chloride was added in one portion. Stirring was continued for six hours. After the completion of the reaction, solvent was evaporated at 35 °C max. Resulting yellow solution was then chromatographed on silica gel (9:1 Hexane:Ethylacetate) to obtain 8.8 g (70%) of diazoacetylacetone **175** as a yellow liquid [48].



**$^1$H-NMR** (400 MHz, $CDCl_3$) 2.44 (s, 6H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) 188.5, 84.7, 28.6

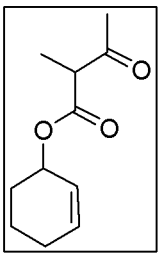
**IR** (KBr, $cm^{-1}$) 2128, 1660

### 3.23 Reaction of 1,3-cyclohexadiene (174) and diazoacetylacetone (175) in benzene with copper (II) acetylacetonate

To a solution of 0.8 g (10 mmol) of cyclohexadiene-ethylene glycol mixture and 0.131 g (0.5 mmol) of copper (II) acetylacetonate in 20 mL benzene was added 1.26

g (10 mmol) of diazoacetylacetone **175** in 10 mL benzene drop wise over 2 hours. Reaction then left for overnight at 80 °C. After the completion of the reaction benzene was evaporated and the residue was chromatographed on silica gel (9:1 Hexane:Ethylacetate) to get compound **178** and **179** with yields 55% and 10% respectively.

**Cyclohex-2-en-1-yl 2-methyl-3-oxobutanoate (178) (diastereomeric mixture)**

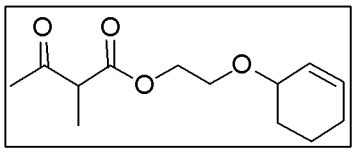


**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 5.97 (dtd, J=10.0, 3.4 and 1.1 Hz, 1H), 5.70 (ddt, J=10.0, 3.6 and 2.2 Hz, 1H), 5.31 (br d, J=3.6 Hz, 1H), 3.49 (q, J= 7.2 and 2.5 Hz, 1H), 3.49 (other diastereomer, q, J= 7.2 and 2.5 Hz, 1H), 2.24 (s, 3H), 2.23 (other diastereomer, s, 3H), 2.02 (m, 2H), 1.80 (m, 2H), 1.71 (m, 2H), 1.33 (d, J=7.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 203.5, 203.6, 170.2, 133.3, 133.2, 125.8, 124.9, 69.2, 69.1, 53.9, 53.8, 28.4, 28.3, 28.1, 28.0, 24.8, 18.7, 18.6, 12.7.

**IR** (KBr, $cm^{-1}$) 2941, 1735, 1711, 1454, 1360, 1241, 1200, 1152, 1097, 1049, 1007, 909, 728.

**2-(Cyclohex-2-en-1-yloxy)ethyl 2-methyl-3-oxobutanoate (179)**



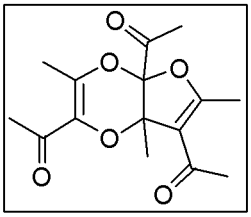
**$^1$H-NMR** (400 MHz, $CDCl_3$) 5.87 (dtd, J=10.1, 3.6 and 1.3 Hz, 1H), 5.72 (ddt, J=10.1 Hz, 1H), 4.25-4.35 (m, 2H), 3.88 (m, 1H), 3.70 (ddd, J=3.9, 5.9 and 11.0 Hz, 2H), 3.70 (other diastereomer, ddd, J=3.9, 5.9 and 11.0 Hz, 2H), 3.53 (q, J=7.1 Hz, 1H), 2.27 (s, 3H), 2.05 (m, 2H), 1.78 (m, 2H), 1.60 (m, 2H), 1.35 (d, J=7.1 Hz, 3H), **$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 203.5, 170.6, 131.3, 127.3, 73.2, 65.6, 64.8, 53.5, 28.5, 28.2, 25.2, 19.1, 12.7

**IR** (KBr, $cm^{-1}$) 3468, 2940, 1740, 1715, 1454, 1359, 1242, 1200, 1154, 1102, 1050, 968, 728.

### 3.24 Reaction of cyclohexene 95 and diazoacetylacetone 175 in the presence of copper metal powder

To a solution of 0.82 g (10 mmol) of cyclohexene **95** and 0.03 g (0.5 mmol) of copper metal powder in 10 mL cyclohexene was added 1.26 g (10 mmol) of diazo acetylacetonate **175** drop wise over 2 hours. Reaction then left for overnight at 80°C. After the completion of the reaction the residue was chromatographed on silica gel (9:1 Hexane:Ethylacetate) to get compound **156**, **178** and **182** with yields of 10%, 55% and 15% respectively.

**1,1',1''-(3,6,7a-trimethyl-4a,7a-dihydrofuro[2,3-b][1,4]dioxine-2,4a,7-triyl) triethanone (182)**



**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 1,96 (s, 3H), 1.45 (s, 3H).

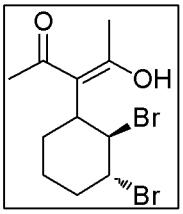
**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 199.8, 196.3, 195.1, 163.5, 149.8, 121.8, 110.8, 103.1, 93.0, 27.9, 26.9, 25.6, 20.2, 18.3, 17.5.

**IR** (KBr, $cm^{-1}$) 3130.6, 1725.5, 1712.3, 1642.6, 1340.3, 1226.1, 741.3.

### 3.25 Synthesis of (E)-3-((2R,3R)-2,3-dibromocyclohexyl)-4-hydroxypent-3-en-2-one (187), 1-(7-bromo-2-methyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-yl) ethanone (188) and 1-(2-methyl-3a,4,5,7a-tetrahydrobenzofuran-3-yl)ethanone (160)

To a solution of 1.8 g (10 mmol) of compound **156** in 50 mL chloroform was added 1.6 g (10 mmol) of bromine in 30 mL chloroform over 2 hours. Afte the completion of the reaction, solvent was evaporated to get compound **187** in 87% yield. Treatment of compound **187** with $Na_2CO_3$ solution produces compound **188** with 93% yield. Further treatment of compound **188** with equimolar of $K_2CO_3$ gives compound **160** with 78% yield.

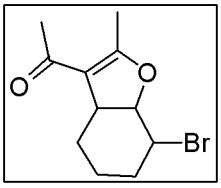
**(E)-3-((2R,3R)-2,3-dibromocyclohexyl)-4-hydroxypent-3-en-2-one (187)**




**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 11.70 (br. s, 1H), 4.91 (dd, J=4.0 and 7.2 Hz, 1H), 4.58 (dt, J=4.0 and 2.3 Hz, 1H), 3.40 (dt, J=7.2 and 6.8 Hz, 1H), 2.72 (s, 3H), 2.53 (s, 3H), 2.08 (m, 2H), 1.70 (m, 2H), 1.25 (m, 2H)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 197.8, 120.5, 89.4, 46.3, 37.8, 29.2, 26.8, 25.6, 23.3, 18.6, 17.7.

**1-(7-bromo-2-methyl-3a,4,5,6,7,7a-hexahydrobenzofuran-3-yl)ethanone (188)**




**$^1$H-NMR** (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 4.49 (dt, J=4.0 Hz, 1H), 3.20 (br. dt, J=7.3 and 9.2 Hz, 1H), 2.25 (d, J=1.8 Hz, 3H), 2.22 (s, 3H), 2.02 (m, 2H), 1.7 (m, 2H), 1.2 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ 194.3, 167.3, 120.5, 85.4, 48.9, 39.3, 29.9, 29.2, 27.2, 18.3, 15.3.

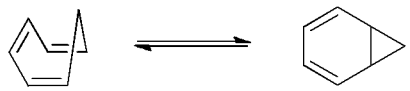
**IR** (KBr, $cm^{-1}$) 3130.6, 1712.3, 1463.5, 1310.3, 1256.1, 749.3.

# CHAPTER 4

# CONCLUSION

Oxidative free radicalic reactions have been a very useful and easy way to form new C-C bonds between two molecules one bearing a π-bond and the other bearing an acidic proton. Manganese (III) acetate is one of the most useful reagents to be used in this type of reactions. However, the mechanism of the reactions in the presence of $Mn(OAc)_3$ have been under investigation since its application in this area.

Cycloheptatriene is also a fascinating molecule in a lot of aspects. Some reactions revealed that CHT **94** has a valance isomer, norcaradiene **93**, which has a six membered planar structure unlike CHT as shown in Scheme 78.



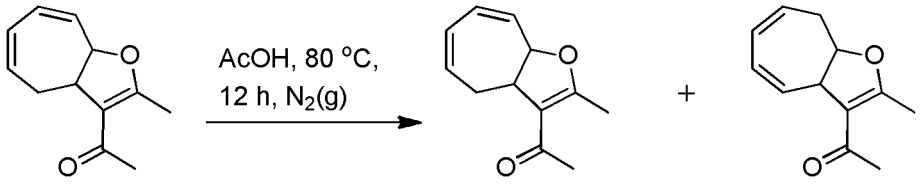
**94** **93**

Scheme 78

In this study we aimed to find out whether CHT or NOR will dominate the products of the reaction of CHT with 1,3-diketone in the presence of different one electron oxidants. We also introduced different substituents on C-7 position of CHT in order to see their effects on isomer choice in the products.

We have found that all the products have CHT form unless CHT has an electron withdrawing or electron releasing group on C-7 position. We have observed NOR derivative products when we introduced –CN group on C-7 position of CHT. All the products from the reaction of CHT with both acetyacetone and dimedone have been

obtained and an equilibrium between the [3+2] addition products have been observed that arises due to thermal [1,5] hydride shift on CHT molecule as shown in Scheme 79.

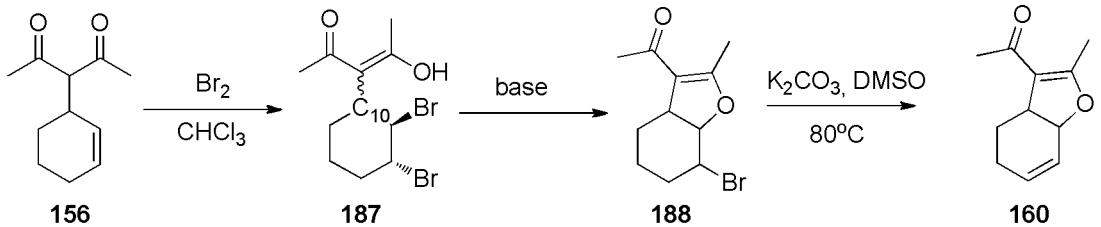



**133** **133** **134**

Scheme 79

We also aimed to find out whether cyclization is going over a cyclopropane intermediate or not. Even though we tried several different metal catalysts with different conditions, we could not obtain acetylacetone derivative cyclopropane compound **173** or dihydrofuran derivative **160** that we were planning to obtain from **173** in order to prove the cyclization mechanism. Therefore we could not proceed our study using diazo mediated cyclopropanation reactions. On the other hand, we have observed that methyl migration takes place on diazoacetylacetone when it is used with Cu derivative catalysts which then undergoes Wolf-rearrangement.

In the second synthetic route towards the synthesis of compound **173**, we obtained the dihydrofuran derivative **160** but unfortunately, reaction did not go over cyclopropane intermediate as shown in Scheme 80.




**156** **187** **188** **160**

Scheme 80

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# APPENDIX

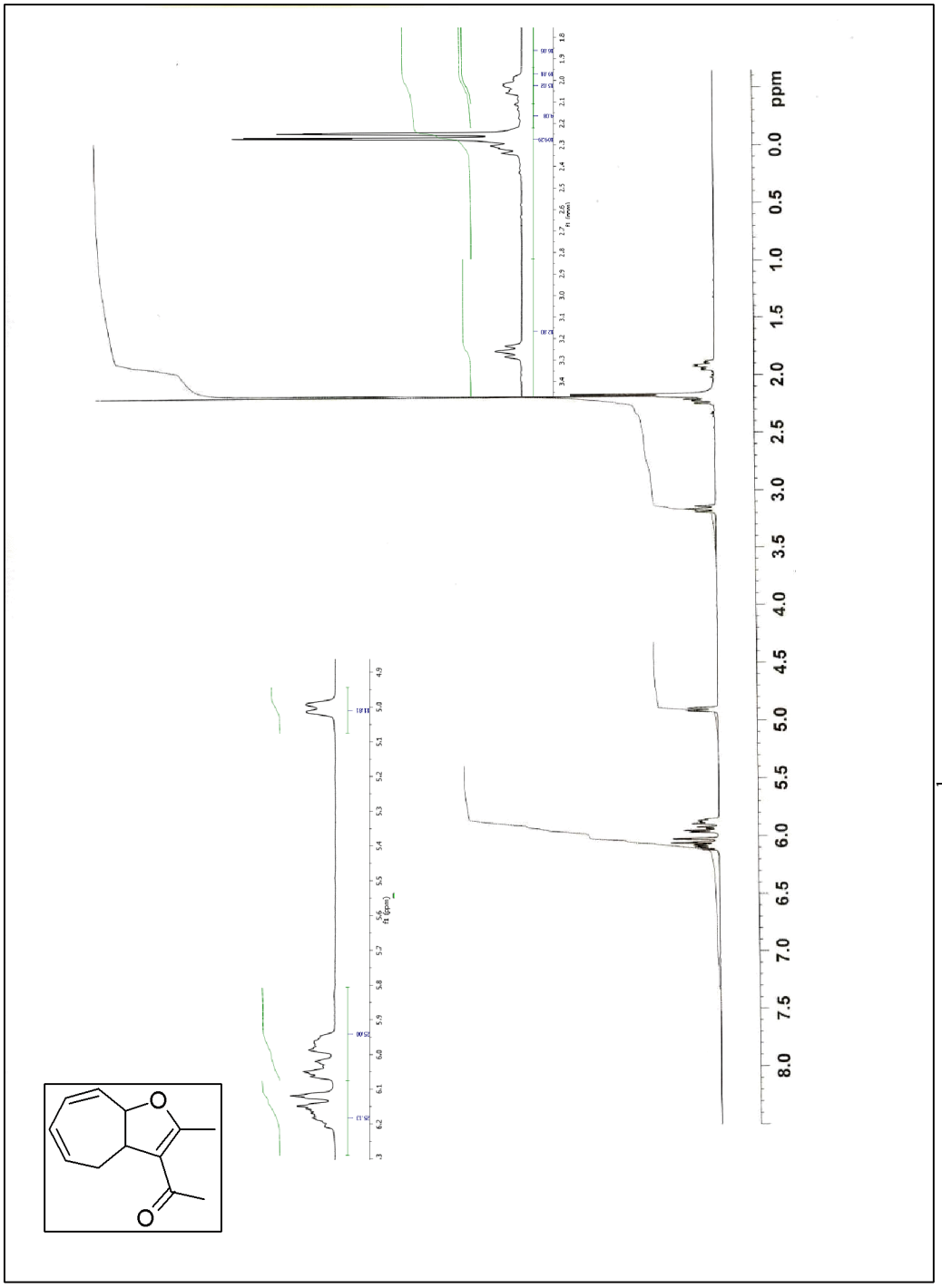


**Figure 10** $^{1}$H NMR spectrum of Compound **133**

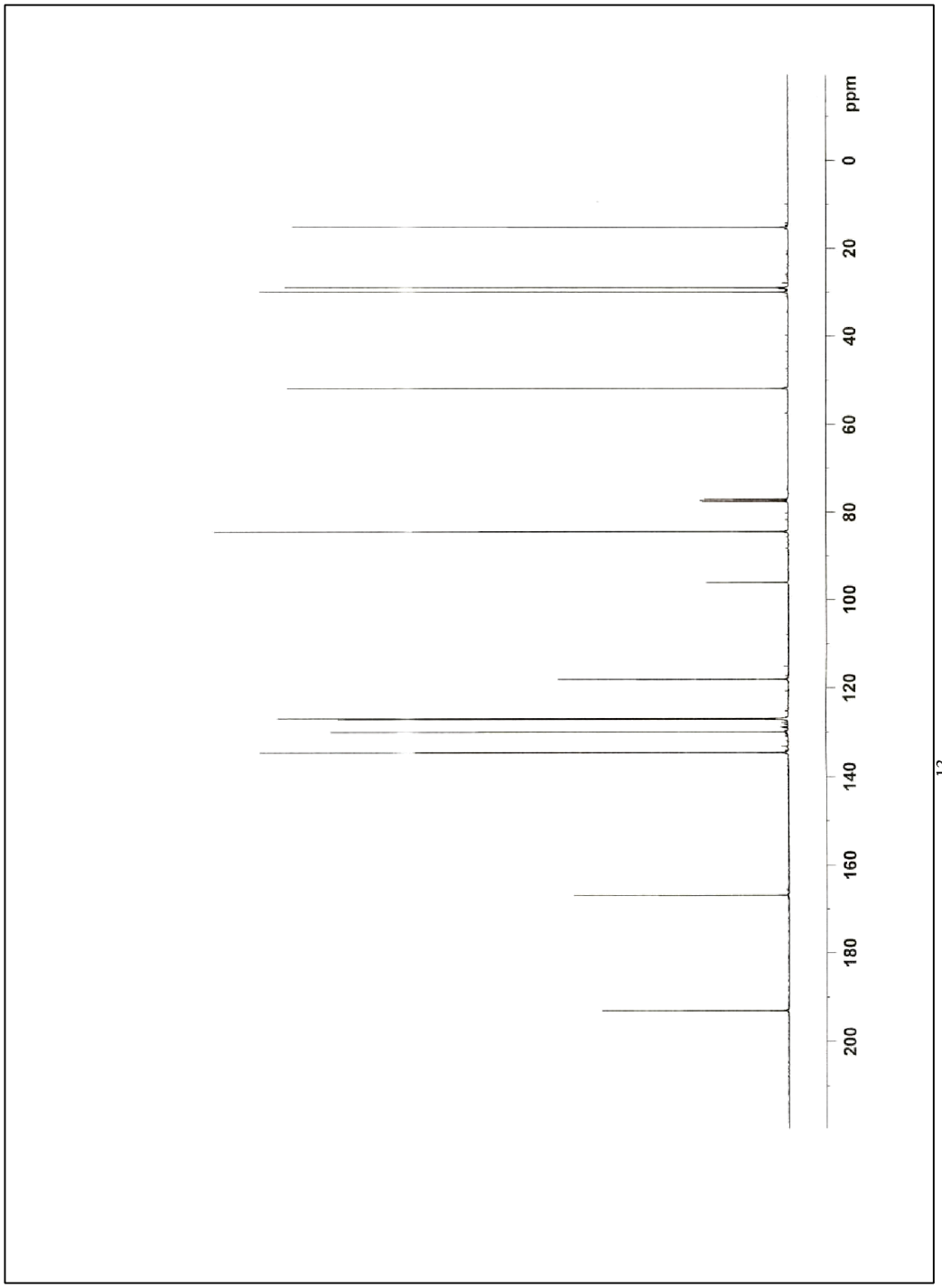


**Figure 11** $^{13}C$ NMR spectrum of Compound **133**

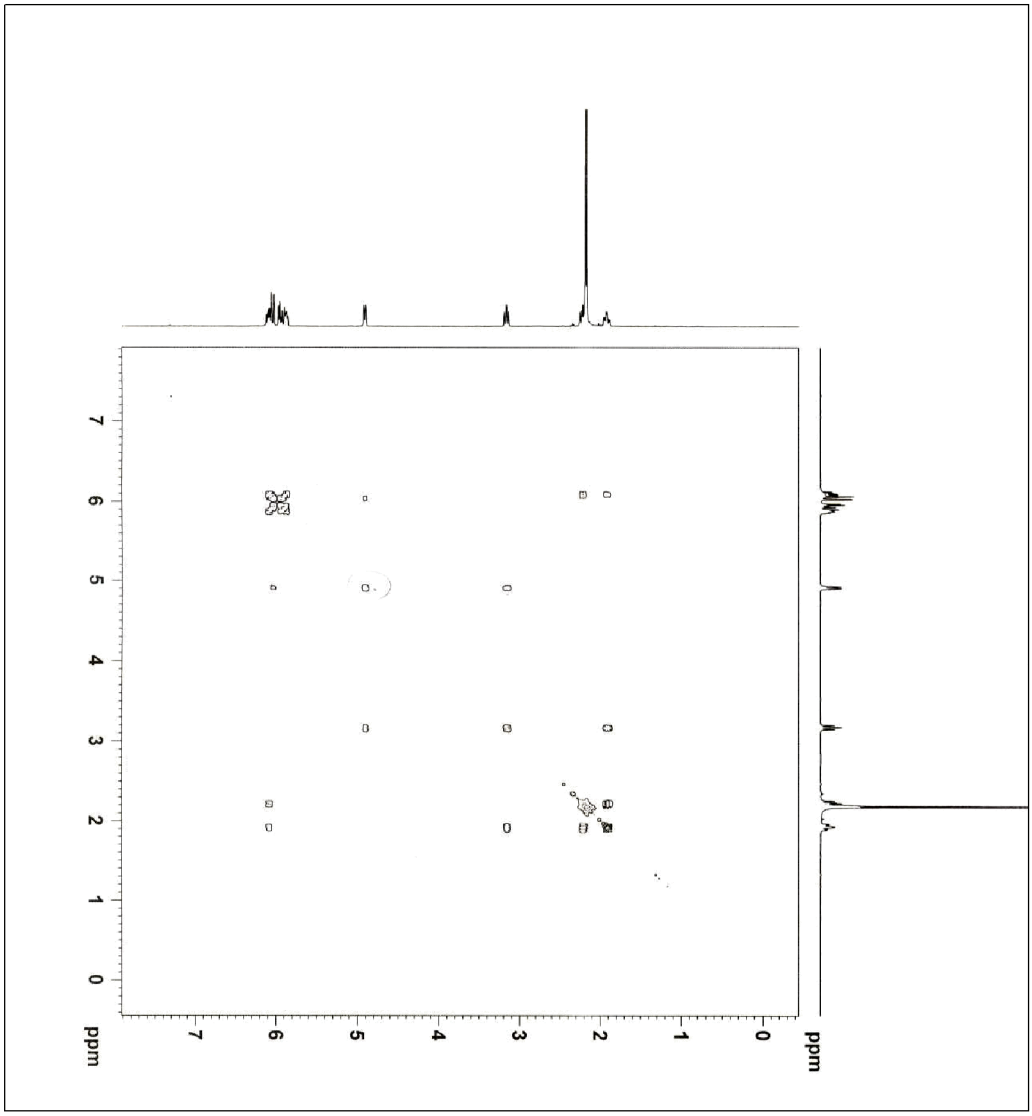


**Figure 12** COSY spectrum of compound **133**

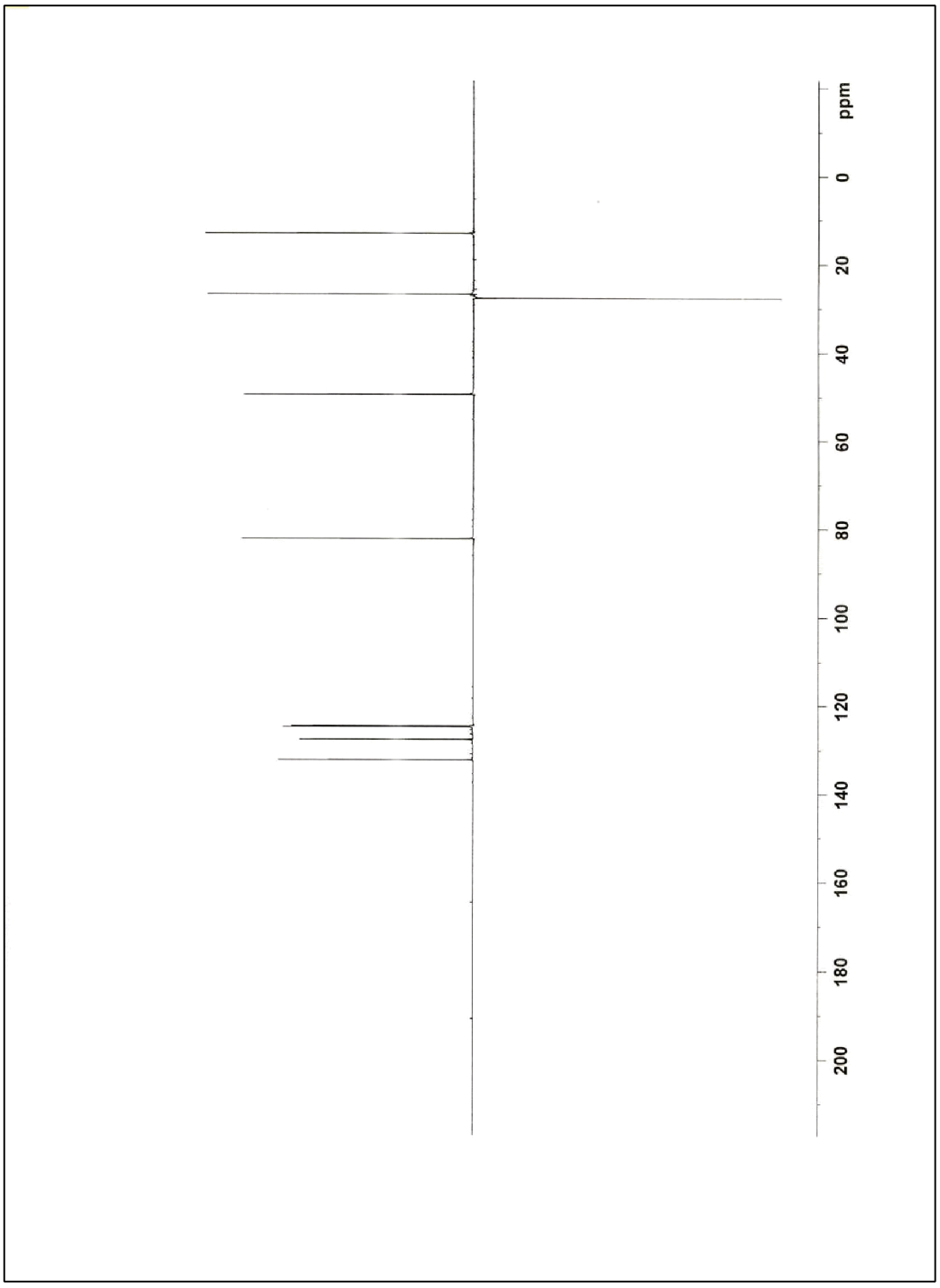


**Figure 13** DEPT 135 spectrum of compound **133**

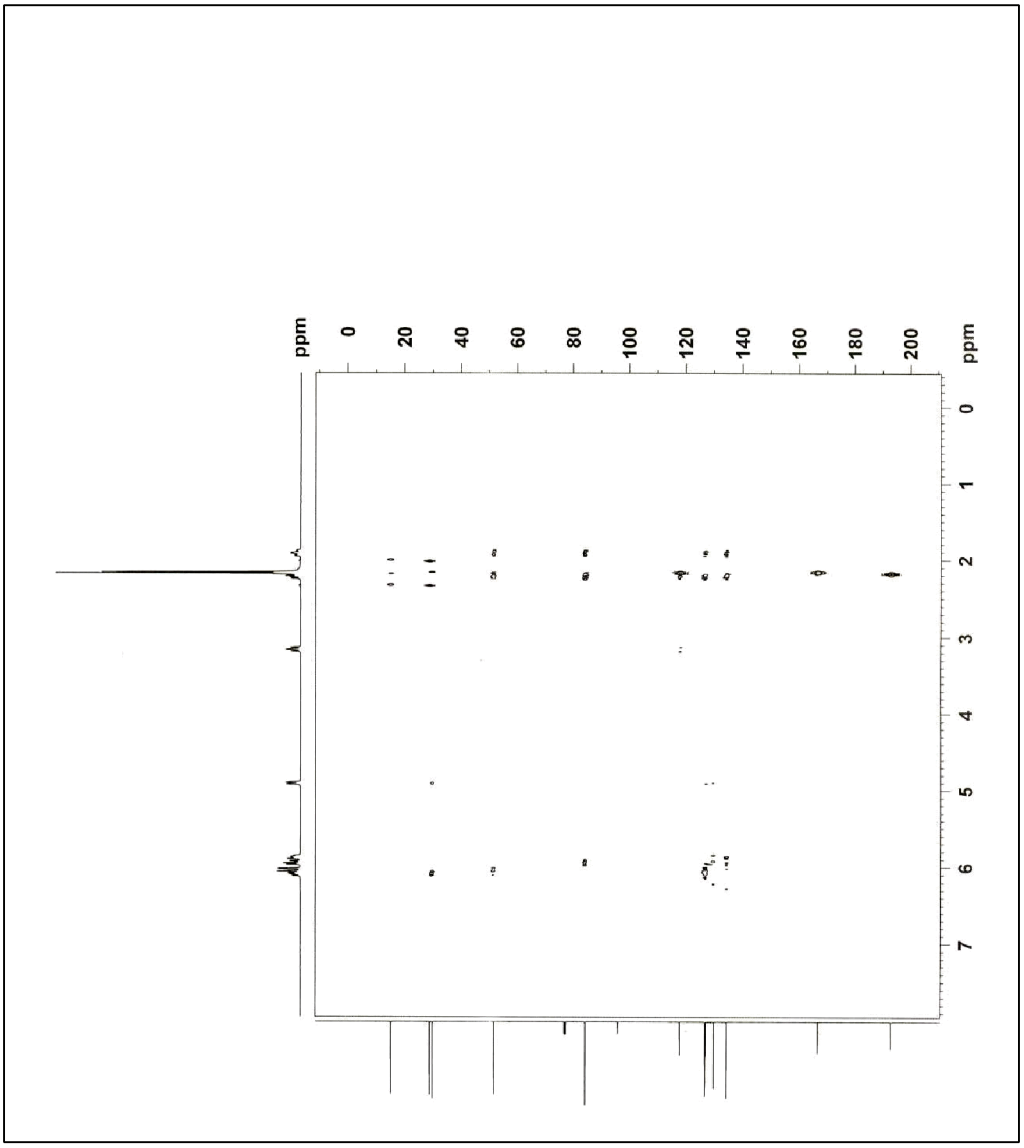


**Figure 14** HMBC spectrum of compound **133**

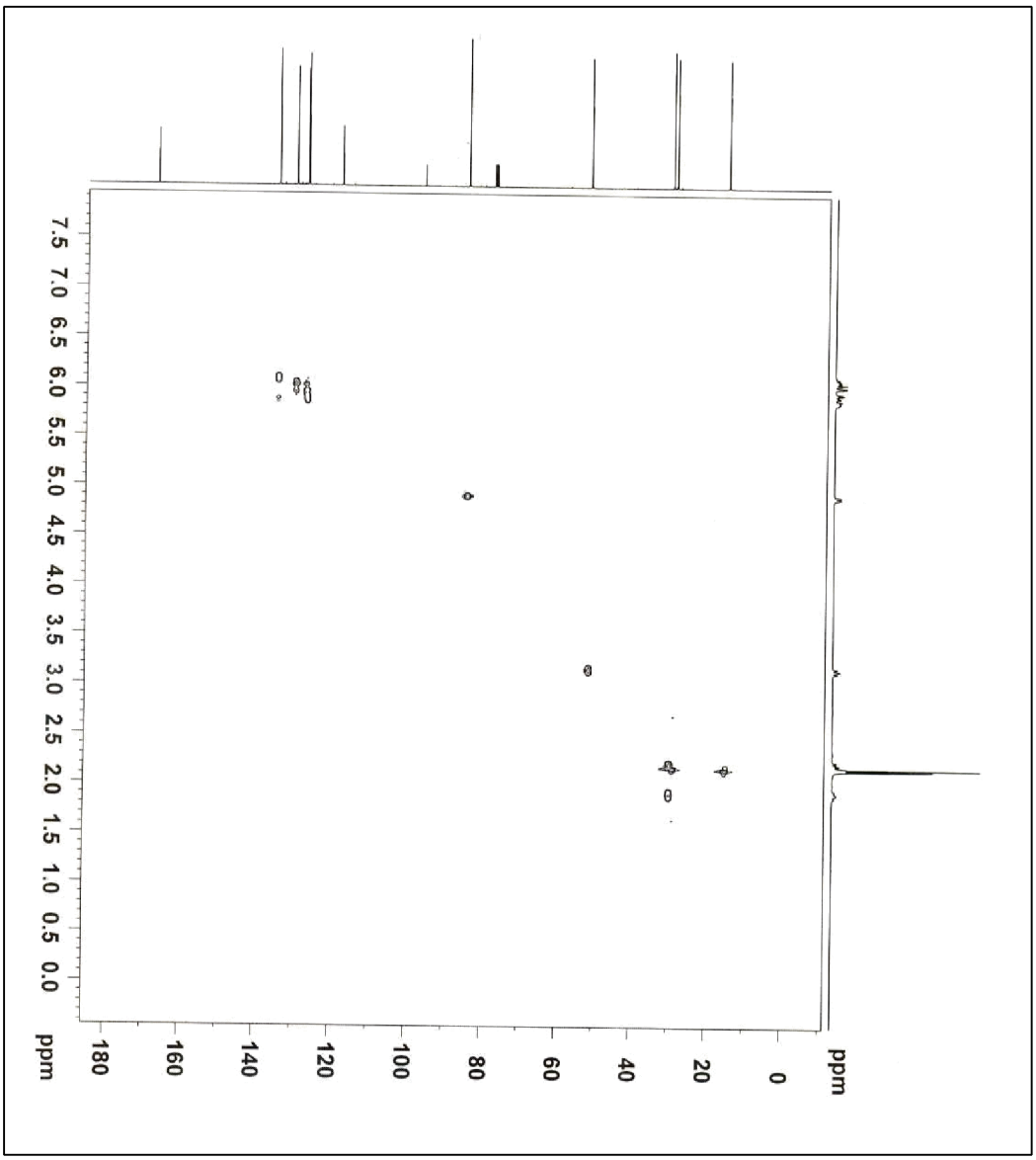


**Figure 15** HSQC spectrum of compound **133**

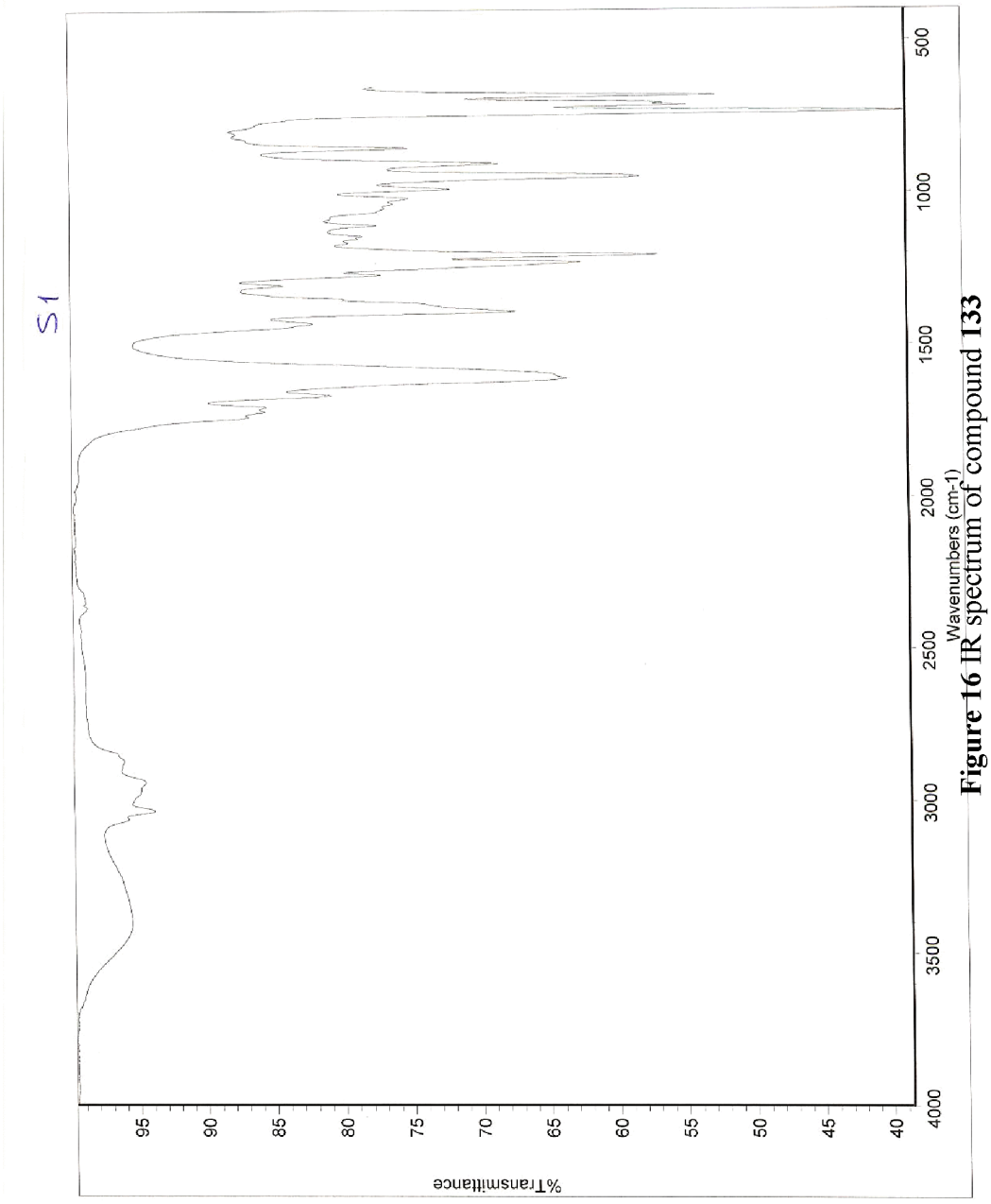


**Figure 16** IR spectrum of compound **133**

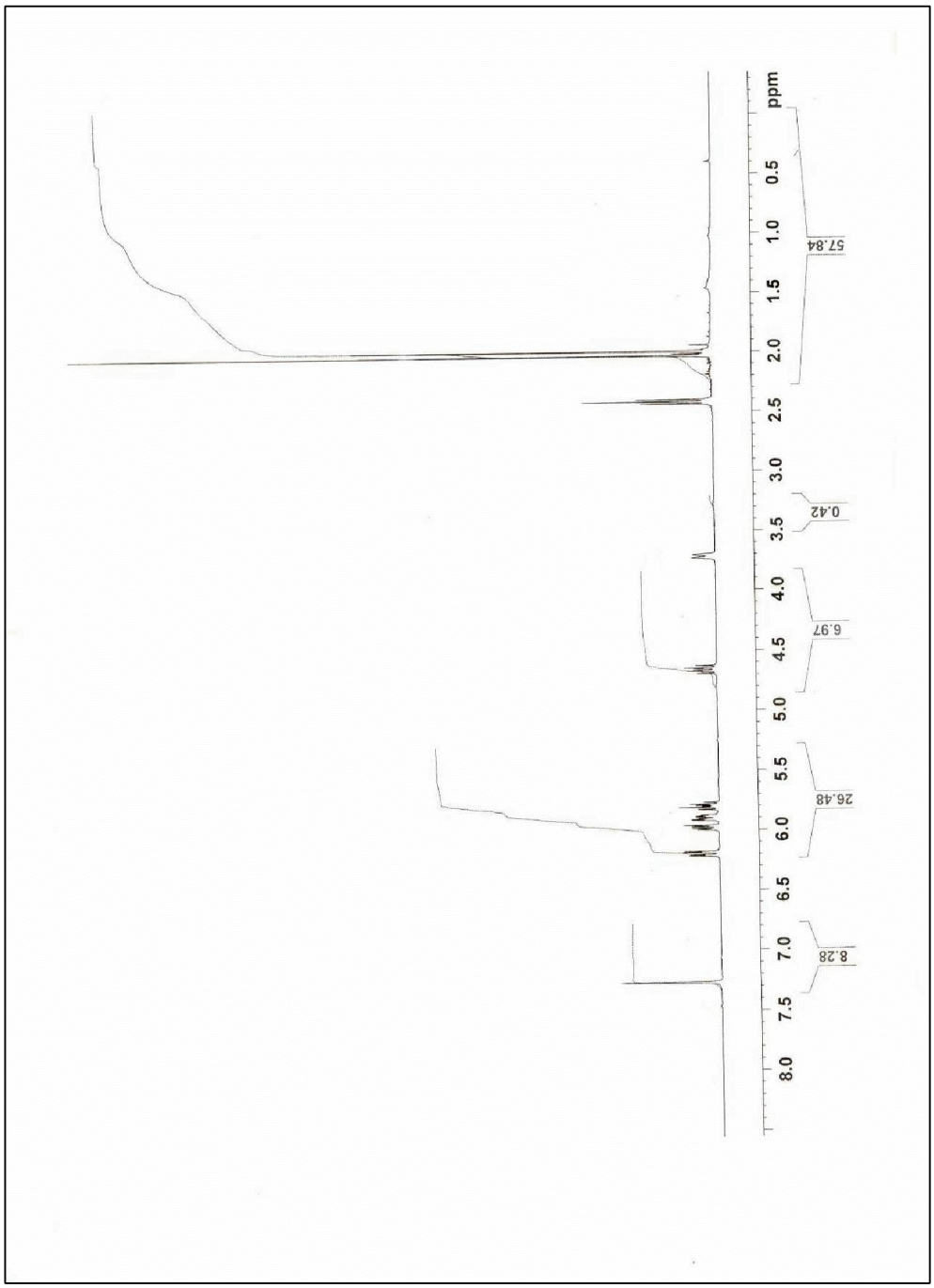


**Figure 17** $^{1}$H NMR spectrum of compound **134**

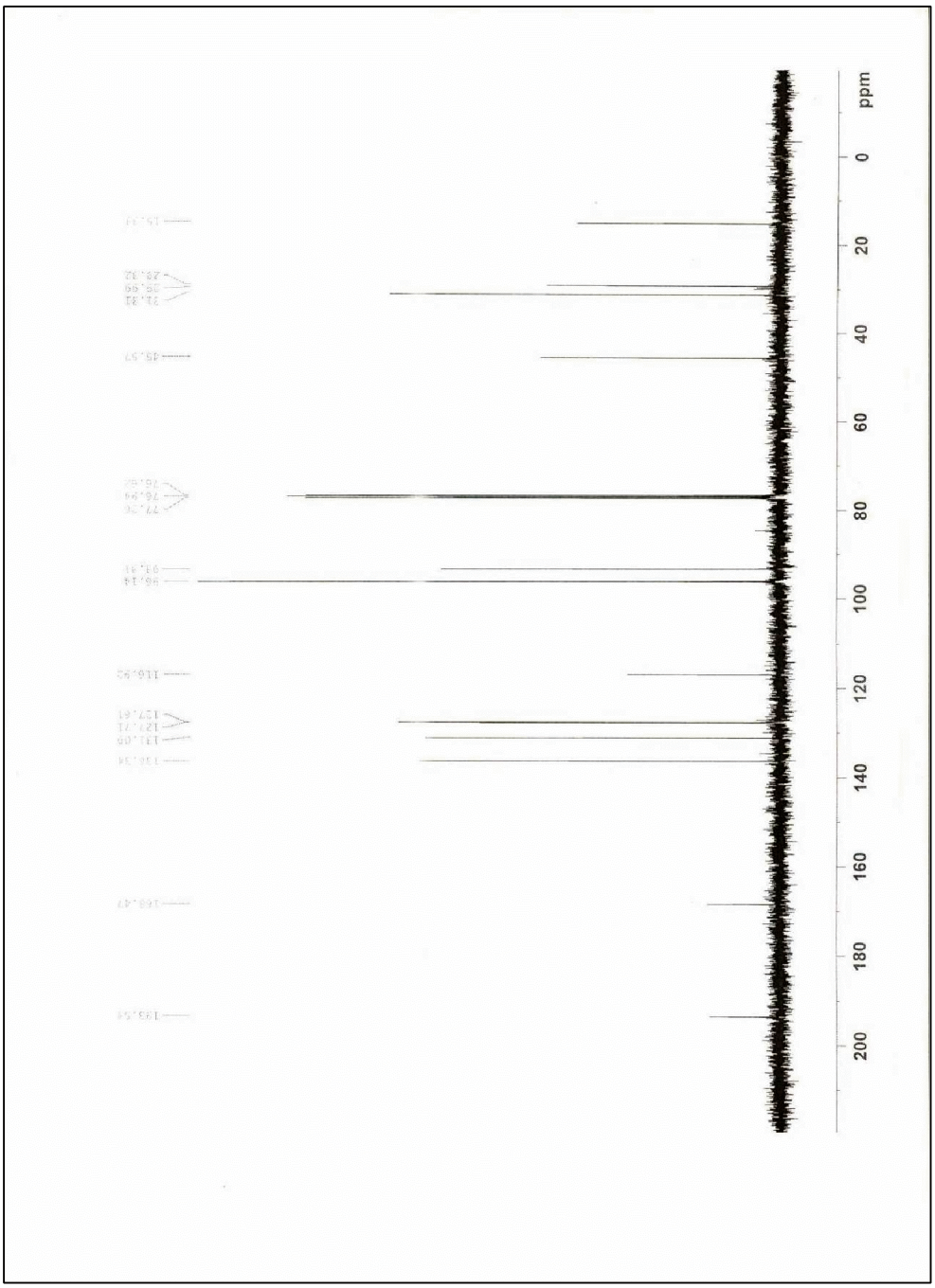


**Figure 18** $^{13}$C NMR spectrum of compound **134**

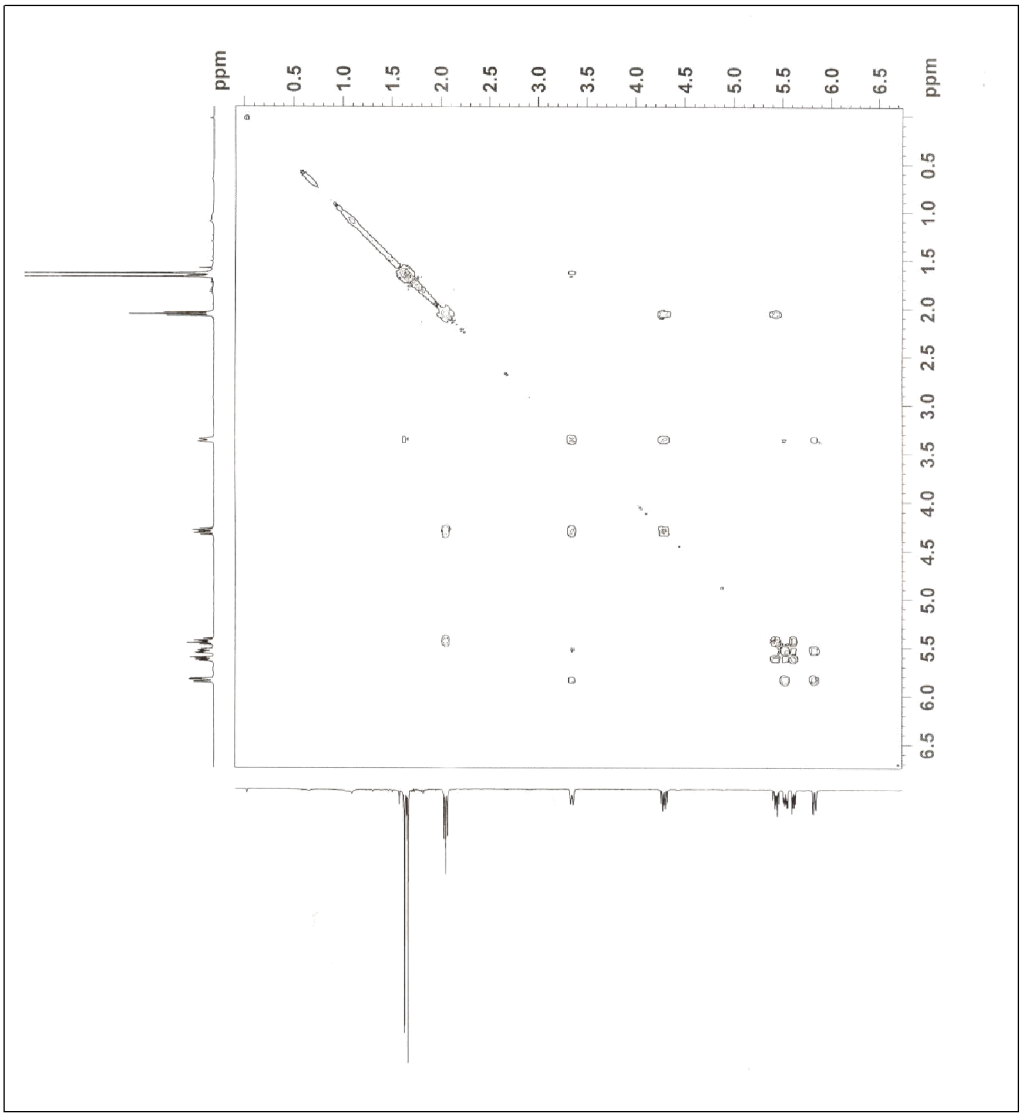


**Figure 19** COSY spectrum of compound **134**

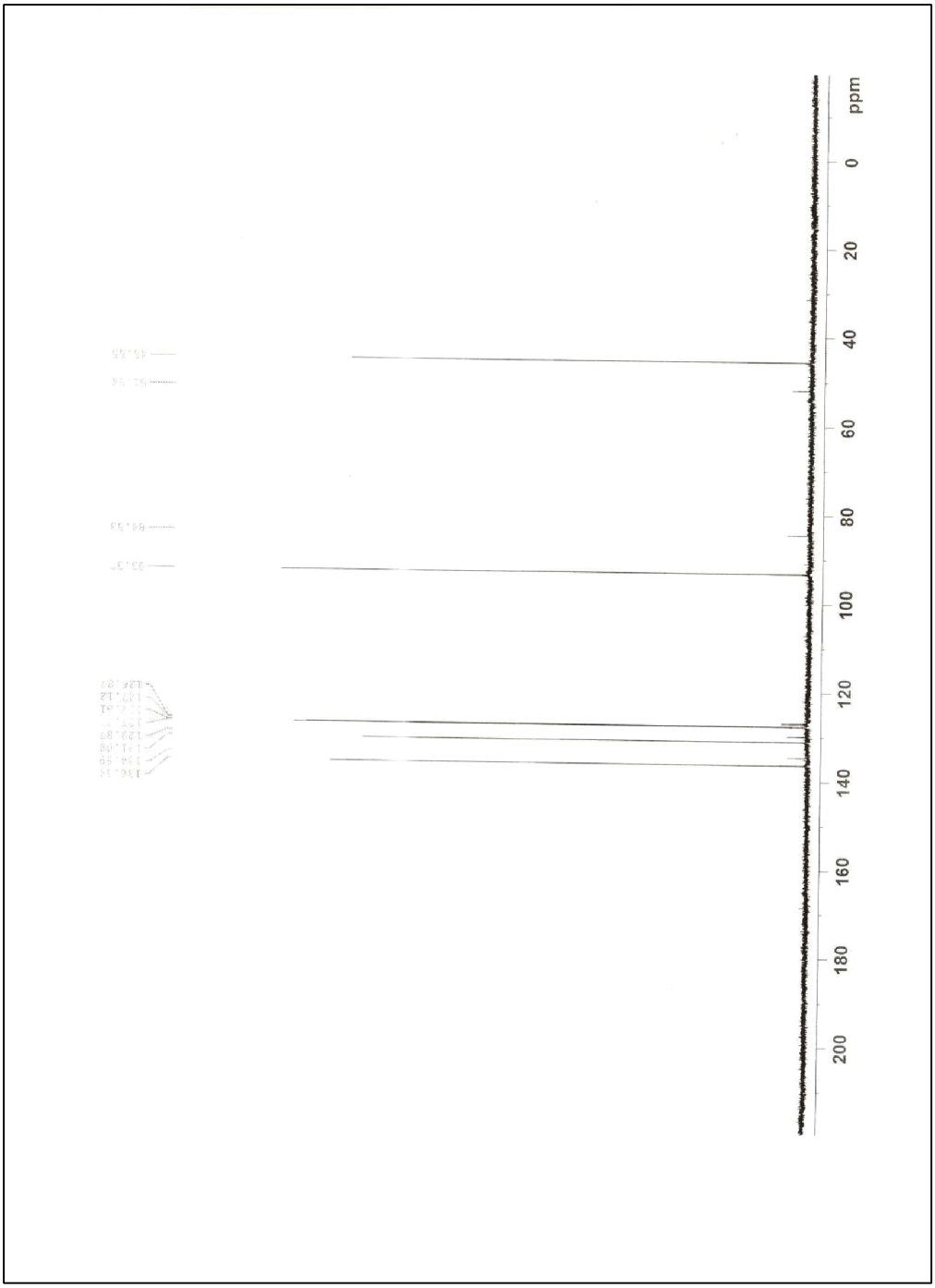


**Figure 20** DEPT 90 spectrum of compound **134**

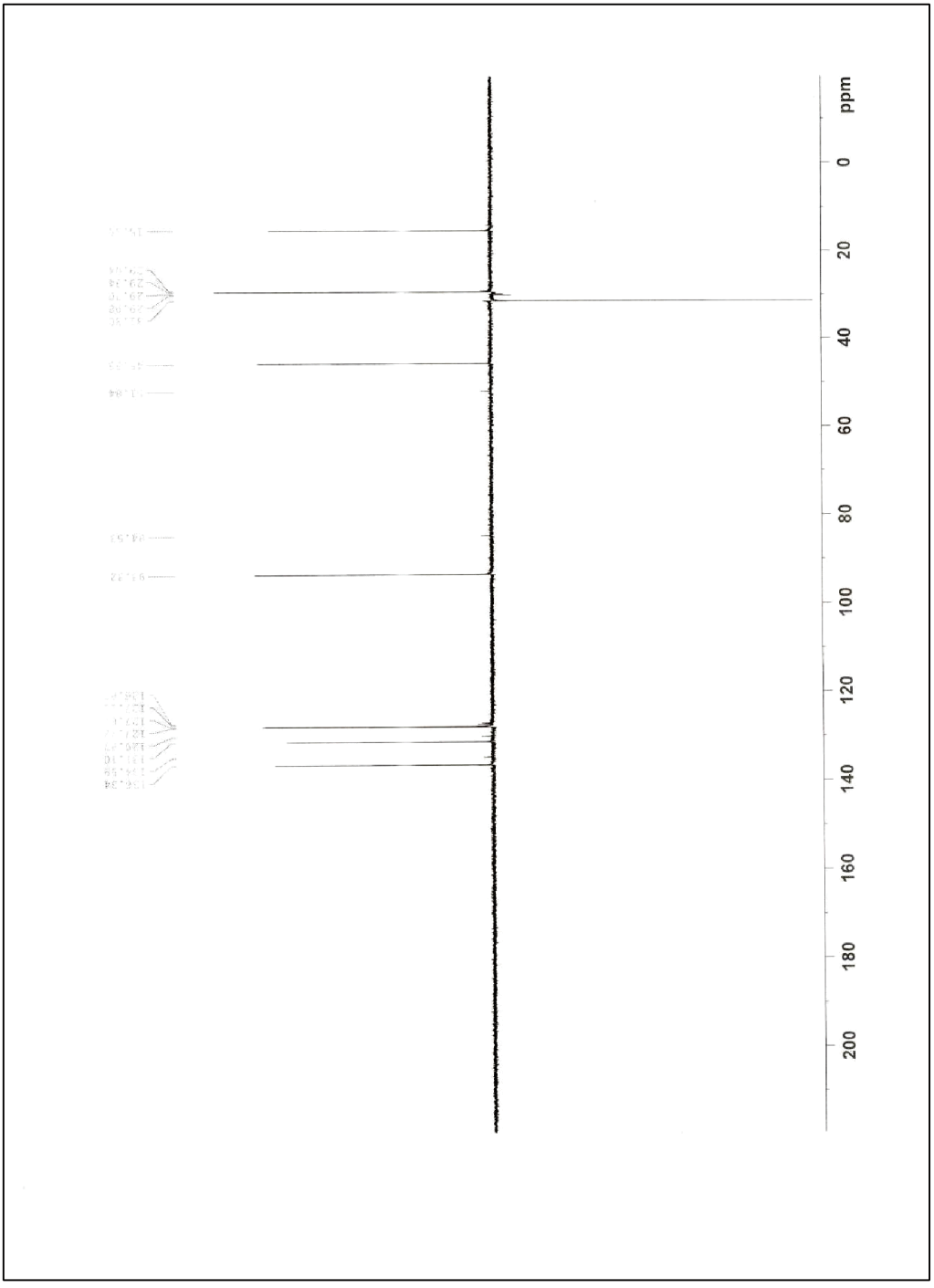


**Figure 21** DEPT 135 spectrum of compound **134**

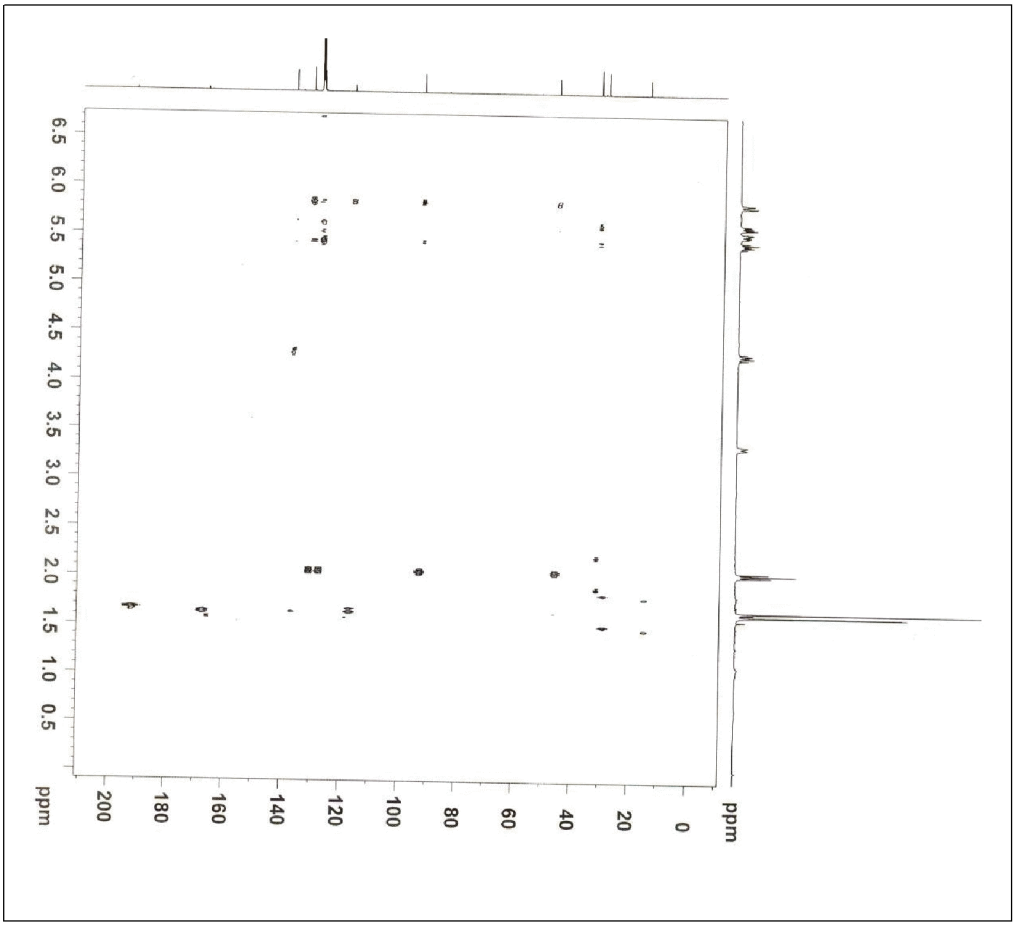


**Figure 22** HMBC spectrum of compound **134**

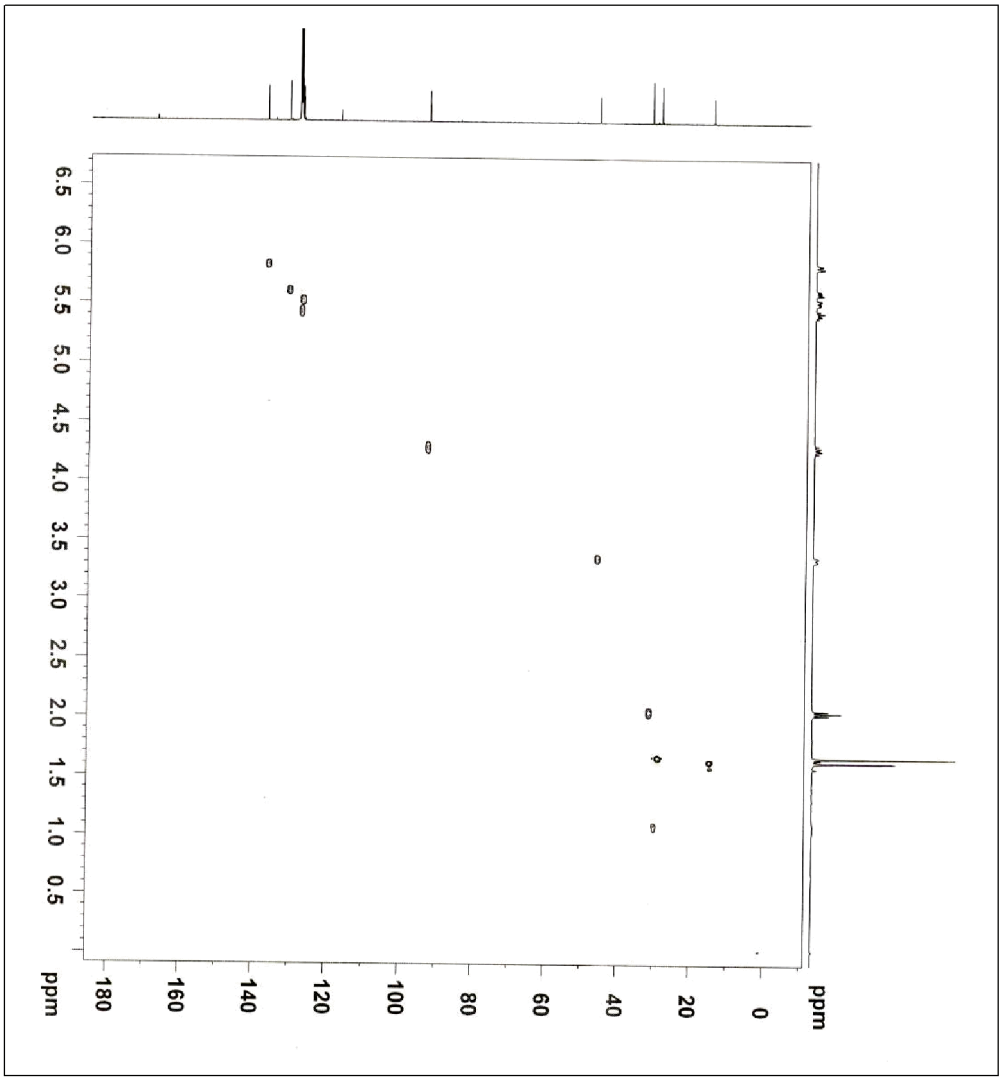


**Figure 23** HSQC spectrum of compound **134**

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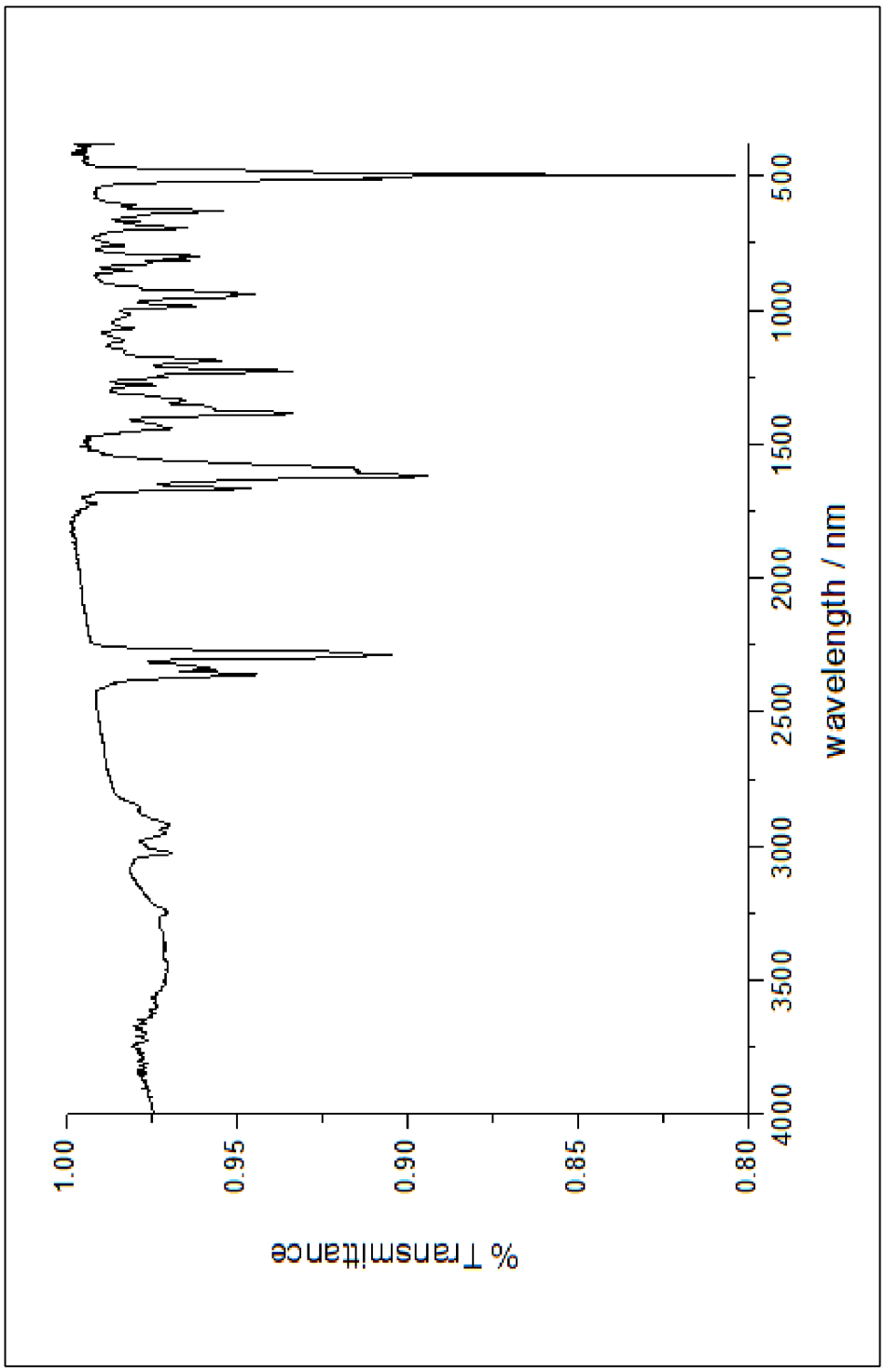


**Figure 24** IR spectrum of compound **134**

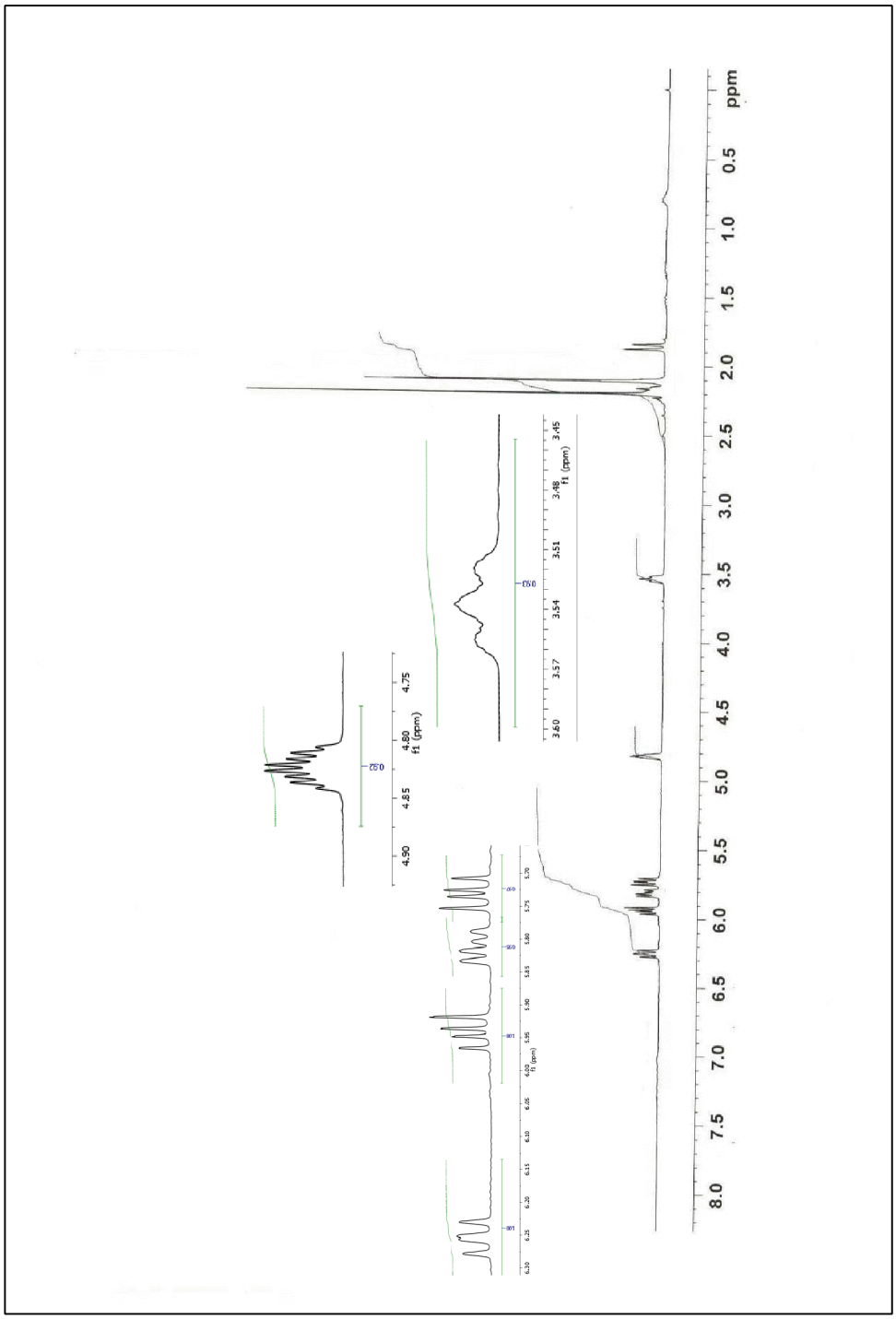


**Figure 25** $^{1}$H NMR spectrum of compound **135**

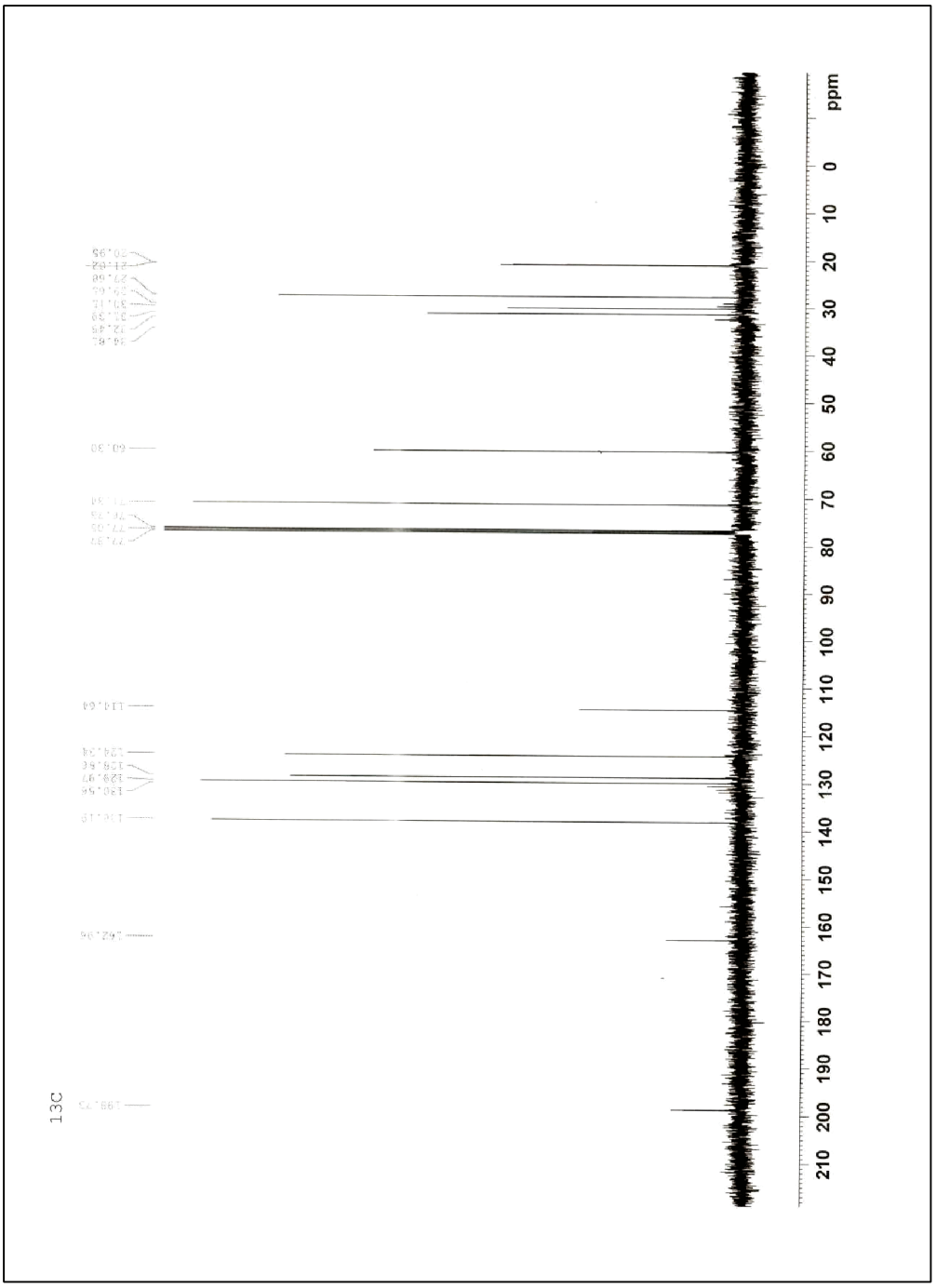


**Figure 26** $^{13}$C NMR spectrum of compound **135**

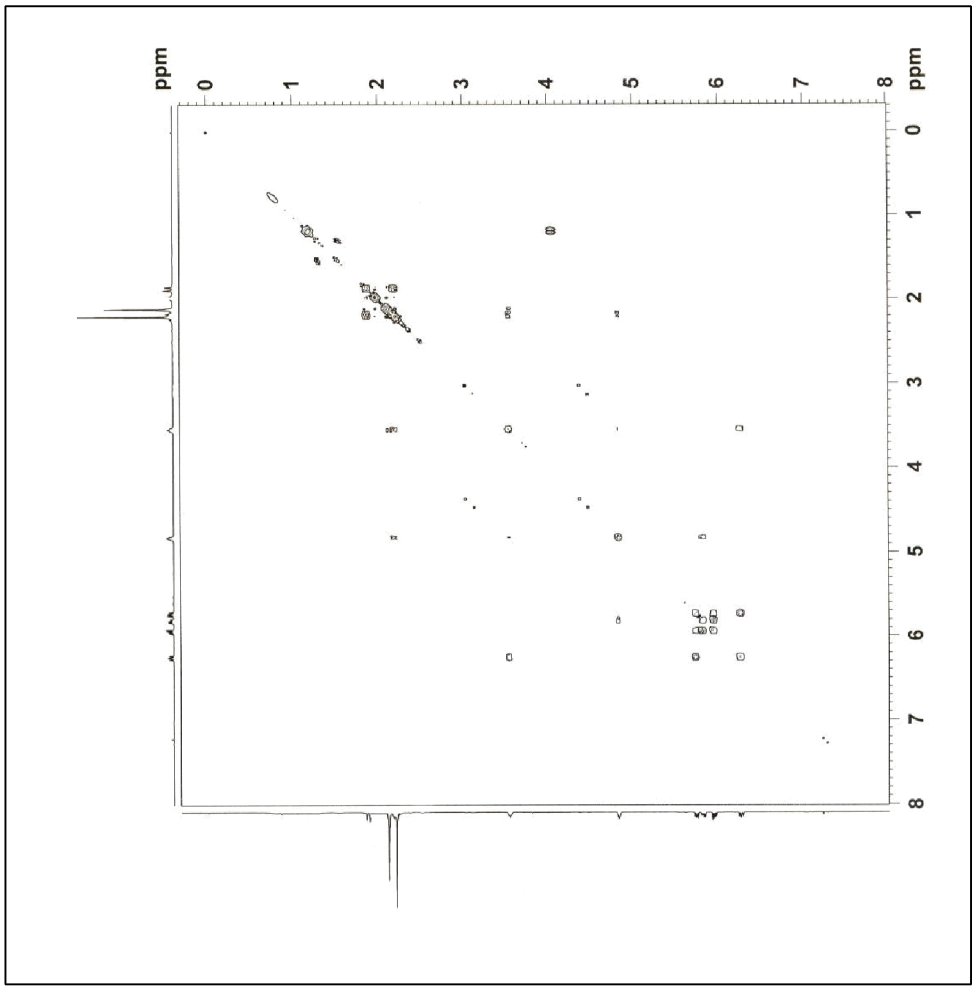


**Figure 27** COSY spectrum of compound **135**

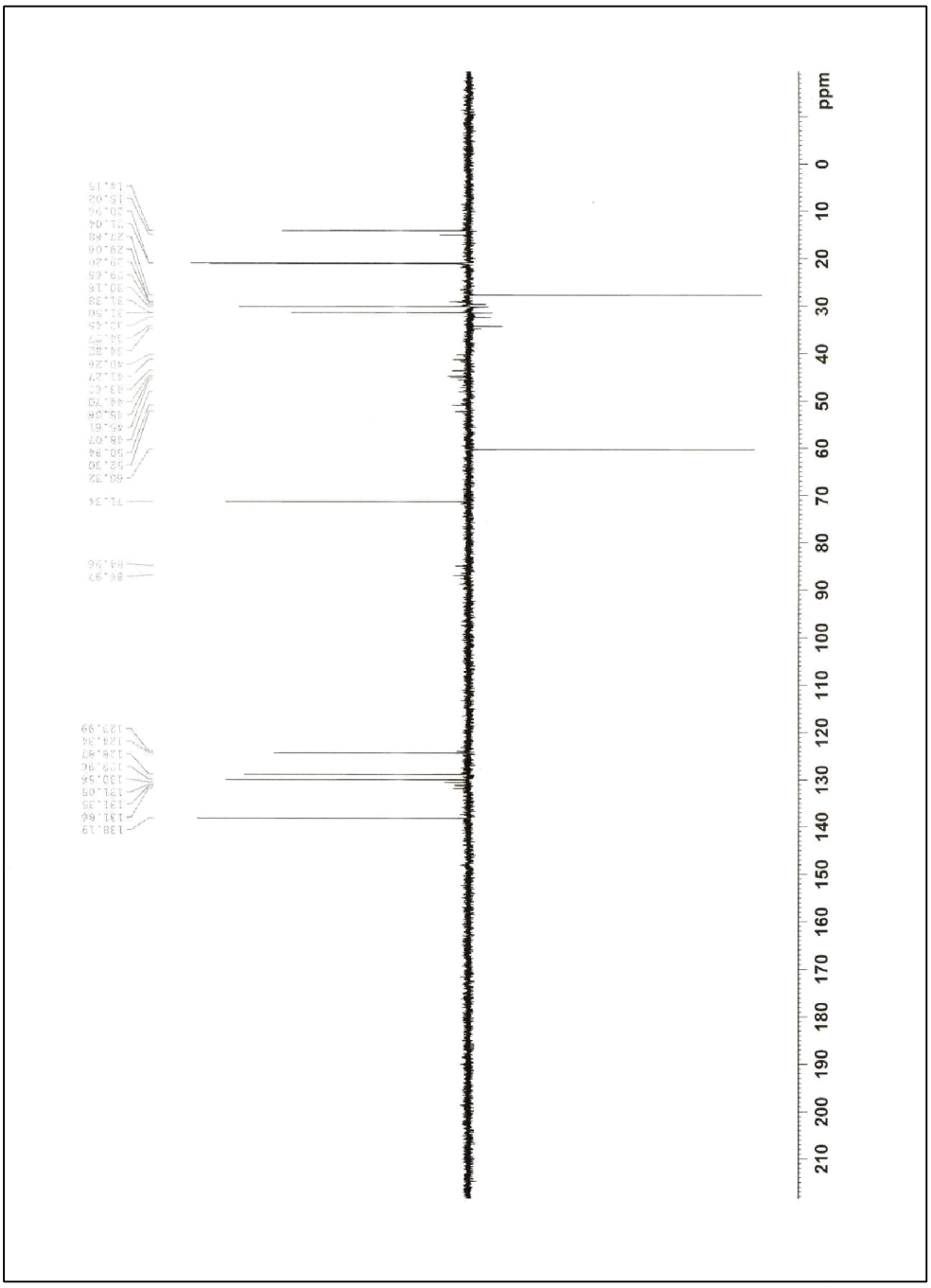


**Figure 28** DEPT 135 spectrum of compound **135**

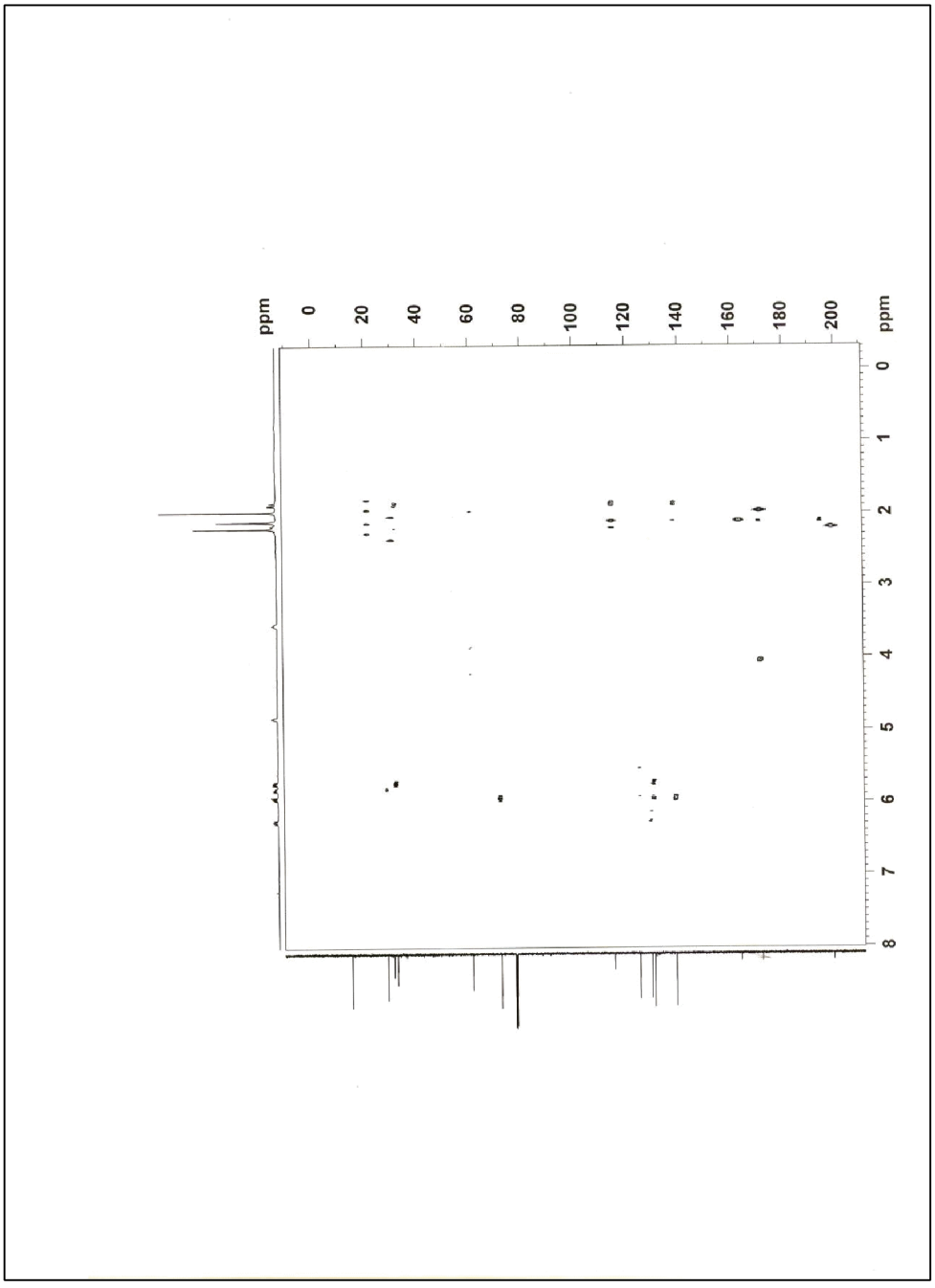


**Figure 29** HMBC spectrum of compound **135**

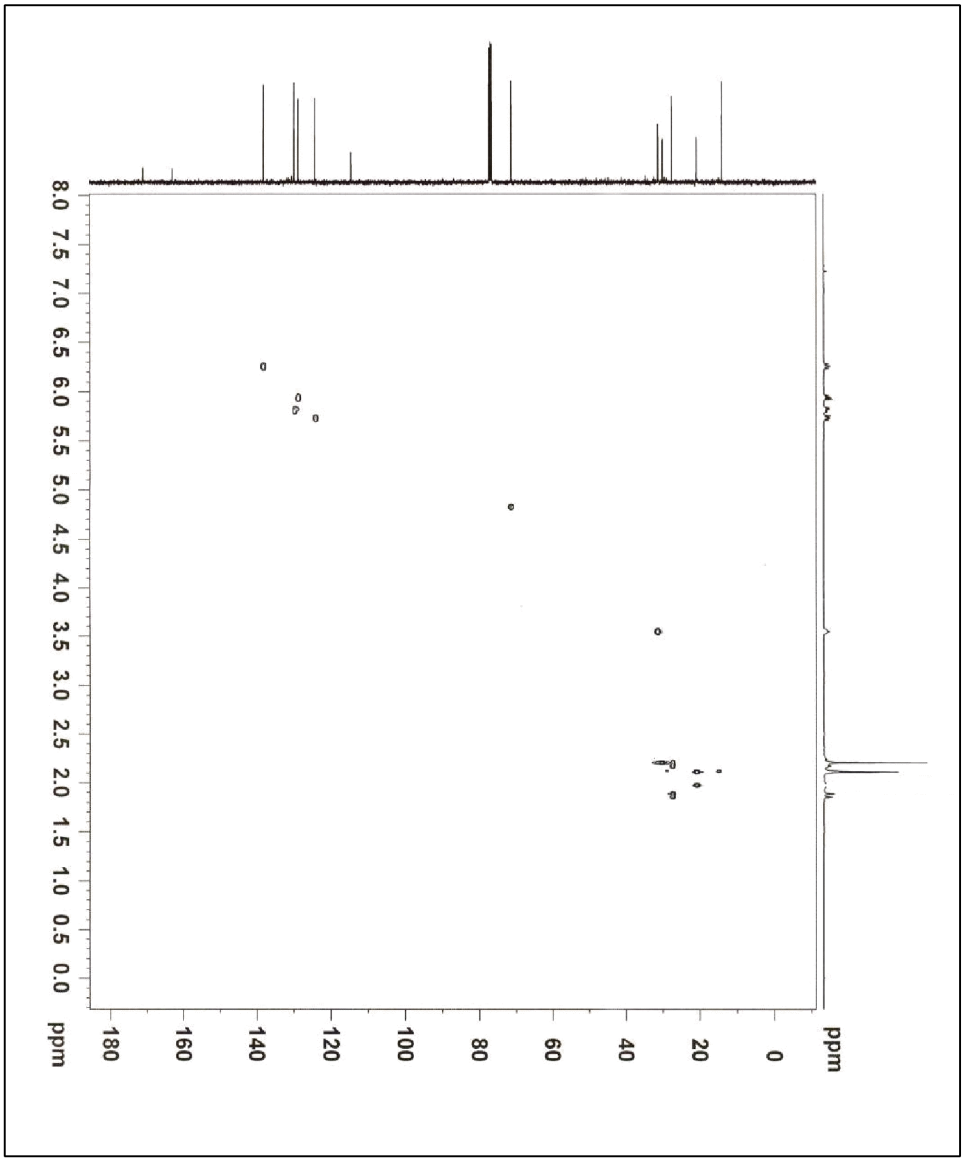


**Figure 30** HSOC spectrum of compound **135**

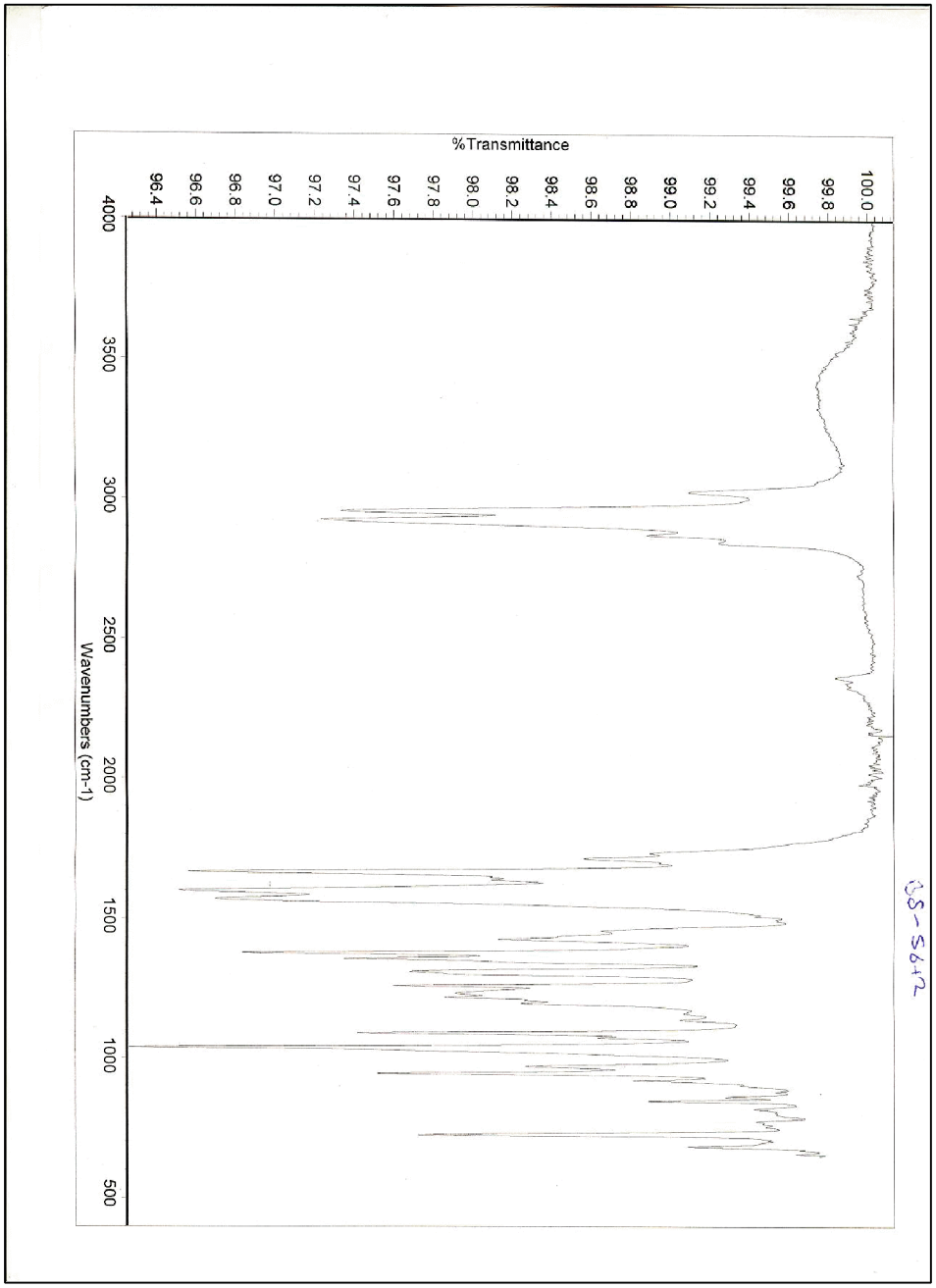


**Figure 31** IR spectrum of compound **135**

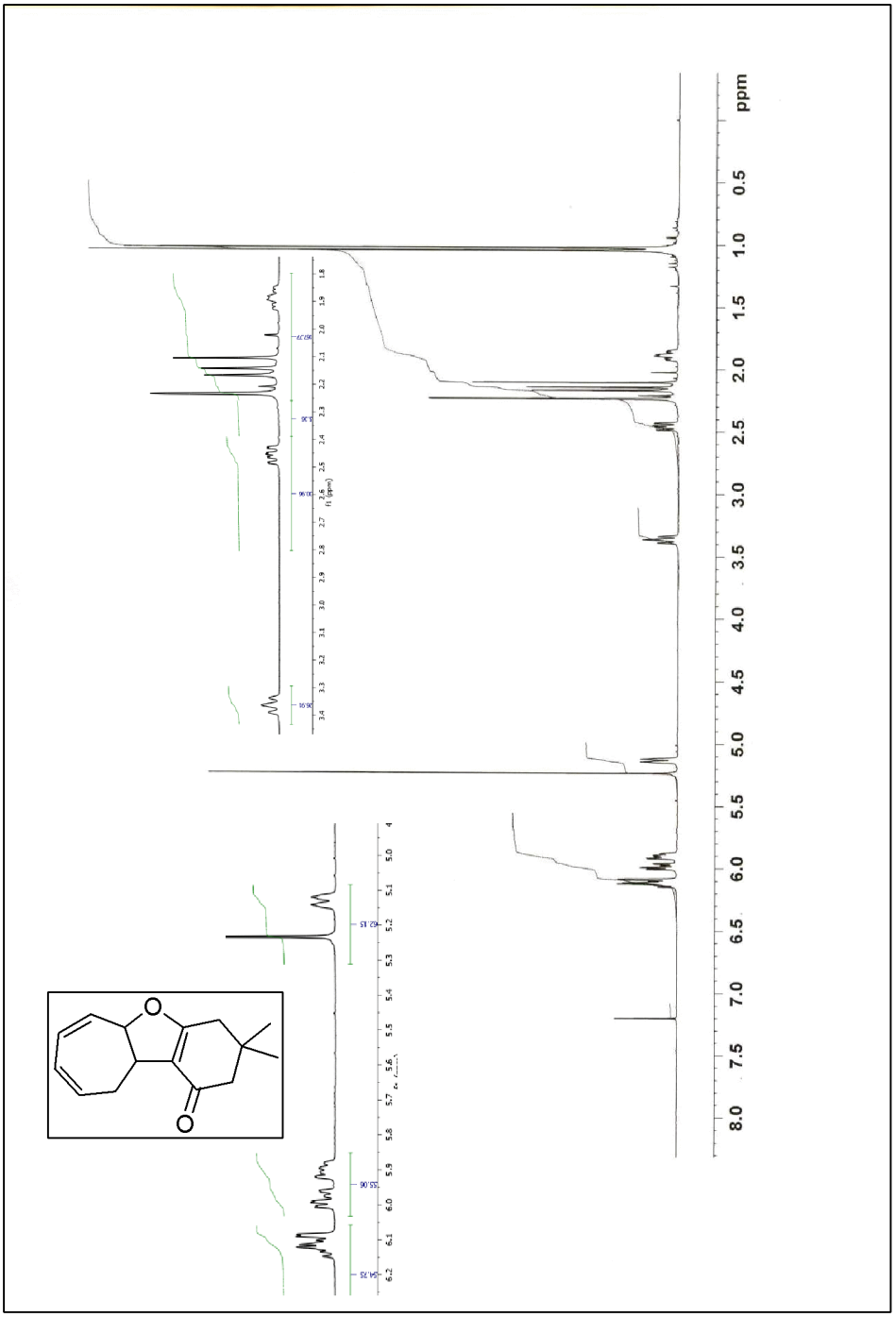


**Figure 32** $^{1}$H NMR spectrum of compound **139**

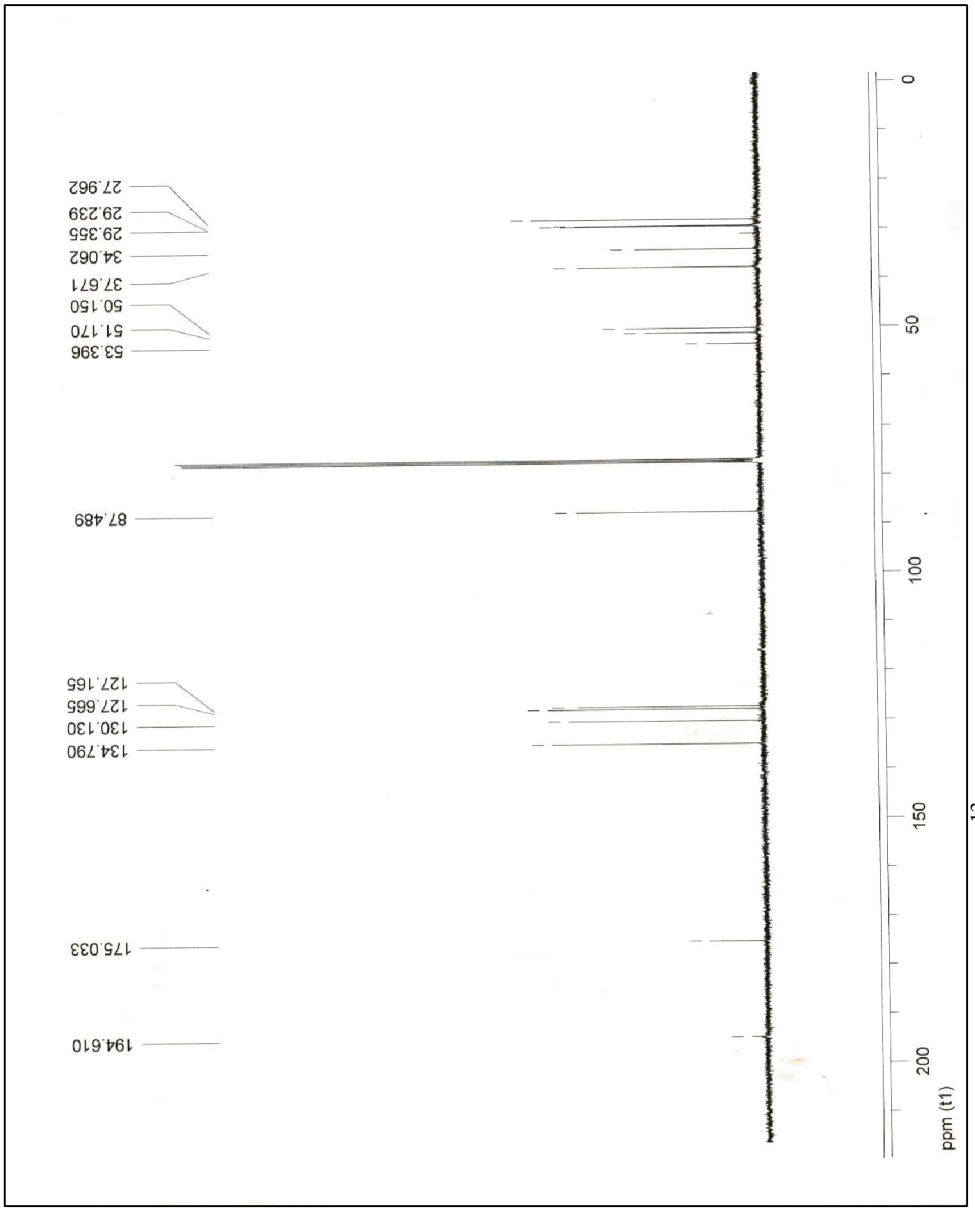


**Figure 33** $^{13}$C NMR spectrum of compound **139**

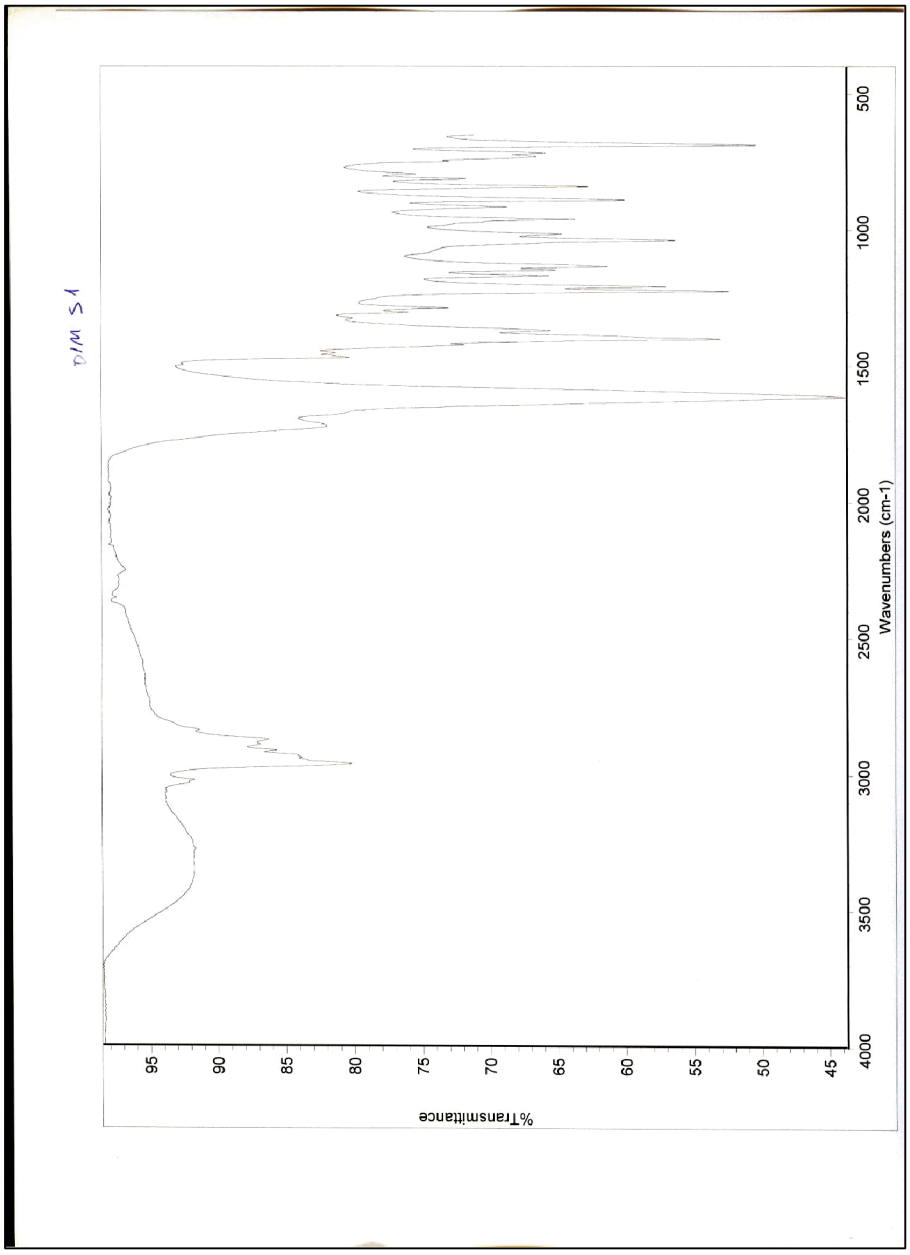


**Figure 34** IR spectrum of compound **139**

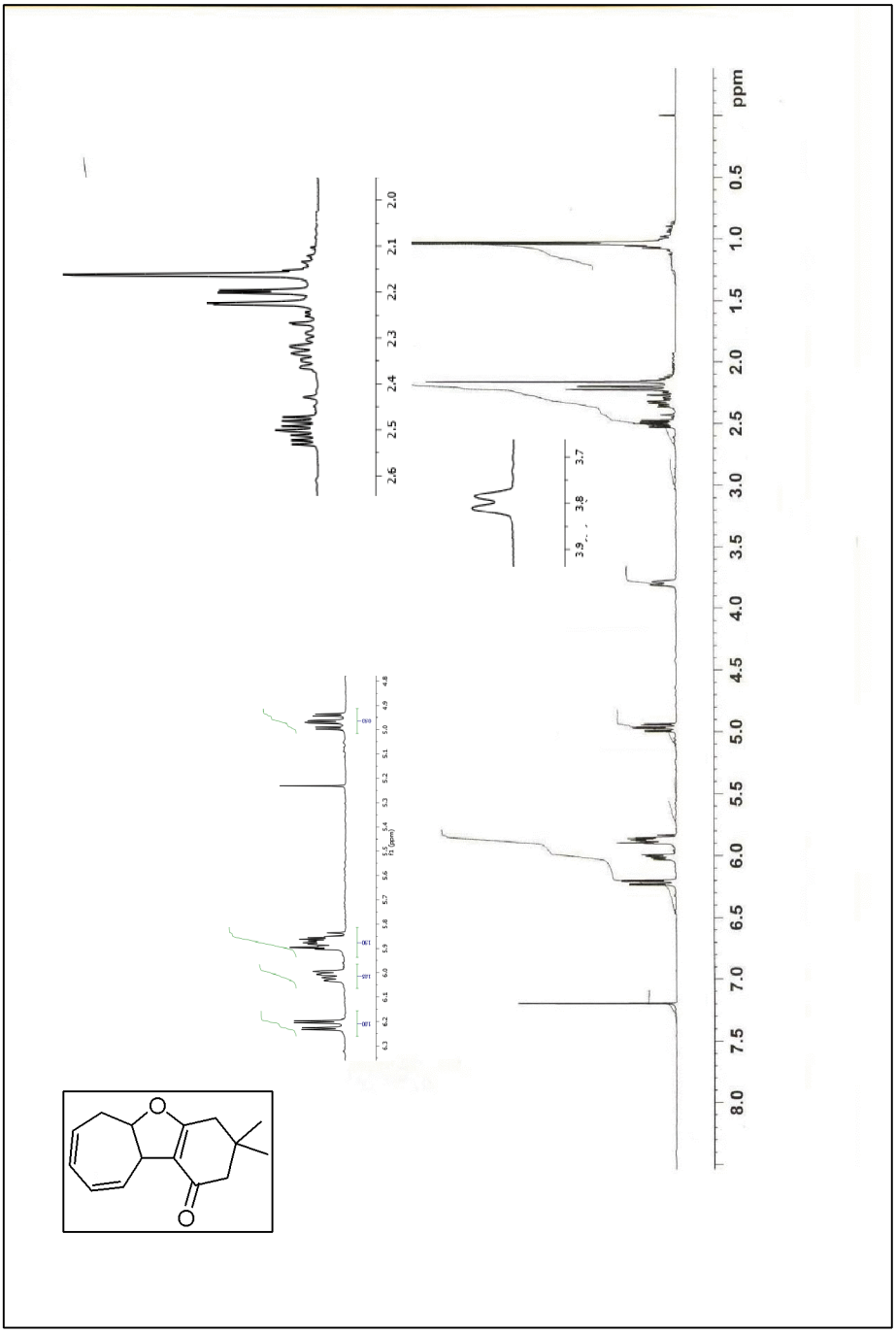


**Figure 35** $^{1}$H NMR spectrum of compound **140**

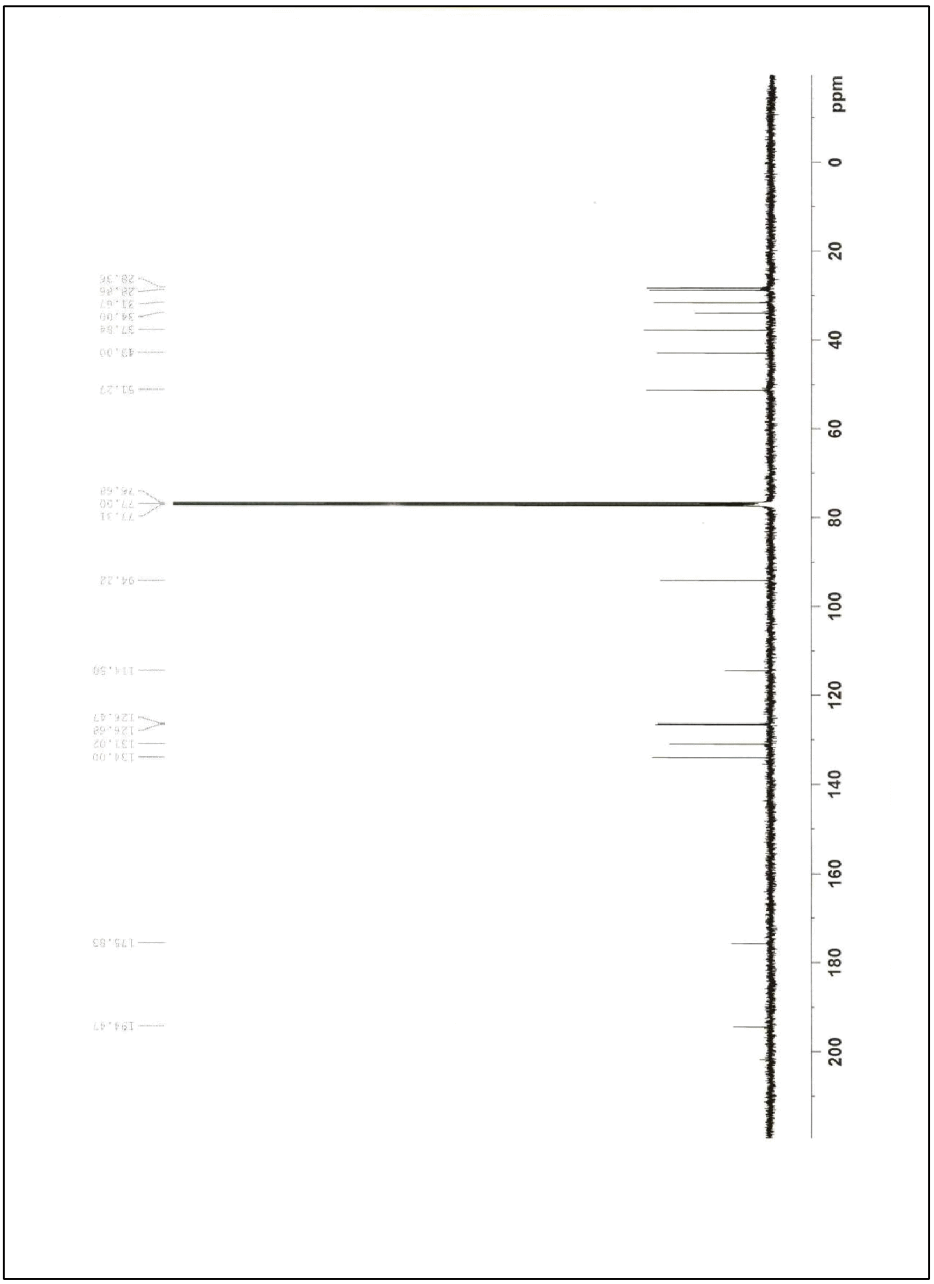


**Figure 36** $^{13}$C NMR spectrum of compound **140**

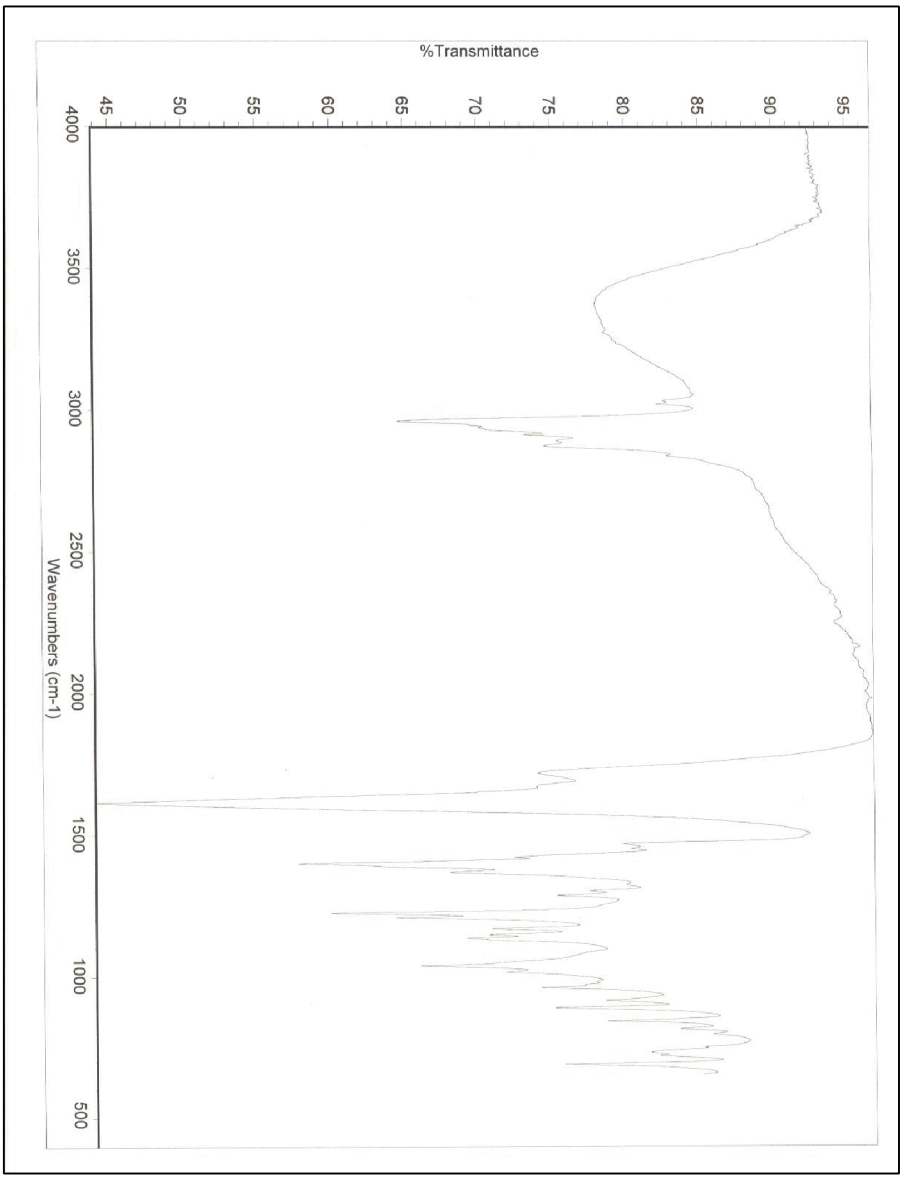


**Figure 37** IR spectrum of compound **140**

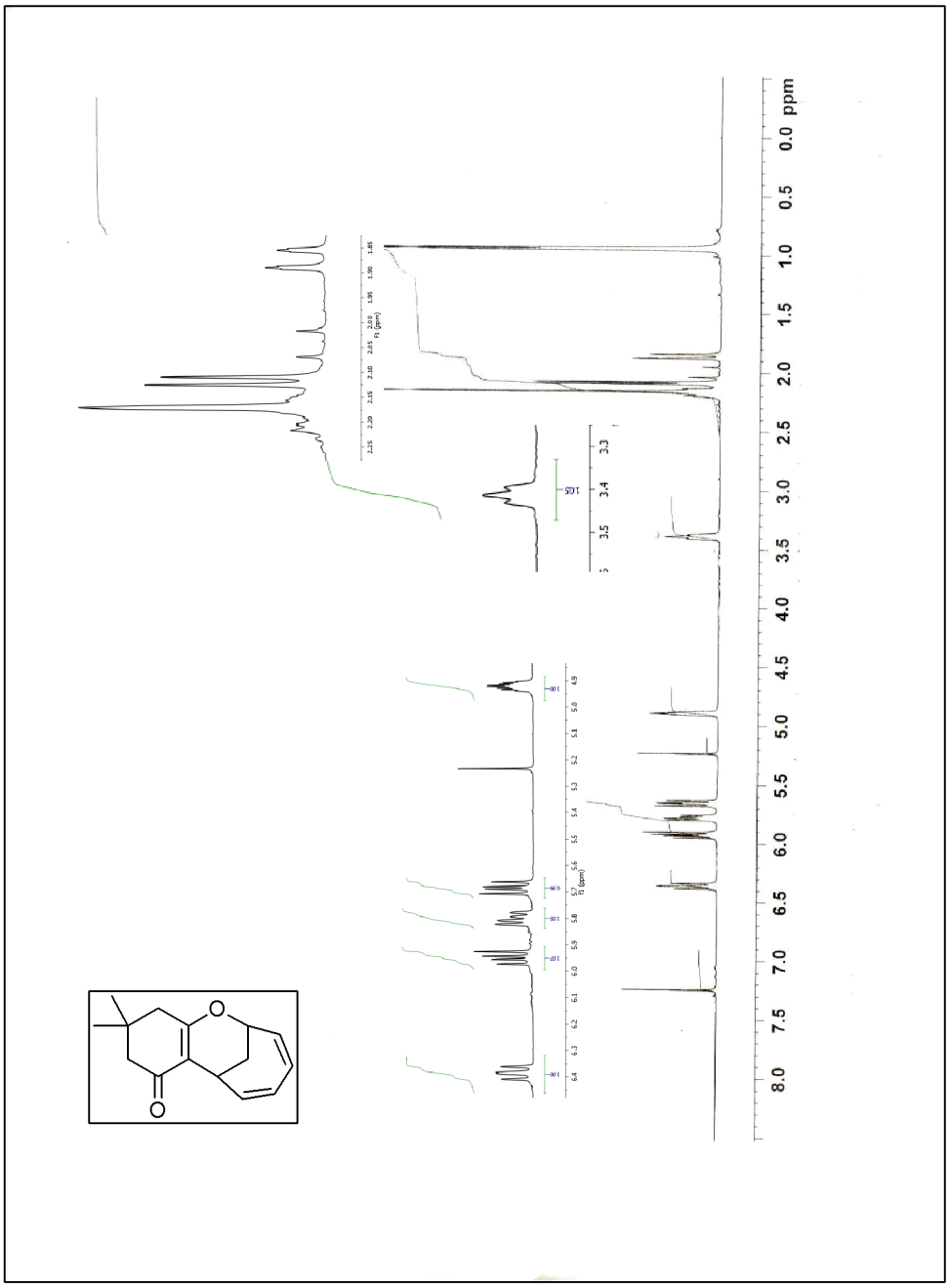


**Figure 38** $^{1}$H NMR spectrum of compound **138**

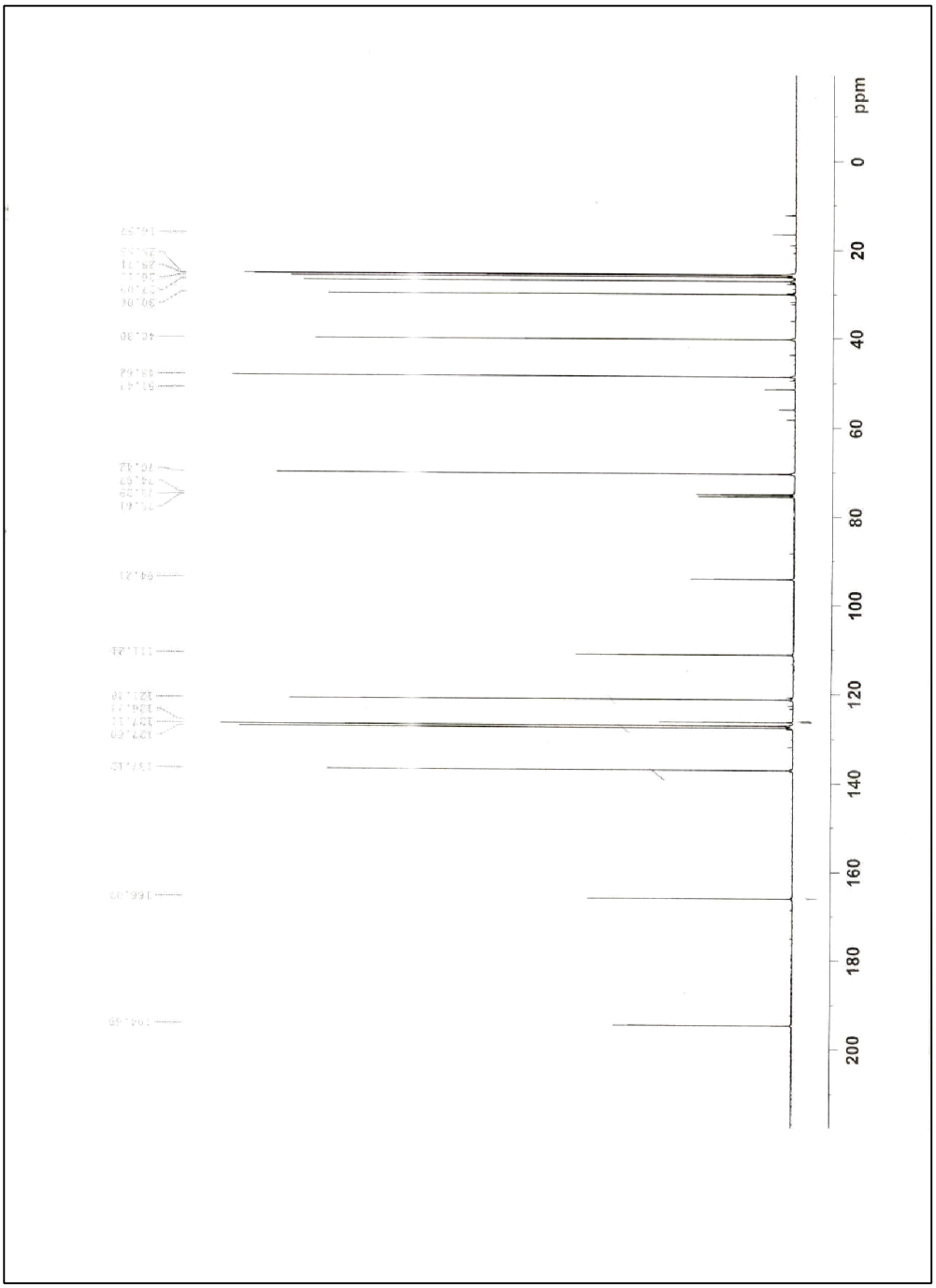


**Figure 39** $^{13}$C NMR spectrum of compound **138**

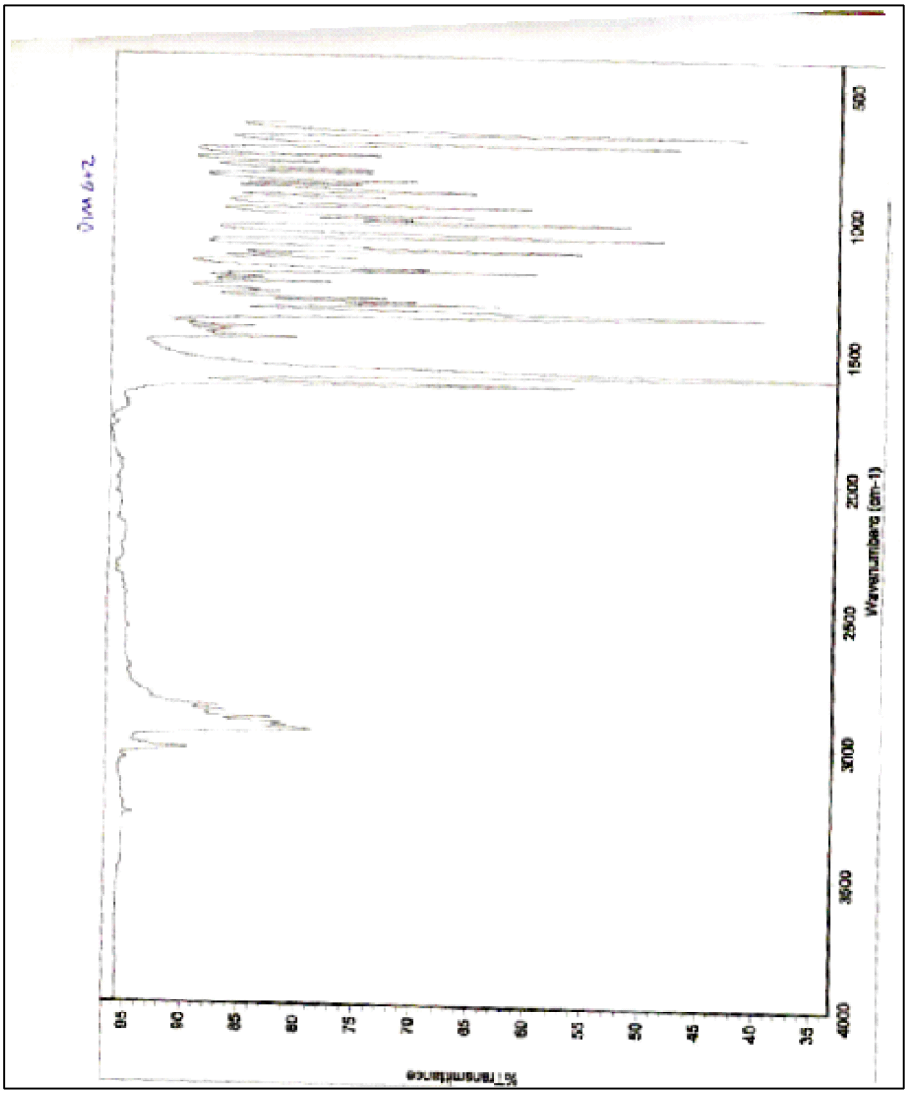


**Figure 40** IR spectrum of compound **138**

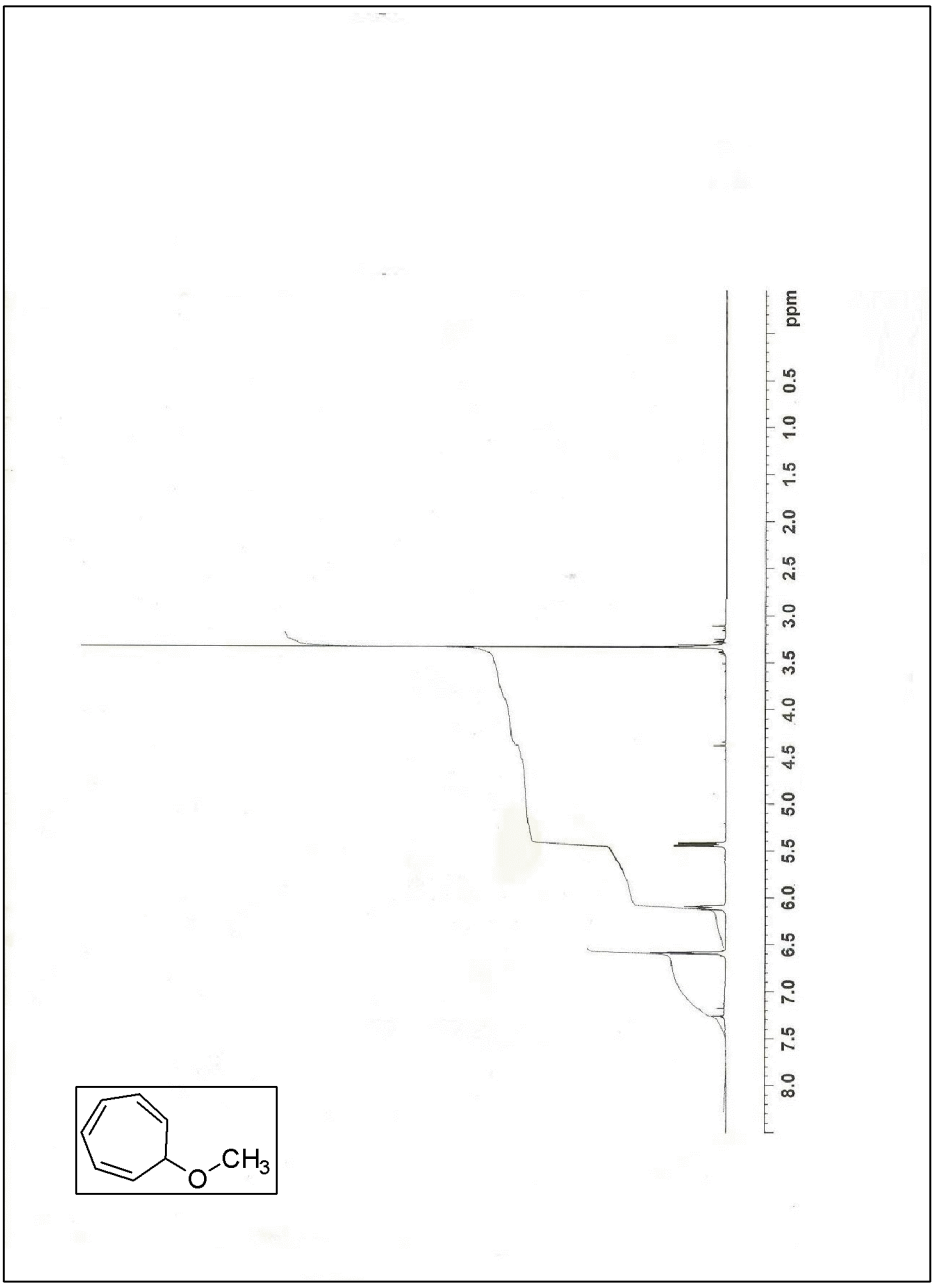


**Figure 41** $^{1}$H NMR spectrum of compound **141**

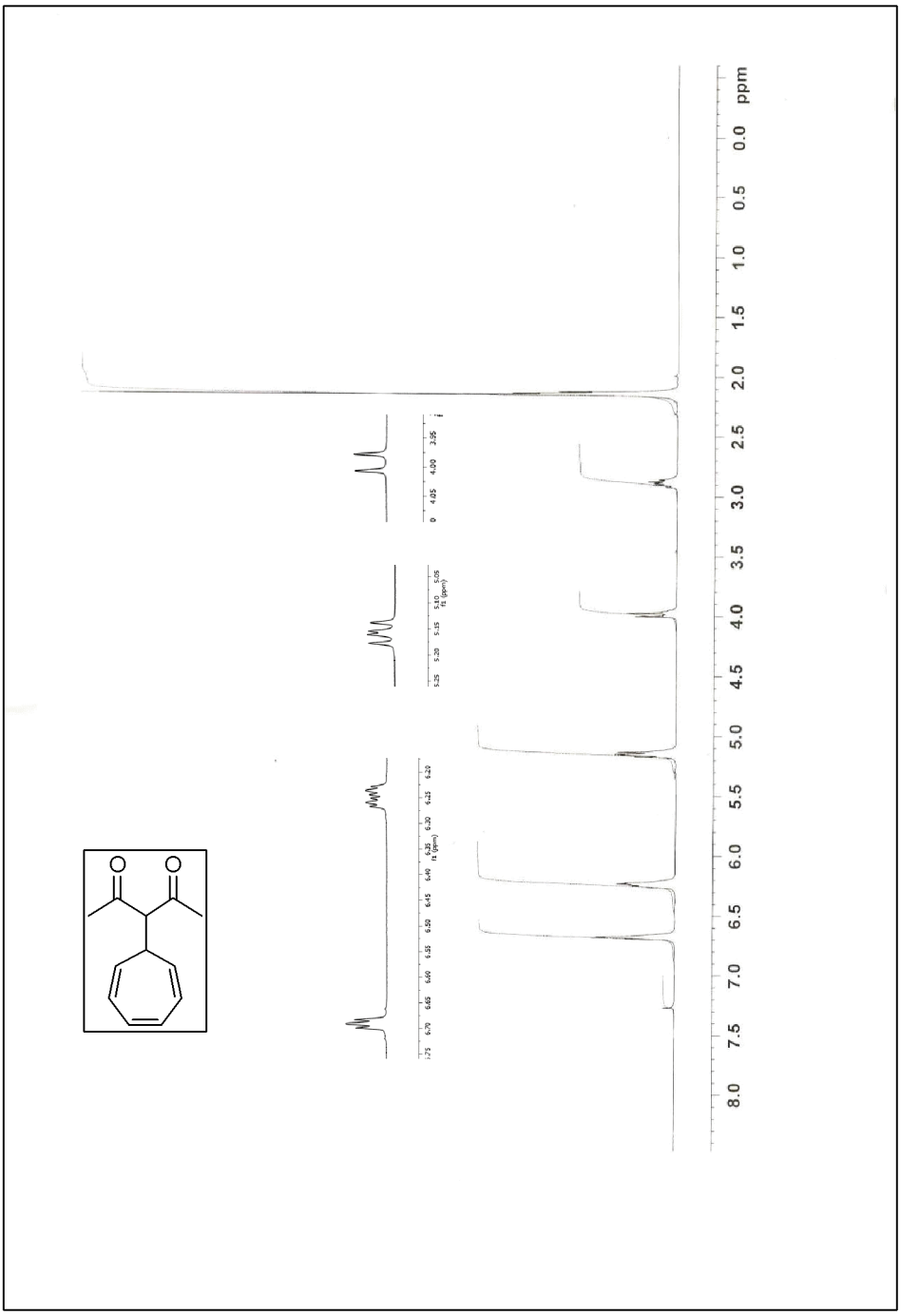


**Figure 42** $^{1}$H NMR spectrum of compound **144**

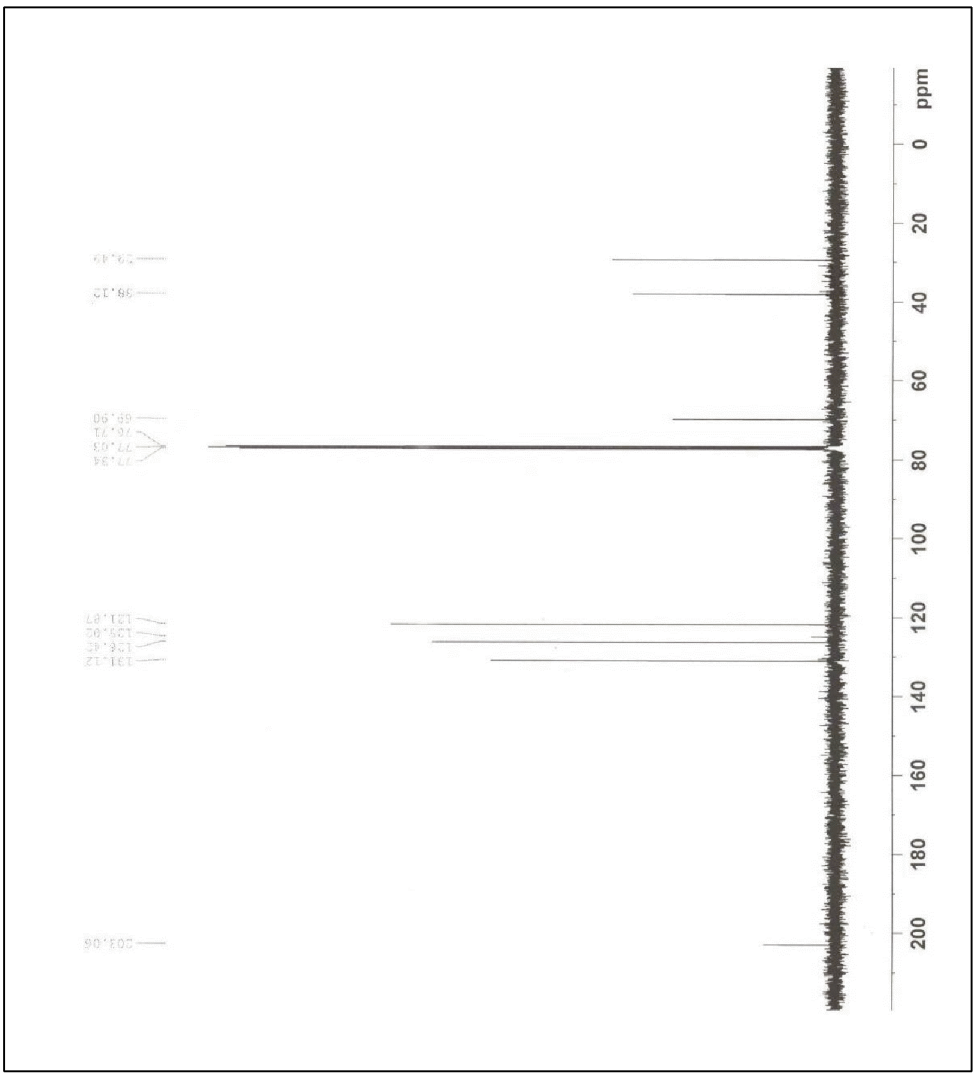


**Figure 43** $^{13}$C NMR spectrum of compound **144**

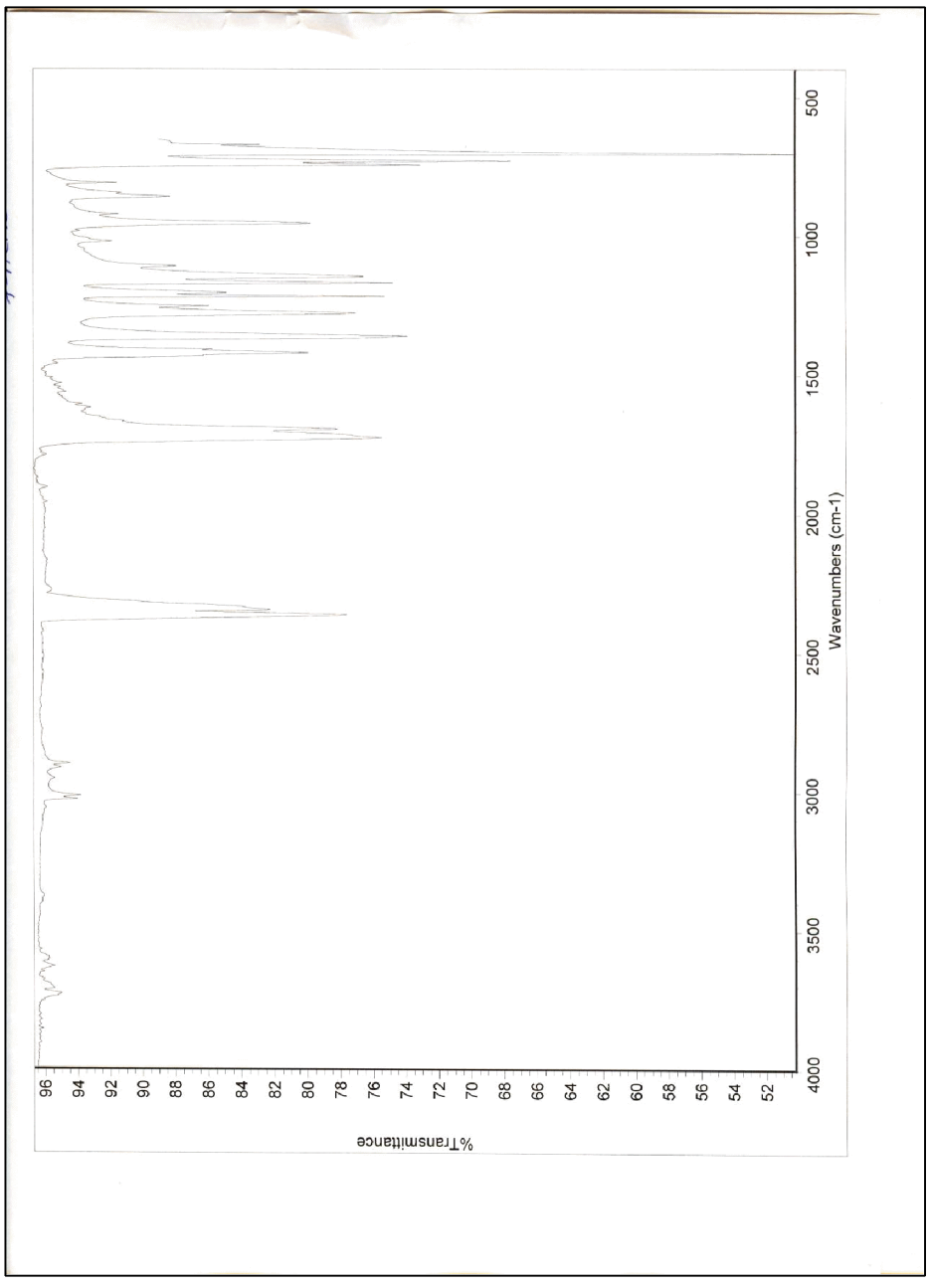


**Figure 44** IR spectrum of compound **144**

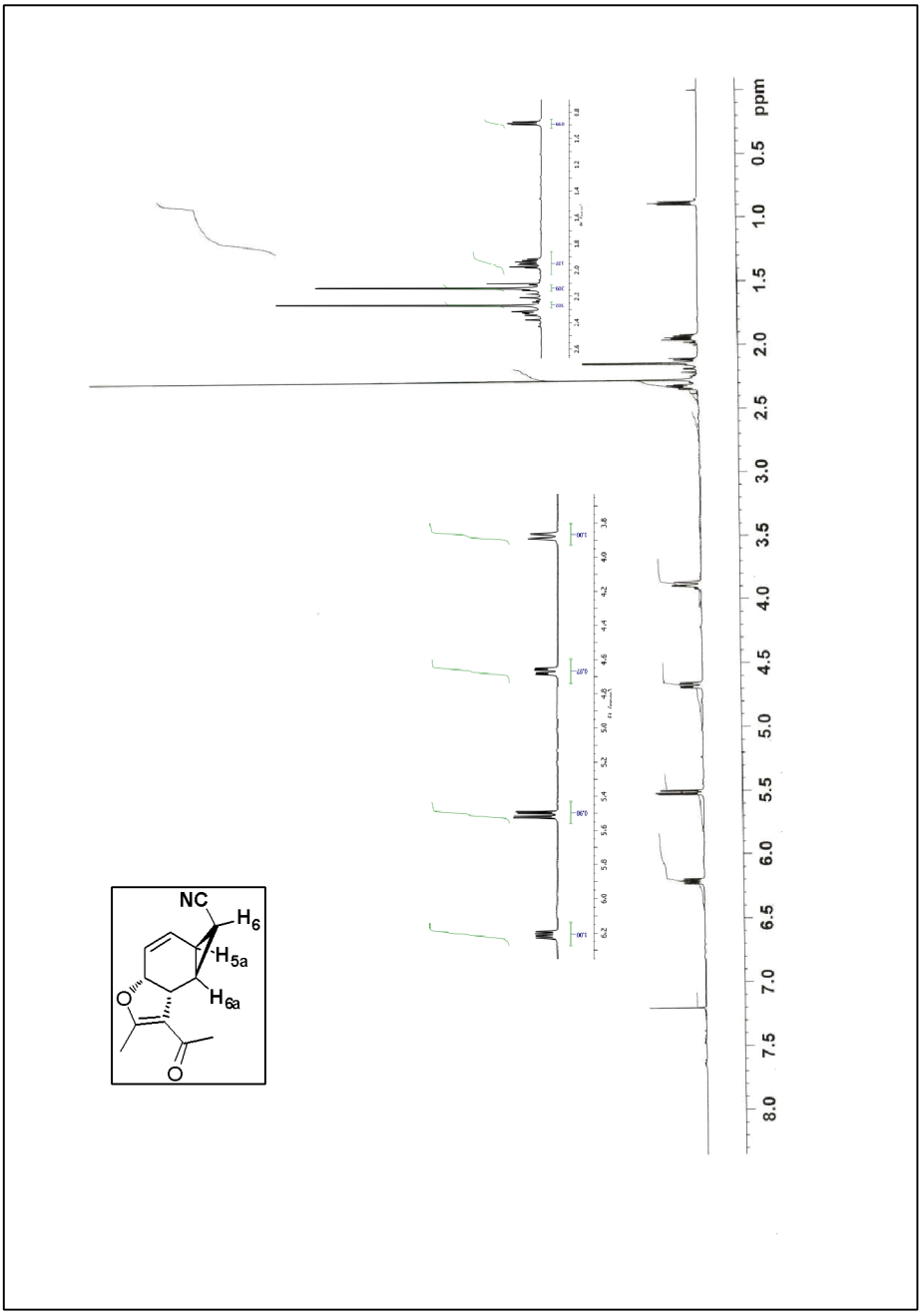


**Figure 45** $^{1}$H NMR spectrum of compound **147**

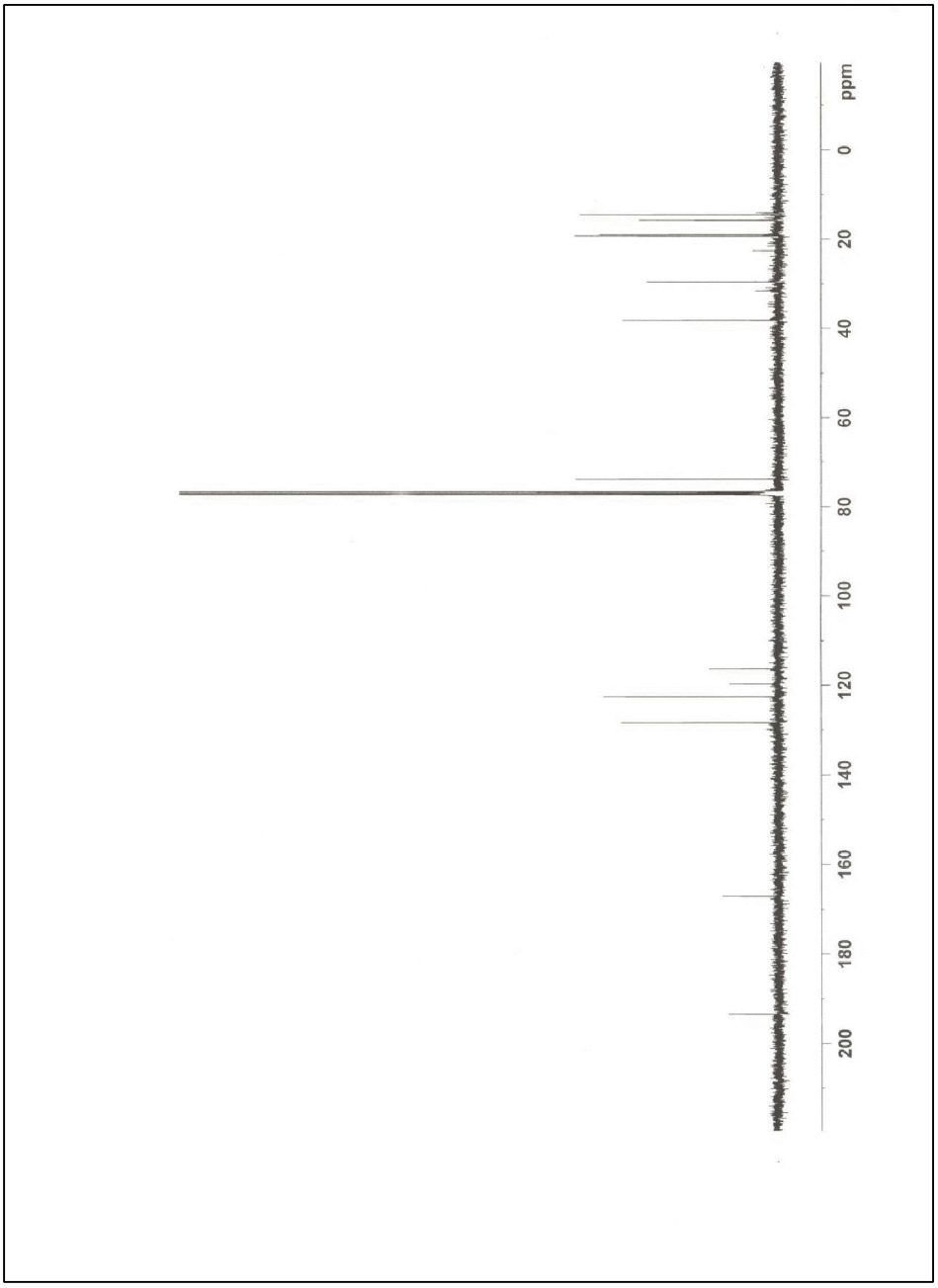


**Figure 46** $^{13}$C NMR spectrum of compound **147**

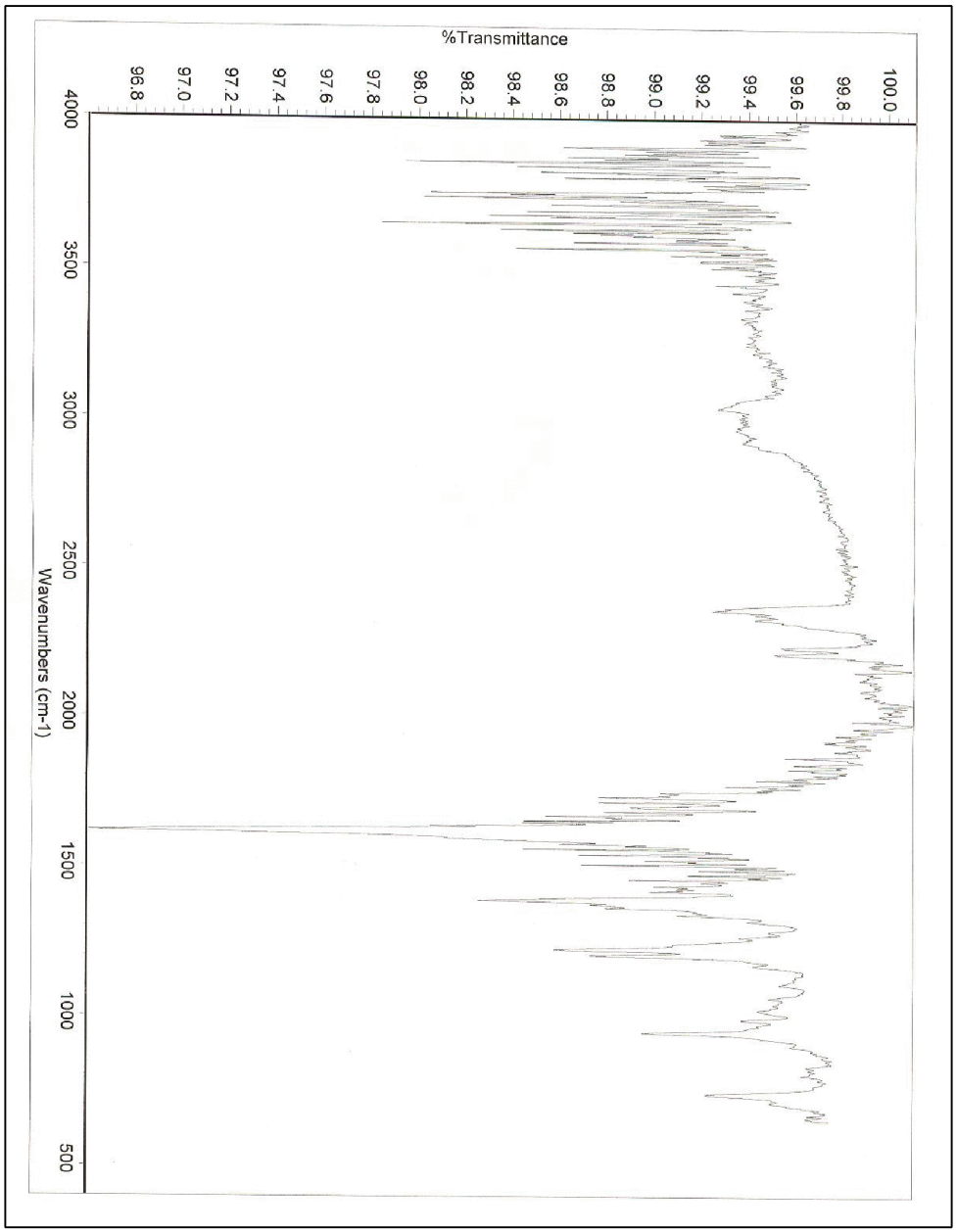


**Figure 47** IR spectrum of compound **147**

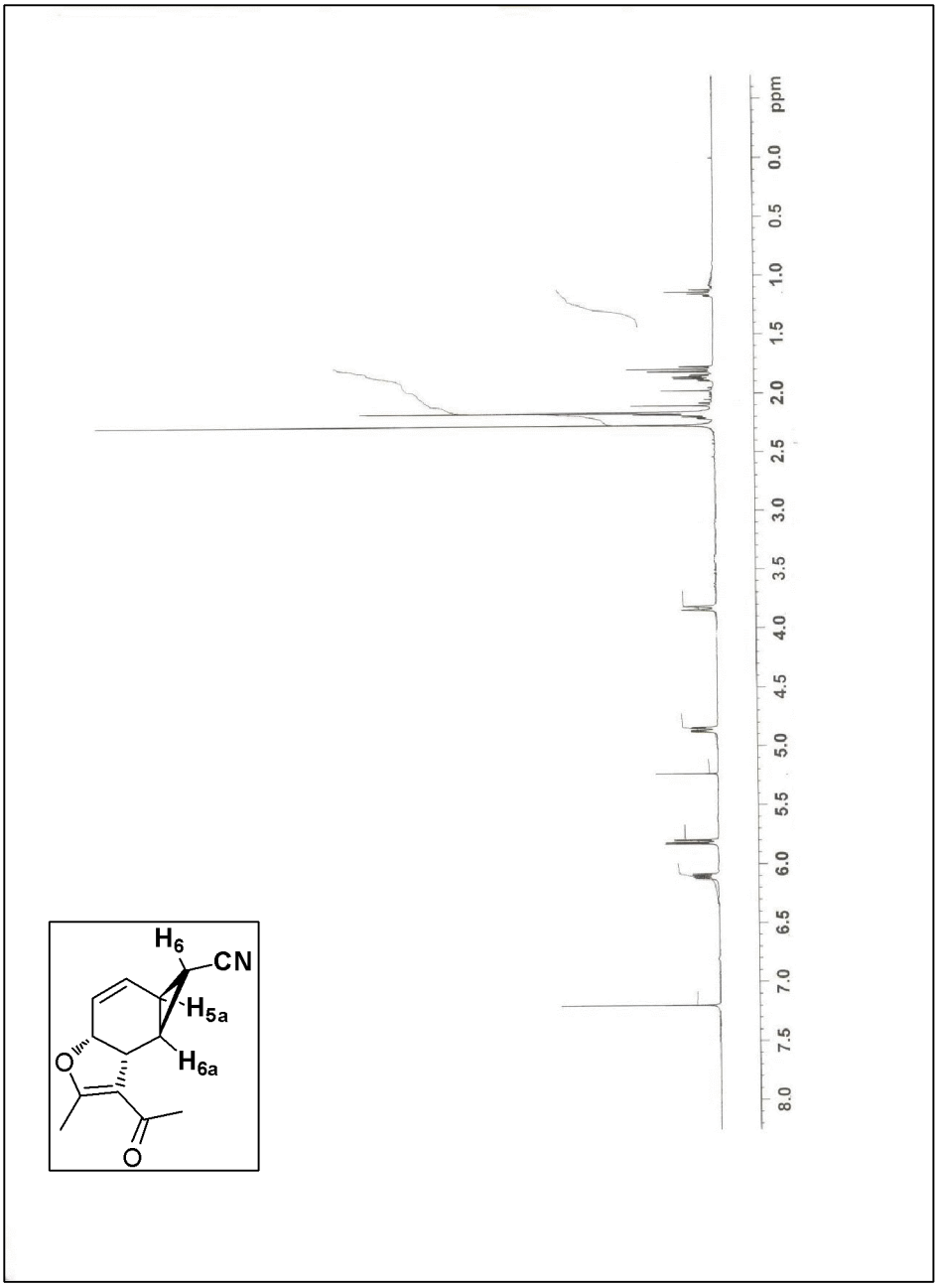


**Figure 48** $^{1}$H NMR spectrum of compound **146**

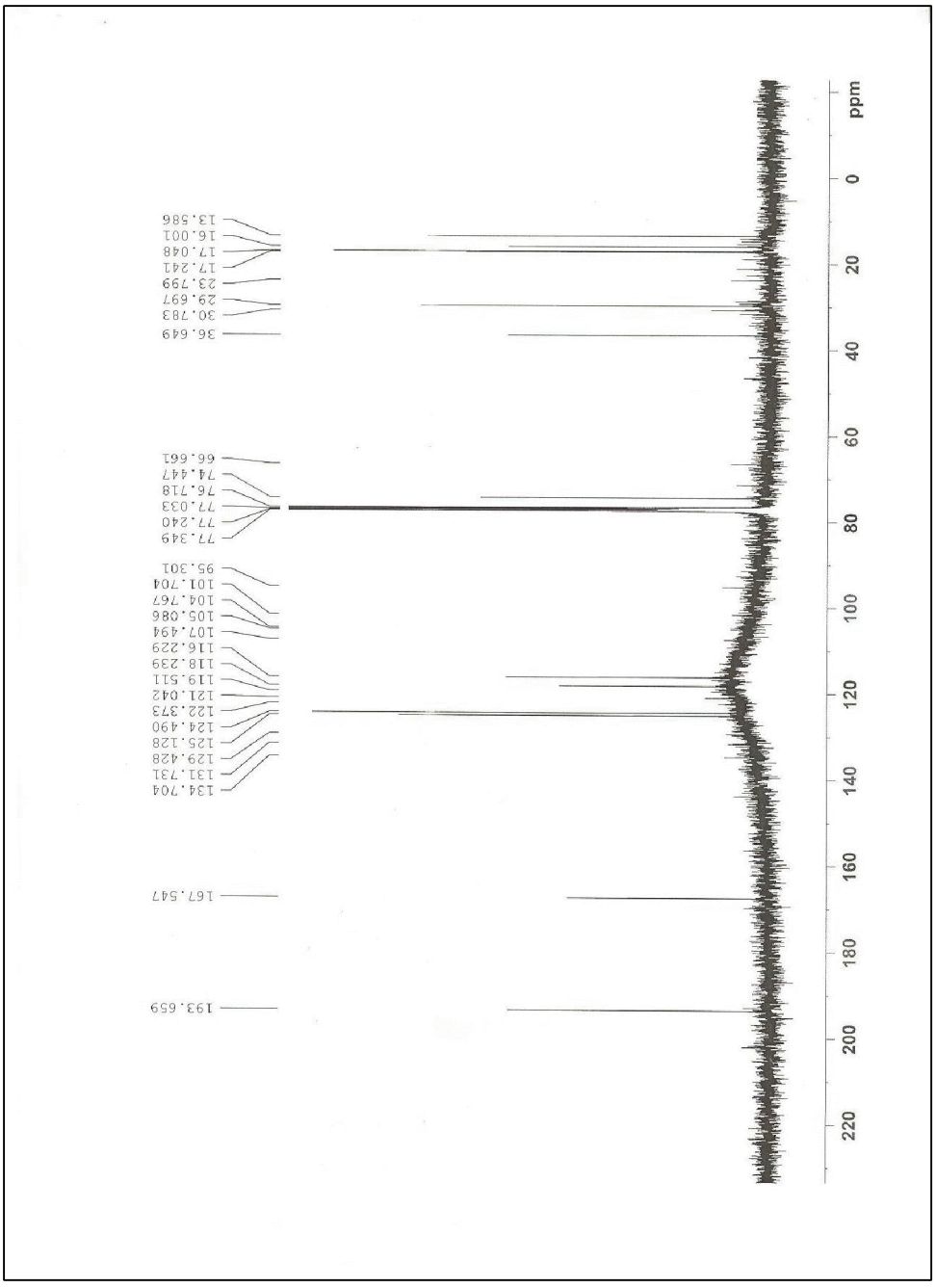


**Figure 49** $^{13}$C NMR spectrum of compound **146**

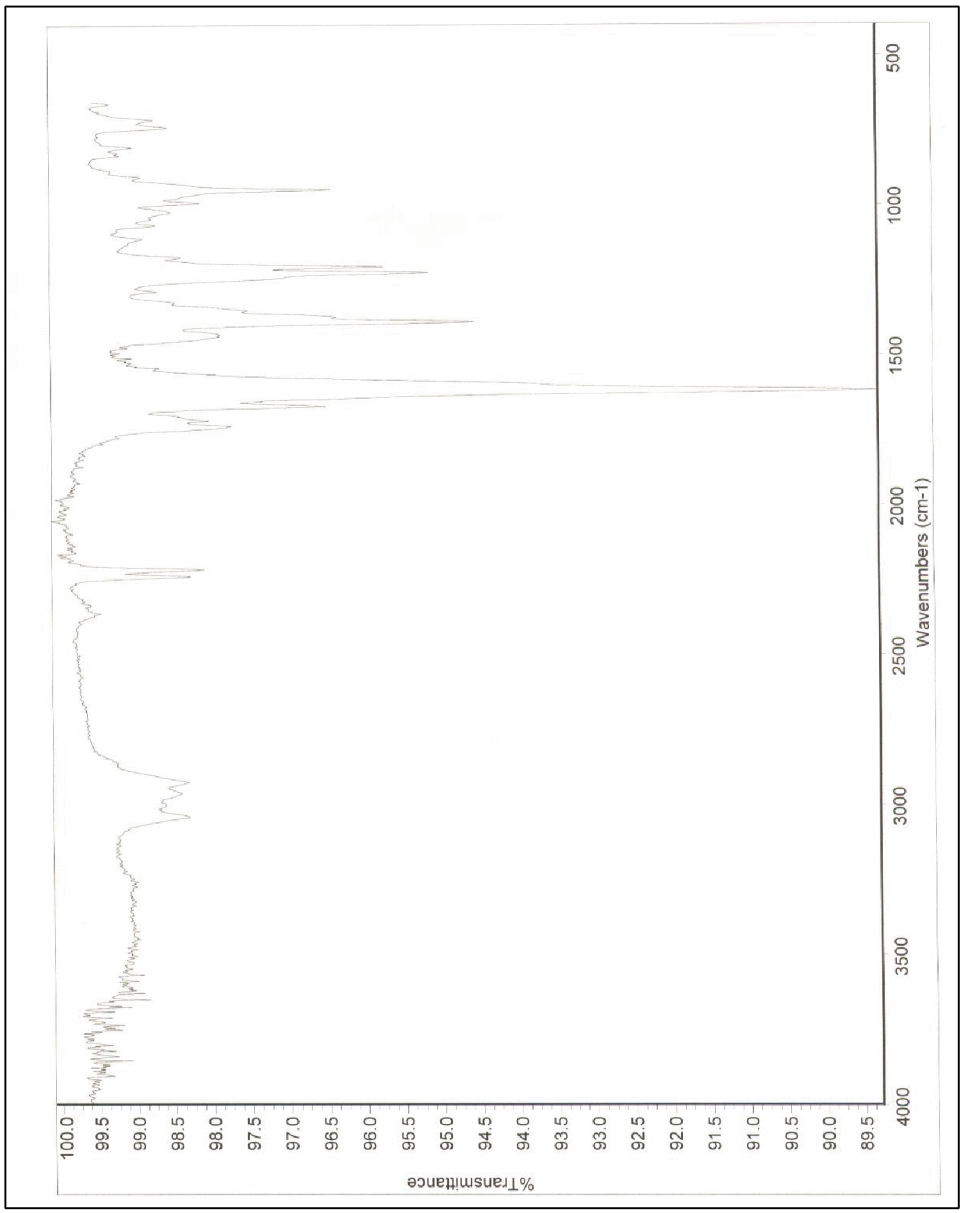


**Figure 50** IR spectrum of compound **146**

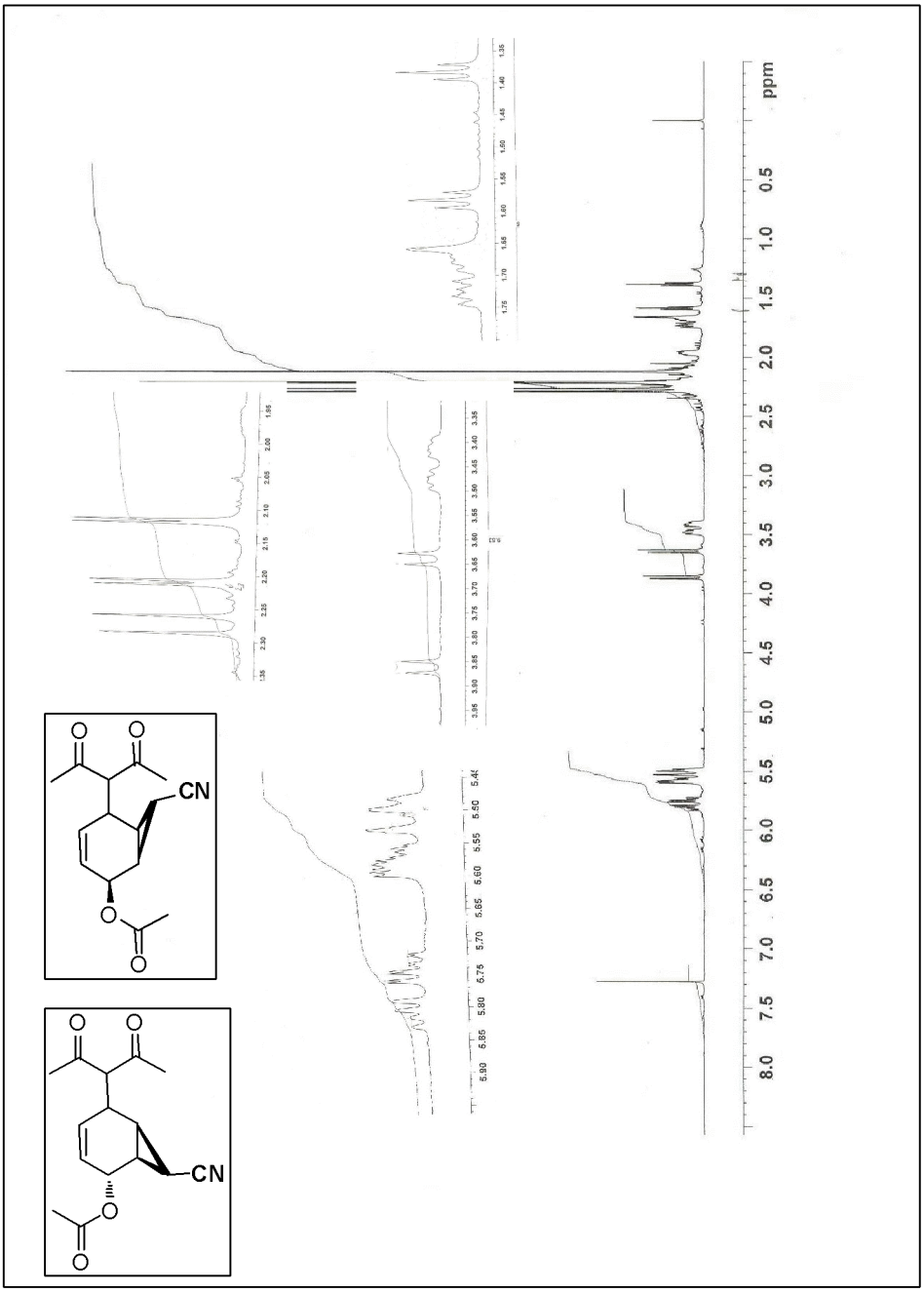


**Figure 51** $^{1}$H NMR spectrum of compounds **148** and **149**

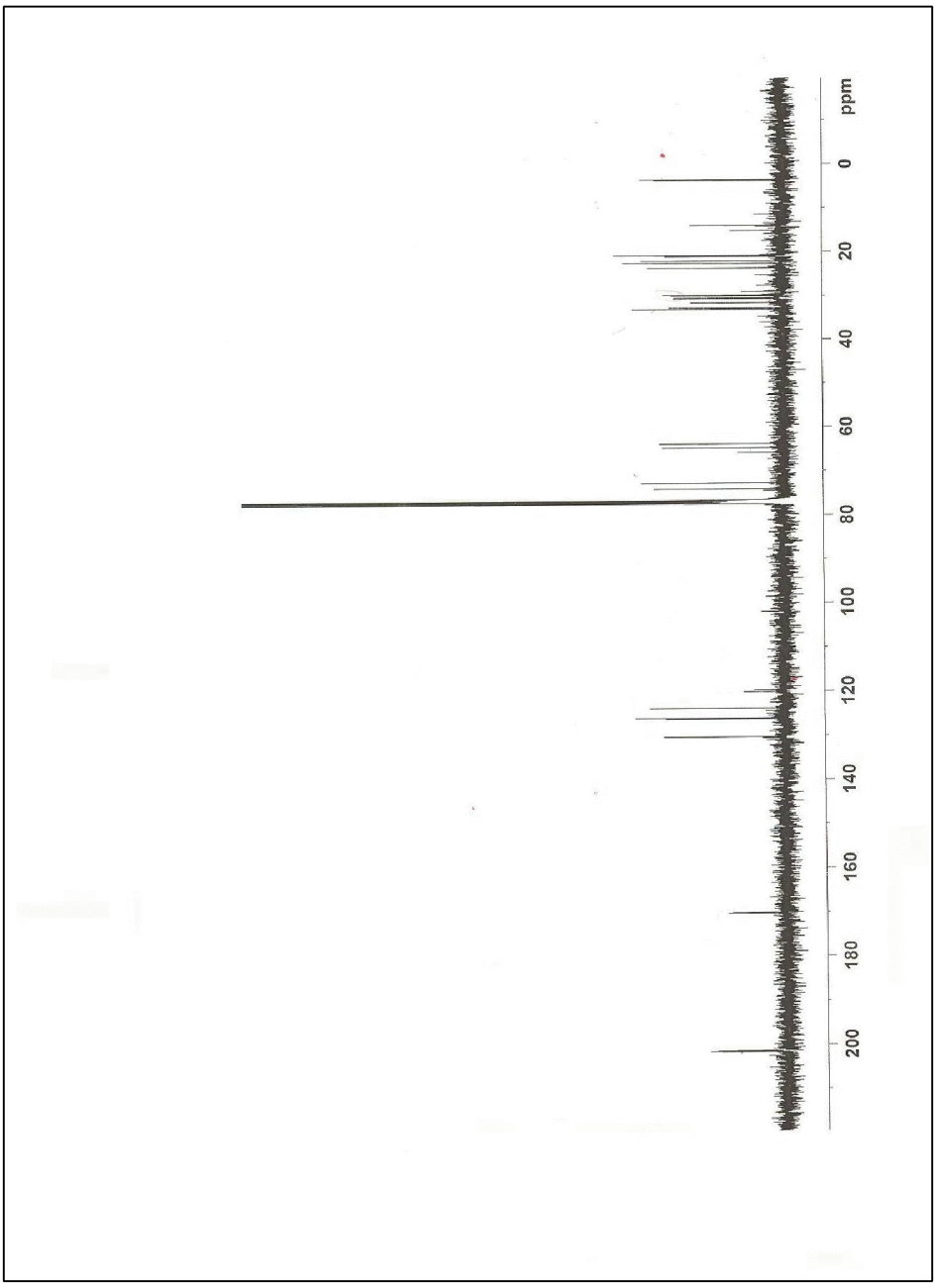


**Figure 52** $^{13}$C NMR spectrum of compounds **148** and **149**

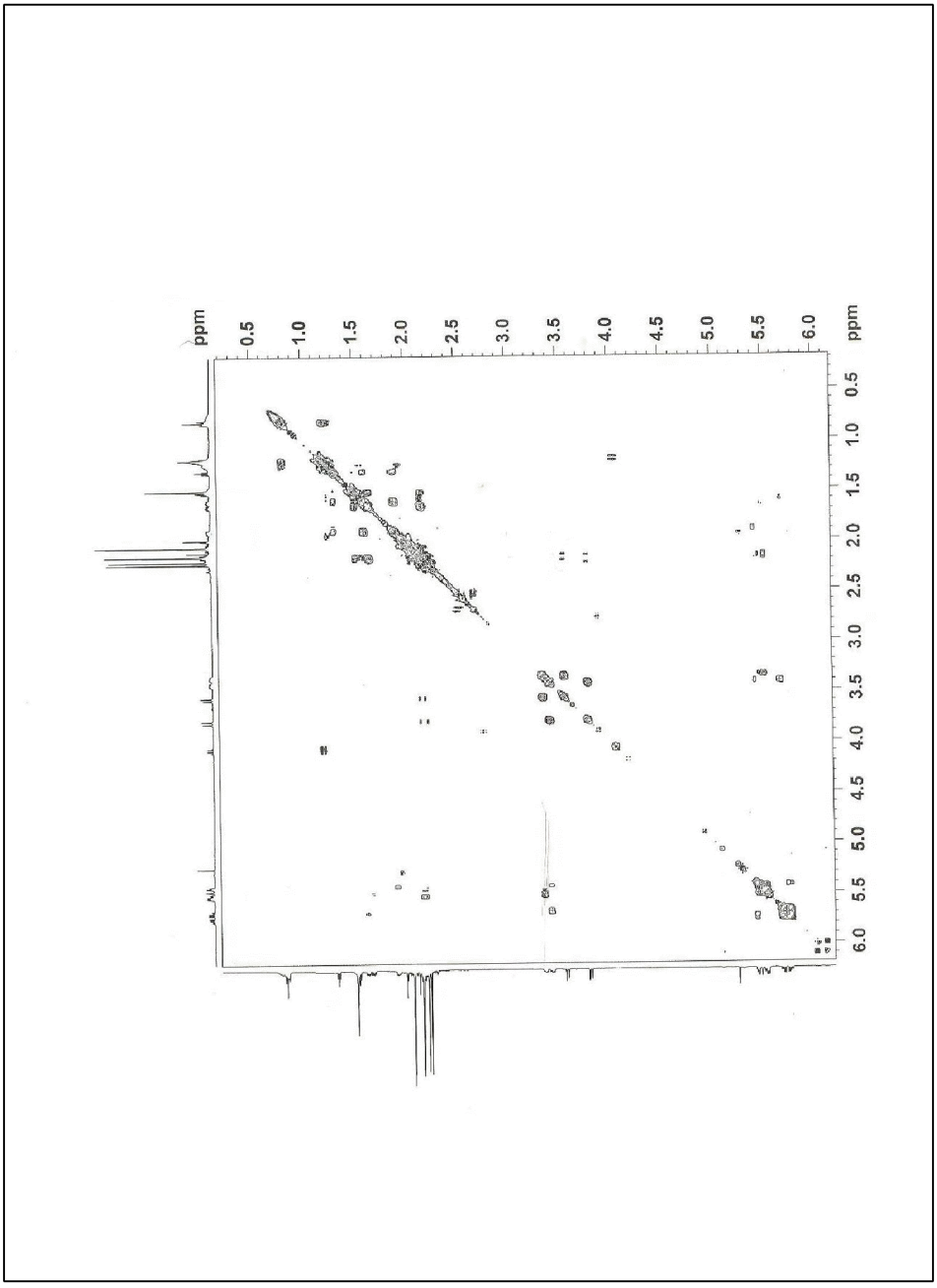


**Figure 53** COSY spectrum of compounds **148** and **149**

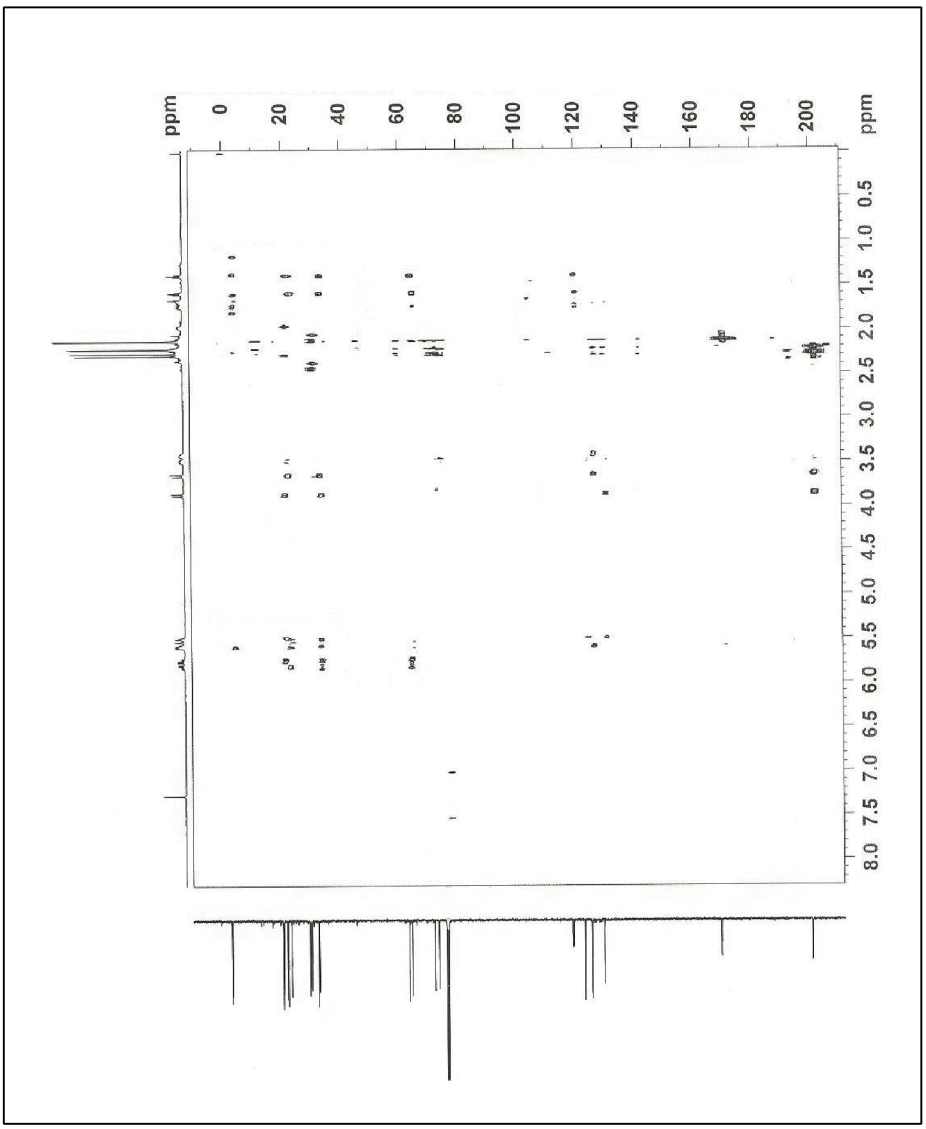


**Figure 54** HMBC spectrum of compounds **148** and **149**

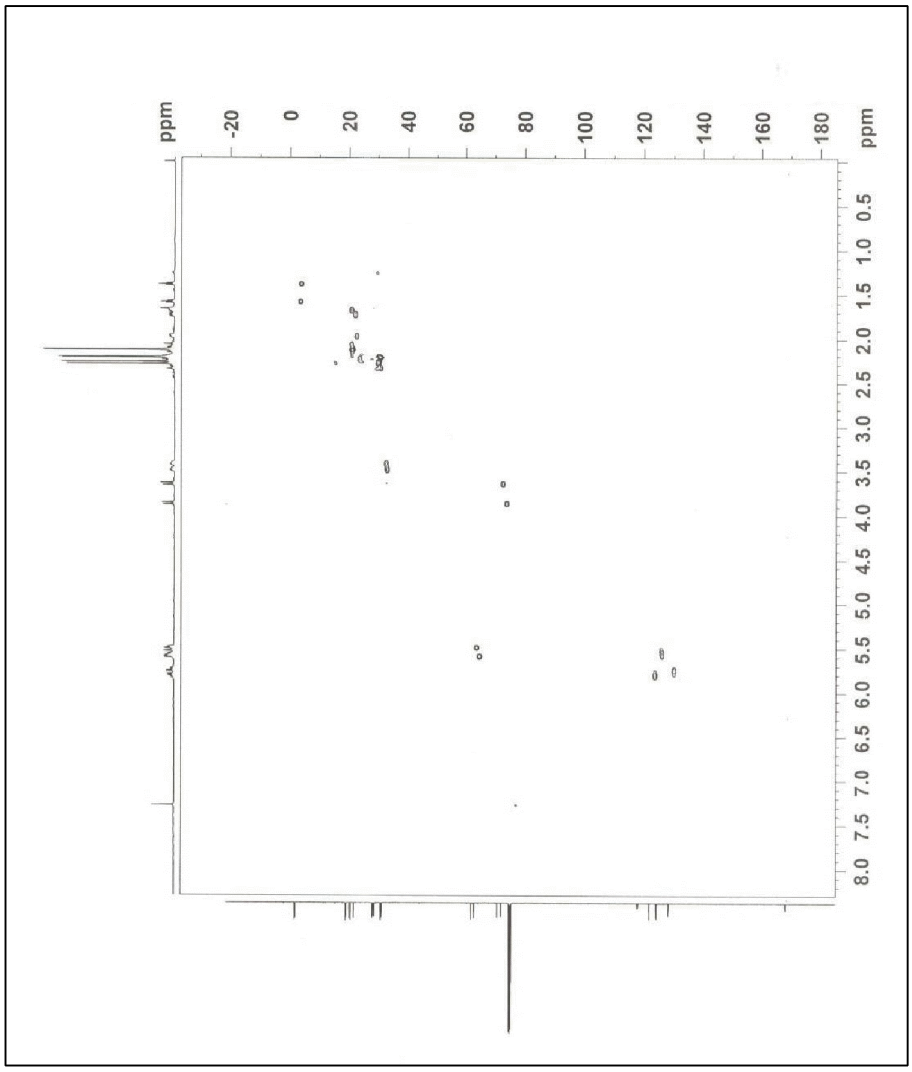


**Figure 55** HSQC spectrum of compounds **148** and **149**

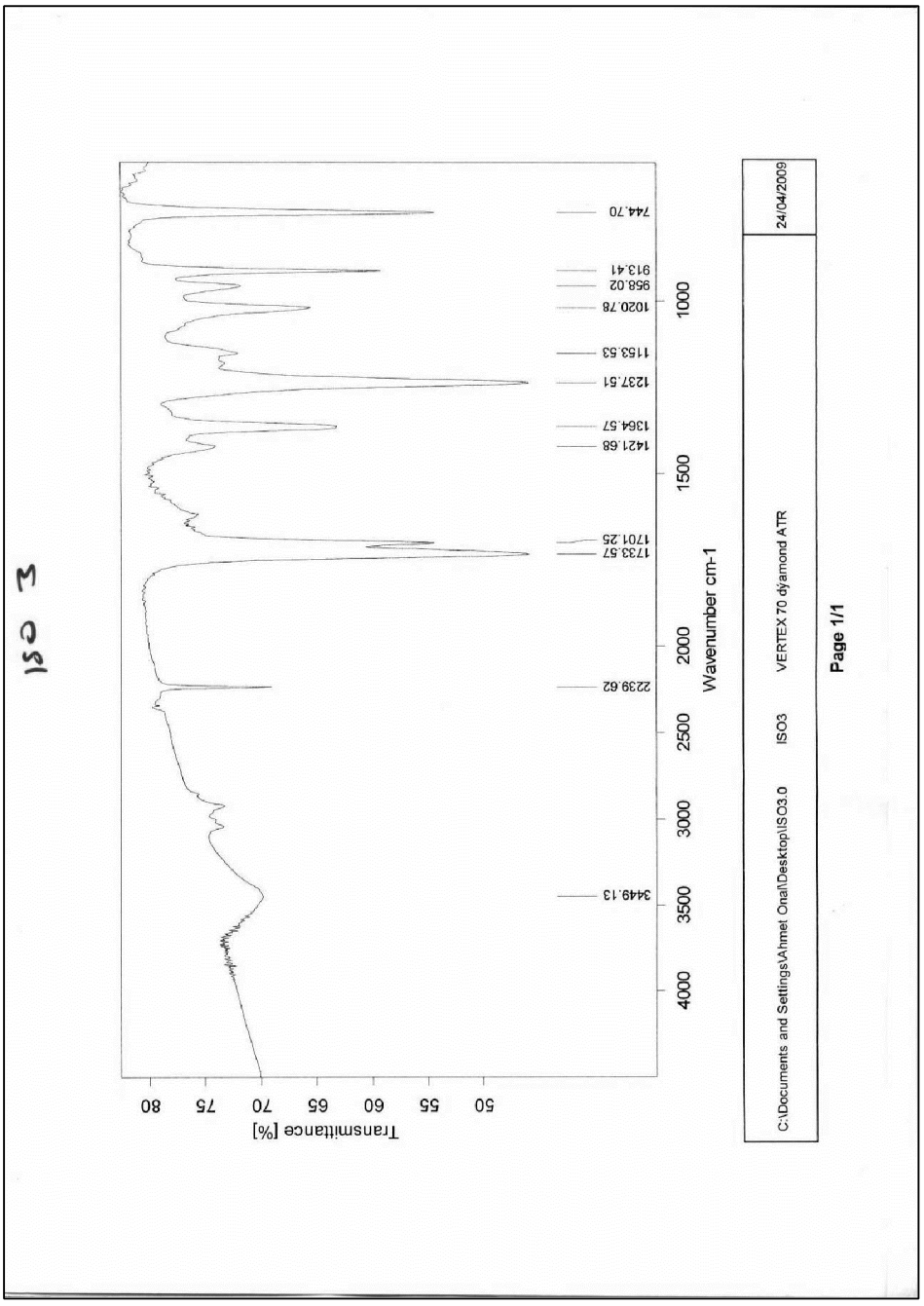


**Figure 56** IR spectrum of compounds **148** and **149**

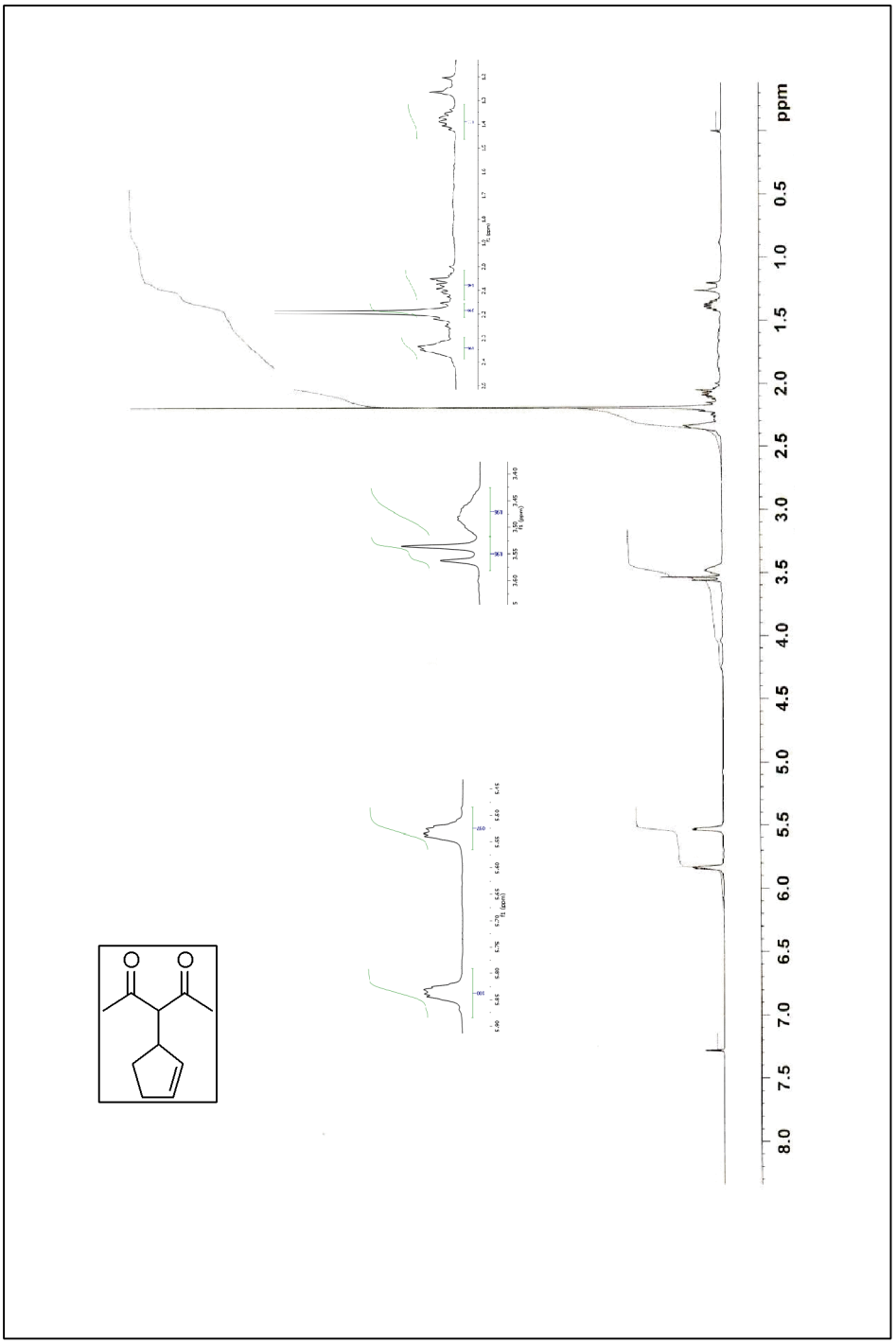


**Figure 57** $^{1}$H NMR spectrum of compound **155**

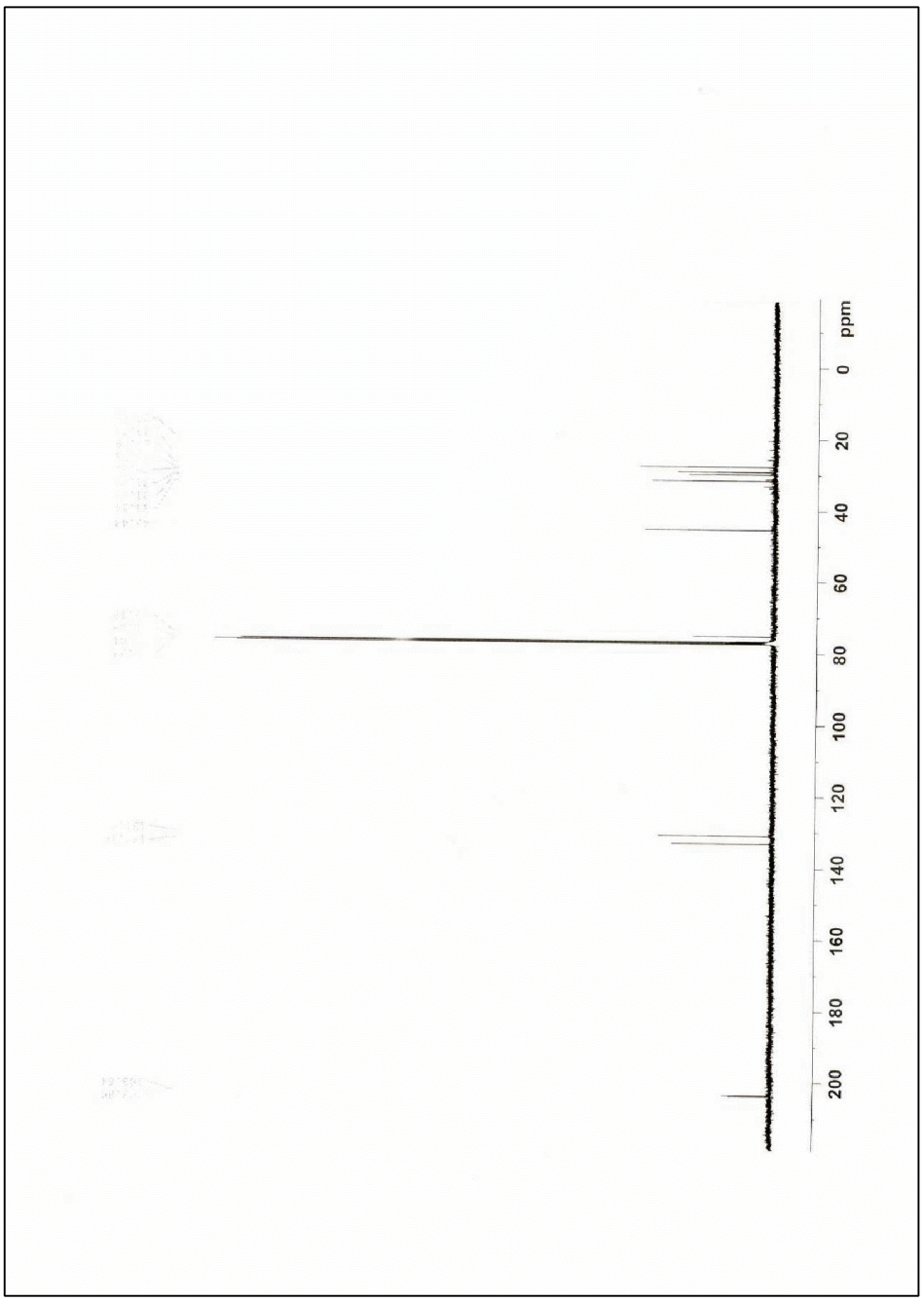


**Figure 58** $^{13}$C NMR spectrum of compound **155**

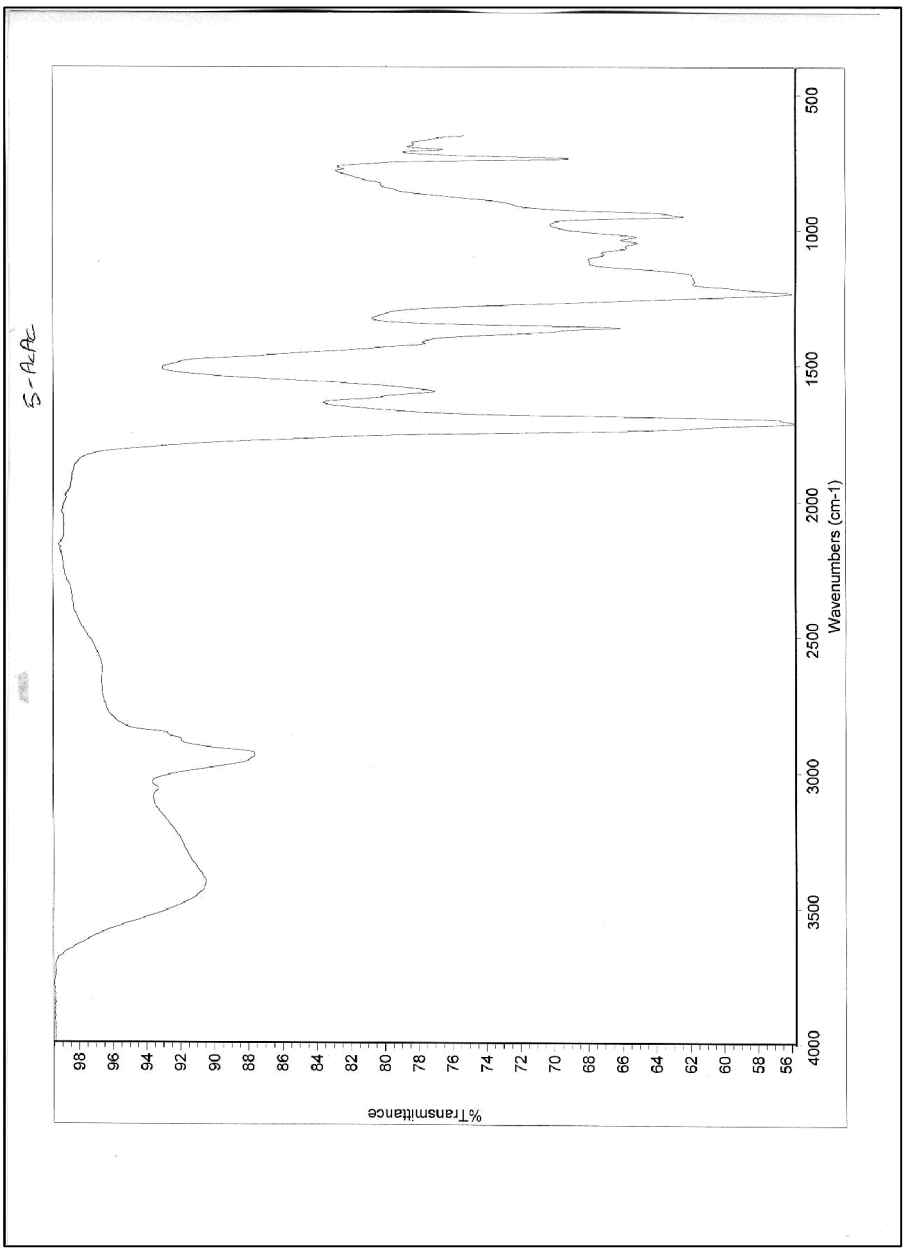


**Figure 59** IR spectrum of compound **155**

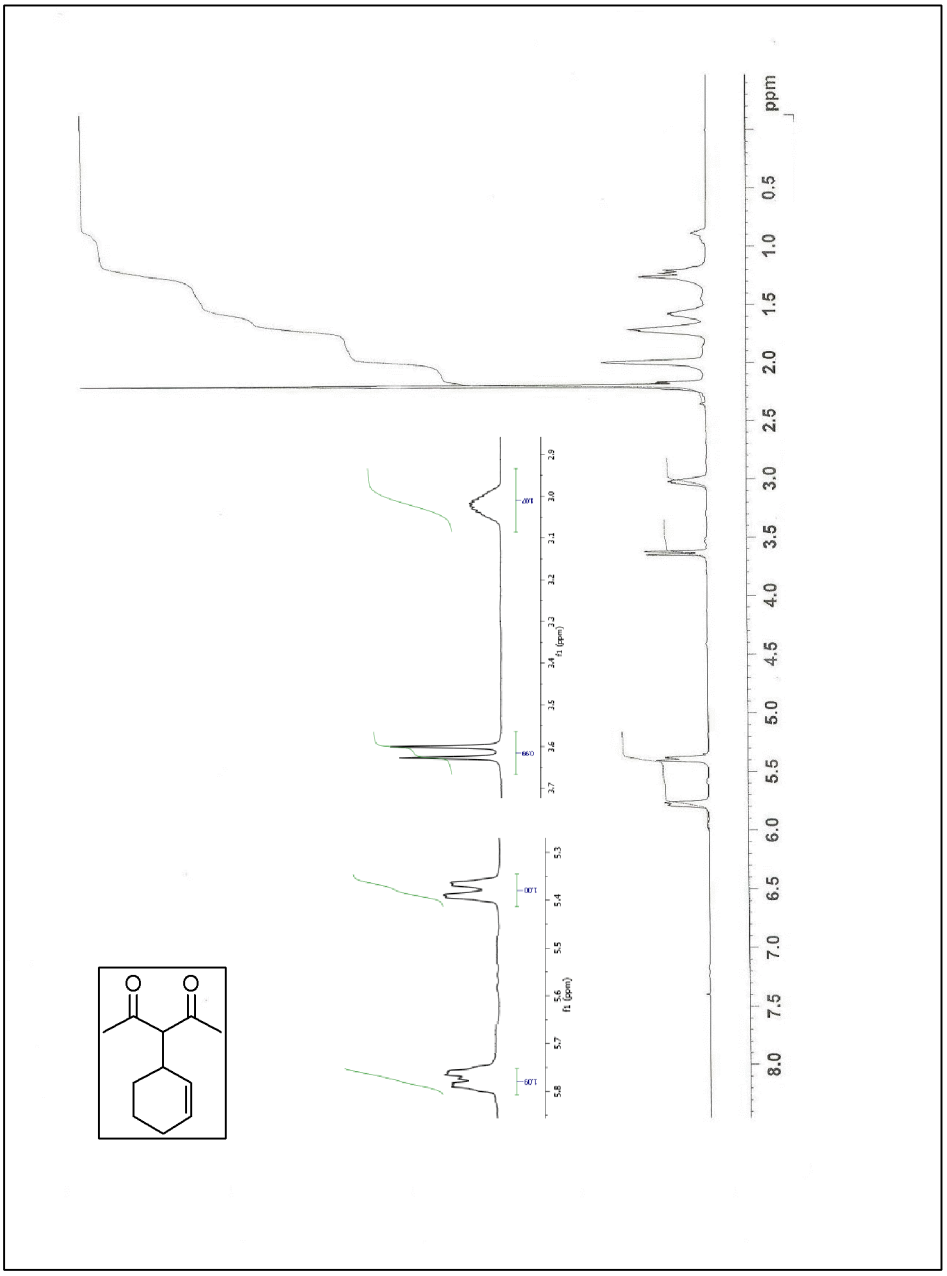


**Figure 60** $^{1}$H NMR spectrum of compound **156**

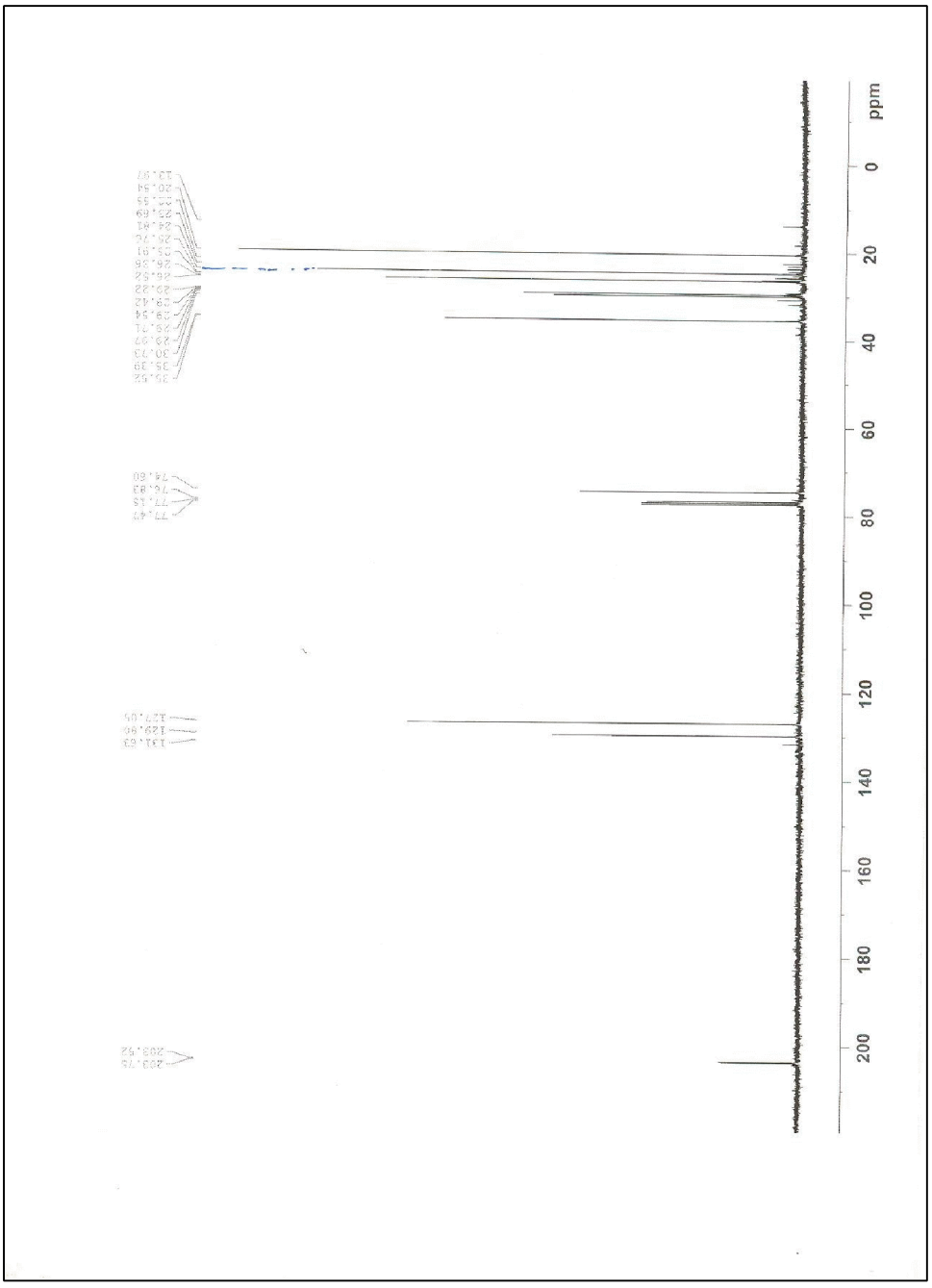


**Figure 61** $^{13}$C NMR spectrum of compound **156**

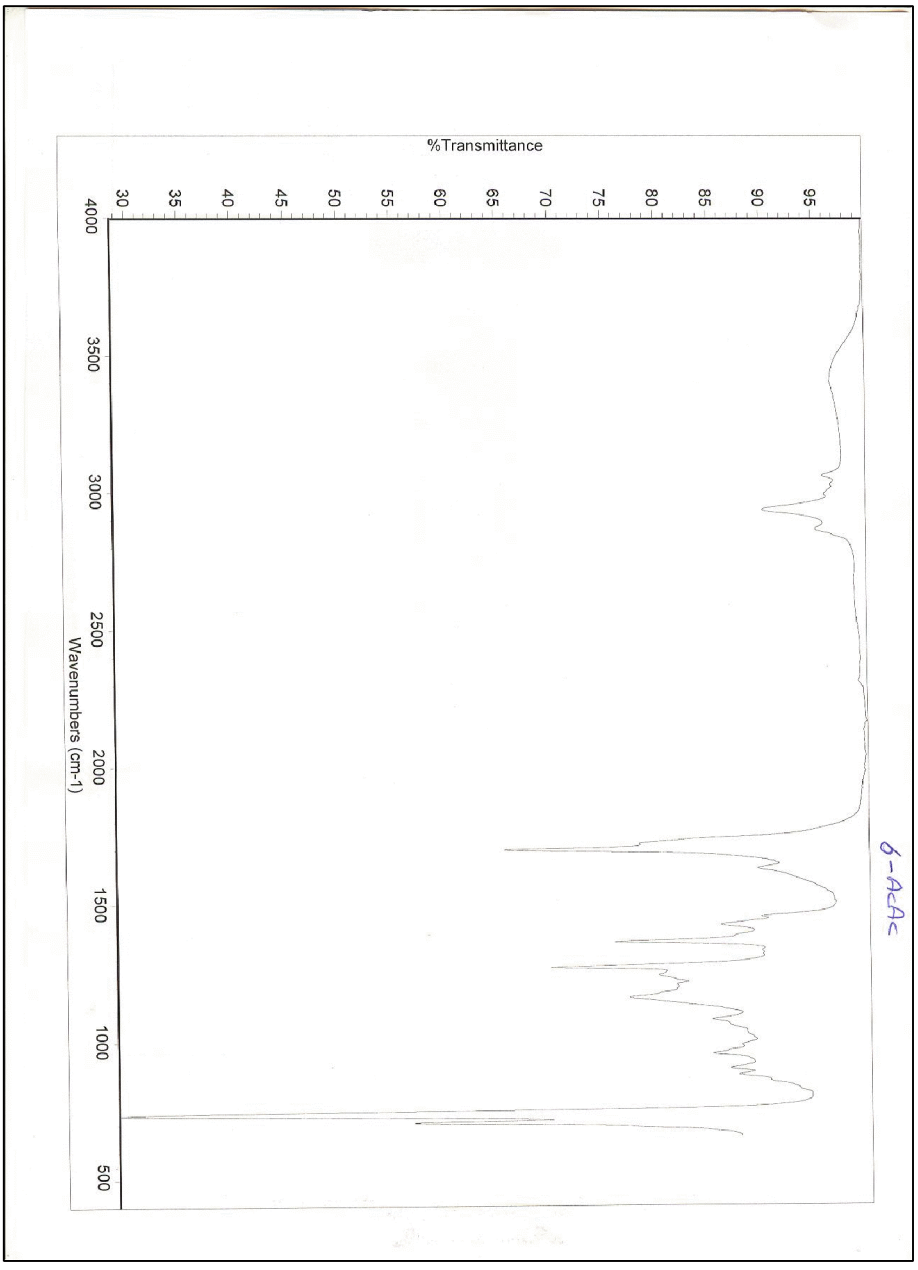


**Figure 62** IR spectrum of compound **156**

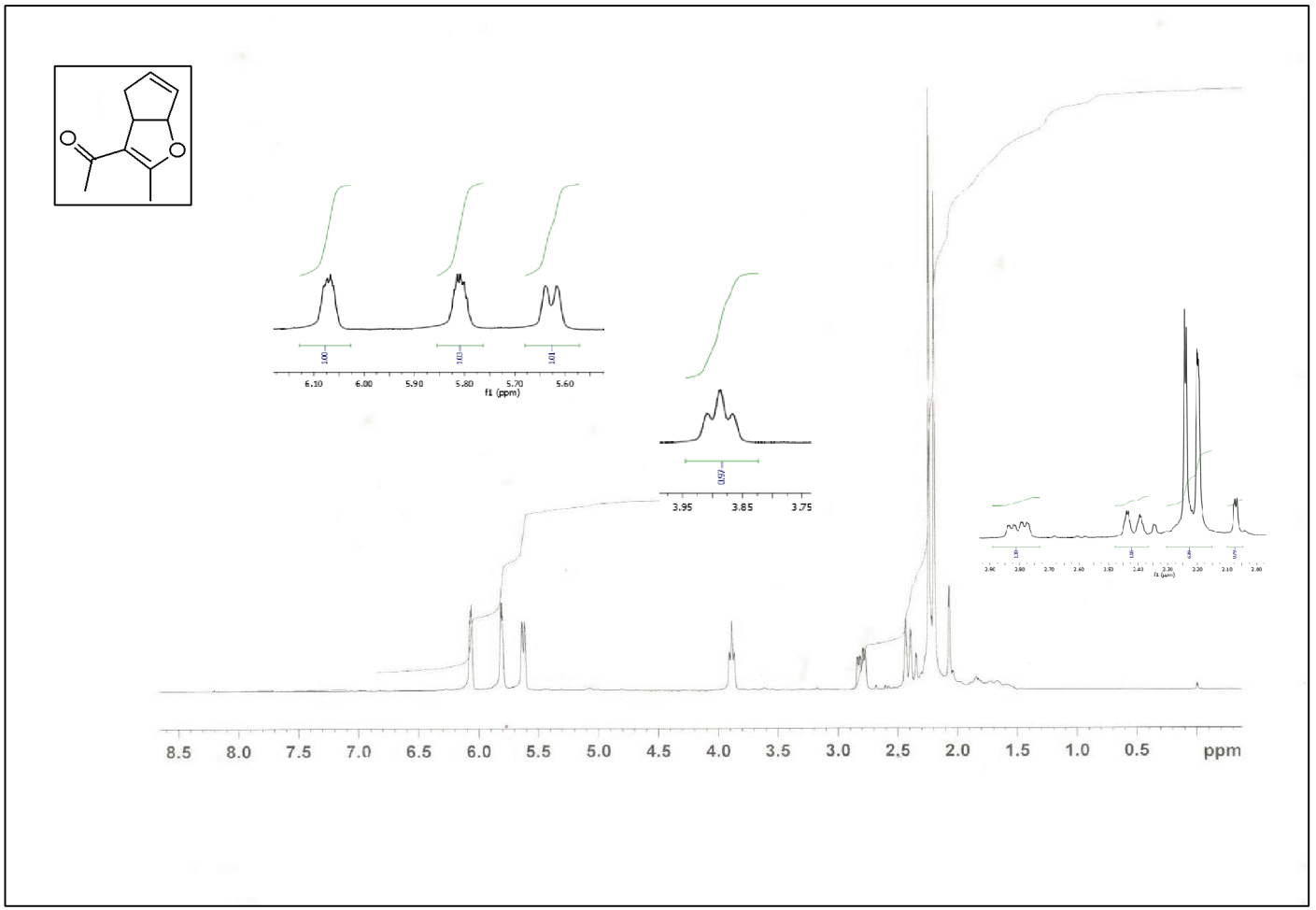


**Figure 63** $^{1}$H NMR spectrum of compound **159**

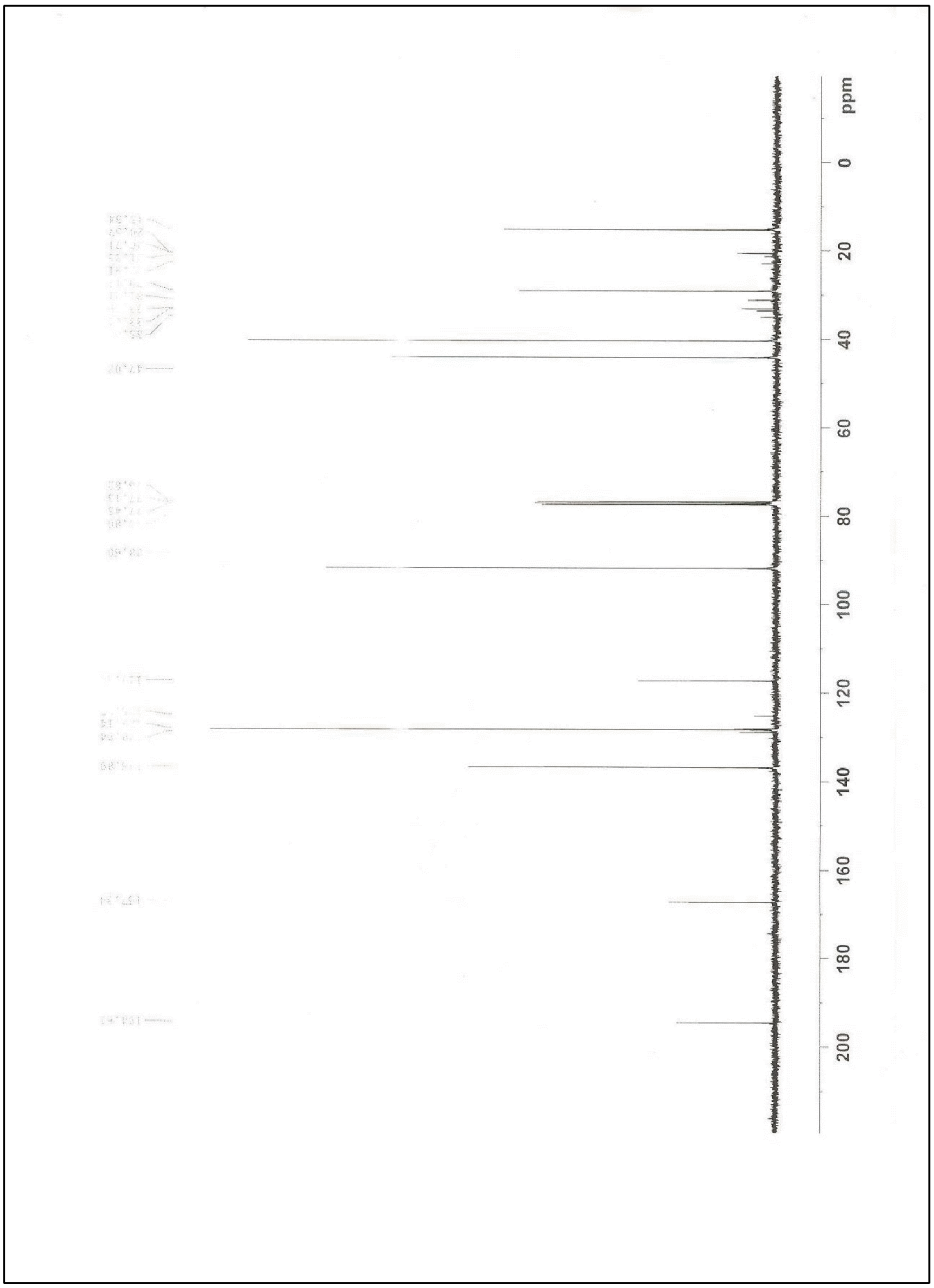


**Figure 64** $^{13}$C NMR spectrum of compound **159**

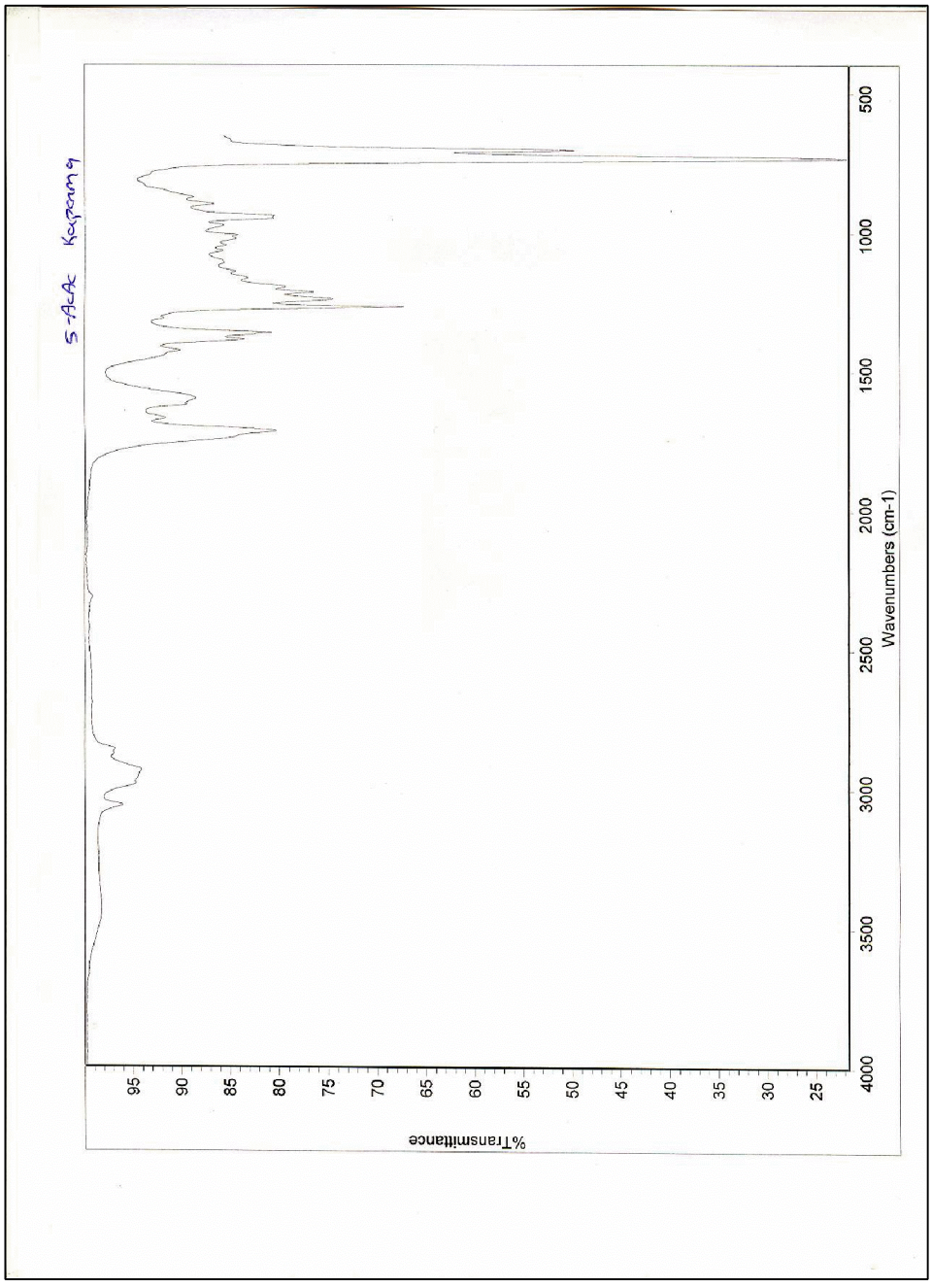


**Figure 65** IR spectrum of compound **159**

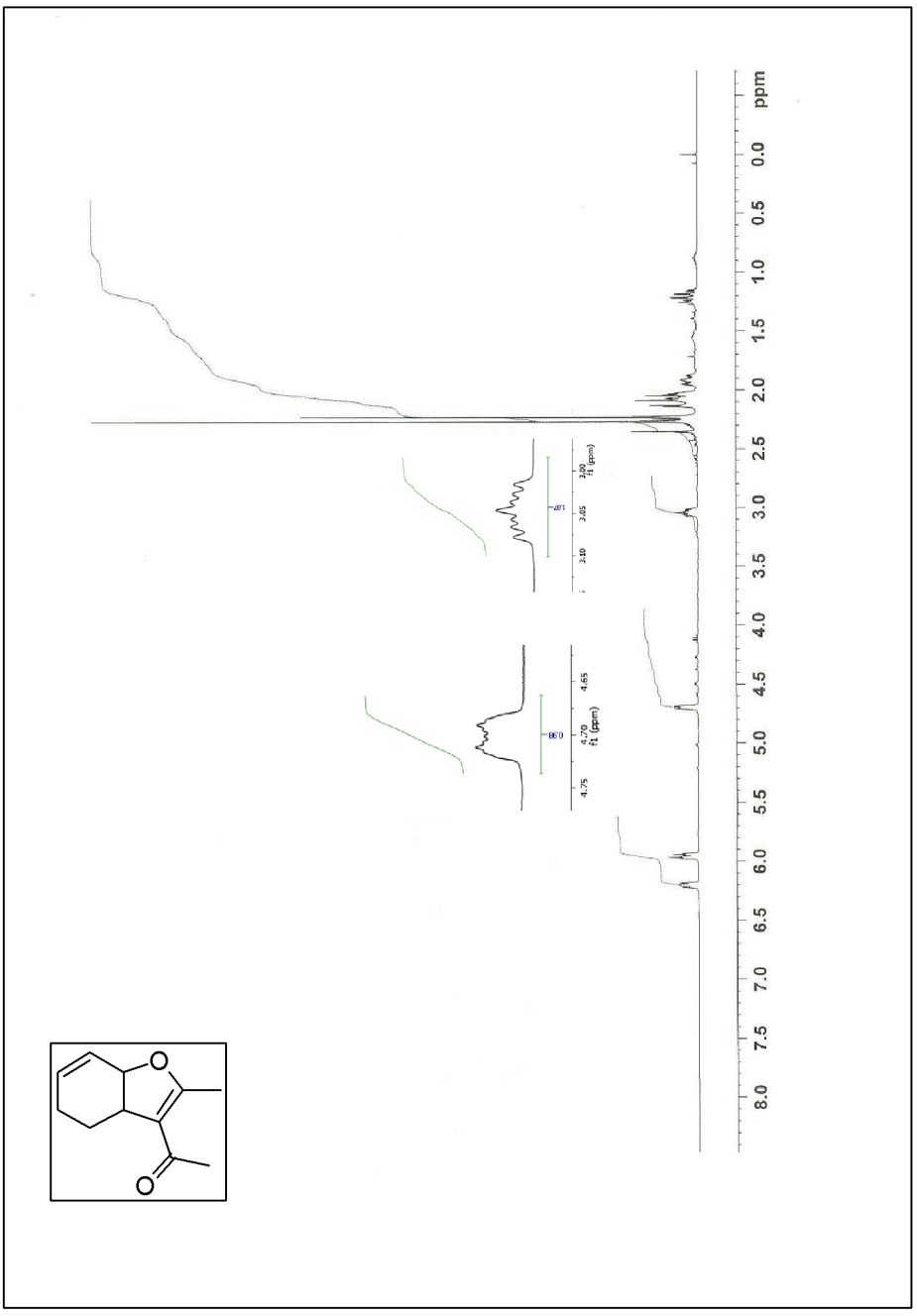


**Figure 66** $^{1}$H NMR spectrum of compound **160**

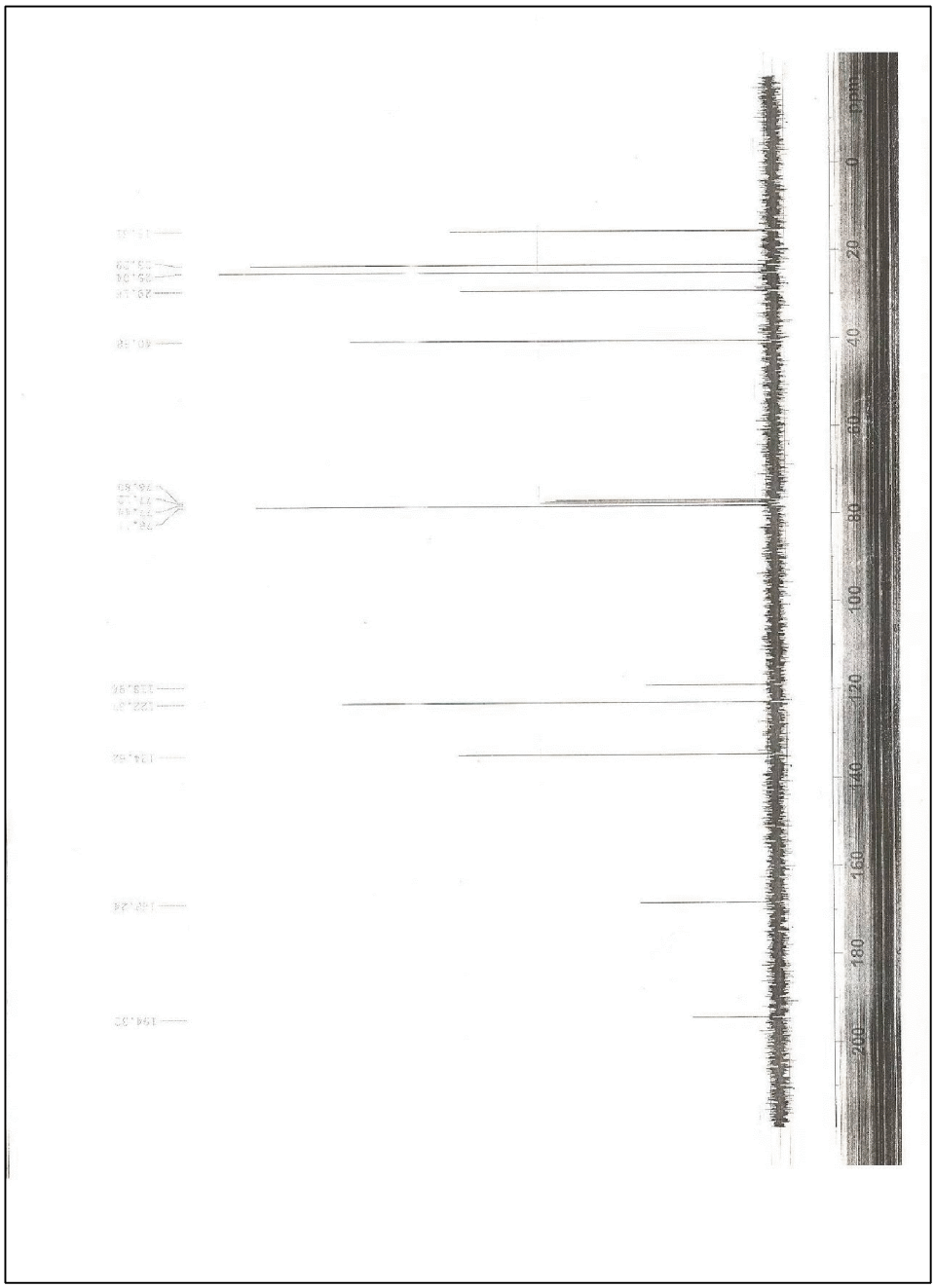

**Figure 67** $^{13}$C NMR spectrum of compound **160**

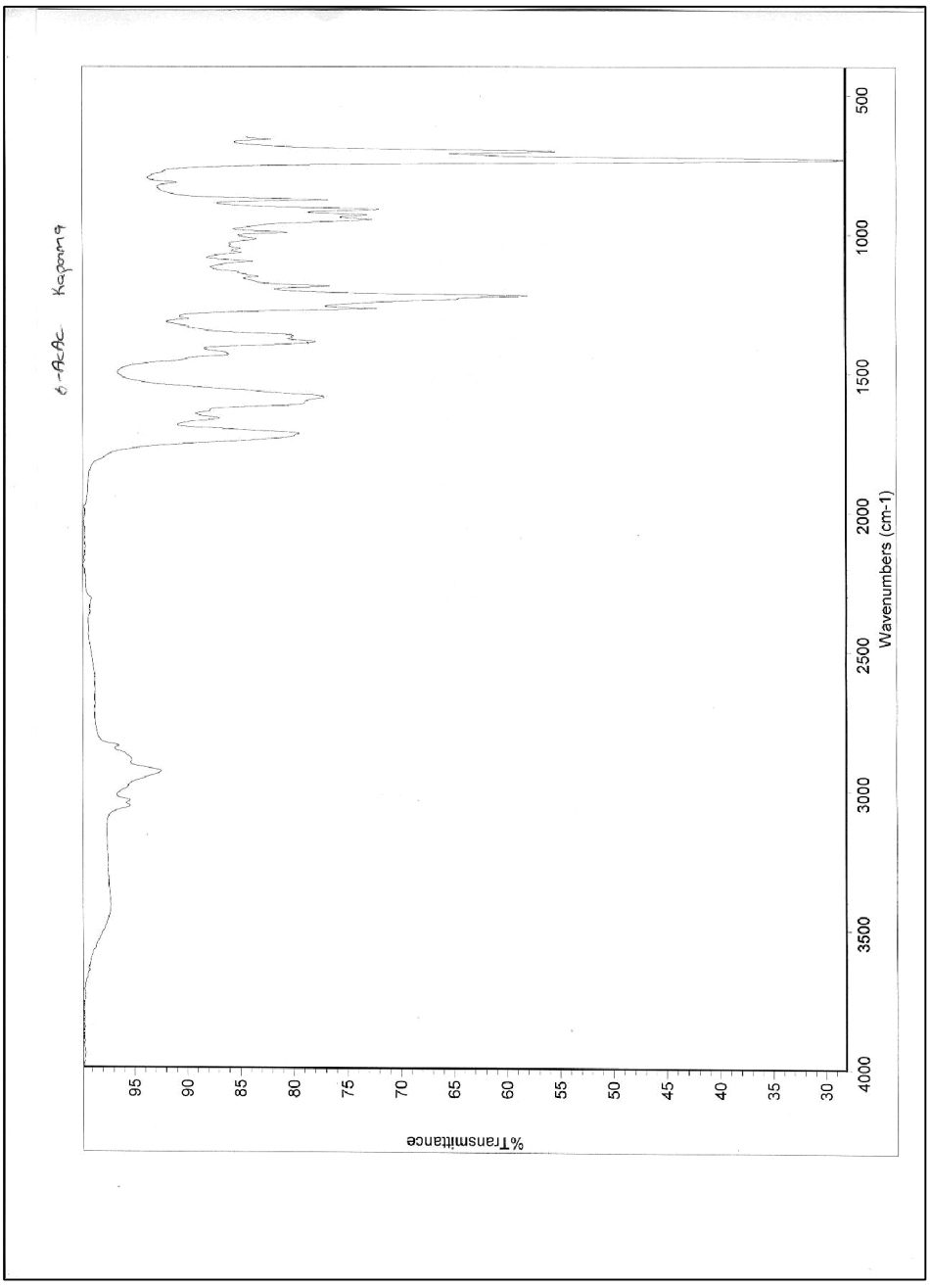


**Figure 68** IR spectrum of compound **160**

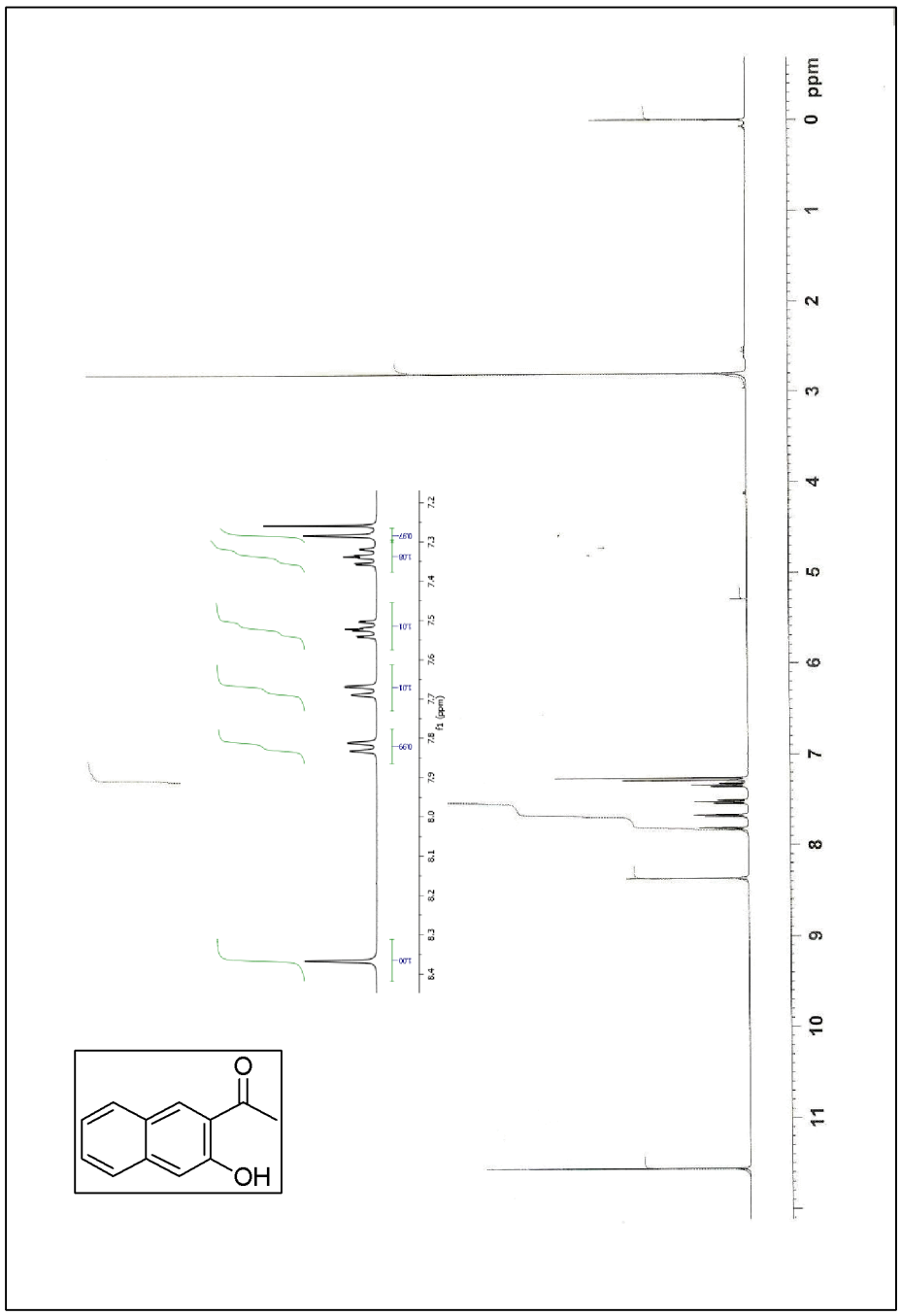


**Figure 69** $^{1}$H NMR spectrum of compound **161**

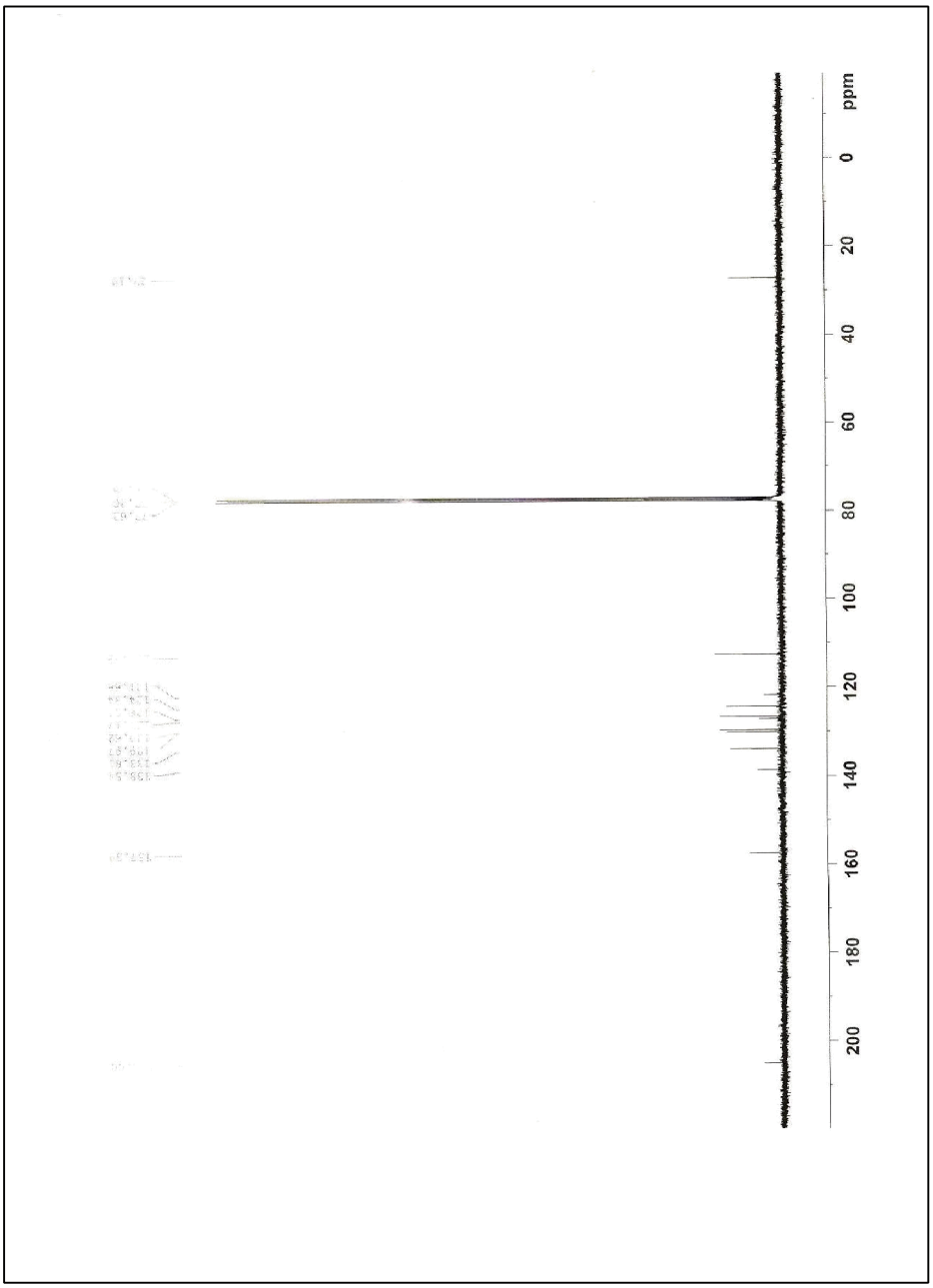


**Figure 70** $^{13}$C NMR spectrum of compound **161**

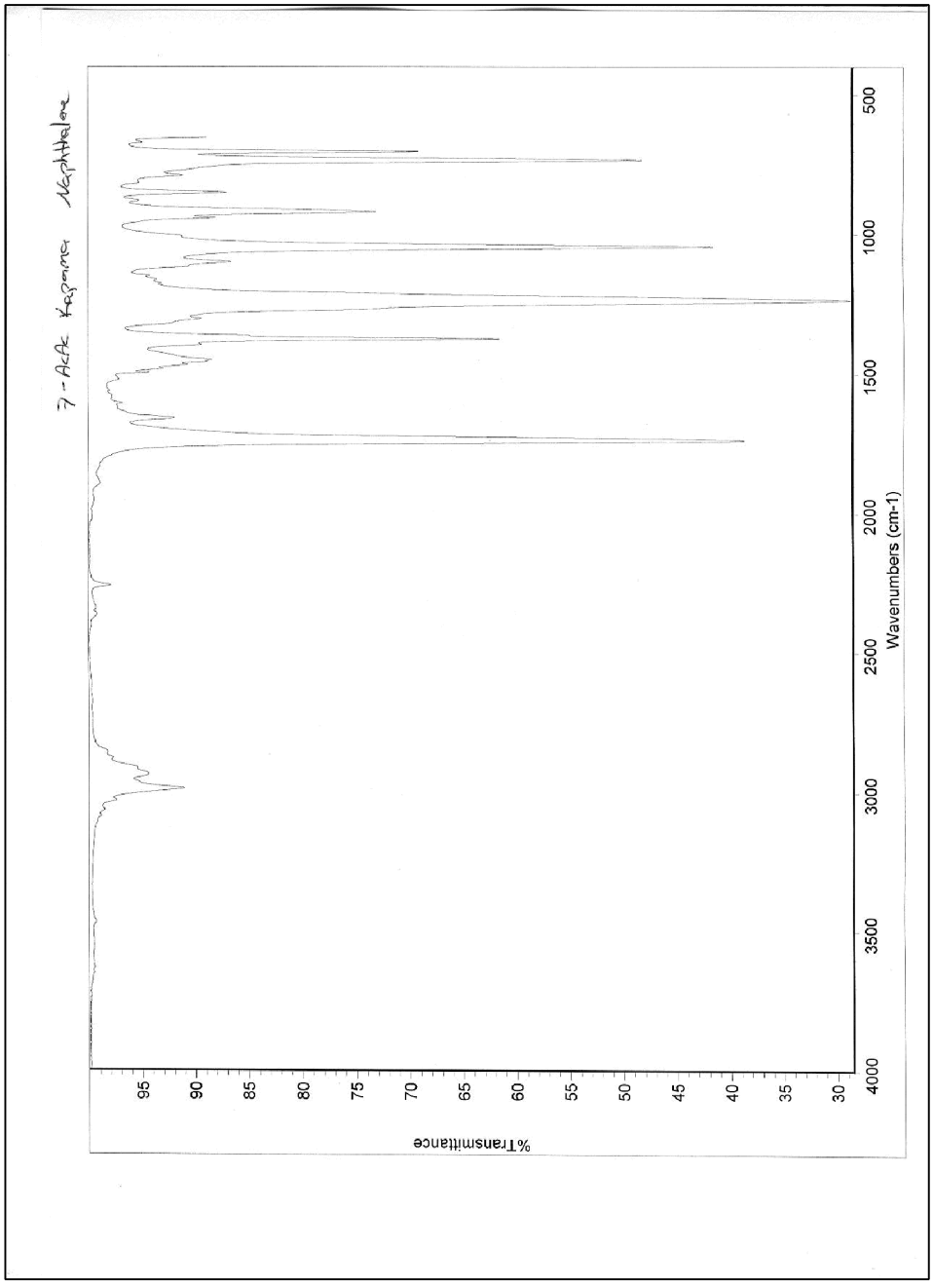


**Figure 71** IR spectrum of compound **161**

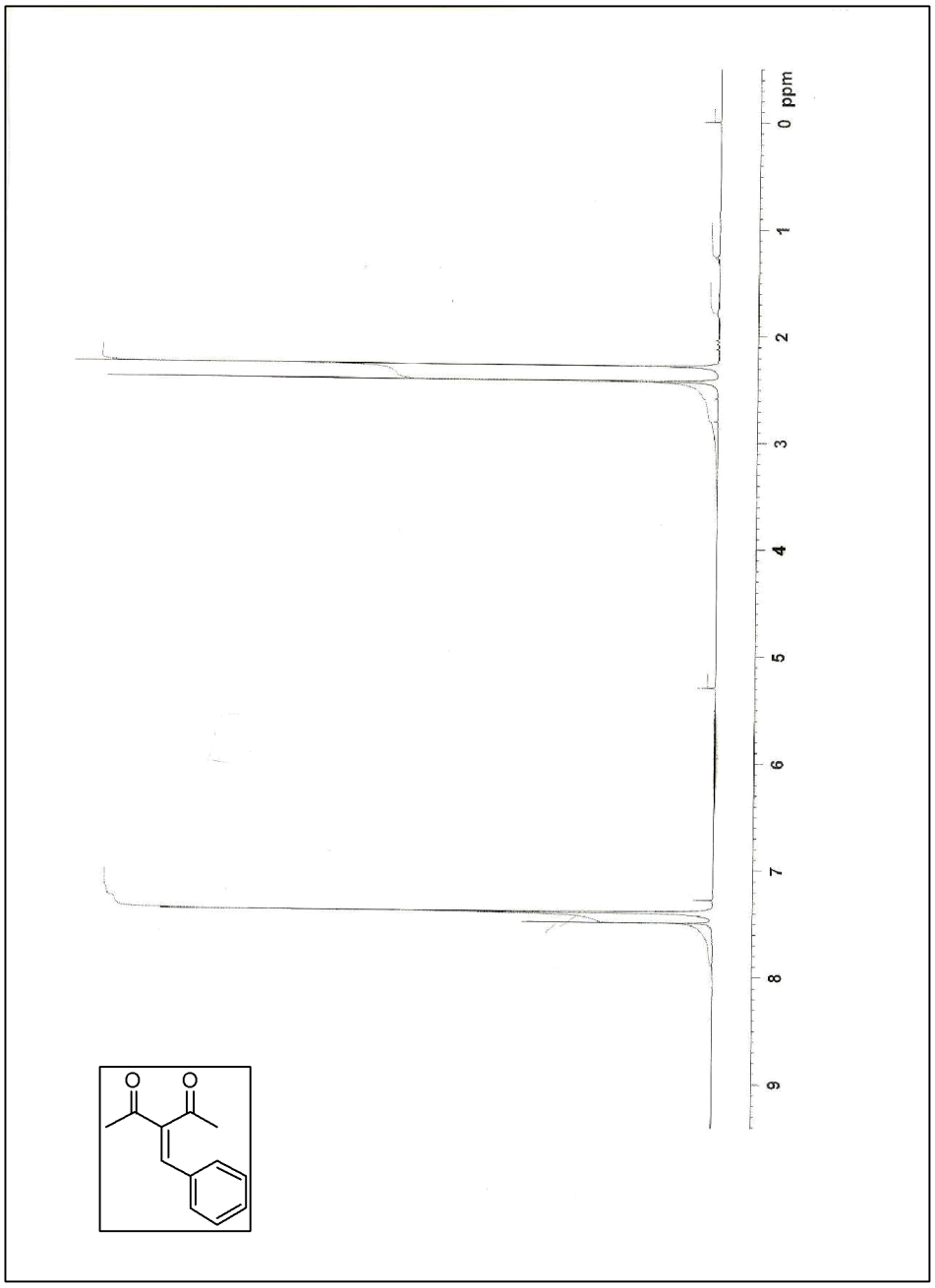


**Figure 72** $^{1}$H NMR spectrum of compound **162**

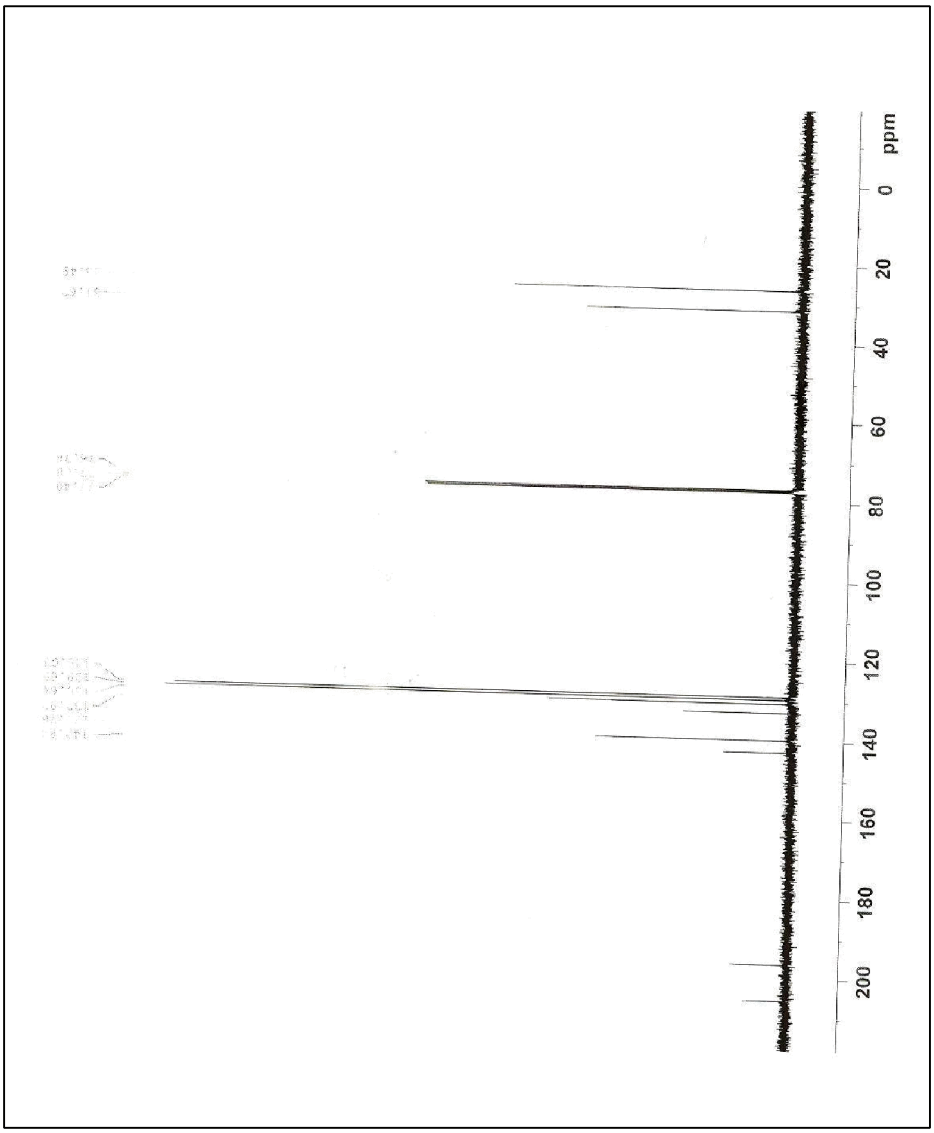


**Figure 73** $^{13}$C NMR spectrum of compound **162**

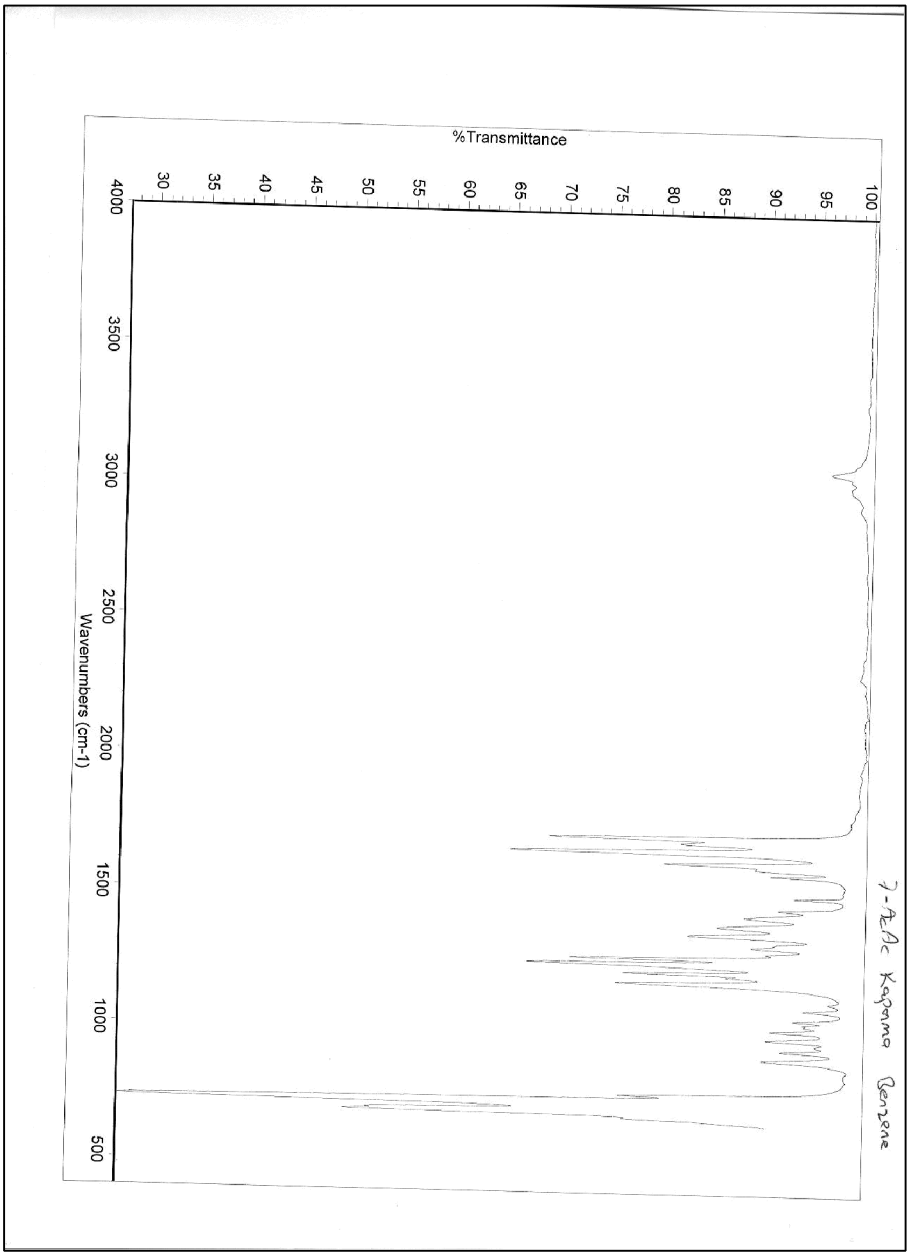


**Figure 74** IR spectrum of compound **162**

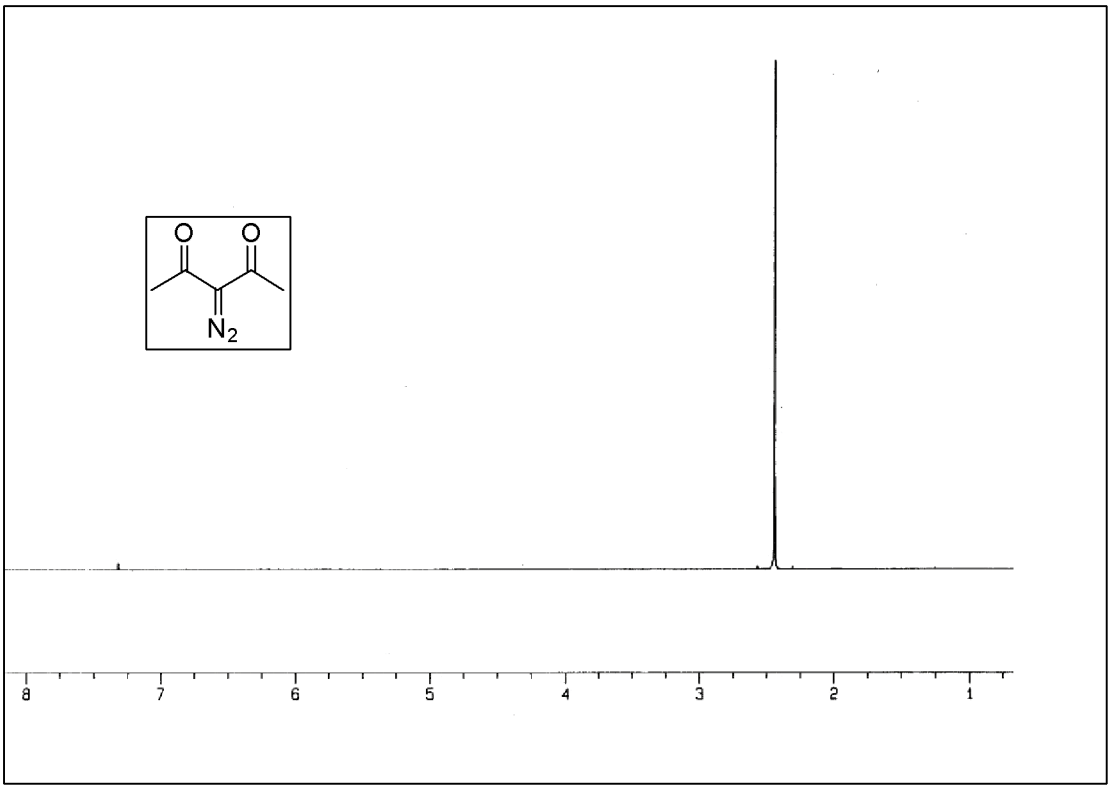


**Figure 75** $^{1}$H NMR spectrum of compound **175**

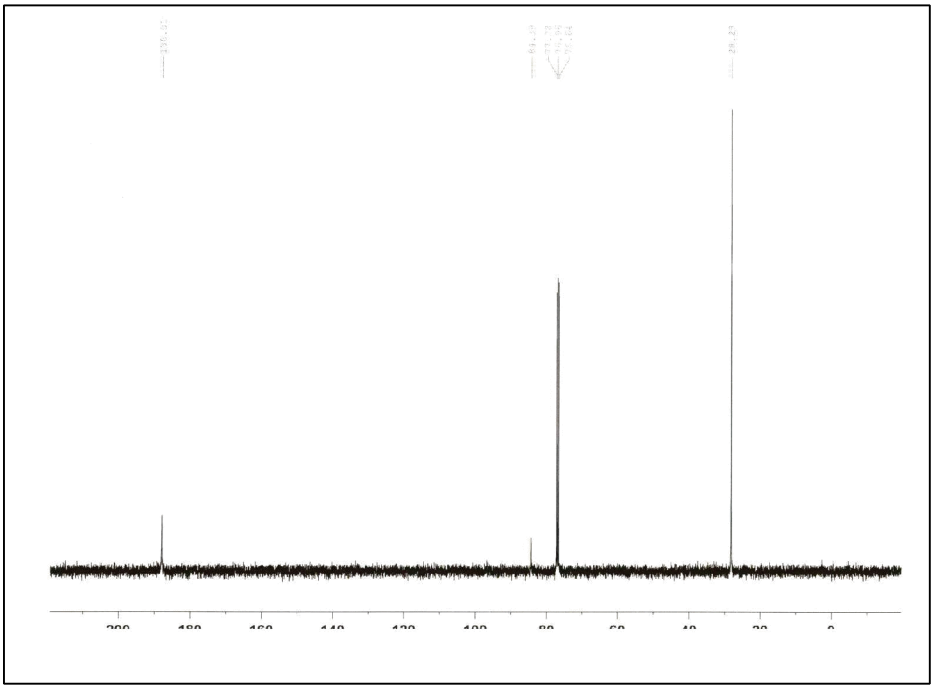

**Figure 76** $^{13}$C NMR spectrum of compound **175**

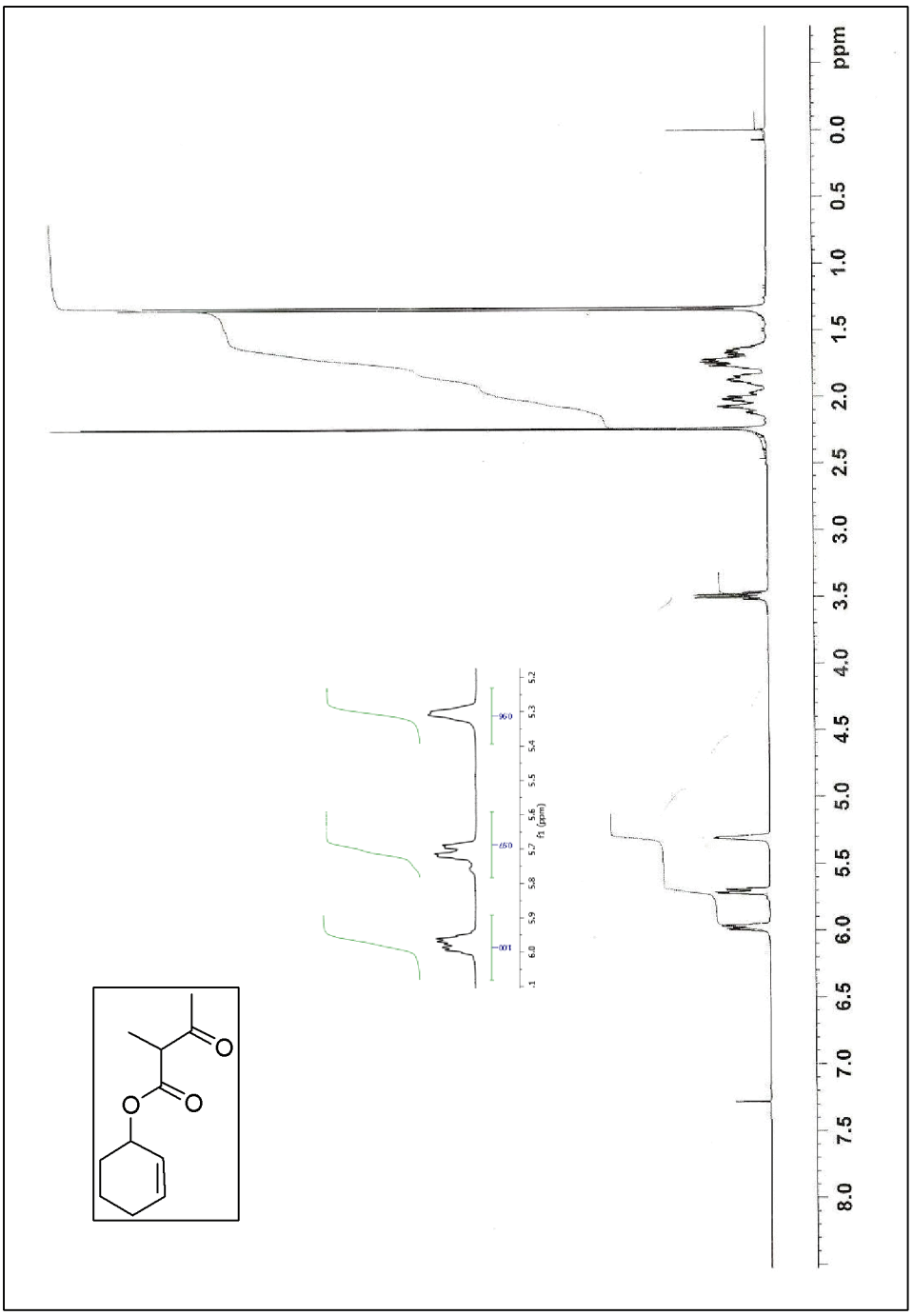


**Figure 77** $^{1}$H NMR spectrum of compound **178**

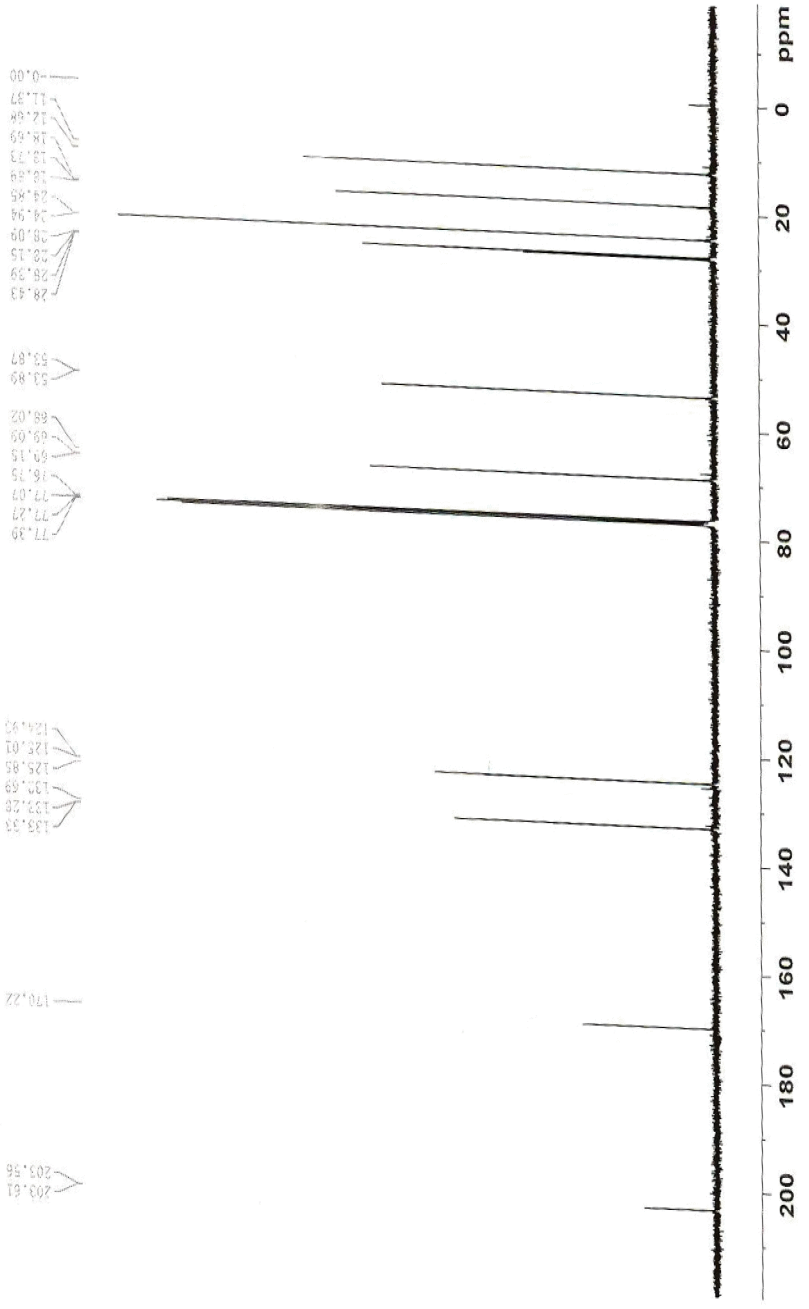


**Figure 78** $^{13}$C NMR spectrum of compound **178**

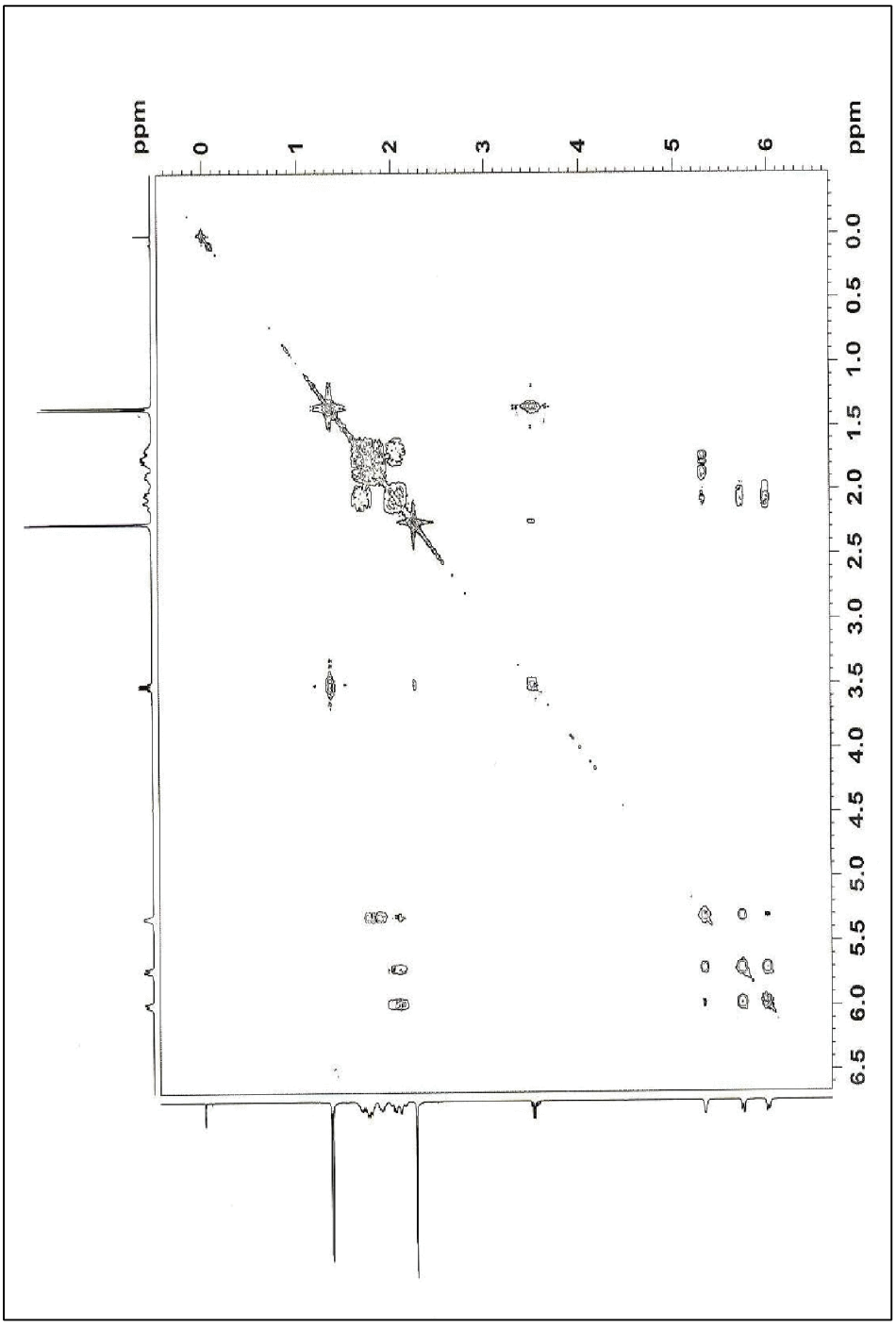


**Figure 79** COSY spectrum of compound **178**

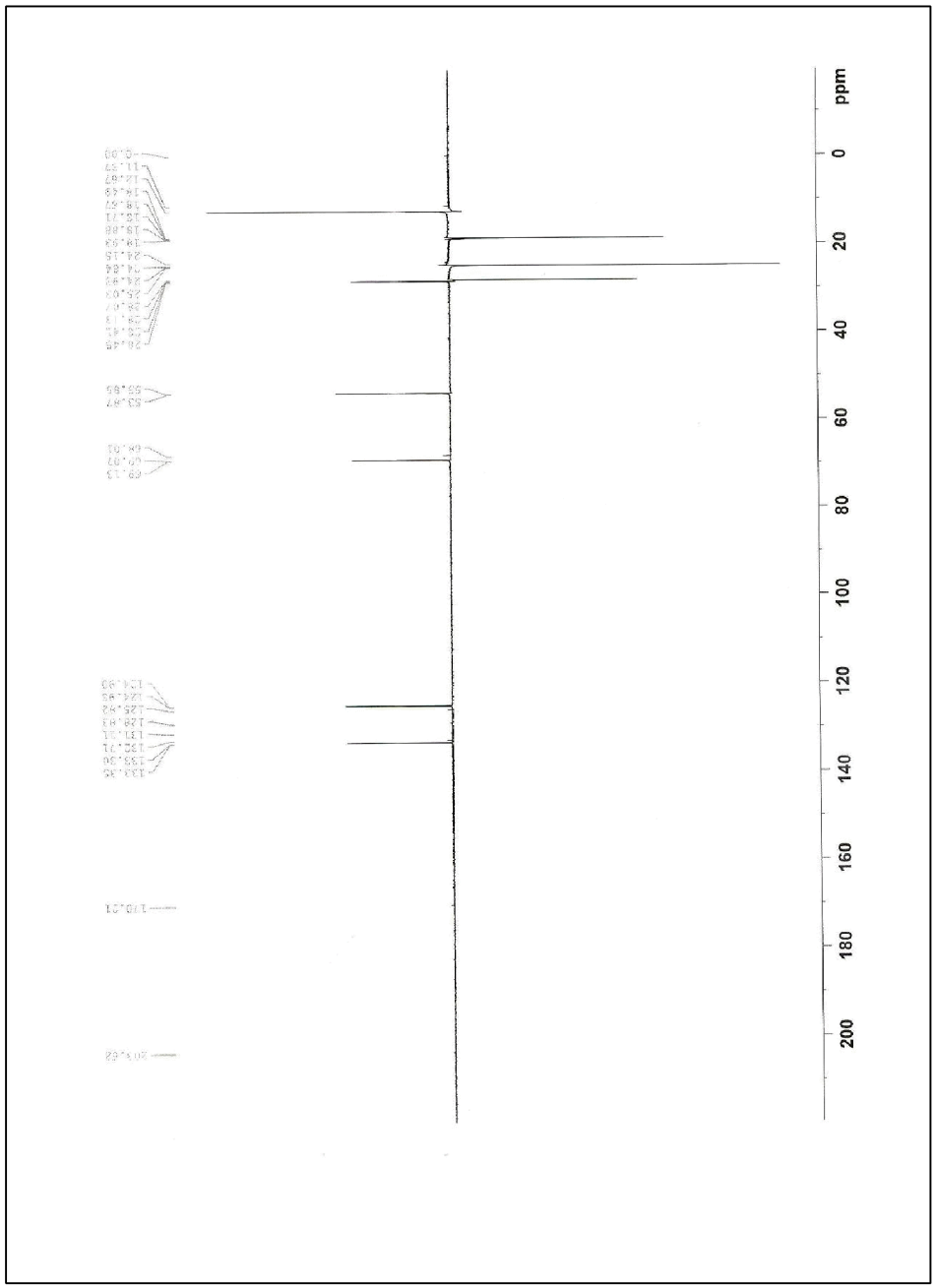


**Figure 80** DEPT 135 spectrum of compound **178**

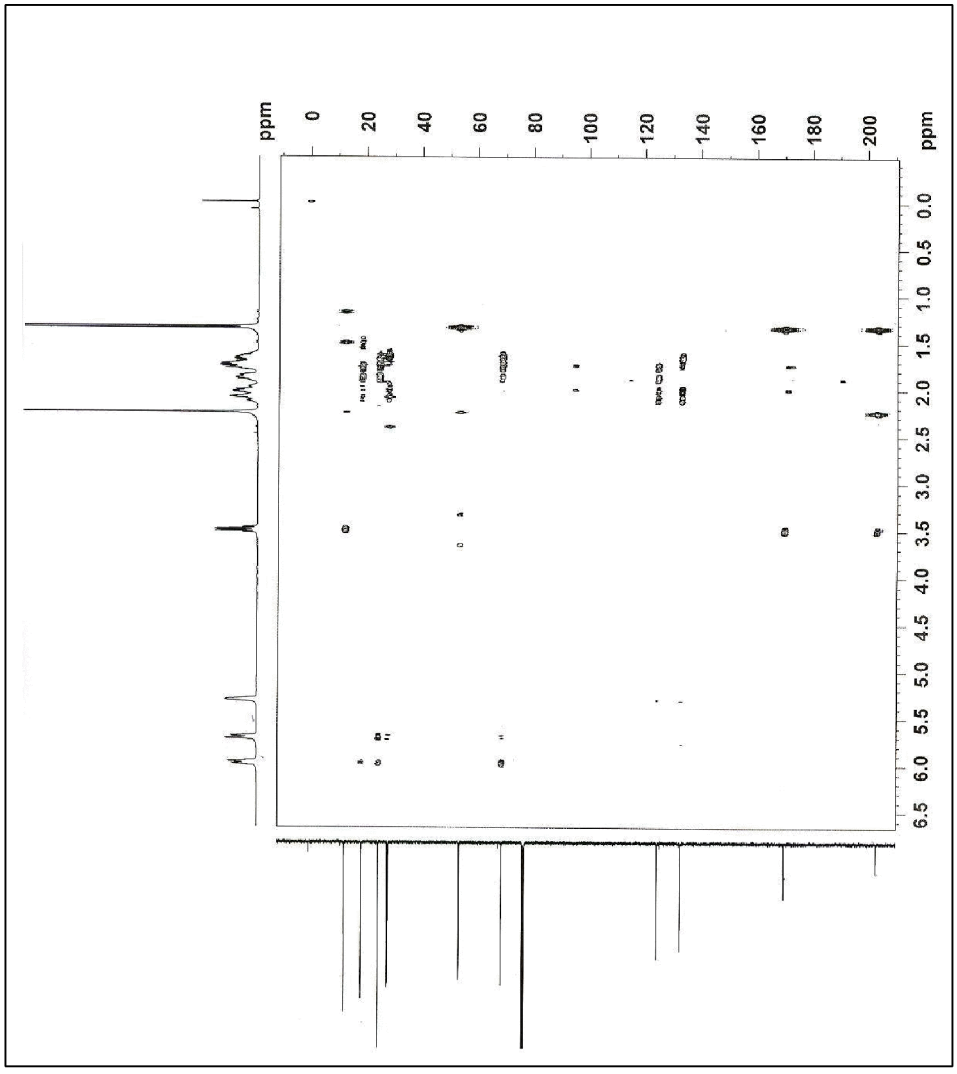


**Figure 81** HMBC spectrum of compound **178**

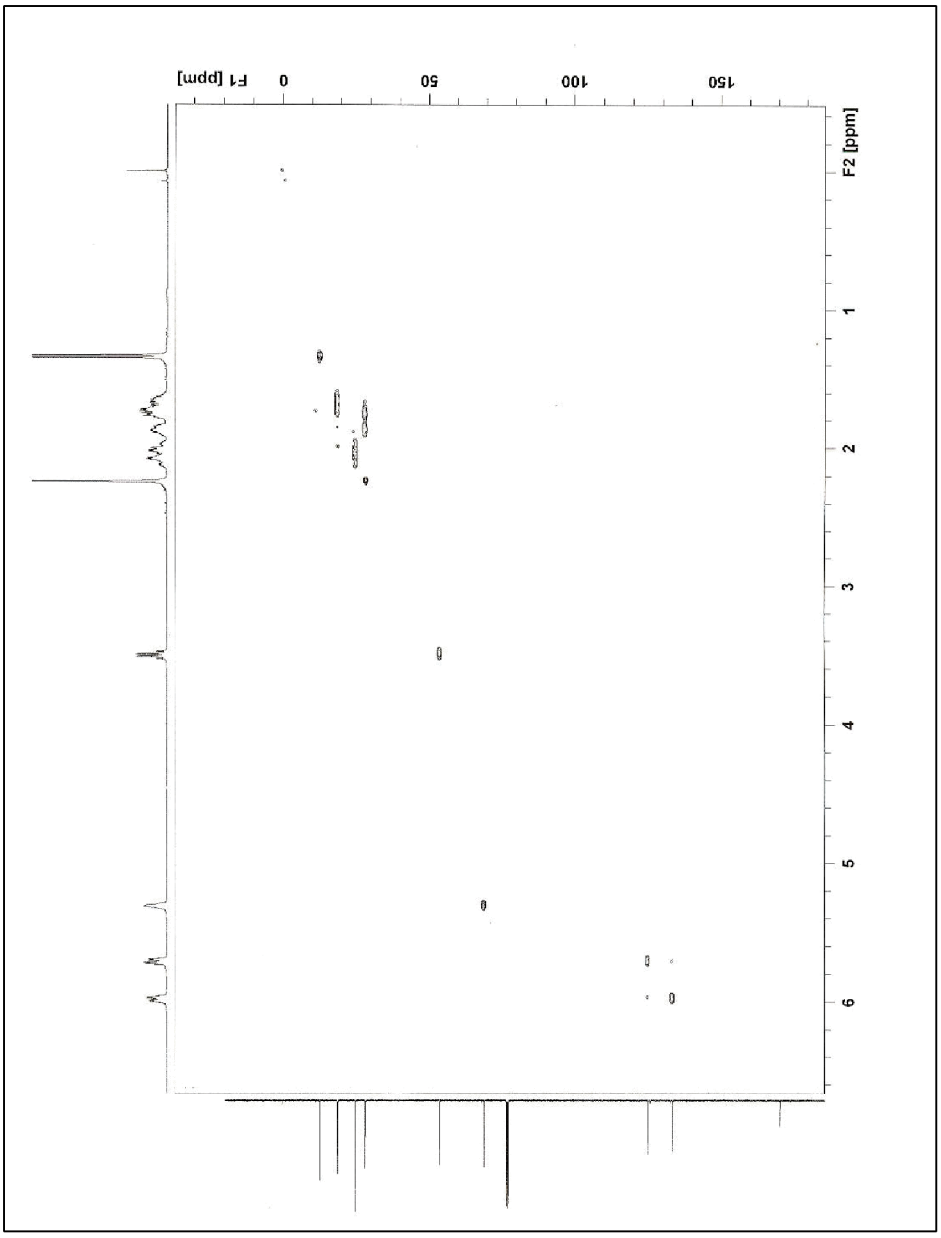


**Figure 82** HSQC spectrum of compound **178**

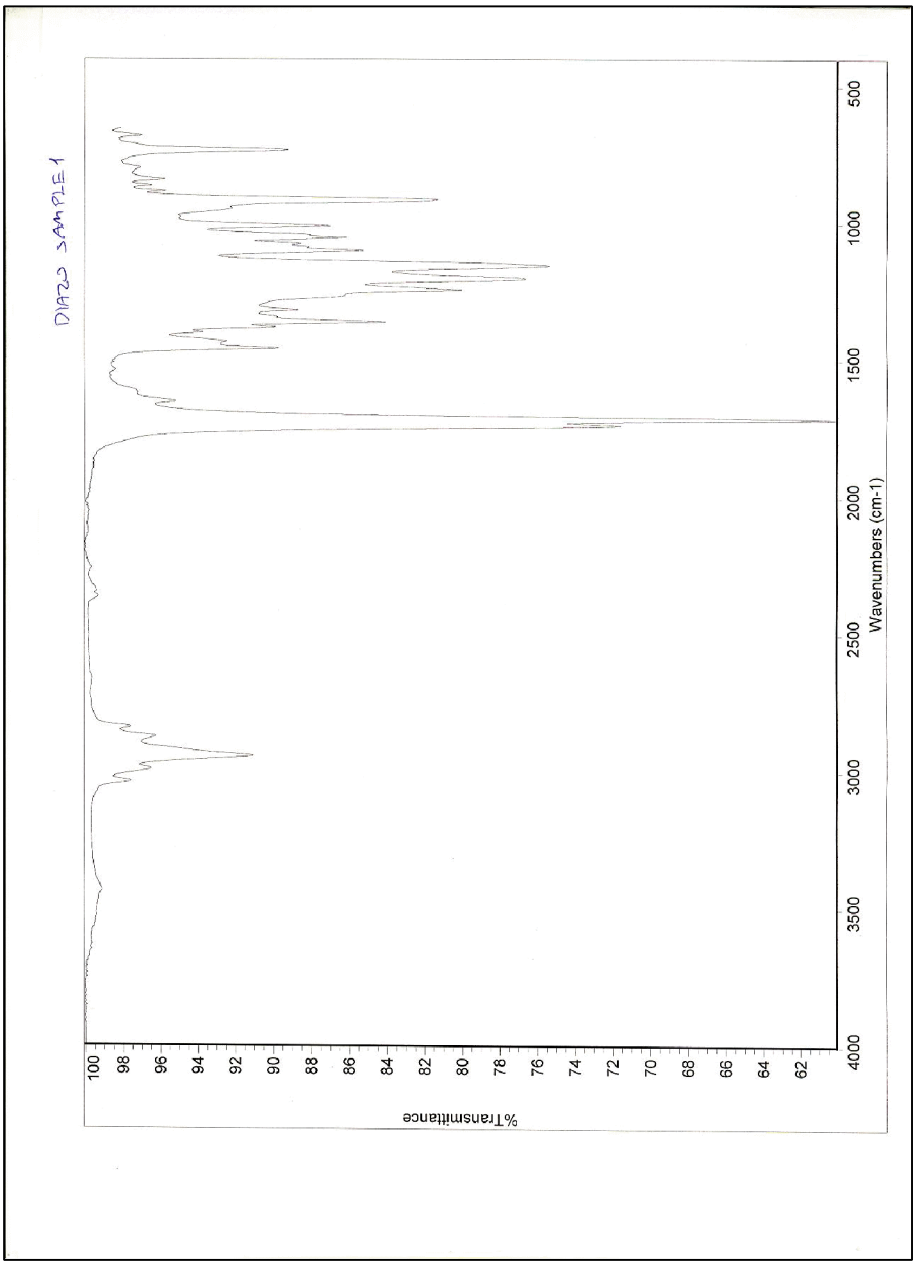


**Figure 83** IR spectrum of compound **178**

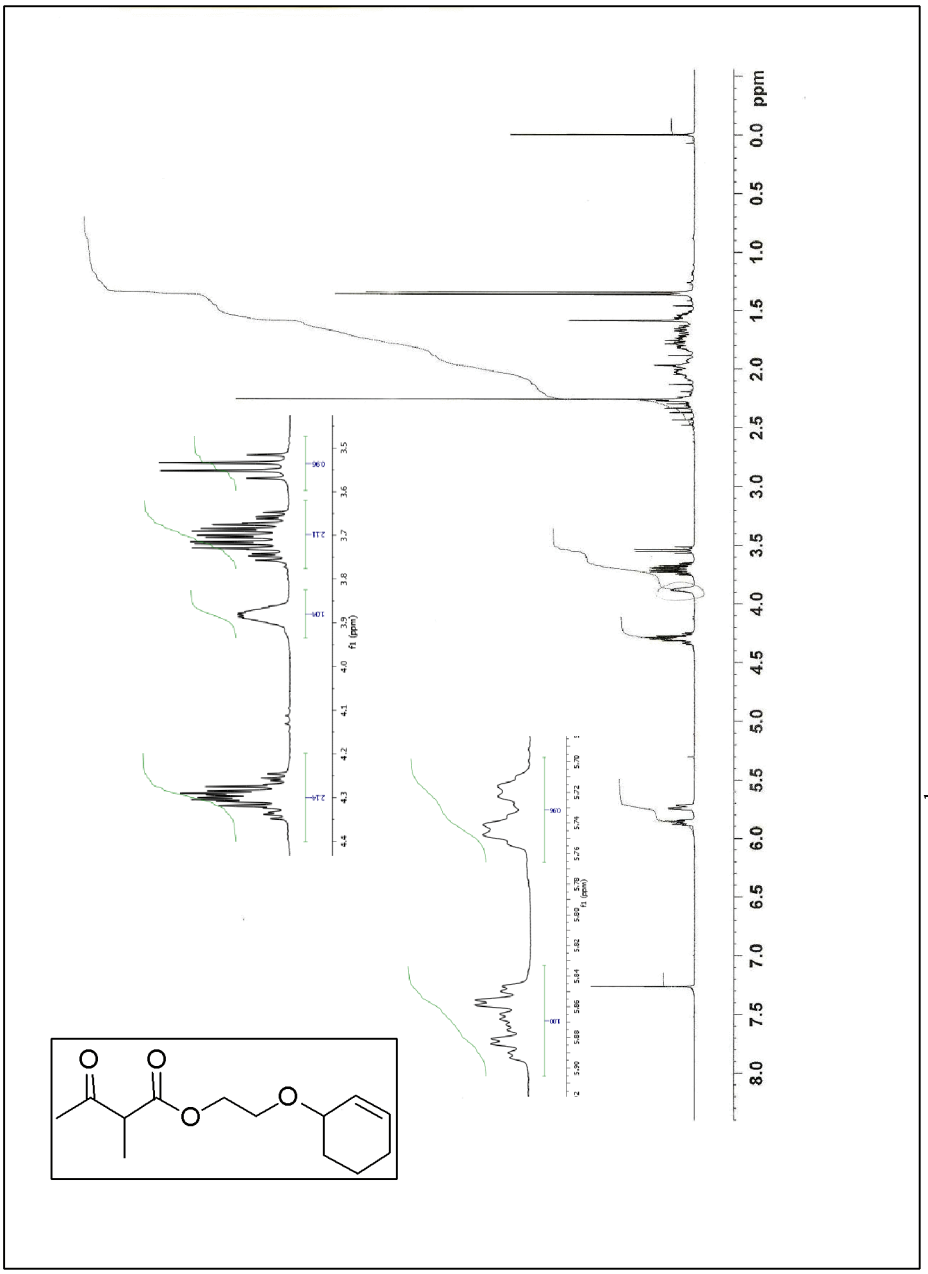


**Figure 84** $^{1}$H NMR spectrum of compound **179**

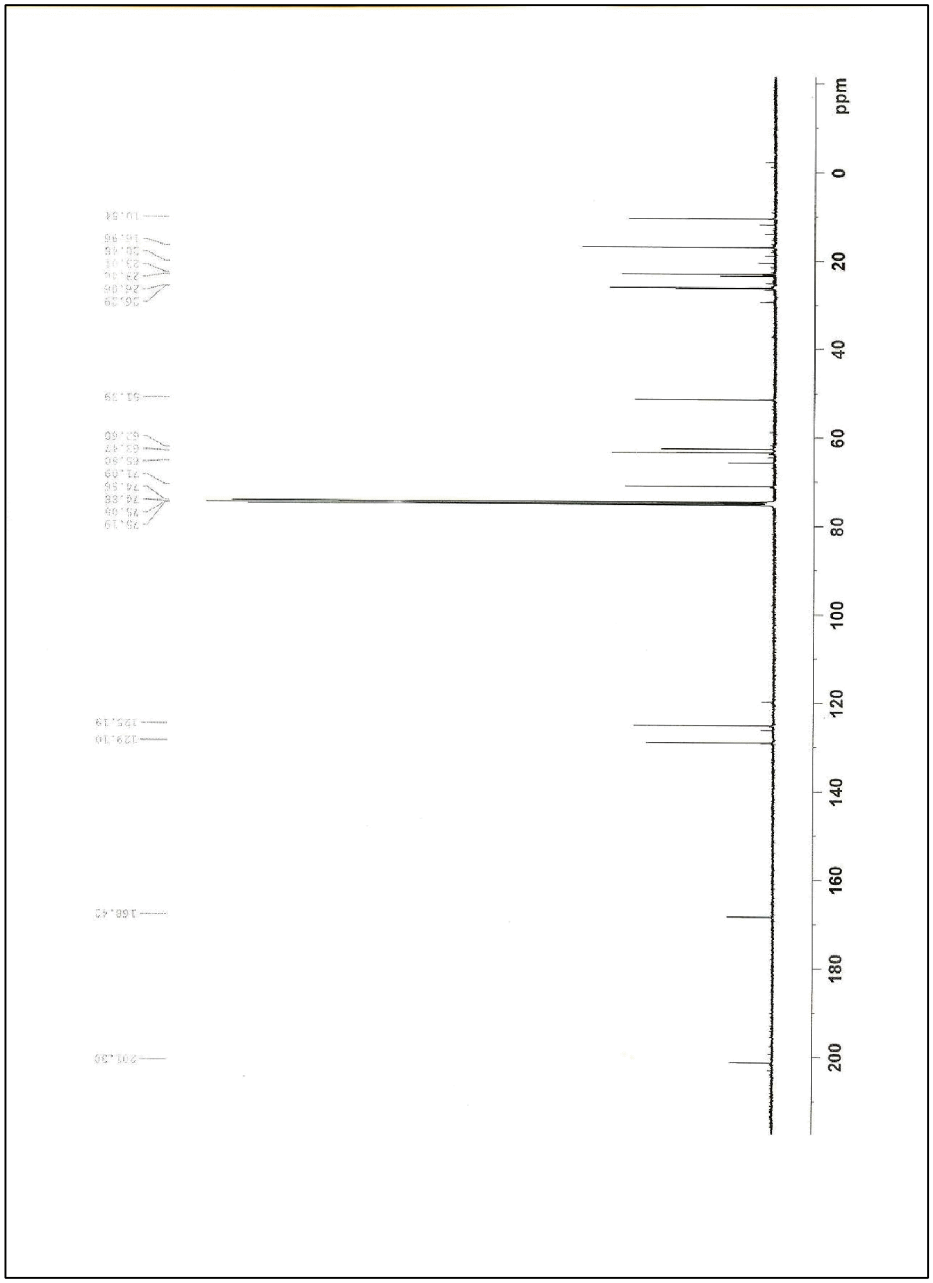


**Figure 85** $^{13}$C NMR spectrum of compound **179**

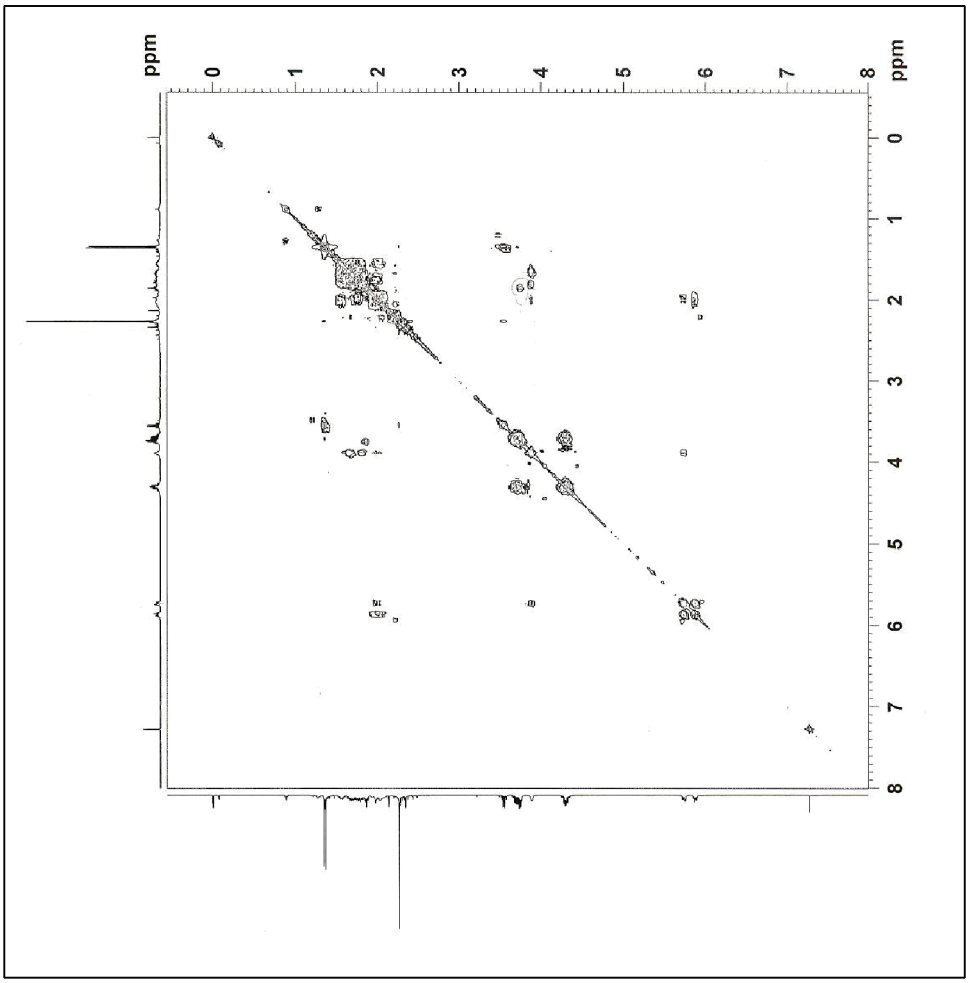


**Figure 86** COSY spectrum of compound **179**

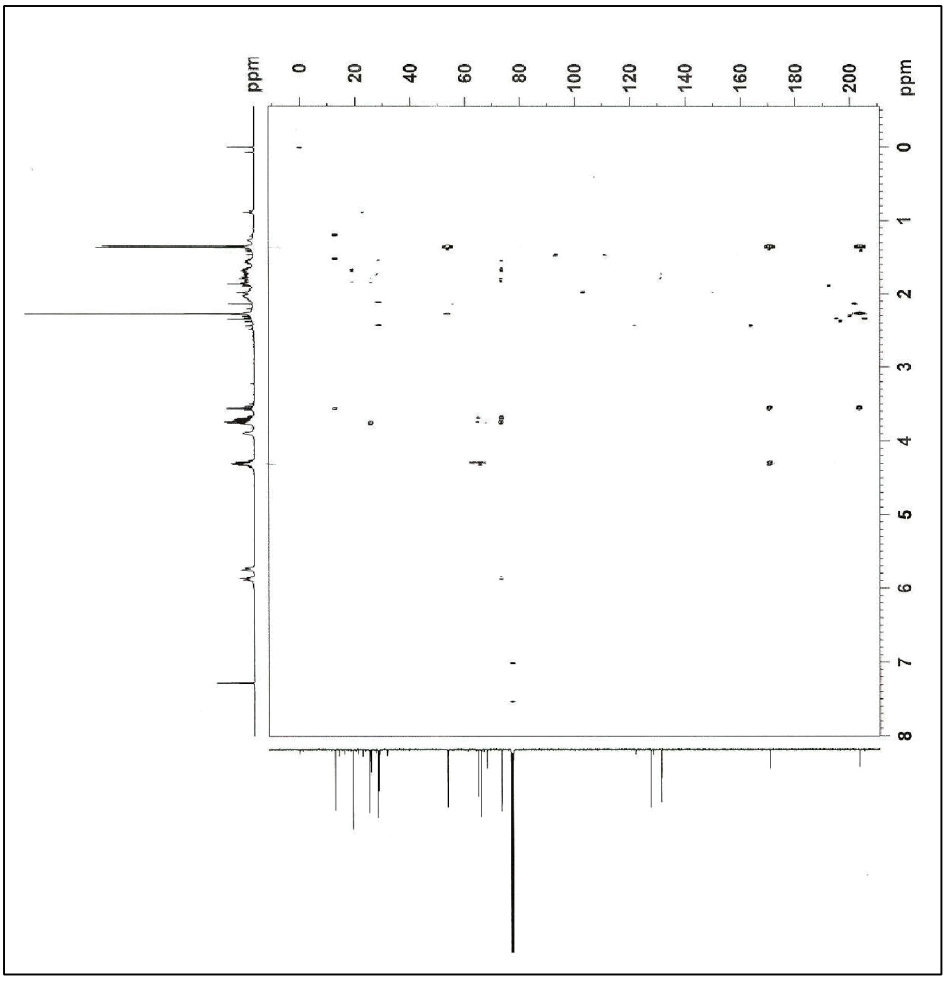


**Figure 87** HMBC spectrum of compound **179**

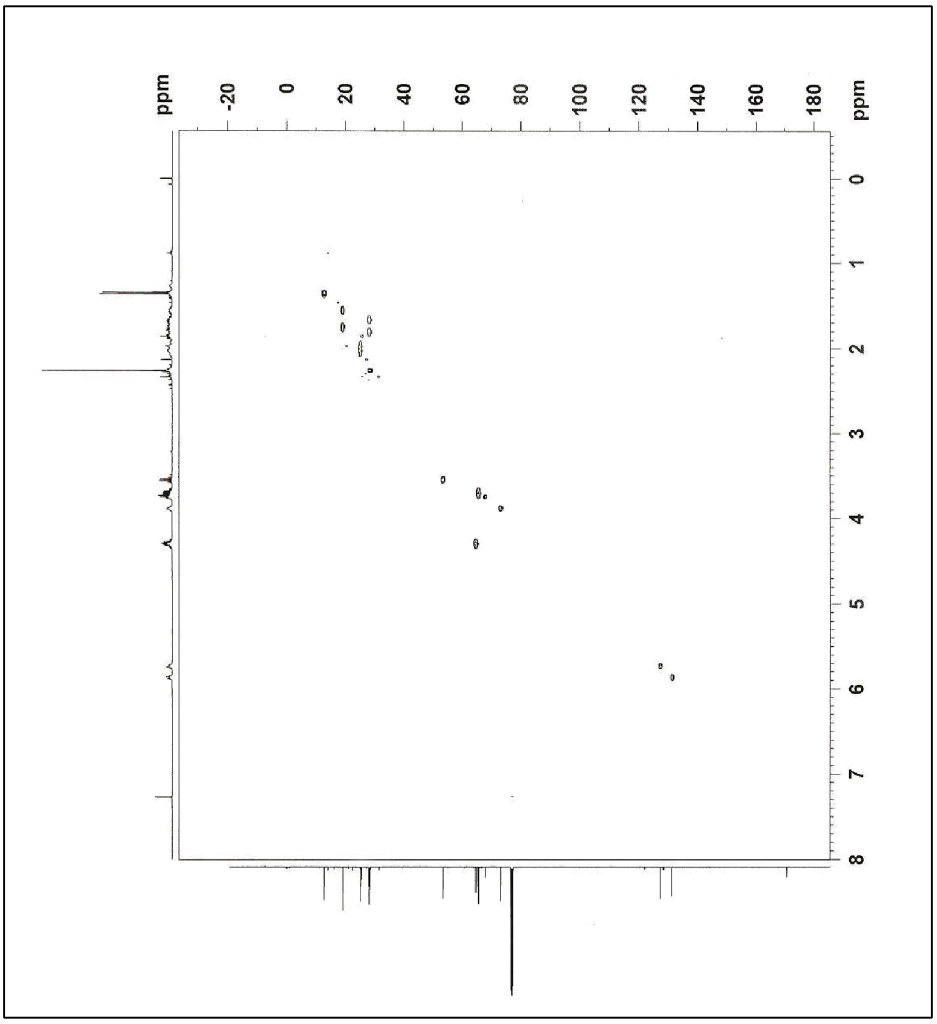


**Figure 88** HSQC spectrum of compound **179**

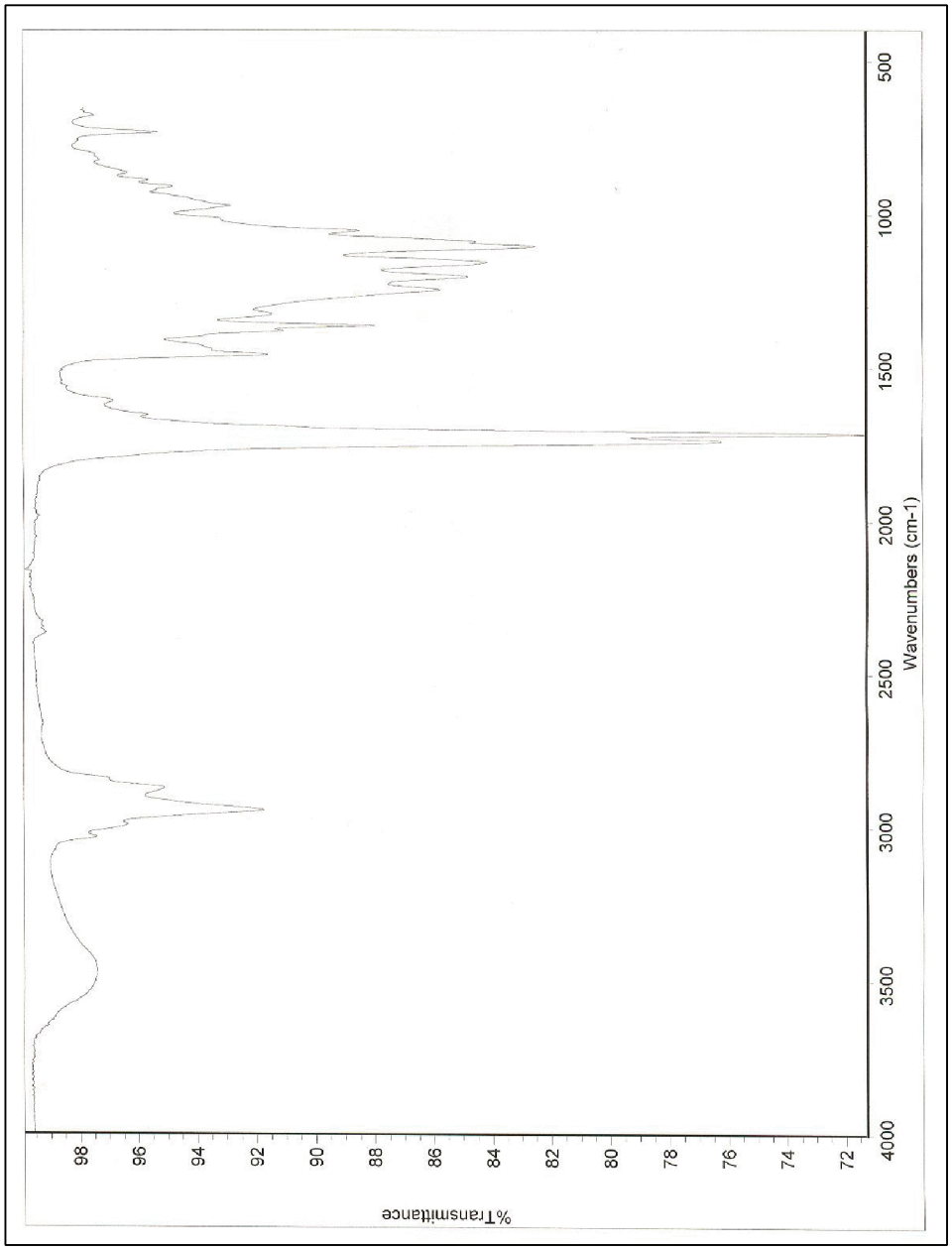


**Figure 89** IR spectrum of compound **179**

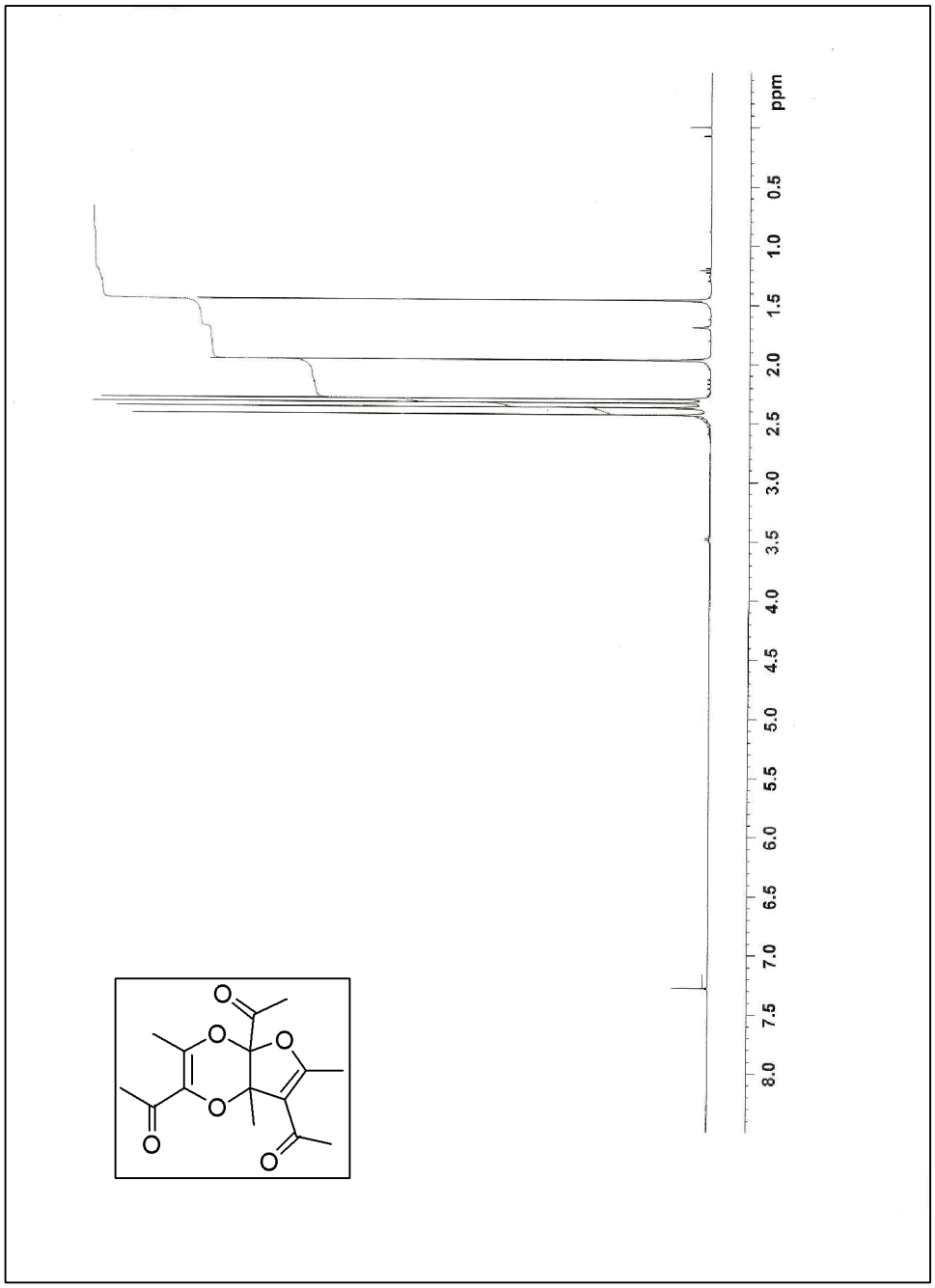


**Figure 90** $^{1}$H NMR spectrum of compound **182**

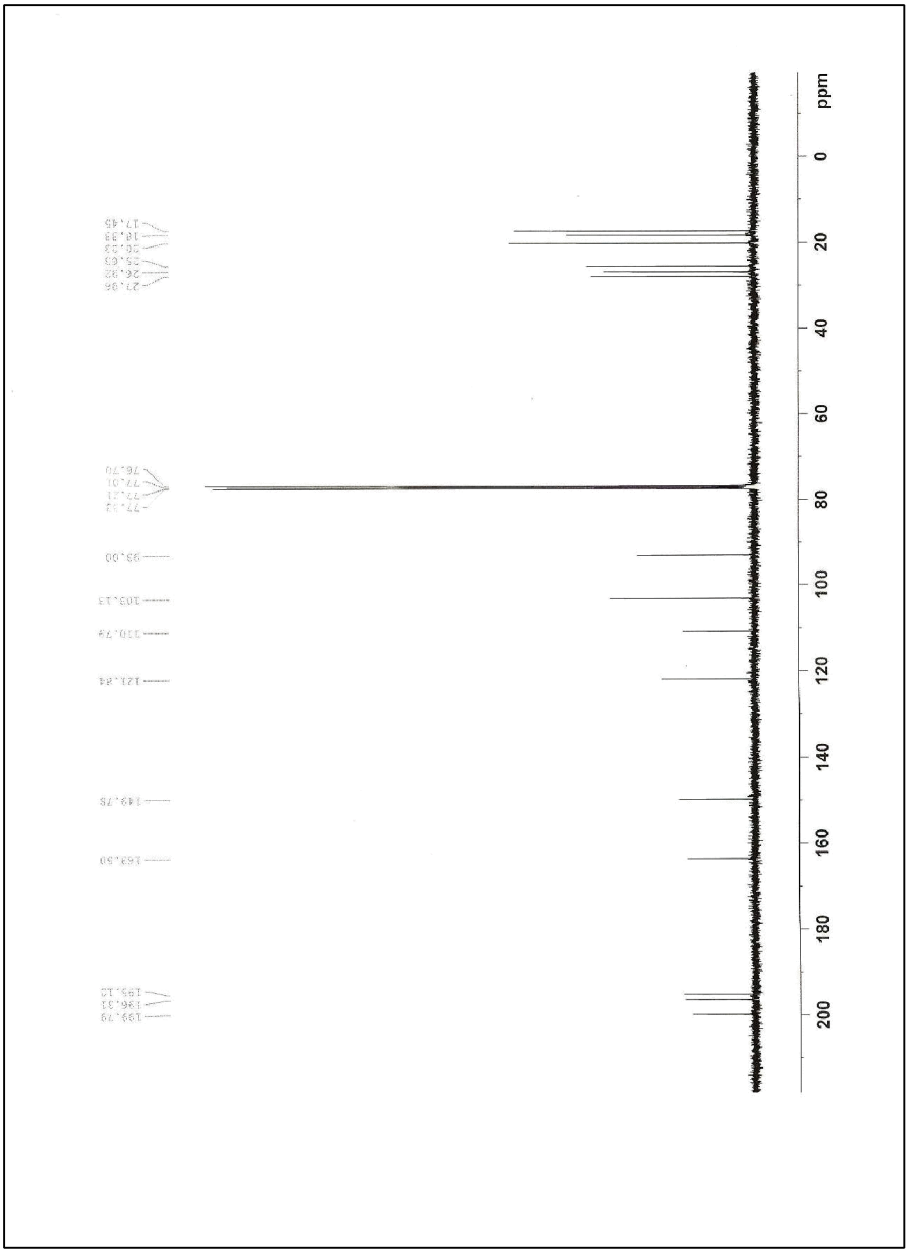


**Figure 91** $^{13}$C NMR spectrum of compound **182**

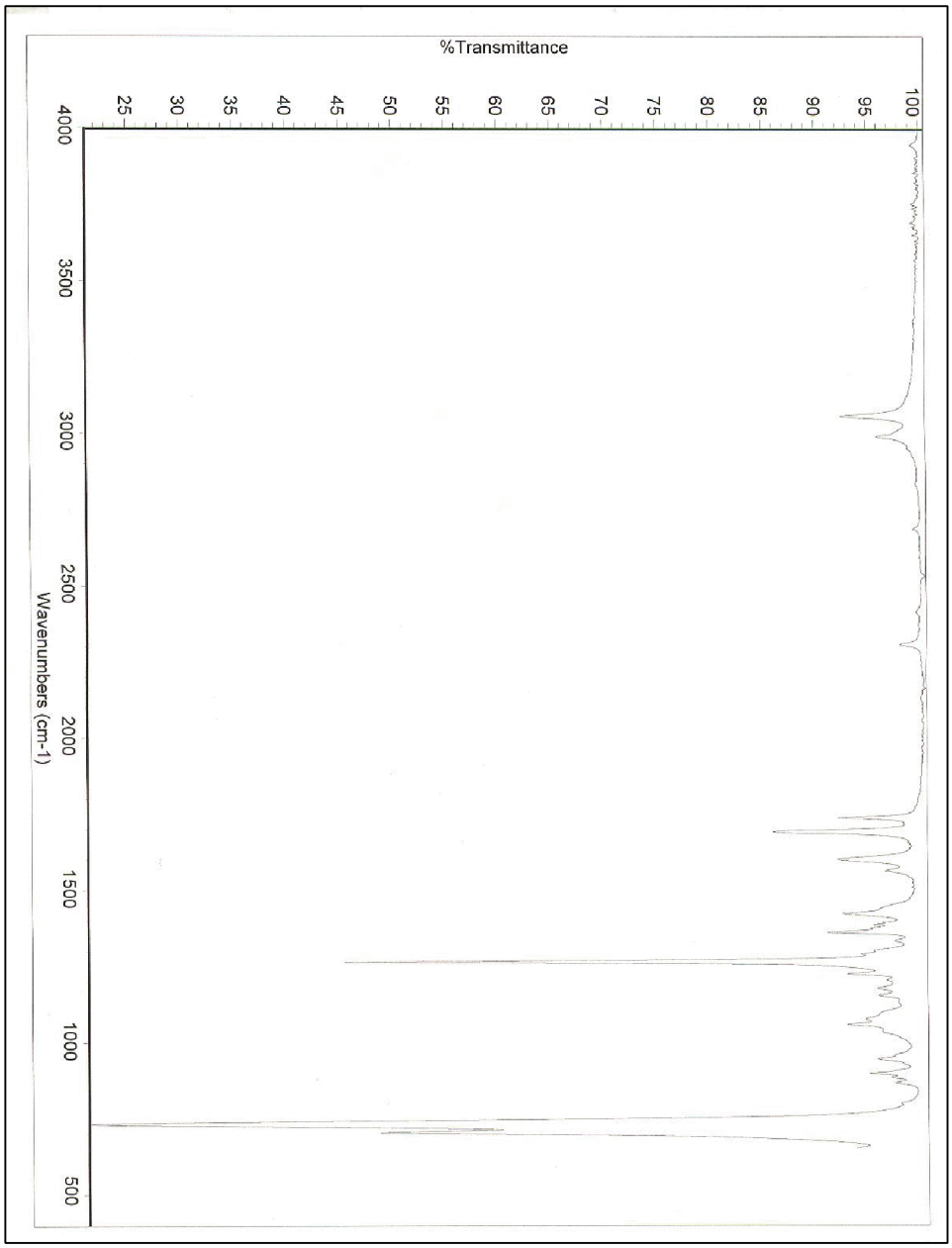


**Figure 92** IR spectrum of compound **182**

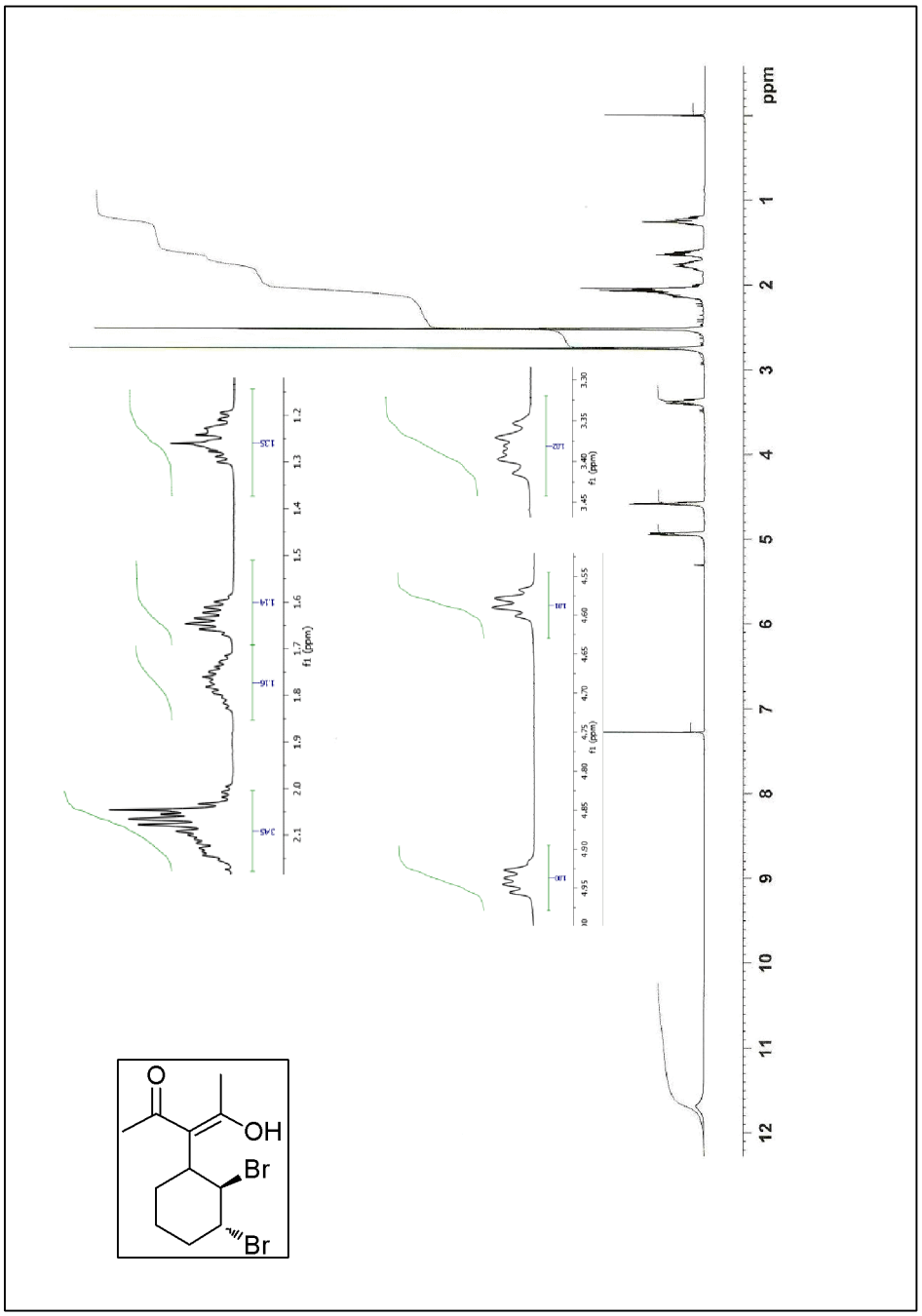


**Figure 93** $^{1}$H NMR spectrum of compound **187**

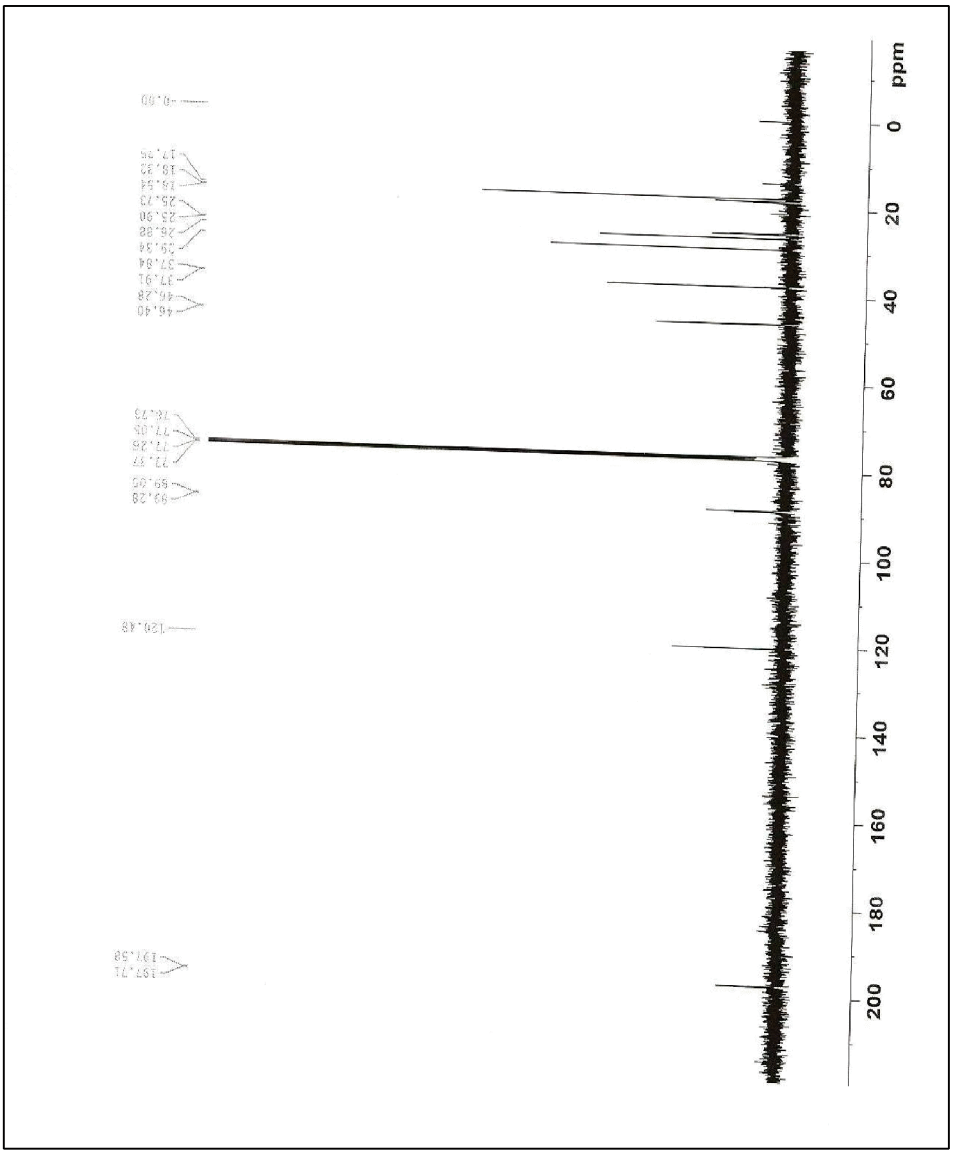


**Figure 94** $^{13}$C NMR spectrum of compound **187**

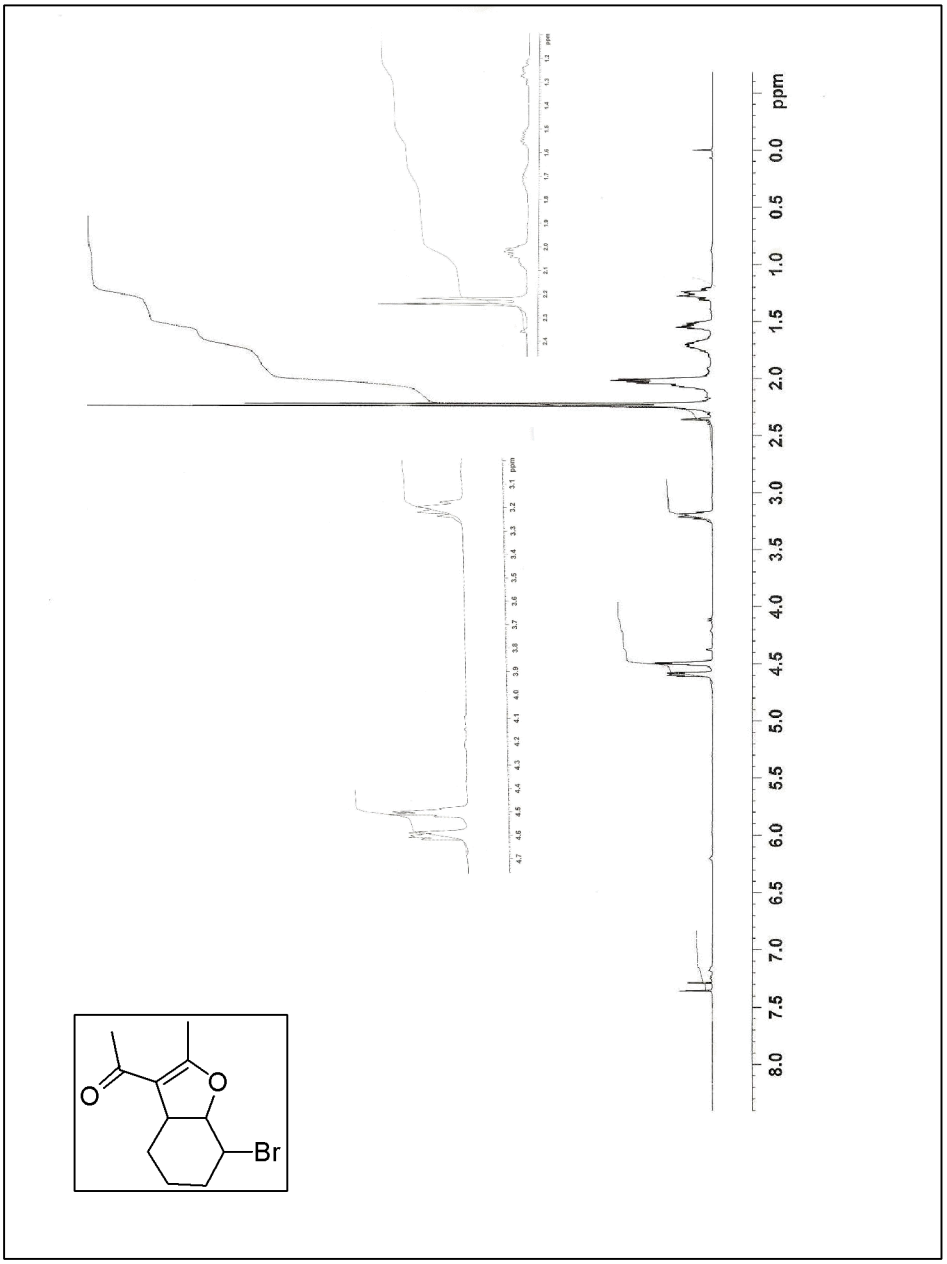


**Figure 95** $^{1}$H NMR spectrum of compound **188**

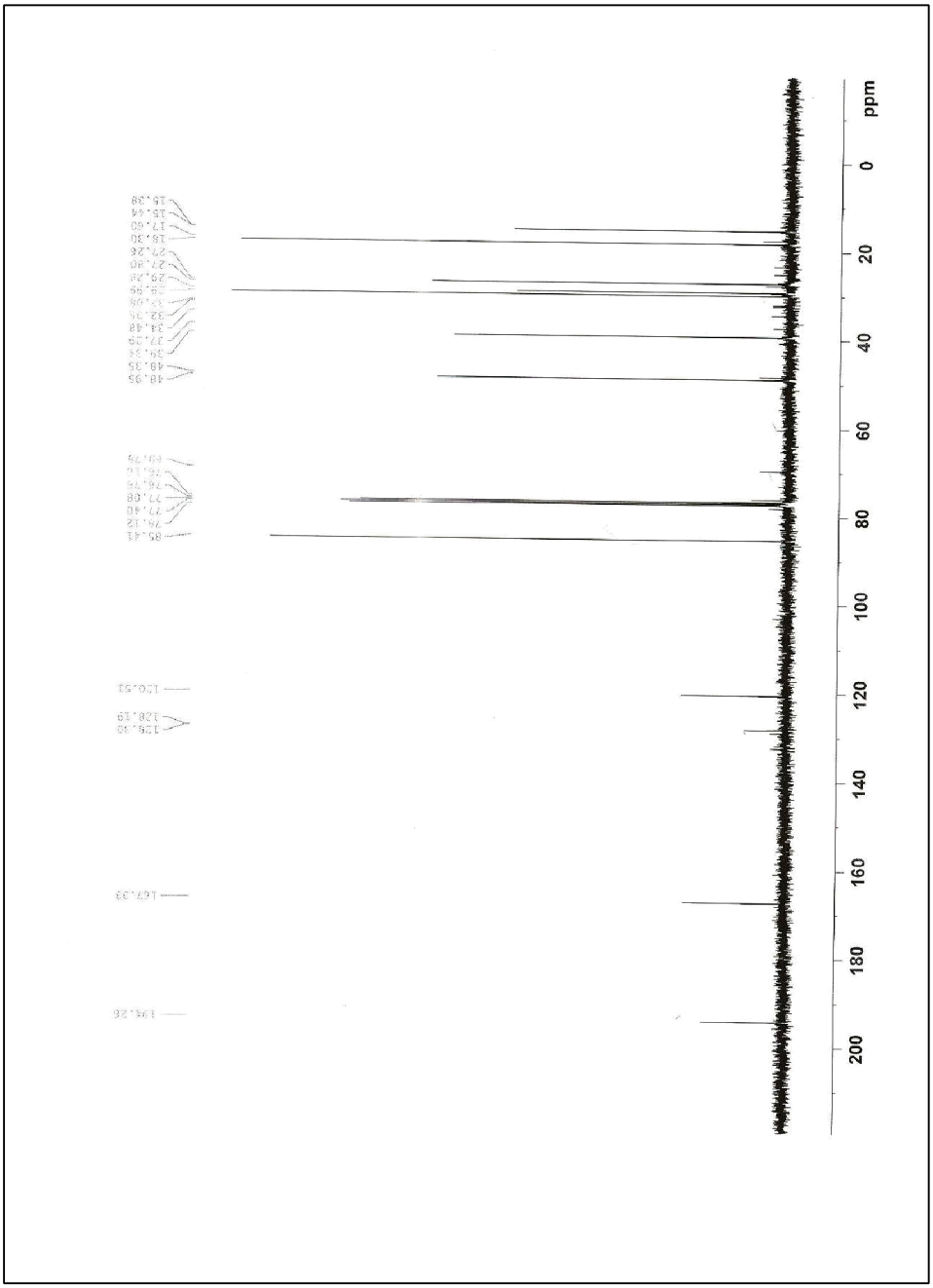


**Figure 96** $^{13}$C NMR spectrum of compound **188**

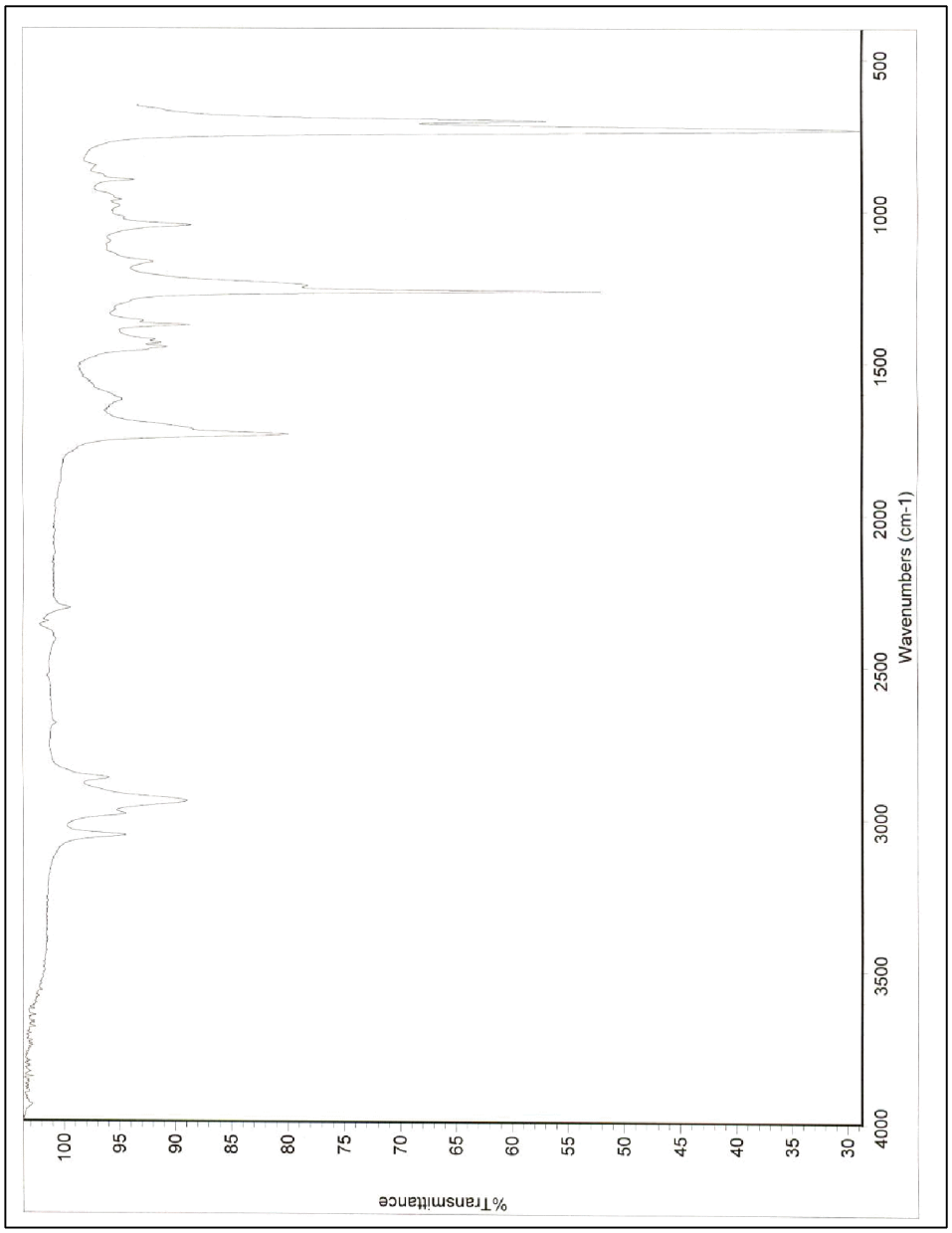


**Figure 97** IR spectrum of compound **188**