ADDITION OF CARBONYL COMPOUNDS TO THE CYCLIC OLEFINS: SYNTHESIS OF CYCLITOLS

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YASEMİN ALTUN

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ADDITION OF CARBONYL COMPOUNDS TO THE CYCLIC OLEFINS: SYNTHESIS OF CYCLITOLS

submitted by **YASEMİN ALTUN** in partial fulfillment of the requirements for the degree of **Master of Sciences in Chemistry Department, Middle East Technical University** by,

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

Prof. Dr. Ahmet M. ÖNAL _____
Head of Department, **Chemistry**

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

Examining Committee Members:

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

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

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

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

Assist. Prof. Dr. Raşit ÇALIŞKAN _____
Chemistry Dept., Süleyman Demirel University

Date: 31.10.2008

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

Name, Last name: Yasemin ALTUN

Signature

ABSTRACT

ADDITION OF CARBONYL COMPOUNDS TO THE CYCLIC OLEFINS: SYNTHESIS OF CYCLITOLS

Altun, Yasemin

M.S., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

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Cyclitols have attracted a great deal of attention in recent years owing to biological activities exhibited by them and also their usefulness in the synthesis of other natural products and pharmaceuticals. Carbasugars are also a derivative of cyclitols and they are cyclic monosaccharide analogues which posses $–CH_2OH$ group in their structure. In this study, novel synthetic strategies leading to cyclitol derivatives were investigated and the synthesis of tetraol (**72**) and pentaol (**73**) derivatives containing $–CH_2OH$ group were achieved successfully. Moreover, by the use of manganese(III) acetate oxidation reactions having considerable synthetic utilities in organic chemistry we developed new synthetic methodologies for the cyclitol derivatives. 1,3- and 1,4-Cyclohexadiene (**71** and **10**) were synthesized from easily available starting materials in order to be used as key compounds. The use of manganese(III) acetate oxidation reaction provides the creation of $–CH_2OH$ group and one of the hydroxyl groups and the remaining hydroxyl groups were introduced into the key compounds by the use of singlet oxygen reaction. As a result of this, we had considerable advance in the synthesis of cyclitol derivatives.

Keywords: Quercitols, tetraols, cyclitols, manganese(III) acetate oxidation, singlet oxygen.

ÖZ

KARBONİL BİLEŞİKLERİNİN SİKLİK OLEFİNLERE KATILMASI: SİKLİTOL TÜREVLERİNİN SENTEZİ

Altun, Yasemin
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Ekim 2008, 160 sayfa

Siklitoller, çeşitli biyolojik aktiviteleri ve bazı doğal bileşiklerin ve ilaçların sentezinde kullanılabilir olmaları nedeniyle son yıllarda büyük ilgi çekmektedir. Karbaşekerler de yapılarında $–CH_2OH$ grubu içeren monosakkarit benzeri yapılardır ve siklitol türevi bileşiklerdir. Bu çalışmada siklitol türevlerine ulaşabilmek için yeni sentetik yöntemler incelenmiş ve $–CH_2OH$ grubu içeren tetrol (**72**) ve pentol (**73**) türevleri başarıyla sentezlenmiştir. Bununla birlikte, organik kimyada oldukça önemli sentetik faydaları olan mangan(III) asetat oksidasyon reaksiyonlarının kullanımı ile siklitol türevleri için yeni sentetik yöntemler geliştirilmiştir. 1,3- ve 1,4-siklohekzadien (**71** ve **10**), oldukça kolay temin edilebilen başlangıç maddelerinden sentezlenip anahtar bileşikler olarak kullanılmışlardır. Hedef moleküllerdeki bir hidroksil ve $–CH_2OH$ grubu mangan(III) asetat oksidasyon reaksiyonu ile geri kalan hidroksil grupları singlet oksijen reaksiyonu ile takılmıştır. Sonuç olarak siklitol türevlerinin sentezinde büyük bir yol alınmıştır.

Anahtar Kelimeler: Quersitoller, tetroller, siklitoller, mangan(III) asetat oksidasyonu, singlet oksijen.

To my brother

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INTRODUCTION

1. 1 CYCLITOLS

Cyclitols are cyclic compounds which contain two or more hydroxyl groups, each attached to a different ring carbon atom [1]. Recently, cyclitols take great deal of attention, as these structural entities not only constitute important segments of a diverse range of natural products, e.g. antibiotics, but also exhibit promising biological activity profiles ranging from glycosidase inhibitors to antidiabetes and anticancer agents [2]. Some of the better known examples of cyclitols are conduritols (**1**), quercitols (**2**) and inositols (**3**).

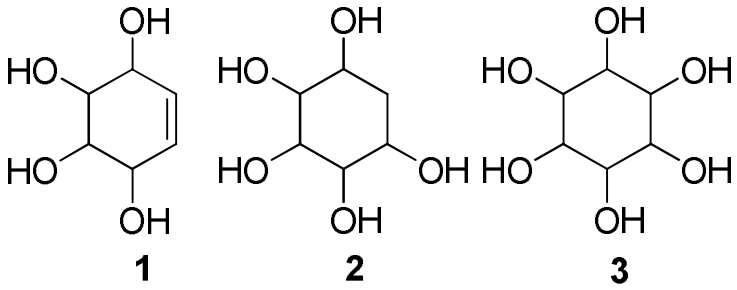


Figure 1 Cyclitol derivatives

1. 2 CONDURITOLS

Conduritols (**1**), 1,2,3,4-tetrahydroxycyclohexenes, constitute an important class of cyclitols due to their biological activities and synthetic role as starting material in the preparation of bioactive molecules, such as glycosidase inhibitors [3]. A number of conduritols and their derivatives have been found to possess antibiotic, antileukemic, and tumor-inhibitory effect [4]. Conduritol was firstly isolated from the bark of the vine *Marsdenia condurango* by Kübler in 1908. 30 years later, the constitution and configuration of this compound were established by Dangschat and Fischer to be conduritol-A. There are six possible diastereomers of conduritol and they have been labeled A, B, C, D, E and F assigned in the order of their discovery (Figure 2).

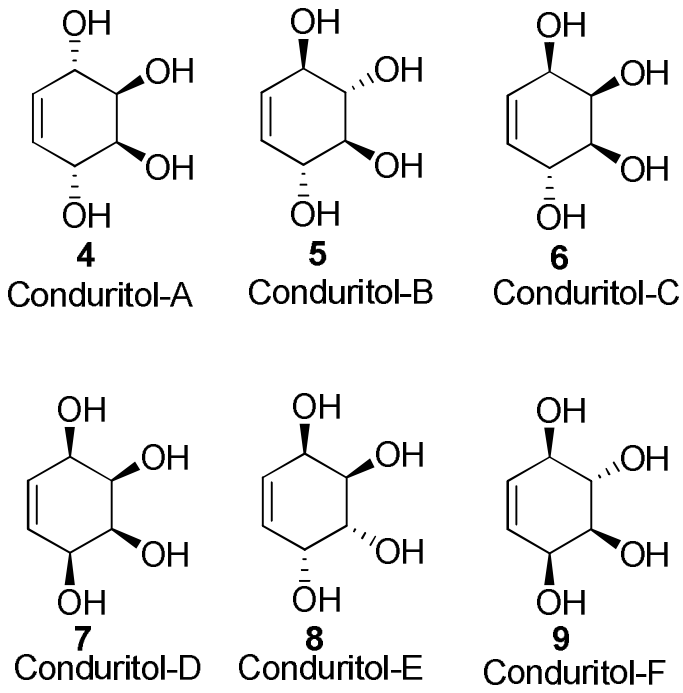


Figure 2 Conduritol diastereomers

Conduritol A and D are symmetrical; the others exist as enantiomeric pairs. The existence of only conduritols A and F have been established in nature [5].

All possible conduritol isomers have been synthesized and their biological importance has been studied. In this part, synthesis of the first conduritol derivative, conduritol-A (**4**) will be discussed as an example. The first successful but non-streospecific synthesis of conduritol-A was performed by Nakajima *et al.* starting from *trans*-benzenediol [5]. Twenty-five years later Knapp *et al*. performed the first stereospecific synthesis of conduritol-A from p-benzoquinone but in a multistep reaction chains. However, Balcı *et al*. showed an efficient and also stereoselective method for the synthesis of conduritol-A starting from readily available 1,4-cyclohexadiene (**10**). Their strategy was based upon the introduction of two oxygen functionalities at the C1 and C4 positions by photooxygenation of the diene, then applying of thiourea reduction for the cleavage of peroxide-linkage in **12** and subsequent hydrolysis [9].

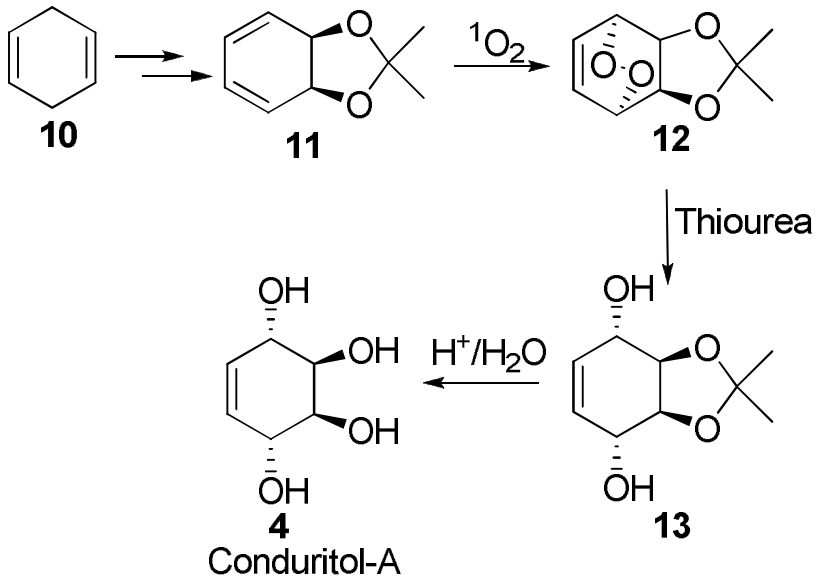


Figure 3 Synthesis of conduritol-A

1. 3 QUERCITOLS

As a generic term for cyclohexanepentol, quercitol has been used. The family of quercitols may be the largest all-known family of diastereoisomers in organic chemistry [6]. The structure of quercitol may exist in 16 stereoisomeric forms, of which 4 are symmetric, and the 12 others being classified in 6 pairs of optical mirror images. In nature only three optically active forms have been found so far. They only exist in plants; the two of them are (+)-*proto*-quercitol, (-)-*proto*-quercitol, and the other one is (-)-*vibo*-quercitol [7].

In 1849, (+)-protoquercitol was isolated from the acorns of an oak tree (genus *Quercus*) by Braconnot. Plouvier found (-)-*proto*-quercitol in 0.55% yield in the leaves of *Eucalyptus populnea*; (-)-*vibo*-quercitol, the third naturally occurring quercitol derivative, exists in many plants, including *gymnema sylvestre, stephania hernandifolia menispennum canadanse, especially vibumurn tinus* [7].

So far ten possible diastereomer for quercitols have been synthesized by many different methods and in all previously reported syntheses, starting materials were natural products or compounds that need many steps to synthesize [8].

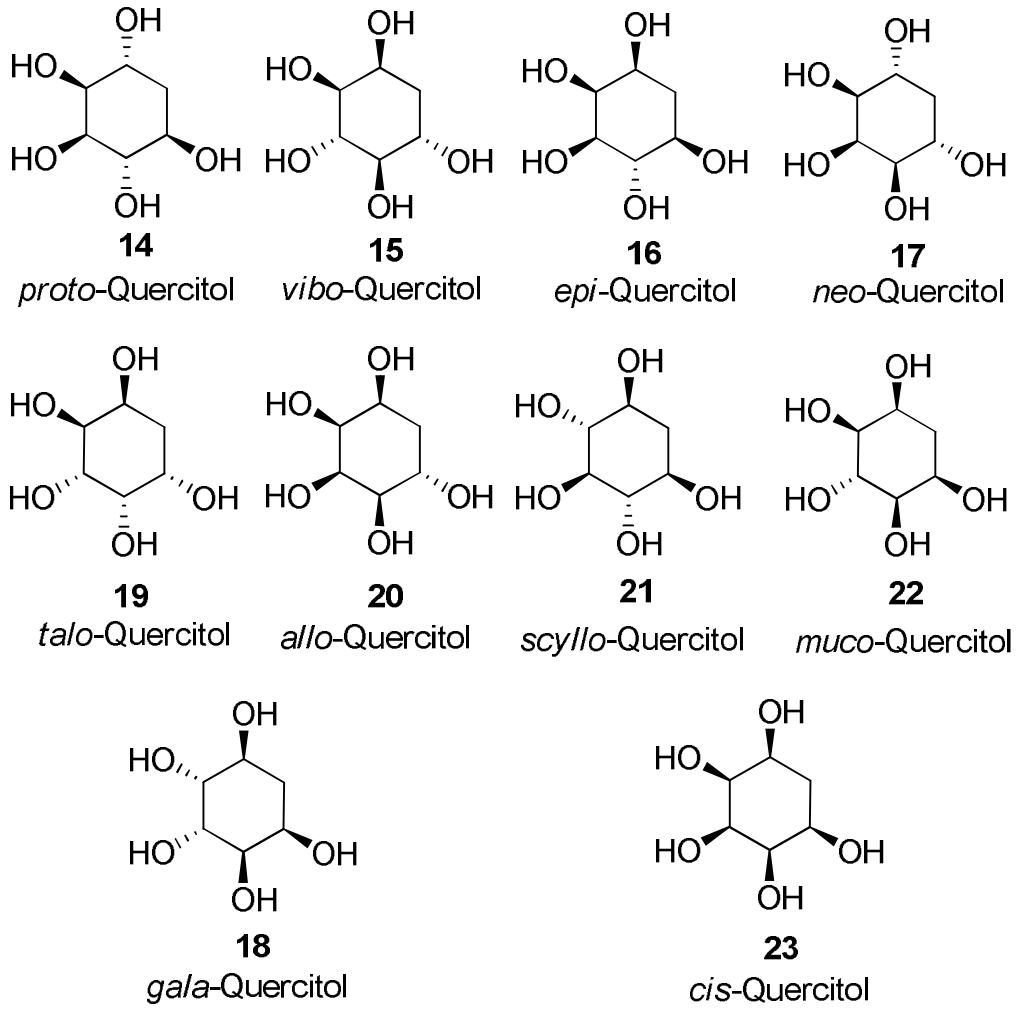


Figure 4 Quercitol stereoisomers

proto-Quercitol was successfully synthesized by McCasland using (-)- *chiro*-inositol. Suami started from DL-1,2-anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol whereas Cambie used conduritol-A as starting material. In all those syntheses, they used natural products as the starting materials or their starting materials required many steps to synthesize. Balcı *et al.* described a concise and convenient three step synthesis of *proto*- and *gala*-quercitols starting from commercially available 1,4-cyclohexadiene (**10**). Herewith a singlet oxygen ene reaction combined with the singlet oxygen [2+4] addition was applied to the synthesis of *proto*- and *gala*-quercitols successfully for the first time by Balcı and his coworkers [10].

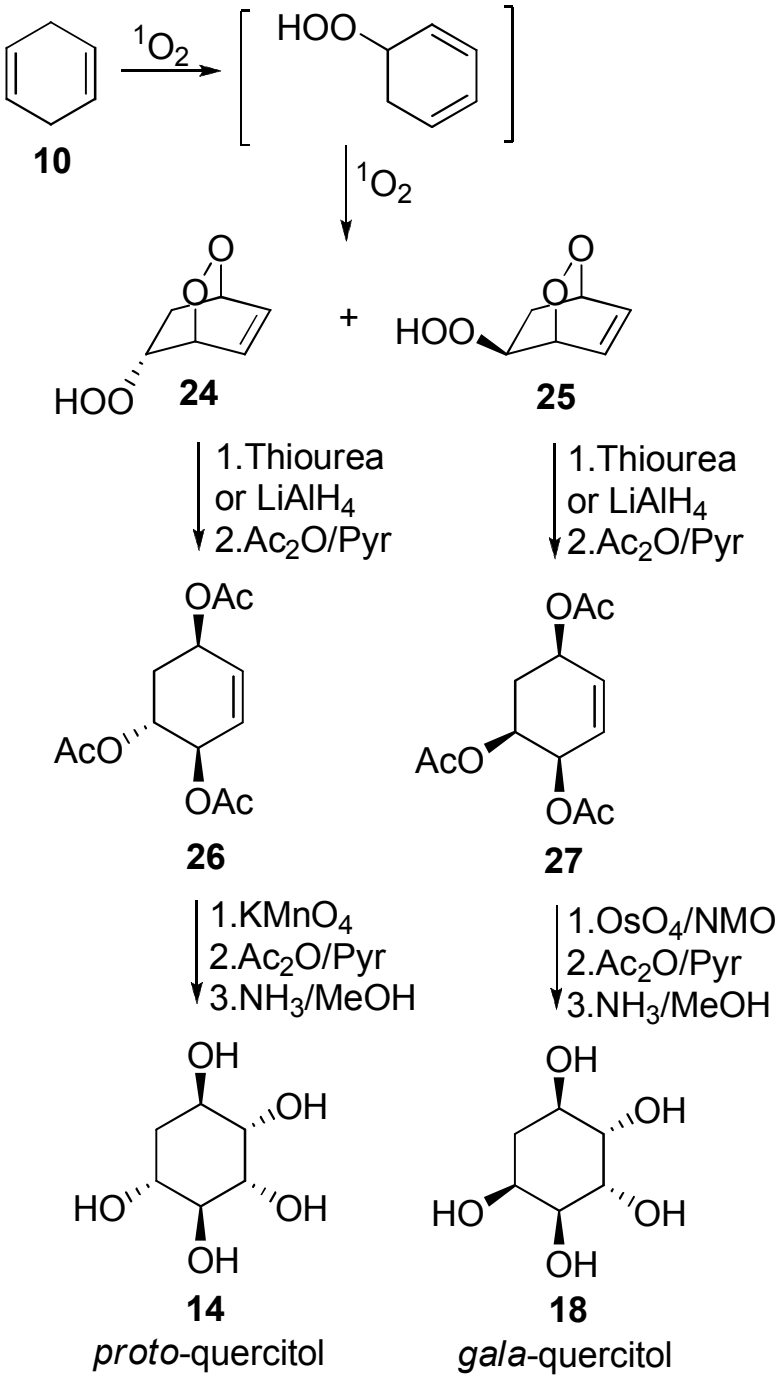


Figure 5 Synthesis of *proto*- and *gala*-quercitols

1. 4 INOSITOLS

In 1850, the first cyclohexanehexol was isolated from meat by Scherer, which was an optically inactive *myo*-inositol **(31)** isomer [11]. 'Inositol' has been used as a generic term for cyclohexanehexols. There are nine steroisomers predicted for inositols shown in Figure 6.

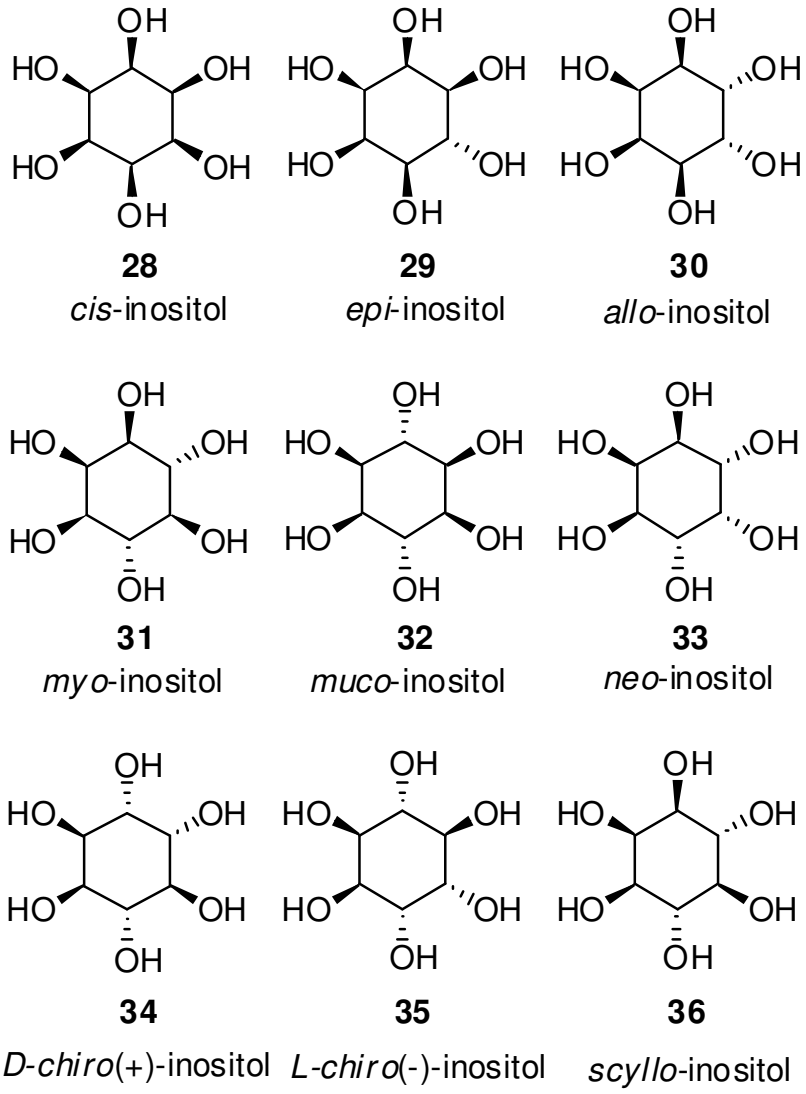


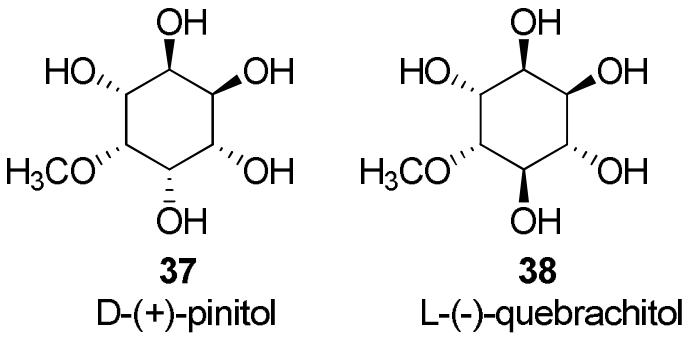
Figure 6 Inositol stereoisomers

All nine isomers are known and four isomers; *myo-, neo-, chiro-*, and *scyllo*-inositol have been recognized to occur in nature, while the other four are *cis-, epi-, allo-*, and *muco*-inositol are unnatural synthetic isomers [12].

Inositols have been prepared from halobenzenes, benzene, sugars, tetrahydroxyquinone, and transformation of conduritol [11]. Chung *et al.* accomplished the first general synthesis of six inositol streoisomers via conduritol intermediates [13].

The most widely distributed isomer is *myo*-inositol (**31**). It exists; both free and combined, in the tissues of nearly all living species. In animals and microorganisms the combined *myo*-inositol (**31**) is mostly present in the form of phospholipids.

The next mostly encountered inositol isomers are the optically active isomers D-(+)- and L-(-)-*chiro*-inositol (**34** and **35**). They are present in higher plants, mostly as the methyl ester, D-(+)-pinitol (**37**) and L-(-)-quebrachitol (**38**).



37 D-(+)-pinitol **38** L-(-)-quebrachitol

Figure 7 Some inositol isomers

cis-Inositol, with three *syn*-axial hydroxyl groups in its chair conformations, can form strong complexes with metal cations and with oxyacid anions. *scyllo*-Inositol has been isolated from animals and plants and it has been suggested that certain human diseases are associated with *scyllo*-inositol depletion [14].

Inositol phosphates became a major research theme in organic chemistry due to their biological roles. Various inositol phosphate derivatives, including D-*myo*-inositol 1,4,5-trisphosphate and D-*myo*-inositol 1,3,4,5-tetrakisphosphate and phospholipids play important roles in intracellular signal transduction events [14].

1. 5 CARBASUGARS

From 1966 to 1968, McCasland *et al.* synthesized a series of cyclitol derivatives in which the ring oxygen of a monosaccharide had been replaced by a methylene group [15] and they named the term *pseudosugars* for this family of compounds, however, now they are known as ***carbasugars***. They hypothesized that their structures resembles to the parent sugars and this resemblance provide them to recognize by enzymes or other biological systems in place of the related true sugars [17].

McCasland *et al.* prepared 5a-carba-α-DL-talopyranose **(39)** (the first reported carbasugar), 5a-carba-α-DL-galactopyranose **(40)** [15] and 5a-carba-β-DL-gulopyranose [16] **(41)** and 7 years later of those syntheses, 5a-carba-α-DL-galactopyranose was isolated as a true natural product from a fermentation broth of *Streptomyces* sp. MA-4145 [17].

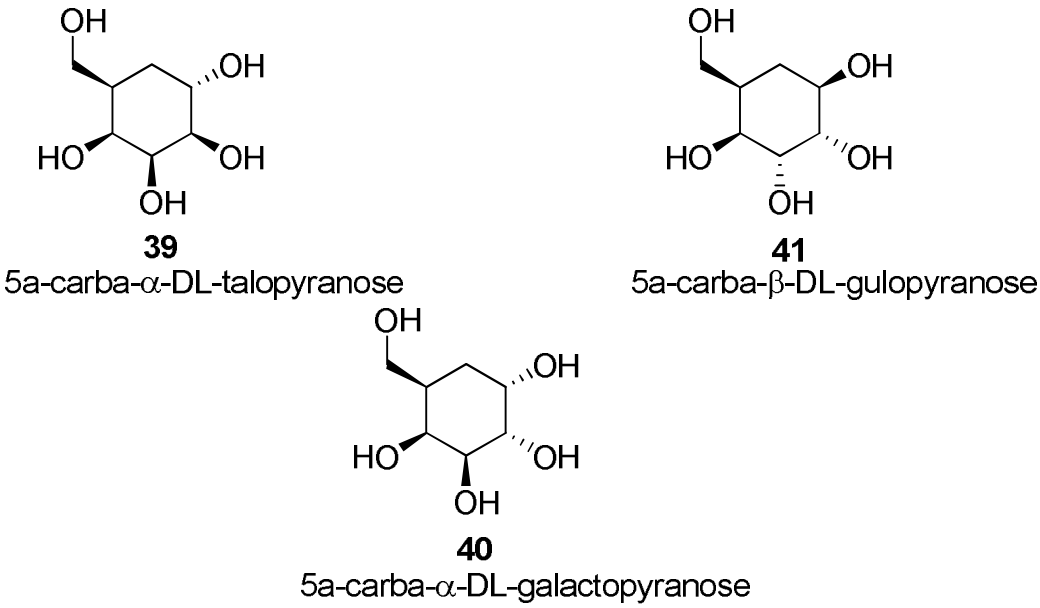


Figure 8 Racemic carbasugars prepared by McCasland *et al.* and the corresponding 'True' Sugars.

Carbafuranoses have not been encountered free in nature but are subunits of products isolated from natural sources, in particular carbanucleosides [17]. However, there are two five-membered cyclitol derivatives; caryose (**42**) [18] and calditol (**43**) [19] have been isolated as natural products and there are no other examples of five-membered carbocyclic carbohydrate analogues reported from natural sources [17].

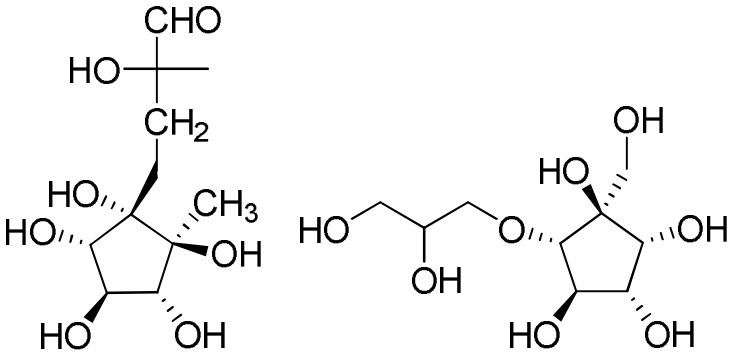


Figure 9 Naturally occurring carbafuranoses

The only information about the biological activity of carbafuranoses was that carboxylic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP) has an enzymatic inhibitory activity against the enzyme 5-phosphoribosyl-α-1-pyrophosphate (PRPP) synthetase. This enzyme reacts with ATP in the presence of Mg ion, to give PRPP, a compound involved in the biosynthesis of histidine and tryptophan [20].

Carbapyranoses have been found in nature rarely, but they are abundant as subunits of other natural products. Compounds such as carba-α-D-galactopyranose (**40**) [21], cyclophellitol (**44**) [22] (isolated from *Phellinus* sp.), or MK7607 (**45**) (isolated from *Cur*V*ularia eragestrides*) were isolated directly from natural sources, whereas aminocarbasugars such as valienamine (**46**) and validamine (**47**) have been mainly found as subunits of several, more complex molecules [17].

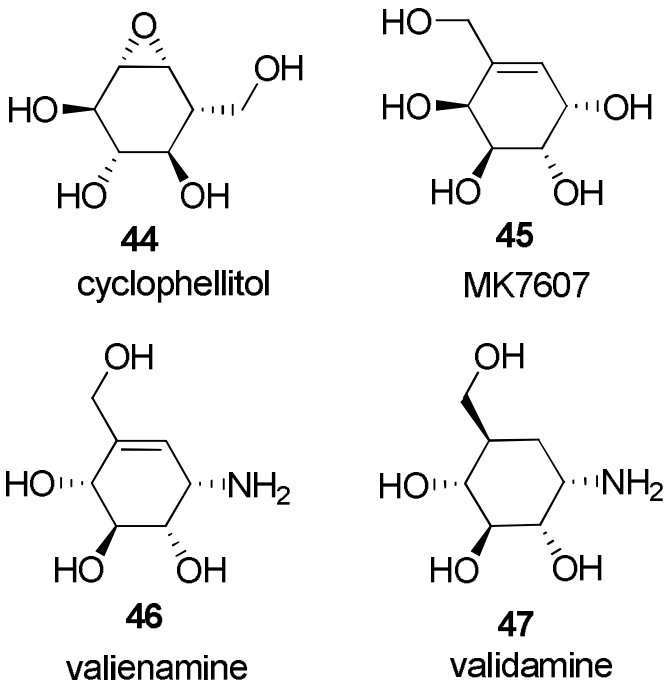


Figure 10 Naturally occurring carbapyranose and aminocarbapyranose derivatives

In 1966, McCasland anticipated that 'pseudo-sugars may be found acceptable in place of corresponding true sugars.' In this context, synthetic carba-β-DL-glucupyranose (**48**) and D-glucose are not able to be distinguished by taste, and synthetic 6a-carba-β-DL-fructopyranose (**49**) was found to be almost as sweet as D-fructose [17].

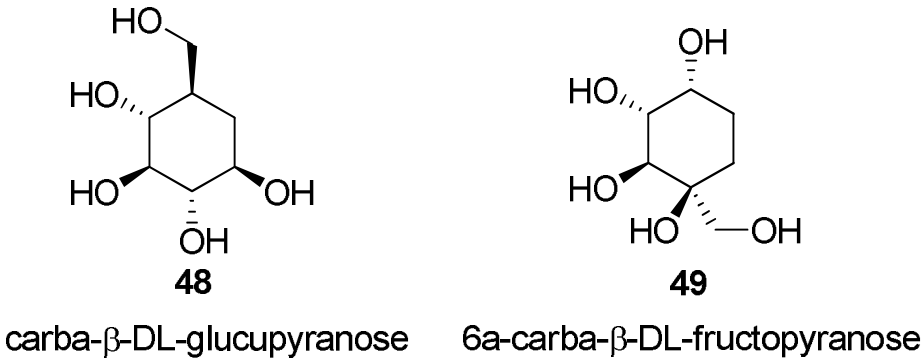


Figure 11 Racemic carbasugars (Only D-enantiomers are shown)

In addition, previously mentioned carbasugars such as cyclophellitol (**44**) and MK7607 (**45**) have relevant biological activities. Cyclophellitol has a potent inhibitory effect of β-glucosidases with potential inhibition of the human immunodeficiency virus (HIV) and with possible antimetastic therapeutic activity. The unsaturated carbapyranose (**45**) was found to have an effective herbicidal activity [23].

First reported carbasugar, 5a-carba-α-DL-talopyranose (**39**) was synthesized by McCasland using ketoacid **54** as the key intermediate [15]. The synthesis of compound **54** was previously performed by Daniels *et al.* based on a Diels-Alder reaction of 2-acetoxyfuran (**50**) and maleic anhydride (**51**) [24]. Applying hydroxylation and hydrolysis to the Diels-Alder adduct (**52**) gave diol diacid **53**. Diol diacid reacts with water and undergoes a series of transformations (acetyl migration, opening of the 1,4-oxacyclic ring, carbonyl liberation, and decarboxylation) leading to **54**. Sodium borohydride reduction of **54**, and subsequent esterification with methanol and trifluoroacetic acid, followed by acetylation gave the tetraacetate **55**, which was converted into target carbasugar **39**, by reduction with lithium aluminium hydride followed by hydrolysis [17].

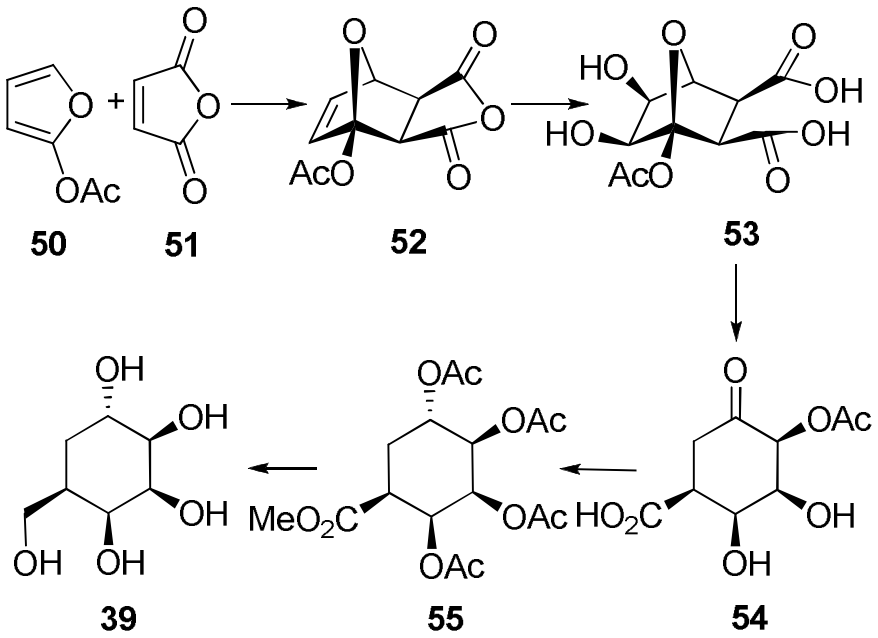


Figure 12 Synthesis of 5a-carba-α-DL-talopyranose

Mehta and co-workers has used bicyclo[2.2.1]heptane system to elaborate carbasugars and 'confused' carbasugars. According to the authors, 'confused' carbasugars have the same oxygenation level as carbasugars but the location of the hydroxymethyl and the 'para' hydroxyl groups are different. They synthesized 5a-carba-α-DL-talopyranose pentaacetate (**59**) and 'confused' carbasugar (**60**) starting from 7-ketonorbornane (**56**) which was prepared from *endo*-2-acetyoxy-7-nobornene ketal or derivatives [25].

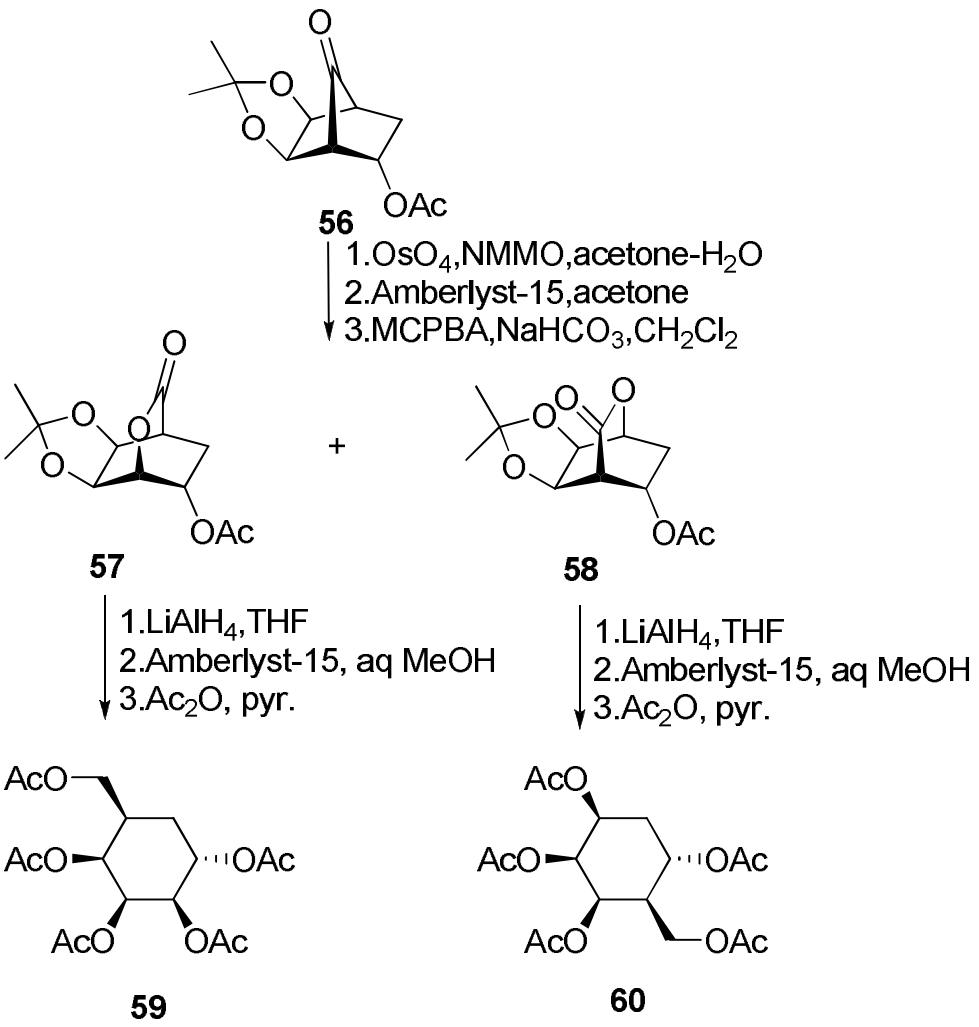


Figure 13 Synthesis of 5a-carba-α-DL-talopyranose and 'confused' carbasugar

1. 6 SINGLET OXYGEN

Although the existence of singlet molecular oxygen has been recognized since 1924, its chemistry has developed dramatically during the last four decades. Not only have chemists contributed to the exponentially growing chemistry of singlet oxygen, but other scientists such as biologists and biochemists have also shown substantial interest in this field. This interest has grown considerably since the recognition of the biochemical roles of the excited state of oxygen in certain blood diseases, in cancer-inducing mechanisms, in a possible free-radical like aging mechanism, in the role of bacterial activities of phagocytes, and in metabolic hydroxylation. In addition to

investigations into role of singlet oxygen in these phenomena and the mechanism of its reactions, its synthetic applications have also been explored and their utility has been demonstrated [26].

Singlet oxygen is most often generated in laboratory by *photosensitization reactions*. If certain molecules are illuminated with light of a given wavelength they absorb it and the energy raises the molecule into an excited state. The excitation energy can be transferred onto an adjacent oxygen molecule, converting it to the singlet state whilst the photosensitizer molecule returns to the ground state (Figure 14)

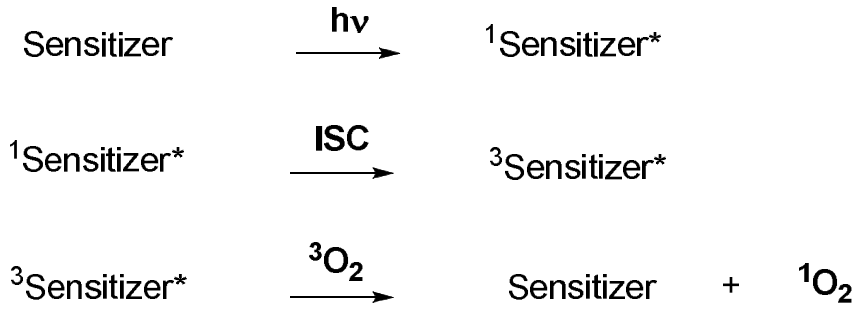


Figure 14 Formation of singlet oxygen with sensitizer

The most important step in the formation of singlet oxygen by energy transfer is annihilation of triplet oxygen with triplet sensitizer and it is called triplet-triplet annihilation. The sensitizers must have lower ability to the oxidation with themselves and their triplet energies must be bigger than the energies of the two states of singlet oxygen.

There are some other chemical methods for generating singlet oxygen in solution including the reaction of hydrogen peroxide with sodium hypochlorite, the thermolysis of triaryl phosphite ozonides, and the decomposition of 9,10-diphenylanthracene peroxide and the dye-synthesized photochemical excitation of triplet oxygen [27]. The latter technique is, by far the most efficient method and has been employed in the vast majority of synthetic applications of singlet oxygen. The

mechanism for generating singlet oxygen involves the excitation of an appropriate dye (such as Rose Bengal, methylene blue etc.) with visible light to form the corresponding excited singlet state. Rapid intersystem crossing generates the excited triplet state of the sensitizer which undergoes an energy transfer with triplet oxygen to form singlet oxygen, generating the ground state sensitizer.

The three most common modes of reaction of singlet oxygen with olefins are the ene reaction of leading to a hydroperoxide, the Diels-Alder type of cycloadditon forming an endoperoxide and the direct addition of $^1O_2$ to an activated double bond resulting in the formation of a 1,2-dioxetane. All three types of singlet oxygen reaction have been utilized in organic synthesis for the regiospecific and stereoselective oxidation of olefins [27].

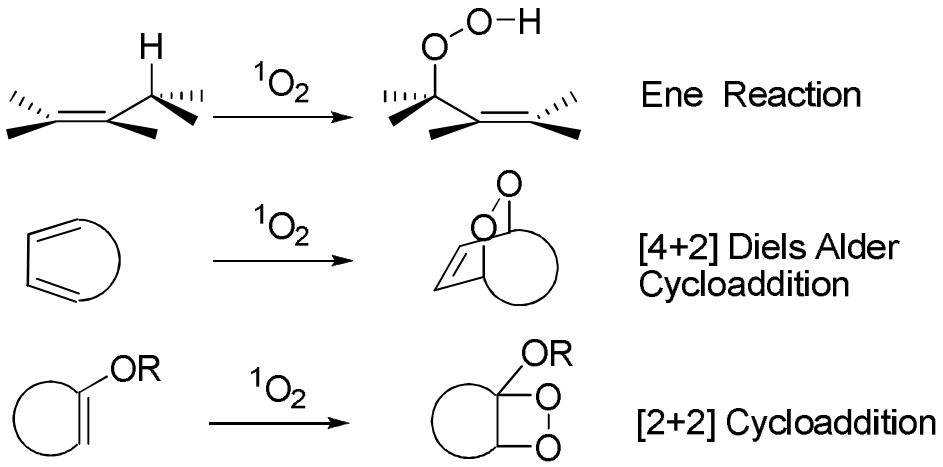


Figure 15 Types of singlet oxygen reactions

1. 7 MANGANESE (III) ACETATE OXIDATION REACTIONS

According to an X-ray study, anhydrous manganese (III) acetate is an oxo-centered triangle of three manganese atoms held together by six bridging acetate ligands. A

single manganese (III) acetate unit can perform up to three sequential one-electron oxidations of a substrate while each Mn (III) is reduced to Mn (II) [28].

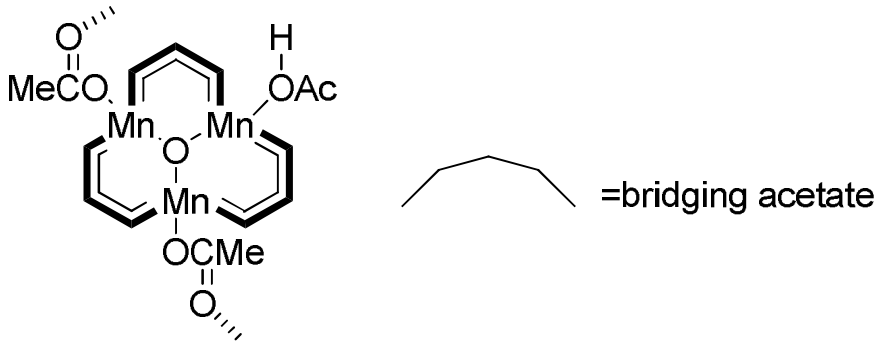


Figure 16 A single manganese (III) acetate unit

Heiba and Dessau and 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. Refluxing the one-electron oxidant $Mn(OAc)_3$ in acetic acid at 115°C produces the carboxymethyl radical **62**. This adds to alkenes to give a radical, which is oxidized by a second equivalent of $Mn(OAc)_3$ to give γ-lactone **64** [29][30].

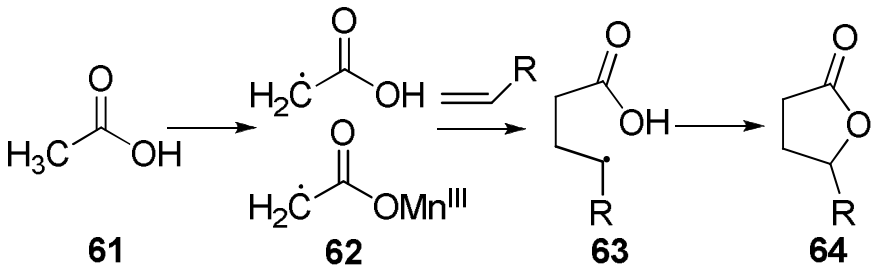


Figure 17 General demonstration of lactonization with $Mn(OAc)_3$

Unfortunately, unsaturated acids do not give oxidative cyclization reactions by the oxidation of Mn (III) since the optimal solvent for this reaction; acetic acid will be oxidized preferentially.

Heiba and Dessau investigated in 1974 that β-keto esters and related dicarbonyl compounds are oxidized to radicals at 25-70^{o}C in acetic acid. The oxidation of ethyl acetoacetate in the presence of styrene results in a dihydrofuran **68** [29].

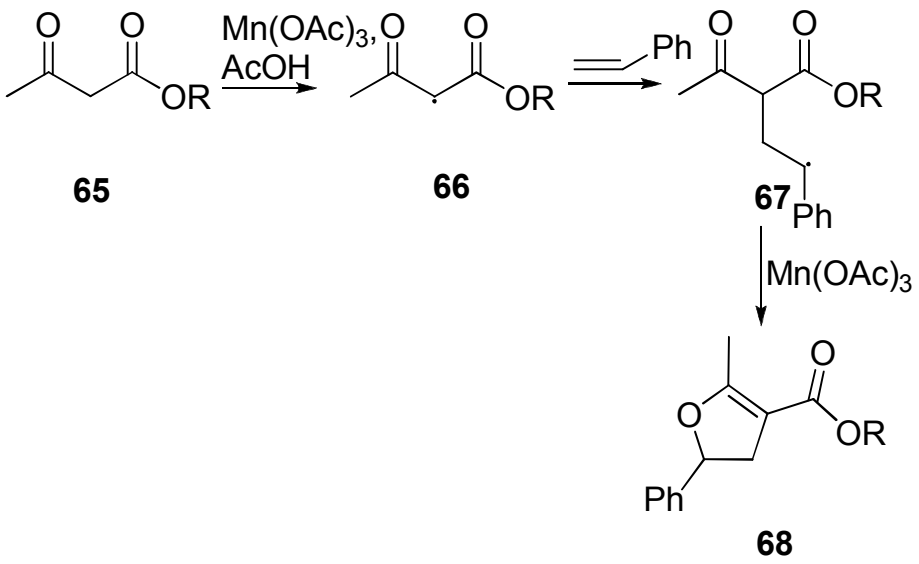


Figure 18 Synthesis of a kind of dihydrofuran by the oxidation of $Mn(OAc)_3$

The application of Mn (III) to oxidative free-radical cyclizations 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 have been named as his own name 'Corey Lactones'. By the oxidative cyclization of β-keto acid **69,** lactone **70** was obtained in 63% yield [31].

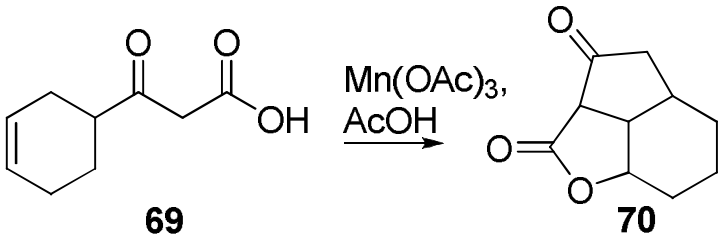


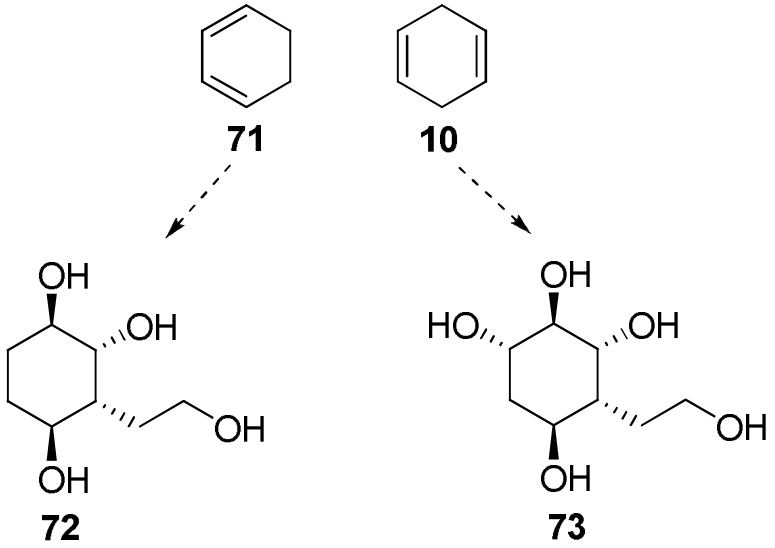
Figure 19 Synthesis of 'Corey Lactone'

1. 8 AIM OF THE STUDY

Cyclitols have attracted a great deal of attention from the synthetic community due to their glycosidase inhibition activities and their versatility as synthetic intermediates. Carbasugars are also a derivative of cyclitols and they are cyclic monosaccharide analogues in which the endocyclic oxygen atom is replaced by a methylene group. As a result of this substitution, they are hydrolytically stable analogues of their parent sugars towards degradation by glycosidases.

Our aim was to develop a synthetic methodology leading to the formation of cyclitols **72** and **73**. In these compounds; the endocyclic oxygen atom replaced by a methylene group and this creates a similarity with carbasugars. Owing to the importance of these compounds our aim is to develop a new and short strategy based on $Mn(OAc)_3$ oxidation reaction and singlet oxygen reaction for the synthesis of cyclitol derivatives. In our target molecules, $–CH_2OH$ group and one hydroxyl group are created with applying $Mn(OAc)_3$ oxidation reaction and the other hydroxyl groups are coming from the singlet oxygen reaction.

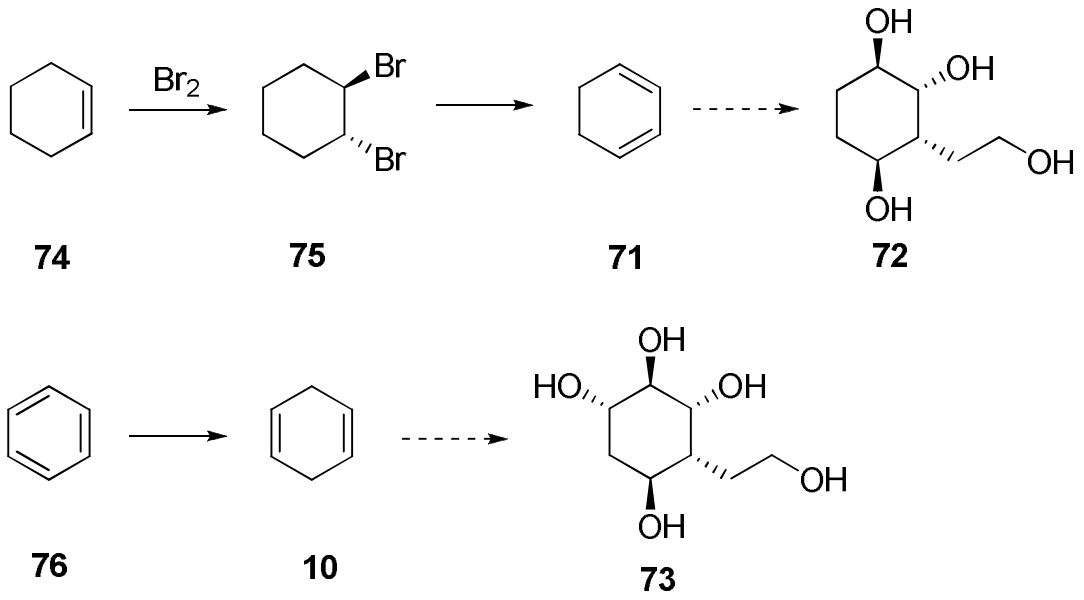
1,3- and 1,4-cyclohexadiene (**71** and **10**) are aimed to be the key compounds and the corresponding target compounds are shown below.



CHAPTER 2

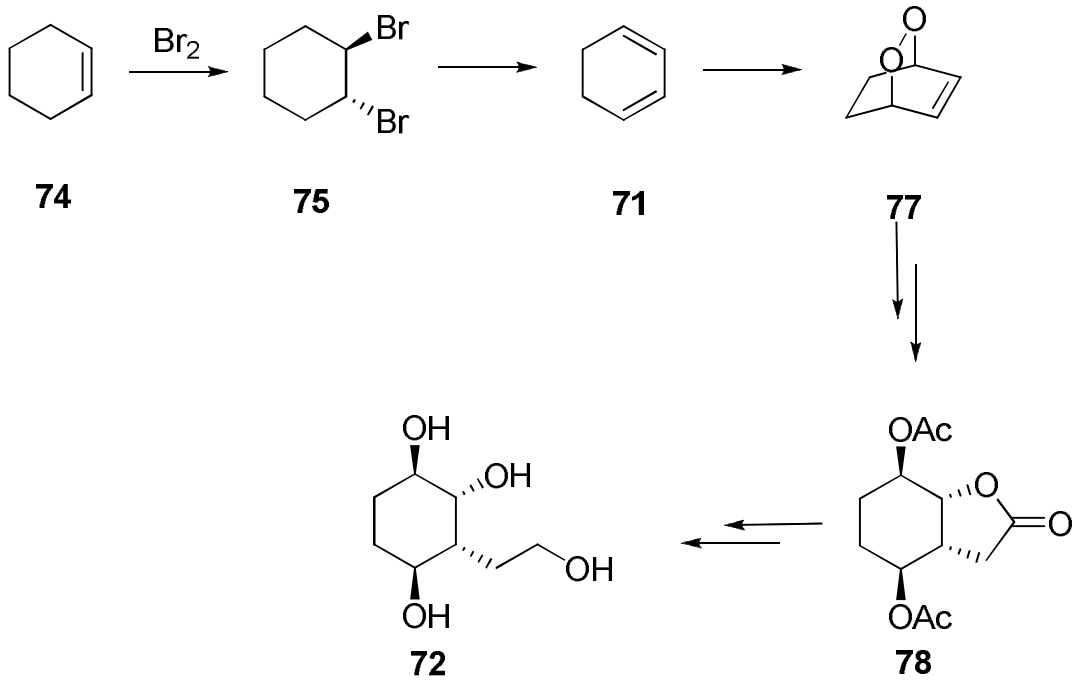
RESULTS AND DISCUSSION

For the synthesis of cyclitol derivatives **72** and **73**, commercially available and inexpensive starting materials such as cyclohexene (**74**), benzene (**76**) and bromine were used. In our synthetic strategy, the compounds 1,3- and 1,4-cyclohexadiene (**71** and **10**) were planned to be the key compoundst. The introduction of oxygen moiety into our key compounds were provided by applying manganese(III) acetate and singlet oxygen reactions.



2.1 SYNTHESIS OF 3-(2-HYDROXYETHYL) CYCLOHEXANE-1,2,4-TRIOL (TETRAOL DERIVATIVE) (72)

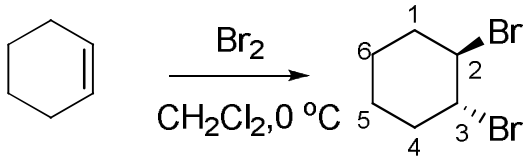
To obtain the target compound, key compound **71** was synthesized for the application of Diels-Alder type singlet oxygen reaction to introduce two hydroxyl groups in molecule **72**. After performing singlet oxygen reaction, a double bond remained so that the introduction of hydroxyethyl group and another hydroxyl group was achieved by using $Mn(OAc)_3$ oxidation reaction. As a consequence, the following synthetic route was developed.



2.1.1 Synthesis of 1,3-Cyclohexadiene (71)

The compounds including 1,3-diene unit are very useful precursors for the synthesis of cyclitol derivatives. Moreover, to posses this unit in the molecule has a great importance since we aimed to use [4+2] cycloaddition reaction of singlet oxygen basically. That is why 1,3-cyclohexadiene (**71**) was our first key compound.

The key compound **71** was synthesized by bromination of cyclohexene (**74**) and subsequent dehydrobromination. Initially, bromine was added to cyclohexene (**74**) dropwise at 0 ^{o}C and pure *trans*-1,2-dibromocyclohexane (**75**) was obtained in a yield of 92%.

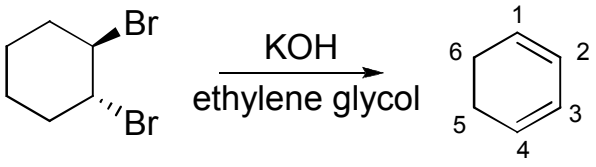


74 **75**

The product could easily be identified with ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectrum of compound **75** consists of multiplets at 4.45 ppm for H_2 and H_3, at 2.48 and 1.90 ppm for H_1 and H_4, at 1.82 and 1.52 ppm for H_5 and H_6 protons.

The ^{13}C NMR spectrum was also consistent with the structure. There are three different carbons which resonate at 55.1, 31.9 and 22.4 ppm.

Secondly, to obtain **71,** dehydrobromination of **75** with KOH was performed.

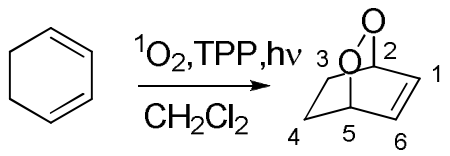


75 **71**

The ^{1}H NMR spectrum of diene **71** was consistent with the structure. Olefinic protons resonate at 5.89-5.87 and 5.80-5.77 ppm as two separated multiplets. There also exists a broad singlet at 2.14 ppm arising from H_5 and H_6.

2.1.2 Synthesis of 2,3-dioxabicyclo[2.2.2]oct-5-ene (77)

To introduce two oxygen functionalities in the 1,4-positions of compound **71** a Diels-Alder type cycloaddition reaction was performed. Photooxygenation reaction was applied to 1,3-cyclohexadiene (**71**) by using a sensitizer, tetraphenylporphyrin (TPP), and the endoperoxide **77** was formed.



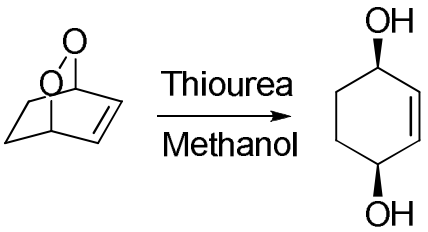
71 **77**

In ^{1}H NMR spectrum of **77**, the two equivalent olefinic protons (H_1 and H_6) resonate as quasi triplet at 6.59 ppm and the two bridgehead protons (H_2 and H_5) give a broad singlet at 4.56 ppm. There is also an AA′BB′ system corresponds to four methylenic protons.

In ^{13}C NMR spectrum, there are three different carbon resonances. The olefinic carbons, the bridgehead carbons and the methylene carbons resonate at 131.6, 70.2 and 21.1 ppm, respectively.

2.1.3 Synthesis of cyclohex-2-ene-1,4-diol (79)

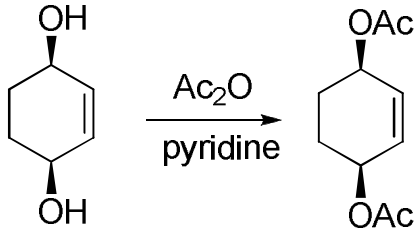
Bicyclic endoperoxides can be readily reduced by lithium aluminum hydride or thiourea to give 2-ene-1,4-diols. Catalytic hydrogenation normally leads to further reduction to 1,4-diols. Thiourea reduction has some advantages over both catalytic hydrogenation and lithium aluminum hydride reduction in that it reduces only the oxygen-oxygen bond thus preserves most other functional groups in the molecule [26]. As a result, thiourea reduction was applied to the endoproxide **77** in methanol and *cis*-diol **79** was obtained.



77 **79**

2.1.4 Synthesis of cyclohex-2-ene-1,4-diyl diacetate (80)

Acetylation of hydroxyl groups in compound **79** was performed with acetic anhydride in the presence of pyridine.



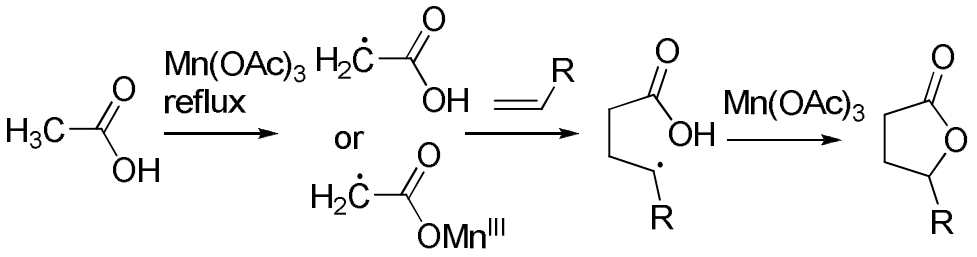
79 **80**

The resulting diacetate **80** was characterized on the basis of ^{1}H NMR spectrum and it is consistent with the structure. The olefinic protons resonate at 5.88 ppm as a broad singlet. The protons which are attached to the carbon atom bearing acetate groups resonate as singlet at 5.19 ppm. The two acetate's methyl groups give a singlet at 2.03 ppm and finally there is a multiplet between 1.79-1.90 ppm resulting from the two methylenic protons.

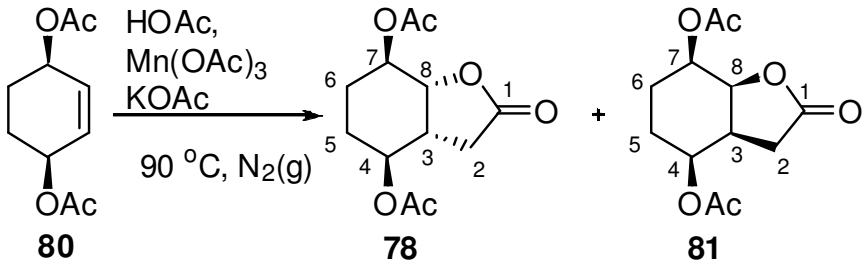
In addition, ^{13}C NMR spectrum also reveals the consistency of the structure. The peak at 170.4 ppm belongs to the carbonyl carbons and the peak at 130.2 ppm belongs to olefinic carbons. There are three other peaks which are carbons next to oxygen atom at 67.2 ppm, methylene carbons at 24.7 ppm and acetate methyl's at 21.2 ppm.

2.1.5 Application of Manganese(III) acetate Oxidation to cyclohex-2-ene-1,4-diyl diacetate (80)

It has been known for some time that manganese (III) acetate in acetic acid at reflux converts a variety of olefins to γ-lactones [31].



In order to provide -CH_2OH functionality in molecule **72**, $Mn(OAc)_3$ oxidation reaction was applied to compound **80** in the presence of acetic acid and potassium acetate at 90 ^oC and two different lactones **78** and **81** were obtained.



The formation ratio of the lactones **78** and **81** is 7:3 and this ratio results from stereochemistry of the acetate groups. Since they are in axial-equatorial positions and creating a steric hindrance, the addition from the backside of the acetate groups is more preferable.

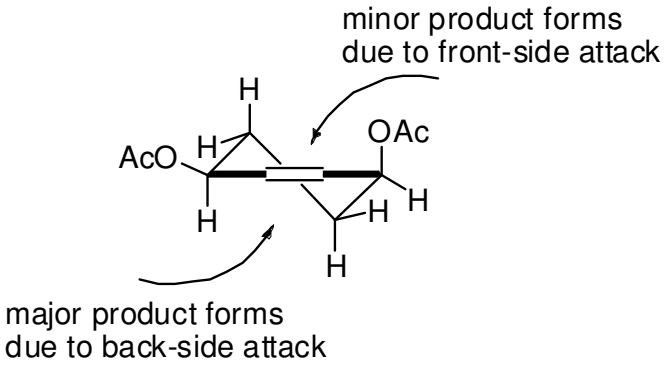


Figure 20 Chair conformation of compound **80**

The two isomers were separated by using column chromatography eluting with ethyl acetate-hexane mixture and both of them were crystallized from ethanol-hexane mixture.

The structures and the stereochemistry of the two isomers were identified by using ^{1}H and ^{13}C NMR. In the ^{1}H NMR spectrum of the major lactone **78**, the H_7 proton gives a multiplet between 5.03-4.99 ppm, the H_4 proton gives a doublet of triplets at 4.85 ppm, the H_8 proton gives a triplet at 4.53 ppm and the H_3 proton gives a quintet at 2.77 ppm. In addition, in the spectrum there is an AB-system arising from methylenic protons located in the lactone ring. Both parts of the AB-system are further split into doublet of doublets due to the coupling with the adjacent protons. A-part of the system resonates at 2.61 ppm and B-part of the system resonates at 2.41 ppm. The singlets at 2.08 and 2.09 ppm belong to acetate's methyl groups and the multiplet between 1.93-1.75 ppm belongs to the H_5 and H_6 methylenic protons. ^{1}H-NMR was used for investigating the stereochemistry of the lactone ring. The coupling constant value of H_8 proton is J = 6.0 Hz indicating an axial-axial interaction of the interacting protons. As a result of this interaction, we assumed that the addition occurs from the *anti*-side of the molecule.

The ^{13}C NMR also verifies the structure of the major lactone **78**. There are three carbonyl carbon signals at 174.2, 170.0, 169.8 ppm. C_8, C_4 and C_7 carbons resonate at 79.2, 70.2, and 69.6 ppm and the carbon C_2 resonate at 32.7 ppm. The tertiary

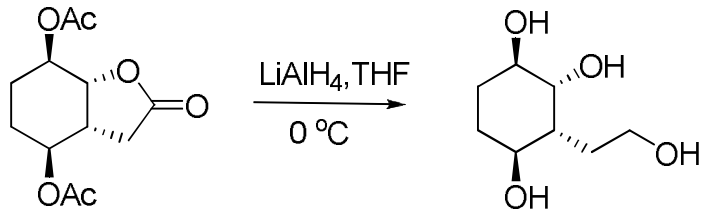
carbon (C_3), the methylene carbons (C_6 and C_5) and the acetate's methyl carbons resonances are observed at 39.7, 23.6, 23.2, 21.1 and 21.0 ppm, respectively.

In the ^1H NMR of the minor lactone **81**, H_4 and H_7 protons are overlapped and resonate between 5.11-5.07 ppm, as a multiplet. The H_8 proton gives a triplet at 4.85 ppm, and the H_3 proton gives a quintet at 2.91 ppm. There is also an AB-system resulting from the H_2 protons that both parts are split into doublet of doublets and A-part and B-part of the system resonate at 2.53 and 2.48 ppm, respectively. In the higher field of the spectrum, at 2.09 and 2.06 ppm the acetate's methyl peaks appear and finally, two different multiplets are observed for the H_6 protons between 2.0-1.9 ppm and for the H_5 protons between 1.72-1.60 ppm. For finding the relative stereochemistry of compound **81** coupling constants were used again. The coupling constant between H_8 and H_3 was measured as J = 4.9 Hz indicating an axial-equatorial interaction of the corresponding protons. As a result of this interaction, it was assumed that the addition occured from the *syn*-side of the molecule.

The ^{13}C NMR spectrum indicated that carbon C_1 appears at 175.7 ppm and the two acetate carbonyls appear at 169.9 ppm, the carbon which is attached to oxygen atom (C_8) resonates at 76.8 ppm and the other lower field carbons C_4 and C_7 arise at 68.2 ppm. The tertiary carbon (C_3) appears at 38.5 ppm and the methylene carbons C_2, C_5 and C_6 resonate at 31.7, 23.8 and 20.8 ppm, respectively.

2.1.6 Synthesis of 3-(2-hydroxyethyl)cyclohexane-1,2,4-triol (72)

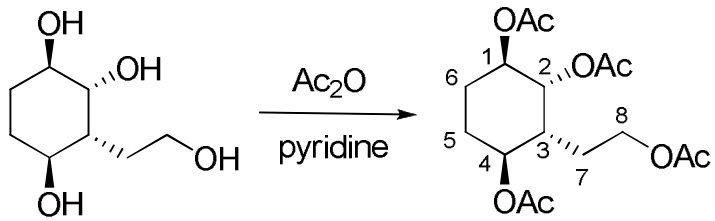
The next step was the reduction of lactone **78** to form compound **72**. The reaction was done with lithium aluminum hydride in tetrahydrofuran at 0 ^oC and we succeded in the synthesis of **72**. For the purification of the tetraol, the compound was converted into the corresponding tetraacetates.



78 72

2.1.7 Synthesis of 3-(2-acetoxyethyl)cyclohexane-1,2,4-triyl triacetate (82)

In order to characterize and purify compound **72,** it was acetylated under mild condition by means of acetic anhydride in pyridine.



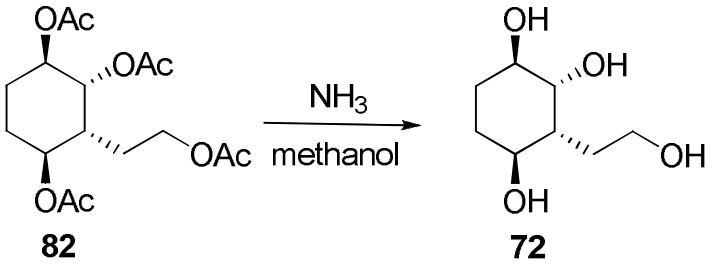
72 82

The resulting product **82** was identified on the basis of ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR spectrum there is a triplet at 5.08 ppm for H_2, and there are multiplets between 4.85-4.79 ppm for H_1 and H_4, between 4.09-3.98 ppm for H_8, between 2.13-2.05 ppm for H_3, between 1.84-1.76 ppm for H_6 and one of H_5 protons, between 1.70-1.51 ppm for H_7 and one of H_5 protons and there are two singlets at 2.01 and 1.97 ppm for acetate methyl groups.

The ^{13}C NMR is also consistent with the structure. In the spectrum, there are four carbonyl carbons resonating at 170.8, 170.3, 169.6, 169.7 ppm. The acetoxy carbons appear at 72.0 (C_4), 71.1(C_2), 68.1(C_1) and 62.5 (C_8) ppm. The tertiary carbon C_3 has a signal at 38.1 ppm and the C_5, C_7 and C_6 carbons resonate at 26.1, 25.1, 24.0 ppm respectively. Finally, acetate methyl groups appear at 21.2, 21.0, 20.9 and 20.8 ppm.

2.1.8 Synthesis of 3-(2-hydroxyethyl)cyclohexane-1,2,4-triol (72)

After characterization and purification of compound **82**, the acetate groups were hydrolyzed to obtain **72**. The hydrolysis was performed with NH_3 gas in methanol.



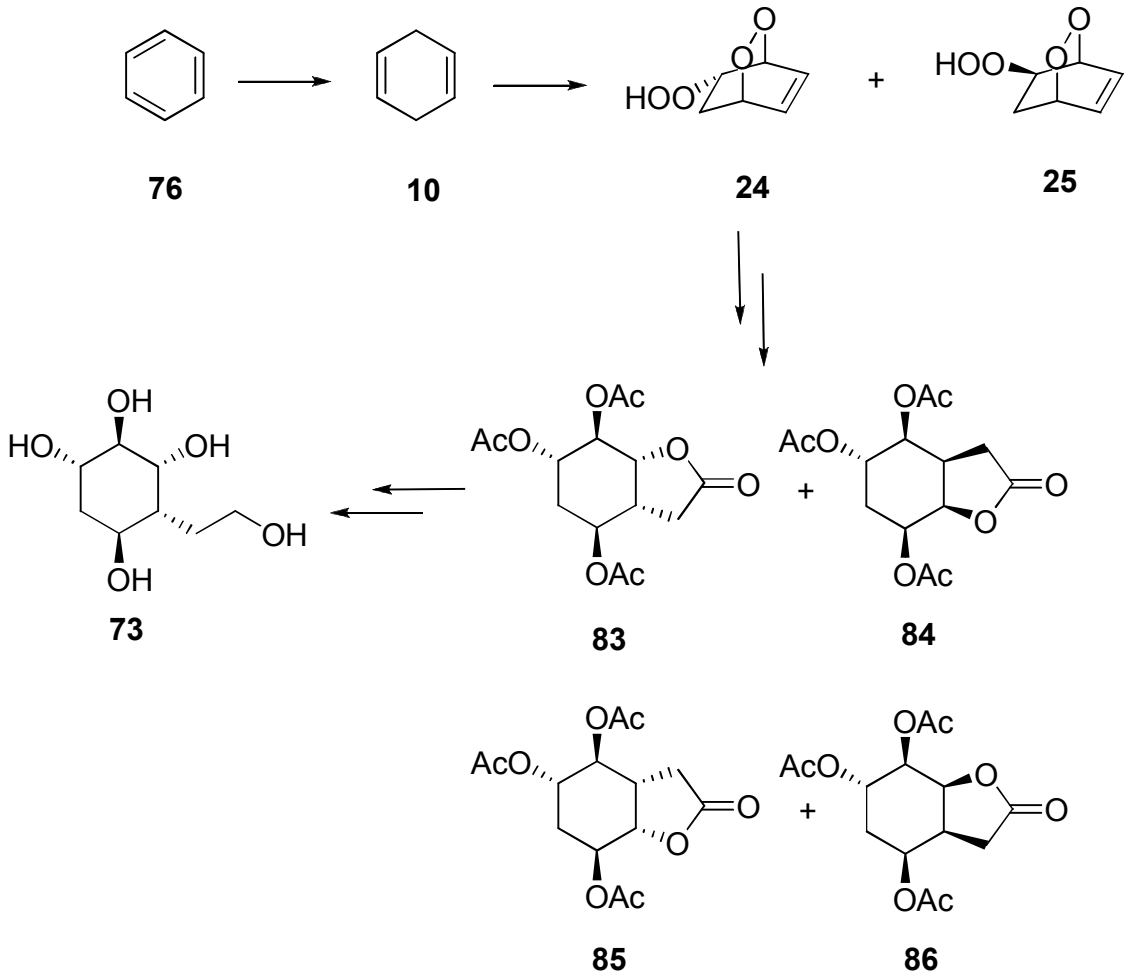
82 **72**

Compound **72** was characterized on the basis of ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR spectrum protons next to hydroxyl groups resonate as multiplet between 3.74-3.72 ppm, 3.68-3.64 ppm and 3.63-3.54 ppm. The other methylene protons and one tertiary proton appear between 1.77-1.47 as a multiplet.

In ^{13}C NMR spectrum there are eight lines. The alkoxy carbon atoms give signals at 71.7, 69.4, 68.9 and 60.1 ppm. The low field resonances can be explained by inductive effect of oxygen atom. Other saturated carbons give signals at 41.0, 29.0, 27.2 and 25.6 ppm.

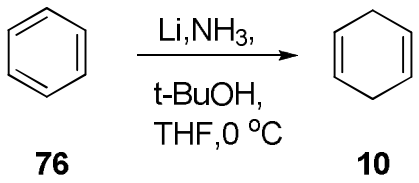
2.2 SYNTHESIS OF 4-(2-HYDROXYETHYL) CYCLOHEXANE-1,2,3,5-TETRAOL (PENTAOL DERIVATIVE) (73)

In this part of the study, target compound **73** was synthesized by starting with another kind of diene. Singlet oxygen ene reaction combined with the singlet oxygen [2+4] addition was applied to 1,4-cyclohexadiene (**10**) for the introduction of three oxygen functionalities [8]. After the singlet oxygen reaction there should have remained a double bond in the molecule so that lactonization could be possible with $Mn(OAc)_3$ oxidation for introducing hydroxyethylene group and another oxygen functionality. As a result, the following synthetic pathway was planned.



2.2.1 Synthesis of 1,4-cyclohexadiene (10)

The key compound diene **10** was synthesized by using Birch reduction. The reduction was applied to benzene with NH_3 and lithium in the presence of tert-butanol and THF at 0 °C.

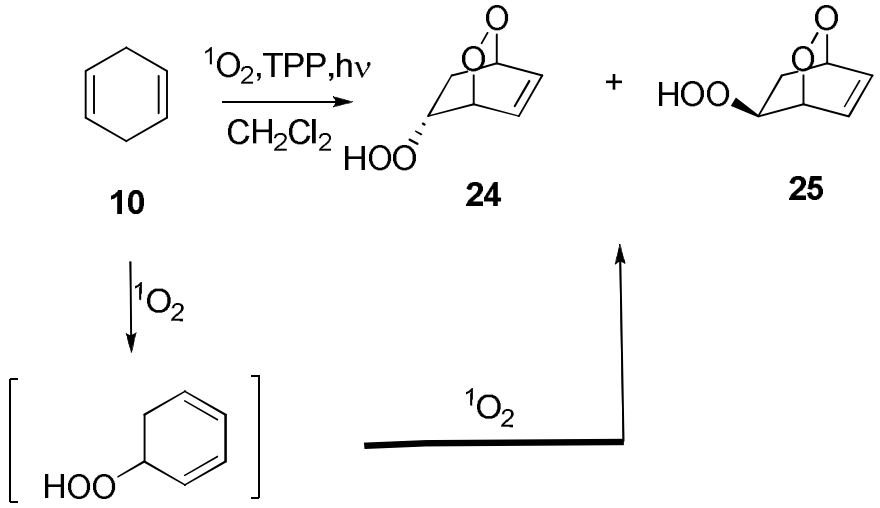


The compound **10** was characterized on the basis of ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR spectrum, the four olefinic protons resonate at 5.71 ppm as a singlet and the four methylene protons give a singlet at 2.69 ppm.

In ^{13}C NMR spectrum, there are two lines. Olefinic carbons resonate at 124.5 ppm and the saturated carbons resonate at 25.7 ppm.

2.2.2 Synthesis of *anti*-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide (24)

Tetraphenylporphyrin-sensitized photooxygenation of 1,4-cyclohexadiene (**10**) in methylene chloride at room temperature resulted in the formation of the bicyclic endoperoxides **24** and **25** in a ratio of 88:12. The reaction mixture was chromatographed on silica gel column with ether/hexane (1:1) as an eluant and the synthetic route was continued with endoperoxide **24**.



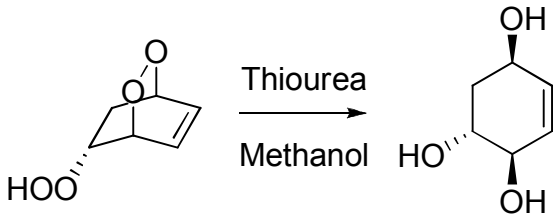
For the formation of those endoperoxides **24** and **25,** the following mechanism is suggested 1,4-cyclohexadiene (**10**) first undergoes an ene reaction with the double-activated methylene groups to give the intermediate product hydroperoxide. Because of the unfavorable arrangement of double bonds, a [2 + 4] cycloaddition can be excluded. On the other hand, formation of dioxetane by addition of singlet oxygen to

one of these double bonds can occur only with certain activated double bonds. Addition of singlet oxygen to the diene unit results in isolated products **24** and **25**.

The structure of **24** was assigned by ^{1}H and ^{13}C NMR and they are consistent with the literature [8].

2.2.3 Synthesis of cyclohex-5-ene-1,2,4-triol (87)

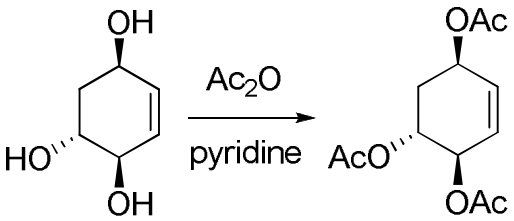
Bicyclic endoperoxides can be readily reduced by lithium aluminum hydride or thiourea to give 2-ene-1,4-diols. Since only the oxygen-oxygen bonds are broken in this reaction, it preserves the configuration at all three carbon atoms. Thiourea in methanol was used to cleave the peroxide linkage in compound **24**.



24 **87**

2.2.4 Synthesis of cyclohex-5-ene-1,2,4-tryl triacetate (26)

The reduced product **87** was acetylated with acetic anhydride in the presence of pyridine to give triacetate **26**.



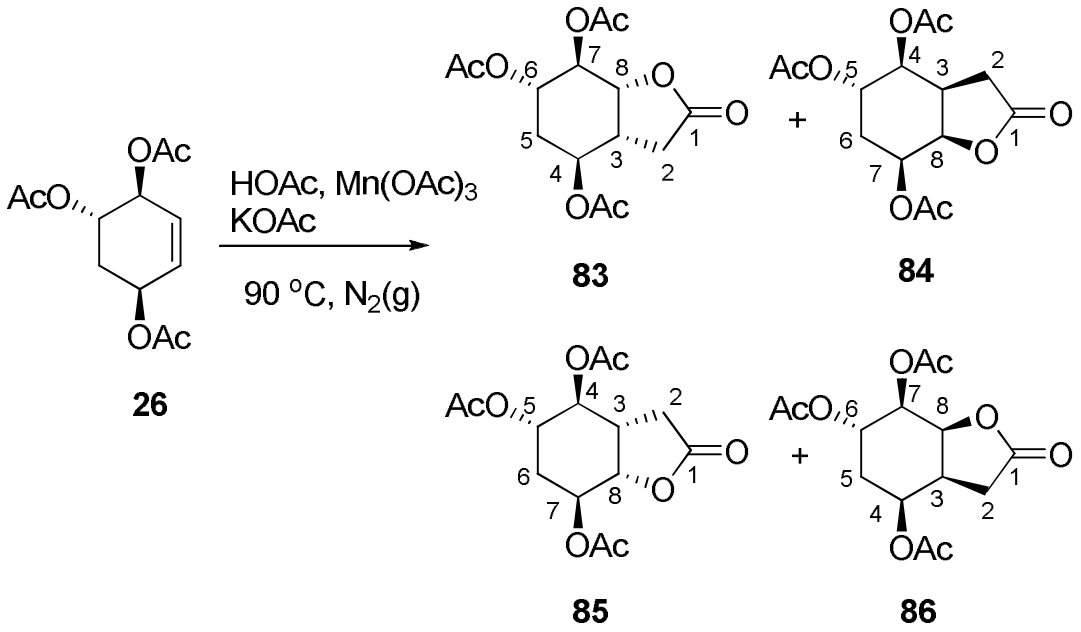
87 **26**

The resulting product was characterized on the basis of ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR, there is an AB-system at 5.86 and 5.73 ppm arising from the olefinic protons, which is further split into doublet of doublets by the adjacent acetoxy protons. There are also three multiplets between 5.32-5.35 ppm, 5.18-5.14 ppm, 2.02-1.98 ppm.

The ^{13}C NMR spectrum reveals the carbonyl carbons at 170.3, 170.2, 170.0 ppm, the olefinic carbons at 128.8, 128.7 ppm, the acetoxy carbons at 70.0, 68.6, 66.2 ppm and the saturated carbons at 31.0, 21.0, 20.9 ppm.

2.2.5 Application of Manganese(III) acetate Oxidation to cyclohex-5-ene-1,2,4-tryl triacetate (26)

$Mn(OAc)_3$ oxidation reaction was applied to compound **26** for the purpose of introducing $-CH_2OH$ functionality compound **73**. The reaction mixture was consisting of acetic acid, potassium acetate and manganese III acetate and it was mixed magnetically at 90 ^{o}C until the color of the mixture became lighter (white). At the end of the reaction four different isomers **83**, **84**, **85** and **86** were observed and the mixture was chromatographed on silica gel column with ethyl acetate/hexane (65:35). Since the R*f* values of isomers **83** and **84** were approximately the same it was not possible to separate them by column chromatography, they were separated by crystallization.



The formation ratio of the compounds **83**, **84**, **85** and **86** is 46:31:15:8 and this ratio can be attributed to stereochemistry of the acetate groups in the cyclohexane ring. It is likely that the radical generated from the acetic acid approaches the double bond from the less crowded side of the molecule to give **83** and **85**. Although the acetate groups which are *cis* to each other create a large steric hindrance, the compounds **84** and **86** are also the products of this reaction. It can be explained with the stereochemistry of the remaining acetate group. The acetate group which is *trans* to the other acetate groups also creates a steric hindrance and addition from the more crowded side of the molecule is also possible.

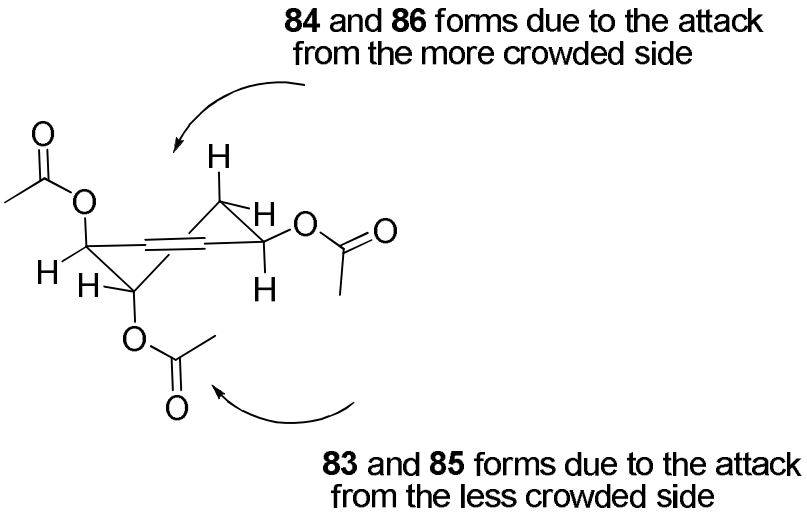


Figure 21 Chair conformation of compound **26**

The stereochemistry and regiochemistry of the isomers **83**, **84**, **85** and **86** were determined by ^{1}H and ^{13}C NMR spectra in conjunction with 2D-NMR (DEPT-90, DEPT-135, COSY, HMQC and HMBC) experiments.

For the major isomer **83**, the data were consistent with the structure. Firstly, the regiochemistry of the compound **83** was found with the help of 2D-NMR spectrum. In DEPT-135 spectrum, the positive signals belong to C_3, C_4, C_6, C_7, C_8 and the acetates' methyl carbons whereas, the negative signals belong to C_2 and C_5.

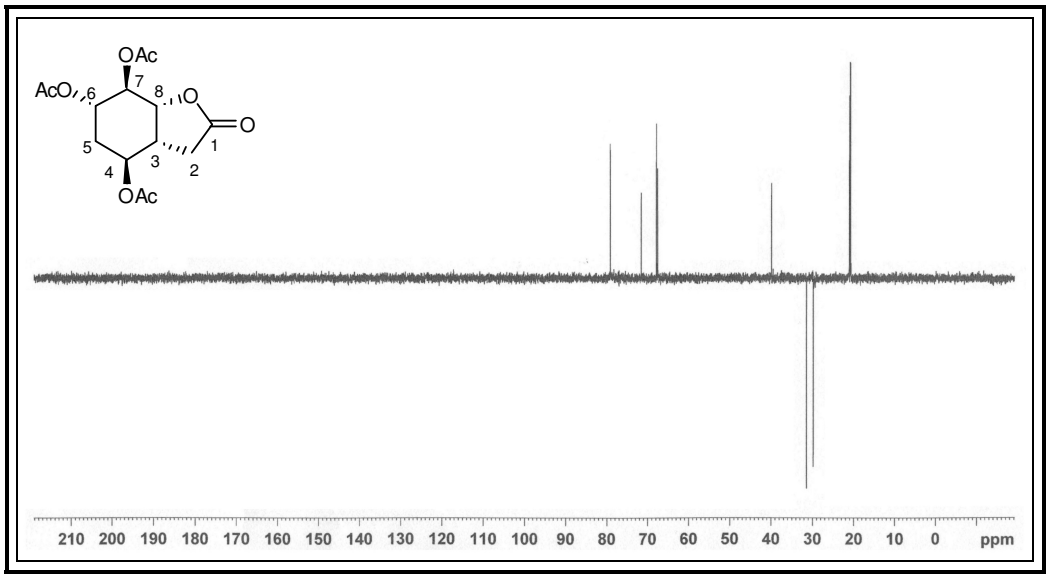


Figure 22 DEPT-135 spectrum of compound **83**

In DEPT-90 spectrum, signals belong to C_3, C_4, C_6, C_7, and C_8 carbons in brief, the –CH carbons. So by examining DEPT-90 and DEPT-135 the carbon signals were correctly assigned.

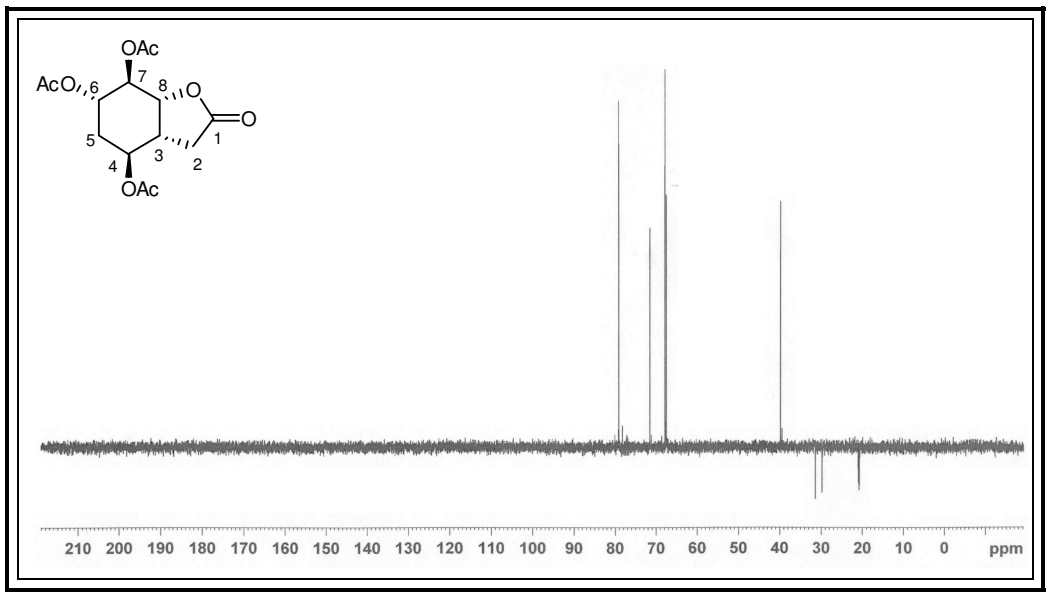


Figure 23 DEPT-90 spectrum of compound **83**

Comparing the overall ^{13}C NMR spectrum with HMQC, it is easily understood which carbon signal belongs to which proton except H_4, H_6 and H_7 because their signals are overlapped in the ^{1}H NMR spectrum. Therefore, they were established by using COSY and HMBC.

For the determination of the regiochemistry of **83**, the place of the acetate group which is *trans* to the other acetate groups, is established. Therefore, COSY and HMBC were used to find the exact structure.

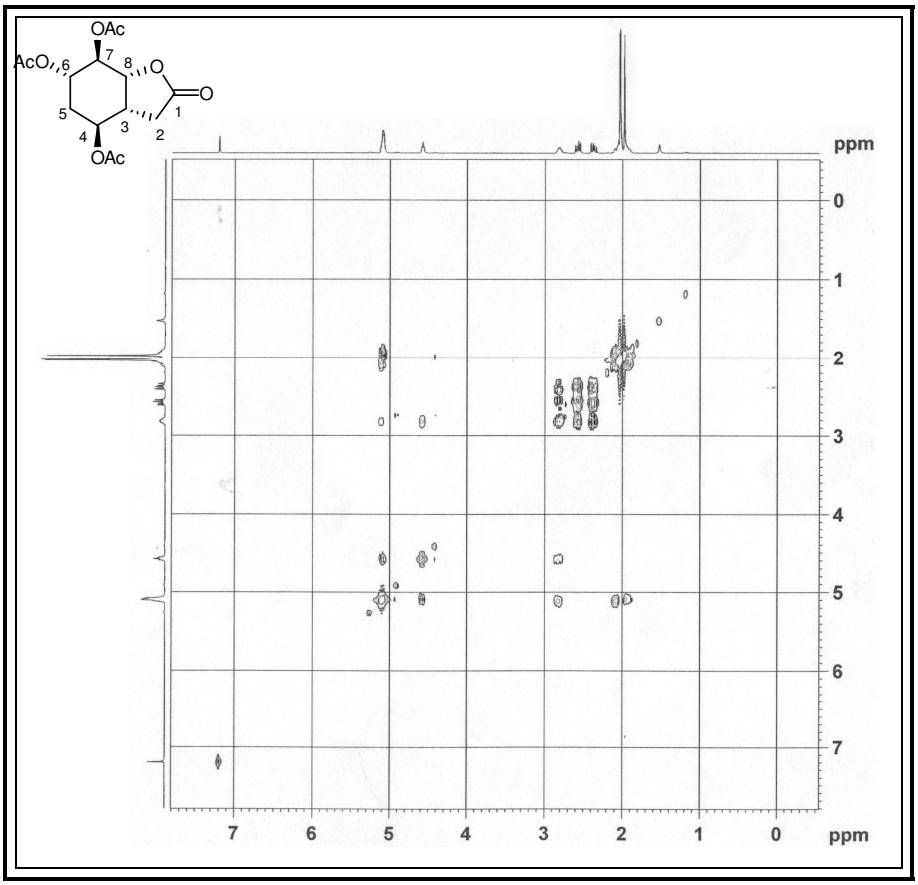


Figure 24 COSY spectrum of compound **83**

First of all, it is well-known that the triplet at 4.67 ppm is H_8 and the H_5 methylene protons' peaks are under the acetate peaks. Starting from this point, H_3 and H_2 are determined from the COSY spectrum. However, the place of the H_4, H_6 and H_7

protons can not be found because of overlapping as mentioned before. That is why, the place of the acetate group next to C_6 is not found, so HMBC becomes crucial for deciding about the exact structure.

In HMBC spectrum, the three bond interaction of methylene (C_5) carbon is checked with H_8 or H_3 protons and it is easily noted that H_3 has a strong correlation with C_5 carbon and the H_8 has no correlation. So the exact place of the acetate that is to say the regiochemistry of the lactone **83** was established.

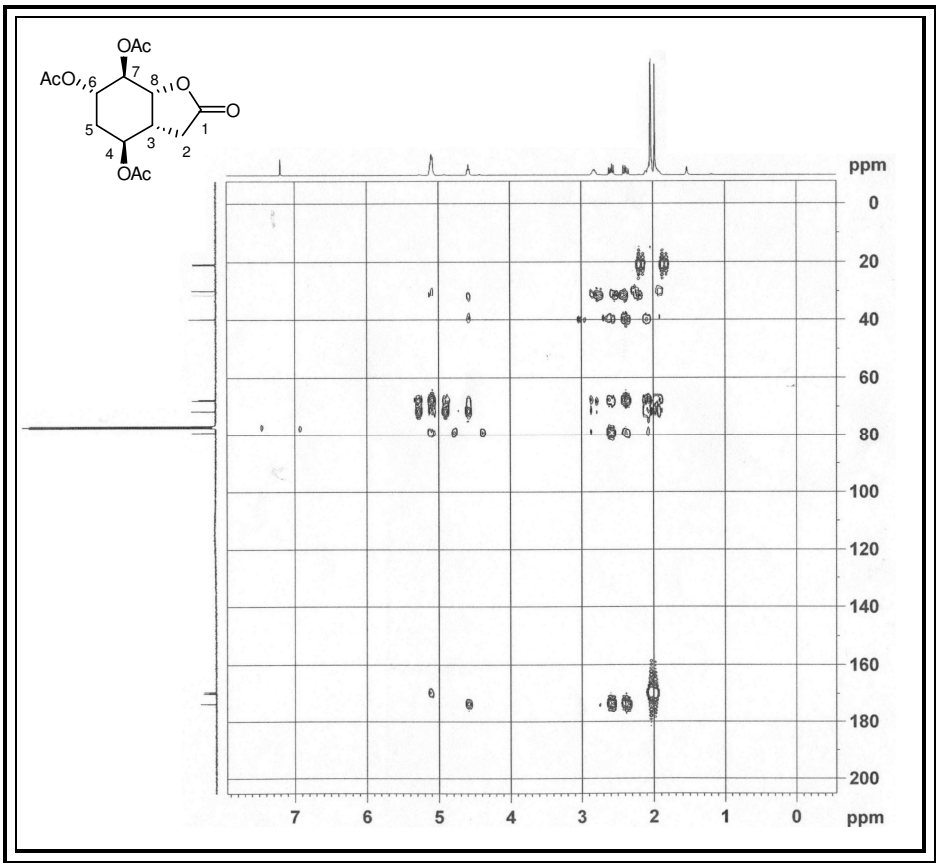


Figure 25 HMBC spectrum of compound **83**

Coupling constants were used to investigate the relative stereochemistry of the lactone ring in **83**. The coupling constant $J_{8,7}$ was used to determine the stereochemistry of the acetate group attached to C_7 carbon atom. The measured

coupling $J_{8,7}$ = 6.9 Hz is indicating an axial-axial interaction of the relevant protons. As a result of this, we assume that the addition occurs from the *anti*-side.

In ^{1}H NMR spectrum of **83**, there is a multiplet between 5.12-5.08 ppm for H_4, H_6 and H_7, a triplet at 4.67 ppm for H_8, a quintet at 2.91 ppm for H_3. AB-system also appears for H_2 protons. The A-part of the system resonates as doublet of doublets, at 2.67 ppm and the B-part of the system also resonates as doublet of doublets, at 2.45 ppm. Finally, there are three singlets at 2.13, 2.12 and 2.07 ppm.

In ^{13}C NMR, there are four peaks for carbonyl carbons at 173.4, 169.9, 169.7 and 169.4 ppm at the lower field of the spectrum. The carbons next to oxygen appear at 79.1, 71.5, 67.8 and 67.5 ppm, the two methylene and the tertiary carbon give signals at 39.8, 31.4 and 29.8 ppm and also the methyl peaks resonate at 20.9, 20.8 and 20.7 ppm.

The regiochemistry of **84** was easily determined just by examining the COSY spectrum. The H_6 proton's resonance is overlapped with acetate peaks; fortunately the interaction of H_6 with H_5 and H_7 is strong enough so that the place of acetate group is easily distinguishable.

The stereochemistry of **84** was established by measuring the coupling constants between H_3 and H_4 and between H_7 and H_8. Small value of $J_{3,4}$ ($J_{7,8}$) (5.2-5.3 Hz) indicate that there is an axial-equatorial interaction with the adjacent protons and one can conclude that the addition occurs from the *syn*-side of the molecule.

In ^{1}H NMR of **84** there is a doublet of doublets at 5.24 ppm for H_4, a doublet of triplets at 5.10 ppm for H_5, a quartet at 4.91 ppm for H_7, a triplet at 4.42 ppm for H_8, a quintet at 2.74 ppm for H_3 and an AB-system arising from H_2. The A-part of the system is split into doublet of doublets at 2.60 ppm and the B-part of the system also resonates as doublet of doublets at 2.56 ppm. Three methyl groups' peaks appear at 2.05, 2.01 and 1.98 ppm.

The ^{13}C NMR spectrum of **84** reveals carbonyl carbons at 173.7, 169.8, 169.7 and 169.4 ppm, the alkoxy carbon atoms at 78.2, 71.2, 68.6 and 67.6 ppm, the other tertiary and methylene carbons appear at 39.5, 33.5 and 29.3 ppm and the methyl carbons give signals at 20.9, 20.8, 20.7 ppm.

^{1}H NMR spectrum of **85** indicates that there are two doublet of triplets at 5.24 and 5.11 ppm for H_7 and H_4, there is a triplet at 4.66 ppm for H_8, a quintet at 3.02 ppm for H_3, and an AB-system for H_2. Both parts of the system are further split into doublet of doublets at 2.46 and 2.41 ppm. In addition, there are two doublet of doublet of doublets for H_6 protons at 2.19 and 1.82 ppm. At 2.04 and 2.01 ppm the methyl groups' signals appear.

^{13}C NMR spectrum of **85** is also consistent with the structure. The carbonyl carbons give signals at 175.0, 169.9, 169.8 and 169.7 ppm. The alkoxy carbon atoms resonate at 68.0, 67.6, 67.5 and 66.6 ppm due to inductive effect of oxygen, the tertiary and the methylene carbons resonate at 36.7, 31.8 and 26.1 ppm and lastly, the methyl carbons appear at 20.8, 20.7 and 20.5 ppm.

The structure of the last isomer **86** was also determined by ^{1}H, ^{13}C and 2D-NMR experiments.

For the determination of regiochemistry of the isomer **86**, COSY spectrum was used. H_2, H_3, H_5 and H_7 protons were well-established but H_4 and H_6 were not determined exactly just by examining COSY spectrum because of overlapping of the signals, thus HMBC was used. It is easy to notice that H_4 has an interaction with H_3, however H_6 does not have any interaction with H_3. As a consequence, the structure of **86** was certainly established.

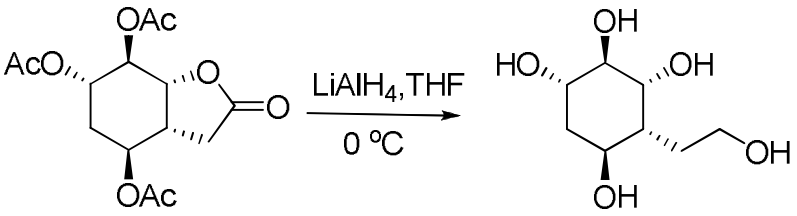
For the determination of stereochemistry of the lactone ring **86** ^{1}H NMR was used. The coupling constants between H_3 and H_4 and between H_7 and H_8 are measured and small value of $J_{3,4}$ ($J_{7,8}$) (5.0-5.4 Hz) indicate that there is an axial-equatorial interaction with the adjacent protons and as a result of this we assume that the addition occurs from the *syn*-side of the molecule.

In ^{1}H NMR spectrum of **86** there is a doublet of triplets at 5.27 ppm for H_4, a multiplet between 5.24-5.20 ppm for H_6, a doublet of doublets at 5.09 ppm for H_7, a triplet at 4.78 ppm for H_8 and a quintet at 2.90 for H_3. An AB-system also appears in the spectrum both parts of the system are split into doublet of doublets at 2.45 and 2.39 ppm. Moreover, there are two doublet of doublet of doublets that belong to H_5 protons which resonate at 2.16 and 1.76 ppm. Lastly, the methyl groups' protons give signals at 2.04, 2.02 and 1.99 ppm.

In ^{13}C NMR of **86**, there are four peaks arising from carbonyl carbons at 175.0, 170.0, 169.7 and 169.4 ppm at the lower field of the spectrum. The alkoxy carbons resonate at 76.8, 69.6, 67.4 and 66.3 ppm. Two methylenic carbons and the tertiary carbon give signals at 33.0, 31.6 and 30.1 ppm, and also the methyl groups' peaks resonate at 20.8, 20.7 and 20.7 ppm.

2.2.6 Synthesis of 4-(2-hydroxyethyl)cyclohexane-1,2,3,5-tetraol (73)

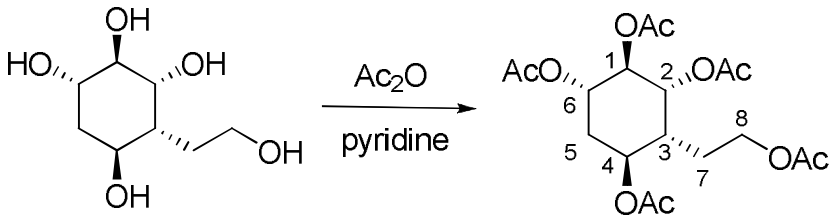
The next step was the reduction of major lactone **83.** Treatment of **83** with lithium aluminum hydride in tetrahydrofuran at 0 ^{o}C gave **73**. For the purification of the pentaol, the compound was converted into the corresponding pentaacetates.



83 **73**

2.2.7 Synthesis of 4-(2-hydroxyethyl)cyclohexane-1,2,3,5-tetraacetate (88)

In order to characterize and purify **73,** it was acetylated under mild condition by means of acetic anhydride in pyridine.



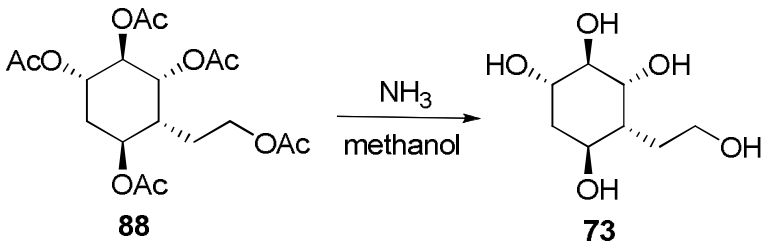
73 **88**

The structure of molecule **88** was elucidated on the basis of the ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR spectrum, the tertiary protons H_1, H_2, H_4 and H_6 overlap and resonate as a multiplet between 5.19-5.06 ppm and other lower field H_8 protons give a triplet at 4.05 ppm. H_3 proton appears between 2.30-2.22 ppm as a multiplet and methyl protons appear at 2.04, 1.99, 1.98 and 1.97 ppm. One of H_5 protons resonates as a multiplet between 1.86-1.79 ppm and one of H_7 protons as a doublet of quartet at 1.56 ppm. The other H_5 and H_7 protons were not observed in the spectrum because of overlapping with the methyl peaks and this was verified by the HMQC spectrum.

The ^{13}C NMR spectrum of **88** also reveals three different carbonyl carbon signals at 169.8, 168.8 and 168.6 ppm, five acetoxy carbons at 69.5, 69.4, 68.7, 68.3 and 61.5 ppm. The tertiary carbon C_3 resonates at 37.7 ppm and C_5 and C_7 carbons appear at 28.9 and 24.4 ppm. Finally, there are 5 lines at 20.1, 19.9, 19.8, 19.7 and 19.6 ppm which are resulting from the acetate groups.

2.2.8 Synthesis of 4-(2-hydroxyethyl)cyclohexane-1,2,3,5-tetraol (73)

After characterization of compound **88**, the acetate groups were hydrolyzed to obtain pure pentol **73**. The hydrolysis was performed with NH_3 gas in methanol.



88 **73**

Compound **73** was characterized on the basis of ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectrum of **73** indicates that there are two doublet of doublets at 3.98 and 3.81 ppm. There are also four proton resonances at the lower field of the spectrum due to inductive effect of oxygen. One of them appears as a multiplet between 3.73-3.63 ppm, two of them overlap and give a multiplet between 3.61- 3.54 ppm and the last one resonates as a triplet at 3.65 ppm. In the higher parts of the spectrum, there is a quartet at 1.93 ppm, a doublet of triplets at 1.85 ppm and a doublet of quartets at 1.22 ppm . In addition, a doublet of doublet of doublets and a doublet of triplets appear at 1.80 and 1.67 ppm, respectively.

In ^{13}C NMR spectrum there are eight lines. The alkoxy carbon atoms give signals at 74.5, 72.1, 70.3, 68.3 and 60.7 ppm. Other saturated carbons give signals at 48.8, 33.9 and 27.9 ppm.

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 ($CDCl_3$), deuterowater (D_2O) as the solvents. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols; s:singlet, d:doublet, t:triplet, q:quartet, dd:doublet of doublet, ddd:doublet of doublet of doublet. Infrared spectra were 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. Thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Fuluka.

All the solvent purifications were done as stated in the literature [32].

3. 2 Synthesis of trans-1,2-dibromocyclohexane (75)

20.5 g of cyclohexene (**74**) (0.25 mole) is dissolved in 30 mL of dichloromethane and cooled to 0^{o}C in an ice bath. Equimolar of bromine (0.25 mole, 40 g) is dissolved in 80 mL dichloromethane is given drop wise. When the dropping is completed, the solvent is removed away by using a rotary evaporator and 63 g product is obtained in a yield of 92% [33].

^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 55.1, 31.9, 22.4.

3. 3 Synthesis of 1,3-cyclohexadiene (71)

63 g of trans-1,2-dibromocyclohexane (**75**), 72 g potassium hydroxide and 177 mL ethylene glycol is heated up 150-170 ^{o}C in an oil bath. The mixture is continuously stirred mechanically throughout the reaction. The product is collected as two phase via distillation through a condenser. The temperature as the product collected is recorded as around 58 ^{o}C. The two phase product is separated and oily organic phase is washed with dilute hydrochloric acid (0.1N) and dried over calcium chloride. 11.3 g of product is obtained in a yield of 60% [33].

^{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).

3. 4 Synthesis of 2,3-dioxabicyclo[2.2.2]oct-5-ene (77)

6.2 g of 1,3-cyclohexadiene (**71**) (0.077 moles) and a catalytic amount of tetraphenylporphin (TPP) were dissolved in 250 mL of CH_2Cl_2 in the flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (500W) for 24 hours while the dry oxygen was bubbled through with a constant rate at room

temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30°C. 5.5 g of product is obtained in a yield of 88% [33].

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (t, *J*=3.8, 2H), 4.56 (s, 2H), 2.2 (AA' part of AA'BB' system, 2H), 1.4 (BB' part of AA'BB' system, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 70.2, 21.1.

3.5 Synthesis of cyclohex-2-ene-1,4-diol (79)

1.0 g of (1R,4S)-2,3-dioxabicyclo[2.2.2]oct-5-ene (**77**) (8.92 mmoles) was dissolved in methanol and 1.36 g (17.81 mmoles) thiourea was added. The reaction was stirred magnetically for 2 hours at room temperature. The mixture was filtrated and the solvent was removed by a rotary evaporator [34].

3.6 Synthesis of cyclohex-2-ene-1,4-diyl diacetate (80)

1.87 g of diol (**79**) (16.4 mmoles) was dissolved in 27 mL of pyridine and 6.8 g of acetic anhydride was added. The reaction was stirred magnetically for 6 hours at room temperature. After 6 hours the reaction mixture was poured to a 400 mL 1 N HCl solution which was cooled to 0°C. Organic phase was obtained by the extraction with ether (3x100 mL). Organic phase was firstly washed with saturated 35 mL $NaHCO_3$ solution and then with 20 mL water. Overall organic phase was dried over Na_2SO_4 and the ether was removed by rotary evaporator (40°C). 1.43 g of product is obtained in a yield of 74% [34].

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 2H), 5.19 (s, 2H), 2.03 (s, 2-CH_3), 1.90-1.79 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.2, 67.2, 24.7, 21.1.

3.7 Synthesis of 2-oxooctahydrobenzofuran-4,7-diyl diacetate (78 and 81)

1.65 g (8 mmol) cyclohex-2-ene-1,4-diyl diacetate (**80**), 15 g $Mn(OAc)_3.2H_2O$, 5 g KOAc and 250 mL acetic acid were mixed and refluxed at 90 ^oC in an oil bath until the reaction mixture turned to white. When the reaction was completed the mixture was washed with CH_2Cl_2 (3x100mL). The CH_2Cl_2 phase was washed with saturated $NaHCO_3$ solution and then with water. Overall organic phase was dried over $MgSO_4$ and the solvent was removed by rotary evaporator (45 ^oC). The yield of crude product was 70% for two isomers. From the ^1H NMR of the reaction mixture, it was observed that the two isomers **78** and **81** have a ratio of 7:3. Mixture was chromatographed on silica gel column with ethyl acetate/hexane (1:1) and the two isomers were separated.

2-oxooctahydrobenzofuran-4,7-diyl diacetate (78)

Ethanol/hexane solvent mixture was used for crystallization. Colorless crystalline product was observed, m.p. 130.3 ^oC

^1H NMR (400 MHz, $CDCl_3$) δ 5.03-4.99 (m, 1H), 4.85 (dt, *J*=6.5 and 3.3 Hz, 1H), 4.53 (t, *J*=6.0, 1H) 2.77 (quintet, *J*=6.9 Hz, 1H), 2.61 (dd A-part of AB-system, *J*=17.2 and 7.7 Hz), 2.41 (dd B-part of AB-system, *J*=17.3 and 7.3 Hz), 2.09 (s,-CH_3), 2.08 (s,-CH_3), 1.93-1.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.0, 169.8, 79.2, 70.2, 69.6, 39.7, 32.7, 23.6, 23.2, 21.1, 21.0.

IR (KBr, cm^{-1}) 2959, 1776, 1731, 1376, 1173, 1021.

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.03; H, 6.18.

2-oxooctahydrobenzofuran-4,7-diyl diacetate (81)

Ethanol/hexane solvent mixture was used for crystallization. White crystalline product was observed, m.p. 151.5 ^oC

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11-5.07 (m, 2H), 4.65 (t, *J*=4.8 Hz, 1H), 2.91 (quintet, *J*=5.9 Hz, 1H), 2.53 (dd A-part of AB-system, *J*=17.3 and 6.3 Hz), 2.48 (dd B-part of AB-system, *J*=12.3 and 2.9 Hz), 2.09 (s,-CH_3), 2.06 (s,-CH_3), 2.0-1.9 (m, 2H), 1.72-1.6 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.9 (2C), 76.8, 68.9, 68.2 (2C), 38.5, 31.7, 23.8, 20.9, 20.8 (2C).

IR (KBr, cm^{-1}) 2963, 1783, 1729, 1377, 1213.

Anal. Calcd for C_{12} H_{16} O_6: C, 56.24; H, 6.29. Found: C, 56.04; H, 6.19.

3.8 Synthesis of (2-hydroxyethyl)cyclohexane-1,2,4-triol (72)

165 mg $LiAlH_4$ was dissolved in 32 mL dry THF and cooled to 0 ^oC. While reaction was stirring magnetically, the reaction medium was saturated with nitrogen gas. 500 mg (1.95 mmoles) of lactone **78** which was dissolved in 25 mL dry THF, was added to $LiAlH_4$ solution drop wise in 3 hours. After addition of **78**, 10 g silica gel and ether was added to the reaction mixture and waited for one night. For completion of the hydrolysis 35 mL methanol was added and filtered. The solvent was removed by rotary evaporator (50 ^oC). 285 mg of product was obtained in a yield of 57% [34].

3.9 Synthesis of 3-(2-acetoxyethyl)cyclohexane-1,2,4-triyl triacetate (82)

285 mg of tetraol **72** (1.76 mmoles) was dissolved in 5 mL of pyridine and 800 mg of acetic anhydride was added. The reaction was stirred magnetically for 6 hours at room temperature. After 6 hours the reaction mixture was poured to a 200 mL 1 N HCl solution which was cooled to 0 ^oC. Organic phase was obtained by the extraction with ether (3x100 mL). Organic phase was firstly washed with saturated 35 mL $NaHCO_3$ solution and then with 20 mL water. Overall organic phase was dried over Na_2SO_4 and the ether was removed by rotary evaporator (40 ^oC) 250 mg of product was obtained in a yield of 87% [34].

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (t, *J*=3.8 Hz, 1H), 4.85-4.79 (m, 2H), 4.09-3.98 (m, 2H), 2.13-2.05 (m,1H), 2.01 (s, 3-CH_3), 1.97 (s, -CH_3), 1.84-1.76 (m, 3H), 1.70-1.51 (m,3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.3, 169.6, 169.7, 72.0, 71.1, 68.1, 62.5, 38.1, 26.1, 25.1, 24.0, 21.2, 21.0, 20.9, 20.8.

IR (KBr, cm^{-1}) 2957, 1737, 1369, 1233, 1027.

Anal. Calcd for C_{16} H_{24} O_8: C, 55.81; H, 7.02. Found: C, 55.49; H, 6.74.

3.10 Synthesis of 3-(2-hydroxyethyl)cyclohexane-1,2,4-triol (72)

250 mg **82** was dissolved in 50 mL methanol and NH_3 gas was bubbled into the reaction mixture for 3 days at room temperature. When the reaction was complete the solvent was removed by rotary evaporator (55 ^oC). 120 mg product was obtained in a yield of %48.

^{1}H NMR (400 MHz, D_2O) δ 3.74-3.72 (m, 1H), 3.68-3.64 (m, 1H), 3.63-3.54 (m, 3H), 1.77-1.47 (m, 7H).

^{13}C NMR (100 MHz, D_2O) δ 71.7, 69.4, 68.9, 60.1, 41.0, 29.0, 27.2, 25.6.

IR (KBr, cm^{-1}) 3339, 2938, 1664, 1287, 1054, 1010.

3. 11 Synthesis of 1,4-cyclohexadiene (10)

In a three necked flask 27.3 g dry benzene, 72 g tert-buthanol, 120 mL THF was added and the medium was saturated with NH_3 gas at 0 ^oC. 7.35 g lithium was added to the reaction mixture with very small portions in 5 minutes. The reaction was refluxed for one night. Then small portions of ice wad added until there was no more lithium left. The mixture was washed with saturated NH_4Cl solution and water. After washing, it was dried over $CaCl_2$ and filtered. 17.75 g diene **10** was obtained.

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

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

3. 12 Synthesis of *anti*-2,3-Dioxabicyclo[2.2.2]oct-7-en-5-yl Hydroperoxide (24)

1 g of 1,4-cyclohexadiene (**10**) (12.5 mmoles) and a catalytic amount of tetraphenylporphin (TPP) were dissolved in 100 mL of CH_2Cl_2 in the flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (500W) for 2 days while the dry oxygen was bubbled through with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 ^oC. From the ^{1}H NMR spectrum of the reaction mixture the ratio of **24** and **25** was determined as 88:12. The crude product was purified with column chromatography by using 50% ether: hexane solvent mixture [34]. ^{1}H and ^{13}C-NMR are consistent with the literature [34].

3. 13 Synthesis of (1,2,5)-cyclohex-3-en-triol (87)

1.0 g of *anti*-2,3-dioxabicyclo[2.2.2]okt-7-en-5 yl hydroperoxide (**24**) (6.94 mmoles) was dissolved in 50 mL methanol and 1.06 g (13.88 mmoles) thiourea was added. The reaction was stirred magnetically for 2 hours at room temperature. The mixture was filtrated and the solvent was removed by a rotary evaporator [34].

3. 14 Synthesis of Triasetoksi-3-cyclohexene (26)

0.4 g (3.07 mmoles) (1,2,5)-cyclohex-3-en-triol (**87**) was dissolved in 5 mL of pyridine and 1.25 g of acetic anhydride was added. The reaction was stirred magnetically for 6 hours at room temperature. After 6 hours the reaction mixture was poured to a 200 mL 1 N HCl solution which was cooled to 0 ^oC. Organic phase was obtained by the extraction with ether (3x100mL). Organic phase was firstly washed

with saturated 25 mL $NaHCO_3$ solution and then with 10 mL water. Overall organic phase was dried over Na_2SO_4 and the ether was removed by rotary evaporator (40^oC) [34] 260 mg product was obtained in a yield of %65.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (dd, A-part of AB-system, *J*=10.1 and 1.6 Hz), 5.73 (d, B-part of AB-system, *J*=9.7 Hz), 5.32-5.35, (m,2H), 5.18-5.14 (m, 1H), 2.02-1.98 (m, 11H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.0, 128.8, 128.7, 70.0, 68.6, 66.2, 31.0, 21.0, 20.9 (2C).

3.15 Synthesis of 2-oxooctahydrobenzofuran-4,6,7-triyl triacetate (83 and 86) and 2-oxooctahydrobenzofuran-4,5,7-triyl triacetate (84 and 85)

1.28 g (5 mmol) triasetoksi-3-cyclohexene (26), 7.75 g $Mn(OAc)_3.2H_2O$, 3.2 g KOAc and 160 mL acetic acid were mixed and refluxed at 90 ^oC in an oil bath until the reaction mixture turned to white (4 days). When the reaction was completed the mixture was washed with CH_2Cl_2 (3x100mL). The CH_2Cl_2 phase was washed with saturated $NaHCO_3$ solution and then with water. Overall organic phase was dried over $MgSO_4$ and the solvent was removed by rotary evaporator (45 ^oC). The yield of crude product was 60% for four isomers. From the ^{1}H NMR spectrum of the reaction mixture, it was observed that the four isomers **83**, **84**, **85** and **86** have a ratio of 46:31:15:8 respectively. The mixture was chromatographed on silica gel column with ethyl acetate/hexane (65:35).

2-oxooctahydrobenzofuran-4,6,7-triyl triacetate (83)

Ethanol/hexane solvent mixture was used for crystallization. White crystalline product was observed. m.p.130.1 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12-5.08 (m, 3H), 4. 67 (t, *J*=6.9 Hz, 1H), 2.81 (quintet, *J*=3.5 Hz, 1H), 2.67 (dd A-part of AB-system, *J*=17.3 and 8.2 Hz), 2.45

(dd B-part of AB-system, *J*=17.3 and 10.5 Hz), 2.13 (s,-CH_3), 2.12 (s,-CH_3), 2.07 (s,-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.9, 169.7, 169.4, 79.1, 71.5, 67.8, 67.5, 39.8, 31.4, 29.8, 20.9, 20.8, 20.7.

IR (KBr, cm^{-1}) 2944, 1787, 1733, 1430, 1235, 1051, 1015.

Anal. Calcd for C_{14} H_{18} O_8: C, 53.50; H, 5.77. Found: C, 52.58; H, 5.60

2-oxooctahydrobenzofuran-4,5,7-triyl triacetate (84)

Ethanol/hexane solvent mixture was used for crystallization. White crystalline product was observed. m.p. 150 ^oC

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (dd, *J*= 9.8 and 4.8 Hz,1H), 5.10 (dt, *J*=8.5 and 3.9 Hz, 1H), 4.91 (t, *J*=7.6 Hz, 1H), 4.42 (t, *J*=5.2 Hz, 1H), 2.74 (quintet, *J*=5.3 Hz, 1H) 2.60 (dd A-part of AB-system, *J*=7.2 and 6.6 Hz), 2.56 (dd B-part of AB-system, *J*=7.3 and 5.5 Hz), 2.05 (s,-CH_3), 2.01 (s,-CH_3), 1.98 (s,-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.8, 169.7, 169.4, 78.2, 71.2, 68.6, 67.6, 39.5, 33.5, 29.3, 20.9, 20.8, 20.7.

IR (KBr, cm^{-1}) 2958, 1787, 1744, 1377, 1234, 1158, 1054.

Anal. Calcd for C_{14} H_{18} O_8: C, 53.50; H, 5.77. Found: C, 53.22; H, 5.65

2-oxooctahydrobenzofuran-4,5,7-triyl triacetate (85)

As a difference from the other isomers **83**, **84** and **86,** this isomer **85** is in a viscous liquid form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (dt, *J*=9.8 and 3.9 Hz, 1H), 5.11 (dt, *J*=6.1 and 2.7 Hz, 1H), 5.05 (t, *J*=5.8 Hz, 1H), 4.66 (t, *J*=4.7 Hz, 1H), 3.02 (quintet, *J*=5.7 Hz, 1H) 2.46 (dd A-part of AB-system, *J*=17.2 and 7.8 Hz), 2.41 (dd B-part of AB-system, *J*=17.2 and 5.5 Hz), 2.19 (ddd, *J*=14.2, 9.8 and 2.8 Hz, 1H) 2.04 (s,-CH_3), 2.01 (s, 2-CH_3), 1.82 (ddd, *J*=13.9, 6.3 and 4.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 169.9, 169.8, 169.7, 68.0, 67.6, 67.5, 66.6, 36.7, 31.8, 26.1, 20.8, 20.7, 20.5.

IR (KBr, cm^{-1}) 3505, 2916, 2848, 1788,1743, 1372, 1226, 1033, 768.

2-oxooctahydrobenzofuran-4,6,7-triyl triacetate (86)

Ethanol/hexane solvent mixture was used for crystallization. Colorless crystalline product was observed. m.p. 141 ^oC

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (dt, *J*=8.4 and 3.6 Hz, 1H), 5.24-5.20 (m, 1H), 5.09 (dd, *J*=8.2 and 4.4 Hz, 1H), 4.78 (t, *J*=4.9 Hz, 1H), 2.90 (quintet, *J*=5.7 Hz, 1H) 2.45 (dd A-part of AB-system, *J*=17.2 and 7.7 Hz), 2.39 (dd B-part of AB-system, *J*=17.3 and 5.3 Hz), 2.16 (ddd, *J*=14.3, 7.0 and 3.8 Hz, 1H) 2.04 (s,-CH_3), 2.02 (s,-CH_3), 1.99 (s,-CH_3) 1.76 (ddd, *J*=13.7, 8.6 and 3.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 170.0, 169.7, 169.4, 76.8, 69.6, 67.4, 66.3, 33.0, 31.6, 30.1, 20.8, 20.7, 20.7.

IR (KBr, cm^{-1}) 3462, 2359, 1786, 1740, 1373, 1228, 1051, 913, 743.

Anal. Calcd for C_{14} H_{18} O_8: C, 53.50; H, 5.77. Found: C, 53.27; H, 5.80

3.15 Synthesis of 4-(2-hydroxyethyl)cyclohexane-1,2,3,5-tetraol (73)

45 mg $LiAlH_4$ was dissolved in 15 mL dry THF and cooled to 0 ^oC. While reaction was stirring magnetically, the reaction medium was saturated with nitrogen gas and 140 mg (0.44 mmoles) of lactone **83** which was dissolved in 13 mL dry THF added to $LiAlH_4$ solution drop wise in 3 hours. After addition of **83**, 6 g silica gel and ether was added to the reaction mixture and waited for one night. For completion of the hydrolysis 25 mL methanol was added and filtered. The solvent was removed by rotary evaporator (50 ^oC). 70 mg of product was obtained in a yield of 50 % [34].

3.16 Synthesis of 4-(2-acetoxyethyl)cyclohexane-1,2,3,5-tetraacetate (88)

70 mg (0.36 mmol) of pentaol **73** was dissolved in 1 mL of pyridine and 200 mg of acetic anhydride was added. The reaction was stirred magnetically for 6 hours at room temperature. After 6 hours the reaction mixture was poured to a 75 mL 1 N HCl solution which was cooled to 0^oC. Organic phase was obtained by the extraction with ether (3x50 mL). Organic phase was firstly washed with saturated 10 mL $NaHCO_3$ solution and then with 5 mL water. Overall organic phase was dried over Na_2SO_4 and the ether was removed by rotary evaporator (40 ^oC) 40 mg of product was obtained in a yield of 57% [34].

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.06 (m, 4H), 4.05 (t, *J*=6.6 Hz, 2H), 2.30-2.22 (m, 1H), 2.04 (s, -CH_3), 1.99 (s, -CH_3), 1.98 (s, -CH_3), 1.97 (s, -CH_3), 1.96 (s, -CH_3), 1.86-1.79 (m, 1H), 1.56 (dq, *J*=8.0 and 6.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 168.8, 168.6 (2C), 69.5, 69.4, 68.7, 68.3, 61.5, 37.7, 28.9, 24.4, 20.1, 19.9, 19.8, 19.7, 19.6.

IR (KBr, cm^{-1}) 3467, 2963, 1740, 1260, 1094, 1025, 800.

3.17 Synthesis of 4-(2-hydroxyethyl)cyclohexane-1,2,3,5-tetraol (73)

40 mg **88** was dissolved in 20 mL methanol and NH_3 gas was bubbled into the reaction mixture for 4 days at room temperature. When the reaction was complete the solvent was removed by rotary evaporator (55 ^oC). 15 mg product was obtained in a yield of %38.

^{1}H NMR (400 MHz, D_2O) δ 3.98 (dd, *J*=5.3 and 3.1 Hz, 1H), 3.81 (dd, *J*=9.6 and 5.2 Hz, 1H), 3.73-3.63 (m, 1H), 3.61- 3.54 (m, 2H), 3.65 (t, *J*=9.2 Hz, 1H), 1.93 (q, *J*=4.1, 1H), 1.85 (dt, *J*=13.4 and 3.7, 1H), 1.80 (ddd, *J*= 14.6, 7.3 and 2.5 Hz, 1H), 1.67 (dt, *J*=11.6 and 2.8 Hz, 1H), 1.22 (dq, *J*=8.0 and 6.5 Hz, 1H).

^{13}C NMR (100 MHz, D_2O) δ 74.5, 72.1, 70.3, 68.3, 60.7, 48.8, 33.9, 27.9

CHAPTER 4

CONCLUSION

Cylitols concerning a large group of natural products have attracted a great deal of attention from the synthetic community due to their glycosidase inhibition activities and their versatility as synthetic intermediates. Carbasugars are also a derivative of cyclitols and they are cyclic monosaccharide analogues which posses $–CH_2OH$ group in their structure. Hence, to develop new and short synthesis leading to cyclitols and their derivatives is a field of interest.

In this study, we had two target molecules, **72** and **73** containing a $–CH_2OH$ group in their structure. For the synthesis of these target molecules **10** and **71** were thought as the key compounds.

The synthesis of tetraol and pentaol derivative (**72** and **73**) was achieved successfully. Moreover, by the use of manganese III acetate oxidation reactions having considerable synthetic utilities in organic chemistry we developed new synthetic methodologies for the cyclitol derivatives. The introduction of hydroxyl groups into the molecule was achieved by both singlet oxygen and manganese III acetate oxidation. As a result of this, we had considerable advance in the synthesis of cyclitol derivatives.

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APPENDIX

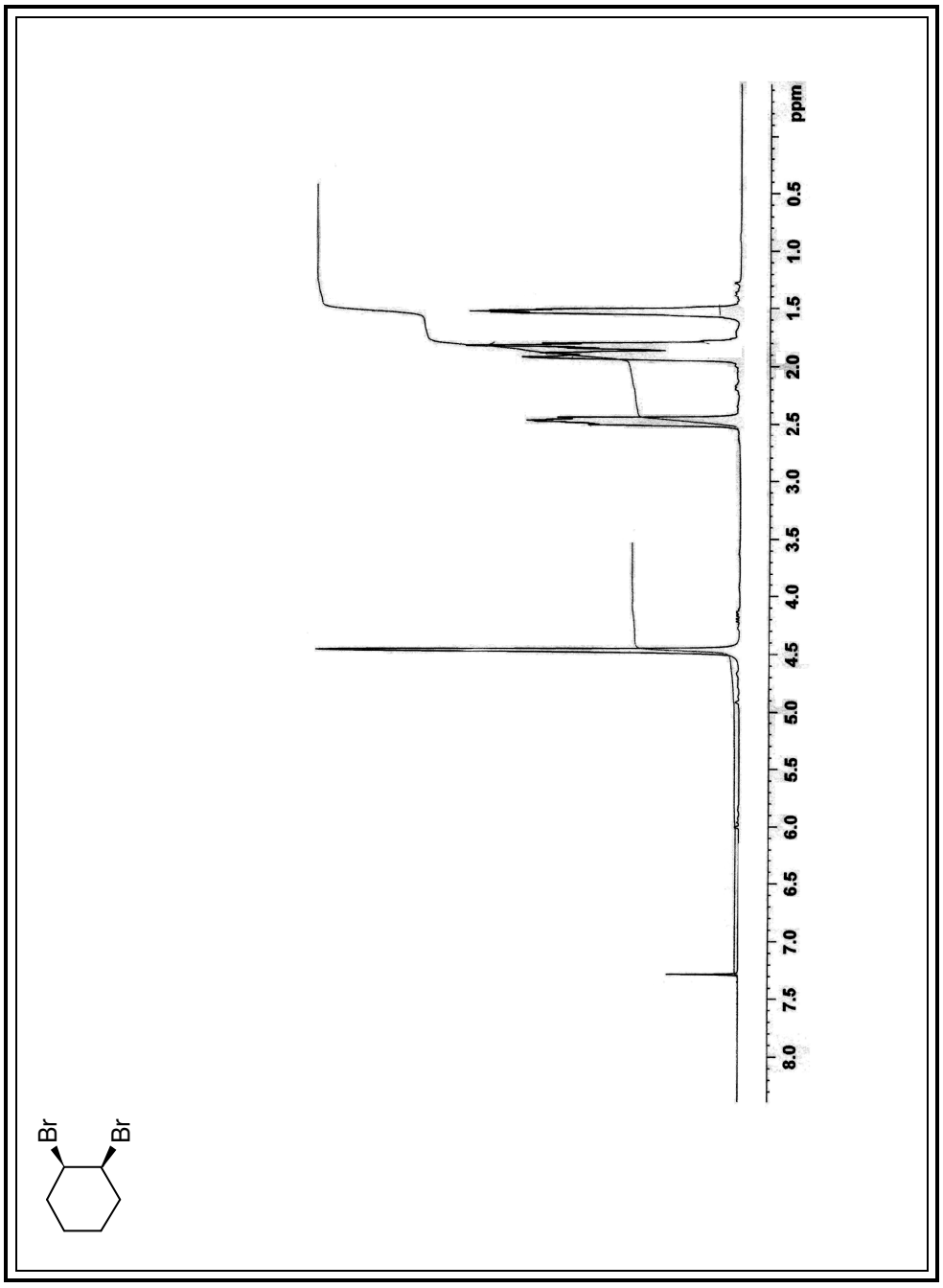

Figure 26 ^{1}H NMR spectrum of compound **75**

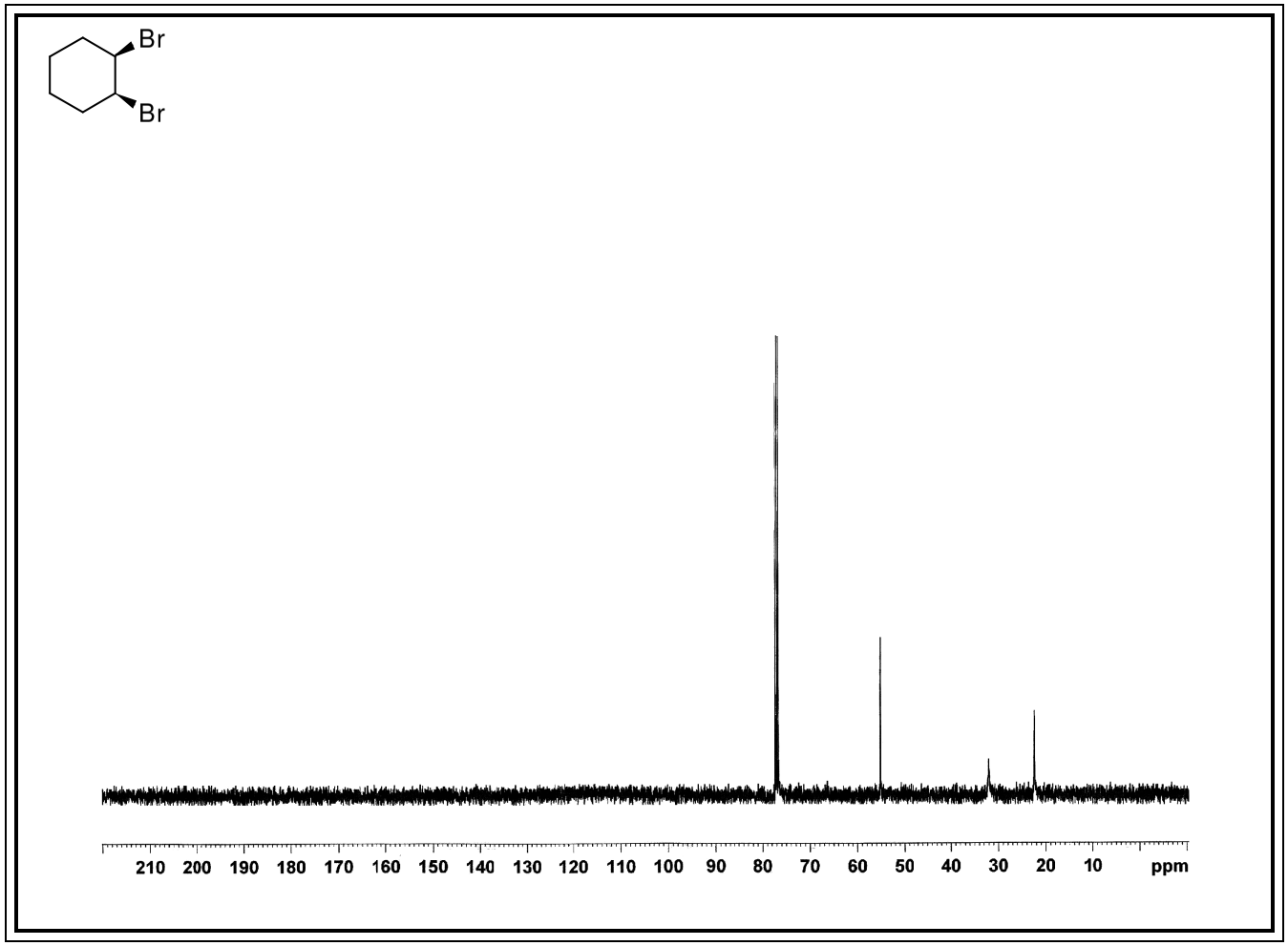

Figure 27 ^{13}C NMR spectrum of compound **75**

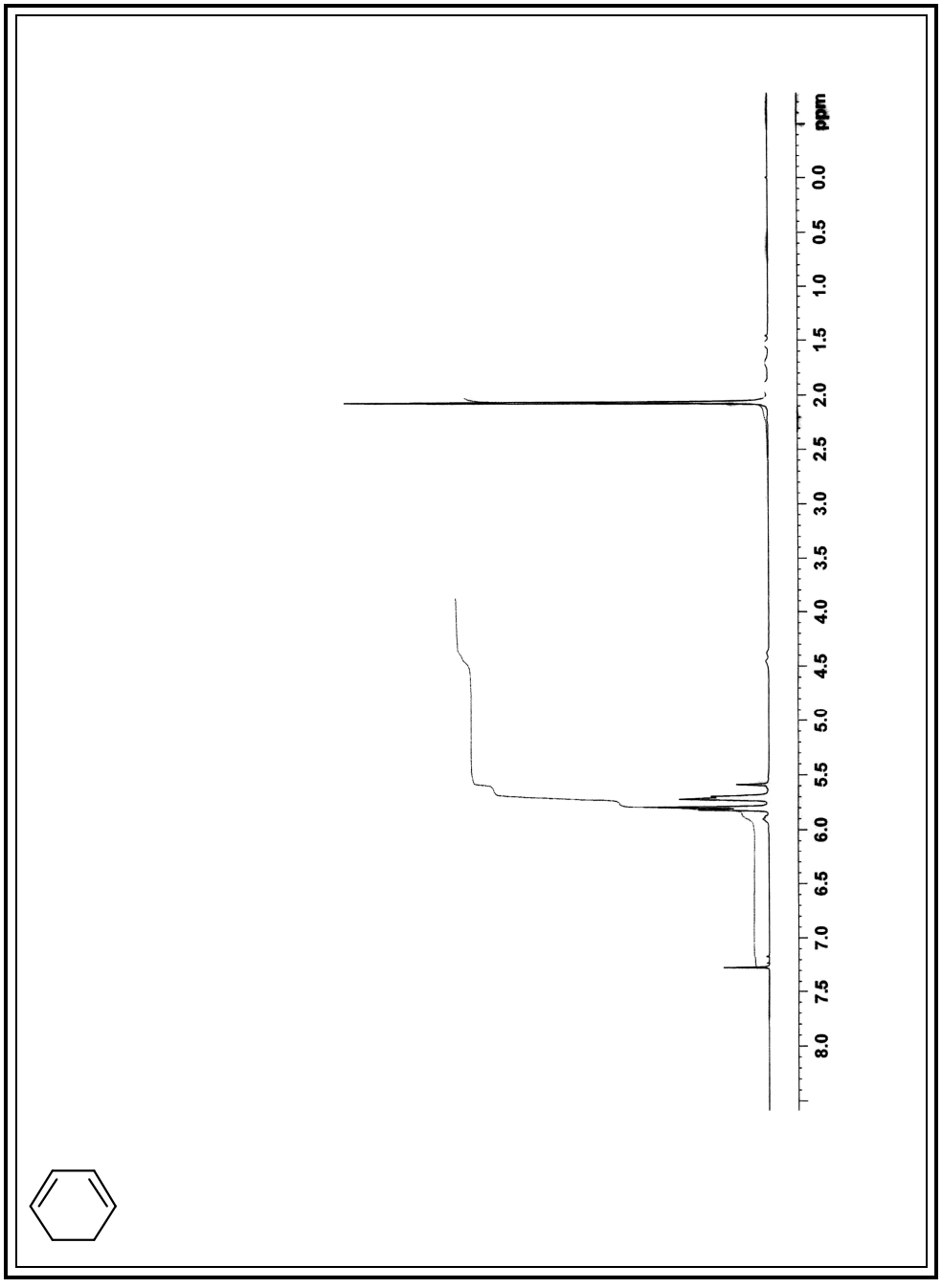

Figure 28 ^{1}H NMR spectrum of compound **71**

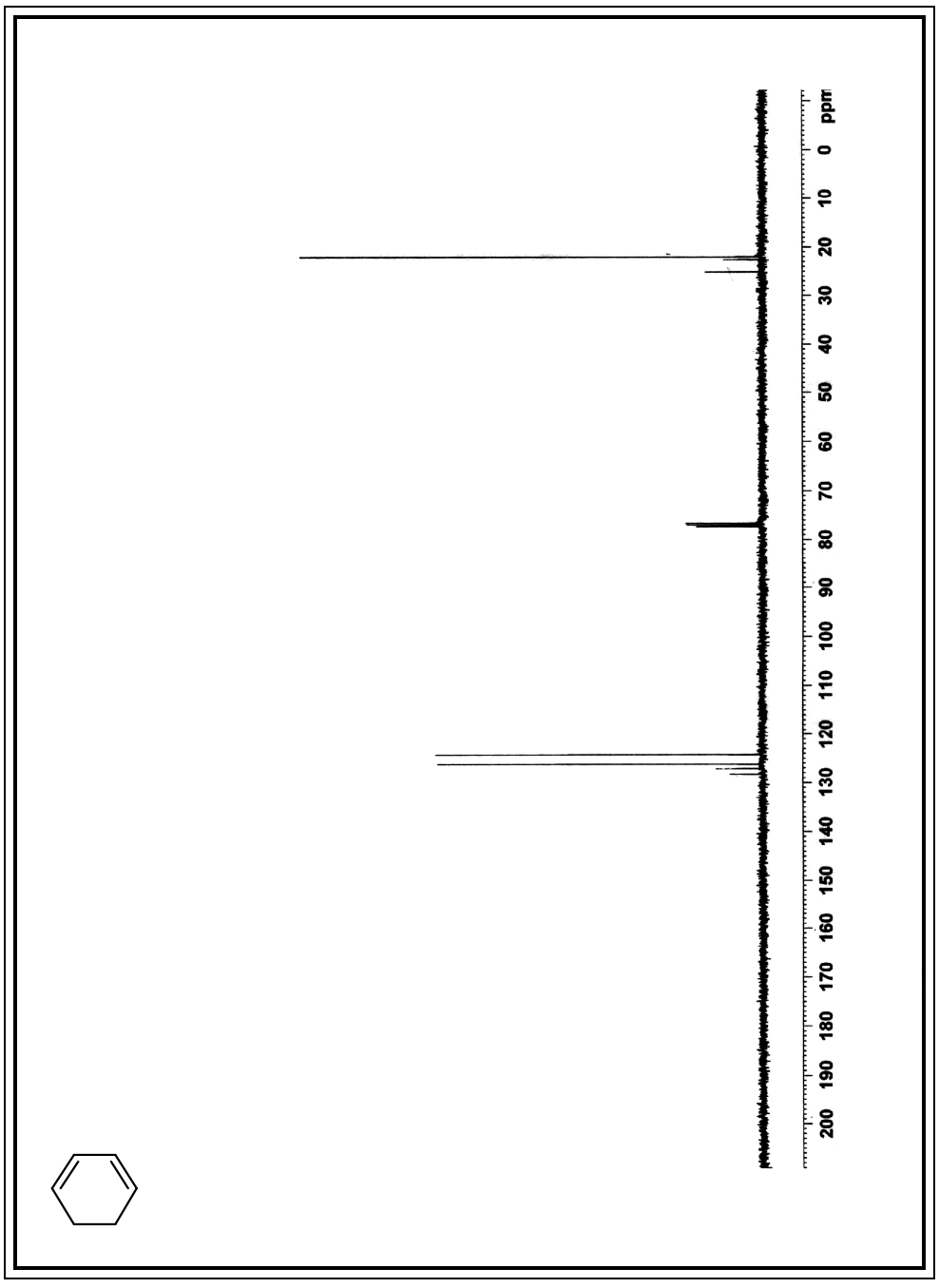

Figure 29 ^{13}C NMR spectrum of compound **71**

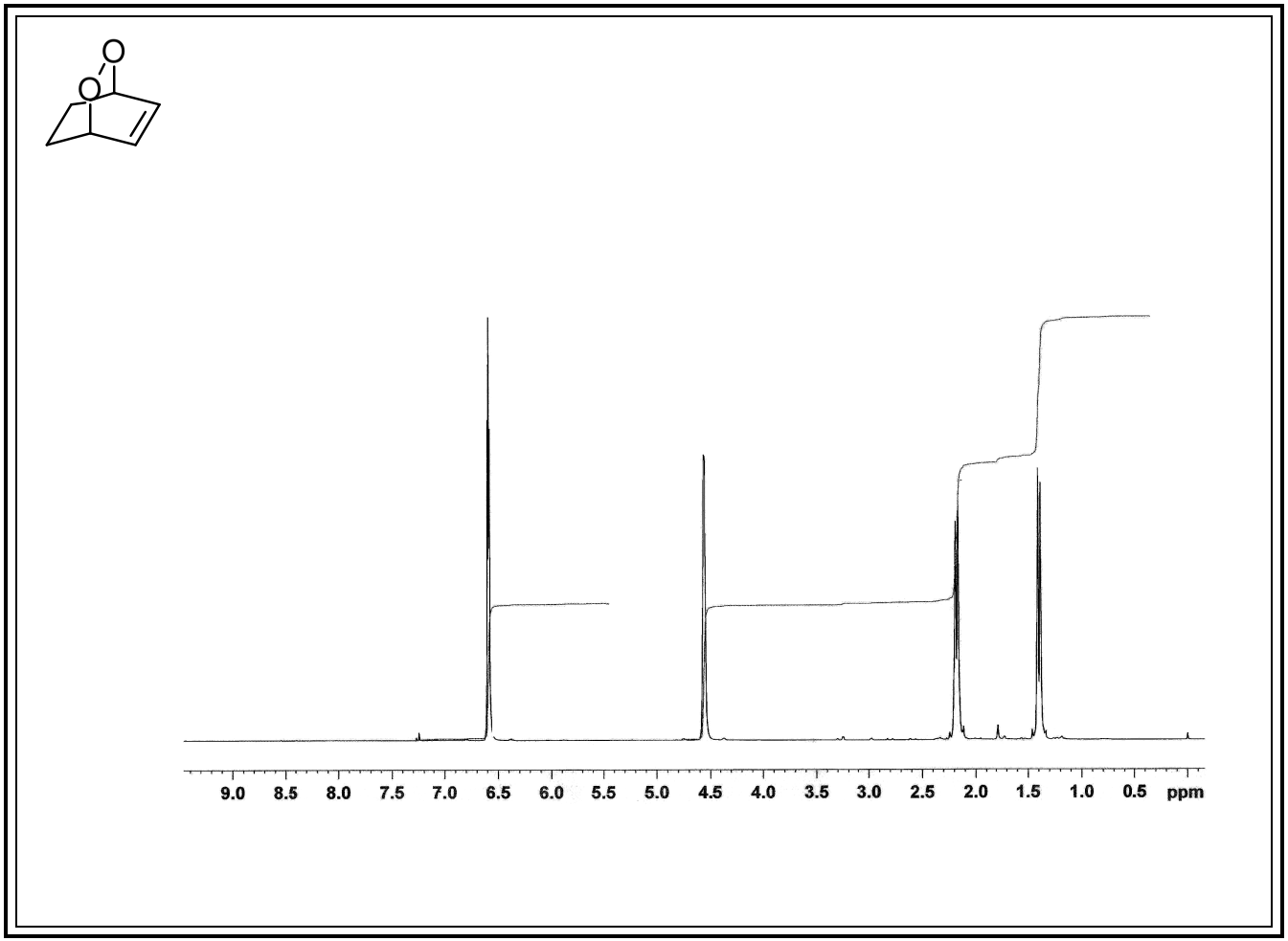

Figure 30 ^{1}H NMR spectrum of compound **77**

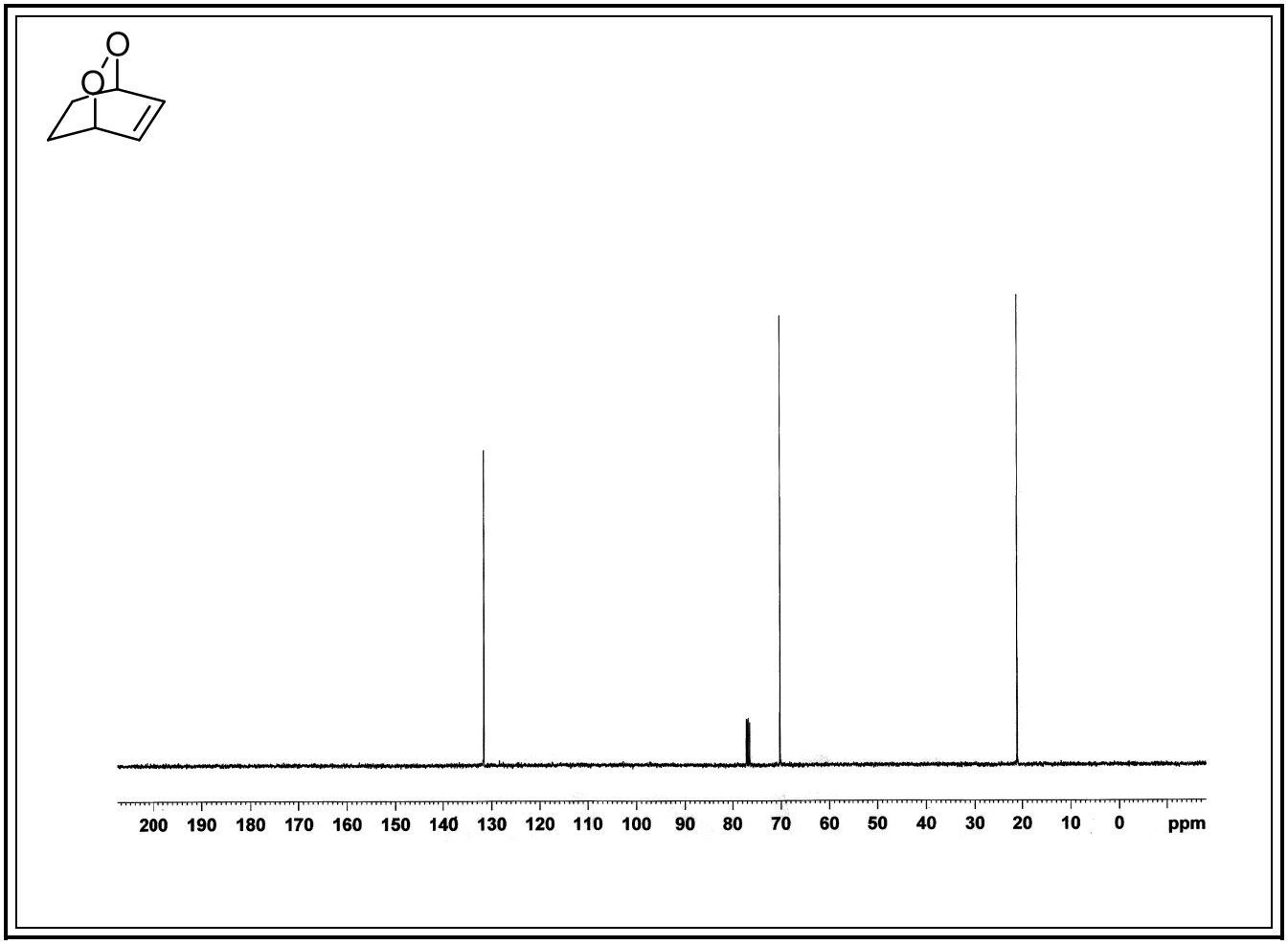

Figure 31 ^{13}C NMR spectrum of compound **77**

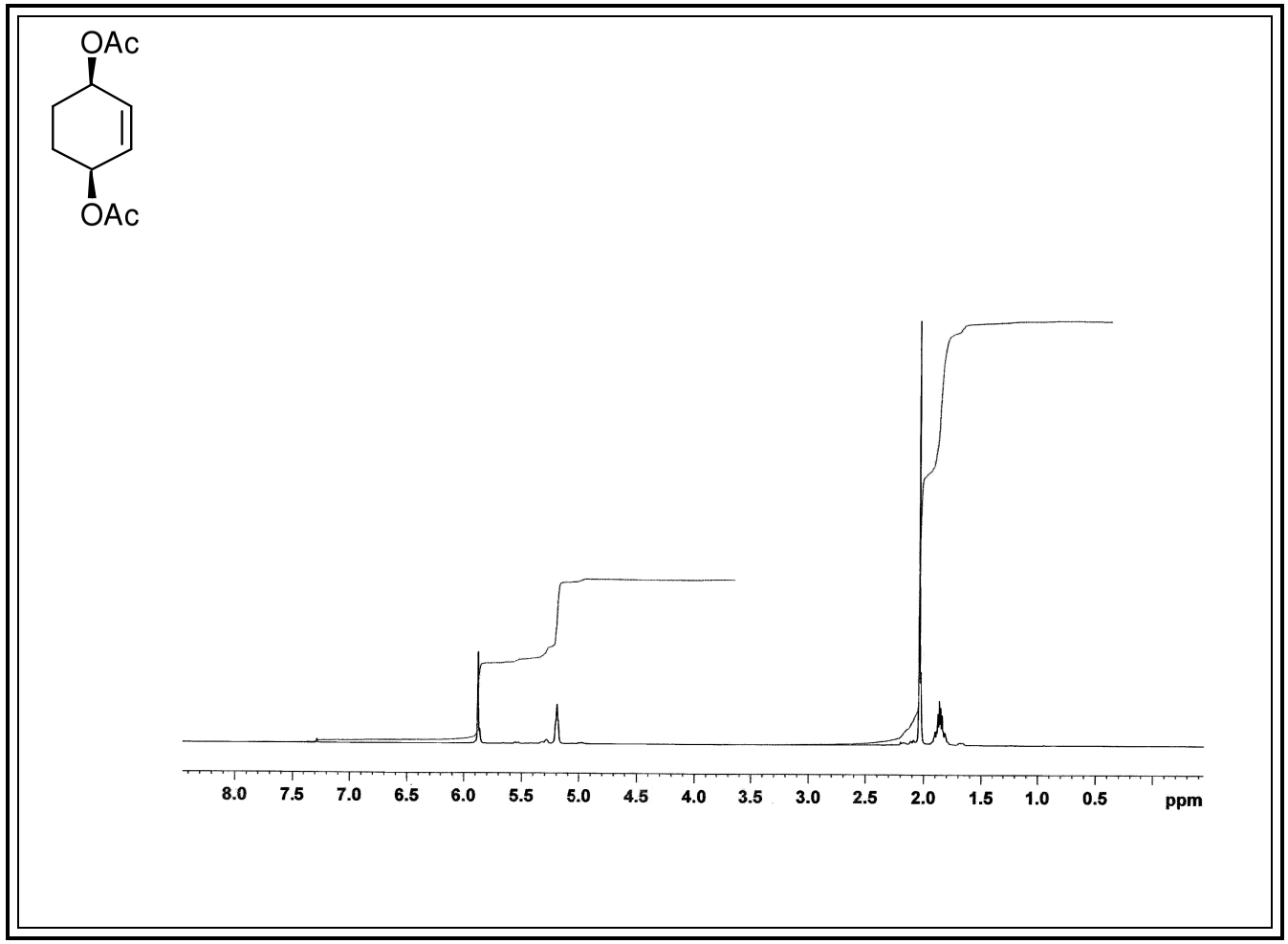

Figure 32 ^{1}H NMR spectrum of compound **80**

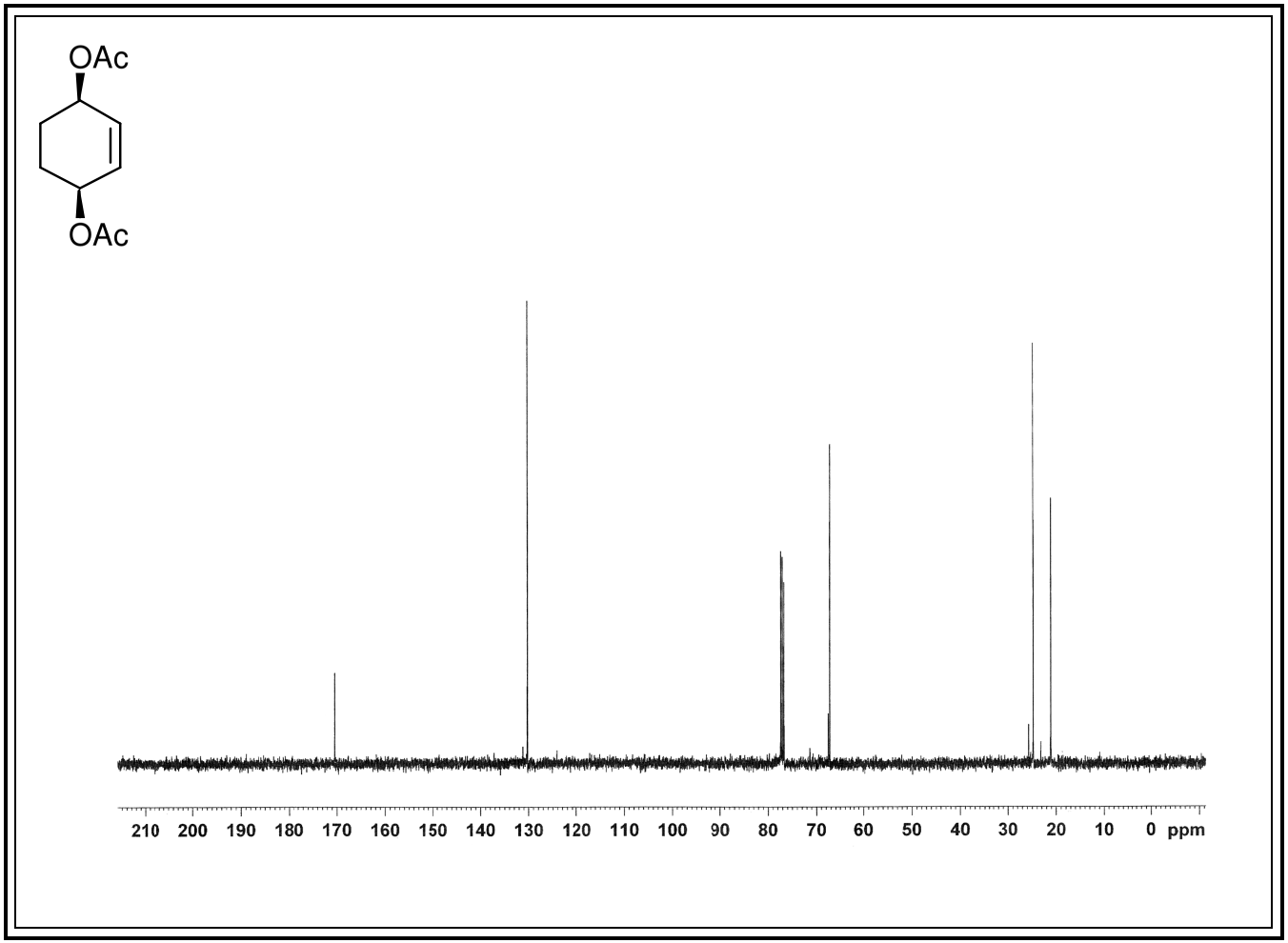

Figure 33 ^{13}C NMR spectrum of compound **80**

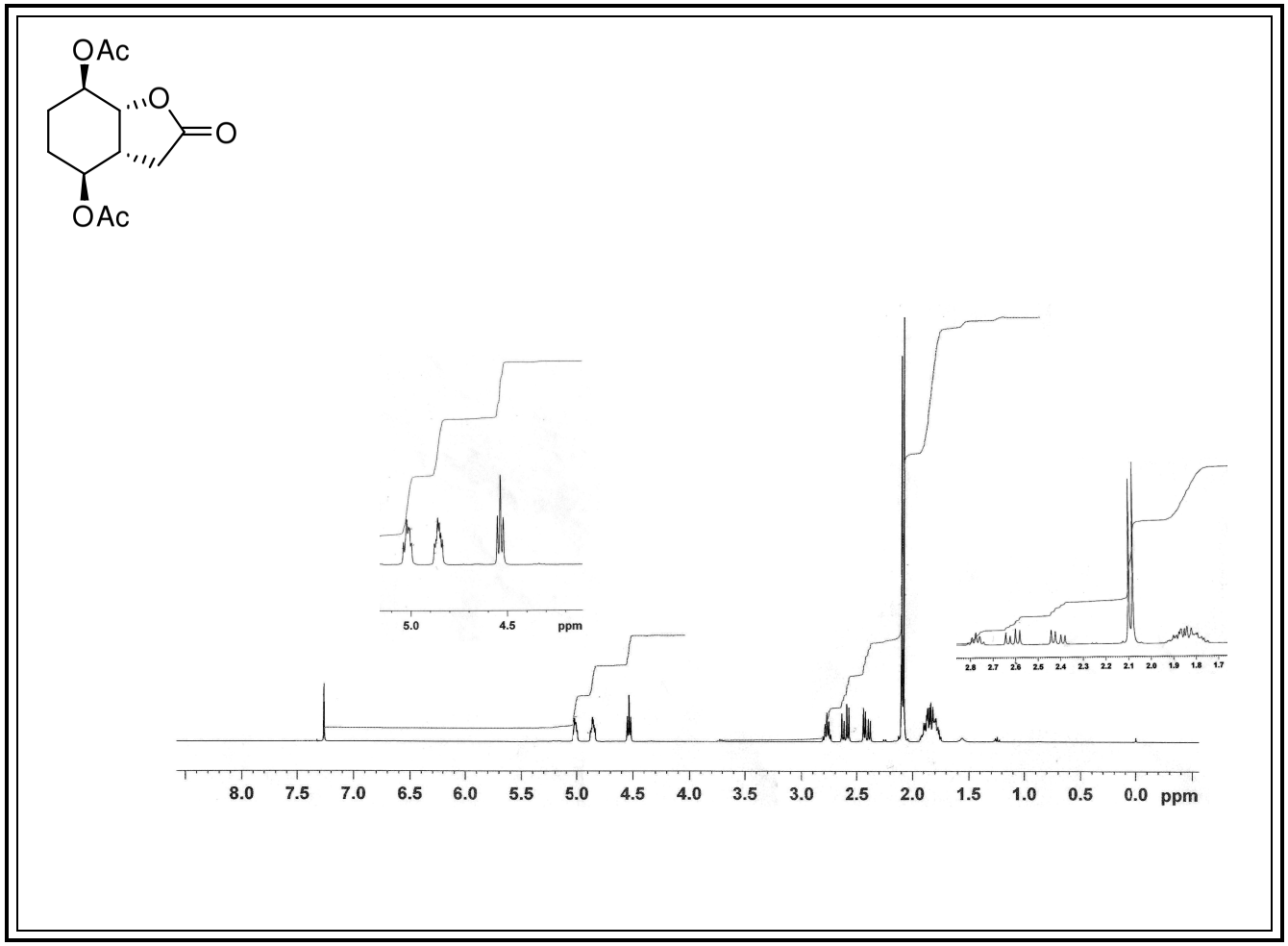

Figure 34 ^{1}H NMR spectrum of compound **78**

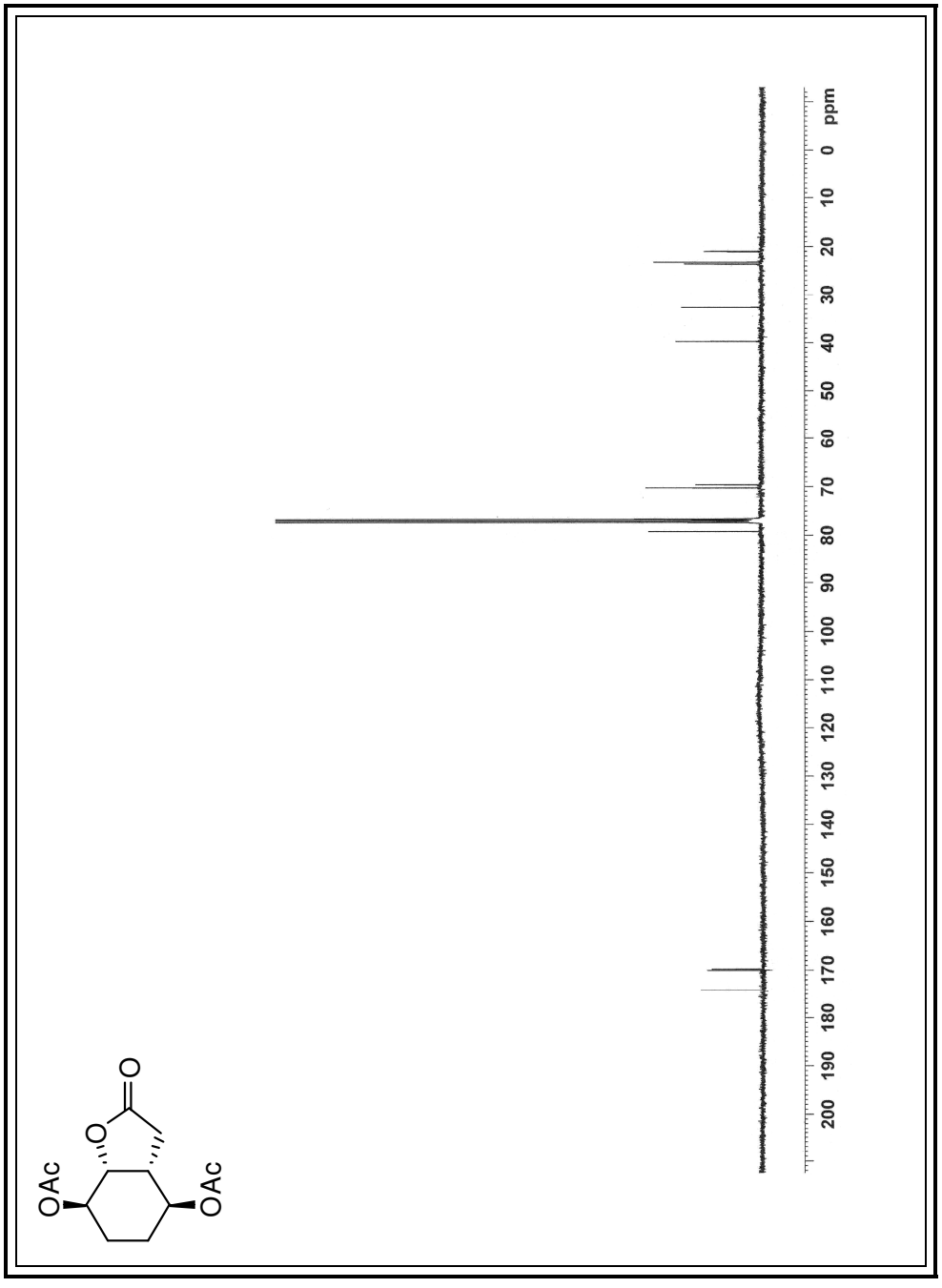

Figure 35 ^{13}C NMR spectrum of compound **78**

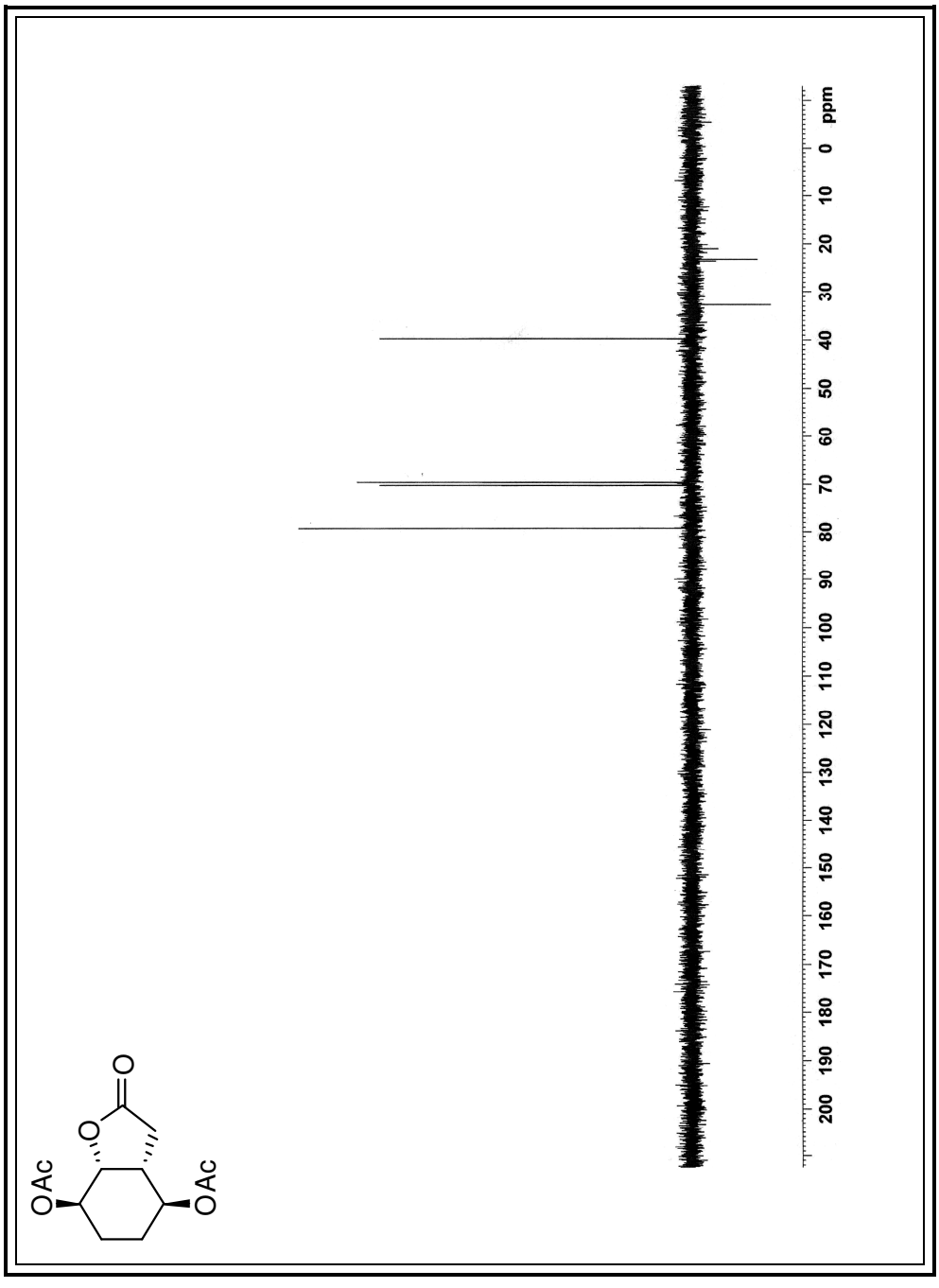

Figure 36 DEPT-90 spectrum of compound **78**

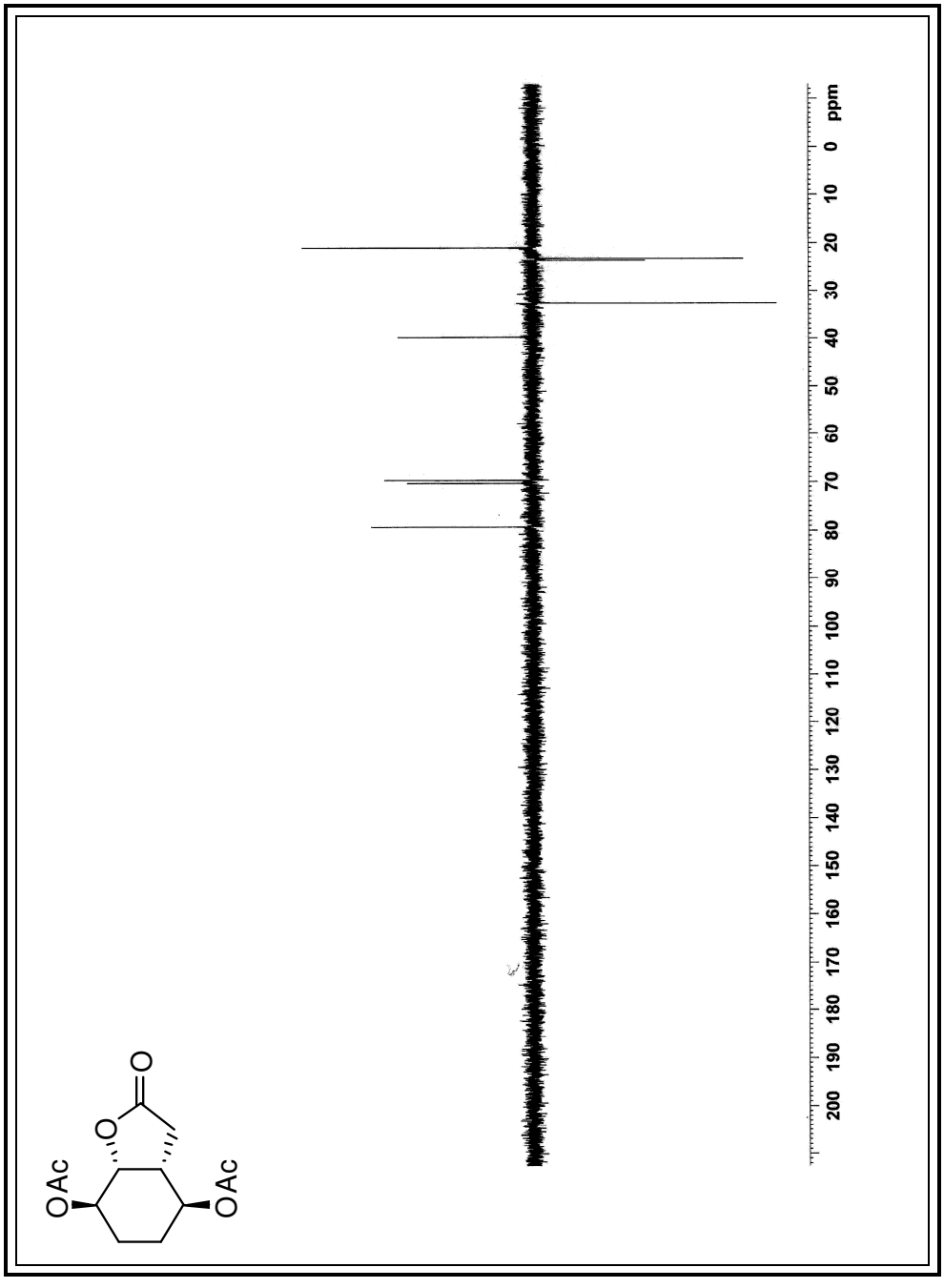

Figure 37 DEPT-135 spectrum of compound **78**

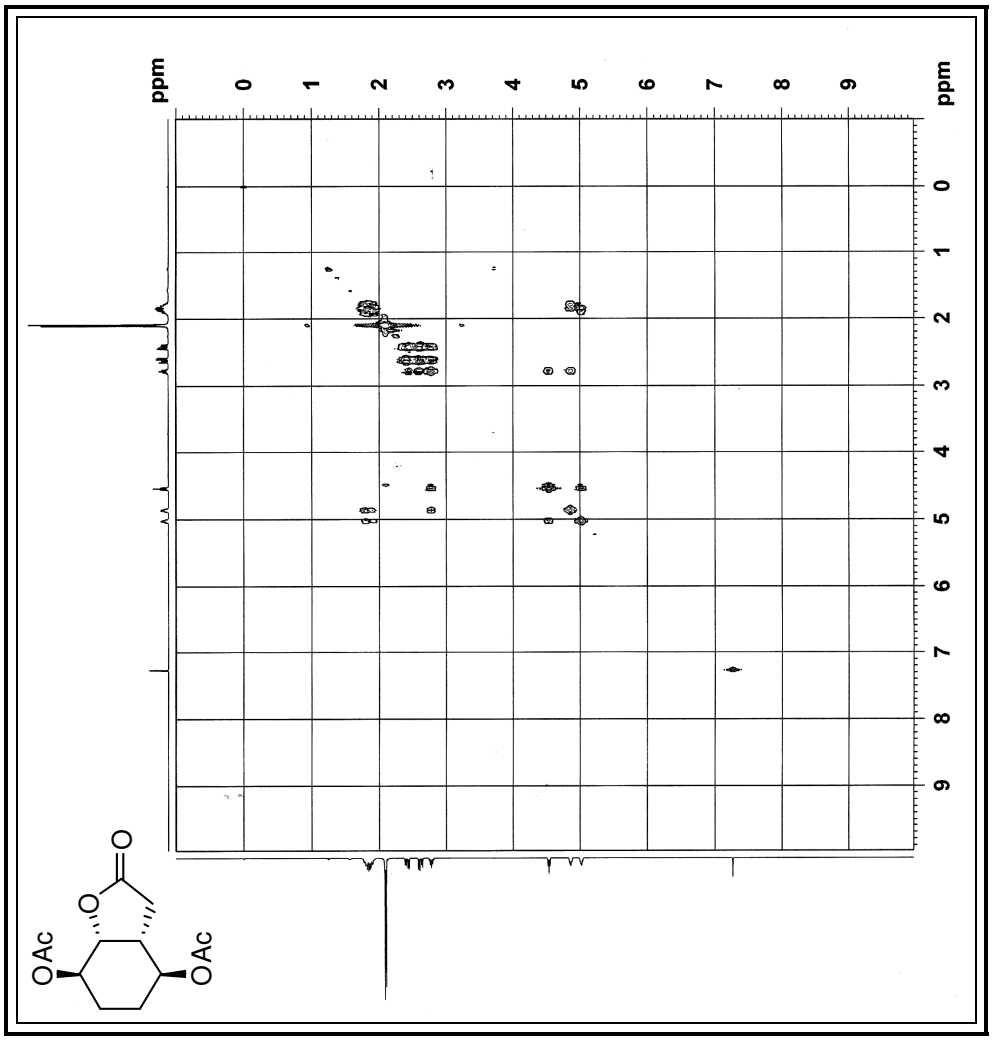

Figure 38 COSY spectrum of compound **78**

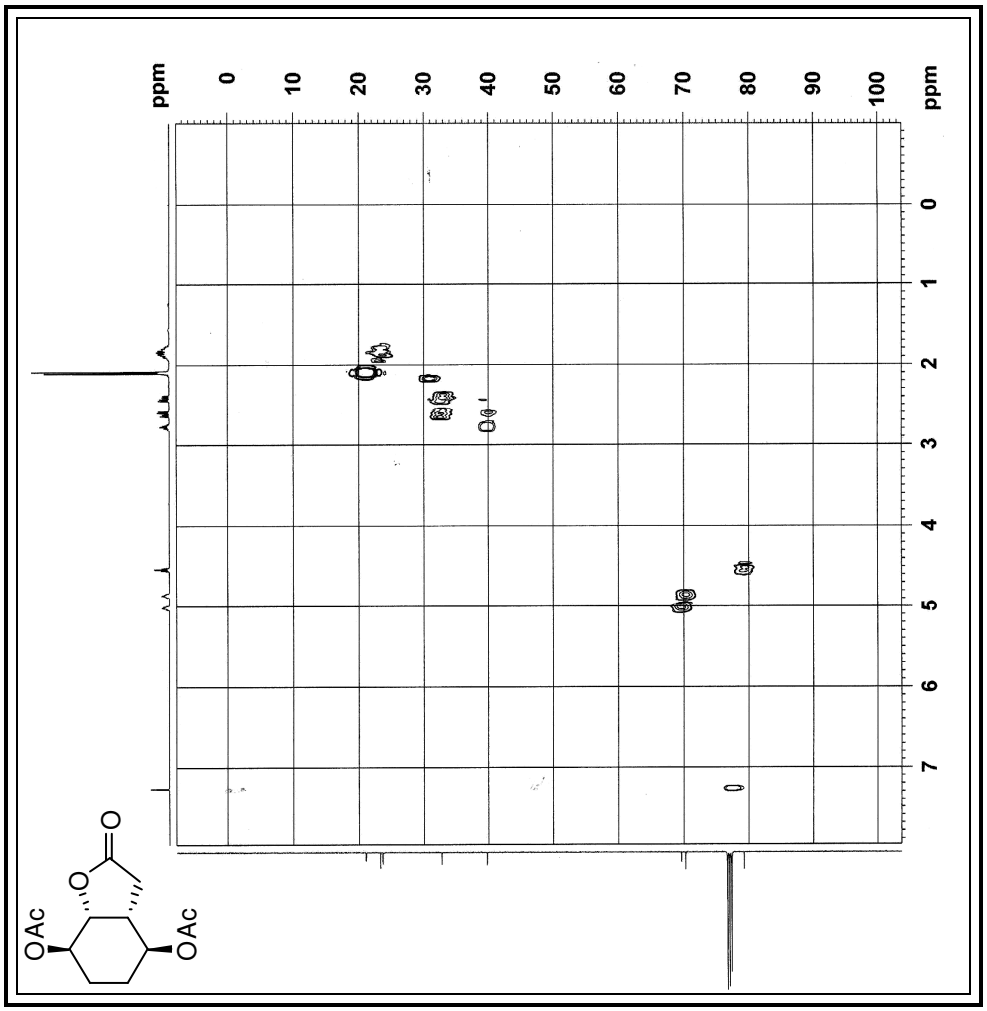

Figure 39 HMQC spectrum of compound **78**

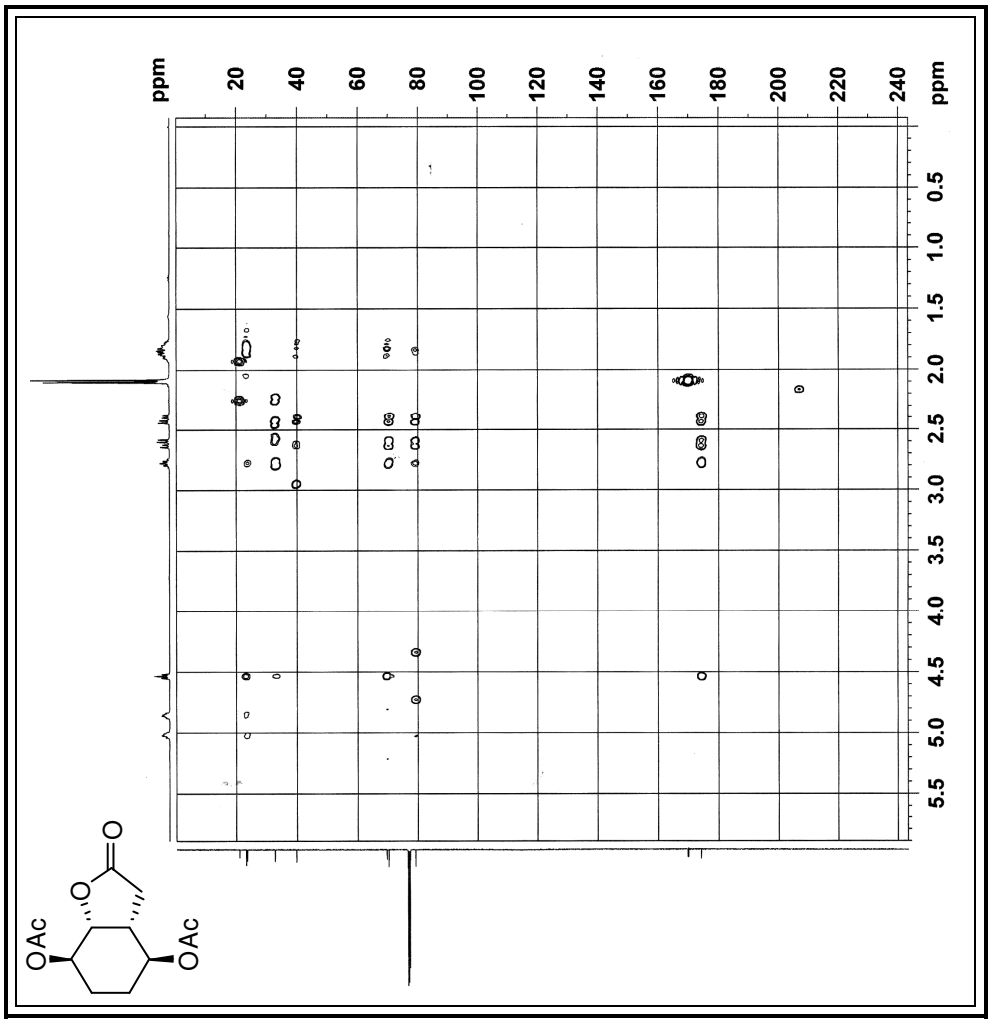

Figure 40 HMBC spectrum of compound **78**

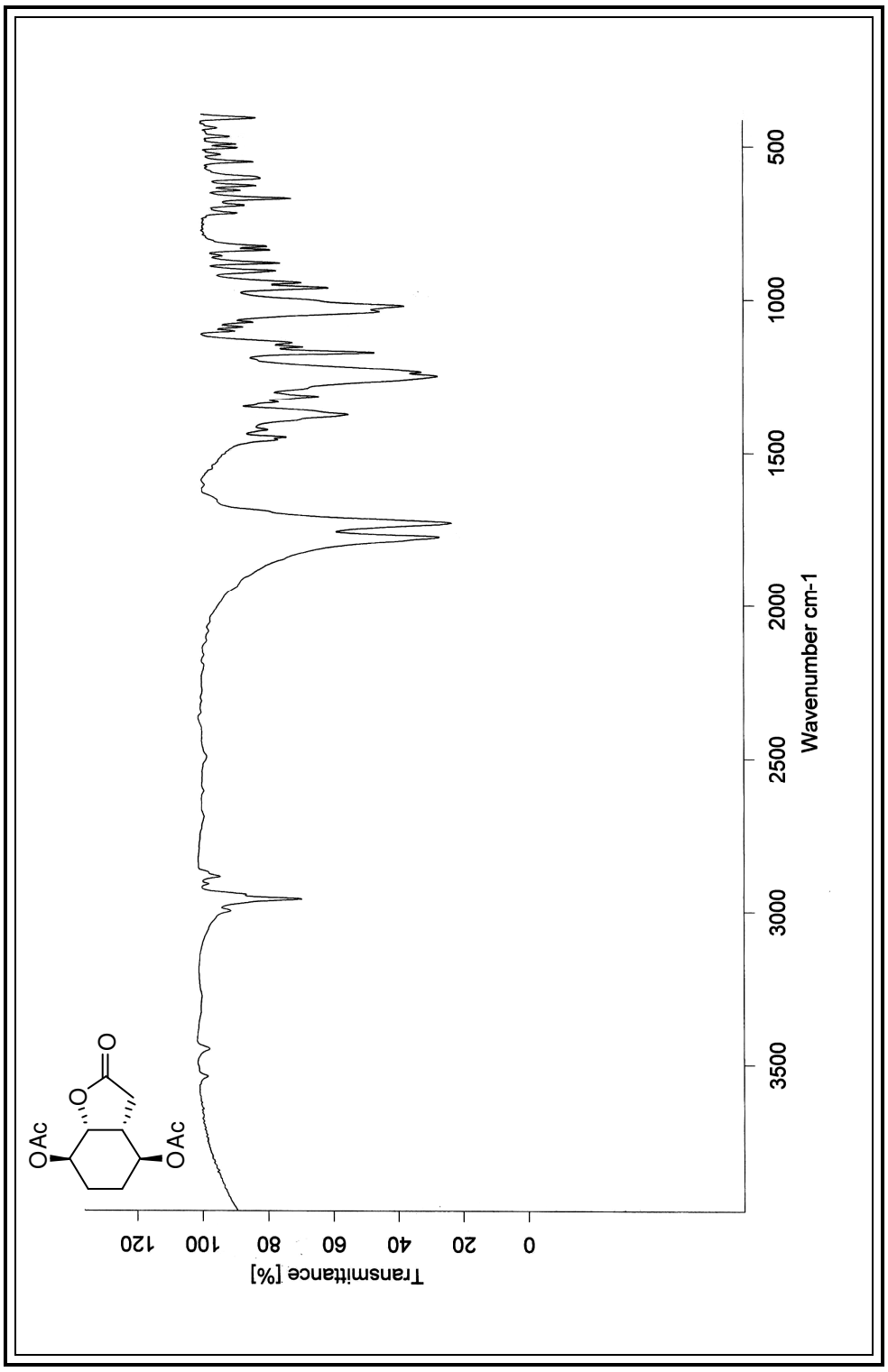

Figure 41 IR spectrum of compound **78**

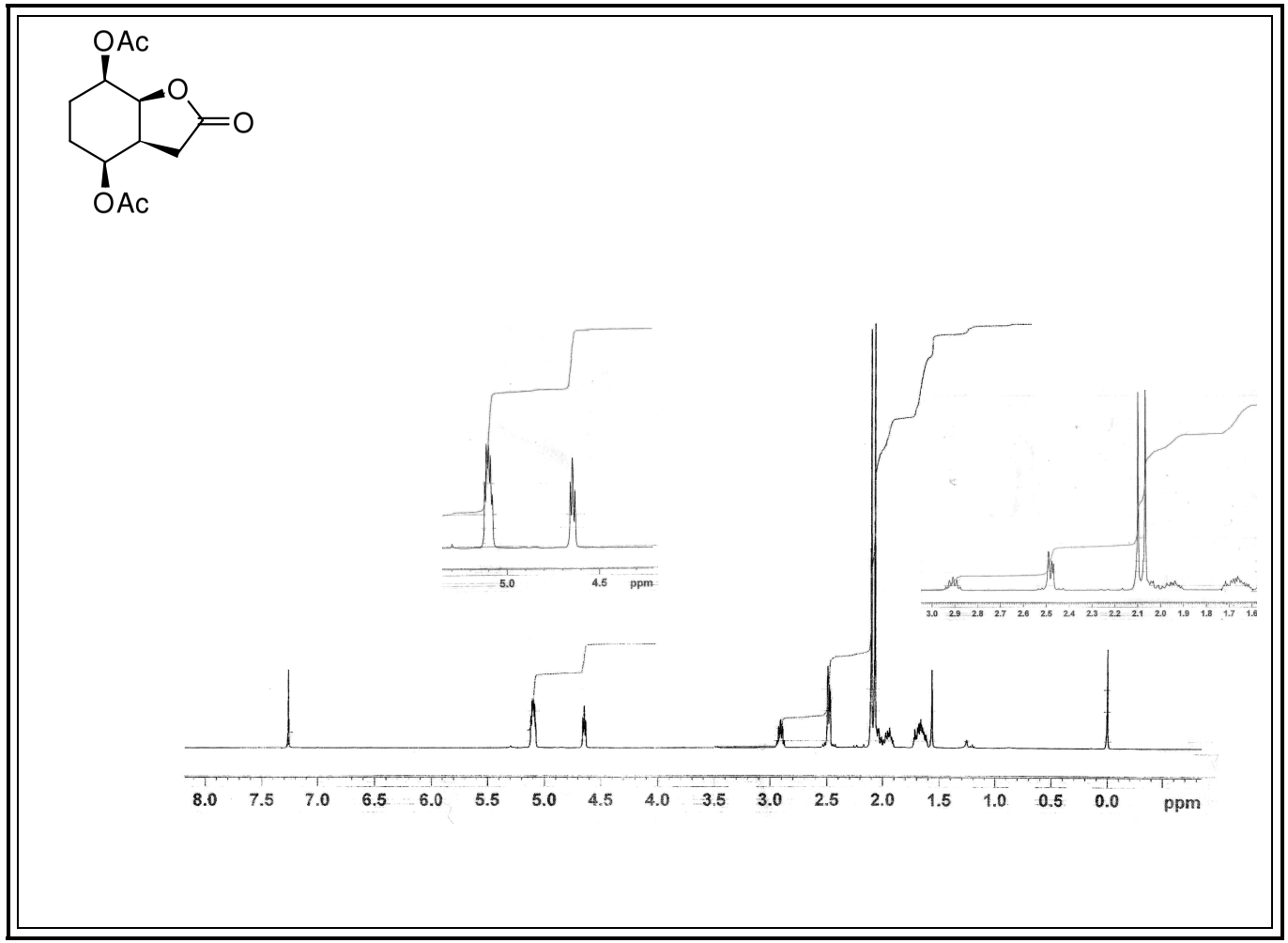

Figure 42 ^{1}H NMR spectrum of compound **81**

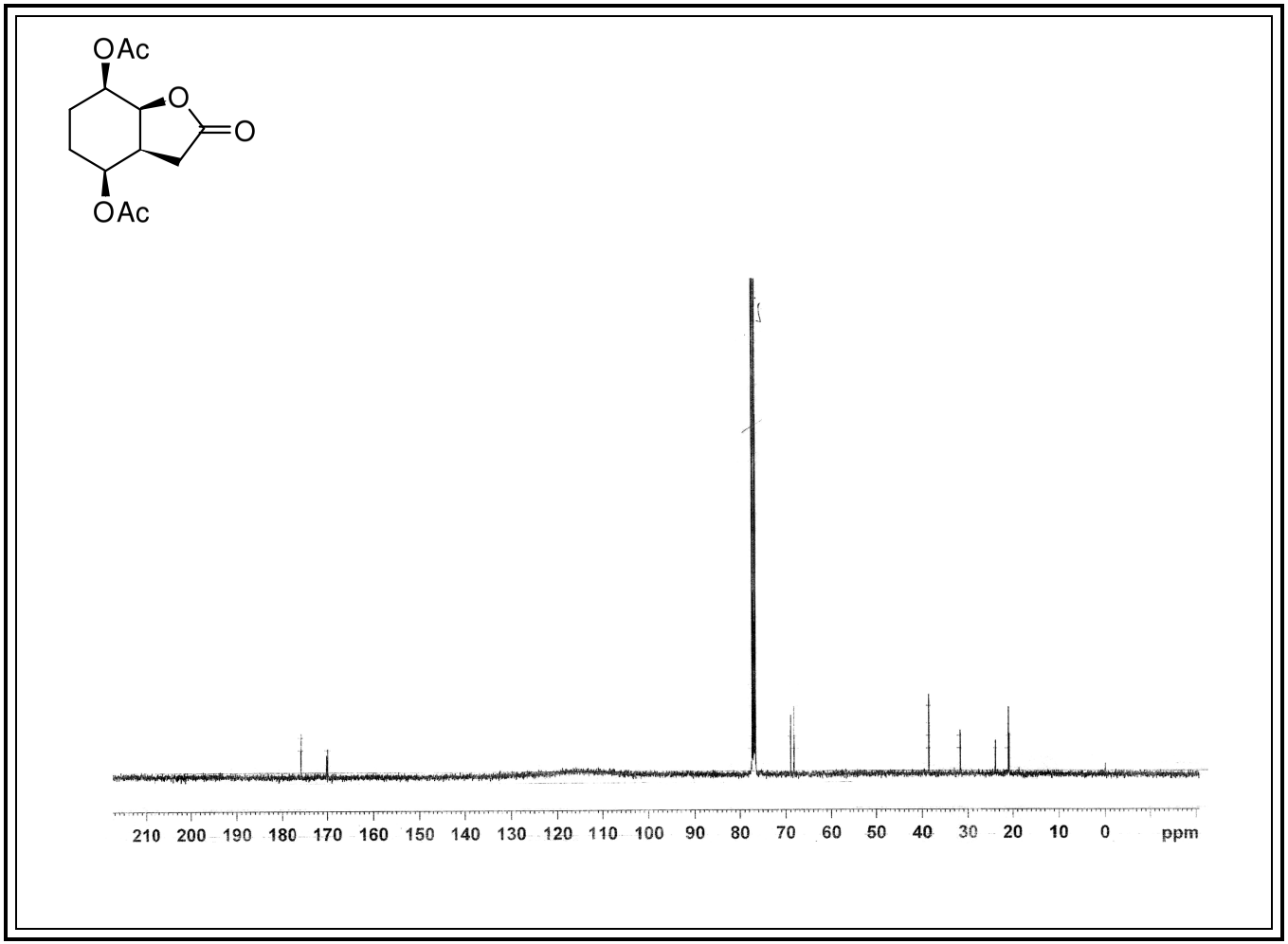

Figure 43 ^{13}C NMR spectrum of compound **81**

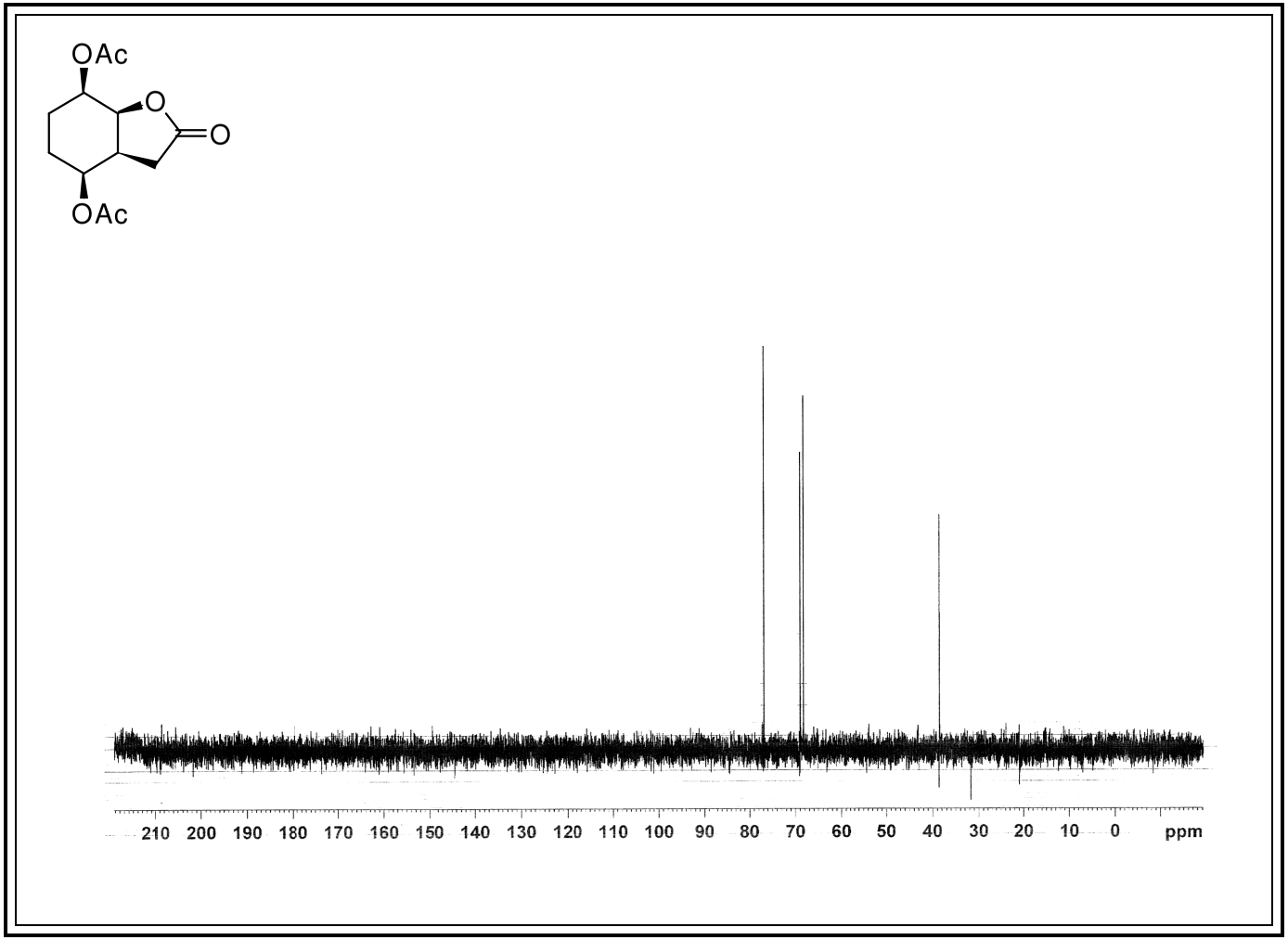

Figure 44 DEPT-90 spectrum of compound **81**

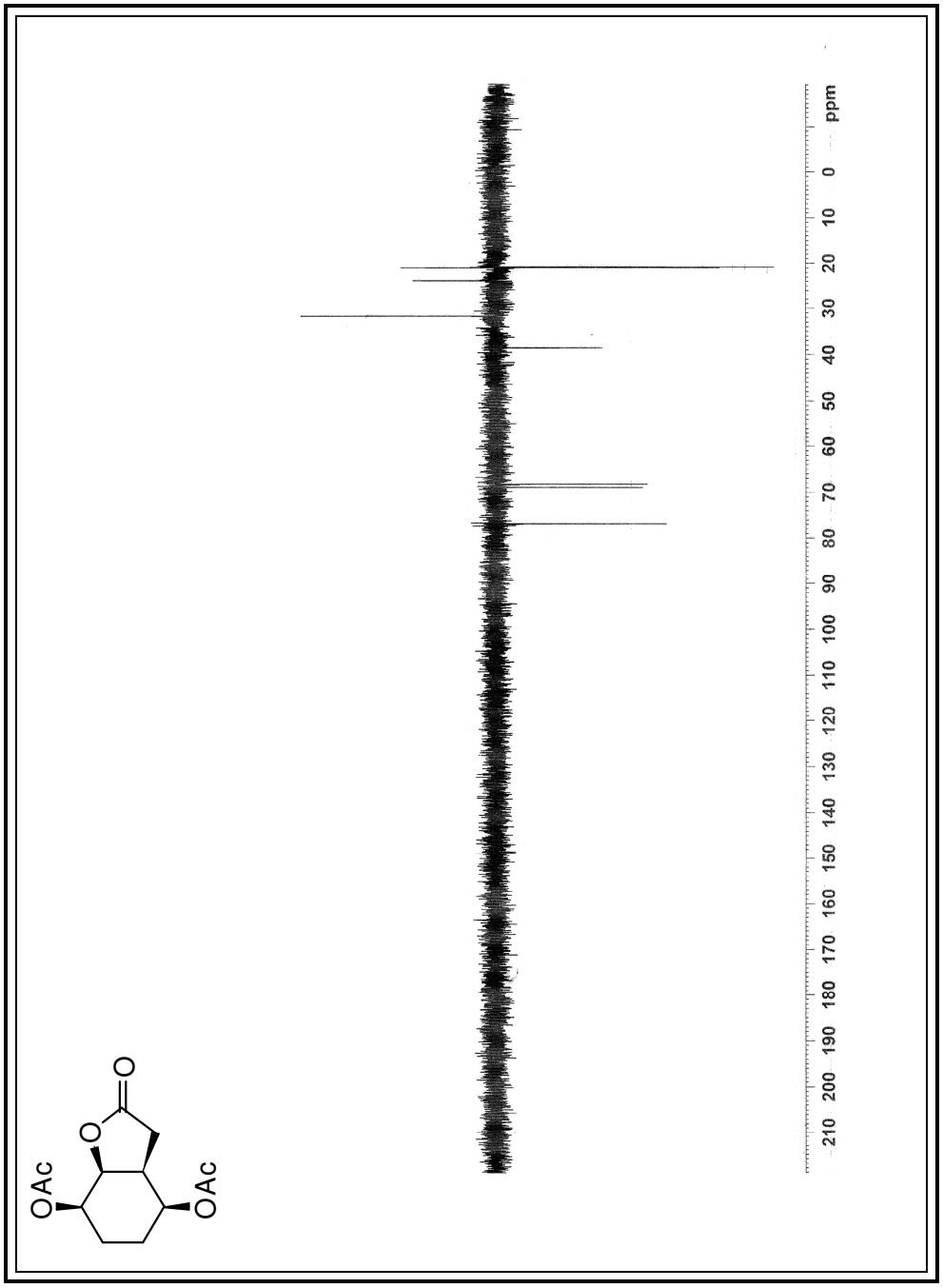

Figure 45 DEPT-135 spectrum of compound **81**

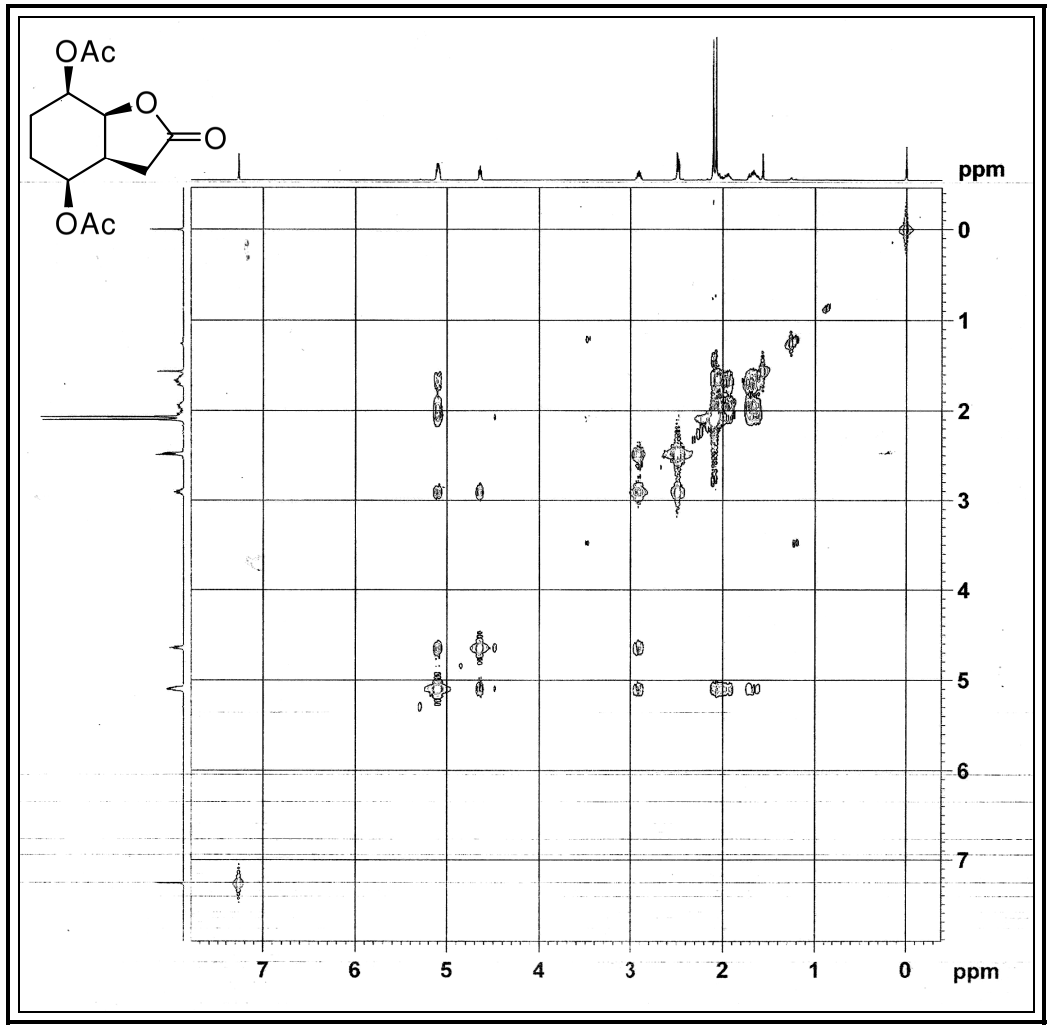

Figure 46 COSY spectrum of compound **81**

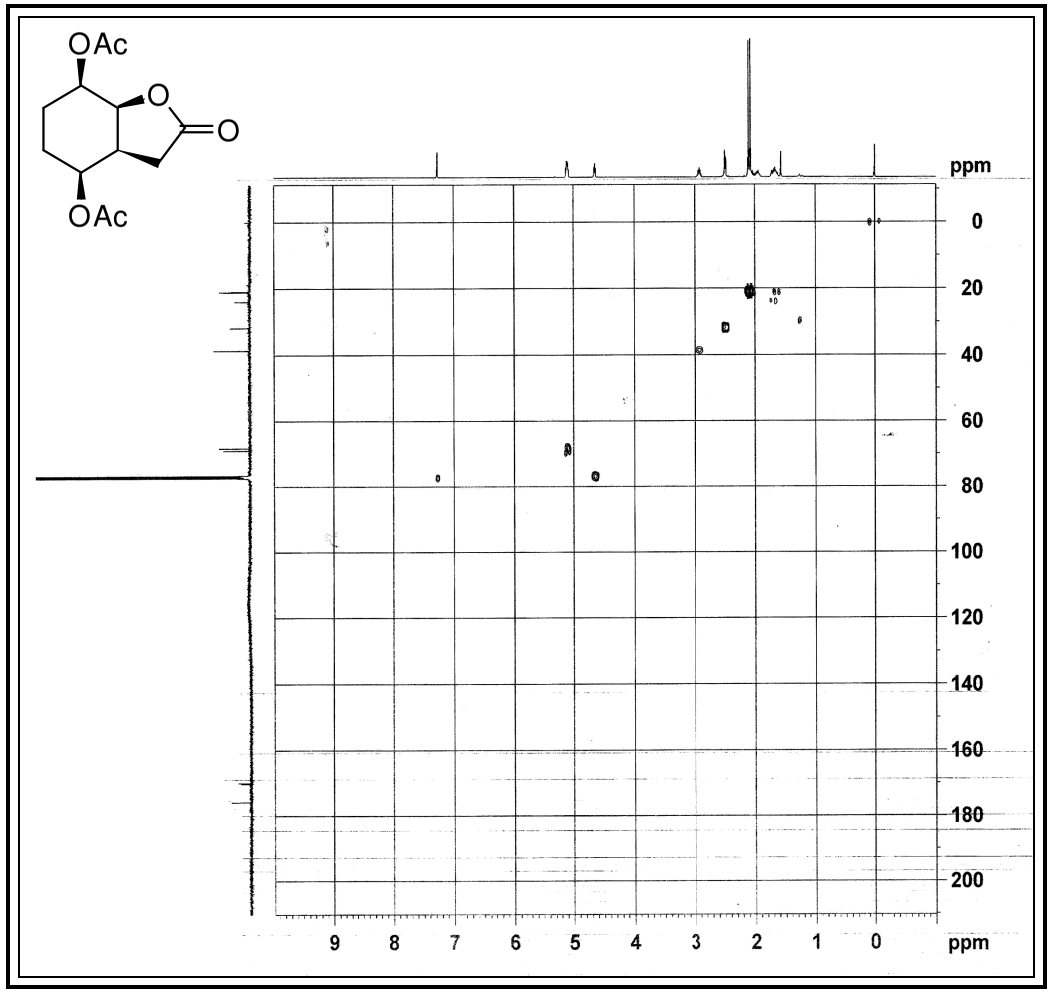

Figure 47 HMQC spectrum of compound **81**

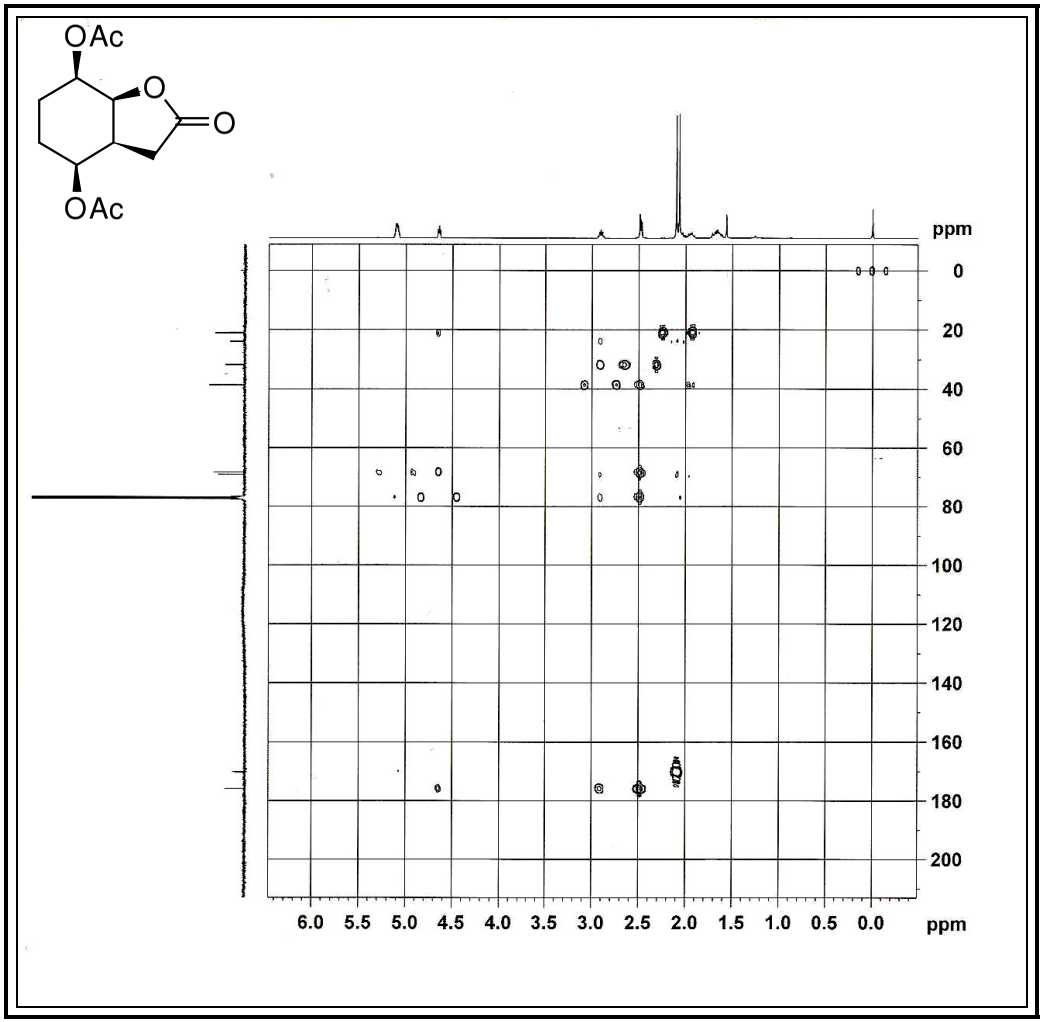

Figure 48 HMBC spectrum of compound **81**

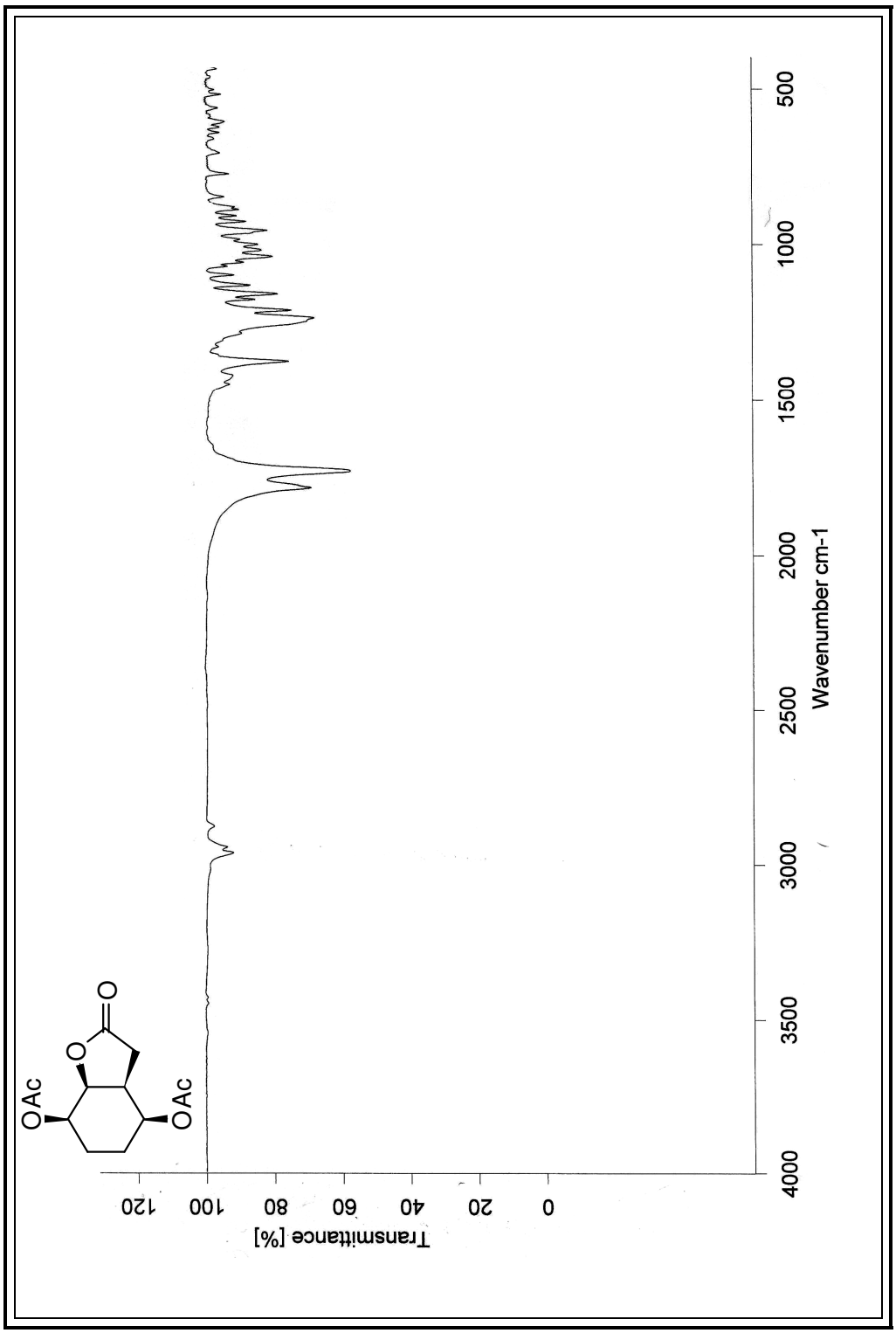

Figure 49 IR spectrum of compound **81**

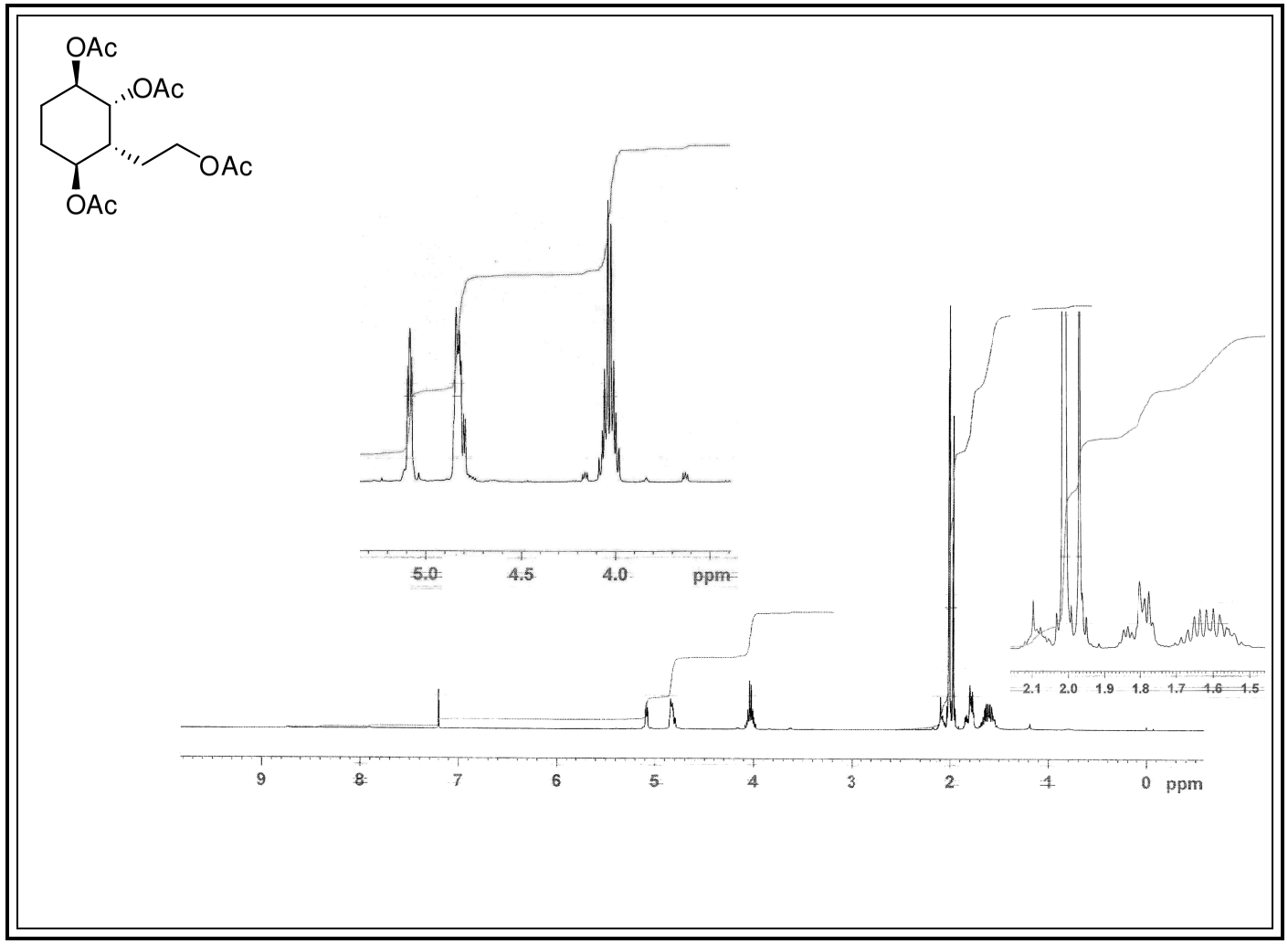

Figure 50 ^{1}H NMR spectrum of compound **82**

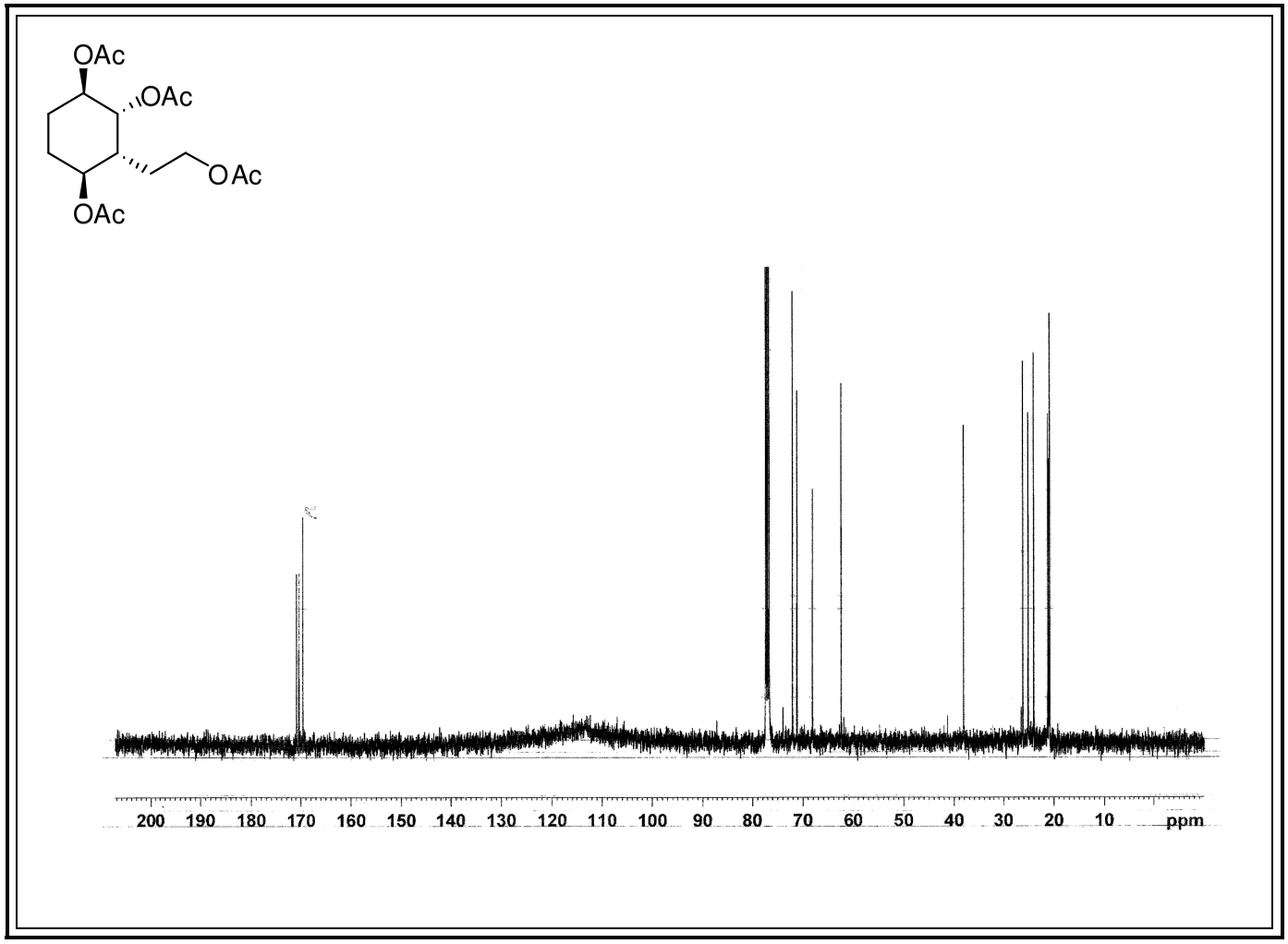

Figure 51 ^{13}C NMR spectrum of compound **82**

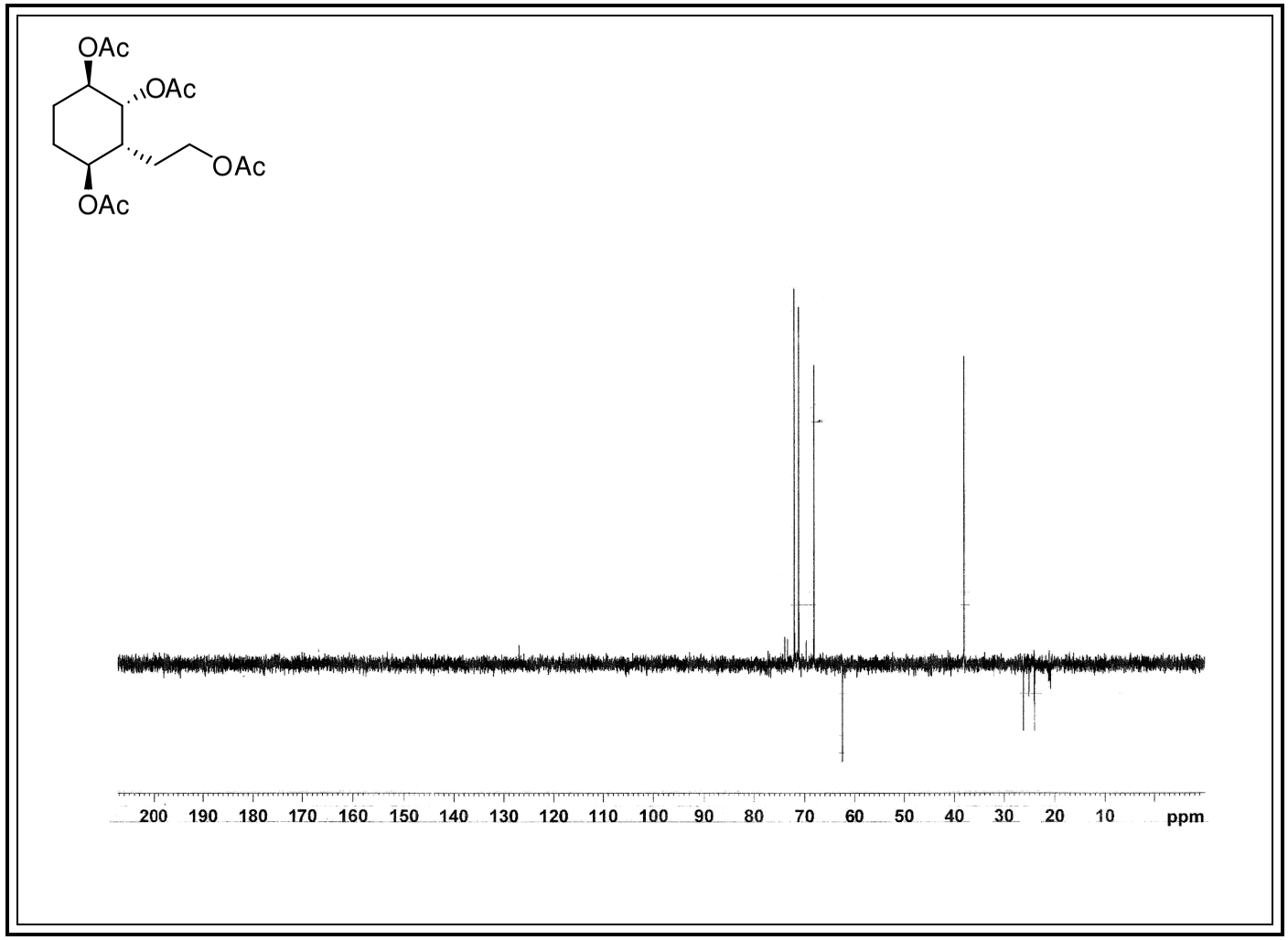

Figure 52 DEPT-90 spectrum of compound **82**

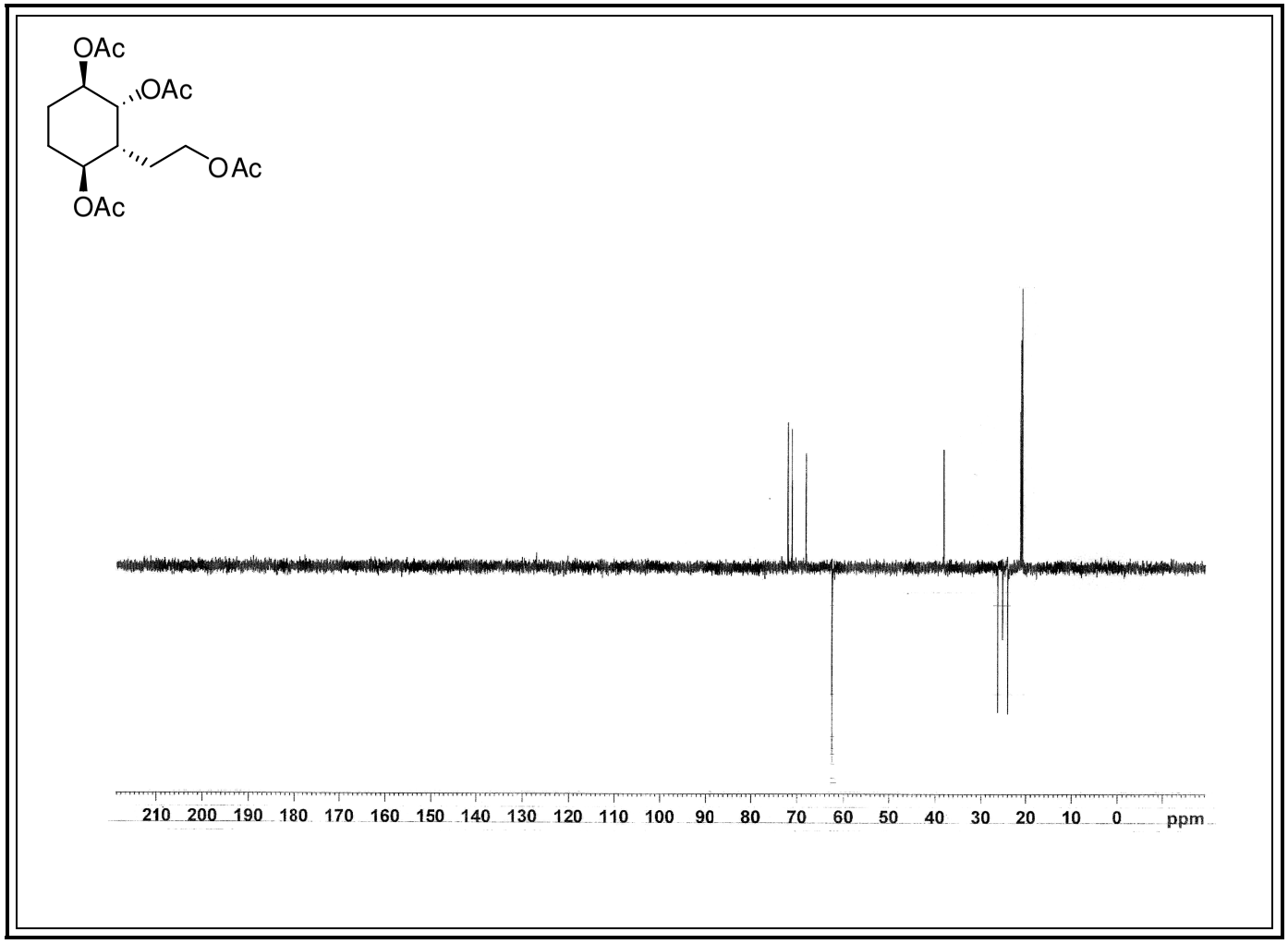

Figure 53 DEPT-135 spectrum of compound **82**

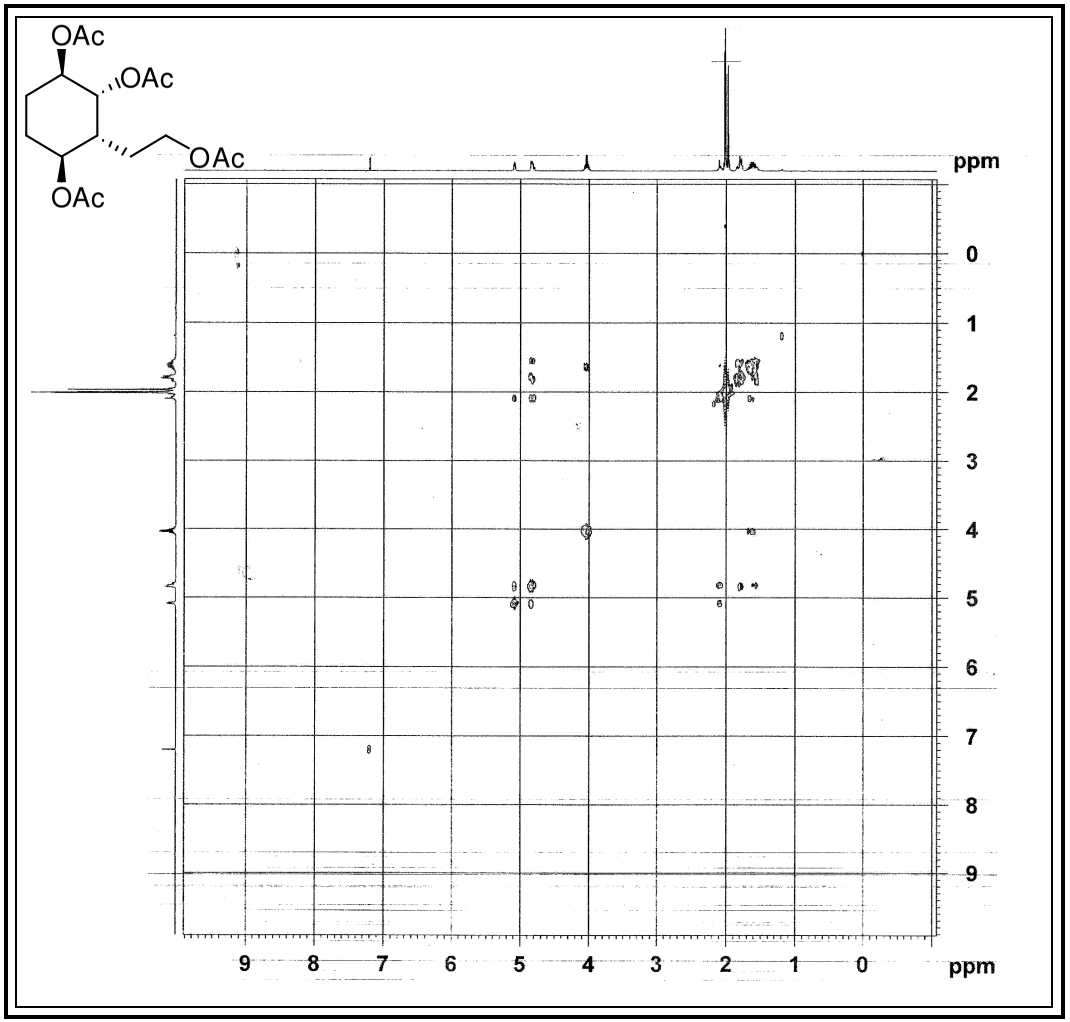

Figure 54 COSY spectrum of compound **82**

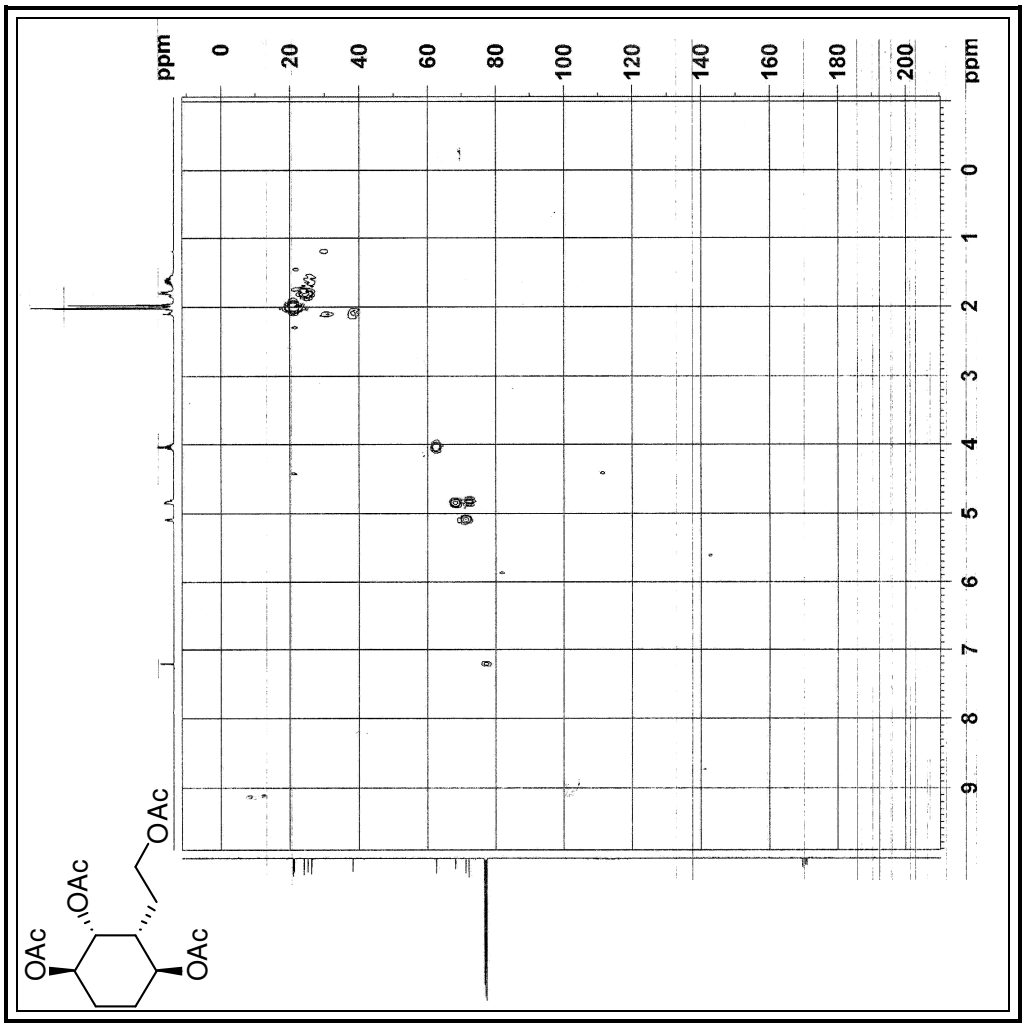

Figure 55 HMQC spectrum of compound **82**

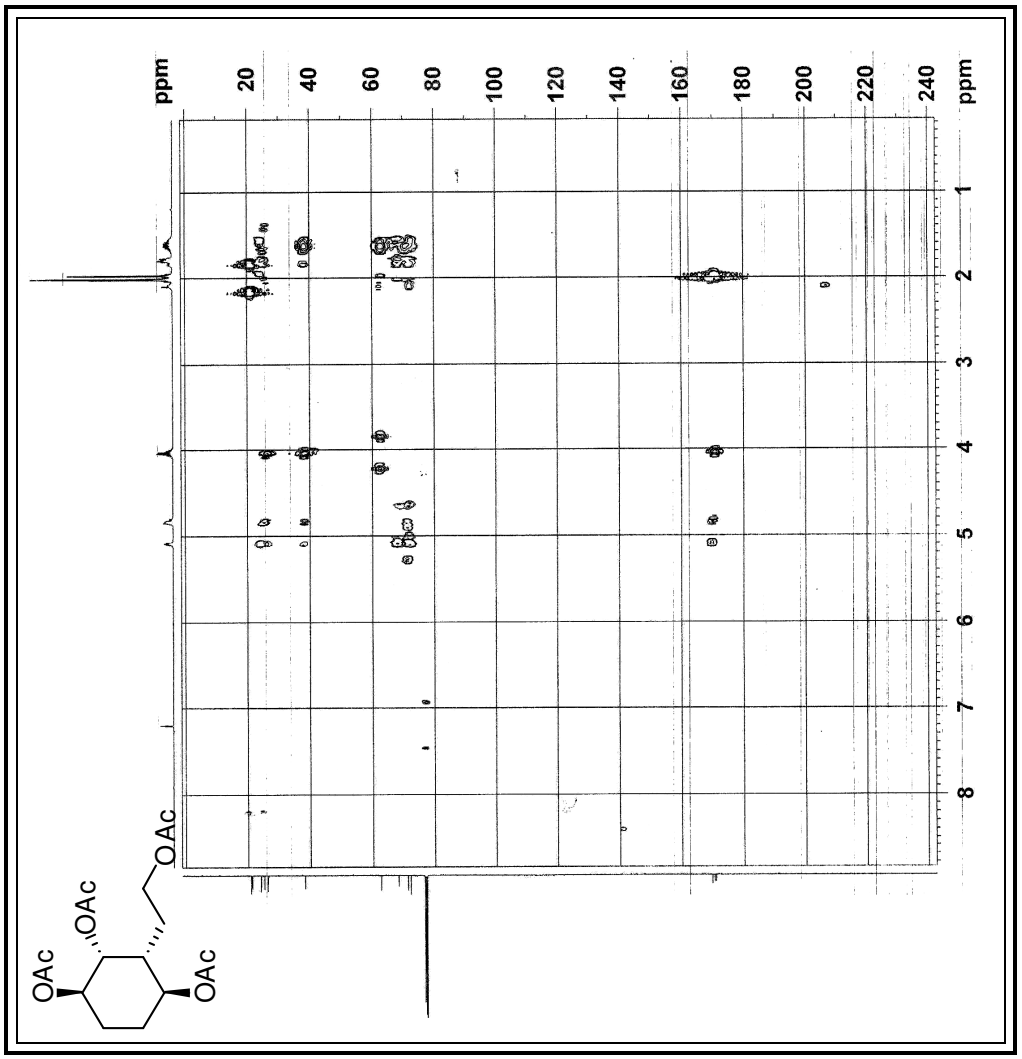

Figure 56 HMBC spectrum of compound **82**

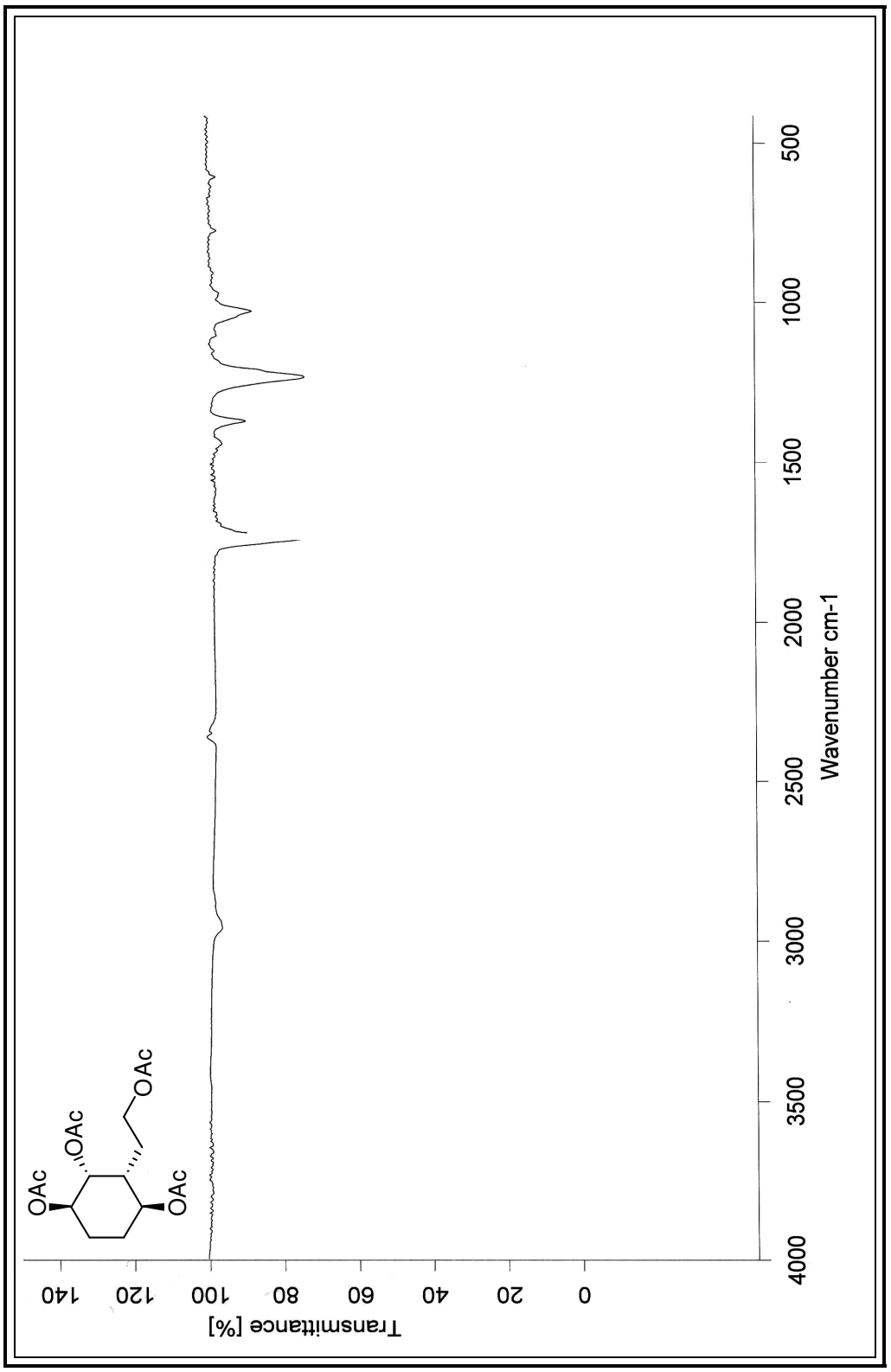

Figure 57 IR spectrum of compound **82**

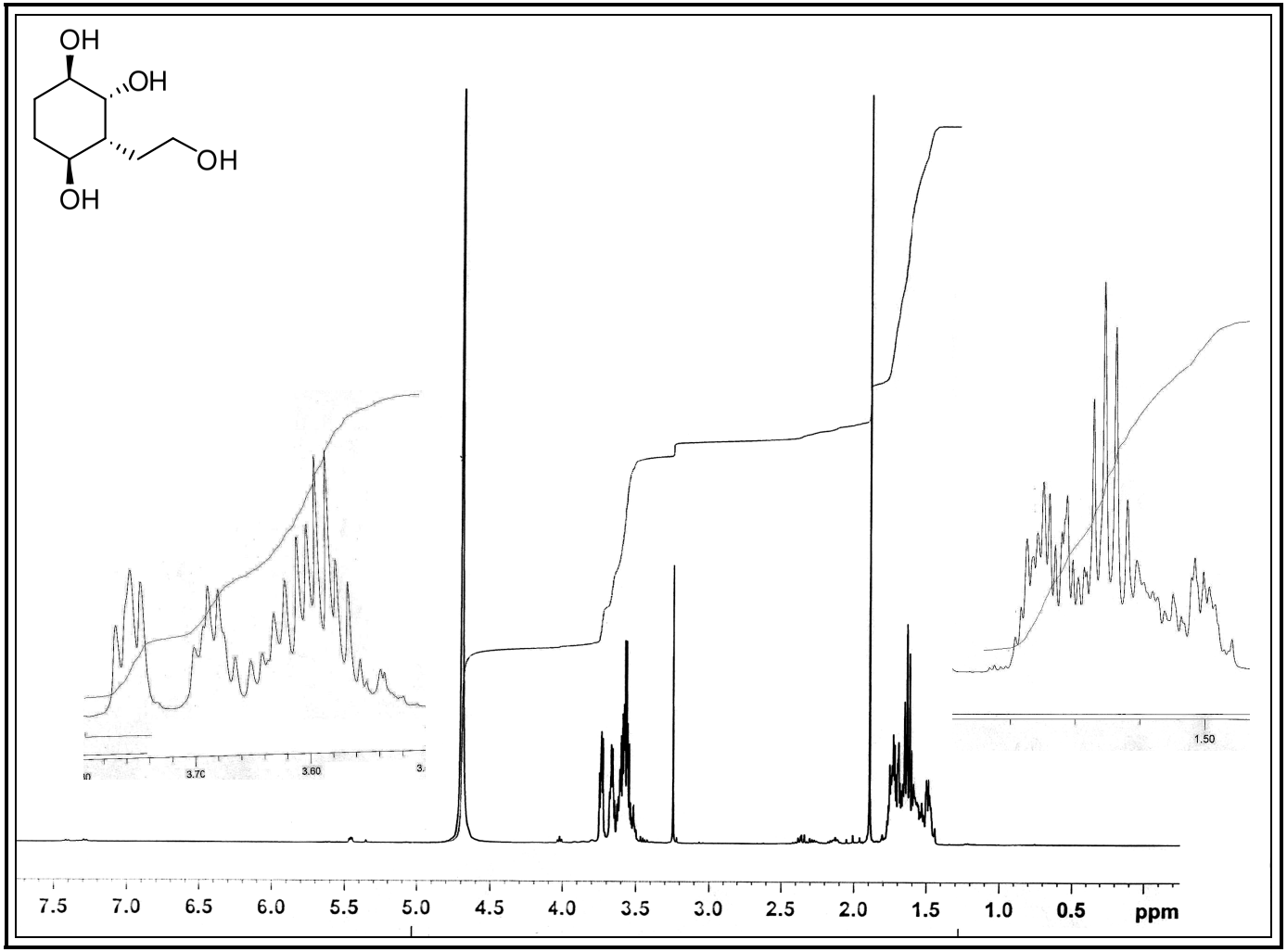

Figure 58 ^{1}H NMR spectrum of compound **72**

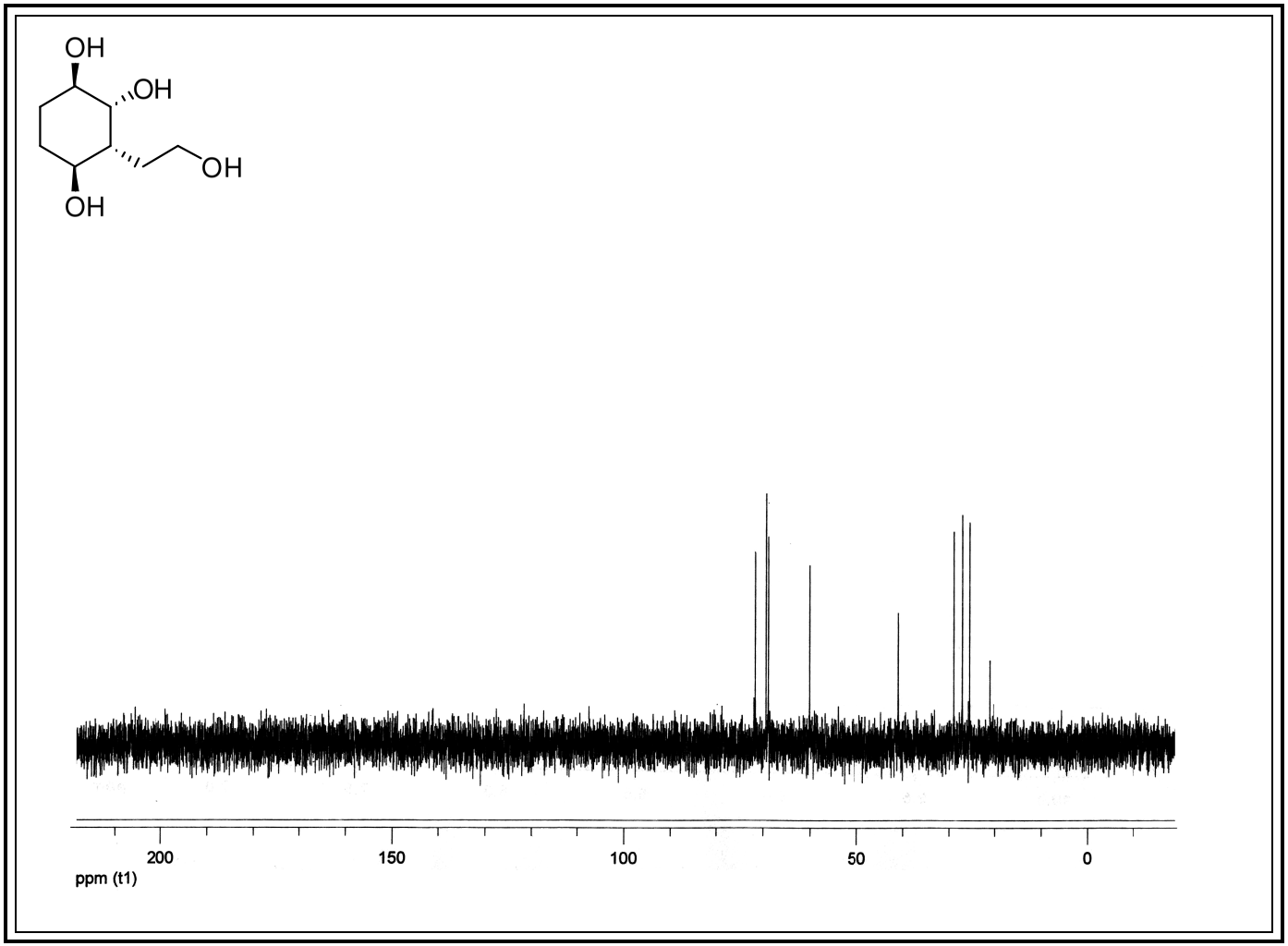

Figure 59 ^{13}C NMR spectrum of compound **72**

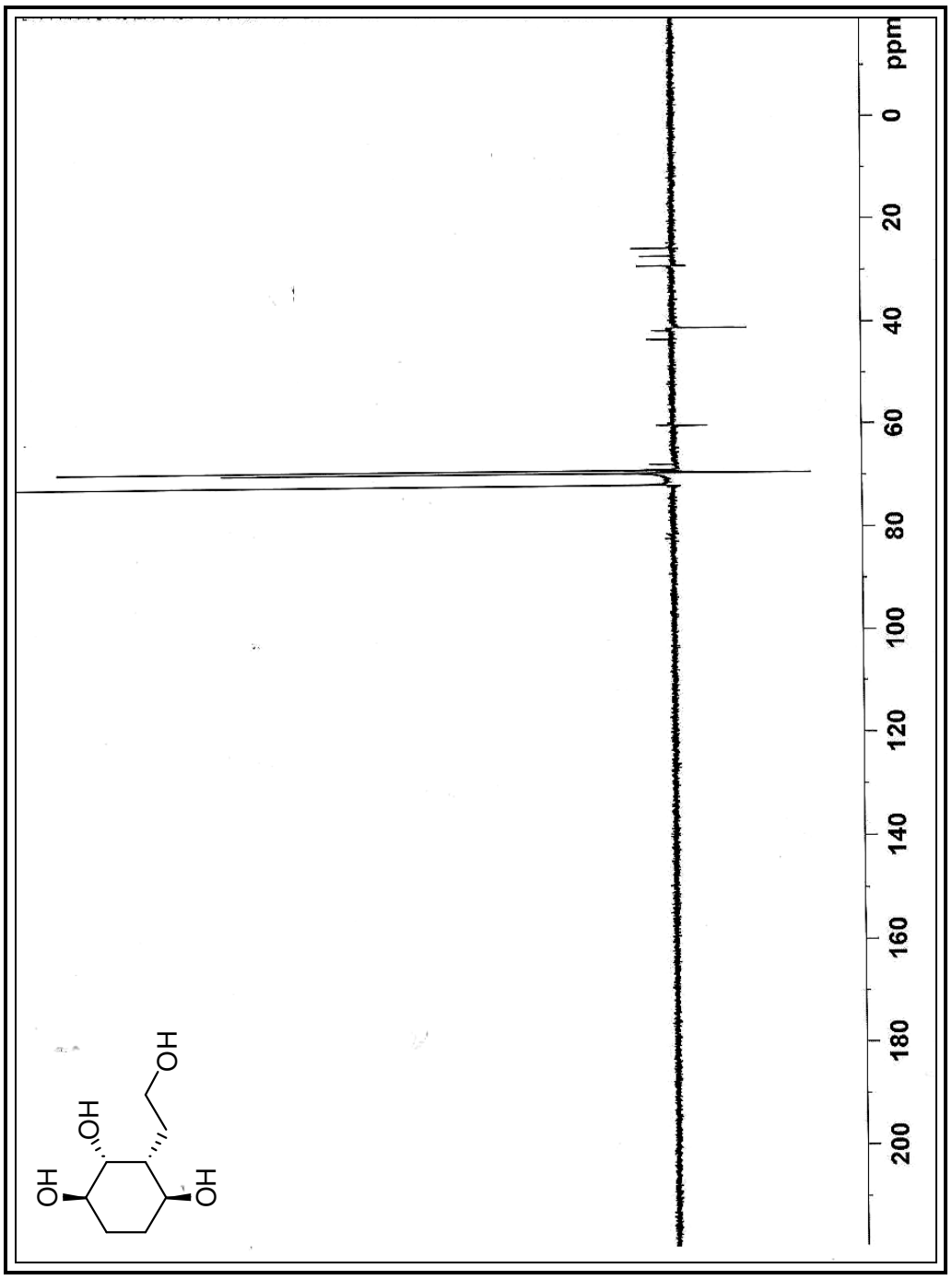

Figure 60 DEPT-90 spectrum of compound **72**

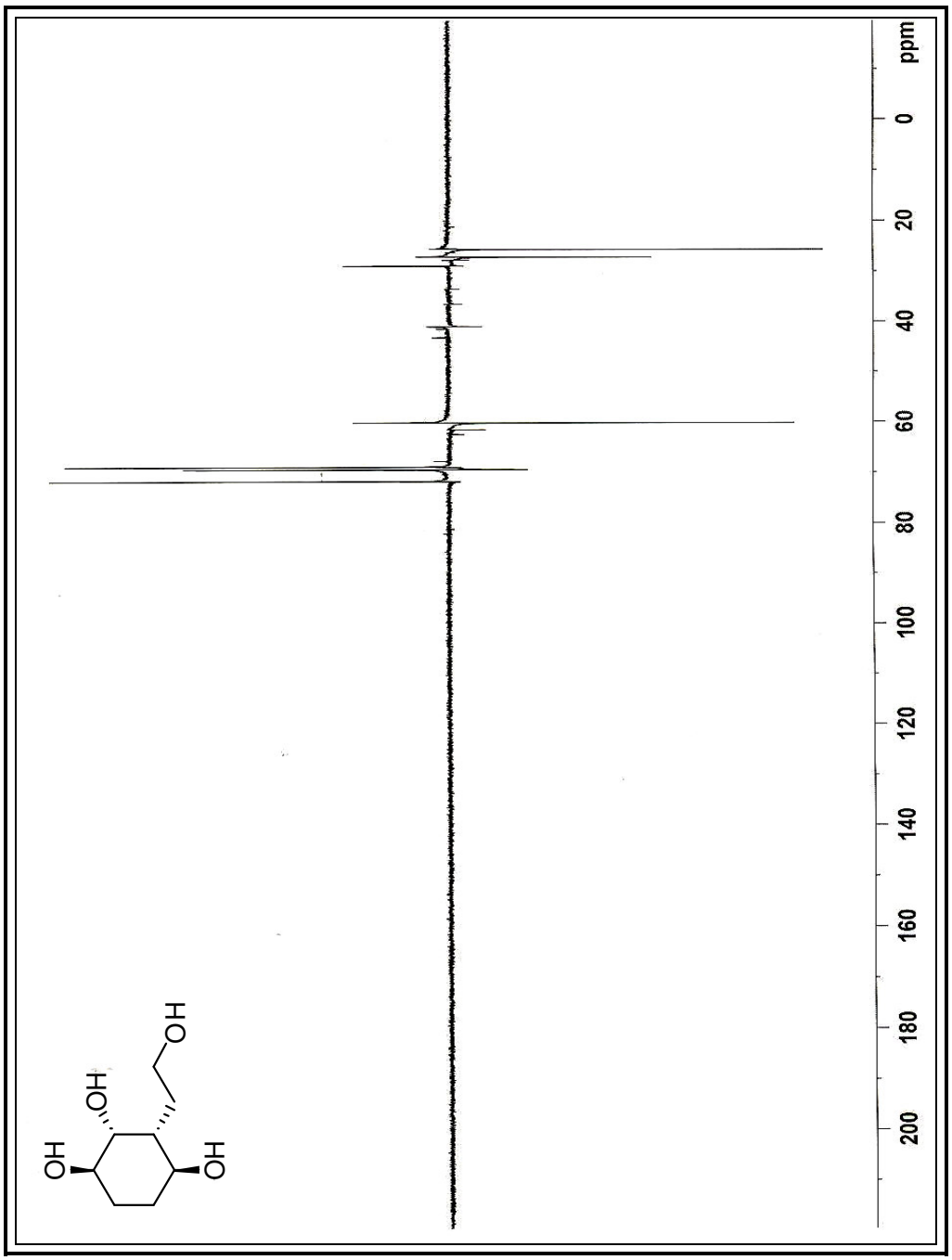

Figure 61 DEPT-135 spectrum of compound **72**

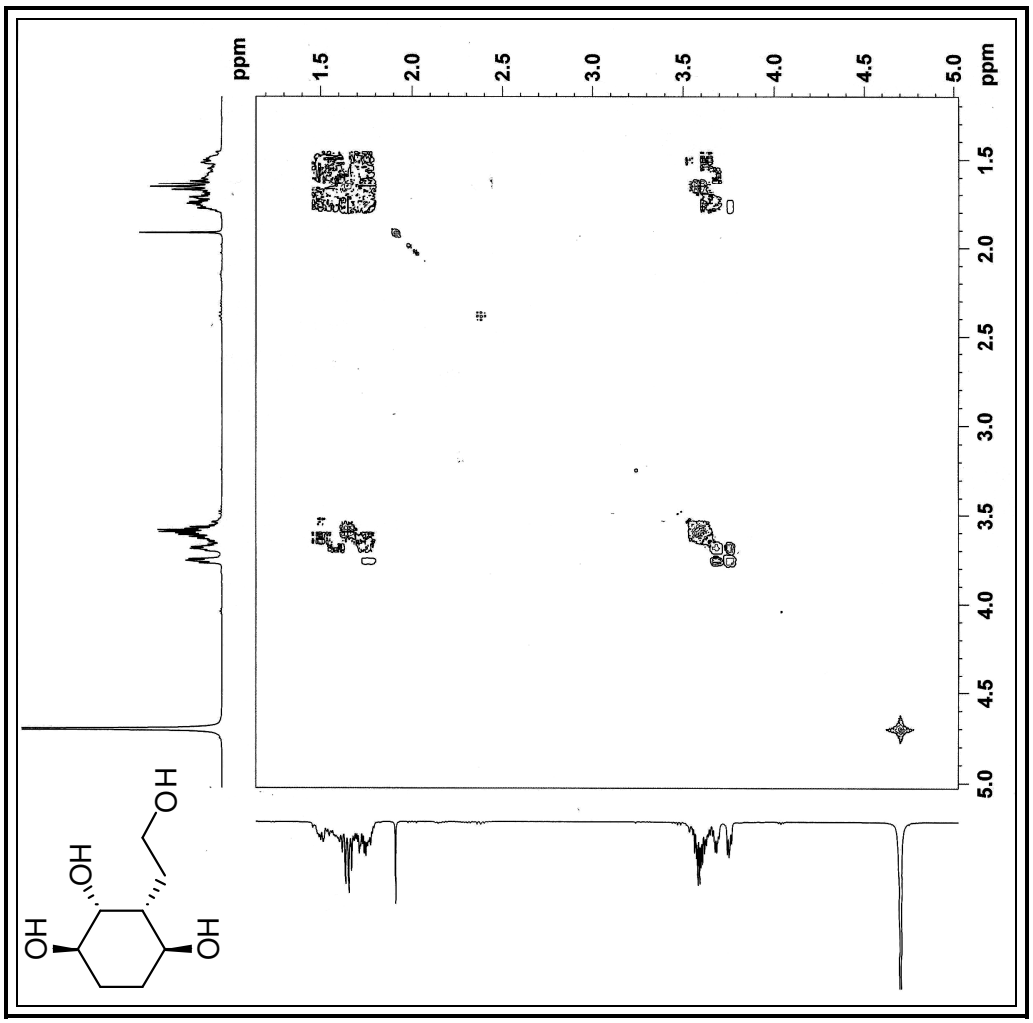

Figure 62 COSY spectrum of compound **72**

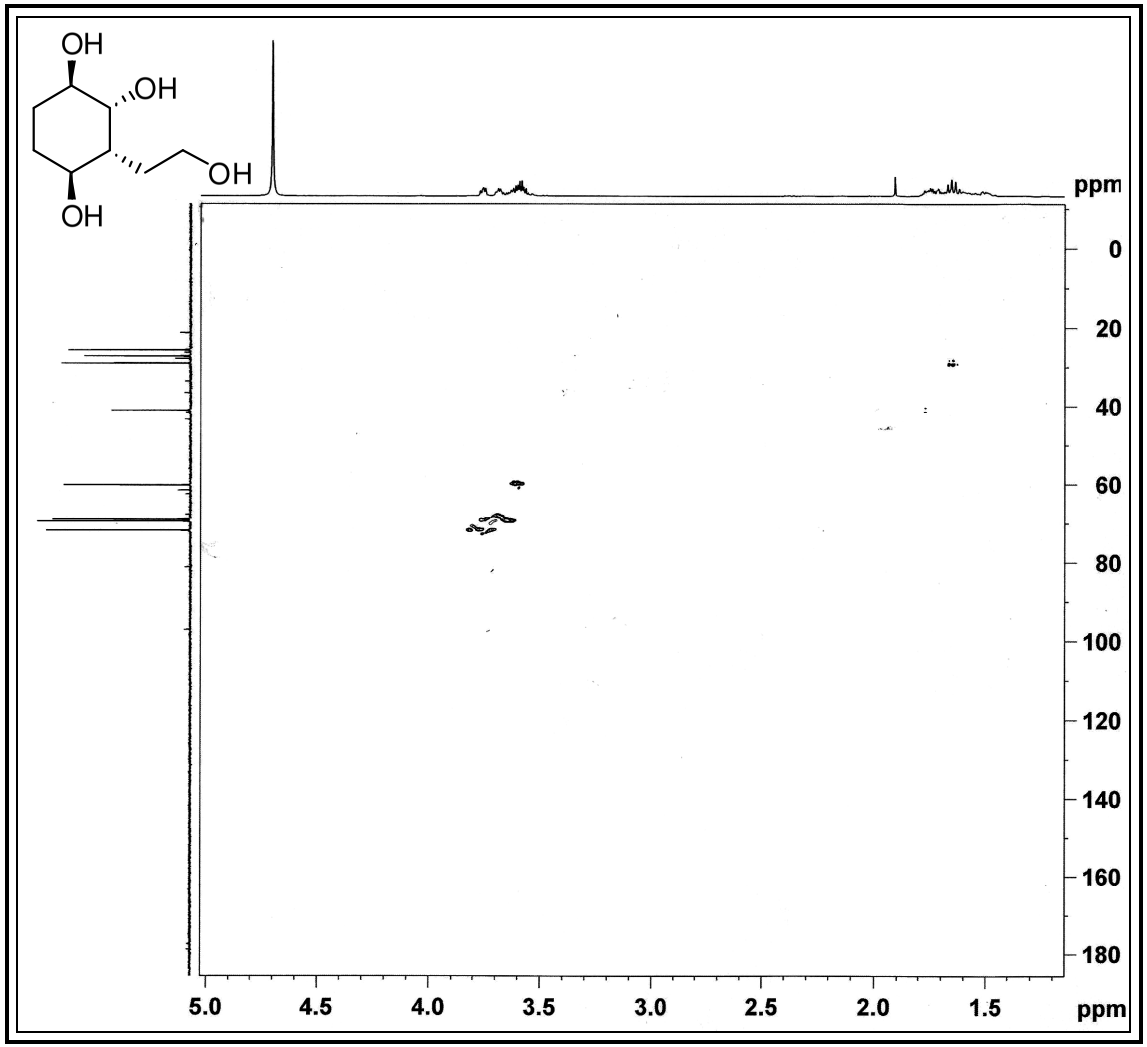

Figure 63 HMQC spectrum of compound **72**

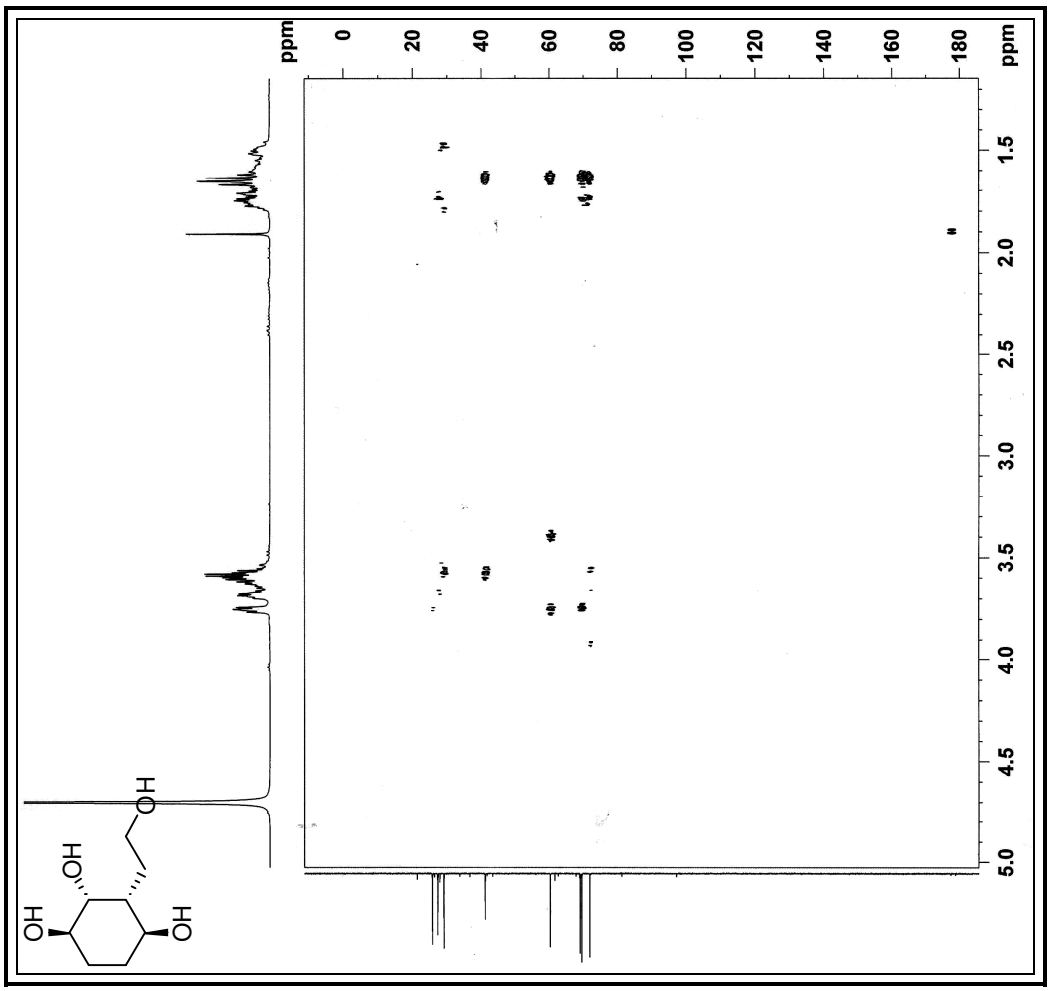

Figure 64 HMBC spectrum of compound **72**

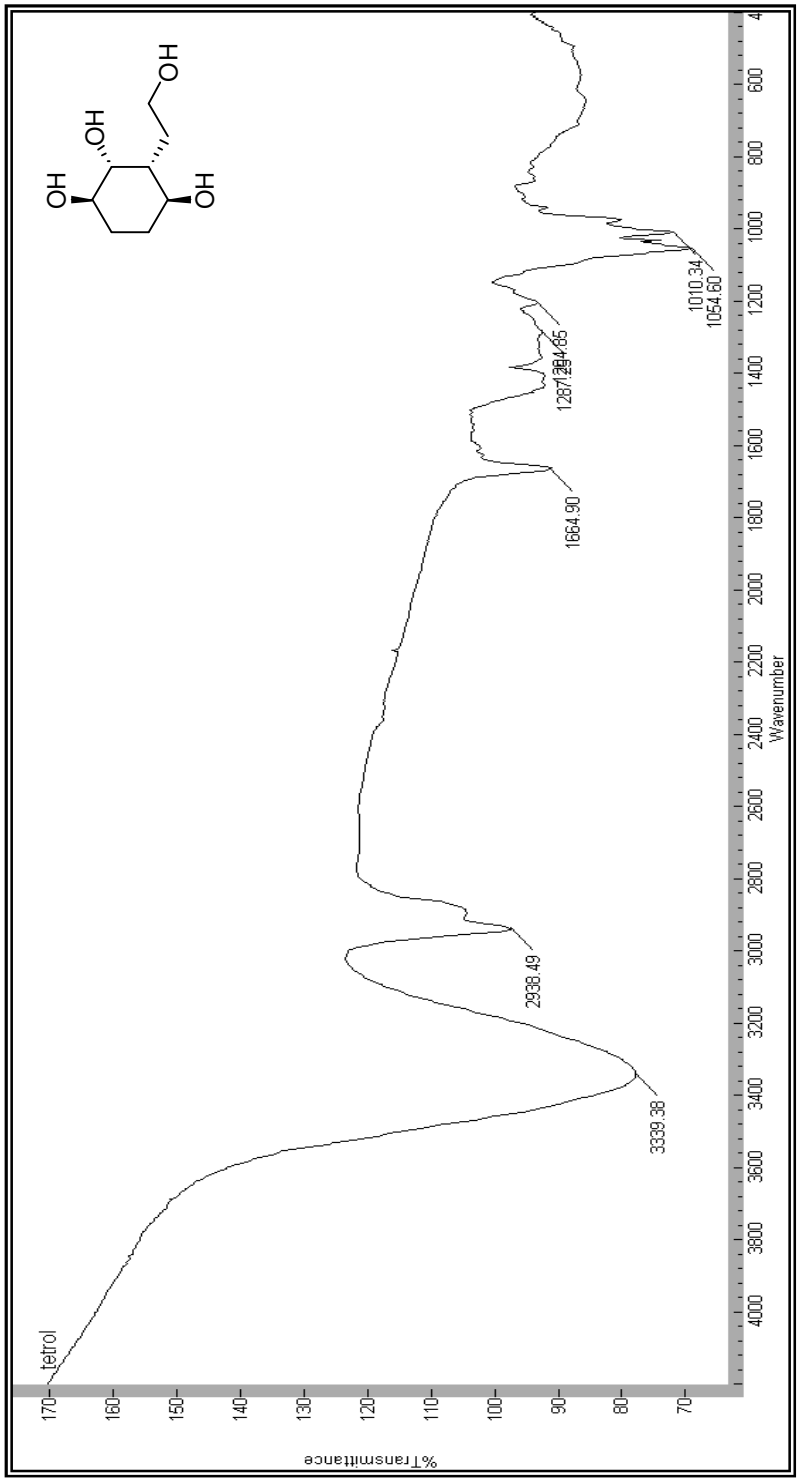

Figure 65 IR spectrum of compound **72**

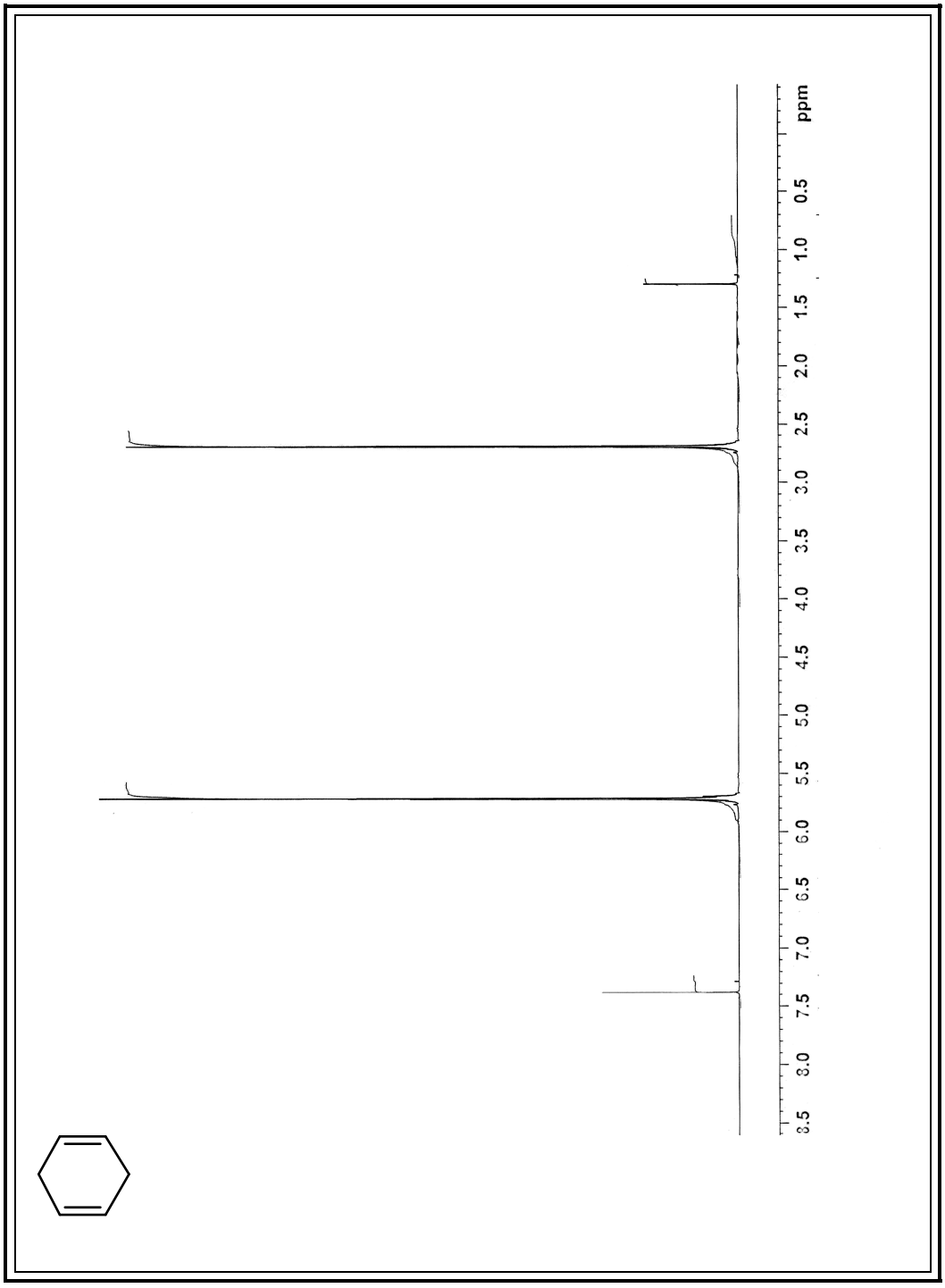

Figure 66 ^{1}H NMR spectrum of compound **10**

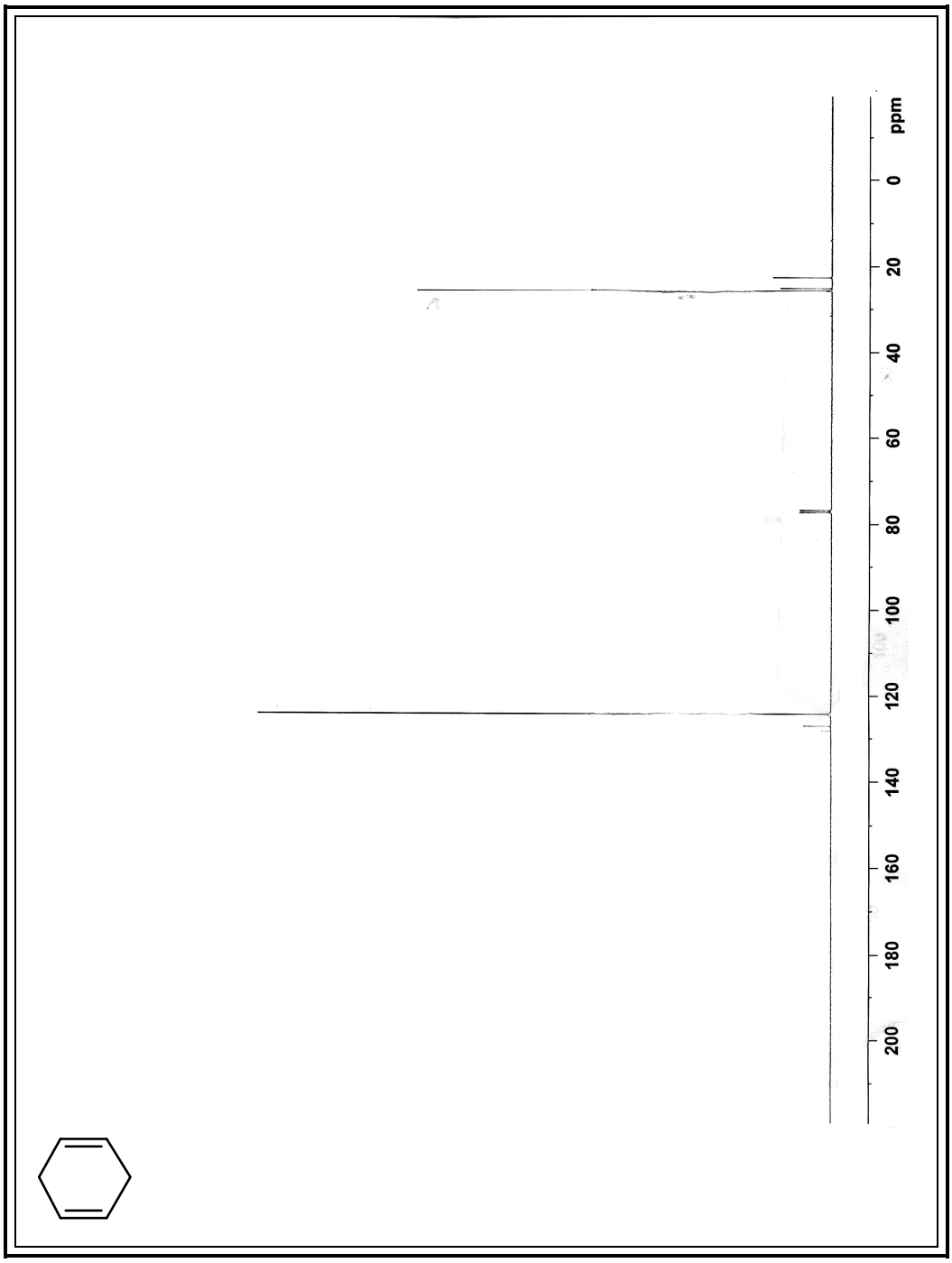

Figure 67 ^{13}C NMR spectrum of compound **10**

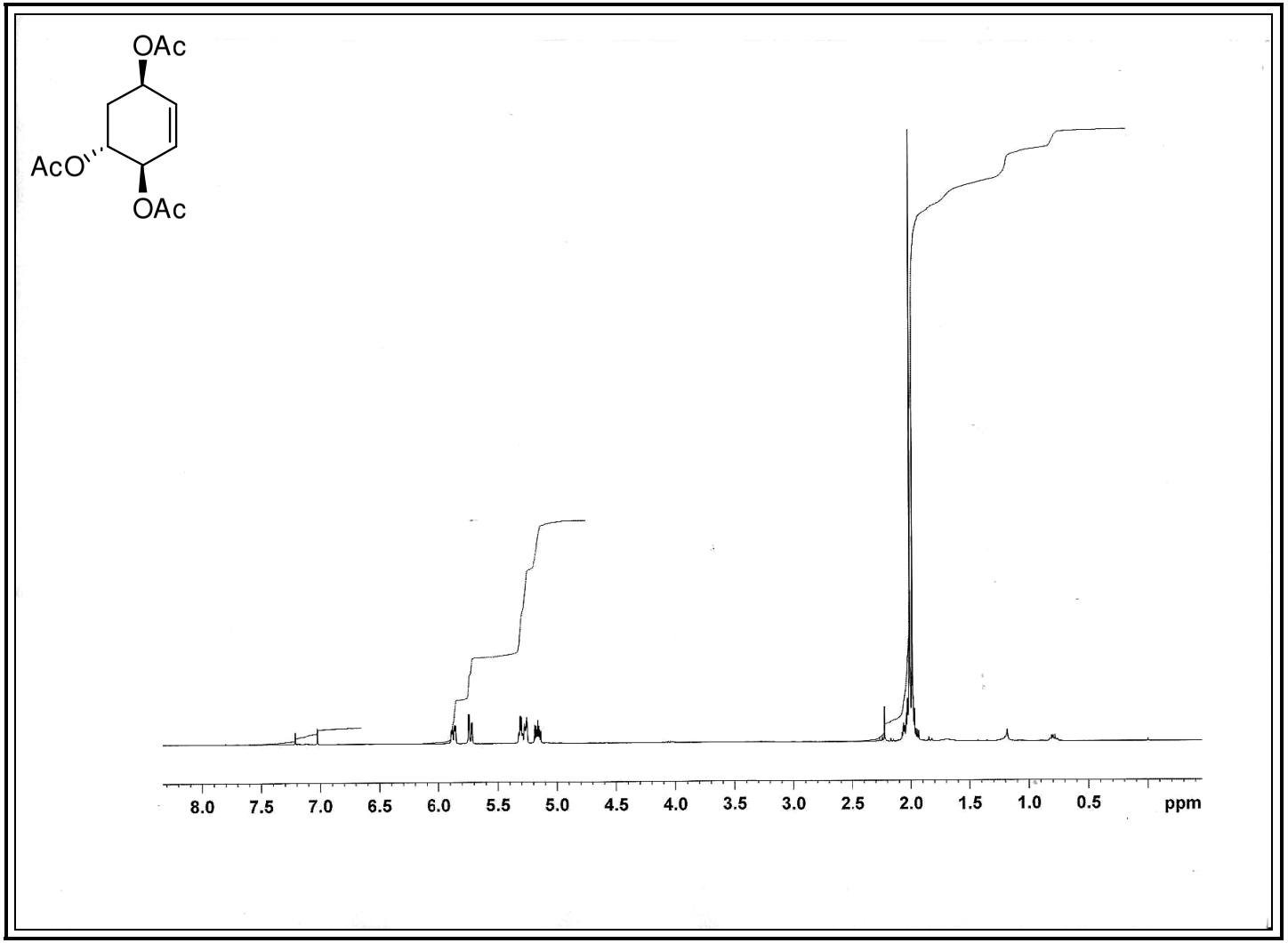

Figure 68 ^{1}H NMR spectrum of compound **26**

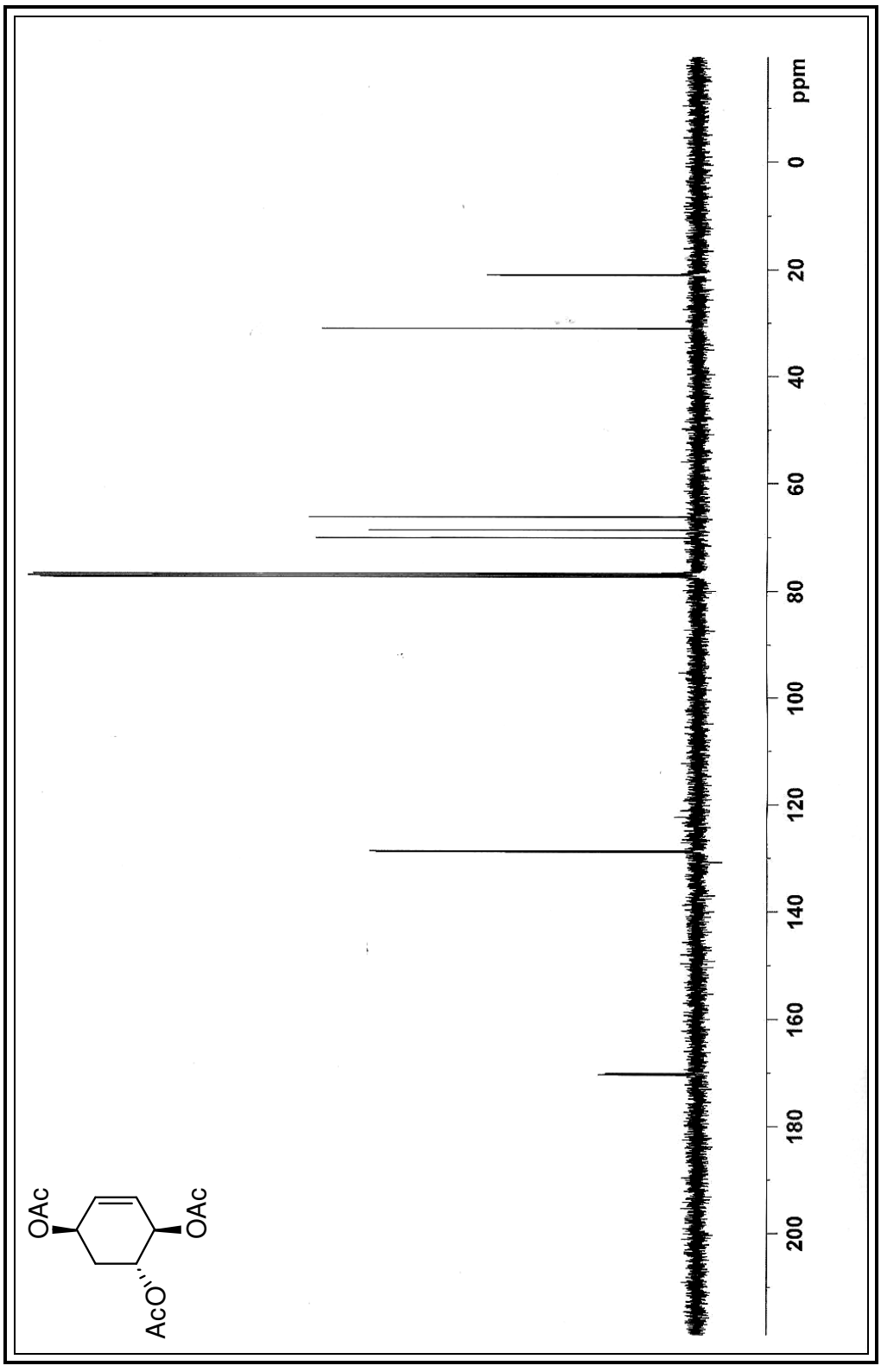

Figure 69 ^{13}C NMR spectrum of compound **26**

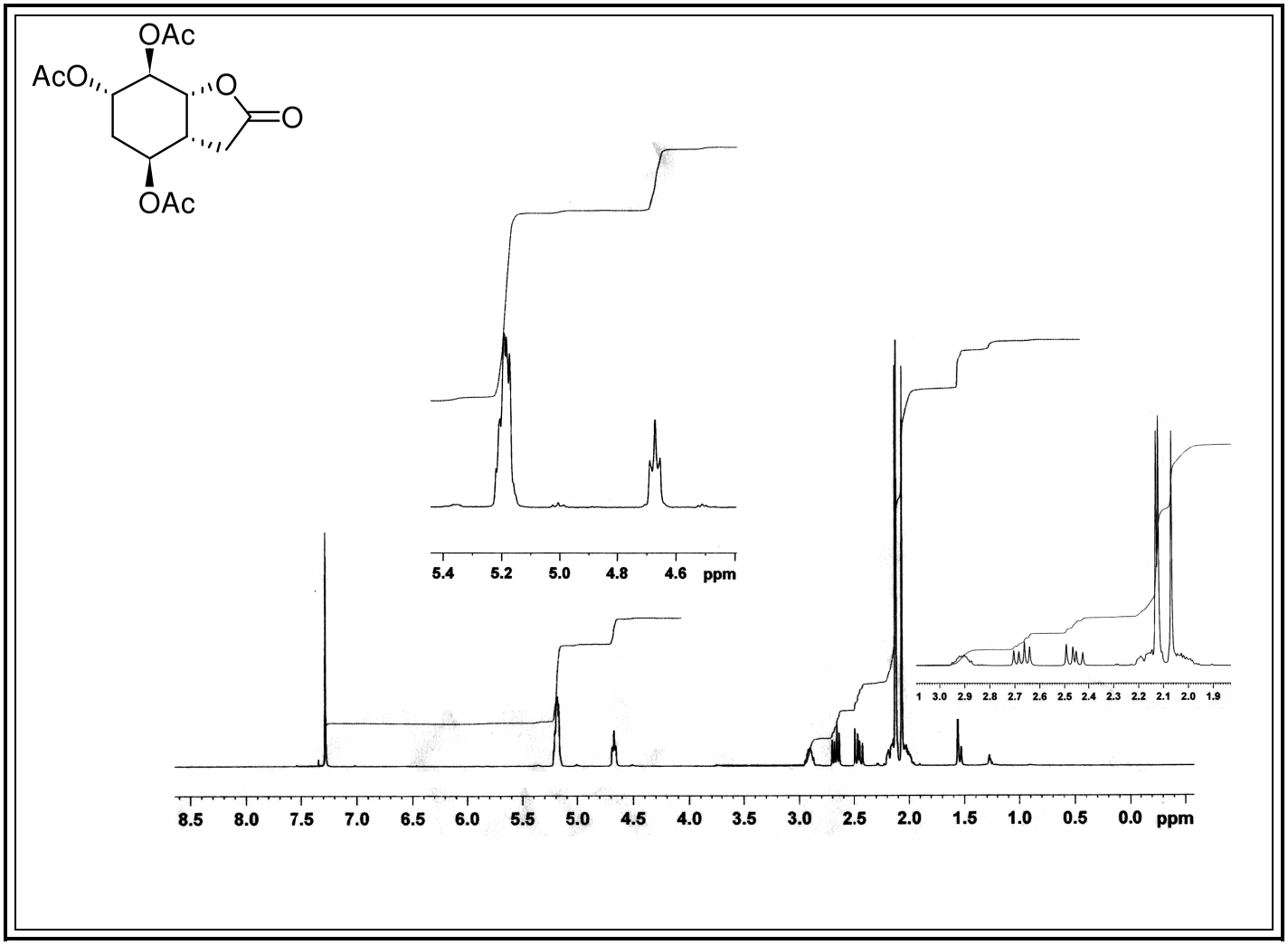

Figure 70 ^{1}H NMR spectrum of compound **83**

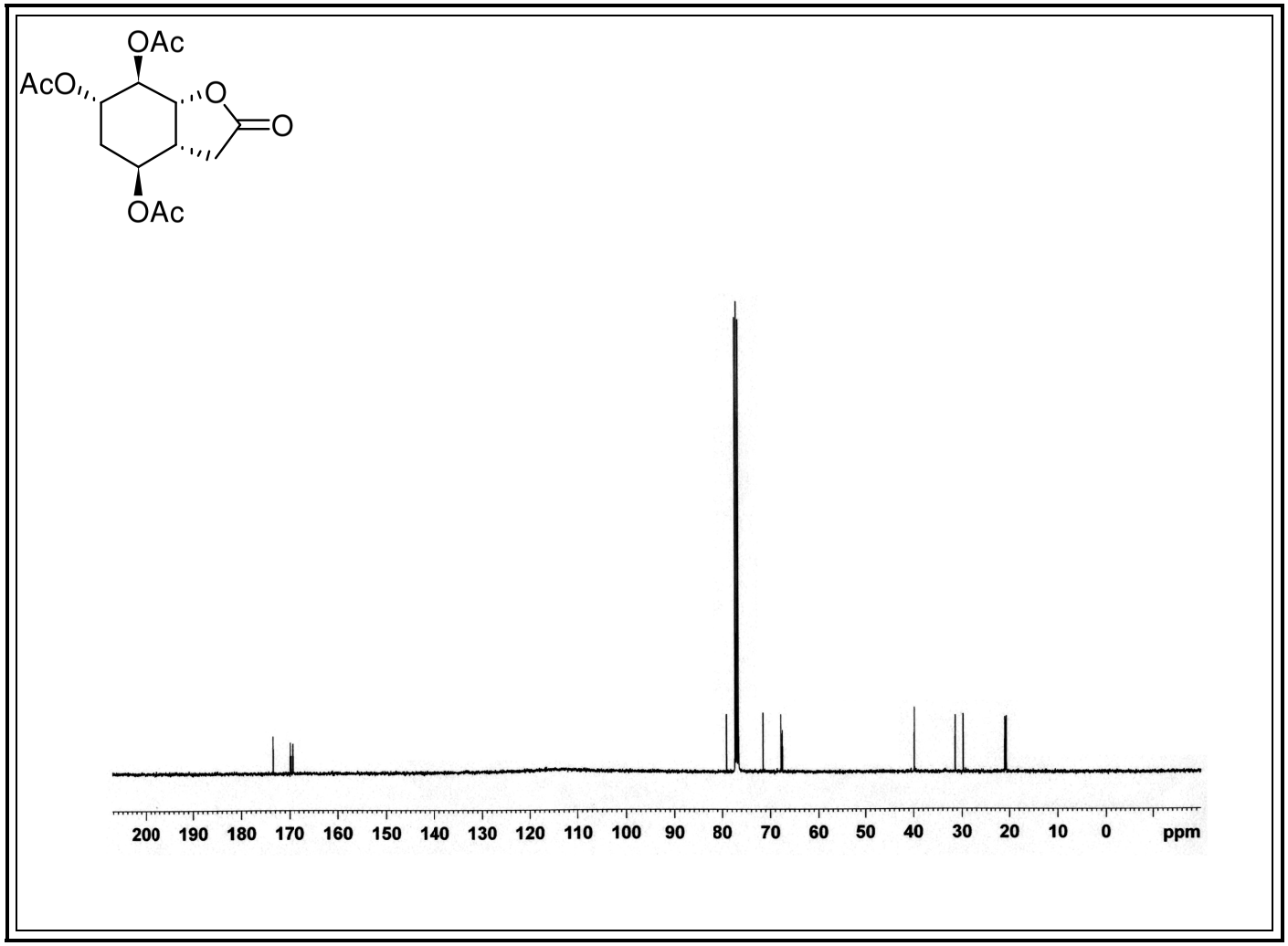

Figure 71 ^{13}C NMR spectrum of compound **83**

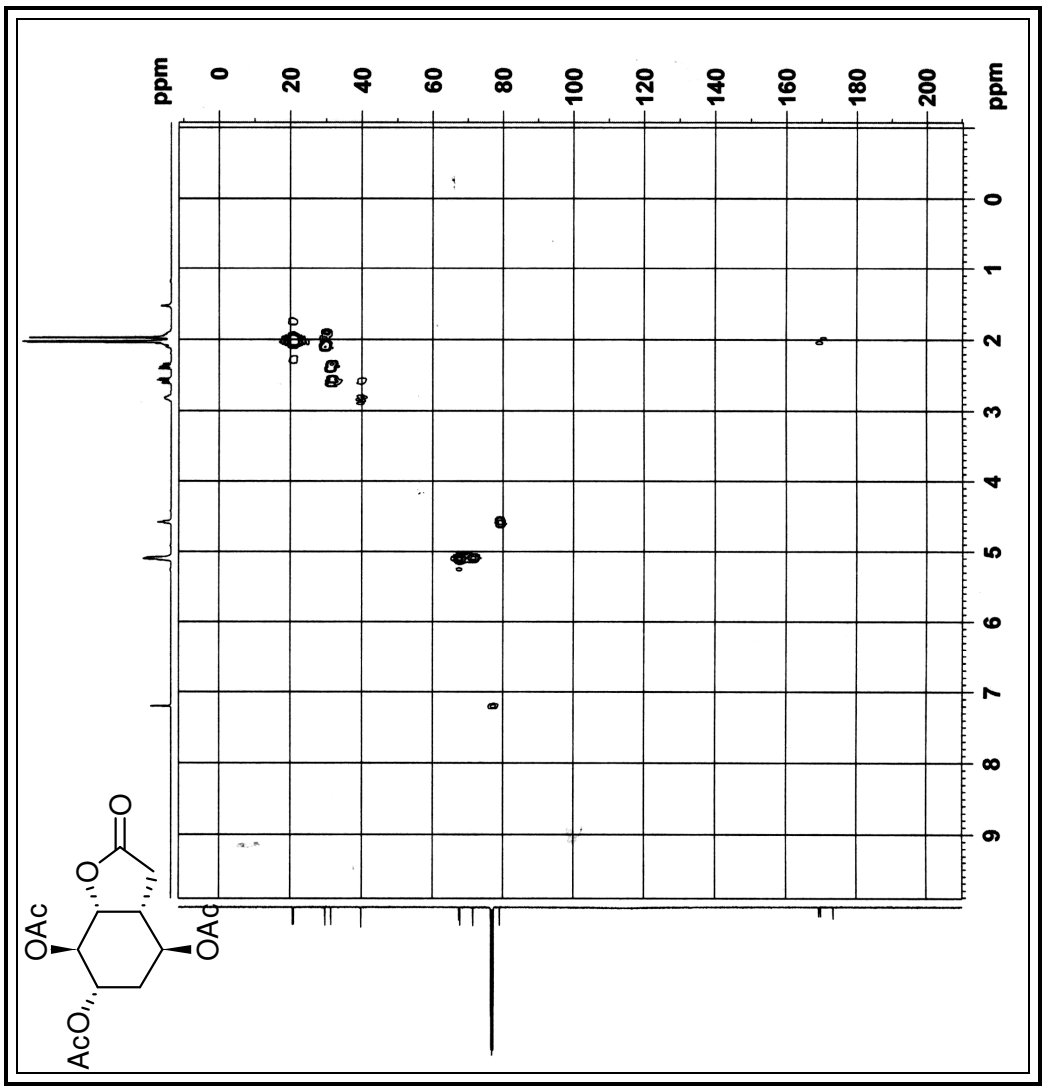

Figure 72 HMQC spectrum of compound **83**

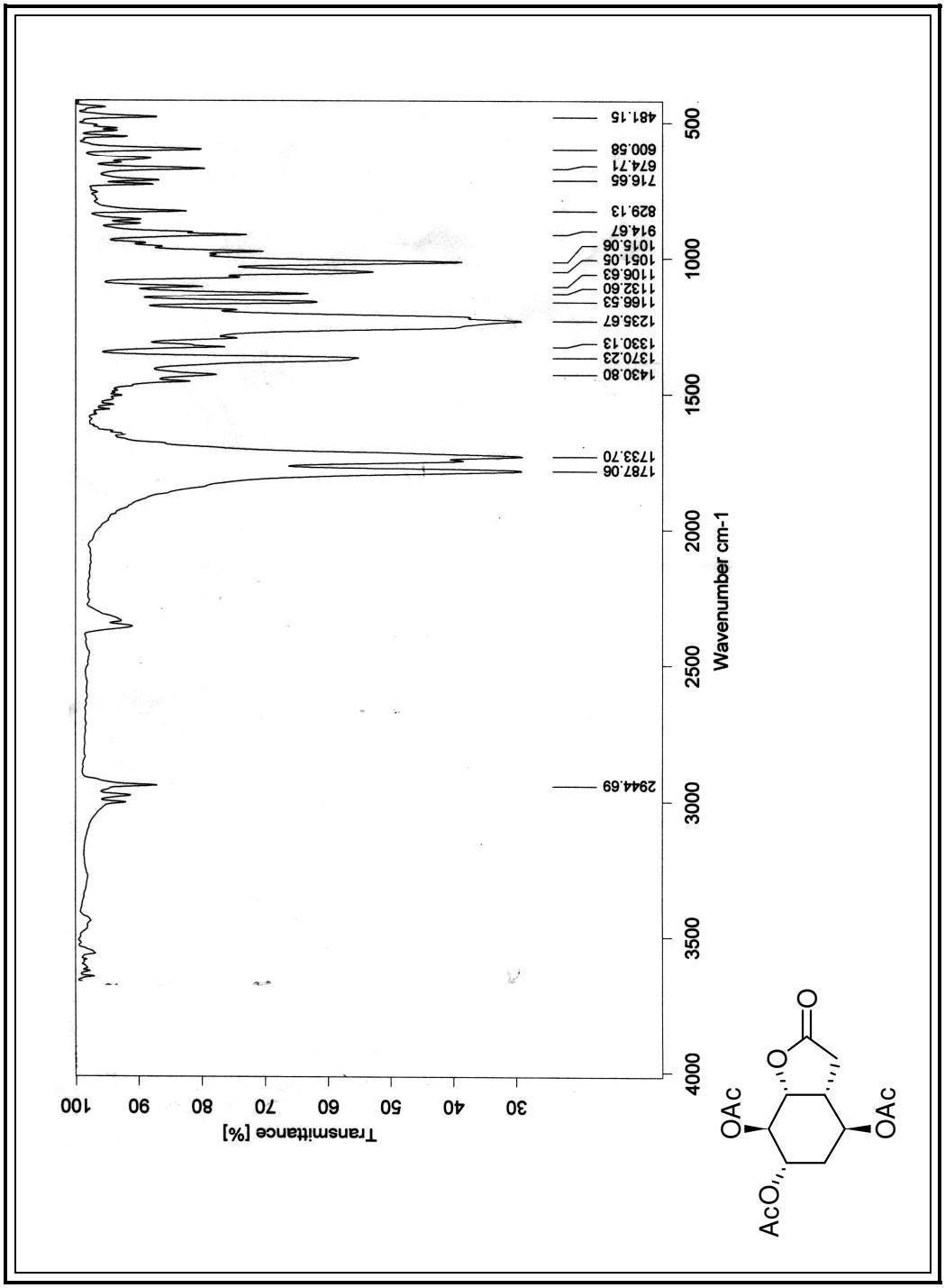

Figure 73 IR spectrum of compound **83**

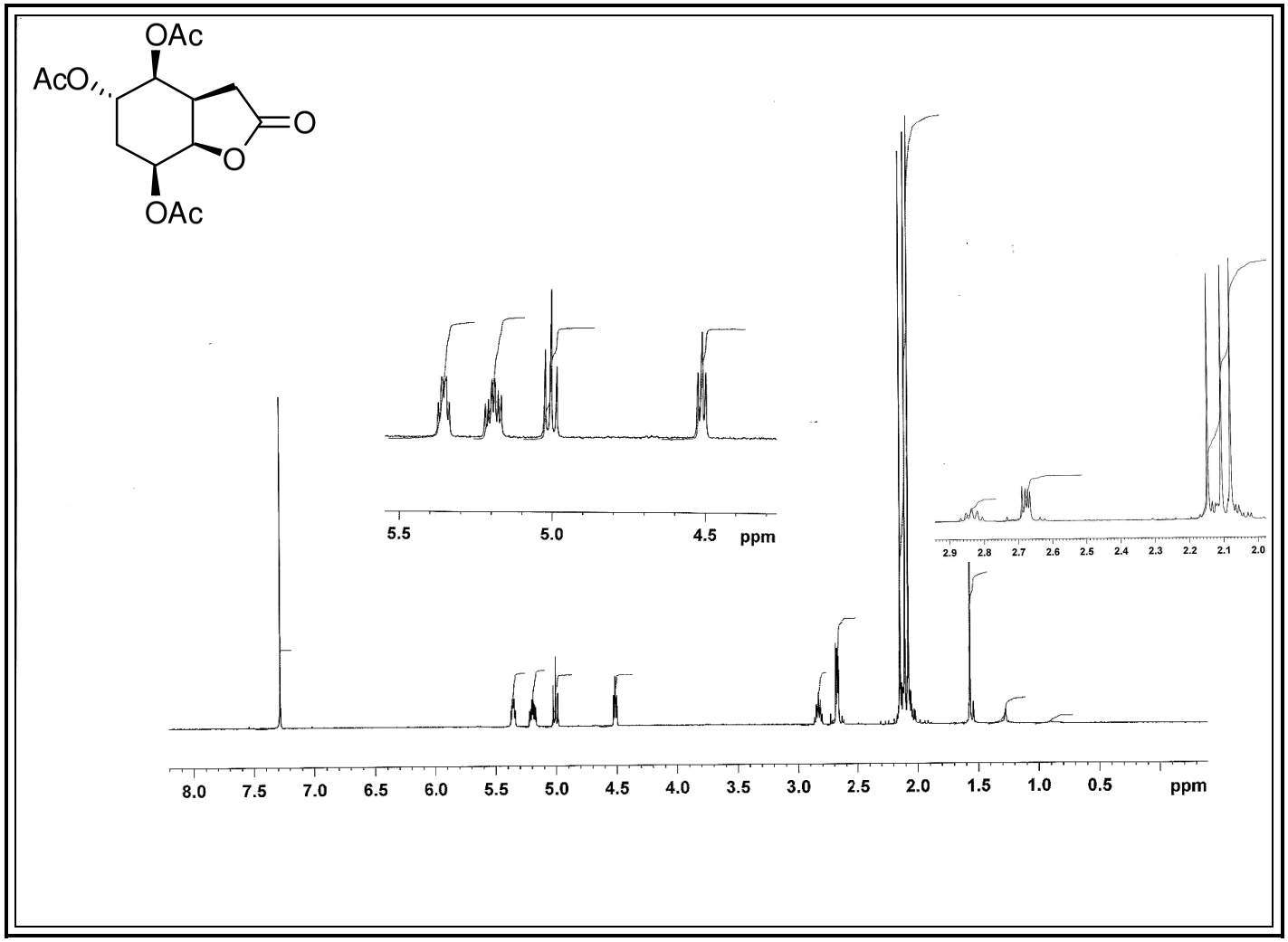

Figure 74 ^{1}H NMR spectrum of compound **84**

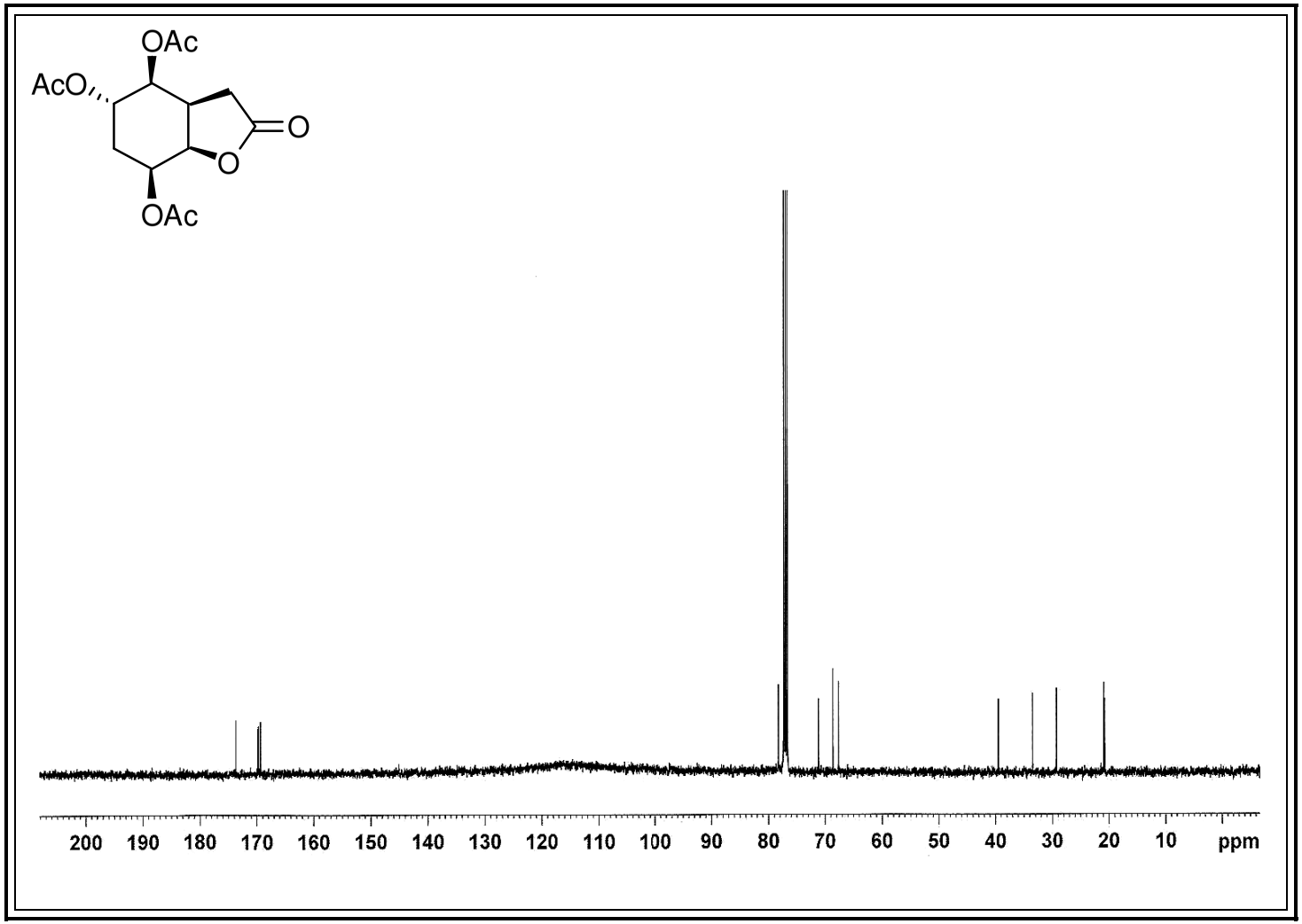

Figure 75 ^{13}C NMR spectrum of compound **84**

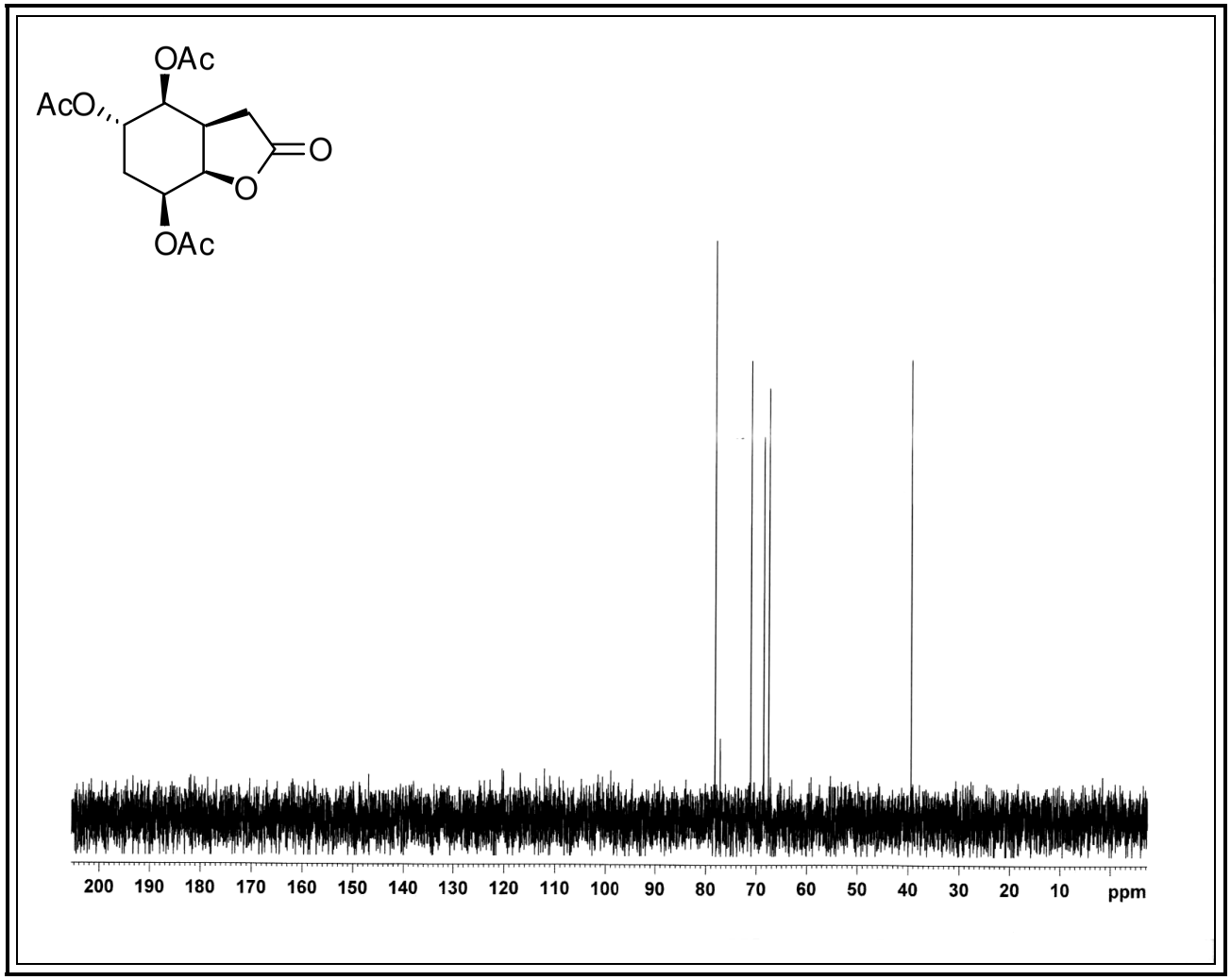

Figure 76 DEPT-90 spectrum of compound **84**

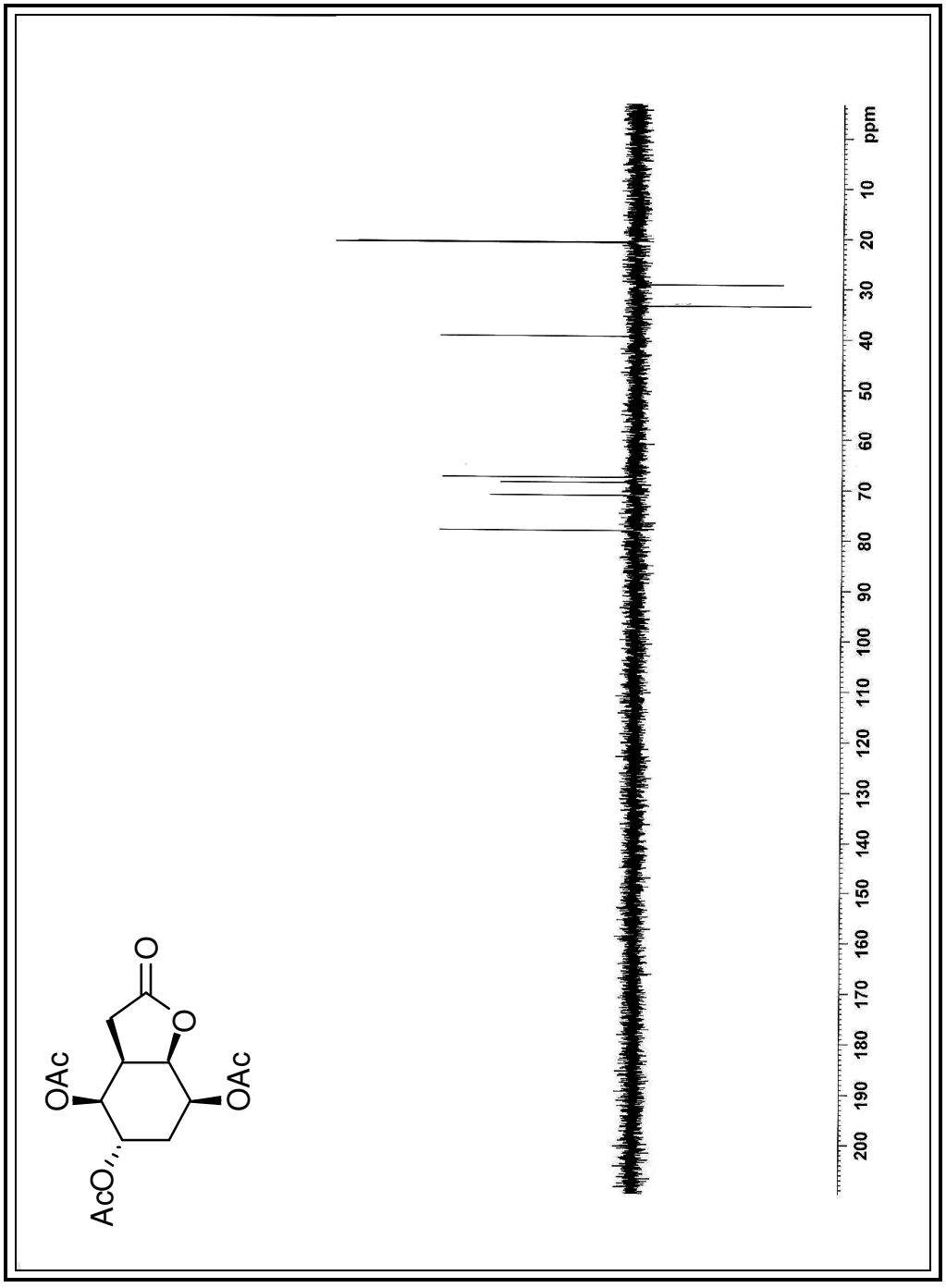

Figure 77 DEPT-135 spectrum of compound **84**

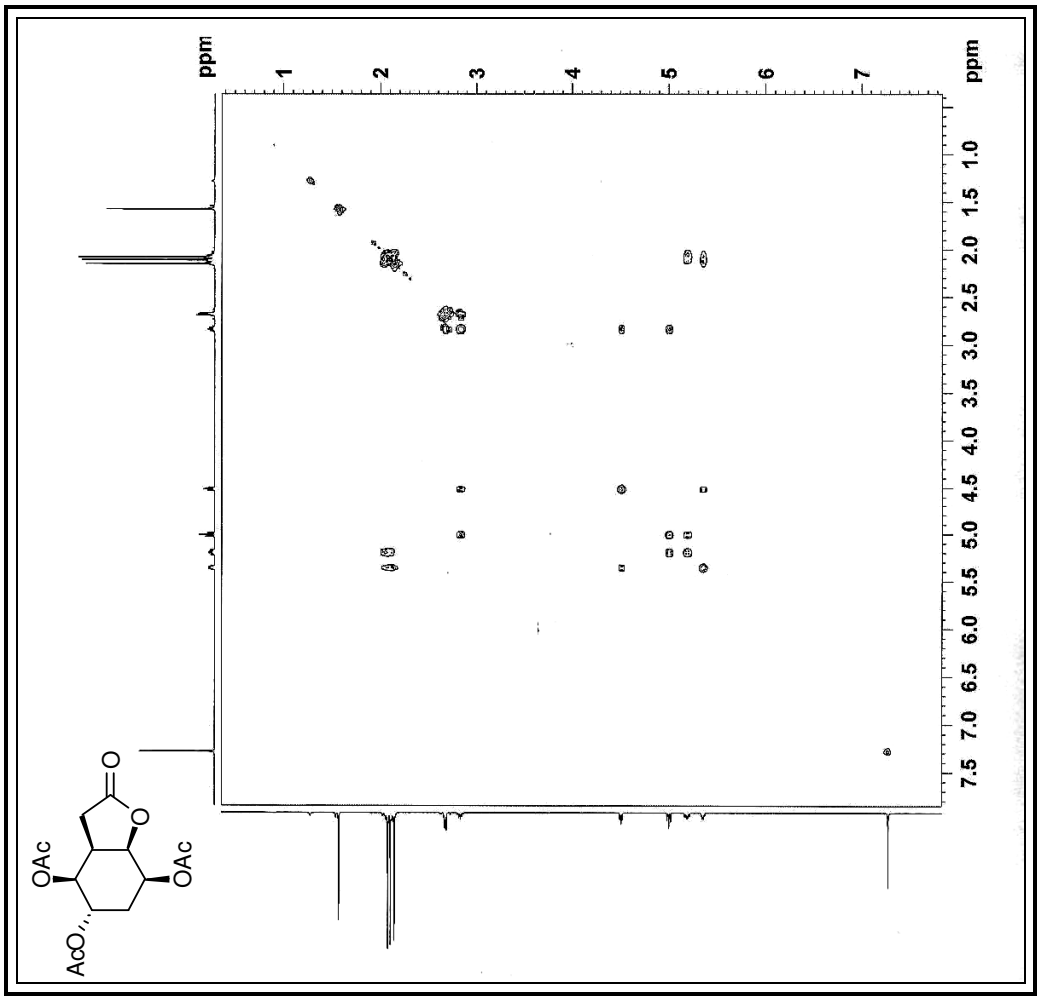

Figure 78 COSY spectrum of compound **84**

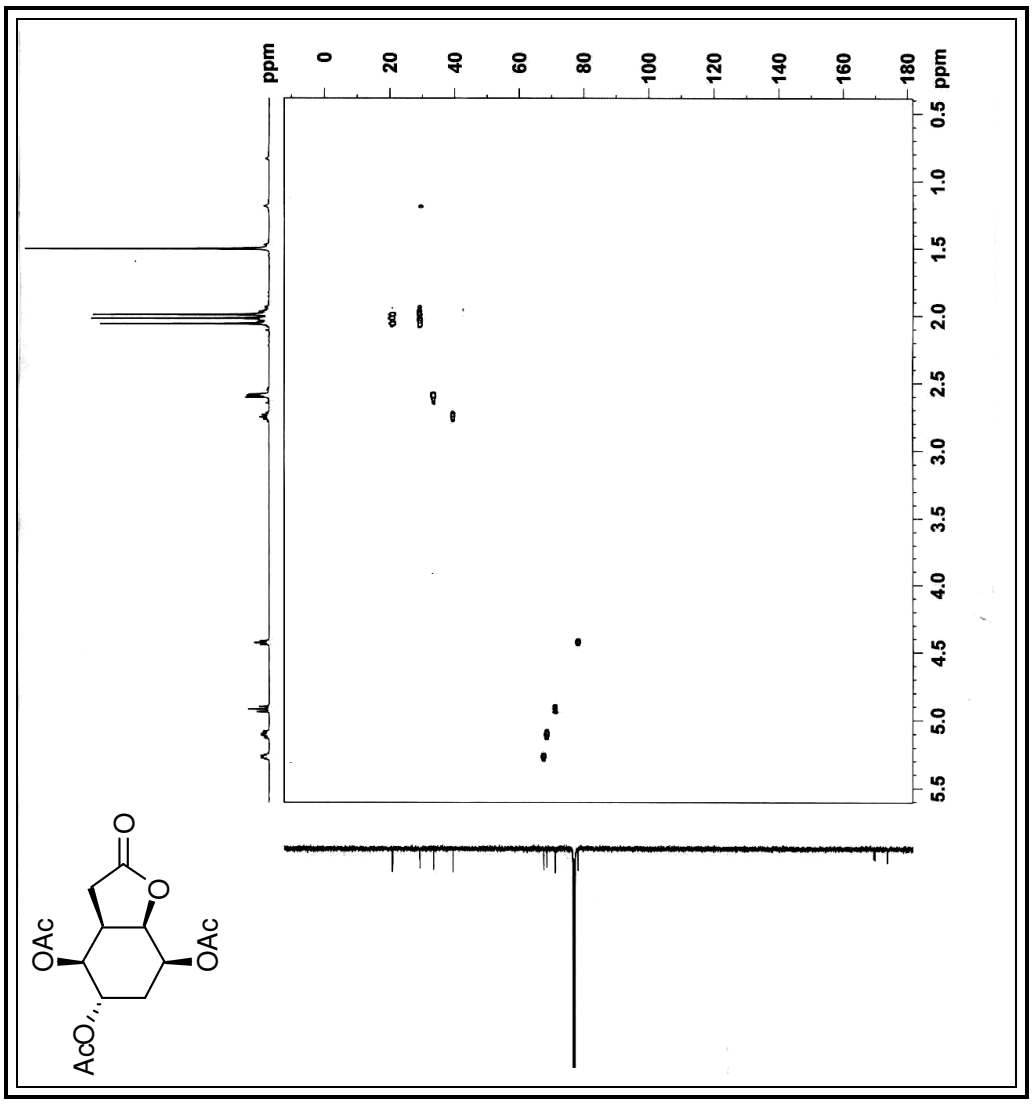

Figure 79 HMQC spectrum of compound **84**

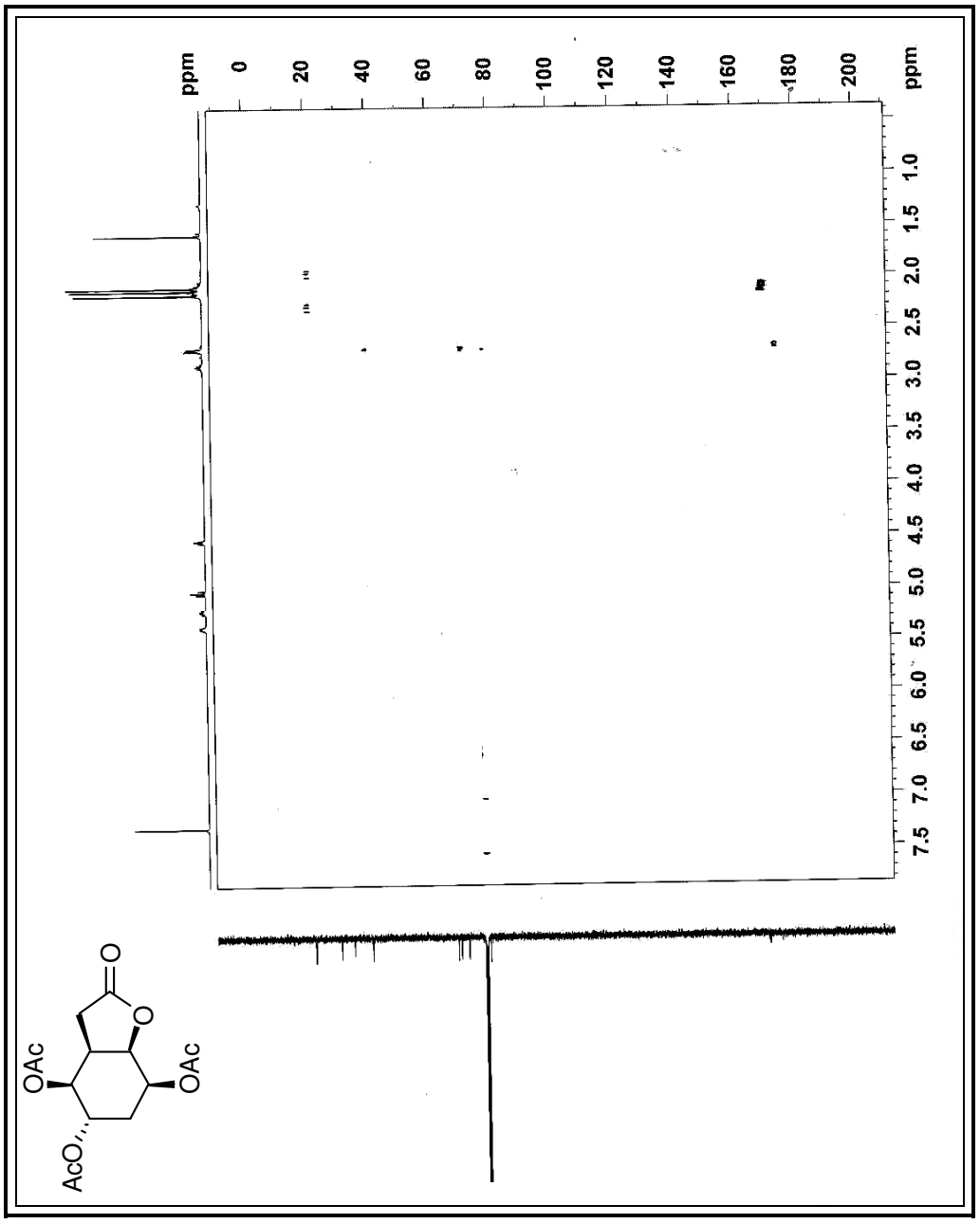

Figure 80 HMBC spectrum of compound **84**

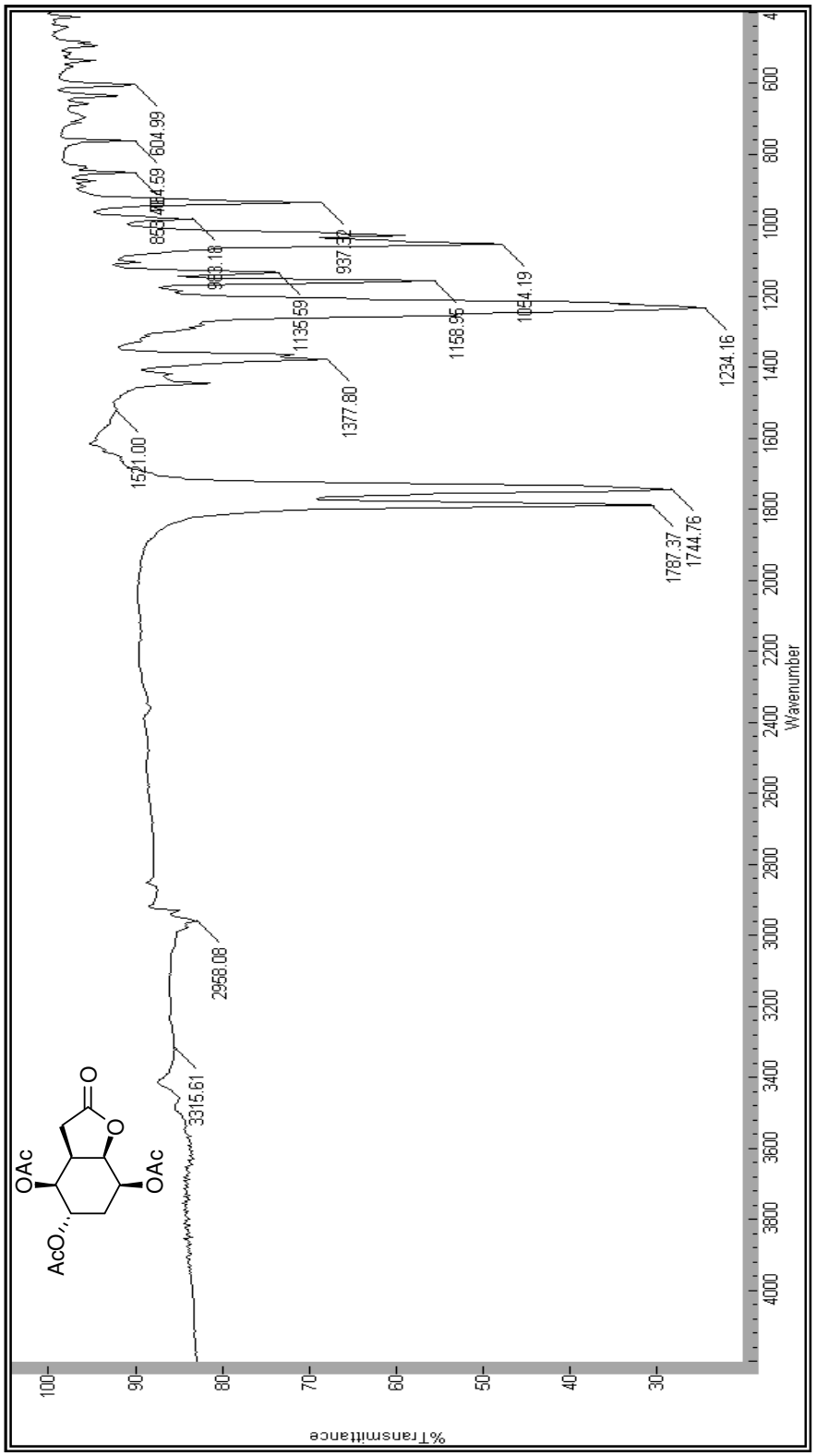

Figure 81 IR spectrum of compound **84**

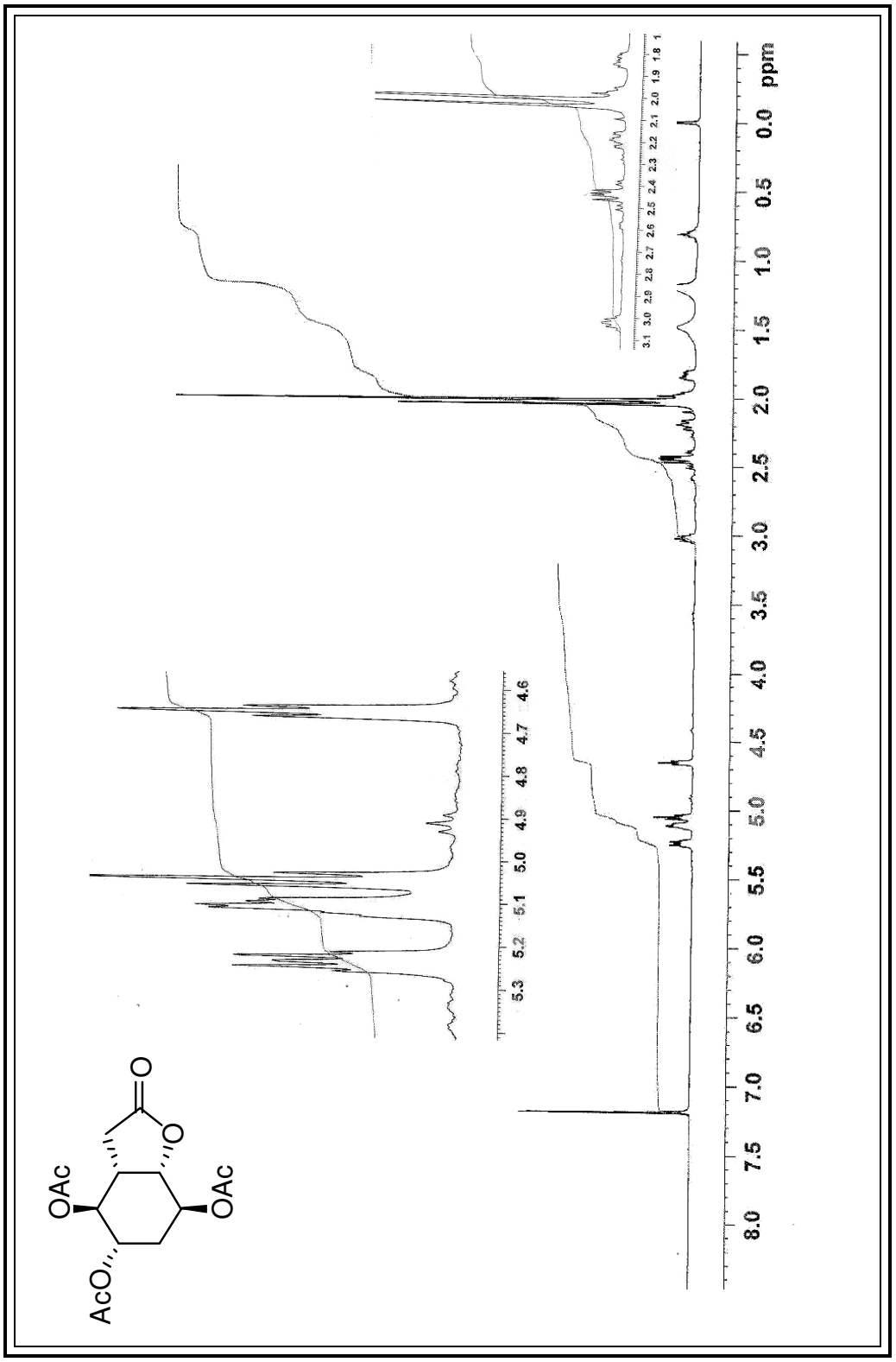

Figure 82 ^{1}H NMR spectrum of compound **85**

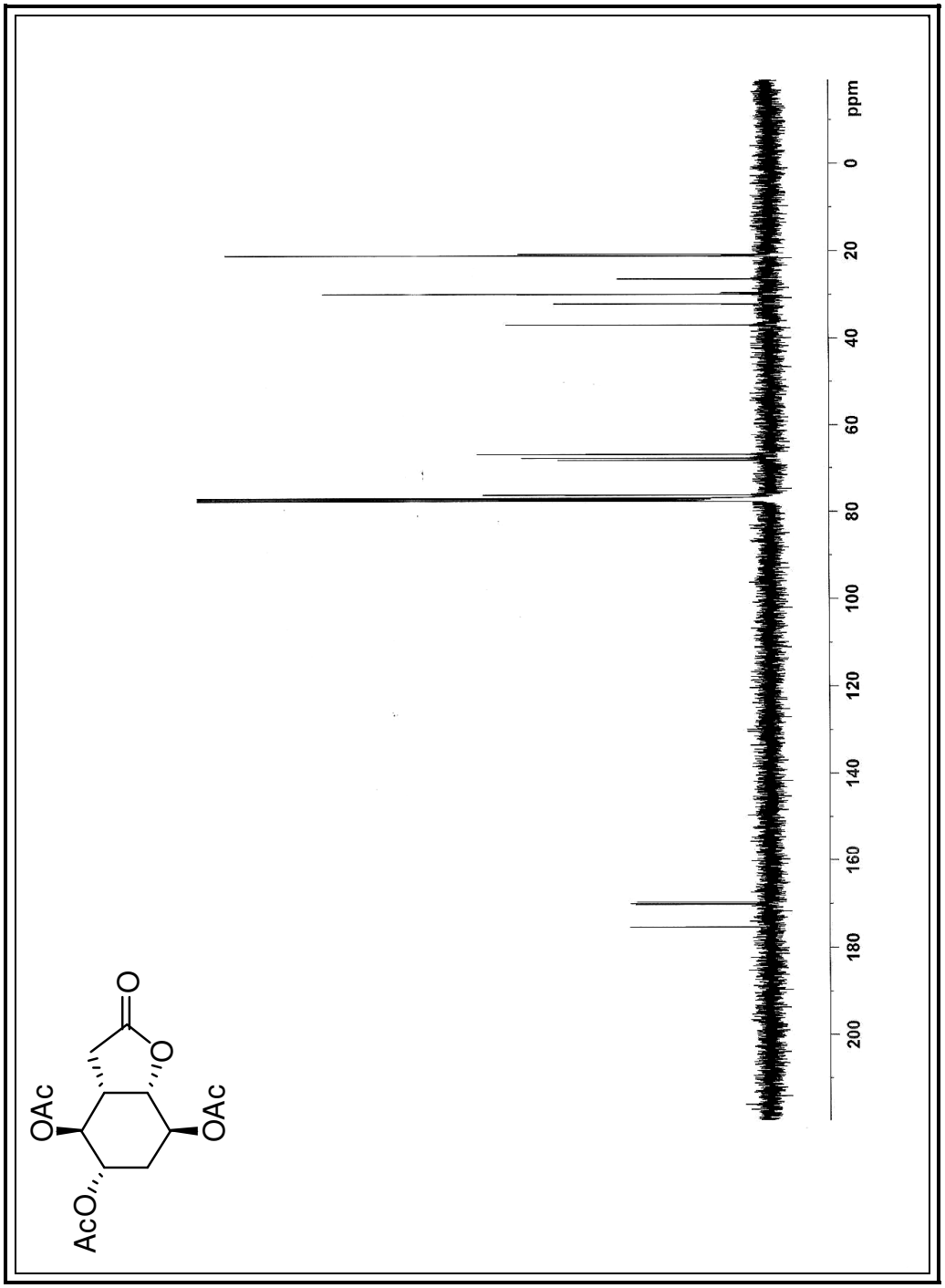

Figure 83 ^{13}C NMR spectrum of compound **85**

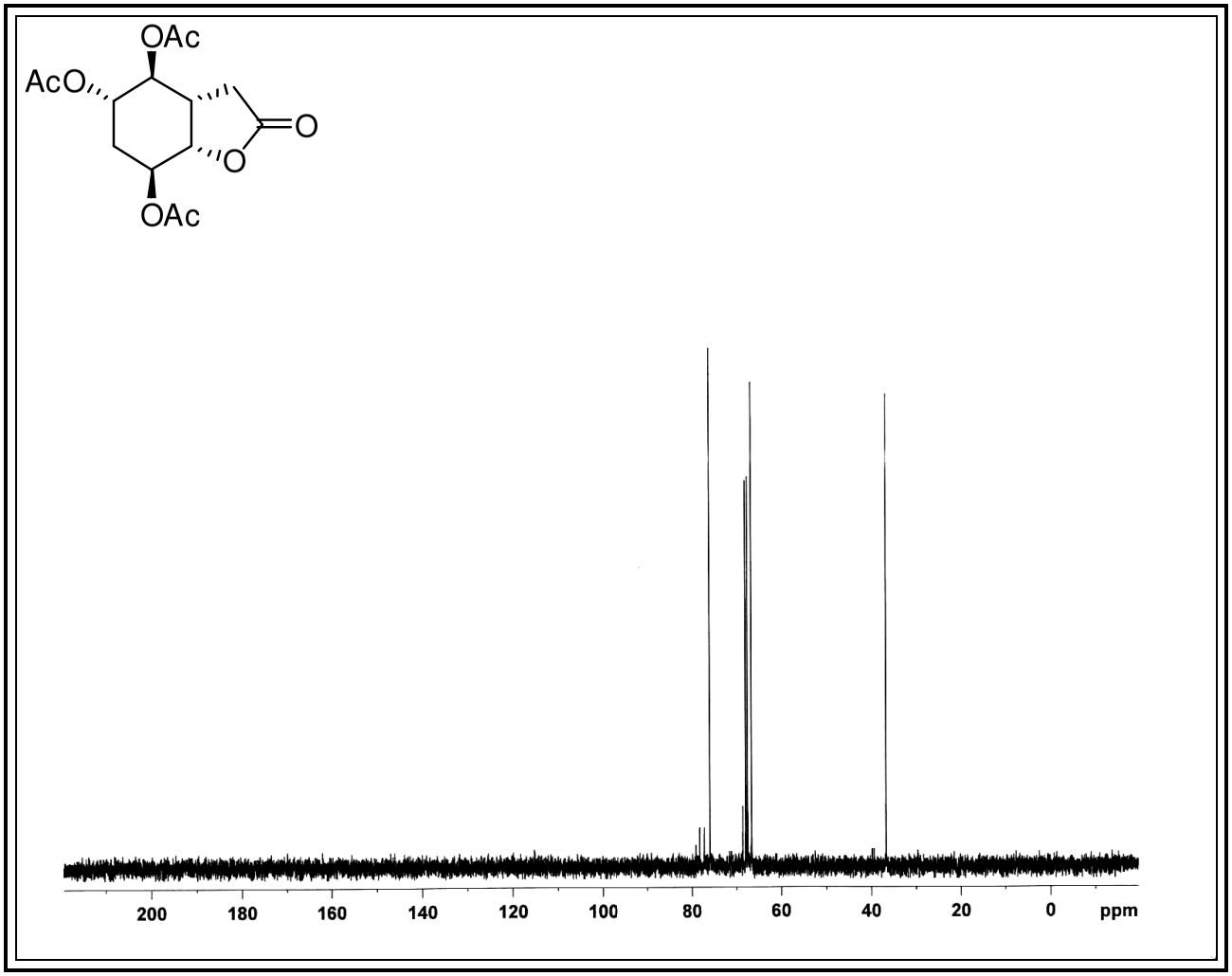

Figure 84 DEPT-90 spectrum of compound **85**

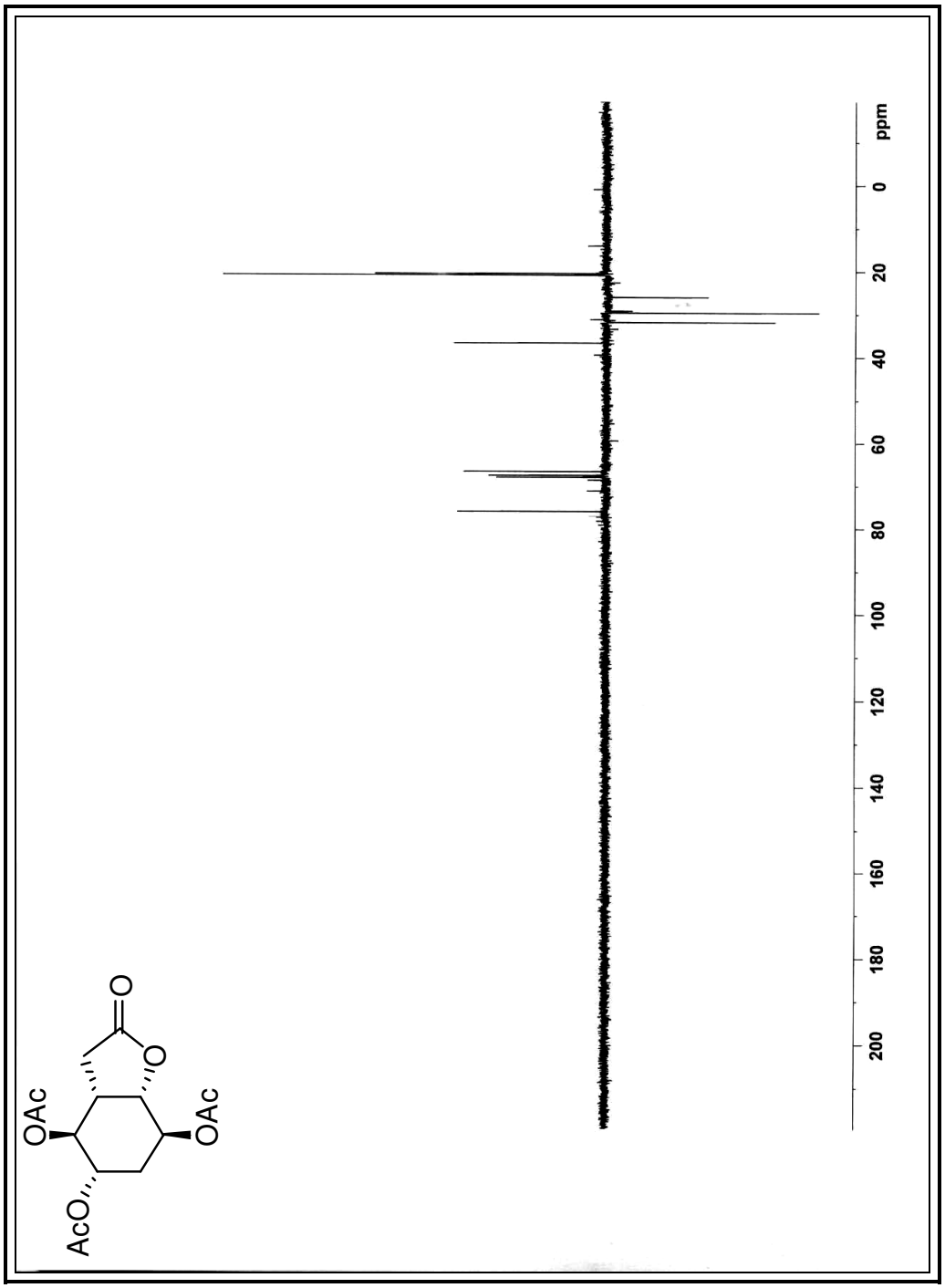

Figure 85 DEPT-135 spectrum of compound **85**

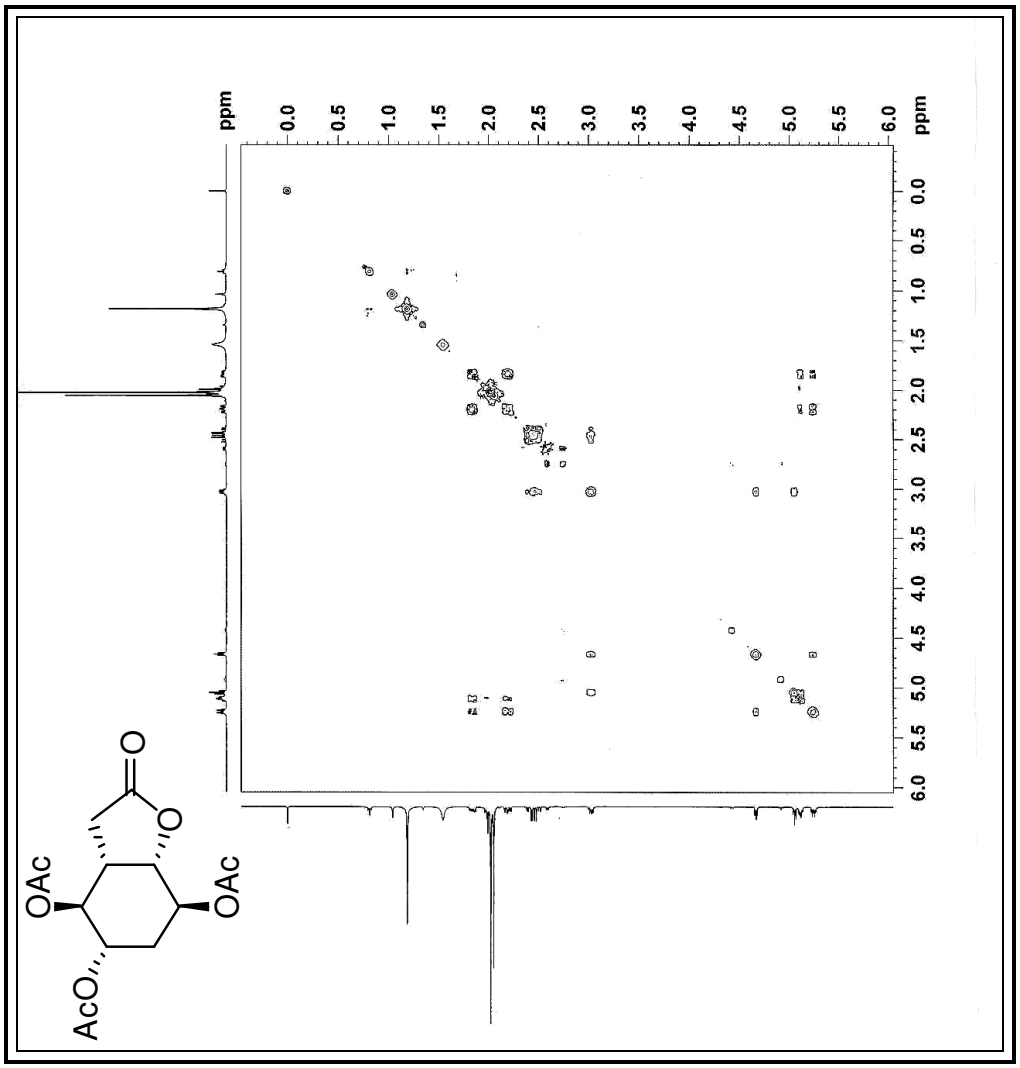

Figure 86 COSY spectrum of compound **85**

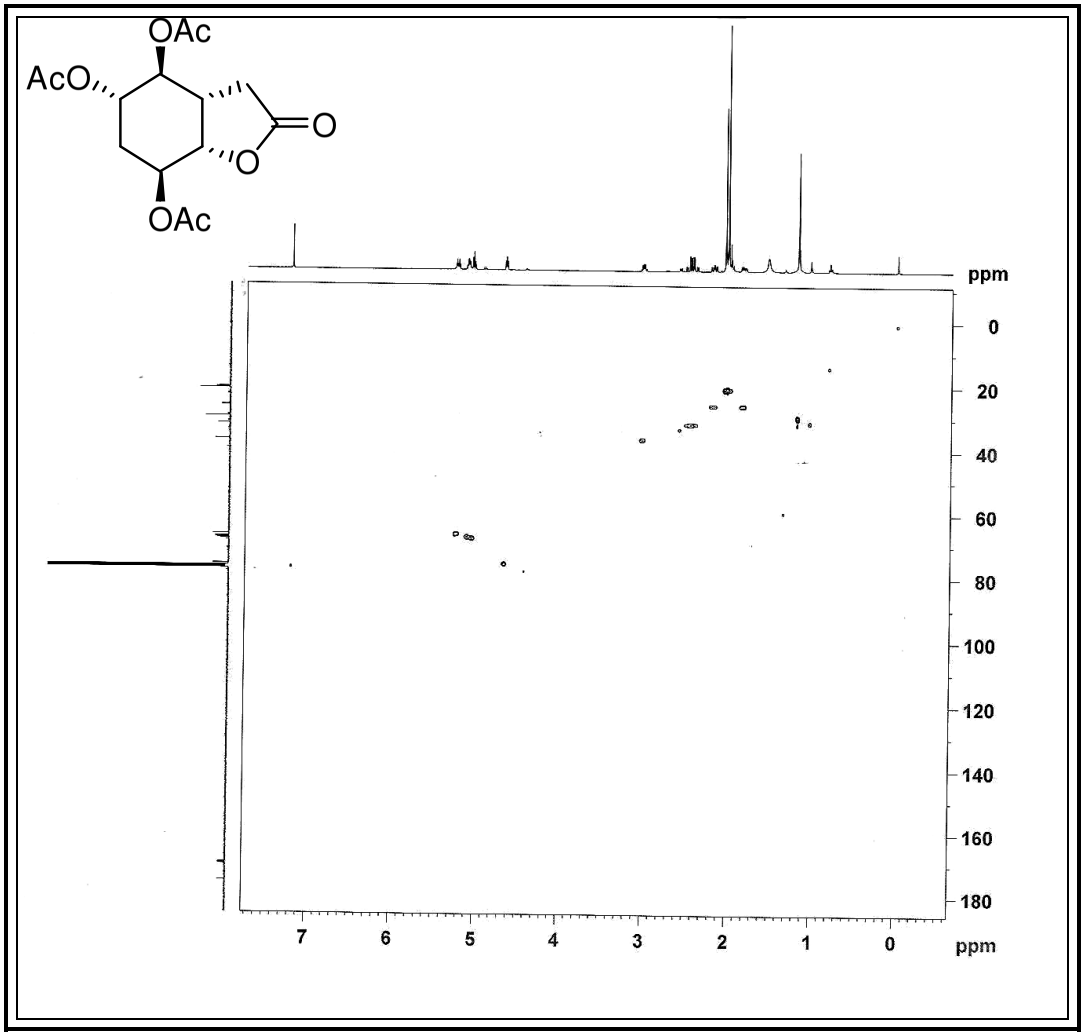

Figure 87 HMQC spectrum of compound **85**

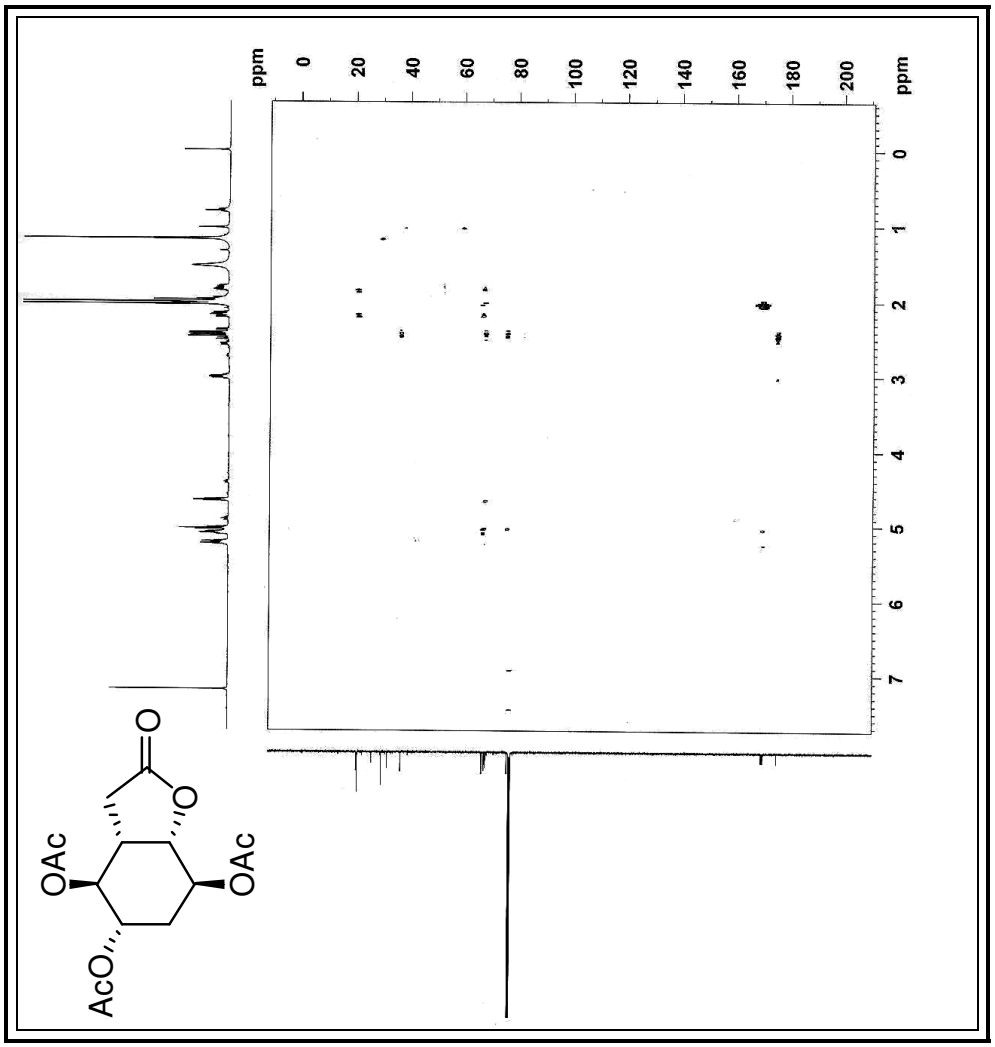

Figure 88 HMBC spectrum of compound **85**

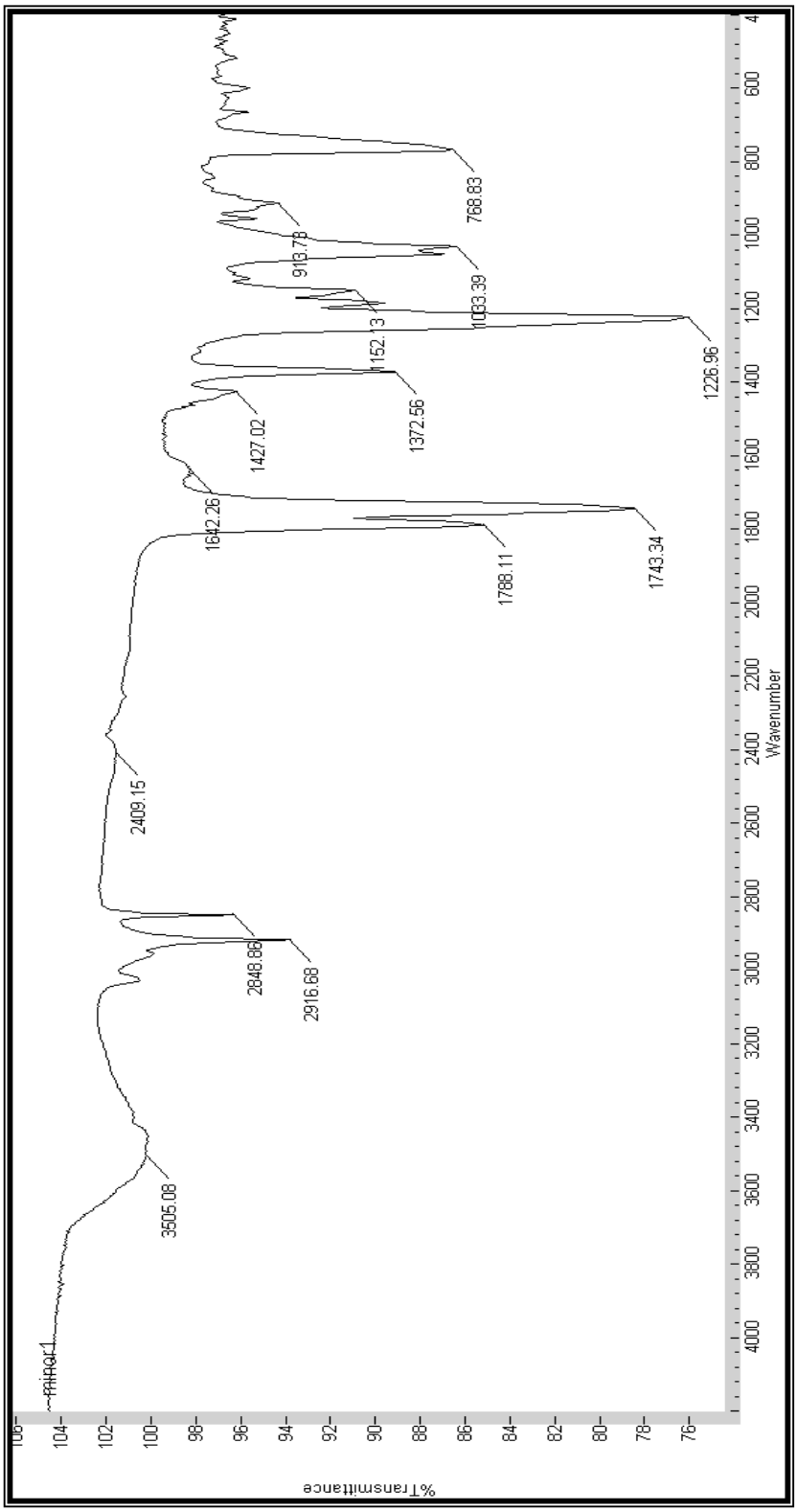

Figure 89 IR spectrum of compound **85**

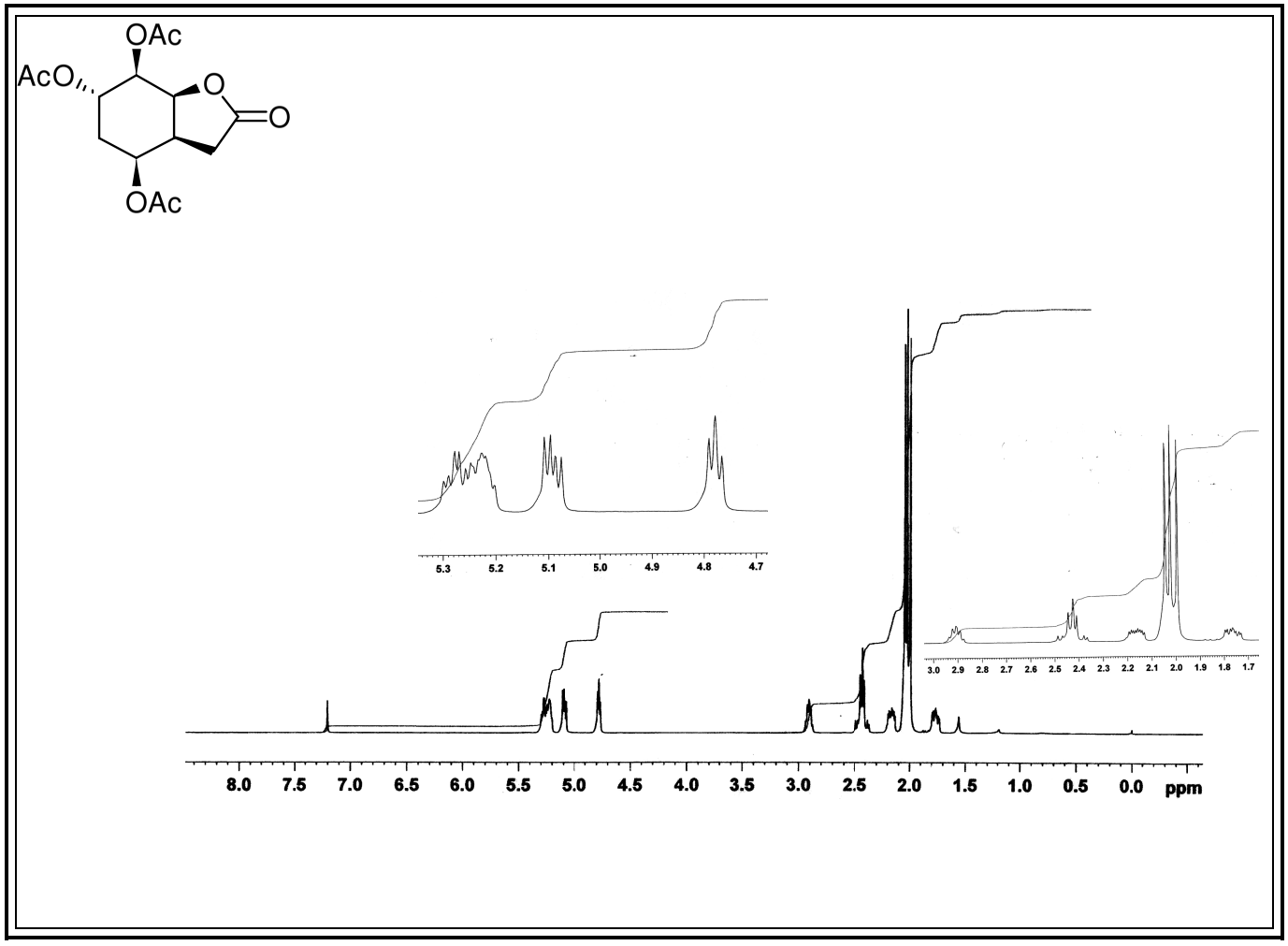

Figure 90 ^{1}H NMR spectrum of compound **86**

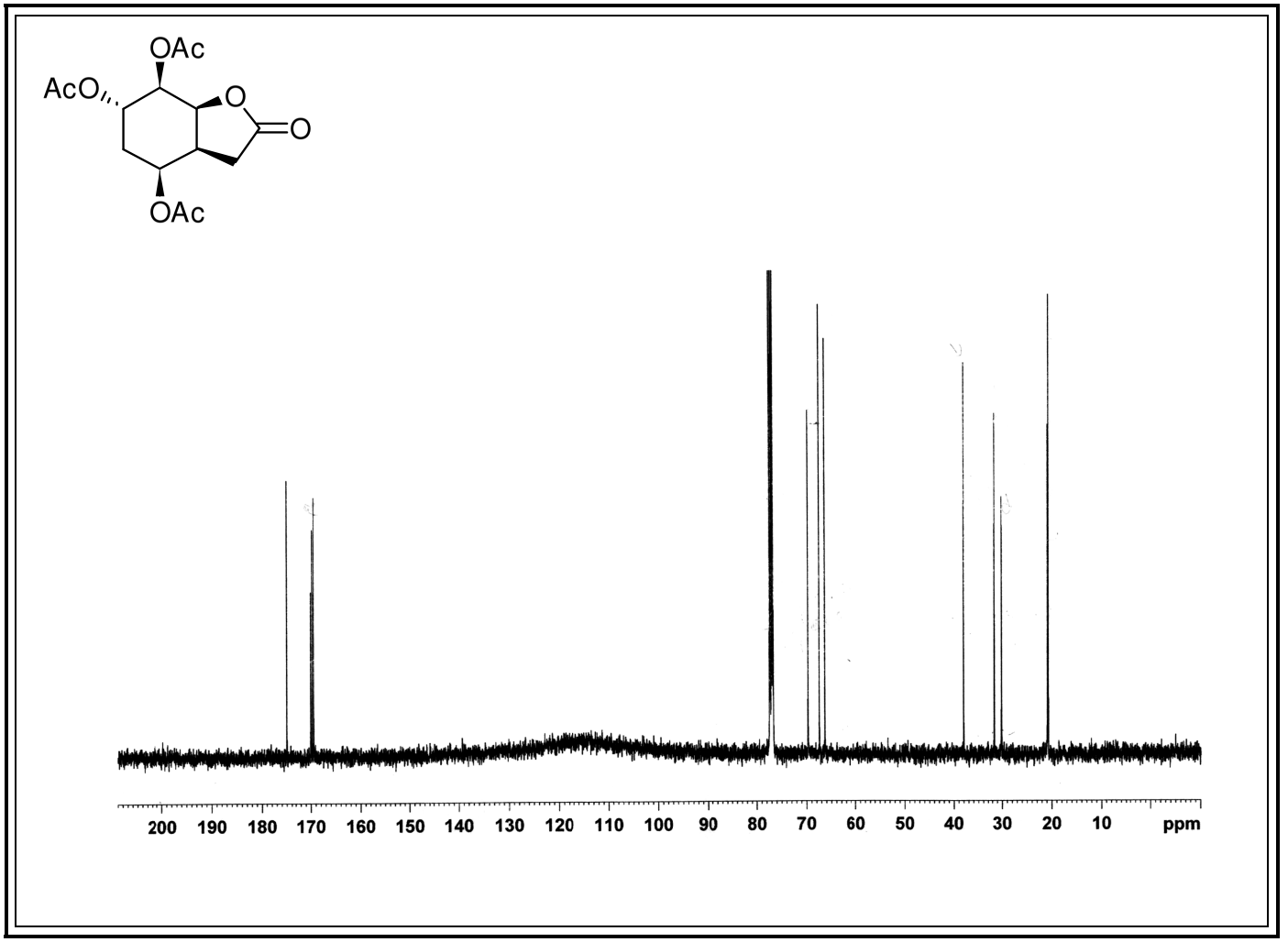

Figure 91 ^{13}C NMR spectrum of compound **86**

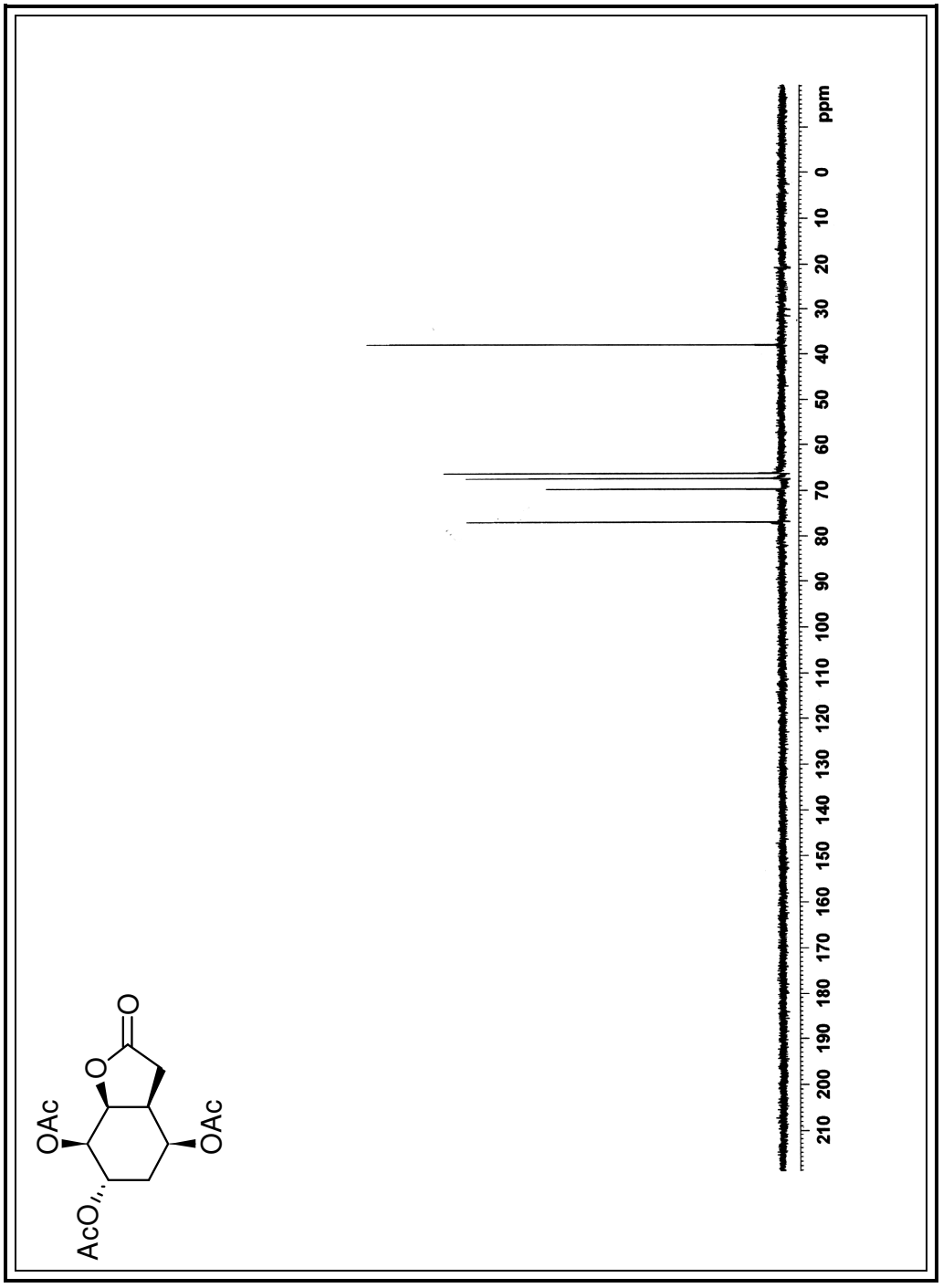

Figure 92 DEPT-90 spectrum of compound **86**

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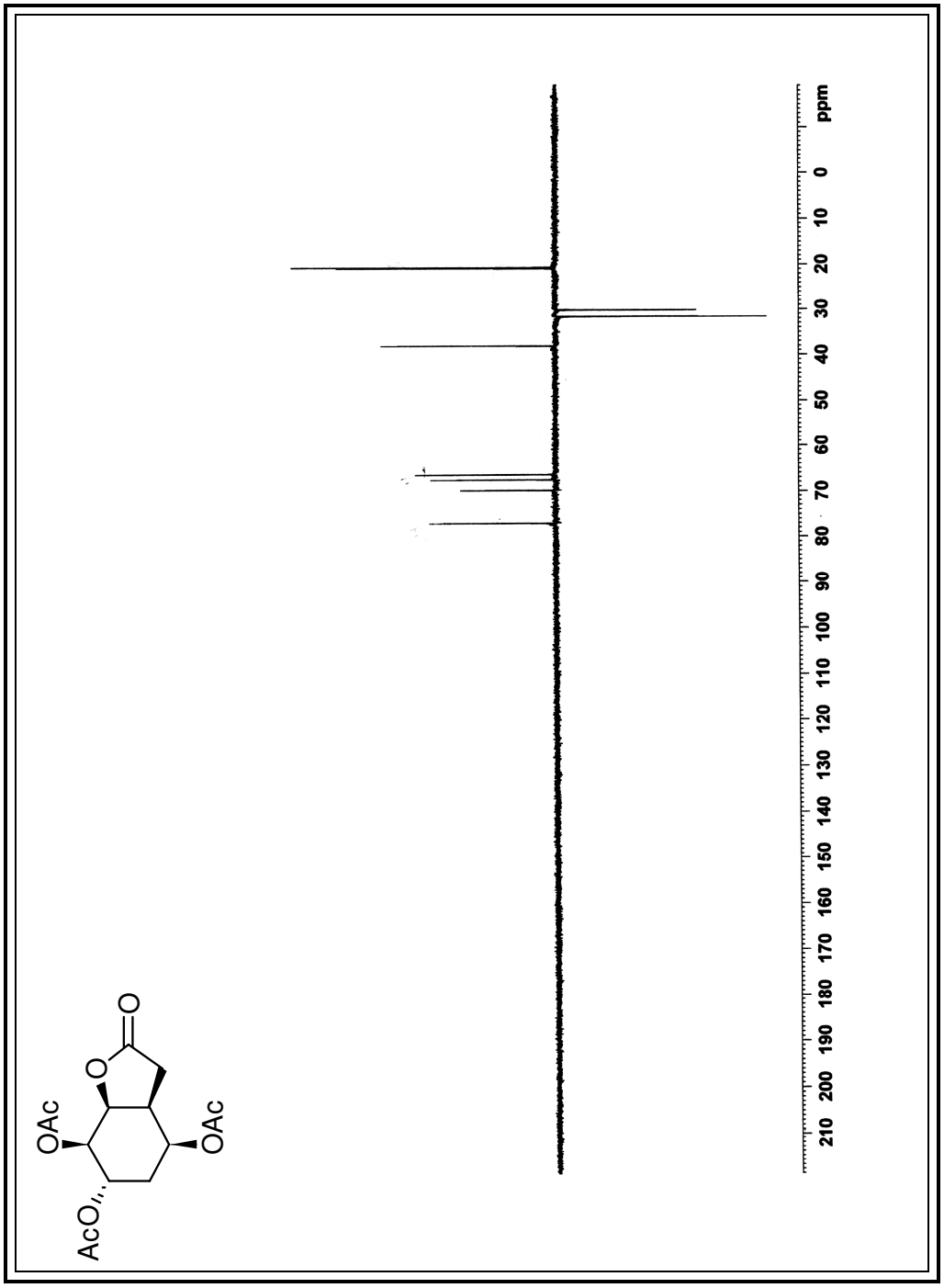

Figure 93 DEPT-135 spectrum of compound **86**

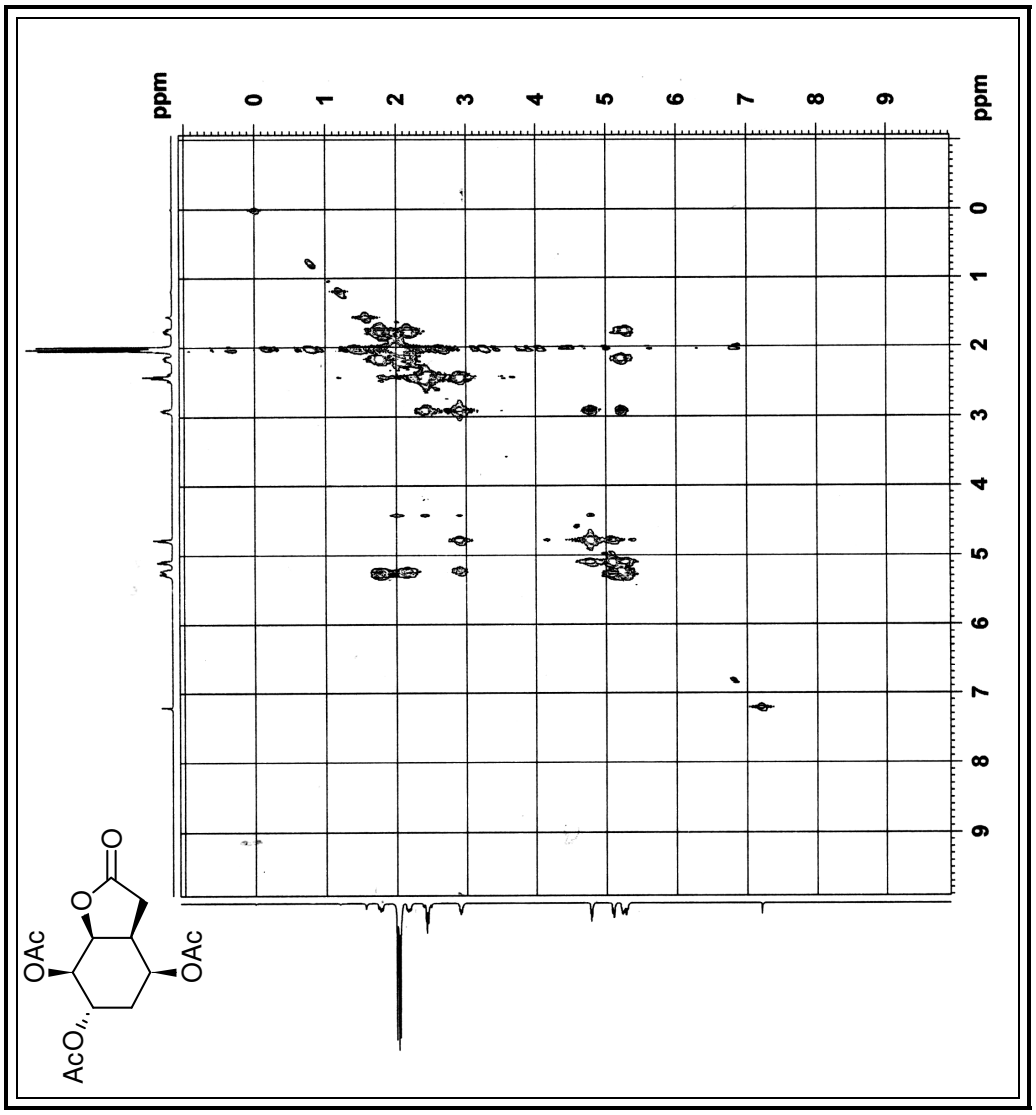

Figure 94 COSY spectrum of compound **86**

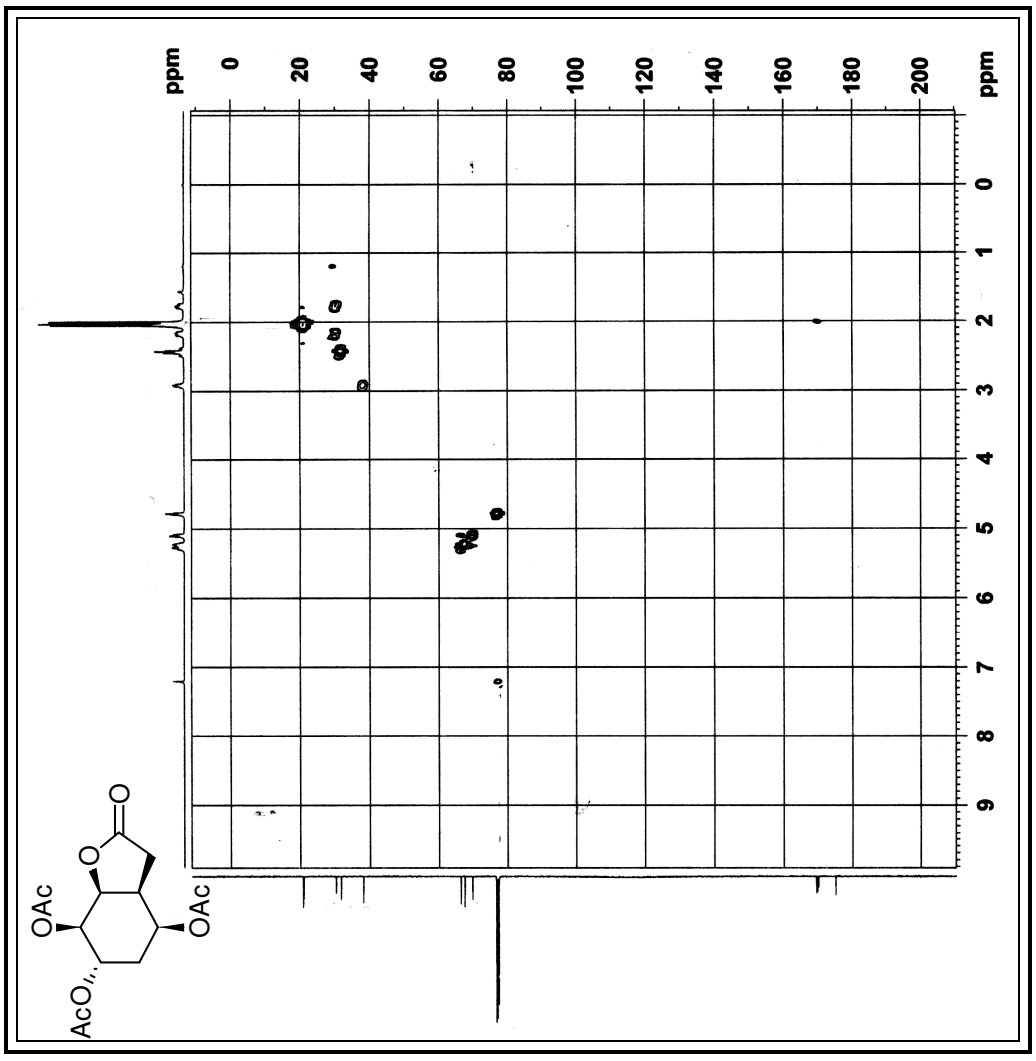

Figure 95 HMQC spectrum of compound **86**

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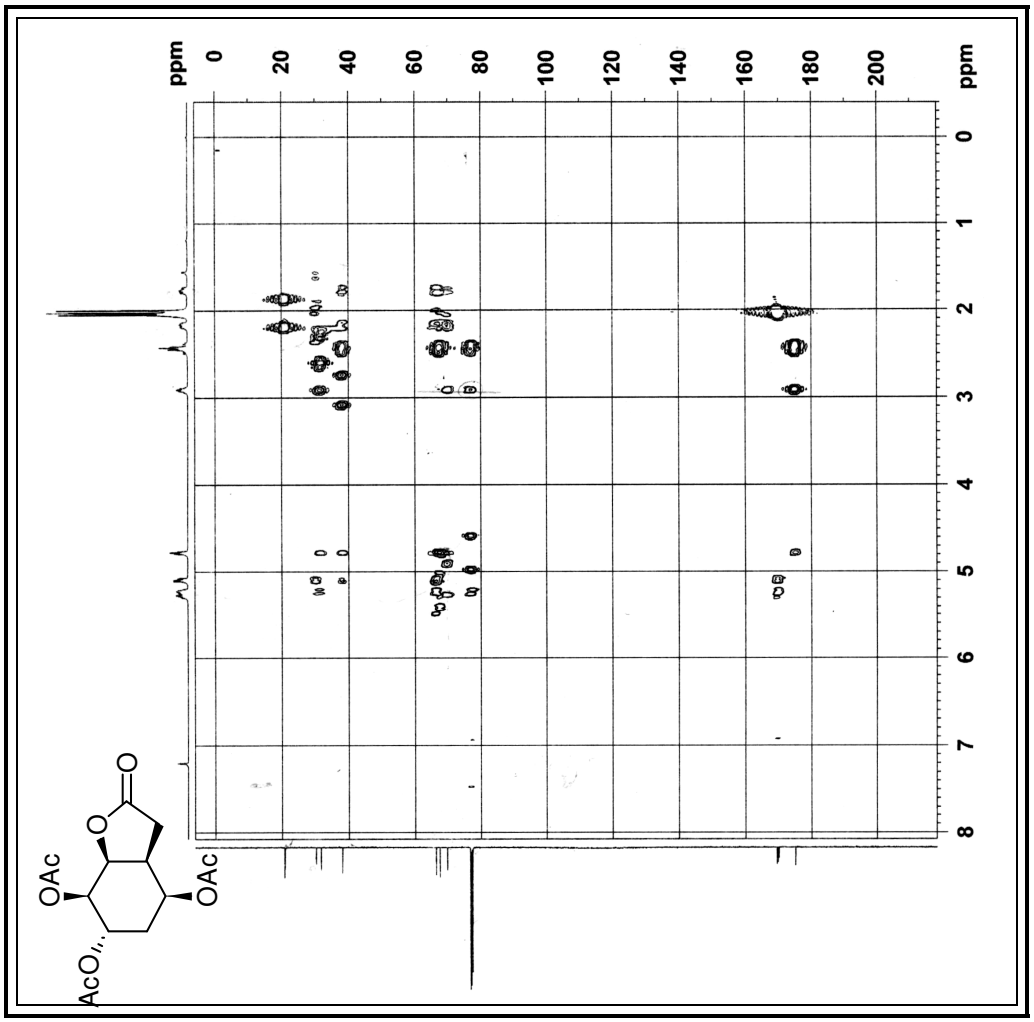

Figure 96 HMBC spectrum of compound **86**

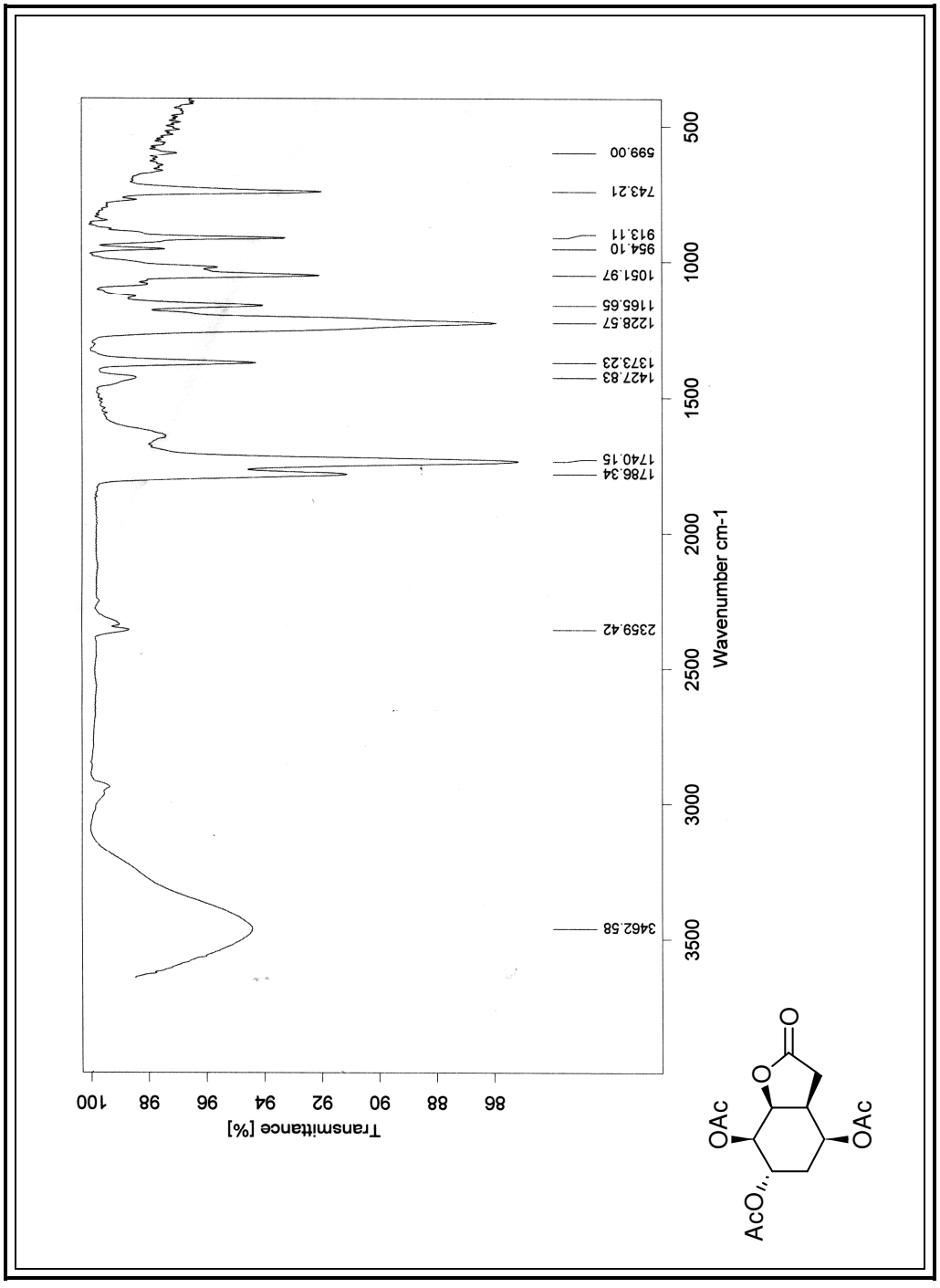

Figure 97 IR spectrum of compound **86**

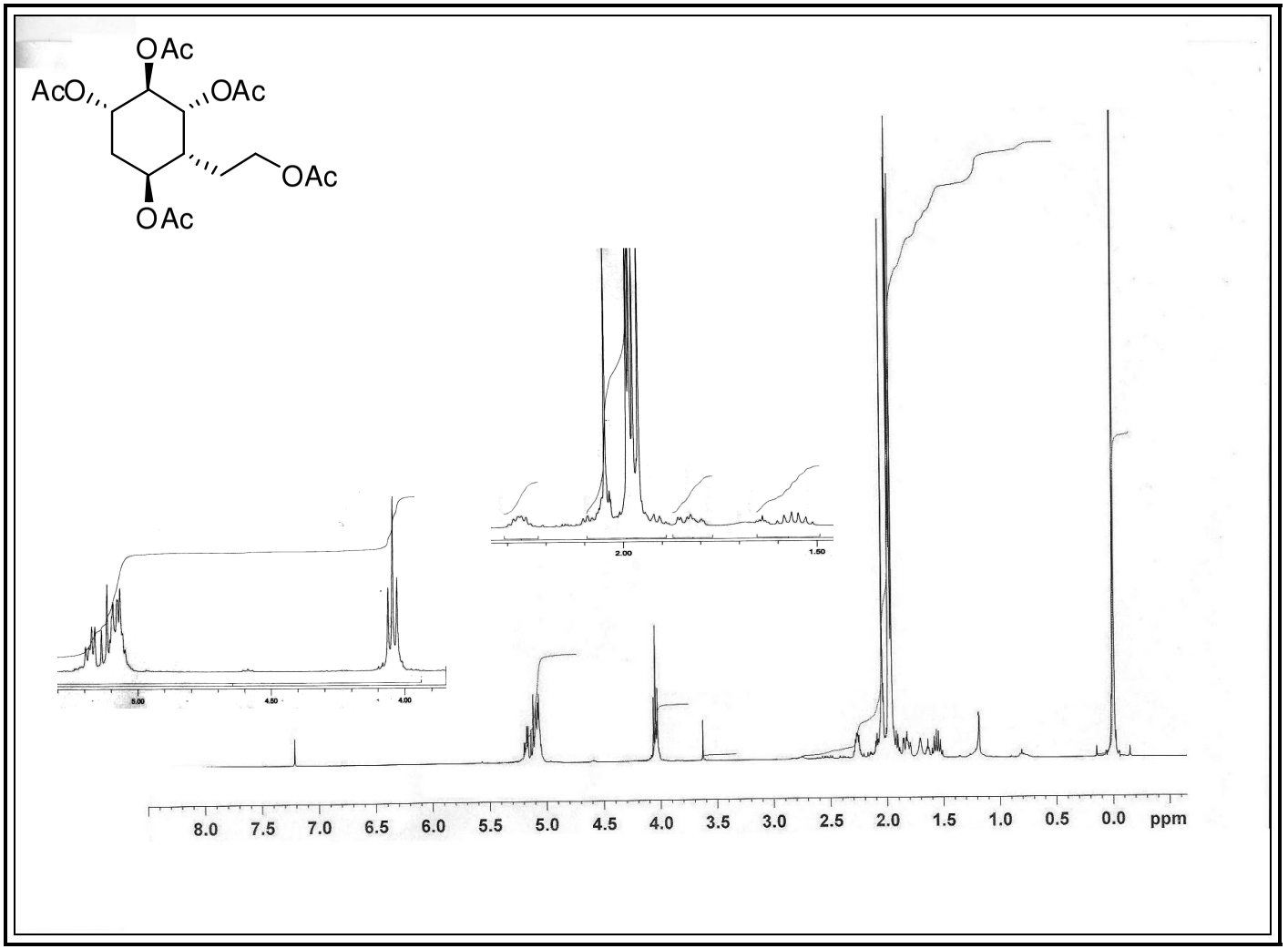

Figure 98 ^{1}H NMR spectrum of compound **88**

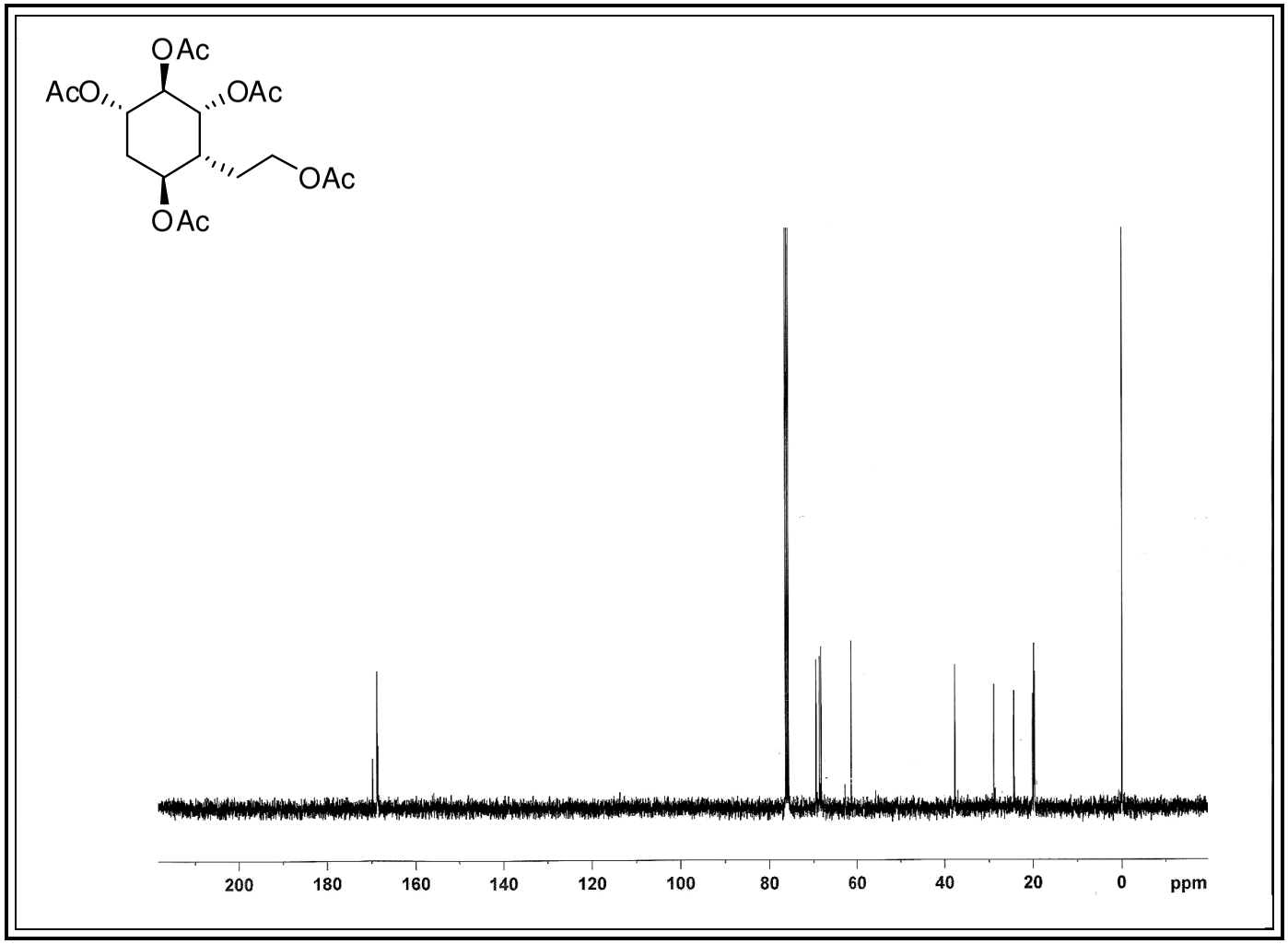

Figure 99 ^{13}C NMR spectrum of compound **88**

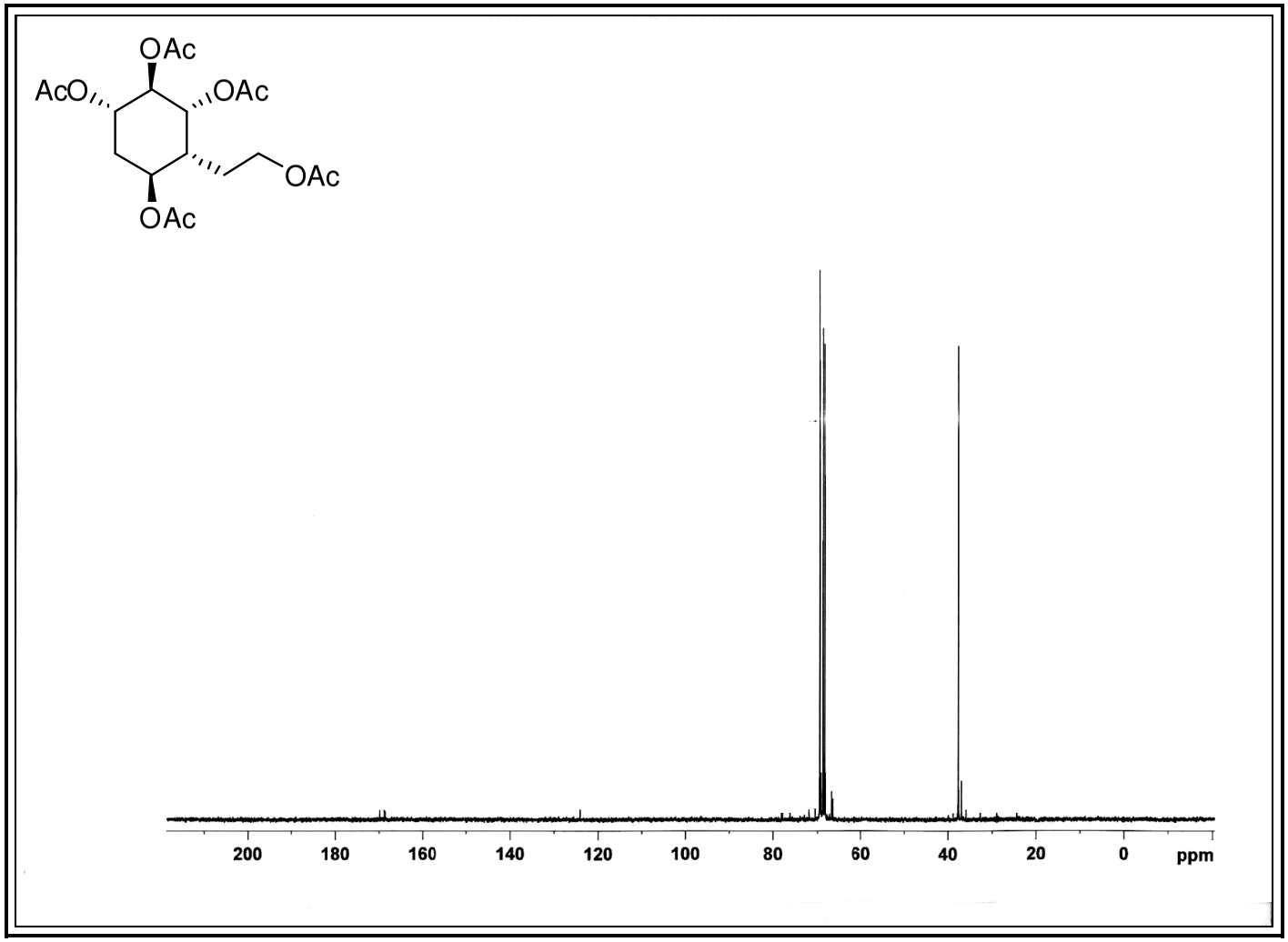

Figure 100 DEPT-90 spectrum of compound **88**

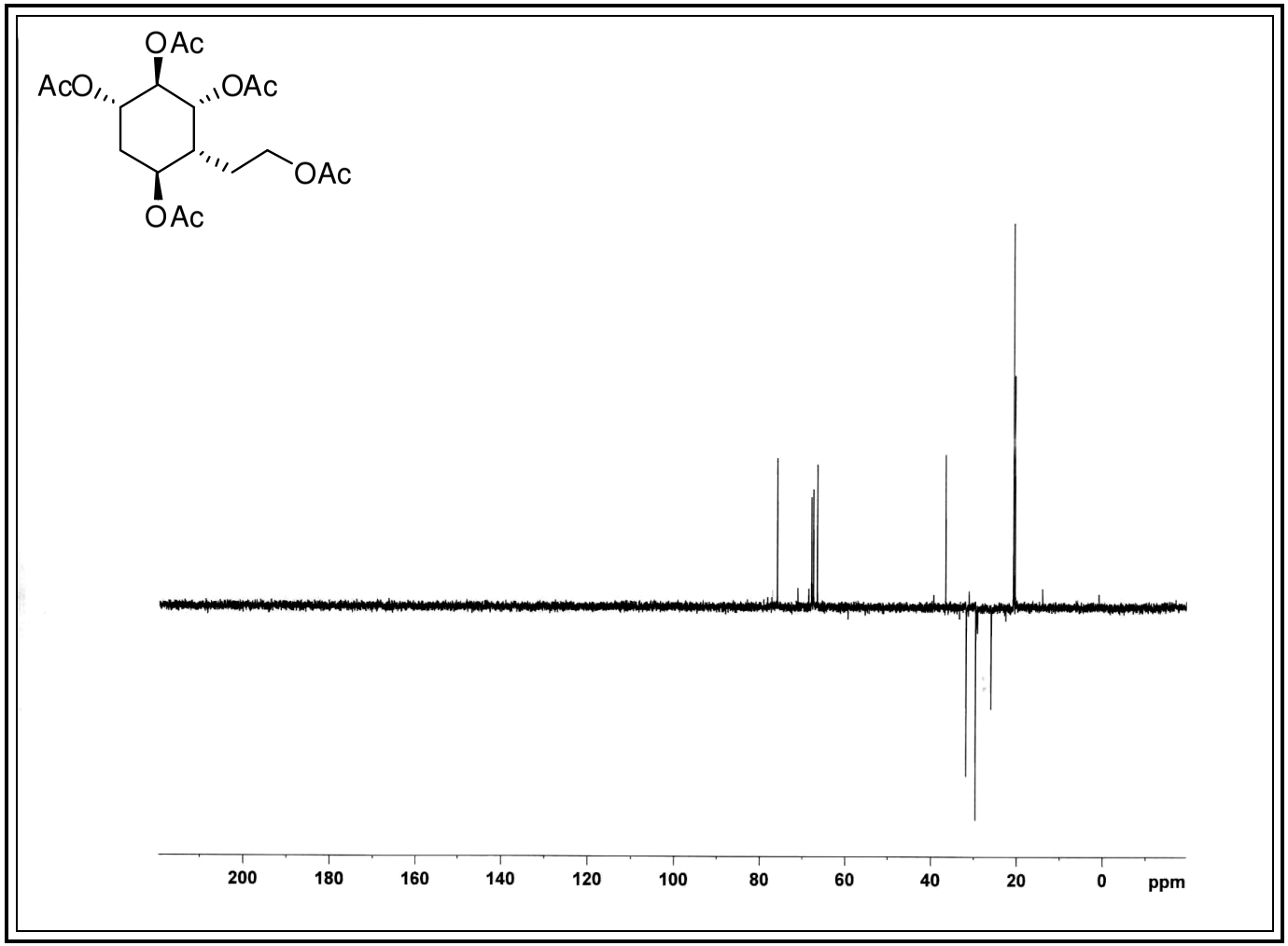

Figure 101 DEPT-135 spectrum of compound **88**

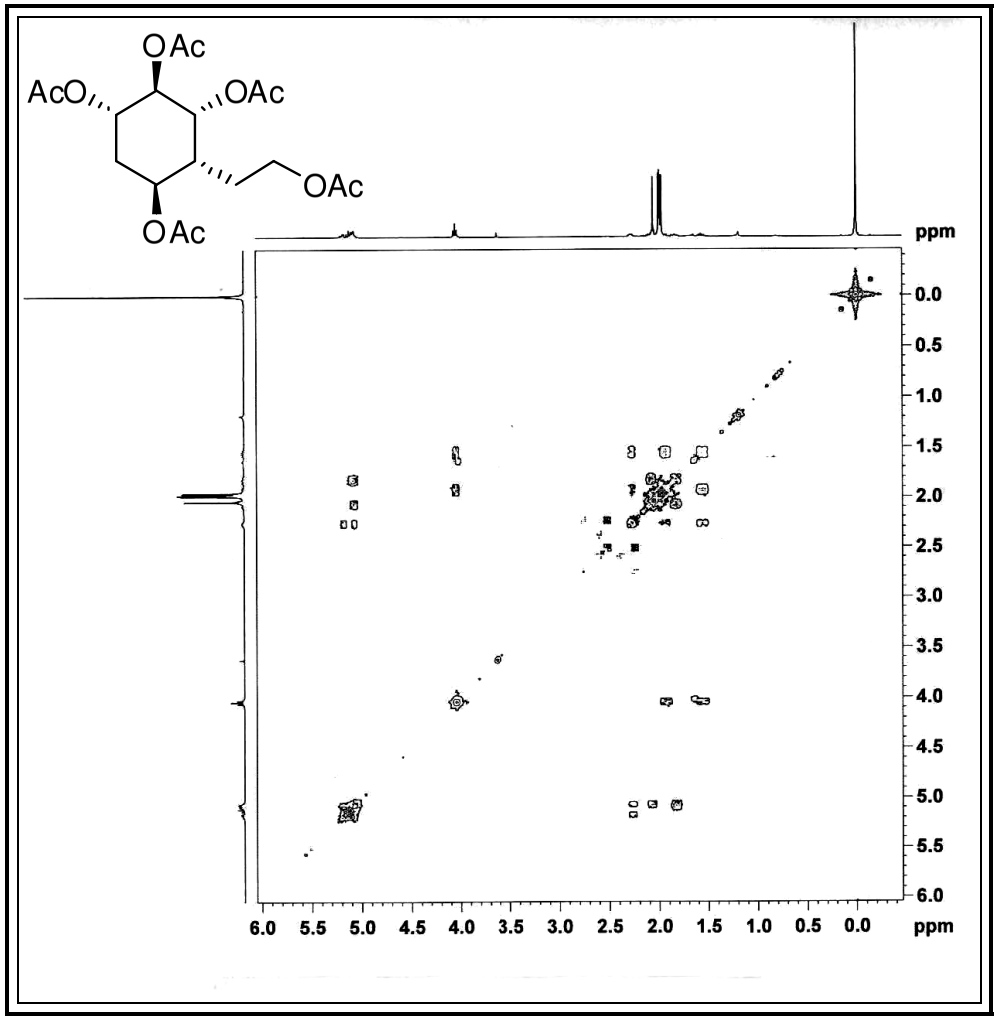

Figure 102 COSY spectrum of compound **88**

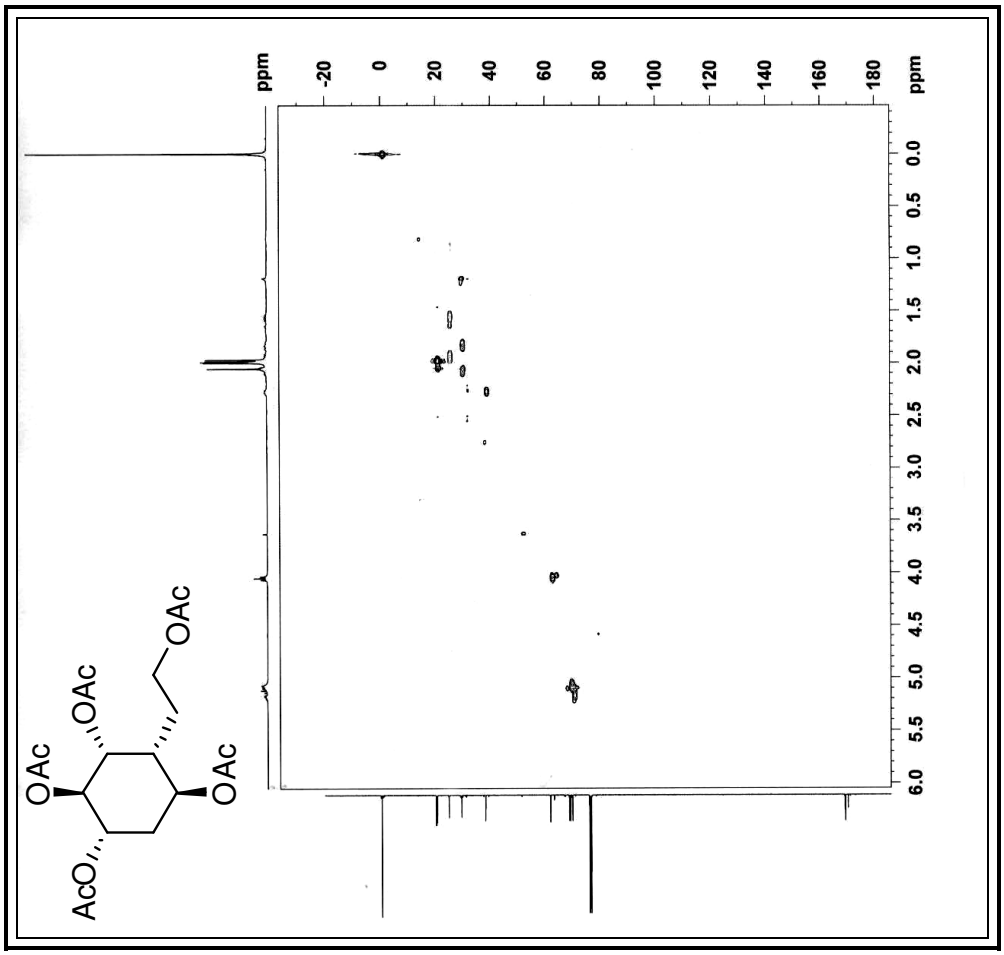

Figure 103 HMQC spectrum of compound **88**

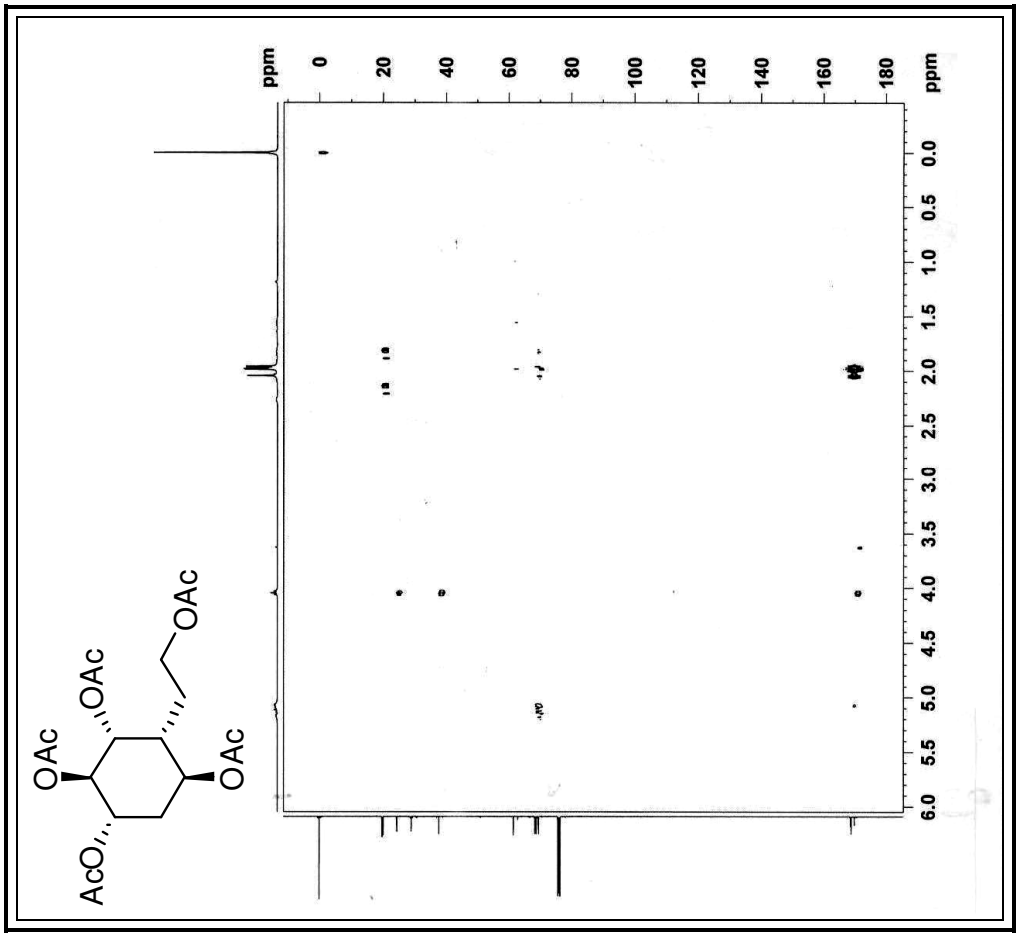

Figure 104 HMBC spectrum of compound **88**

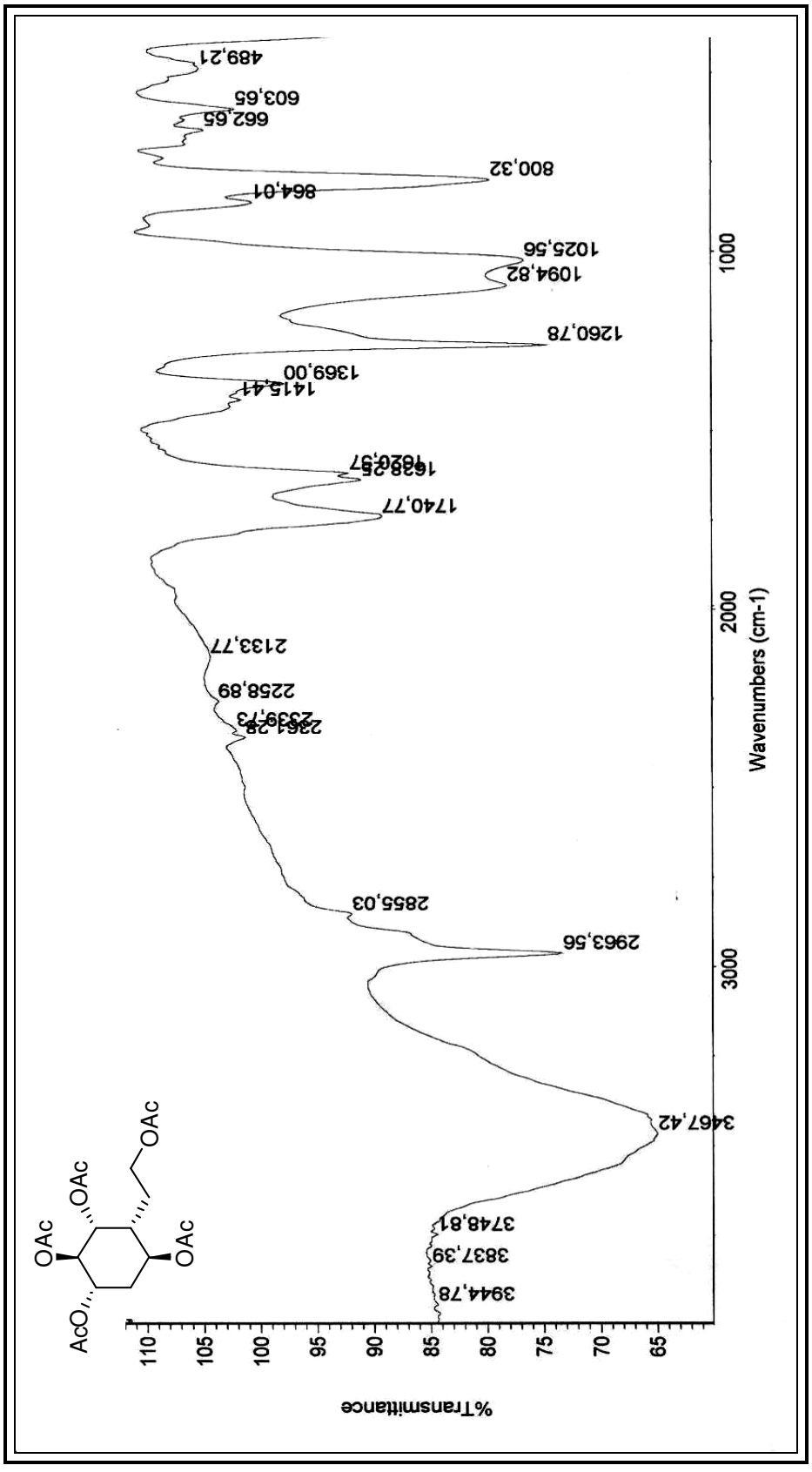

Figure 105 IR spectrum of compound **88**

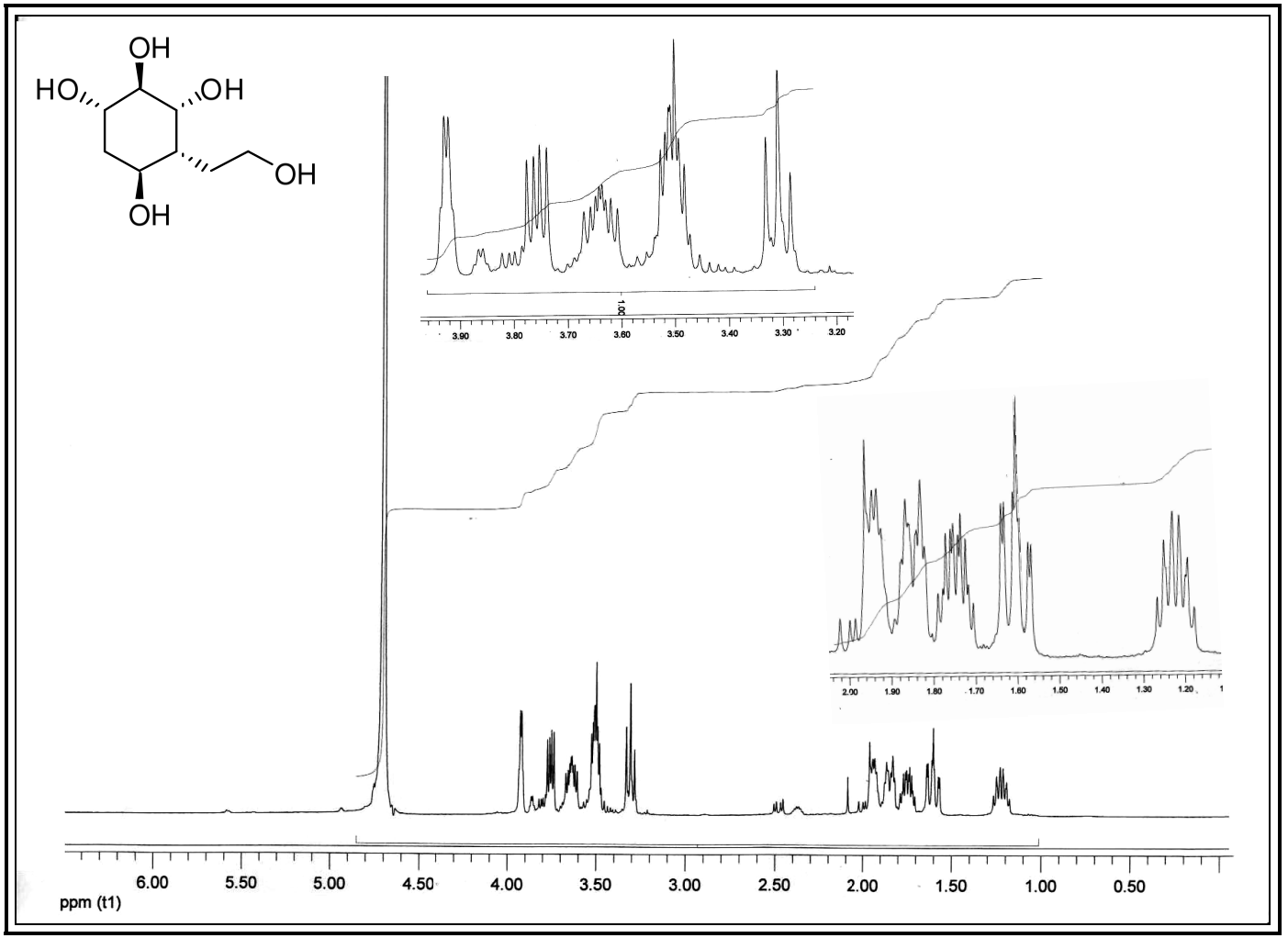

Figure 106 ^{1}H NMR spectrum of compound **73**

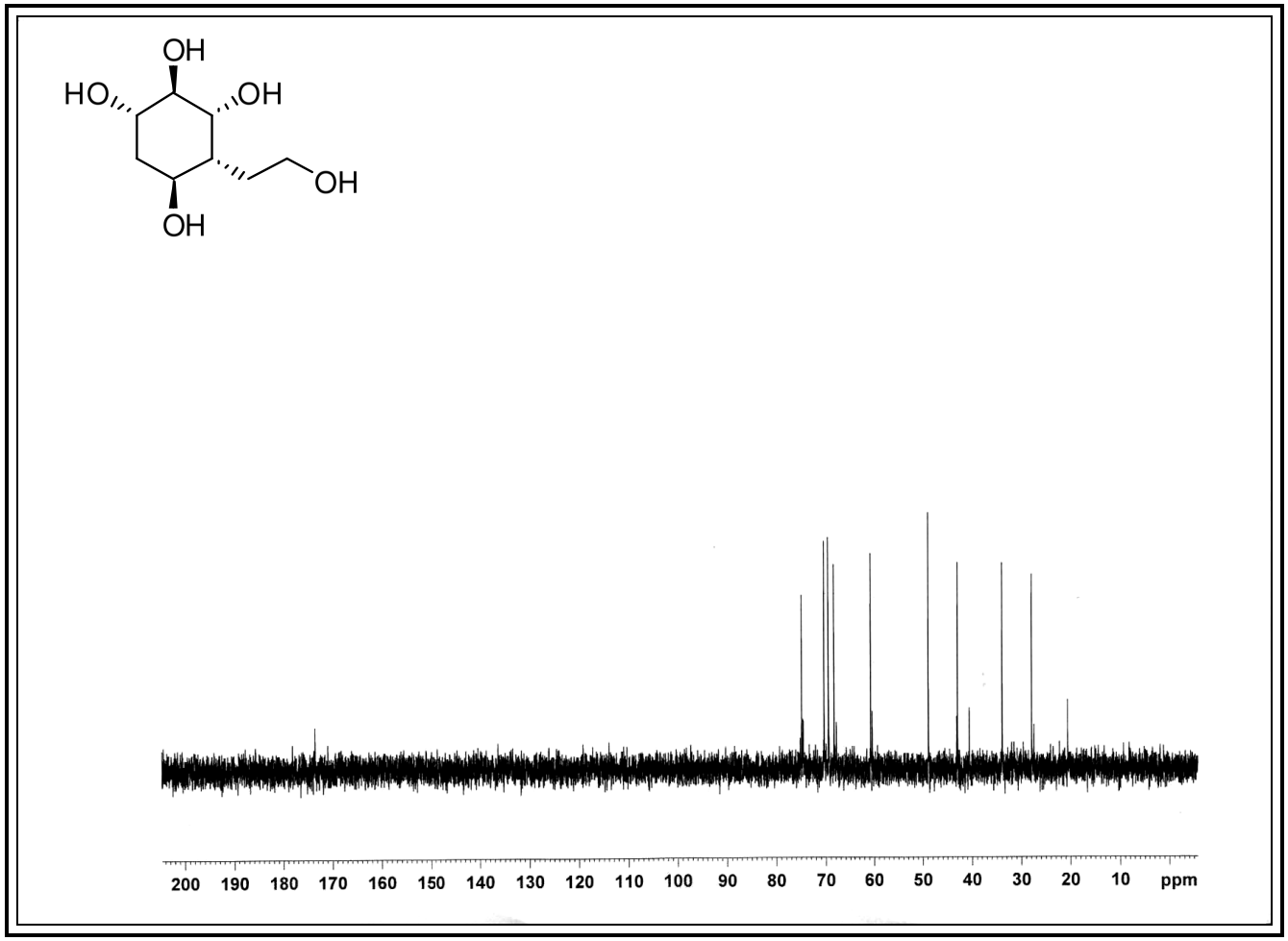

Figure 107 ^{13}C NMR spectrum of compound **73**