DEVELOPMENT OF NEW SYNTHETIC STRATEGIES FOR AMINOCYCLITOLS

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ABSTRACT

DEVELOPMENT OF NEW SYNTHETIC STRATEGIES FOR AMINOCYCLITOLS

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Cyclitols are of great importance due to their biological activities playing a crucial role in living organisms as well as their synthetic usefulness in the synthesis of other natural compounds or pharmaceuticals. In this study, new synthetic strategies leading to the aminocyclitols were investigated. The synthesis of aminoconduritol and aminoinositol derivatives (**173** and **174)** were achieved starting from easily available compound, 7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (**166**) obtained from the Diels-Alder reaction of furan and maleic anhydride. The anhydride functionality in **166** was converted into the half-ester **169** by desymmetrization in methanol. The carboxylic acid moiety in the molecule was used to obtain urethane functionality by making use of Curtius rearrangement. After the cleavage of oxa-bridge with the help of a Lewis acid the aminoconduritol derivative **173** was synthesized. The *cis*-dihydroxylation of **173** with osmium tetroxide resulted in the formation of inositol derivative **174**. Consequently, we developed a new methodology for the synthesis of aminocyclitol derivatives.

Keywords: Aminocyclitols, aminoconduritols, aminoinositols, desymmetrization of anhydride, Curtius rearrangement, ring opening of oxa-bridge.

ÖZ

AMİNOSİKLİTOLLER İÇİN YENİ SENTEZ YÖNTEMLERİNİN GELİŞTİRİLMESİ

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M.S., Department of Chemistry
Tez Yöneticisi: Prof. Dr. Metin BALCI

Temmuz 2003, 109 sayfa

Siklitoller bazı doğal bileşiklerin ve ilaçların sentezinde kullanılabilirliklerinin yanı sıra, canlı organizmalarda hayati önem taşıyan biyolojik aktiviteleri sebebiyle son derece önemli bileşiklerdir. Bu çalışmada aminosiklitollere ulaşabilecek yeni sentetik yöntemler incelenmiştir. Aminokonduritol türevi **173** ve aminoinositol türevi **174**'ün sentezi furan ve maleik anhidritin Diels-Alder reaksiyonu ile kolayca elde edilebilen 7-oksa-bisiklo[2.2.1]hept-5-en-2,3-dikarboksilik anhidrit (**166**) ile başlanarak gerçekleştirilmiştir. **166**'daki anhidrit gurubu metanol içinde desimetrileştirme ile yarı ester **169'**e dönüştürülmüştür. Moleküldeki karboksilik asit kısmı Curtius düzenlenmesi ile üretan gurubu elde edilmesinde kullanılmıştır. Oksa köprüsünün bir Lewis asiti yardımı ile açılmasının ardından aminokonduritol türevi **173** sentezlenmiştir. **173**'ün osmiumtetroksit ile *cis*-dihidroksilasyonu sonucunda inositol türevi **174**'ün sentezi gerçekleştirilmiştir. Sonuç olarak, bu çalışmayla aminosiklitol türevlerinin sentezi için yeni bir sentetik yöntem geliştirilmiştir.

Anahtar Kelimeler: Aminosiklitoller, aminokonduritoller, aminoinositoller, anhidrit desimetrileştirme, Curtius düzenlenmesi, oksa köprüsünün açılımı.

...to my dear lifelong friend, Zafer

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Last but not the least, my deepest appreciation and love are devoted to my dear husband, Zafer. I am grateful to him for everything he made for us to have such a beautiful life.

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INTRODUCTON

1.1 CYCLITOLS

The word *cyclitol* refers to cyclic polyalcohols among which the great majority of work is dedicated to ones bearing cyclohexane skeleton, e.g. conduritols (**1**), quercitols (**2**), and inositols (**3**). During the last era, chemists, as well as biologists and biochemists, have been captivated by the beauty of cyclitols, the attractiveness of which arises from their synthetic diversity and biological activities [1].

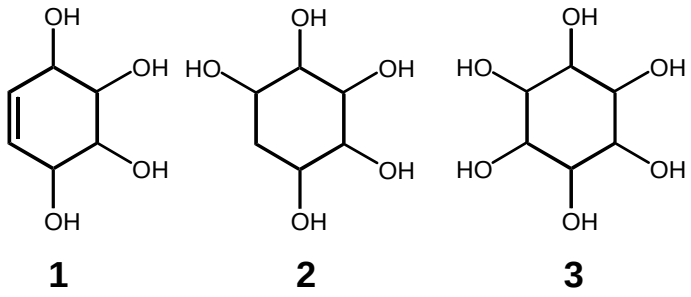


Figure 1. Important Cyclitols

Inositols play a crucial role in signal transduction in living organisms, that is; they act as cell mediators. Quercitols constitute a large group of stereoisomeric family,

some of which were isolated as natural products. Conduritols, aminoconduritols, and their derivatives is of great interest due to their glycosidase inhibitory activity and antibiotic effects [2].

1.2 CONDURITOLS

1.2.1 NATURAL OCCURRENCE AND IMPORTANCE

Conduritols are 1,2,3,4-cyclohexenetetrols having six diastereomers, theoretically. Two of these diastereomers are symmetrical and the others are found in four enantiomeric pairs. To avoid confusion, conduritols are named by letters A, B, C, D, E, and F in the order of their discovery. In nature, only two isomers, Conduritol A (**4**) and Conduritol F (**9**) are found to exist so far [3a].

In 1908, Kübler isolated an alcohol from the bark of the vine *Marsdenia condurango* and he named it as “conduritol”, which was optically inactive and later designated as Conduritol A (**4**). In 1962 Plouver discovered another conduritol isomer from *Crysanthemum Leucanthemum* and it was named as L-Leucanthemitol (Conduritol F) (**9**). Conduritol F can be found at least in traces in almost all green plants, while the abundance of conduritol A is limited to specific subfamilies of tropical plants [4].

Being an extensive subgroup of cyclitols, as it was mentioned before, conduritols are known to have some important biological activities, the most striking of which is that they are inhibitors of glycosidases. Moreover, they have antifeedant, antibiotic, antileukemic, and growth-regulating activity [3a].

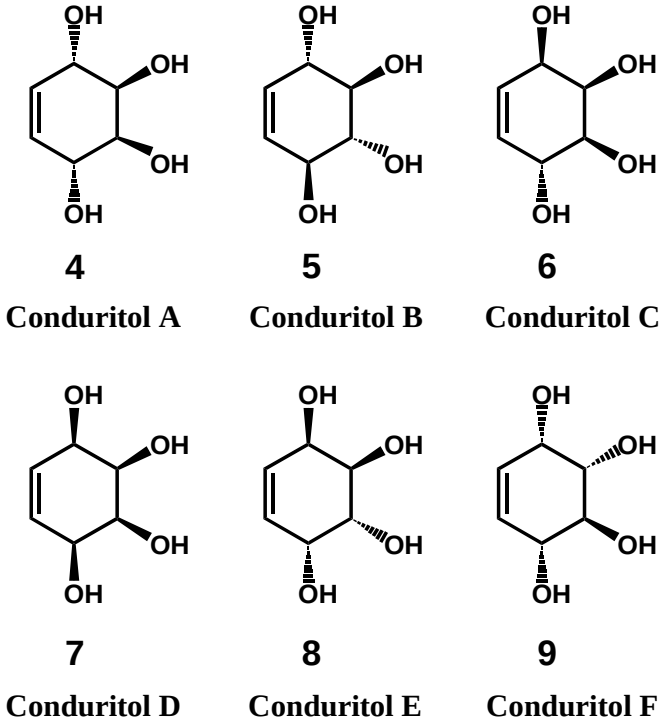
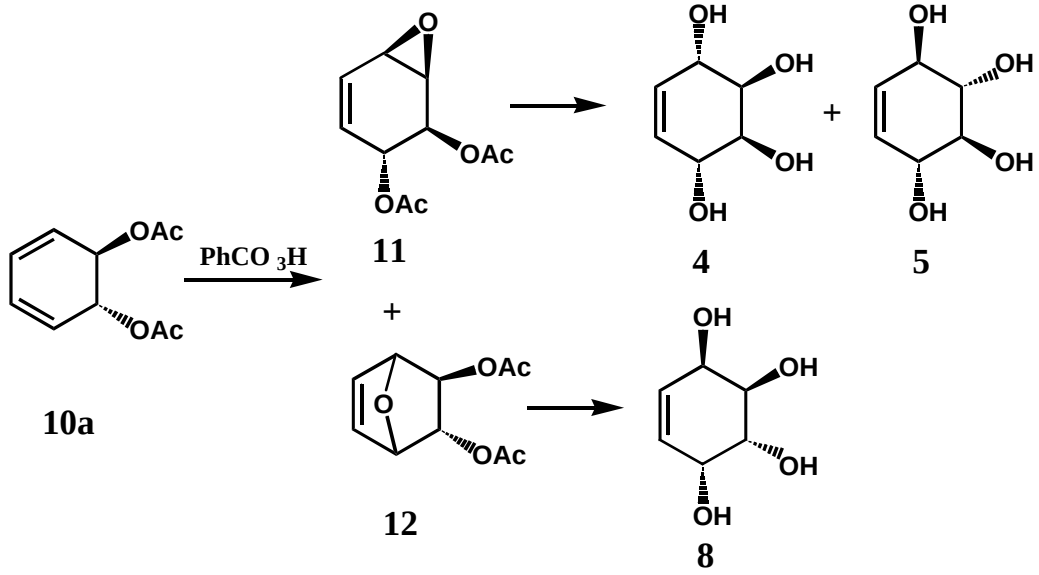


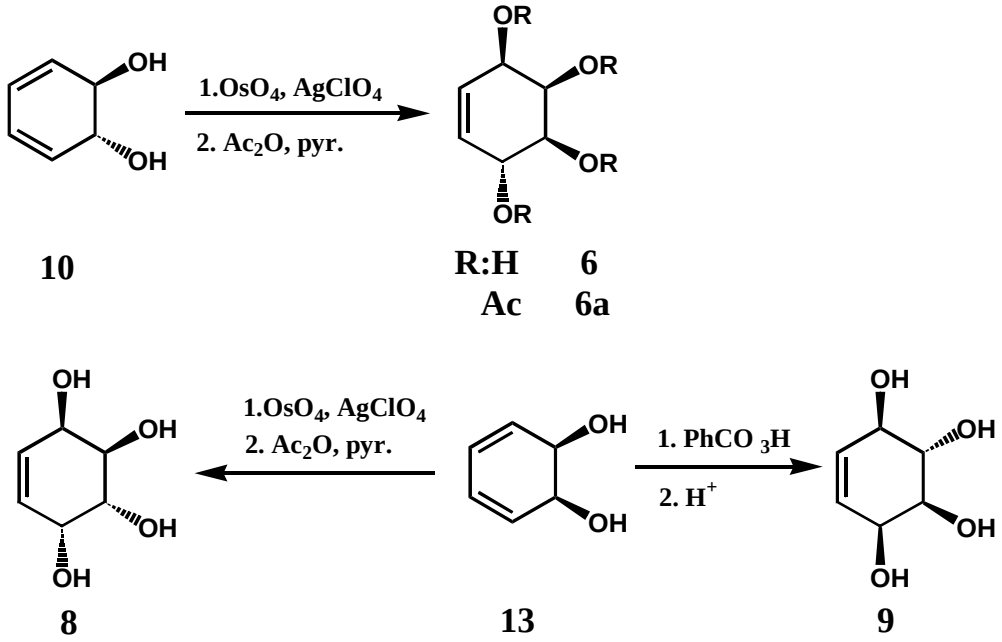
Figure 2. Conduritol isomers

In addition to their biological importance, conduritols and their derivatives involve in many reactions leading to the other interesting compounds like inositols, quercitols, deoxyinositols, aminoconduritols, conduritol epoxides, cyclophellitol, pseudo-sugars, amino sugar analogs, sugar amino acid analogs, etc. which make them synthetically valuable precursors [3b].

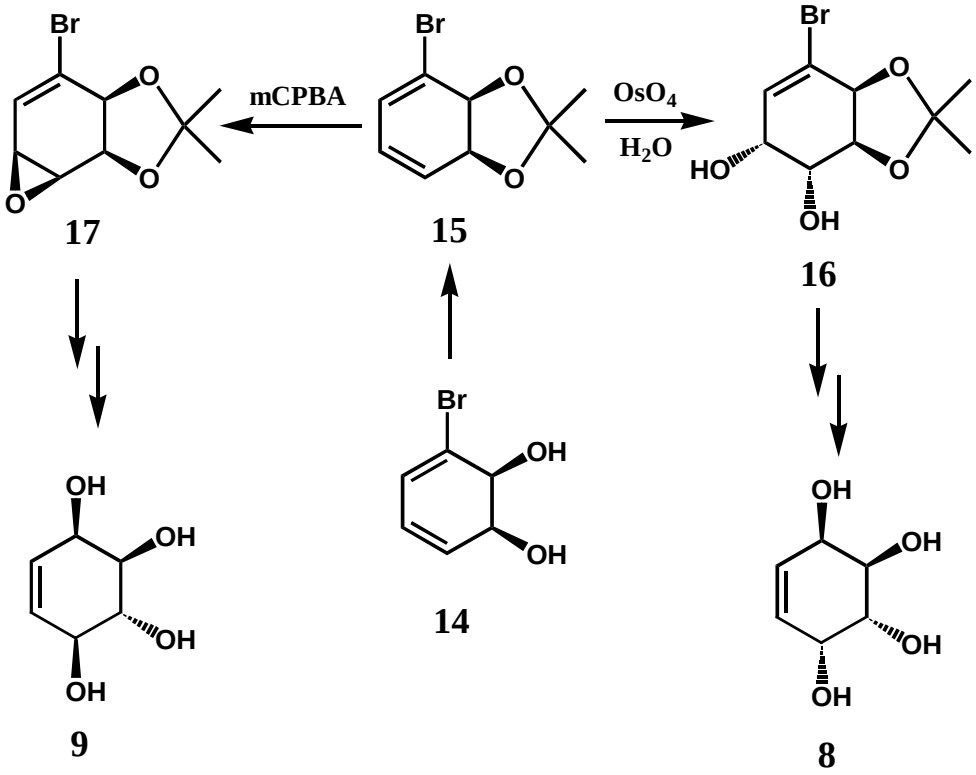
1.2.2 SYSTHESIS OF CONDURITOLS

For the first time, Nakajima *et al.* synthesized some conduritol isomers (A, B, and E) by using *trans*-benzenediol as starting material. After the oxidation of diacetate **10a** with perbenzoic acid, the resultant compounds **11** and **12** were converted into the desired conduritols. In order to obtain Conduritol C tetraacetate (**6a**) and Conduritol E (**8**), they applied osmium tetroxide oxidation to *trans*- and *cis*-benzenediol, respectively, followed by acetylation. They could also isolate Conduritol F (**9**) when *cis*-benzenediol was treated with perbenzoic acid followed by a hydrolysis step [4].

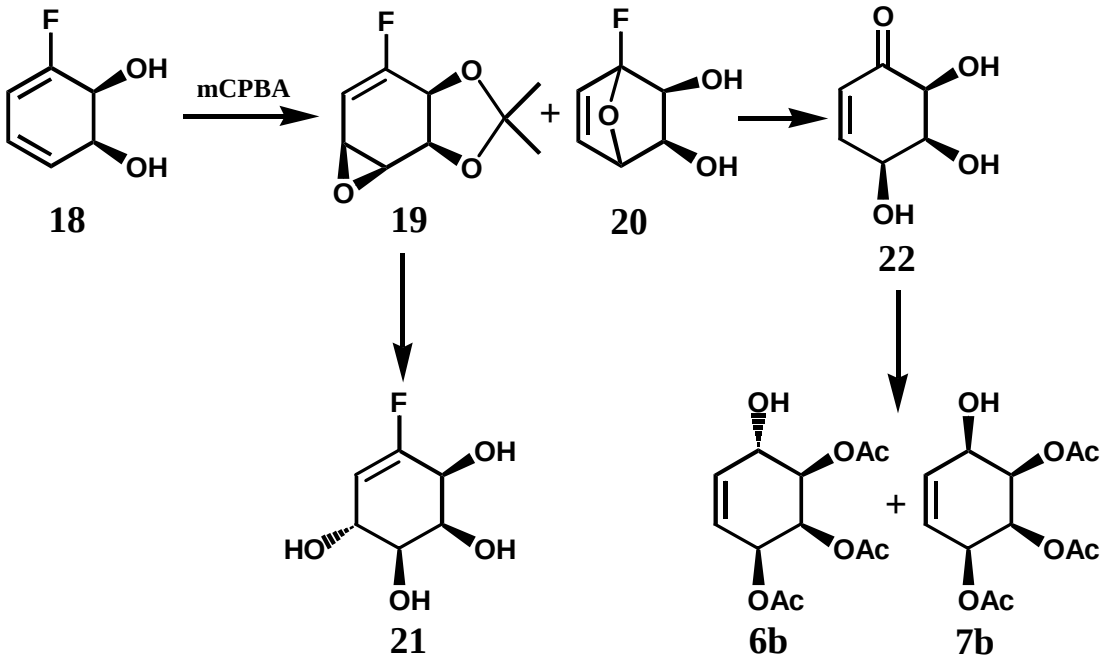




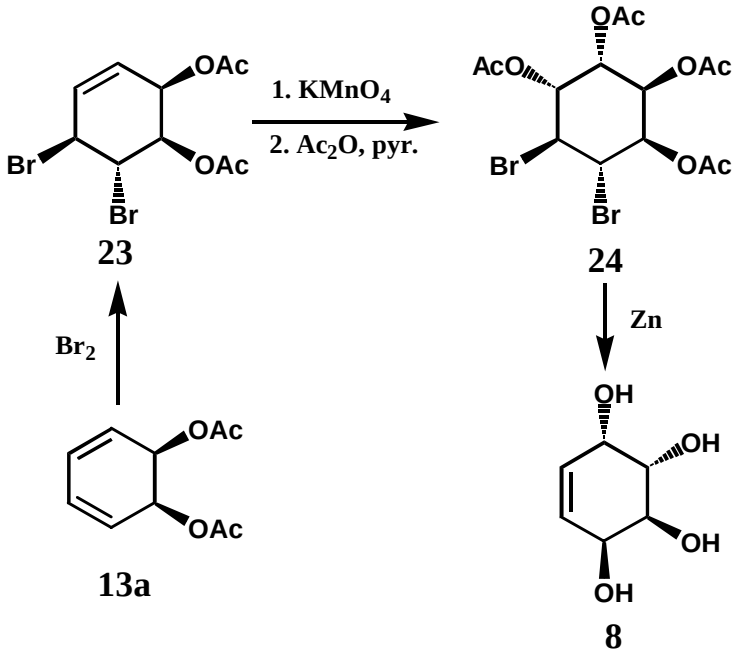
Cis- and *trans*-benzenediols were also used by a good number of groups in the synthesis of conduritols and their derivatives [5]. Among these groups, Hudlicky *et. al.* dedicated most of their works for the use of benzenediols as starting materials. They synthesized both Conduritol E (**8**) and Conduritol F (**9**) starting from a common acetonide **15**, the protected form of bromo-*cis*-benzenediol. The treatment of **15** with osmium tetroxide gave a single diol **16** resulting from reaction of the more electron rich double bond. After the reduction of bromide with tributyl tinhydride and deprotection, Conduritol E (**8**) could be obtained in enantiomerically pure form. On the other hand, a single epoxide **17** was formed by the reaction between *m*-CPBA and acetonide **15**. Opening of epoxide under basic conditions led to the bromotrans-diol, which was reduced by trimethyl tinhydride and deprotected giving Conduritol F (**9**) [6].



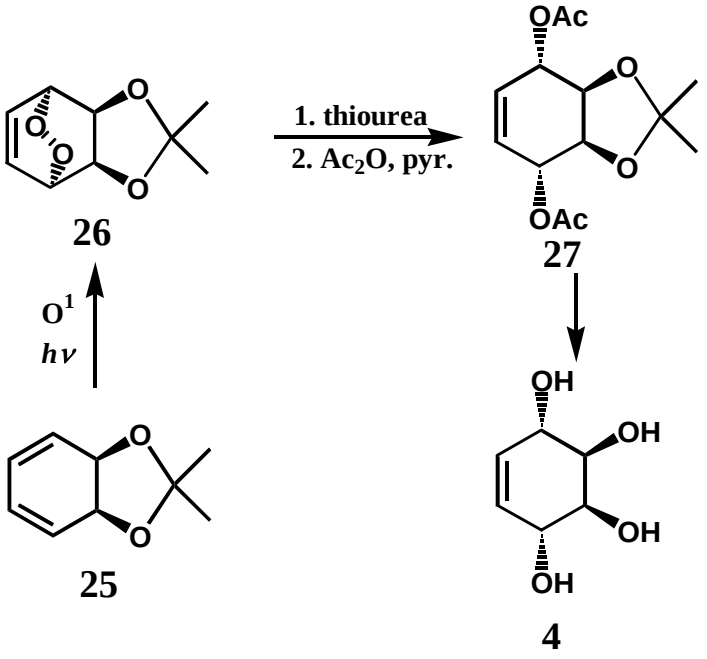
Carless *et. al.* [7] applied a similar methodology by using fluorobenzenediol **18**. After the epoxidation with *m*-CPBA, the formation of two products (**19** and **20**) were reported. The allylic epoxide **19** was converted into the fluoroconduritol **21** in the presence of water. As for compound **20**, it yielded to enone **22**, which was acetylated and reduced by $NaBH_4$ to produce Conduritol C and D derivatives, **6b** and **7b**, respectively. There are many examples of the use of halobenzenediols reported in the literature by Donohoe *et. al.* [8].



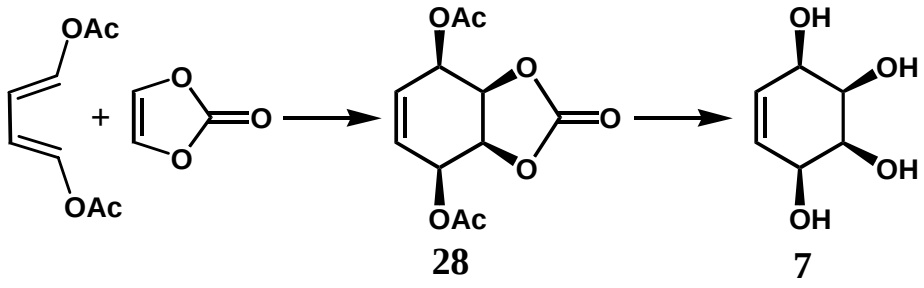
Recently, Balcı *et al.* and Nicolasi *et al.* also reported conduritol syntheses using *cis*-benzenediol [9]. Balcı *et al* have described a short and convenient method to obtain conduritol E (**8**) starting from *cis*-benzenediol [9a]. After the bromination of diacetate **13a**, oxidation with permanganate was performed. By Zn-elimination of vicinal bromides **24** the desired conduritol E (**8**) was isolated.



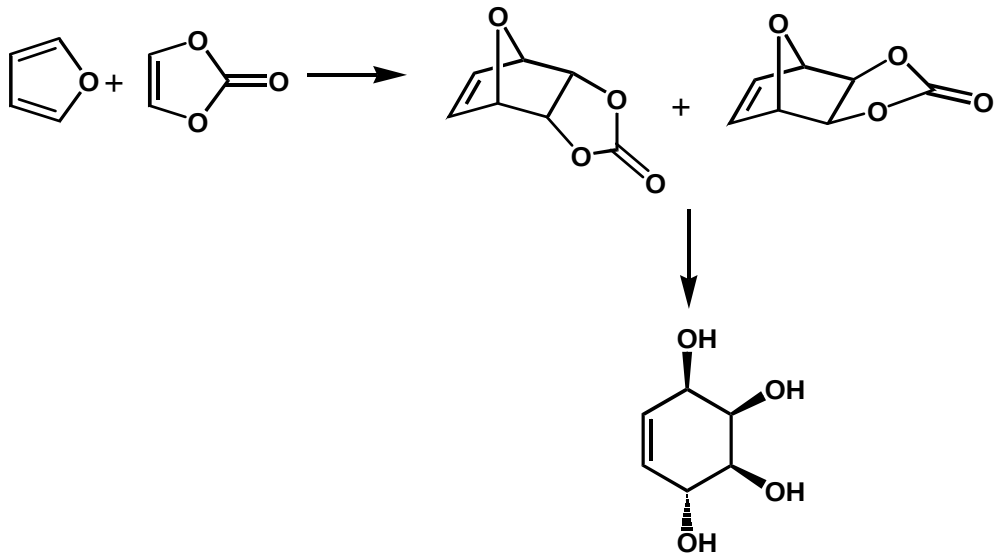
There is an effective and well-known method to introduce the oxygen functionality to the benzenediols by photooxygenation [10]. Balcı *et al.* added singlet oxygen to protected *cis*-benzenediol **25** and obtained only one *endo*-peroxide **26** with high yield. The selective cleavage of peroxide was achieved by thiourea. After hydrolysis of the ketal **27**, conduritol A (**4**) was isolated [10a].



A great number of groups have made use of the versatility of Diels-Alder reaction in their synthesis. Criegee and Becher prepared the Diels-Alder adduct of *trans-trans*-diacetoxybutadiene and vinylenecarbonate at elevated temperatures and high pressures. The desired Conduritol D (**7**) was isolated after the hydrolysis of **28** by barium hydroxide [4].

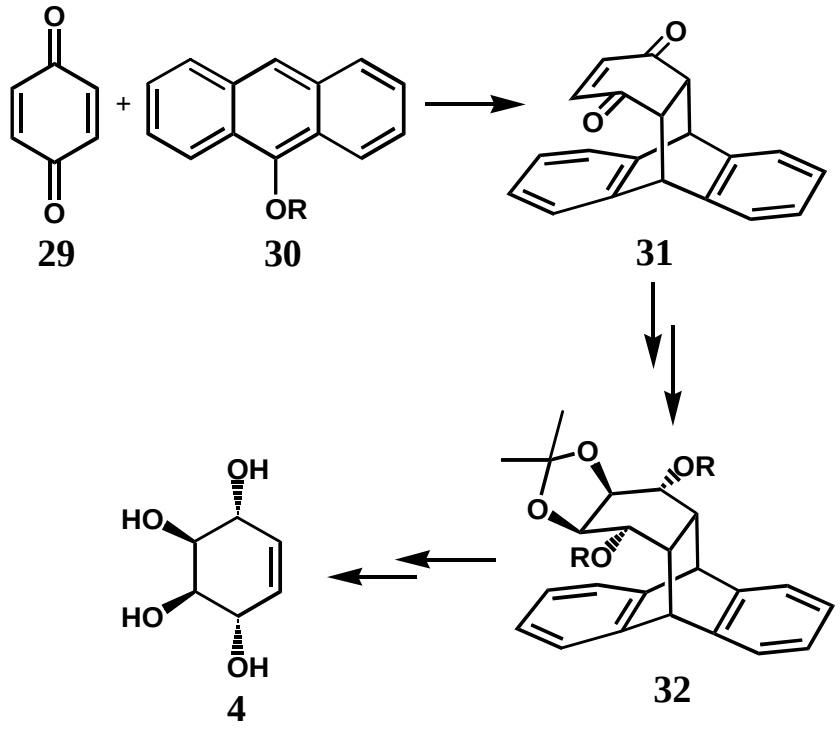


Yurev and Zefirov also developed a short and effective synthesis for conduritol C by using furan and vinylene carbonate [4]. Both Diels-Alder adducts were first acidified and then treated with barium hydroxide to obtain conduritol C (**6**).

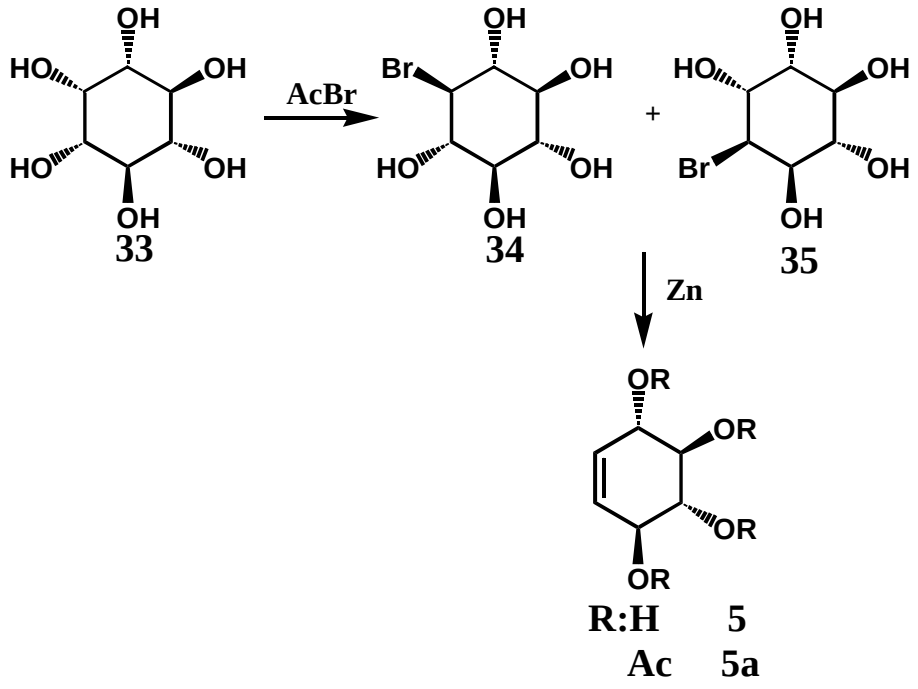


6

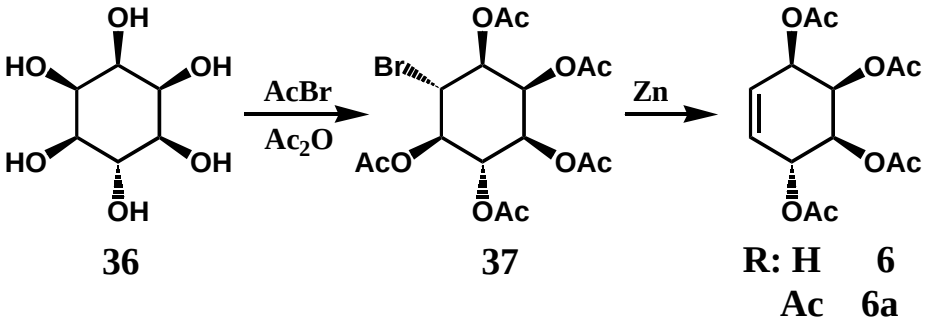
Knapp and coworkers [11a] reported a stereoselective synthesis of conduritol A starting from *p*-benzoquinone and using an anthracene derivative as a protective group. After the reduction of Diels-Alder adduct **31**, the double bond was oxidized by osmium tetroxide. Deprotection followed by retro-Diels-Alder reaction of **32** resulted in the formation of conduritol A (**4**). Later on, this synthetic pathway was modified by Ruthledge *et. al.* [11b].



There were an enormous number of studies beginning with a suitably substituted cyclitol like inositols and quercitols. For example, McCasland and Horswill prepared conduritol B (**5**) by using bromoquercitols **34** and **35** derived from *myo*-inositol **33** by reacting with acetyl bromide. Then the elimination of bromides via zinc gave conduritol B (**5**) [4].

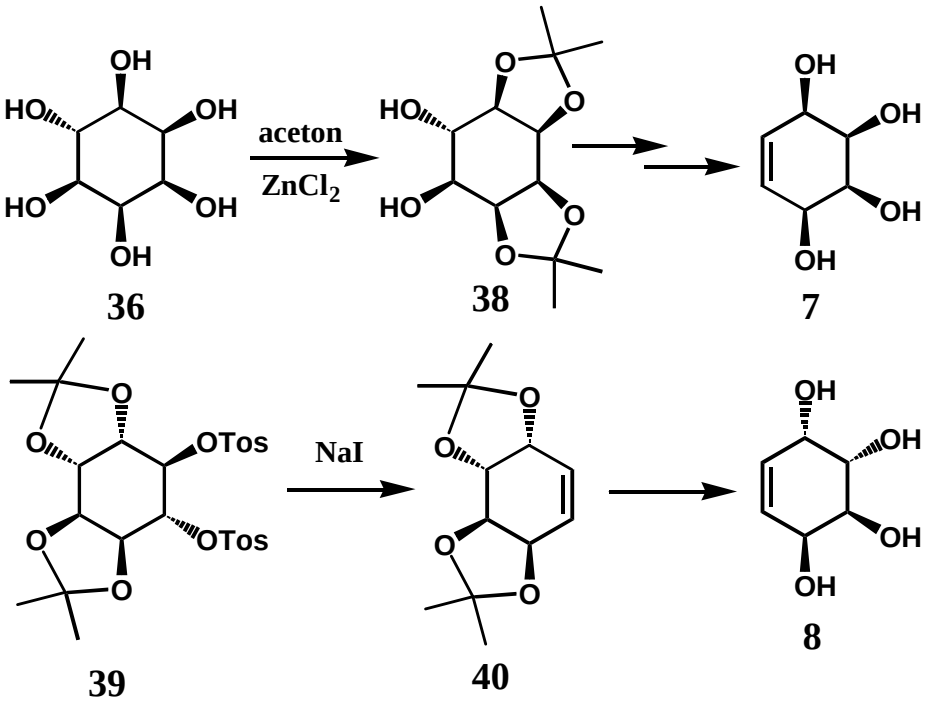


A similar synthetic methodology was applied to *epi*-inositol **36** leading to the synthesis of Conduritol C (**6**) [4].

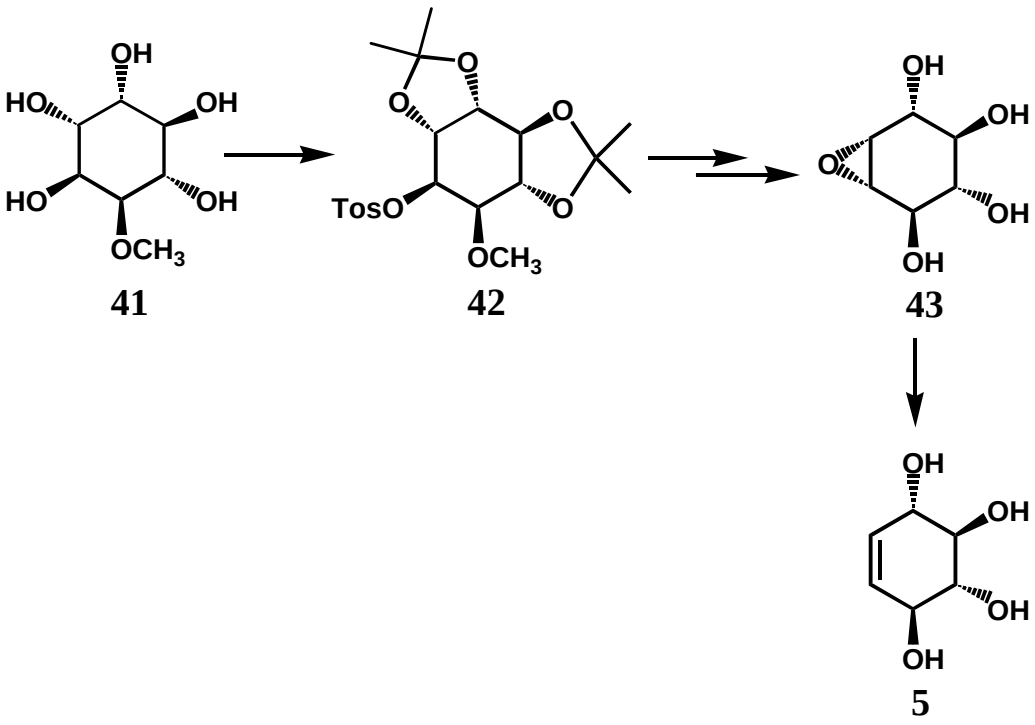


The first synthesis of Conduritol D (**7**) was also achieved from di-O-isopropylidene derivative of *epi*-inositol **38** by Angyal *et al.* The same group was applied a similar approach to achieve the synthesis of Conduritol E (**8**). In this method two vicinal

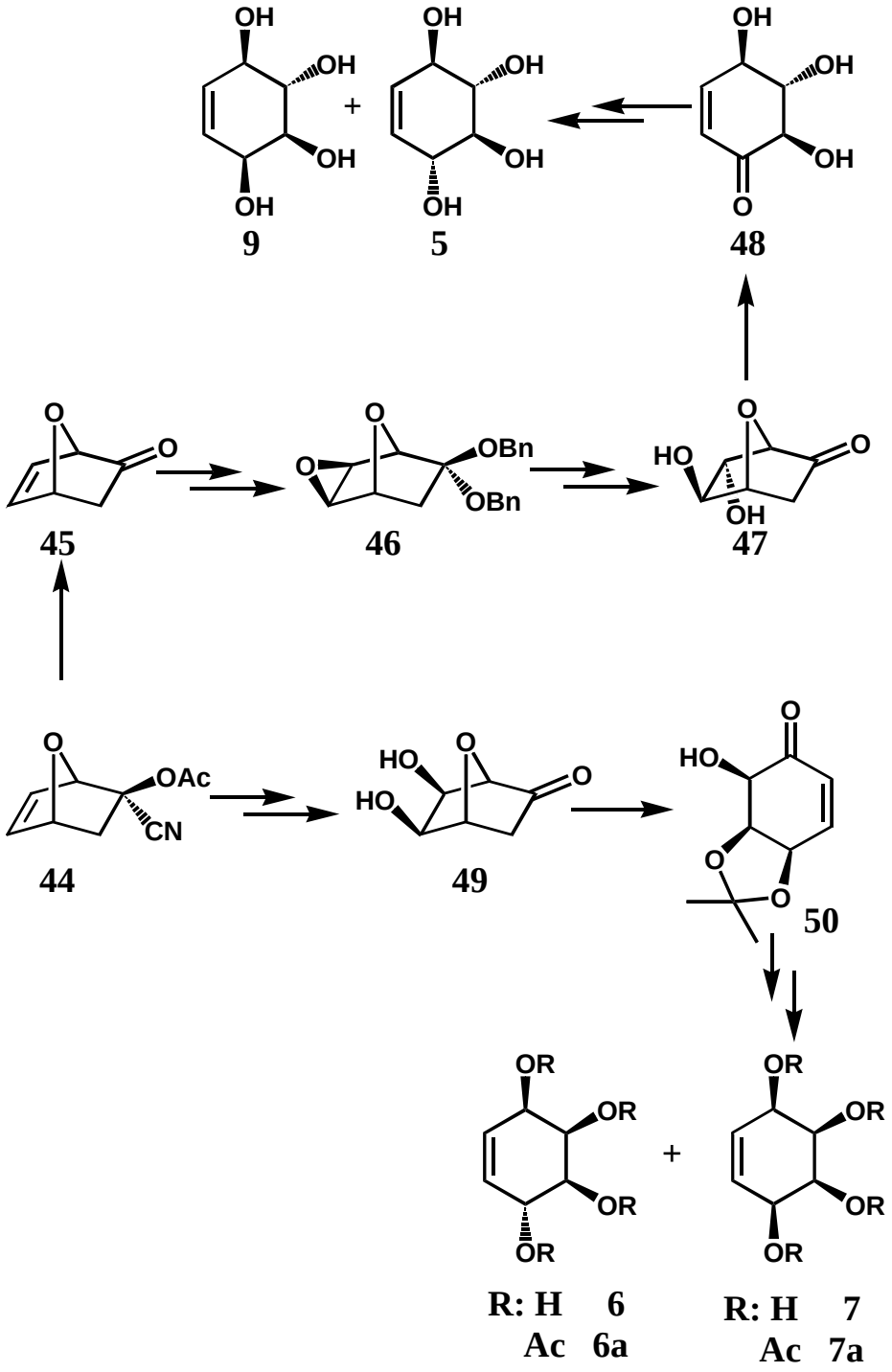
leaving groups in **39** were eliminated by iodide ion. After the hydrolysis of isopropylidene groups the expected conduritols **7** and **8** were obtained [4].



Paulsen *et al.* also made use of suitably substituted inositol derivative, quebrachitol (**41**). The key intermediate **42** was first reduced by 3-methyl-2-(selenoxo)benzothiazole and oxidized to obtain epoxide **43** followed by several steps giving conduritol B (**5**) in high yield. They also synthesized conduritol F (**9**) through a similar route starting from the same compound [12a]. Akiyama and Ozaki reported the synthesis of conduritol B (**5**) and conduritol F (**9**) by using quebrachitol as starting material and following a similar pathway [12b,c].



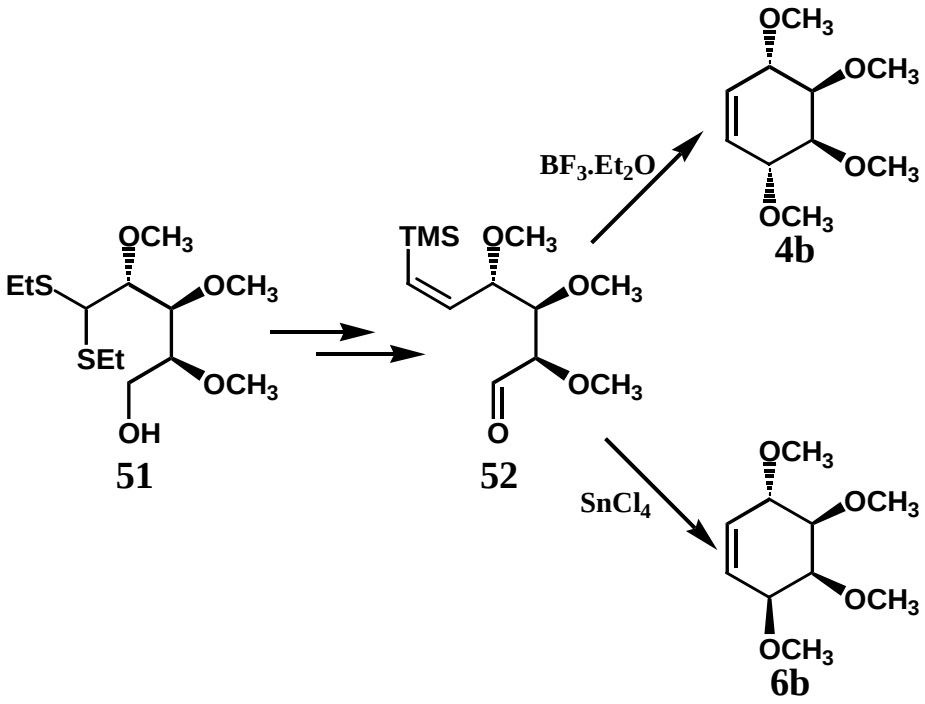
Vogel has developed a different approach for the synthesis of conduritols and related compounds starting from "naked sugar" **44** [13]. In one of these works, *cis*-bis-hydroxylation of the double bond was performed with H_2O_2 followed by protection and saponification steps to yield ketone **49**. Opening of the oxa-bridge was achieved by triethylamine in the presence of trimethylsilyl triflate and then several steps gave conduritol C (**6**) and conduritol D (**7**). For the synthesis of conduritol B (**5**) and conduritol F (**9**) they have used similar pathway the difference of which arose from the oxygenation of the double bond by a peracid instead of osmium tetroxide catalyzed H_2O_2.



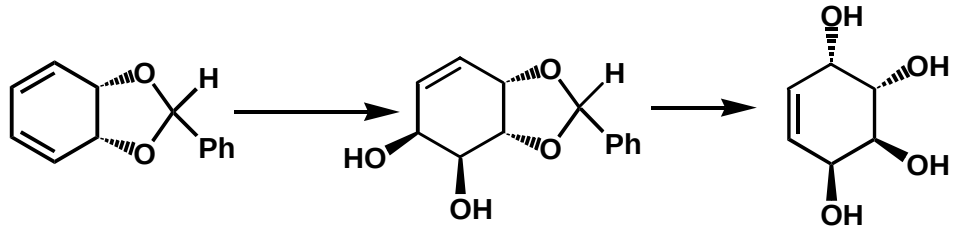
R: H 6
Ac 6a

R: H 7
Ac 7a

Ring closing metathesis was quite popular in the conduritol synthesis [14, 15]. Weinreb *et al.* have reported [14a] the synthesis of conduritol A and conduritol C derivatives by passing through the same key compound **52** which was derived from dithioacetal trimethyl ether **51**. Treatment of vinylsilane-aldehyde **52** with $BF_3.Et_2O$ gave conduritol A derivative **4b**. On the other hand, when vinylsilane-aldehyde **52** was reacted with $SnCl_4$ conduritol C derivative **6b** became the only product.

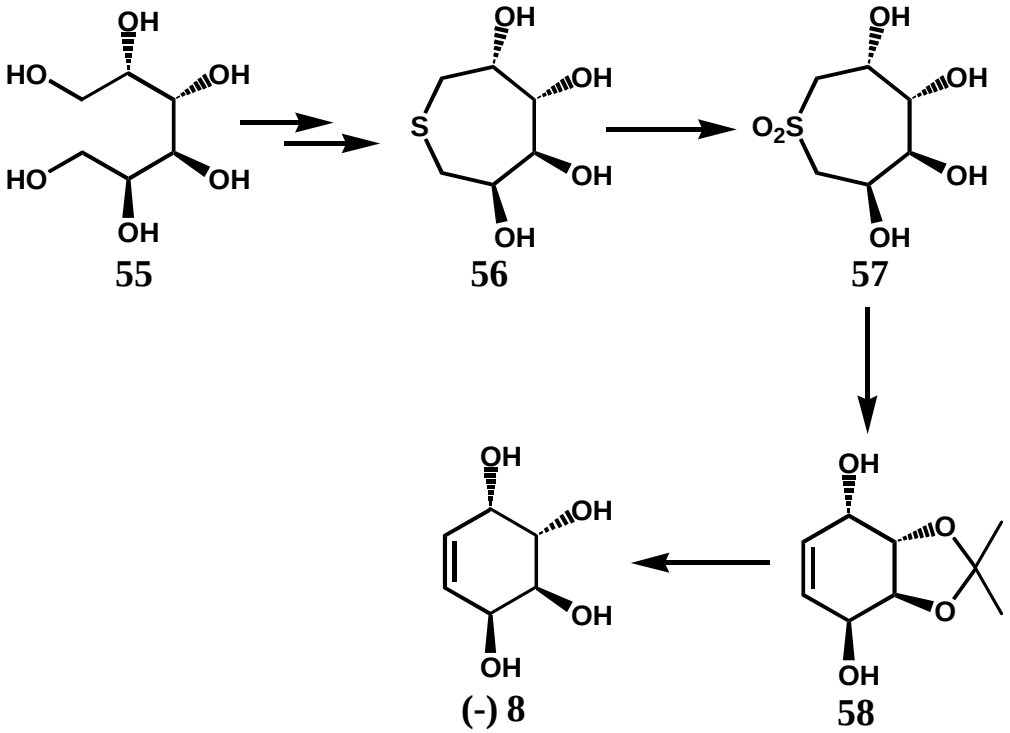


During the last decade, numerous methods have been introduced to the literature for the asymmetric synthesis of conduritols [15, 16]. In one of these studies, an asymmetric dihydroxylation of *cis*-olefin bond was performed by Ogasawara in the synthesis of optically pure conduritol E (**8**) [16]. A *meso*-diene **53** was chosen as starting material which gave optically active compound **54**. After asymmetric dihydroxylation followed by hydrolysis (+)-conduritol E (**8**) was obtained.

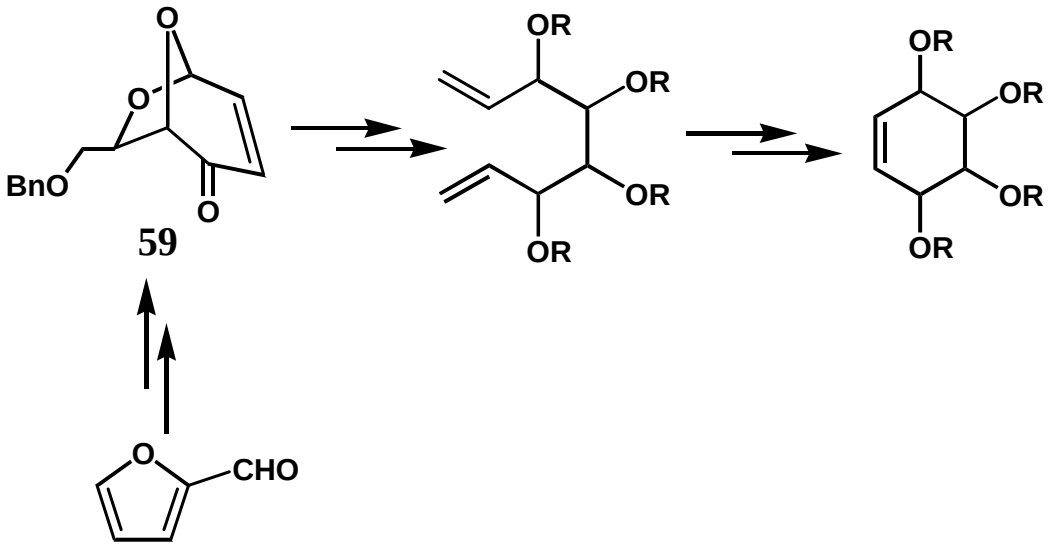


53 **54** **(+) 8**

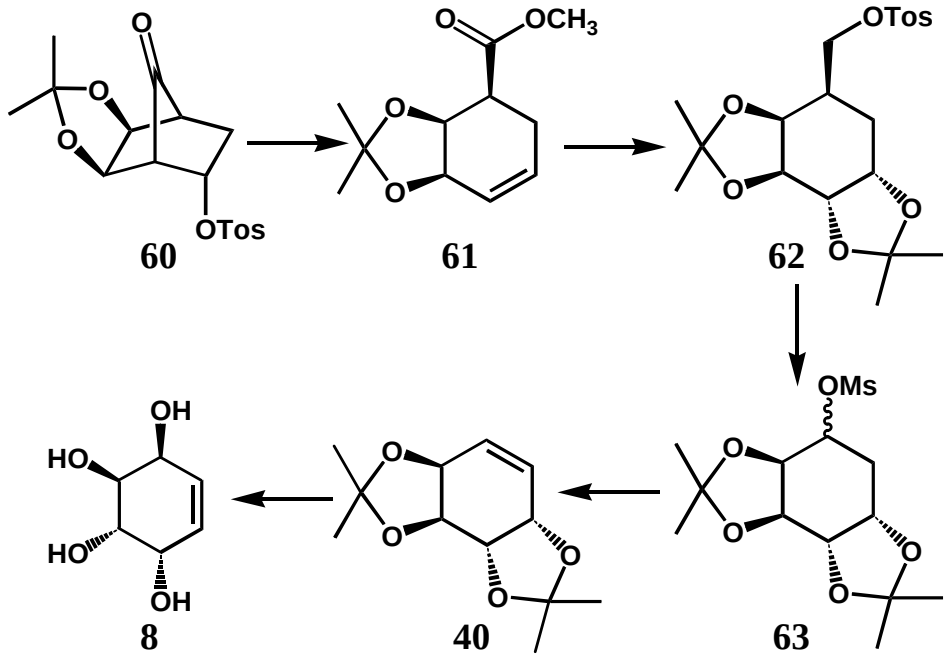
Some recent literature have reported asymmetric conduritol synthesis dealing with ring-closing reactions by applying different methods [15]. Cere *et al*. have revealed an enantioselective synthesis of conduritol B, E and F. D-mannitol **55** was converted into the corresponding thiopane **56** by means of intramolecular thiacyclization. Compound **56** was oxidized to the sulfone **57** and subjected to a Ramberg-Backlund reaction giving rise to a double bond. In order to remove protecting groups $SnCl_4$ was used and (-) conduritol E (**8**) was produced [17a]. Starting from L-iditol and D-sorbitol syntheses of (+) conduritol B (**5**) and (-) conduritol F (**9**) were achieved by applying the same methodology [17b].



Most recently, Ogasawara *et al.* have developed a strategy to synthesize all conduritol isomers starting from a common compound (**59**) derived from furfural. In this study they have made use of the ring closing metathesis after obtaining the suitable dienes [18].



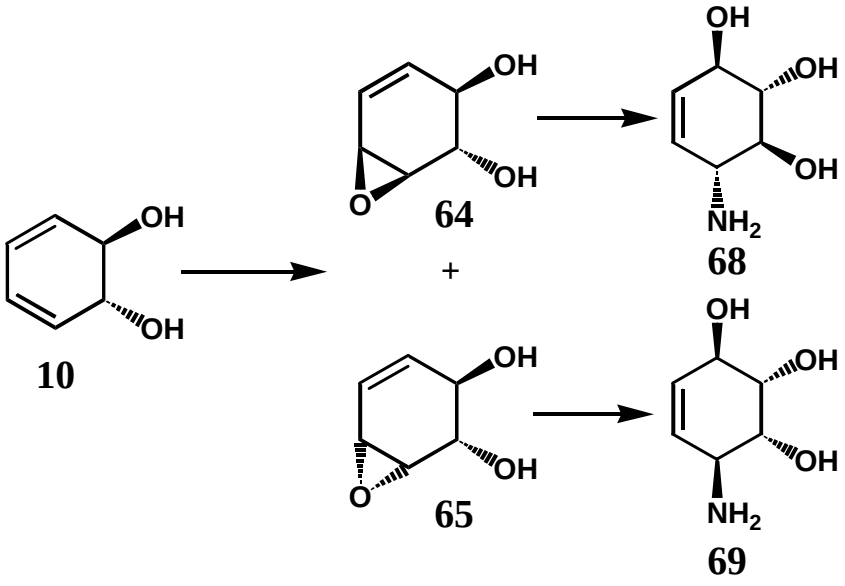
In a recent communication [19], Mehta has reported a new synthesis of conduritol E starting from tricyclic acetonide **60**. First, elimination via iodide gave olefin **61**. After the oxidation and mesylation, compound **63** was obtained. Elimination of mesylate and deprotection steps yielded conduritol E (**8**).

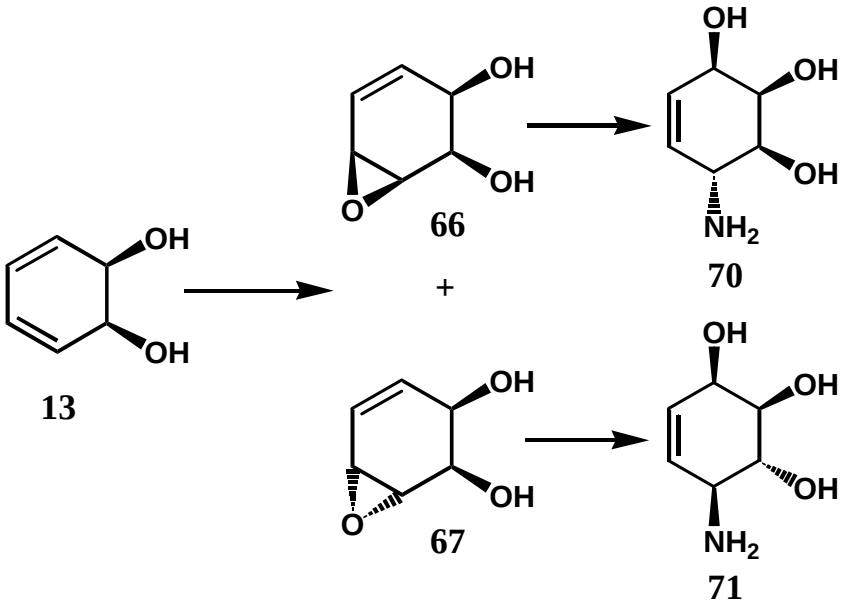


1.2.3 CONDURAMINES (AMINOCONDURITOLS)

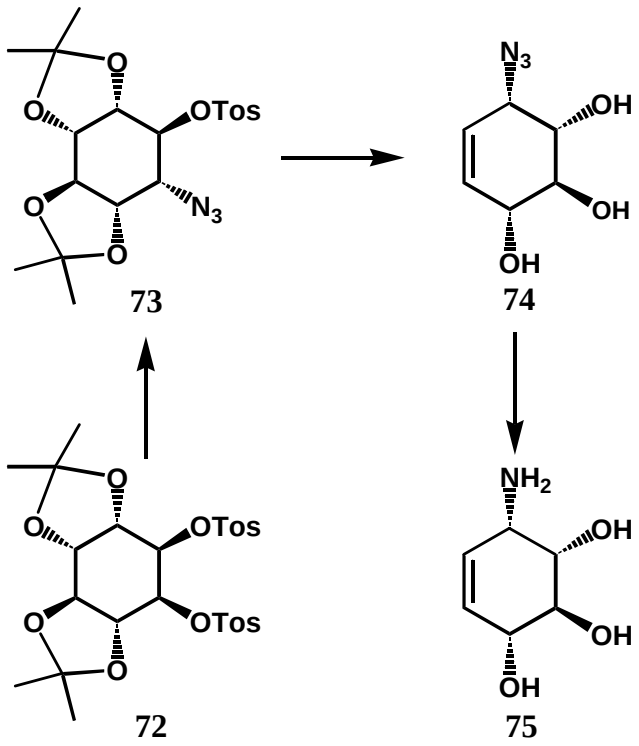
Conduramines are purely synthetic aminocyclohexenetriols formally derived from conduritols. Some conduramines have significant glycosidase inhibitory activity, but they are of much greater impotance as synthetic precursors of amino and diaminocyclitols, many of which constitute an important part of therapeutically useful aminoglycoside antibiotics. In addition, conduramines have been used as intermediates for the preparation of azasugars, aminosugars and some alkaloids [20]. All these points contributes to the importance of conduramines and are the reasons for the great efforts made for the development of new and efficient synthetic routes.

In one of the early studies for the synthesis of simple aminoconduritols, Nakajima *et al.* [4] made use of the epoxidation of both *cis*- or *trans*-benzenediols. After the opening of epoxide rings by ammonia the corresponding aminoconduritols were obtained.

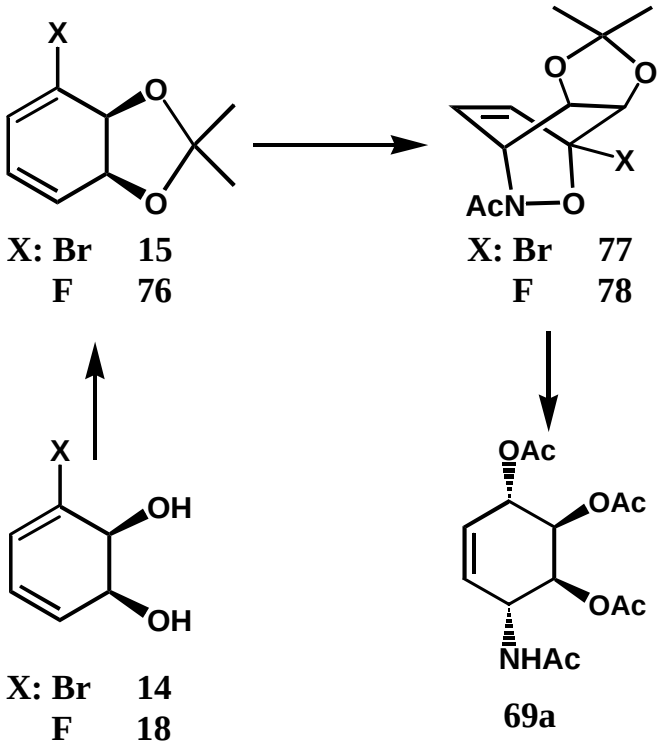

OH
OH
10
OH
OH
O
64
+
OH
OH
OH
NH2
68
OH
OH
O
65
OH
OH
OH
NH2
69


OH
OH
13
OH
OH
O
66
+
OH
OH
OH
NH2
70
OH
OH
O
67
OH
OH
OH
NH2
71

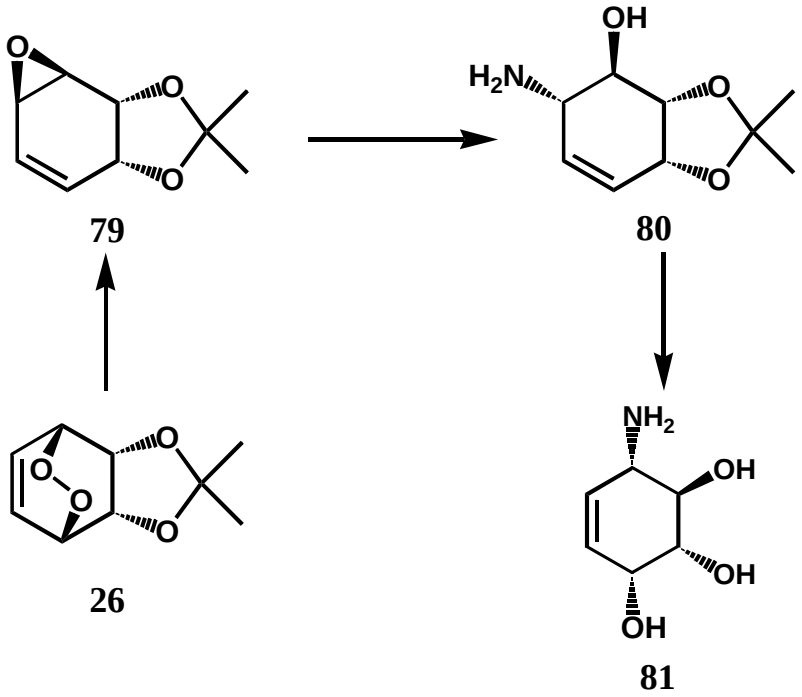
An example for the use of inositols in the synthesis of aminoconduritols was achieved by Paulsen and coworkers [21]. They have obtained the conduramine F-1 (**75**) starting from key compound **73** going through the intermediate azido conduritol **74** which is derived from the corresponding inositol.



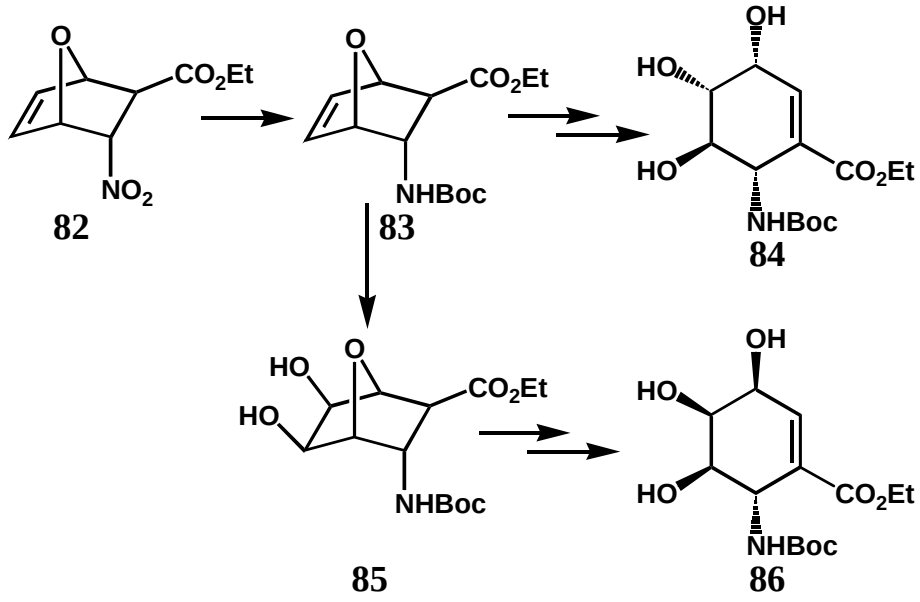
Hudlicky *et al.* made use of halo*cis*-benzenediol in their synthetic strategy. The Diels-Alder reaction of protected diol (**15**/**76**) with a nitrosyl dienophile generated *in situ* gave a single isomer **77** and **78**, respectively. Simultaneous reductive cleavage of N-O bond and dehalogenation followed by acetylation yielded to conduramine A-1 tetraacetate **69a** [22]. Werbitzky *et al*. have synthesized the same compound by a similar pathway [23].



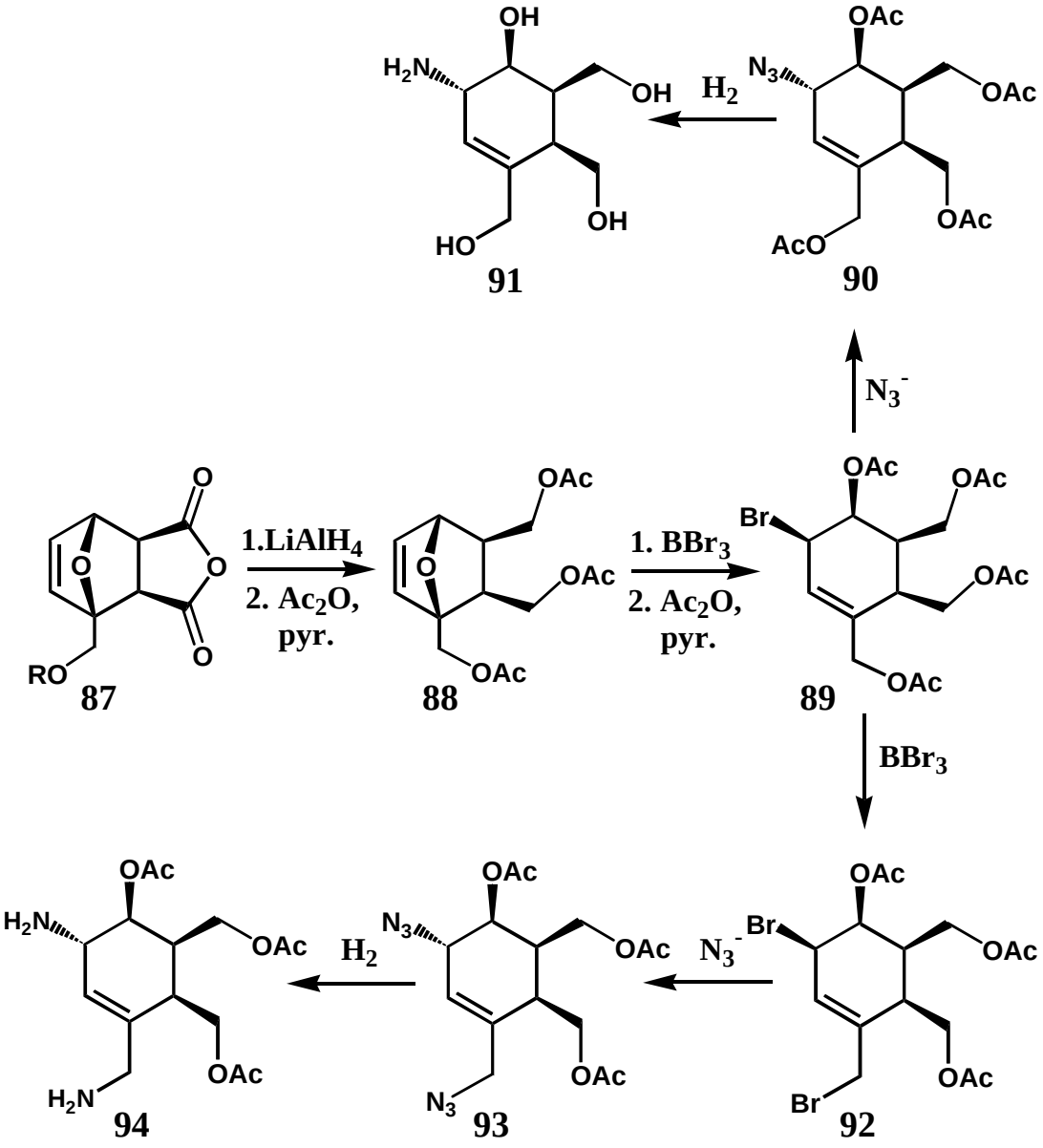
Balcı *et al.* have developed a stereospecific pathway for the synthesis of conduramine F-4. The photooxygenation of cyclohexadiene acetonide and then triethyl phosphite deoxygenation resulted in monoepoxide 7**9**. Opening of epoxide by ammonia followed by hydrolysis gave conduramine F-4 **81** [10d].



Recently, Steel *et. al.* have reported the synthesis of an aminoconduritol derivative starting from the Diels-Alder adduct (**82**) of furan and *β*–nitro acrylate [24]. After the nitro group was reduced, the resulted amine was protected as carbamate **83**. Opening of oxa-bridge followed by dihydroxylation with osmium tetroxide gave **84**. Another isomer **86** was obtained by bishydroxylation of the double bond before the opening of oxa-bridge in order to direct the oxidation with osmium tetroxide. Similar treatments gave the protected form of the desired product **86**.

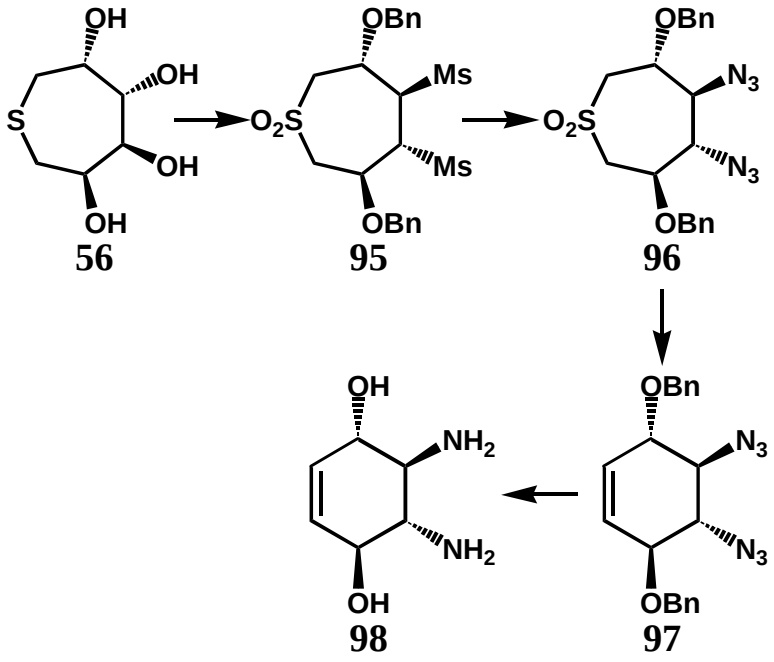


Vogel, has improved a strategy to synthesize some aminocyclitol derivatives including aminoconduritols bearing hydroxymethyl groups [2]. The synthetic route began with 7-oxabicyclo[2.2.1]hept-2-ene derivative **87** as the precursor. First, anhydride part in compound **87** was reduced to dialcohol by $LiAlH_4$ and then acetylated. After opening of the oxa-bridge with BBr_3, it was treated with tetramethyl guanidinium azide to produce **90** catalytic hydrogenation of which yielded **91**. By using similar route they have also synthesized diaminoconduritol derivative **94**.



As in the case of aminoconduritols, diaminoconduritols have inhibitory activity towards $\alpha-$ and β–glycosidases. An example for the synthesis of diaminoconduritols was described by Cere *et al.* [25]. They applied a similar methodology starting from a suitable alcohol as in the case of conduritol B, E, and F synthesis. Before treatment

with NaN_3, tetrol **56** was oxidized to sulfone **95**. Ramberg-Backlund reaction gave diazidoconduritol **97** which was, then, converted to diaminoconduritol **98**.



1.3 INOSITOLS

1.3.1 NATURAL OCCURRENCE AND IMPORTANCE

Of the cyclitols, hexahydroxycyclohexanes or inositols are best known. Nine isomers are possible and it should be noted that all but the *chiro*-inositols are meso and therefore optically inactive compounds [26].

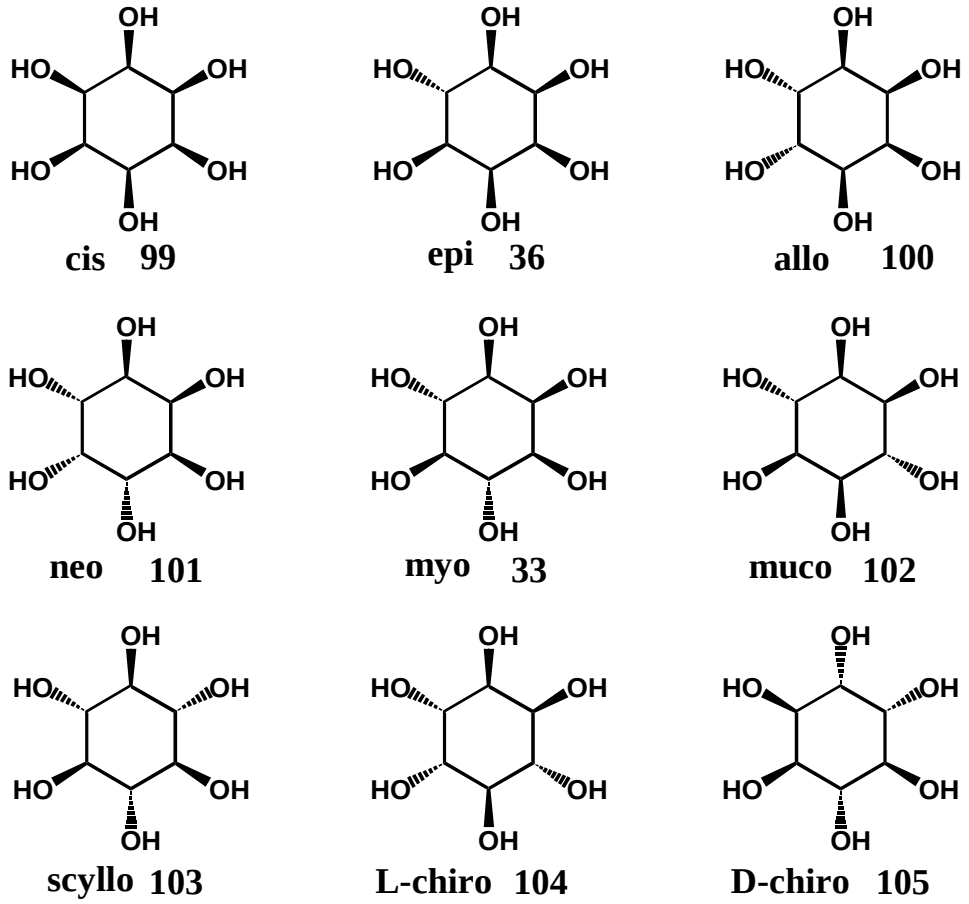


Figure 3. Inositol isomers

Over a hundred years ago Scherer isolated an optically inactive cyclohexanehexol and named it as *inosit*, which was later called as inositol. *myo*-Inositol, often referred to simply as inositol (or misleadingly as *meso*-inositol) occurs widely in nature in the free form and as its derivatives. In animals and microorganisms the combined *myo*-inositol is mostly in the form of phospholipids. Moreover, plants may contain *myo*-inositol as phytate (phosphates) or as methyl ethers. *myo*-Inositol is commercially obtained from steep liquors [27].

The next most abundant inositols are the optically active isomers, D- and L-*chiro*-inositols. They can be found in higher plants as methyl ethers D-pinitol and L-quebrachitol. *scyllo*-Inositol has been isolated from plants, animals, several species of insects, and mammalian urines. Of the remaining inositols, *neo*- has been detected in soil and *muco*- as a mehtyl ether in many plants [27].

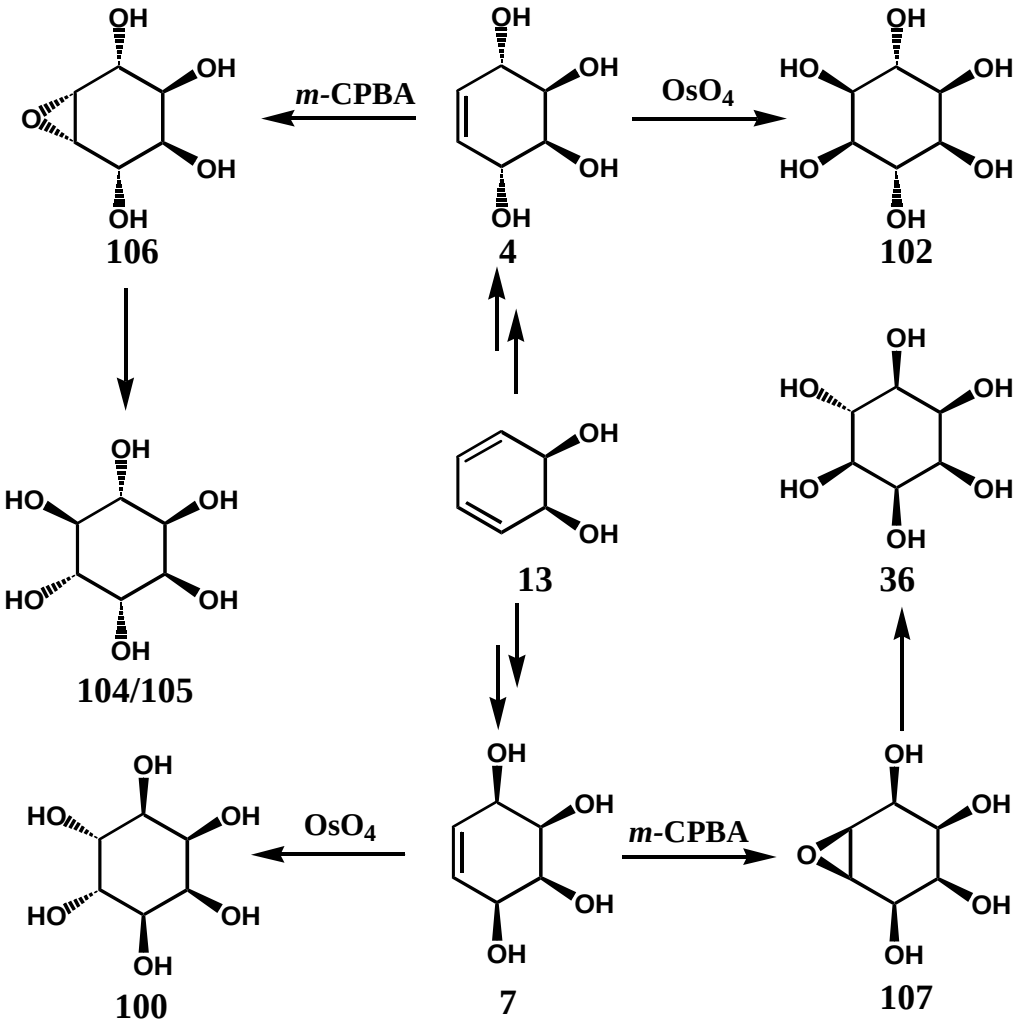
The importance of inositols arises from the discovery of *myo*-inositol as cell-mediator and glycosidase inhibitor. Inhibitors of glycosidase enzymes have potential for the treatment of various disorders and diseases such as diabets, cancer, and AIDS [28]. *myo*-Inositol 1,4,5-triphosphate and related molecules behave as secondary messengers in cellular signal transmission. Some inositols have been linked to antiglycosidic and therefore antiviral activity, while some have shown promise as antidiabetic agents or insulin mimics [29].

1.3.2 SYSTHESIS OF INOSITOLS

Some specific routes to members of the inositol group are available from monosaccharides and further approach involves the use of benzenediol, which is a microbial oxidation product of benzene. Selective hydroxylation processes have been used to obtain some members of the family [30]. Several inositols have been prepared from halobenzenes, tetrahydroxyquinone, conduritols and the most abundant isomer *myo*-inositol [31].

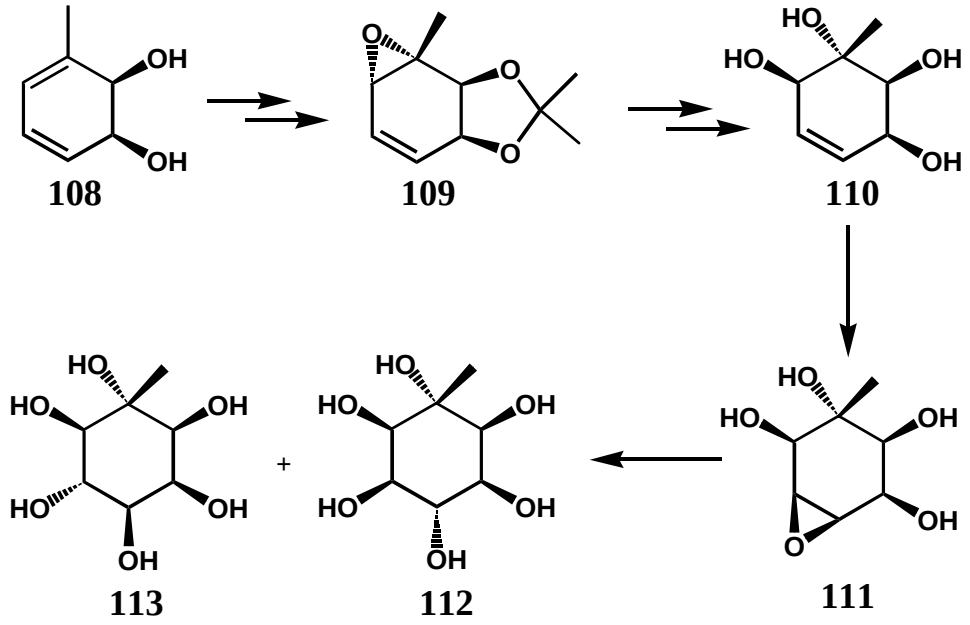
Carless *et al*. [32], used *cis*-benzenediol to synthesize *muco*-, *epi*-, *chiro*-, and *allo*-inositols. This synthesis involved the singlet oxygen addition to *cis*-benzenediol followed by reduction of the endoperoxides with thiourea giving two conduritol isomers, A and D. The epoxidation of conduritol A using *m*-CPBA gave epoxide **106**,

which was hydrolyzed to result in DL-*chiro*-inositols **104** and **105**. Catalytic osmylation of conduritol A produced *muco*-inositol **102**. Similarly, epoxidation of conduritol D followed by several steps gave *epi*-inositol **36** and catalytic osmylation of conduritol D gave *allo*-inositol **100**.



Carless have also reported [33] the total synthesis of (-) laminitol starting from *cis*-diol obtained from the microbial oxidation of toluene. After the protection of diol **108**, selective epoxidation of more substituted double bond with *m*-CPBA was achieved.

After the opening of epoxide ring followed by removal of isopropylidene group gave tetrol **110**. Second epoxidation followed by ring opening produced laminitol **112** and its *muco*- configurated isomer **113** .

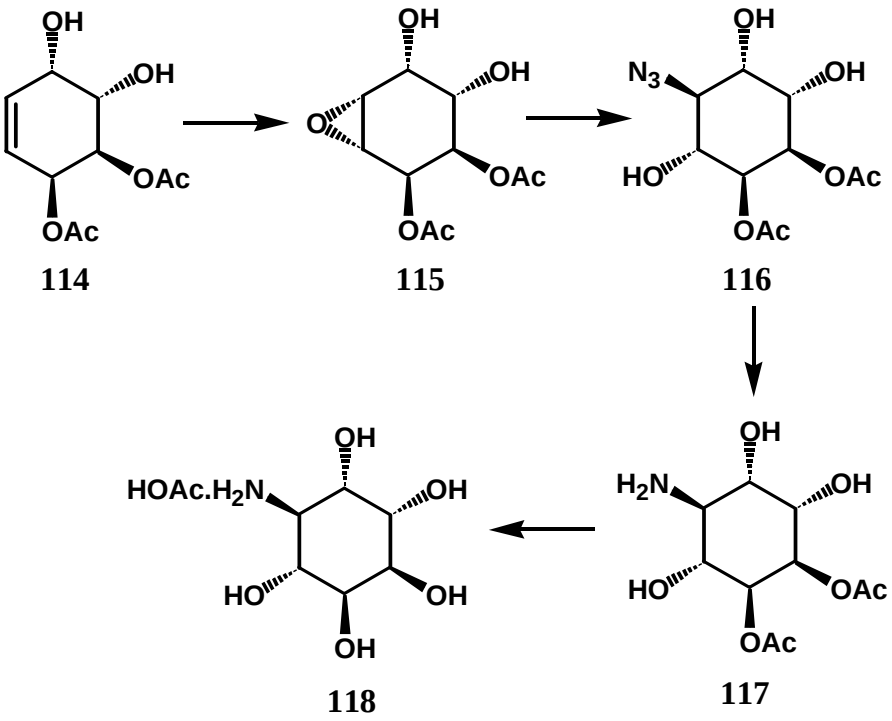


1.3.3 INOSAMINES (AMINOINOSITOLS)

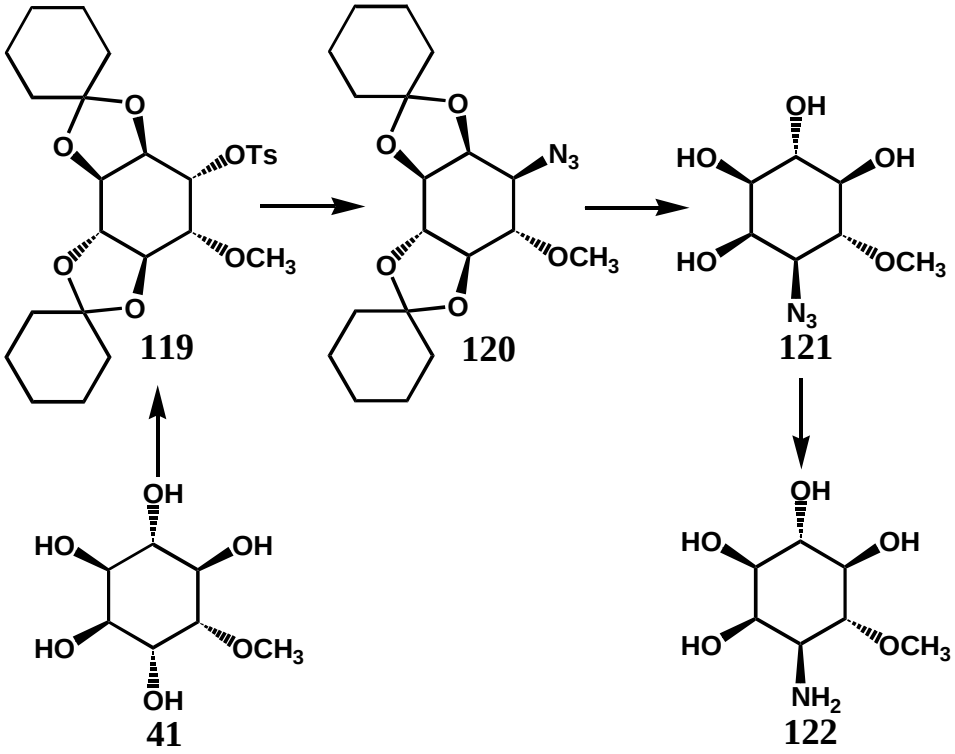
There are numerous examples for azido- and amino derivatives, which have great potential as bioactive molecules. The direct antiproliferative activity on tumour cells of azido *myo*-inositols has been well recognized. Moreover, the enzyme inhibitory activity of glycosidases reported for free and conjugated aminoinositols plays a central role in antibiotic action [34].

Nicolosi *et al.*have described the synthesis of 4-amino-4-deoxy-*chiro*-inositol starting from conduritol E diacetate **114**. Epoxidation of **114** followed by ring opening with

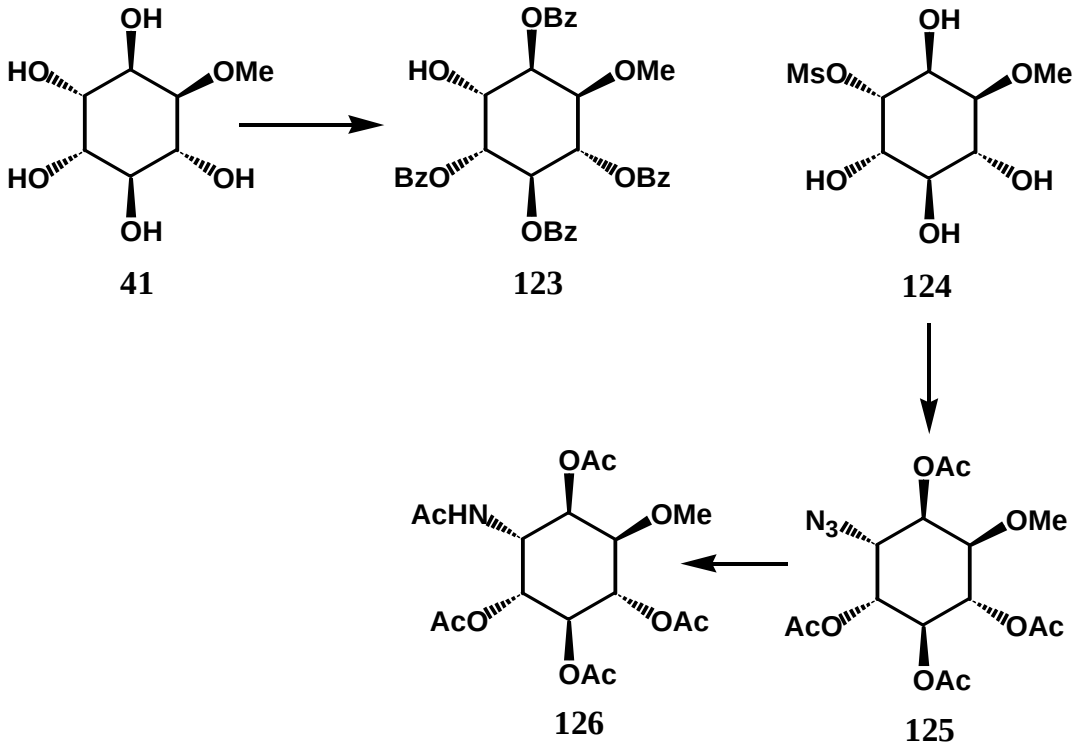
NaN_3 gave partially protected azidoinositol **116**, whose catalytic hydrogenation resulted in corresponding aminoderivative **117**. Reaction of **117** with aqueous NH_4OH furnished 4-amino-4-deoxy-*chiro*-inositol isolated as the salt with acetic acid **118** [34].



Starting from L-quebrachitol, Benjamin and Baker have reported synthesis of azido and amino inositols [35]. The protected inositol was obtained from L-quebrachitol and reacted with p-toluenesulphonyl chloride to give **119**. The treatment of this compound by lithium azide in DMF resulted in azido compound **120**, deprotection of which with trifluoroacetic acid gave azido inositol **121**. After the hydrogenation of **121** amino inositol **122** was obtained.



Recently, De Almedia *et al.* have also reported [36] the synthesis of azido and amino inositol derivatives by using quebrachitol as starting material. Treatment of quebrachitol with benzoyl chloride gave a mixture of products. After purification of compound **123**, it was reacted with methane sulfonyl chloride to yield **124**. Cleavage of benzoyl groups followed by treatment with NaN_3 and acetylation afforded compound **125**. Finally the hydrogenation in the presence of palladium allowed the reduction of azido compound **125** into the corresponding amine derivative **126**.



1.4 CYCLITOLS IN ACTION

Numerous cyclitols isolated from natural sources have been of great interest. Among naturally occurring glycosidase inhibitors, cyclitol epoxides, such as cyclophellitol **127**, senepoxide **128**, and pipoxide **129**, have been extensively studied due to their antibiotic property [37]. Cyclophellitol (**127**), isolated from the mushroom *Phellinus*, is an inactivator of β–glucosidase and an inhibitor of human immunodeficiency virus (HIV) [38]. Pipoxide **129** show significant tumour-inhibitory activity [2].

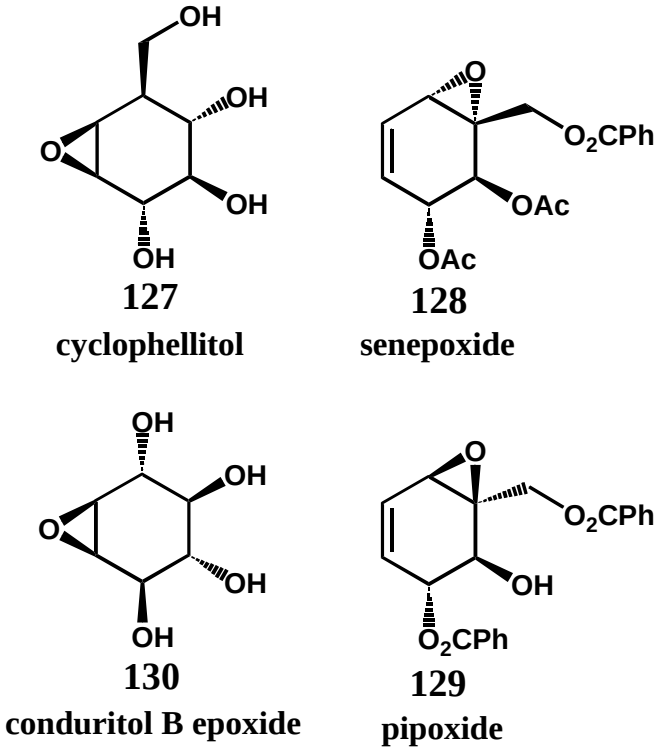


Figure 4. Some important cyclitol epoxides

The D-enantiomer of conduritol B epoxide (1-D-1,2-anhydro-myo-inositol) **130** is an inhibitor for β–glucosidases from a variety of sources, whereas the L-enantiomer inhibits neither α– nor β–glycosidases, but selectively inactivates β–fructofuranosidase from yeast. D-conduritol B epoxide is also an efficient inactivator for acid β–glycosidase and has been used clinically in diagnosis of Gaucher disease [39].

It is worthwhile to pay attention to the most of the cyclitol derivatives concerned involve a hydroxymethyl group as one of the substituents. Previously, it was thought that hydroxymethyl group has steric effects which may distort the conformation of transition state enzyme-substrate interactions. However, it is now clear that there is no distortion, as a matter of fact, interaction of the hydroxymethyl group with the protein

at the transition state are an important contributor to activity [40, 41]. Some naturally occurring cyclitols containing hydroxymethyl group are given as examples.

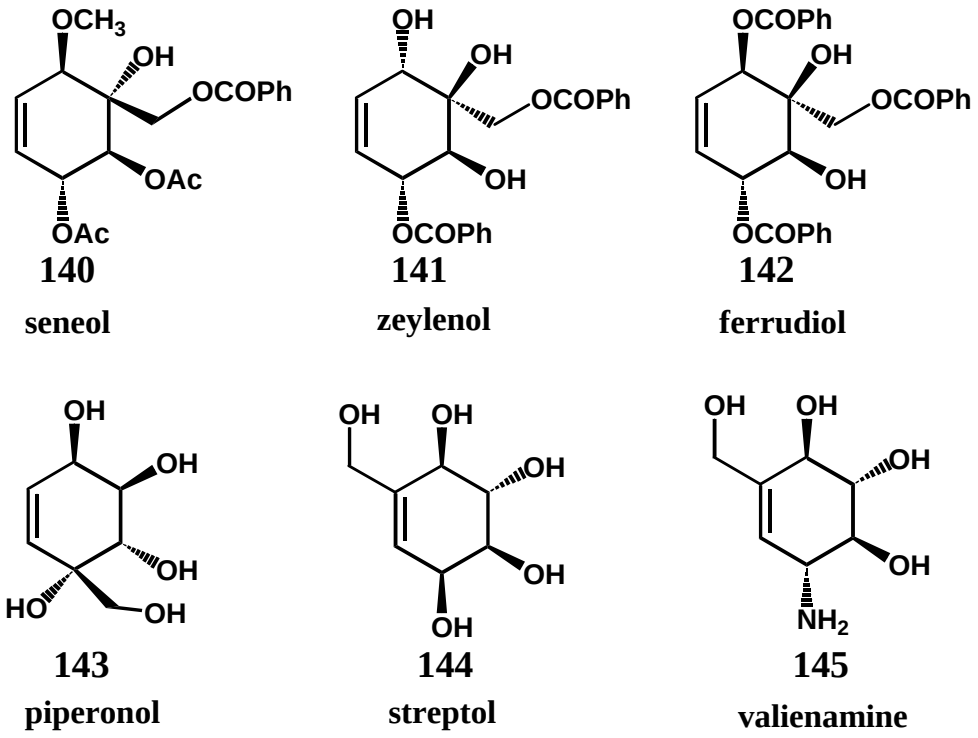
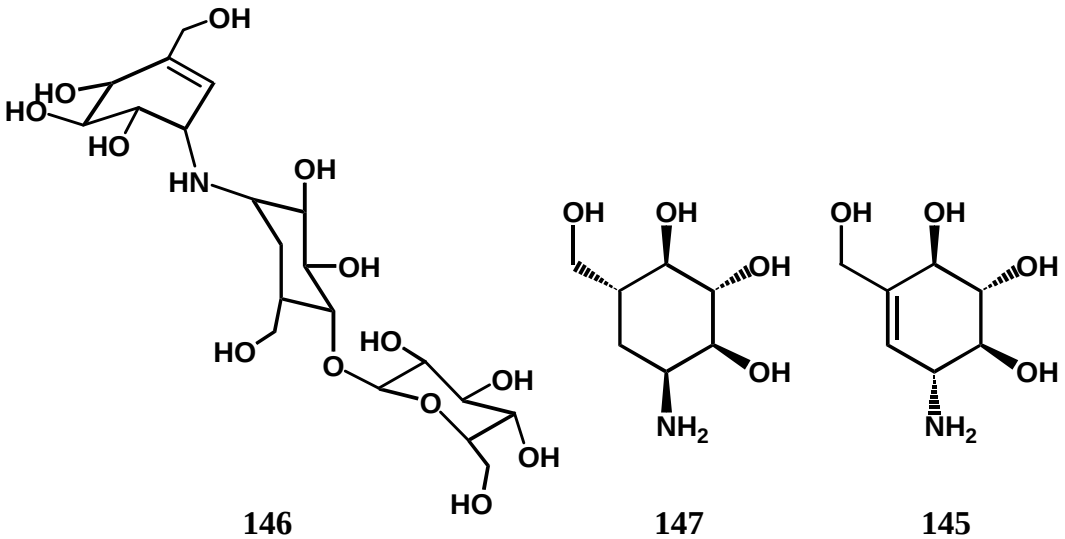


Figure 5. Some hydroxymethyl group containing cyclitols

Conduramines play an important role as glycosidase inhibitors which not only aid in the understanding of glycoprotein processing but also may find applications in immunology, diabetes, virology, and cancer [38]. Conduramines can also be found in certain antibiotics. For instance; validamycin A is major and the most active component of antibiotic validamycins [4, 42]. It has two aminocyclitol moieties, namely validamine and valienamine, in its structure. Valienamine itself has been found to posses both α–glycosidase inhibition and antibiotic activity.



146
validamycin A

147
validamine

145
valienamine

Figure 6. An antibiotic validamycin A and its components

The valienamine moiety linked to D-glucose or 6-deoxy-D-glucose via an imino linkage has been found as an essential unit in a homologous series of pseudo-oligosaccharides like acarbose [43]. Acarbose and voglibose have powerful α–glycosidase inhibitory activity and used in theatment of non-insulino-dependant diabetes [44].

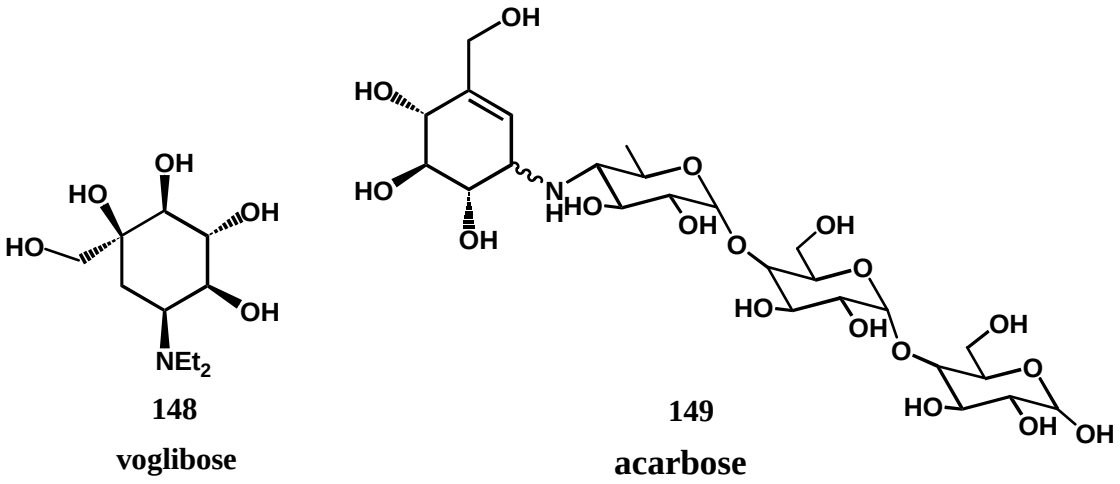


Figure 7. Structures of acarbose and voglibose

Several mehtyl derivatives of inositols, both O-methyl, e.g. D-pinitol and L-quebrachitol, and C-methyl e.g. (-) laminitol occur in nature [30].

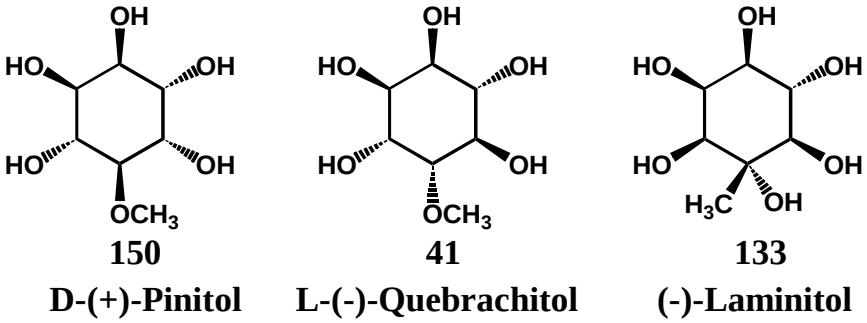
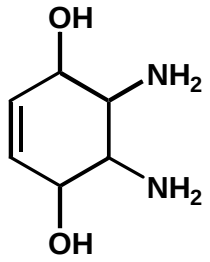


Figure 8. Structures of some methyl derivatives of inositols

1.5 AIM OF THE STUDY

The syntheses of conduritols and inositols have great importance due to their applications in biology and biochemistry. Therefore, there is an increasing interest to find new and efficient routes to synthesize them. Here, we aim to develop a new synthetic strategy leading to cyclitol derivatives containing one or two amino and a hydroxymethyl groups as substituents with a definite configuration relative to each other. The followings will be our target compounds.



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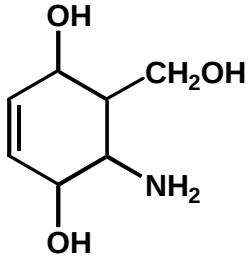

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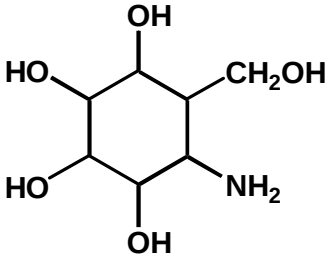
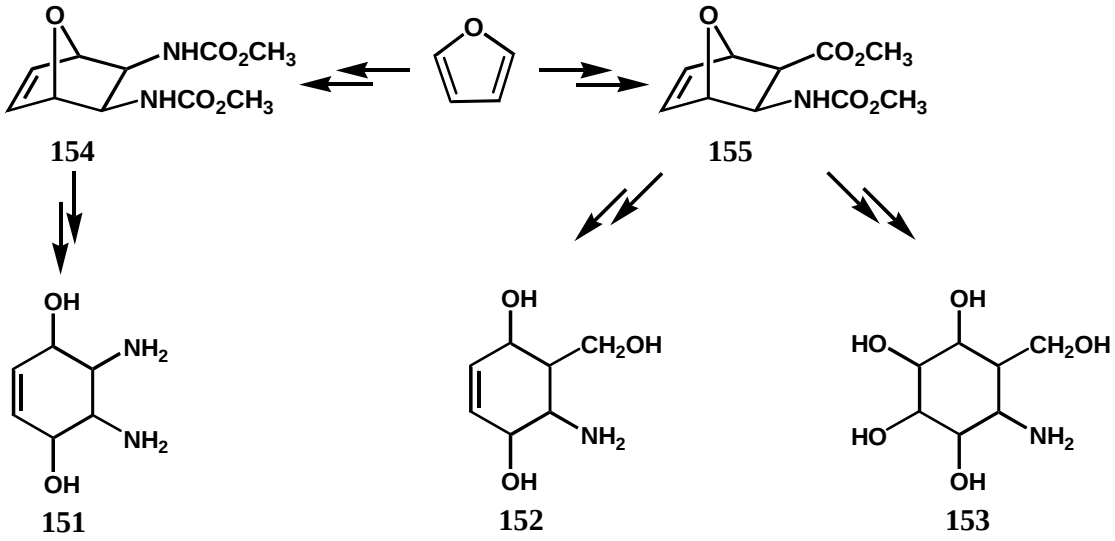


153

CHAPTER 2

RESULTS AND DISCUSSION

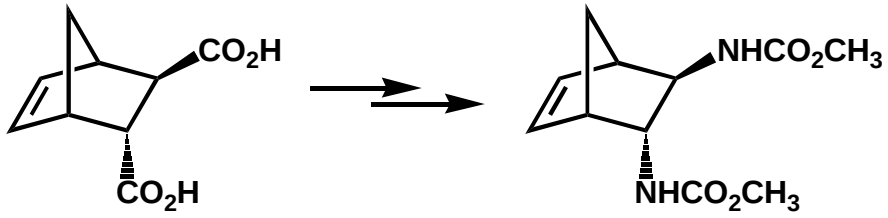
Through the synthesis of target molecules **151, 152,** and **153** starting from easily available and less expensive compounds, like furan, the route consisting of several facile and known reactions is given below. The compounds **154** and **155** were thought to be the key compounds through these syntheses.



The key steps include Curtius rearrangement of an acyl azide providing the amine functionality and the opening of the oxa-bidge with a suitable reagent giving 1,4-diol.

2.1 THE SYNTHESIS OF (3-METHOXYCARBONYLAMINO-BICYCLO[2.2.1]HEPT-5-EN-2-YL)-CARBAMIC ACID METHYL ESTER (157)

Owing to the unstability of oxa norbornene systems we have to test the validity of our methodology by using a more stable system. Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid derived from 1,4-cyclopentadiene and fumaric acid is used as the template to introduce the amine functionality.

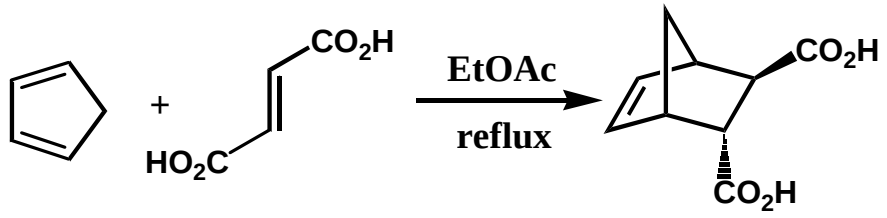


156 **157**

2.1.1 THE SYNTHESIS OF BICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBOXYLIC ACID (156)

Conjugated dienes undergo a [4+2] cycloaddition reaction with multiple bonds to form unsaturated six-membered rings. This reaction has a great synthetic utility and was discovered by two German chemists, Otto Diels and Kurt Alder, who received the Nobel Prize in 1950. Since the reaction mechanism involves a cyclic transition state, it was also classified as a subgroup of pericyclic reactions [45].

The facile Diels-Alder reaction between cyclopentadiene and fumaric acid was achieved in the presence of ethyl acetate as solvent [46]. The identification of the product was done on the basis of its ^{1}H and ^{13}C NMR spectra, which were taken with D_2O as solvent. In ^{1}H NMR spectrum, there is an AB-system arising from the olefinic protons both parts of which were split into doublet of doublets due to the couplings with the bridge-head protons which give rise to two broad singlets at 3.2 and 3.1 ppm. Other two tertiary protons have chemical shifts of 3.3 and 2.5 ppm. Another AB-system due to the bridge protons appears between 1.4 – 1.6 ppm, A part of which gives doublet whereas B part gives doublet of doublets due to the small splitting by one of the bridge-head protons.



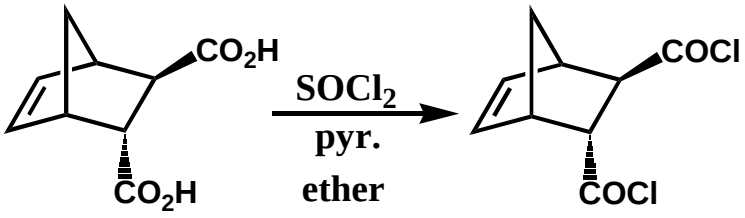
156

^{13}C NMR spectrum is also consistent with the structure. There are two carbonyl peaks at 178.9 and 178.1 ppm. Two olefinic carbons arise at 138.4 and 135.1 ppm while other tertiary carbons resonate between 46.0 – 48.0 ppm.

2.1.2 THE SYNTHESIS OF BICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBONYL DICHLORIDE (158)

The conversion of carboxylic acids into the acyl chlorides can easily be done by using various reagents such as $SOCl_2$, PCl_3 and PCl_5. In order to convert diacid **156** into dichloride **158**, first we used thionyl chloride in excess with pyridine to remove the

formed HCl by converting it to pyridinium chloride. Although the reaction was achieved, the yield was poor and the purification of the product was complicated. Then, we have used ether as the reaction solvent to dilute the medium and added two equivalent of thionyl chloride in the presence of catalytic amount of pyridine. By these modifications we could succeed in the synthesis of dichloride **158** with high yield and purity.



156 **158**

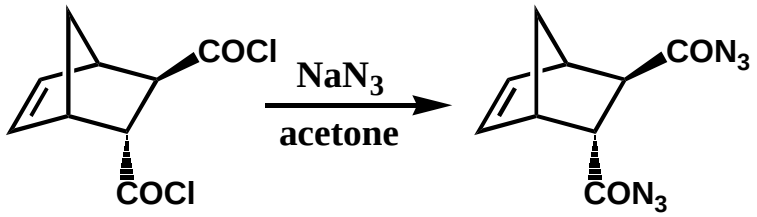
In contrast to diacid **156**, dichloride **158** can easily dissolve in $CDCl_3$, as expected. In the ^1H NMR spectrum a similar pattern was observed since the electronic environments of the protons were not affected so much. Olefinic protons and bridge protons still gave two AB-system between 6.0-6.3 and between 1.4-1.6 ppm, respectively. The chemical shifts of tertiary carbons were at 3.8, 3.5, 3.4 and 3.1 ppm having small differences when compared to the diacid case. Splitting patterns were also similar but with different coupling constants.

In the ^{13}C NMR spectrum, carbonyl carbons resonate at 174.6 and 173.0 ppm while olefinic protons resonate at 138.0 and 135.7 ppm. The saturated carbons appear at 60.2, 59.6, 48.6, 47.6, and 47.1 ppm.

2.1.3 THE SYNTHESIS OF BICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBONYL DIAZIDE (159)

Acyl azides are valuable synthetic precursors for the preparation of amines, amides, uretanes, ureas, etc. by a facile thermal rearrangement to isocyanate. There are several routes to acyl azides. In most of these reactions a carboxylic acid is converted into a more reactive intermediate like acyl chloride and then reacted with the azide ion [46]. There are some methods in the literature about the preparation of acyl azides directly from carboxylic acids. These include the use of acid activators such as methyl or ethyl chloroformate, $SOCl_2$-DMF, trihposgene and cyanuric chloride [47].

Here we have used a very facile procedure by using NaN_3 as the azide source and acetone as the solvent. After stirring a few hours at room temperature the desired diazide **159** was obtained. Since the column chromotography with silica gel resulted in the loss of the product without a satisfactory purification we have done the subsequent reaction by using crude diazide.

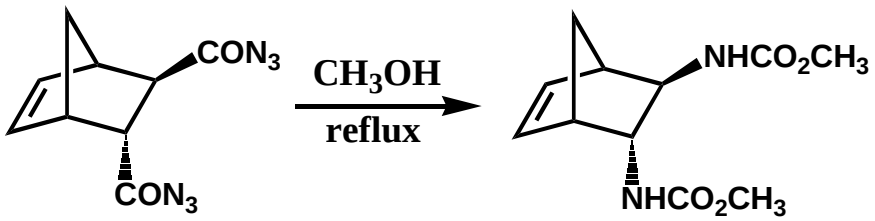


158 **159**

In ^1H NMR spectrum, the similar patterns were observed with small changes in the appearances and the chemical shifts of the peaks like in the case of dichloride. The existence of acyl azide was conformed by taking IR spectrum in which the strong N=N=N bands at 2170 and 2224 cm^{-1} could be seen clearly.

2.1.4 THE SYNTHESIS OF (3-METHOXYCARBONYLAMINO-BICYCLO[2.2.1]HEPT-5-EN-2-YL)-CARBAMIC ACID METHYL ESTER (157)

When an acyl azide is heated, it evolves nitrogen gas to form a nitrene, a reactive intermediate, which rearranges to an isocyanate. The addition of either water or an alcohol to the isocyanate results in a primary amine or an urethane, respectively. The overall process is known as Curtius rearrangement. We have used the advantage of this thermal Curtius rearrangement to obtain a uretane functionality in our system which would be the precursor for the amine functionality. Heating the acyl azide **159** in the presence of methanol as solvent resulted in the formation of diuretane **157**.



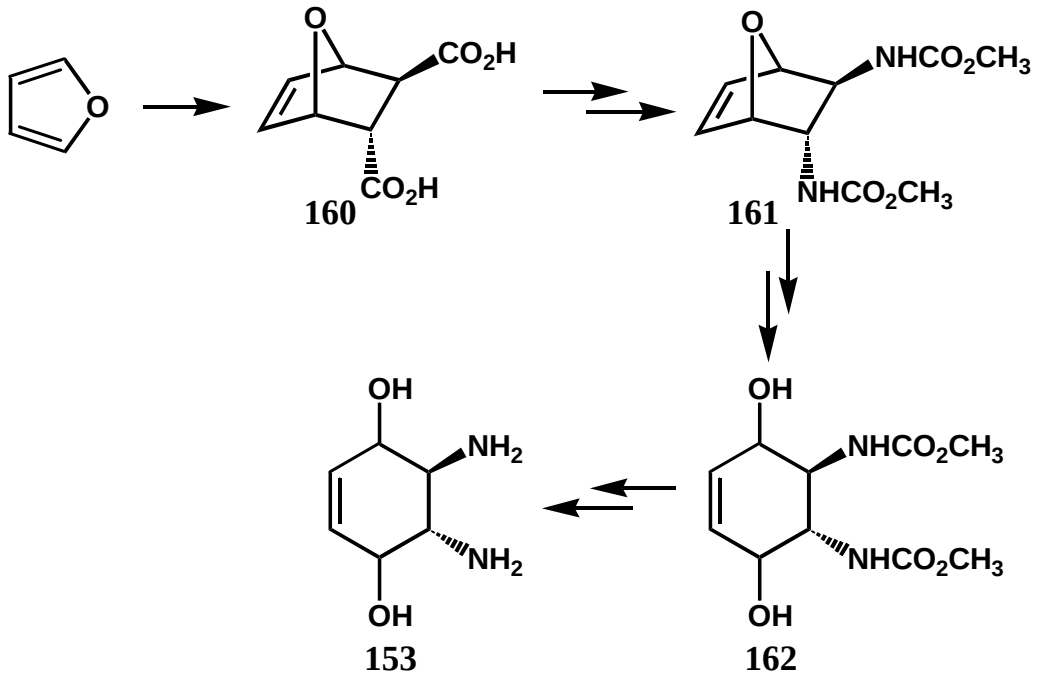
159 **157**

In ^{1}H NMR spectrum, the olefinic protons resonate as an AB-system at 6.4 and 6.2 ppm, both parts of which is further split into doublets. Two protons on the nitrogen atoms appear as two broad singlets at 5.3 and 4.6 ppm due to the inductive effects of nitrogens. Protons attached to tertiary carbons resonate at 3.9, 3.1, 2.9 and 2.8 ppm. The other AB-system arising from bridge protons appears between 1.6 - 1.8 ppm. The newly formed two different methoxy groups are observed as two close singlets at 3.68 and 3.66 ppm.

In ^{13}C NMR, the carbonyl carbons resonate at 156.9 ppm, olefinic carbons at 138.5 and 134.5 ppm. All saturated carbons appear between 61.0 – 45.0 ppm.

2.2 SYNTHESIS OF DIAMINOCONDURITOL 151

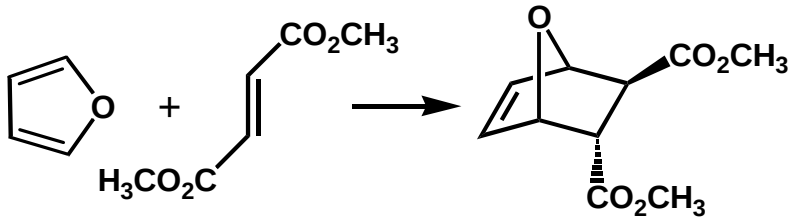
By the synthesis of the diurethane **157**, we could successfully establish the validity of our method to obtain urethane functionality in norbornene systems. The next purpose was to apply this methodology to the oxa norbornene systems. We tried to establish the following synthetic strategy through which the key intermediate is diurethane **161** to obtain the diaminoconduritol **151**.



2.2.1 THE SYNTHESIS OF 7-OXA-BICYCLO [2.2.1] HEPT-5-ENE-2,3-DICARBOXYLIC ACID DIMETHYL ESTER (163)

The first attempted synthesis through the diamino conduritol **151** was the conversion of *trans*-diacid obtained from the Diels-Alder reaction between furan and fumaric acid

into the *trans*-dichloride. However, the reaction between furan and fumaric acid was found to be too slow with a poor yield [48]. Therefore, we decided to obtain *trans*-diacid from the hydrolysis of corresponding dimethyl ester **163**. The reaction between furan and dimethyl fumarate at room temperature gave compound **163** at the end of one month with a yield of 40 %. The purification of the product was achieved by the recrystallization of dimethyl fumarate upto 70 %. However, this resulted in the loss of compound **163** since the reaction is equilibrium and the removal of dimethyl fumarate from the medium caused the decomposition of the product. The attempts to improve the yield of the reaction by repeating it in sealed tube with the excess of furan just decreased the reaction time.

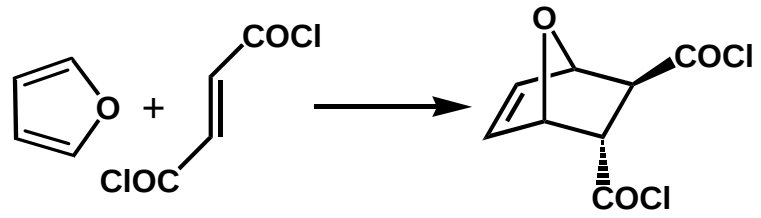


163

Due to the inconvenient reaction conditions such as poor yield and the long reaction time, we decided to end the trials to obtain diuretane **161** from diacid **160**.

2.2.2 THE SYNTHESIS OF 7-OXA-BICYCLO [2.2.1] HEPT-5-ENE-2,3-DICARBONYL DICHLORIDE (164)

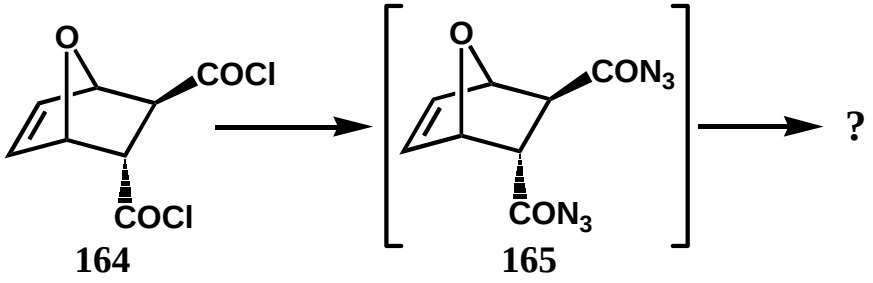
After the dissatisfaction to obtain diacid **160**, we turned our attention to obtain the dichloride in one step by using fumaryl chloride as dienophile. We could synthesize the desired dichloride with a yield of 70 % [49]. Due to the disgusting smell of fumaryl chloride the purification processes was delayed for the following steps.



164

^{1}H NMR spectra of this dichloride **164** shows an AB-system between 6.5-6.6 ppm due to the olefinic protons. Both A and B part are split into doublet of doublets due to further couplings with the bridge-head protons which arise at 5.4 as singlet. Other protons, H-2 and H-3, resonate at 4.1 and 3.4 ppm.

We tried to synthesize diazide by reacting the dichloride with HN_3 solution in benzene at room temperature. This reaction resulted in a complex mixture of unidentified products which were probably including the retro-Diels-Alder product of diazide **165** even at room temperature indicating the unstability of it.

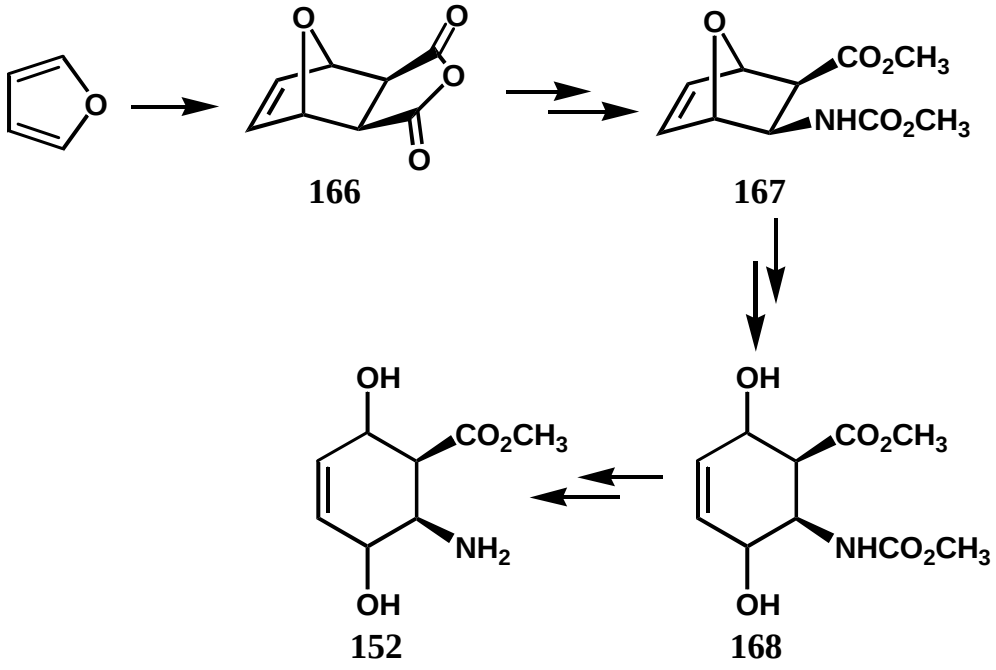


164 **165**

At that point our attempts to synthesize diamino conduritol **153** finished since it was understood that even if dichloride **164** is obtained it will not be possible to convert it to the corresponding diazide which would be the precursor of the diuretane **161**.

2.3 THE SYNTHESIS OF AMINOCONDURITOL DERIVATIVE 152

Through the synthesis of amino conduritol **152** we decided to use the Diels-Alder adduct of furan and maleic anhydride as the key compound. We aimed to follow the synthetic route given below.

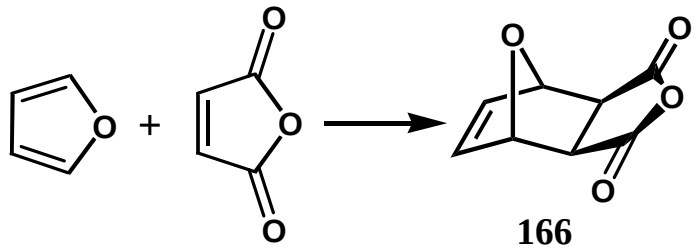


The key steps involve the desymmetrization of anhydride functionality, Curtius rearrangement, and the ring opening reaction of the oxa-bridge with a suitable reagent.

2.3.1 THE SYNTHESIS OF 7-OXA-BICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBOXYLIC ANHYDRIDE (166)

The reaction between furan and maleic anhydride, being one of the most famous examples, was first investigated by Diels and Alder [50]. They assigned the structure

of compound as *endo*-adduct, however, it was proved that the adduct has *exo*-configuration. This *exo*-selectivity arises from the secondary orbital interaction between the empty π-orbitals of carbonyl groups and the lone pairs of the bridge oxygen atom [51].



166

This reaction was further improved by applying different conditions such as temperature, pressure, catalysts, and solvents [52]. Here, we have chosen ether as the reaction solvent. Although the reaction occurs even at room temperature, it was heated to reflux to obtain a homogenious solution by dissolving maleic anhydride. The product can be recrystallized from a variety of solvents like acetone, ether, dichloromethane and ethylacetate causing different crystal patterns. The ^{1}H and ^{13}C NMR data are consistent with the reported ones.

In ^{1}H NMR spectrum, there are only three singlets due to the symmetry in the molecule, as expected. The broadnesses of the signals arise from the small couplings between protons that cannot be resolved.

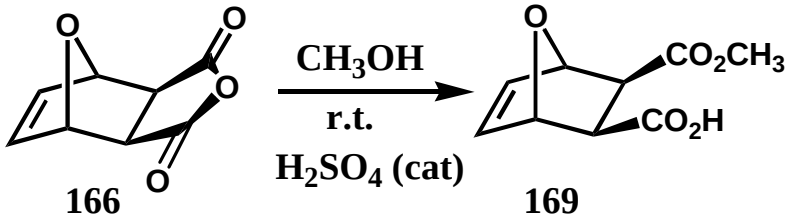
^{13}C NMR spectrum is also consistent with the symmetrical structure of the molecule, which give rise to only four signals. Carbonyl carbons resonate at 170.3 ppm, olefinic carbons resonate at 137.4 ppm. The bridgehead carbons appear at 82.6 ppm, a

relatively lower field due to the inductive effect of oxygen bridge. The other tertiary carbons have a chemical shift of 49.0 ppm.

2.3.2 THE SYNTHESIS OF 7-OXA-BICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBOXYLIC ACID MONOMETHYL ESTER (169)

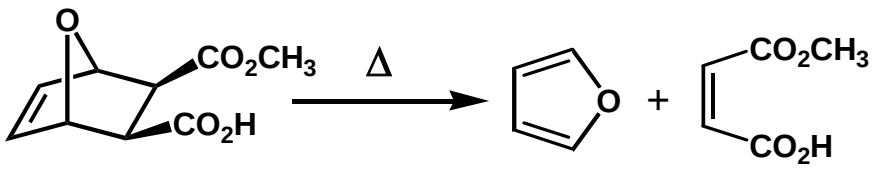
Anhydride functionality is a useful moiety that can have a potential of being converted to many other functional groups like carboxylic acid, ester, amine, alcohol, etc. Here we aimed to obtain a half-ester, containing an ester and a carboxylic acid groups which will then converted into a hydroxymethyl group and an amino group, respectively, in our synthetic strategy. This can be achieved by solvolysis in an alcohol; such as methanol, with or without a Lewis acid catalyst like $BF_3.Et_2O$, $AlCl_3$, and $FeCl_3$ leading to a racemic mixture [53] or by using chiral catalysts to obtain enantioselective ring opening [54]. Half-esters can also be obtained from corresponding diesters by using some enzymes [55].

Since we were not interested in asymmetric synthesis of the cyclitols we run the ring opening reaction in methanol at room temperature giving the desired half-ester **169** quantitatively. The reaction time can be shortened by the addition of sulphuric acid as catalyst.



166 **169**

Increasing the temperature resulted in decomposition of the product to some extent due to the retro-Diels-Alder reaction giving furan and maleic acid monometyl ester **170**. This is due to the extra strain caused by the oxa-bridge in the molecule.



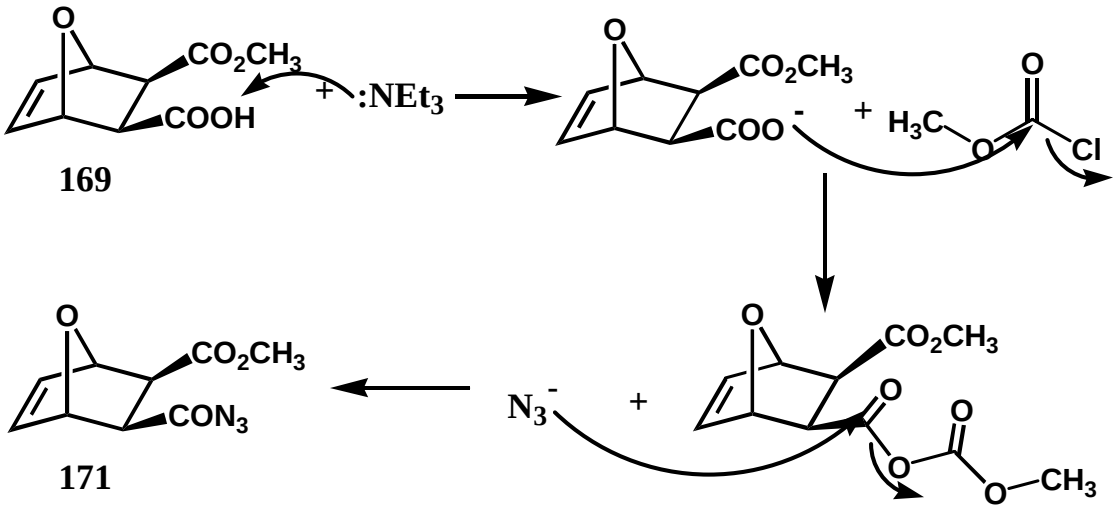
169 **170**

The compound **169** was characterized on the basis of its ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, the acidic proton resonates as a broad singlet at 9.0 ppm. At 6.4 ppm a singlet was observed arising from two olefinic protons indicating that there is no coupling between bridge-head protons (H-1, H-4) which give rise to two different and close singlets at around 5.3 ppm, a characteristic chemical shift for the bridge-head protons in oxa norbornene systems. The methoxy protons resonate as a singlet at 3.7, shifted to lowfield due to the inductive effect of oxygen. Between 2.7 – 2.8 ppm, there is an AB system arising from other two CH- protons (H-2 and H-3) both giving doublets with a coupling constant of 9.0 Hz.

In ^{13}C NMR spectrum, carbonyl carbons resonate at 177.3 and 172.4 ppm, relatively high field resonances when compared to aldehydes and ketones due to the mesomeric effect of oxygen next to carbonyl carbon. Olefinic carbons are quite close to each other and appear at 137.1 and 137.3 ppm. Bridge-head carbons have a chemical shift of 80.7 and 80.9 ppm being shifted to low field by oxygen-bridge. Other saturated carbons resonate at 47.3, 47.6, and 52.7 ppm.

2.3.3 THE SYNTHESIS OF 3-AZIDOCARBONYL-7-OXA-BICYCLO[2.2.1]HEPT-5-ENE-2-DICARBOXYLIC ACID METHYL ESTER (171)

Since our aim is to obtain an amine functional group in the desired cyclitol derivative, we tried to convert the acid group of the half-ester **169** into an acyl azide **171** by the help of an acid activator, methyl chloroformate. The methods involves the formation of an intermediate having a good leaving group *in situ*, and then the addition of azide ion to this intermediate. The addition of triethyl amine is essential since no acyl azide formation was observed in the absence of it.



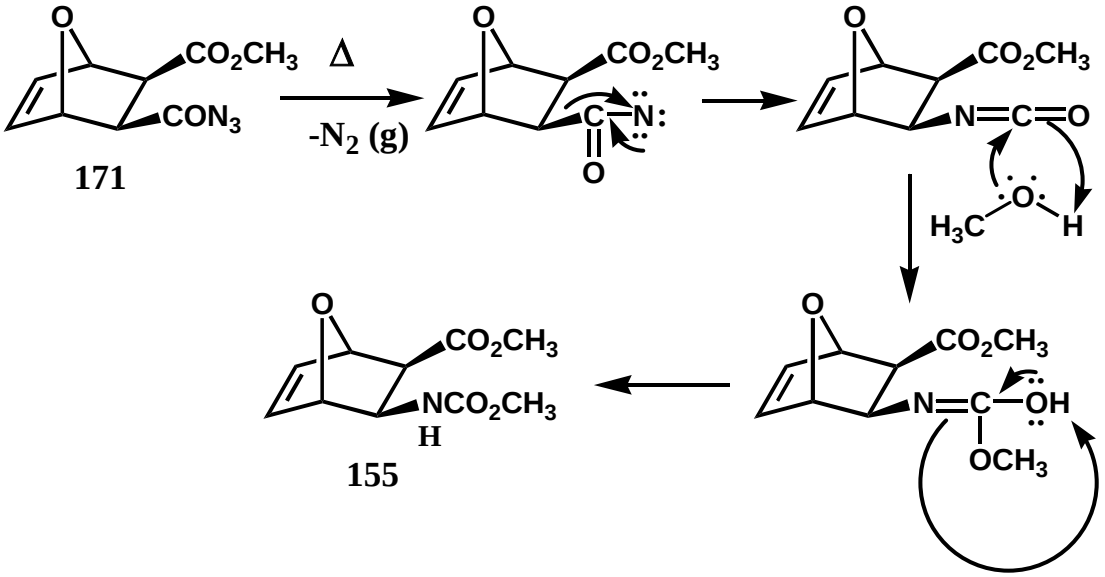
The formation of acyl azide is proved by the azides bands at 2264 and 2162 cm^{-1} in IR spectrum. The ^{1}H NMR spectrum of the acyl azide **171** contains two AB systems arising from the olefinic protons (H-5, H-6) and two saturated protons (H-2, H-3) next to the carbonyl groups. Both parts of AB system of olefinic protons are further split into doublet of doublets with coupling constants of 5.7 and 1.5 Hz control. The small

splittings indicate the interaction of olefinic protons with the bridge-head protons which give rise to two singlets at 5.1 and 5.2 ppm. The methoxy protons resonate at 3.7 while protons H-2 and H-3 resonate between 2.6 and 2.7 as an AB system having a coupling constant of 8.9 Hz.

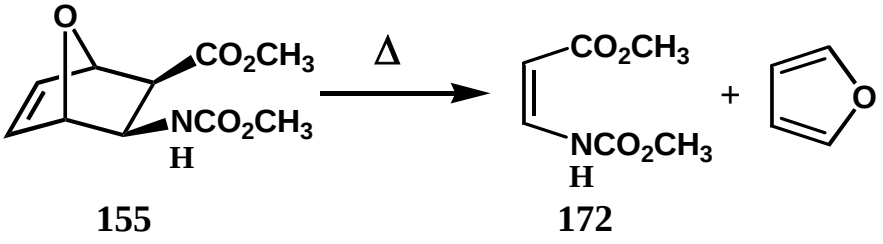
As for the ^{13}C NMR, since the electron density of the molecule is nearly the same in the molecule, the chemical shifts of all carbon atoms are similar to those observed in the case of half-ester **169**. Carbonyl carbons resonate at 171.7 and 179.1, whereas the olefinic protons are at 136.7 and 137.3 ppm. Saturated carbons resonate at 80.9 as bridge-head carbons, 52.6 as methoxy carbon, 47.9 and 49.1 as the carbons next to the carbonyl groups.

2.3.4 THE SYSNTHESIS OF 3-METHOXYCARBONYL AMINO-7-OXA-BICYCLO[2.2.1]HEPTE-5-ENE-2,3-DIARBOXYLIC ACID METHYL ESTER (155)

We aimed to synthesize uretane **155**, the protected form of the amino group, as our second key compound from acyl azide **171** in order to prevent the possible solubility and reactivity problems which may arise from the existence of an amino group, in the following steps.



Although the isolation of isocyanate was possible, it was unnecessary for us. The addition of methanol to isocyanate was done at room temperature since the formed uretane was not so stable. By incresing temperature it underwent retro-Diels-Alder reaction giving furan and 3-methoxycarbonylamino methyl acrylate **172** [56].



It was also possible to perform the synthesis of urethane **155** via formation of isocyanate by using dichloromethane as solvent since its boiling point is low. However, in that case the crude product was contaminated by some unidentified materials. The crude urethane **155** was purified by flash column chromatography technique and then recryslallized from etylacetate-hexane mixture.

The ^{1}H and ^{13}C NMR data were reasonable. The ^{1}H NMR spectrum shows an AB-system for the olefinic protons at 6.4 ppm. The coupling constant is 5.9 Hz between these two protons. The proton attached to nitrogen resonates at 5.4 due to the inductive effect of nitrogen atom. Its multiplicity is doublet arising from the coupling with H-3 (J=9.6 Hz). Chemical shifts of bridge-head protons H-1 and H-4 are 5.0 and 4.7 ppm, respectively. At 4.1 ppm H-3 proton appears as doublet of doublets because of couplings with H-2 and H-7 protons having coupling constants of 9.6 Hz and 7.7 Hz, respectively. H-2 proton resonates at 2.7 ppm as doublet owing to the coupling with H-3 proton. No couplings were obtained between H-2 and H-3 protons with bridgehead protons, H-1 and H-4, respectively, due to the dihedral angles between these protons. The two methoxy protons resonate 3.5 and 3.6 ppm, the broader one belonging to the one in uretane functional group.

When we look at the COSY spectrum of that compound we can easily see the correlations between all protons. There are correlations between olefinic protons and the bridge-head protons which cause them appear as broad singlets in ^{1}H NMR spectrum.

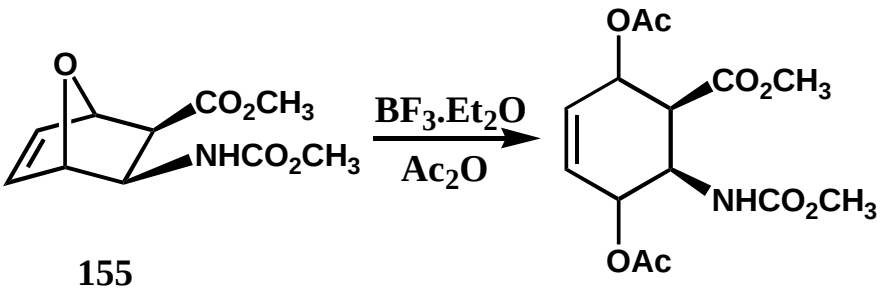
The ^{13}C NMR spectrum consists of 10 lines each corresponding to a different carbon atom. Carbonyl carbons resonate at 175.3 and 159.8 ppm. The one appearing at highfield belongs to the uretane carbonyl since nitrogen has a mesomeric effect on it. The HMBC spectrum also supports this conclusion by showing the corresponding correlations. Two lines at 141.0 and 139.0 ppm appear as olefinic carbons. The bridge-head carbons resonate at 87.0 and 83.1 ppm, as expected. Other saturated carbons resonate at 56.0, 55.4 and 55.2, and 50.0. Since DEPT-90 spectrum shows only CH-protons, we could differentiate the CH- protons (56.0 and 50.0 ppm) from methoxy protons (55.4 and 55.2 ppm).

The HMQC spectrum enabled us to assign every carbon to the protons attached to them. By this way, we are sure that the peak in ^{1}H NMR at 5.4 ppm belongs to the proton attached to the nitrogen atom since there is no correlation of this proton with none of the carbon atoms. Additionally, we could assign the bridge-head protons to their carbon atoms. However, it is not enough to decide which peak in ^{1}H NMR belongs to which bridge-head protons. That can be possible by examining the HMBC (Heteronuclear Multi Bond Coherence) spectrum, which gives long-range couplings between the carbons and the protons. The carbonyl carbon at lower field has correlations with H-1, H-2, and H-3 protons as well as methoxy protons being at lower field, whereas, the carbonyl carbon at higher field correlates with only H-3 proton and methoxy protons being at a higher field. As for the olefinic carbons, the one resonating at lower field correlates to one of the bridge-head protons and H-2 meaning that it has H-6 attached on it, on the other hand, other olefinic carbon at a higher field correlates to the other bridge-head proton and H-3 proton meaning that it has H-5 attached on it. We can conclude that bridge-head proton H-1 resonates at 4.7 and the other one H-4 resonates at 5.0 ppm. The highfield bridge-head carbon has correlation to H-2 and the other one has a correlation with H-3 which also support the previous assignments of bridge-head protons. Remembering the information gained from HMQC, the carbon at 87.0 ppm has H-1 proton attached to it and the carbon at 83.1 has H-4 proton.

2.3.5 THE SYNTHESIS OF 2,5-DIACETOXY-6-METHOXY CARBONYLAMINO CYCLOHEX-3-ENE CARBOXYLIC ACID METHYL ESTER (173)

To obtain the protected form of conduritol, the oxa-bridge should be opened. Literature provides different choices for the oxa-bridge of the norbornene systems including bases like methoxide, acetate ions [57], triethyl amine [58a,b] or acids such as HBr

[59], BBr_3 [2, 60, 61], $TiCl_4$ [40] mediated ring openings as well as enantioselective ones [62, 63]. First, we tried to use H_2SO_4 as the catalyst in the presence of acetic anhydride. Although we have succeeded in the ring opening, some of the product underwent aromatization due to the elimination of acetate groups in acidic medium. Then we have made use of a Lewis acid, $BF_3.Et_2O$, as catalyst to cleave the oxa-bridge, which resulted in the desired product without any aromatization.



155 **173**

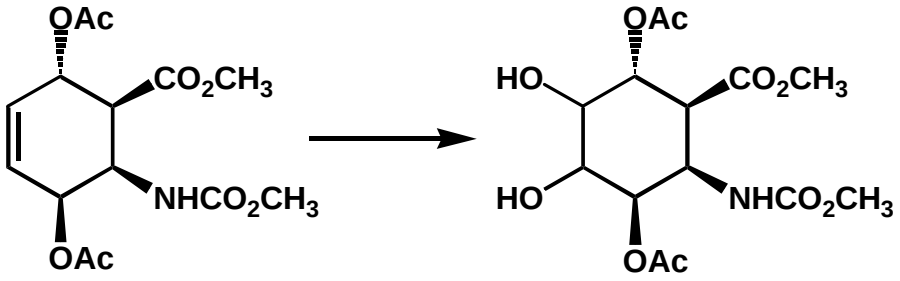
The compound **173** wad identified on the basis of its ^1H, ^{13}C NMR and 2-D NMR spectra. In ^1H NMR spectrum, there is an AB-system arising from olefinic protons, H-3 and H-4. A part of the AB-system (H-3) splitts into doublet of doublets of doublets since it has couplings between bridge-head protons, H-2 and H-5. Small coupling (2.2 Hz) is arising from allylic coupling, which can also be observed from the doublet of that proton, H-5, at 5.3 ppm. B part of the system (H-4) appears as doublet which clearly shows that there is no other couplings of this proton. Bridge-head proton H-2 gives a signal like a triplet indicating the couplings with H-1 and H-3 protons are very close to each other and around 4.2 Hz. H-6 proton resonate at 4.7 ppm as multiplet due to the couplings with H-1, H-5 and H-7 protons which can easily be seen from the COSY spectrum.

In ^{13}C NMR spectrum, there are four different carbonyl carbons at 172.5, 171.6, 170.9, and 159.2 ppm the one appearing at lowfield is shifted due to the inductive effect of nitrogen atom. The olefinic carbons, C-3 and C-4, resonate at 129.6 and 132.3 ppm, respectively, while the saturated carbons appear between 71 and 20 ppm. The bridge-head carbons, C-5 and C-2, resonate at 71.5 and 67.3, respectively. On the basis of HMQC spectrum, two methoxy carbons of ester and urethane groups resonate together at 54.6 and two methoxy carbons from acetoxy groups also resonate together at 23.2 ppm. C-6 and C-1 carbons appear at 49.5 and 47.1, respectively. The HMBC spectrum also supports the above assignments.

By achieving the synthesis of compound **173** we could succesfuly synthesis an amino conduritol derivative which can be converted into our second target molecule **152**.

2.3.6 THE SYNTHESIS OF 2,5-DIACETOXY-3,4-DIHYDROXY-6-METHOXYCARBONYLAMINO-CYCLOHEXANECARBOXYLIC ACID METHYL ESTER (174)

Oxidation of olefins can be performed by several reagents such as peracids for trans hydroxylation, potassium permanganate or osmium tetroxide for cis hydroxylation [5d, 8, 24, 65]. Here we performed the oxidation of compound **173** by using N-methyl morpholine N-oxide in the presence of catalytic amount of osmium tetroxide. The reaction yielded to only one isomer, **174**, exclusively.



173 **174**

The diol **174** was characterized on the basis of its ^{1}H NMR spectrum. In the olefinic region there is no signal which clearly indicates the disappearance of the double bound in the molecule. H-3 and H-4 protons resonate at 5.4 due to the inductive effects of the oxygen atoms. H-5 and H-2 protons appear at 5.0 ppm as doublet of doublets and 4.1 ppm as broad singlet, respectively. Proton attached to nitrogen resonates at 4.7 ppm. H-1 proton resonates as a broad singlet at 3.3 ppm while H-6 proton resonates at 3.8 ppm as doublet coupling with H-5 proton.

The synthesis of this molecule **174** will enable us to obtain amino inositol derivative **153** by the reduction and deprotection steps which can be done simultaneously.

CHAPTER 3

CONCLUSION

Cyclitols concerning a large group of natural products are of great importance due to their known and potential biological activities as well as their synthetic usefulness in the synthesis of other natural or pharmaceutical compounds. Hence, to develop new and efficient synthesis leading to cyclitols and their derivatives is a field of interest.

In this study, there were three target compounds, **151**, **152**, and **153**, the synthetic strategies of which involved the Diels-Alder adducts of furan with different dienophiles. The diuretane **154** and uretane **155** were thought as the key compounds for the synthesis of these target molecules.

For the synthesis of diuretane **154**, we could synthesize dimethyl ester **163** but with a poor yield and a long reaction time. Therefore we decided to try another pathway. The second way was to synthesize the diazide **165** directly from dichloride **164** obtain from the reaction between furan and fumaryl chloride. The azidization of that compound with HN_3 resulted in a complex mixture of products which probably contained the decomposition product of the desired azide as well as the other unidentified compounds. Therefore, the attempted synthesis of the diuretane **154** was failed since we could not obtain the diazide **165**. We thought that the difficulty to isolate it arises from its unstability even at room temperature.

For the synthesis of uretane **155**, we started with the Diels-Alder adduct of furan and maleic anhydride the desymmetrization of which gave half-ester **169**. The acid functionality of half-ester **169** was converted into acyl azide functionality which was converted into uretane **155** by thermal Curtius rearrangement. The cleavage of oxa-bridge with the help of a Lewis acid, $BF_3.Et_2O$, in acetic anhydide resulted in the derivative of the target molecule **152**.

The compound **173** was used for the synthesis of aminoinositol derivative **153**. The cis dihydroxylation of compound **173** with osmium tetroxide gave diol **174** which can be reduced and deprotected to obtain the target molecule **153**.

In concusion, the derivatives of the aminoconduritol (**173**) and aminoinositol (**174**) were synthesized succesfully from easily available and less expensive starting materials through five or six steps with relatively high to moderate yields.

CHAPTER 4

EXPERIMENTAL

4.1 General Considerations

Nuclear Magnetic Resonance (^{1}H, ^{13}C and 2-D) spectra were recorded on a Bruker Instruments Avance Series-Spectrospin DPX-400, Ultra Shield (400 MHz), High Performance digital FT-NMR spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane (TMS) reference and deuterochloroform, $CDCl_3$ as the solvent. Coupling constants (J values) were reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer by using chloroform, $CHCl_3$ as the solvent and KBr pellets. Band positions are reported in reciprocal centimeters (cm^{-1}).

Column chromatographic separations were performed by using Fluka Silicagel 60 (particle size 0.063-0.170 mm) The relative proportions of solvents refer to volume : volume ratio. Routine thin layer chromatography (TLC) was performed by using precoated 0.25 mm silicagel plates purchased from Fluka. All the solvent purifications were done as stated in the literature [64].

4.2 The Synthesis of Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid (156)

3.8 g (0.05 mol) of cold cyclopentadiene was added to a suspension of 5.8 g (0.05 mole) of fumaric acid in 50 ml of ethylacetate. After the mixture was refluxed for 5 hrs, white, solid product was formed. The solvent was evaporated and the product **156** was isolated quantitatively (mp: 186-188 ^{o}C).

^{1}H NMR δ ppm (D_2O): 6.3 (dd, A part of the AB-system, J = 5.3 – 3.2, 1H), 6.1 (dd, B part of the AB-system, J = 5.3 – 2.7, 1H), 3.3 (t, J = 4.5, 1H), 3.2 (s, 1H), 3.1 (s, 1H), 2.5 (dd, J = 4.5 – 1.5, 1H), 1.5 (d, A part of the AB-system, J = 8.3, 1H), 1.4 (dd, J = 8.3 – 1.5, B part of AB-system, 1H).

^{13}C NMR δ ppm (D_2O): 178.9, 178.2, 138.4, 135.1, 48.3, 47.7, 47.6, 47.5, 46.1.

IR: 2996, 2899, 2628, 1427, 1314, 1276, 1215, 1117, 951, 818.

4.3 The Synthesis of Bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride (158)

10.0 g (0.05 mol) of diacid **156** was dissolved in 150 ml of dry ether and (0.20 mol) of thionyl chloride was added all at once. After the addition of catalytic amount of pyridine, the mixture was refluxed for 20 hrs. The solvent and excess thionyl chloride was removed under reduced pressure. The colorless and liquid product was obtained with a yield of 95 %.

^{1}H NMR δ ppm: 6.3 (dd, A part of the AB-system, J = 5.5 – 3.2, 1H), 6.2 (dd, B part of the AB-system, J = 5.5 – 2.7, 1H), 3.8 (t, J = 4.0, 1H), 3.5 (s, 1H), 3.4 (s, 1H), 3.2

(dd, J= 4.2 – 1.4, 1H), 1.6 (dd, A part of the AB-system, J = 9.4 – 1.6, 1H), 1.5 (d, B part of the AB-system, J = 9.4, 1H).

^{13}C NMR δ ppm : 174.6, 172.9, 137.9, 135.7, 60.2, 59.6, 48.6, 47.6, 47.1, 31.1.

4.4 The Synthesis of Bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl diazide (159)

To a solution of 11.0 g (0.05 mol) of dichloride **158** in 250 ml of acetone 8.2 g (0.13 mol) of NaN_3 was added and the solution was stirred for 4 hrs at room temperature. After the filtration of precipitate, the filtrate was concentrated with a rotary evaporator. The compound **159** was obtained as colorless liquid with 85% yield.

^{1}H NMR δ ppm: 6.3 (ddd, A part of the AB-system, J = 8.5 – 5.4 – 3.2, 1H), 6.2 (ddd, B patr of the AB-system, J = 8.5 – 5.6 – 2.8, 1H), 3.3 (t, J = 4.0, 1H), 3.2 (s, 1H), 3.1 (s, 1H), 1.6 (d, A part of the AB-system, J = 9.0, 1H), 1.5 (d, B part of the AB-system, J = 9.0, 1H).

IR: 3367, 3067, 2983, 1817, 1733, 1533, 1417, 1350, 1150, 933, 867.

4.5 The synthesis of (3-Methoxycarbonylamino-bicyclo[2.2.1]hept-5-en-2-yl)-carbamic acid methyl ester (157)

12 g (0.051 mole) of diazide **159** was dissolved in 50 ml of methanol and refluxed for 4 hrs resulting in the formation of diuretane **157**. After the removal of excess methanol the compound **157** was obtained as white solid with a yield of 78 %. The crude product was recystallized from ethyl acetate/dichloromethane mixture (2:1) (mp: 178 ^{o}C).

^{1}H NMR δ ppm: 6.4 (dd, A part of the AB-system, J = 8.3 – 5.2 – 3.0) , 1H), 6.2 (dd, B part of the AB-system, J = 8.3 – 5.5 – 2.6),1H), 5.3 (broad s, 1H), 4.6 (broad s, 1H), 3.9 (broad s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.1 (broad s, 1H), 2.9 (broad s, 1H), 2.8 (broad s, 1H), 1.71 (d, A part of the AB-system, J = 8.5, 1H), 1.68 (d, B part of the AB-system, J = 8.5, 1H).

^{13}C NMR δ ppm : 156.9, 138.5, 134.6, 60.8, 59.9, 52.4, 49.1, 45.9, 45.7.

IR: 3315, 3060, 2983, 2881, 2147, 1686, 1533, 1461, 1338, 1283, 1100, 1031, 933.

4.6 The Synthesis of 7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylicanhydride (166)

To a solution of 4.9 g (0.05 mol) of maleic anhydride in 20 ml of dry ether, 3.4 g of freshly distilled furan was added. After the mixture was stirred for 6 hrs at room temperature, the solvent was evaporated under reduced pressure. The product **166** was recrystallized from hot acetone with a yield of 70 % (mp:125 ^{o}C).

^{1}H NMR δ ppm : 6.5 (s, 2H), 5.3 (s, 2H), 3.1 (s, 2H).

^{13}C NMR δ ppm : 170.3, 137.4, 82.6, 49.1.

4.7 The Synthesis of 7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester (169)

Method I: 6.0 g (0.03 mol) of anhydride **166** was dissolved in 300 ml of absolute methanol and catalytic amount (5 drops) of sulfuric acid was added. The methanolysis

was completed after mixing for 5 hrs at room temperature giving half-ester **169** quantitatively. After the solvent was evaporated, the solid product **169** was recrystallized from ether (mp: 105 ^{o}C).

Method II: 6.0 g (0.03 mol) of anhydride **166** was dissolved in 30 ml of absolute methanol and stirred for 18 hrs at room temperature. After the removal of solvent with a rotary evaporator, the product **169** was recrystallized from ether (mp: 105 ^{o}C).

^{1}H NMR δ ppm : 9.0 (bs, 1H), 6.4 (s, 2H), 5.3 (2s, 2H), 3.7 (s, 3H), 2.8 (d, A part of AB system, J=9.0, 1H), 2.7 (d, B part of AB system, J=9.0, 1H).

^{13}C NMR δ ppm : 177.4, 172.3, 137.1, 136.9, 80.9, 80.7, 52.7, 47.6, 47.3.

IR: 3033, 2954, 2754, 2667, 1739, 1702, 1439, 1366, 1335, 1303, 1259.

4.8 The Synthesis of 3-azidocarbonyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-dicarboxylic acid methyl ester (171)

6.0 g (0.03 mol) of half-ester **169** was dissolved in 20 ml of dry THF. After the mixture was cooled to –20 ^{o}C, 1.2 equivalent (3.7 g, 0.036 mol) of triethylamine was added. The solution was treated with 1.5 equivalent (4.3 g, 0.045 mol) of methyl chloroformate, dropwise. After the additional stirring for 1 hr, a solution of 9.8 g (0.15 mol) of sodium azide in 60 ml of water was added all at once. The reaction was completed after 1 hr mixing at room temperature. The excess methyl chloroformate was removed by the addition of 90 ml of water (2 ml for each mmoles of methyl chloroformate). After the formation of two layers, the organic phase was seperated. The water phase was extracted with first ethylacetate (3 x 50 ml), then with a saturated

solution of sodium bicarbonate and water. It was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The compound **171** was obtained with 95 % yield.

^{1}H NMR δ ppm : 6.4 (dd, A part of AB system, J=5.7-1.5, 1H), 6.3 (dd, B part of AB system, J=5.7-1.5, 1H), 5.2 (s, 1H), 5.1 (s, 1H), 3.7 (s, 3H), 2.7 (d, A part of AB system, J=8.9, 1H), 2.7 (d, B part of AB system, J=8.9, 1H).

^{13}C NMR δ ppm : 179.1, 171.7, 137.3, 136.7, 80.9, 52.6, 49.1, 47.9.

IR: 3359, 3008, 2967, 2876, 2264, 2162, 1750, 1688, 1564, 1440, 1357, 1254.

4.9 The Synthesis of 3-methoxycarbonylamino-7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid methyl ester (152)

A solution of 6.5 g (0.03 mol) of compound **171** in 50 ml of dry benzene was mixed for 12 hrs at 50 ^{o} C to convert it into isocyanate by the help of Curtius rearrangement. The mixture was cooled to room temperature and 3 ml of dry methanol was added. It was stirred for an additional 2 hrs at room temperature. After the concentration by evaporating the solvent in a vacuo, the product **152** was purified by using flash column chromatography technique (ethylacetate/hexane 1:3). The product was further purified by the recrystallization with a yield of 60% (110 - 114 ^{o}C).

^{1}H NMR δ ppm : 6.4 (dd, A part of AB system, J=5.9-1.4, 1H), 6.4 (dd, B part of AB system, J=5.9-1.3,1H), 5.4 (d, J=9.4, 1H), 5.0 (s, 1H), 4.7 (s, 1H), 4.1 (dd, J=9.6-8.2, 1H), 3.6 (s, 3H), 3.5 (s, 3H), 2.7 (d, J=7.7, 1H).

^{13}C NMR δ ppm : 175.3, 159.8, 141.2, 138.6, 87.0, 83.3, 56.0, 55.4, 55.2, 50.2.

IR: 3319, 3038, 3004, 2945, 2846, 1732, 1711, 1534, 1422, 1359, 1253.

4.10 The Synthesis of 2,5-diacetoxy-6-methoxycarbonylamino-cyclohex-3-enecarboxylic acid methyl ester (173)

2.0 g (9 mmol) of uretane **152** was dissolved in 30 ml of acetic anhydride and cooled to 0 ^{o} C. After the addition of 1 ml of BF_3 diethyl ether complex as Lewis acid catalyst, the solution was mixed for 3 hrs by warming the system to room temperature, slowly. Approximately, 100 ml of ice-water mixture was added and extracted with chloroform (3 x 30 ml). The combined organic phases were washed with saturated sodium bicarbonate, and then water. After it was dried over Na_2SO_4, the solvent was removed under reduced pressure. The product **173** was recrystallized from ether with a yield of 40 % (mp: 124 ^{o}C).

^{1}H NMR δ ppm: 5.9 (ddd, A part of AB system, J=10.1-4.3-2.2, 1H), 5.7 (d, B part of AB system, J=10.1, 1H), 5.6 (t?, J=4.2, 1H), 5.4 (d, J=9.3, 1H), 5.3 (d, J=2.2, 1H), 4.7 (t?, J=4.6, 1H), 3.7 (s, 3H), 3.6 (s, 3H), 2.9 (dd, J=4.1-3.0, 1H), 2.0 (2s, 3H, 3H).

^{13}C NMR δ ppm: 173.4, 172.5, 171.9, 160.1, 133.3, 130.1, 72.5, 68.3, 55.5, 49.5, 47.1, 24.1.

IR: 3446, 3046, 3014, 2961, 2905, 1759, 1511, 1415, 1152.

4.11 The Synthesis Of 2,5-Diacetoxy-3,4-Dihydroxy-6-Methoxycarbonylamino-Cyclohexanecarboxylic Acid Methyl Ester (174)

200 mg (0.6 mmol) of compound **173** was dissolved in 50 ml of acetone. 2.5 eqv of N-morpholine N-oxide and catalytic amount of osmium tetroxide was added. The mixture was stirred for 24 hrs. After the addition of aqueous solution of sodium bisulphite, the mixture was filtered through celite to remove the salts. After the solvent was evaporated the liquid compound was obtained with a yield of 80%.

^{1}H NMP δ ppm: 5.4 (m, 2H), 5.0 (dd, J=10.1 – 4.0, 1H), 4.7 (m, 1H), 4.1 (s, 1H), 3.8 (d, J=10.1, 1H), 3.3 (s, 1H).

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APPENDICES

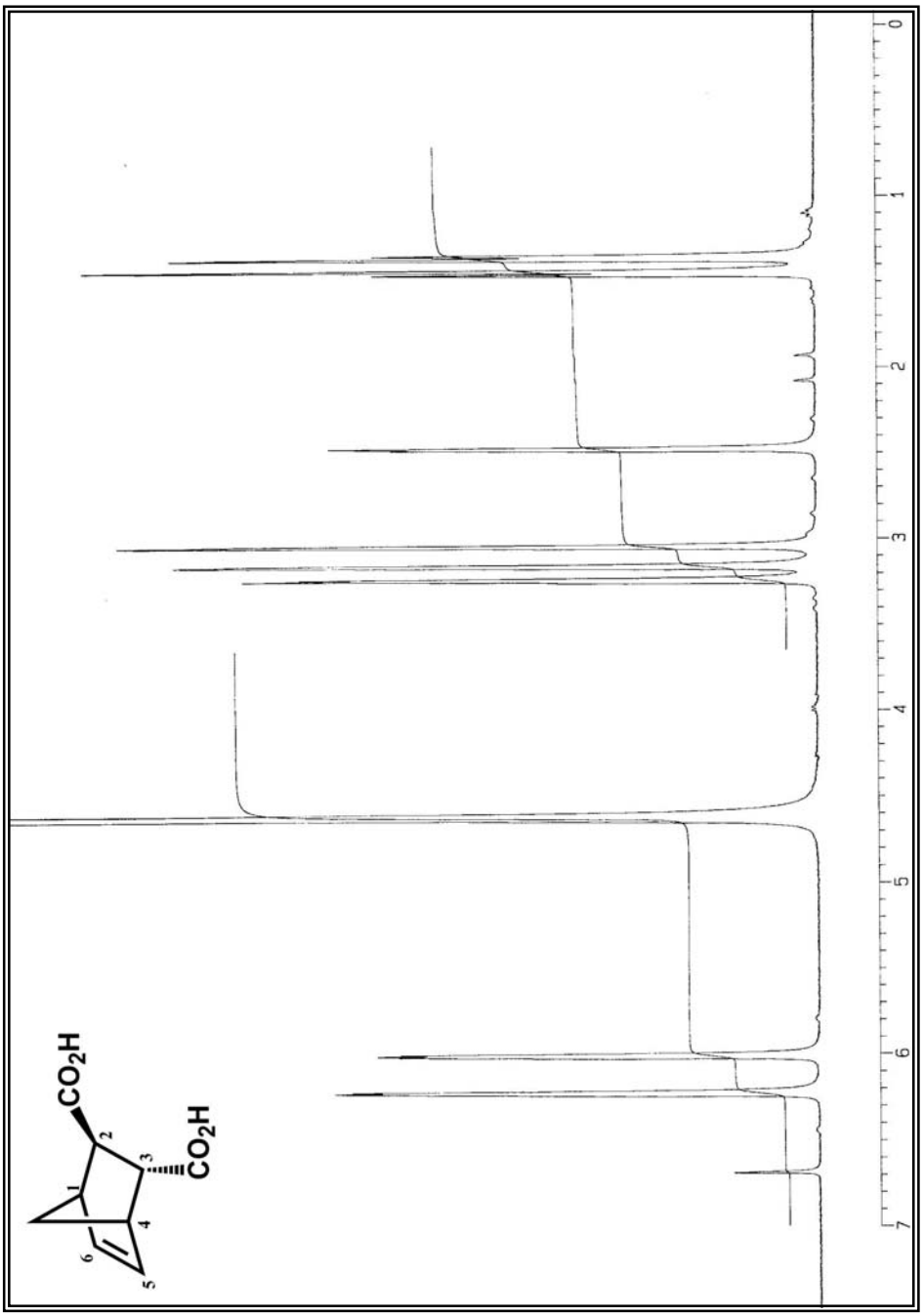

Figure 9. Structure and ^{1}H NMR spectrum of compound **156**

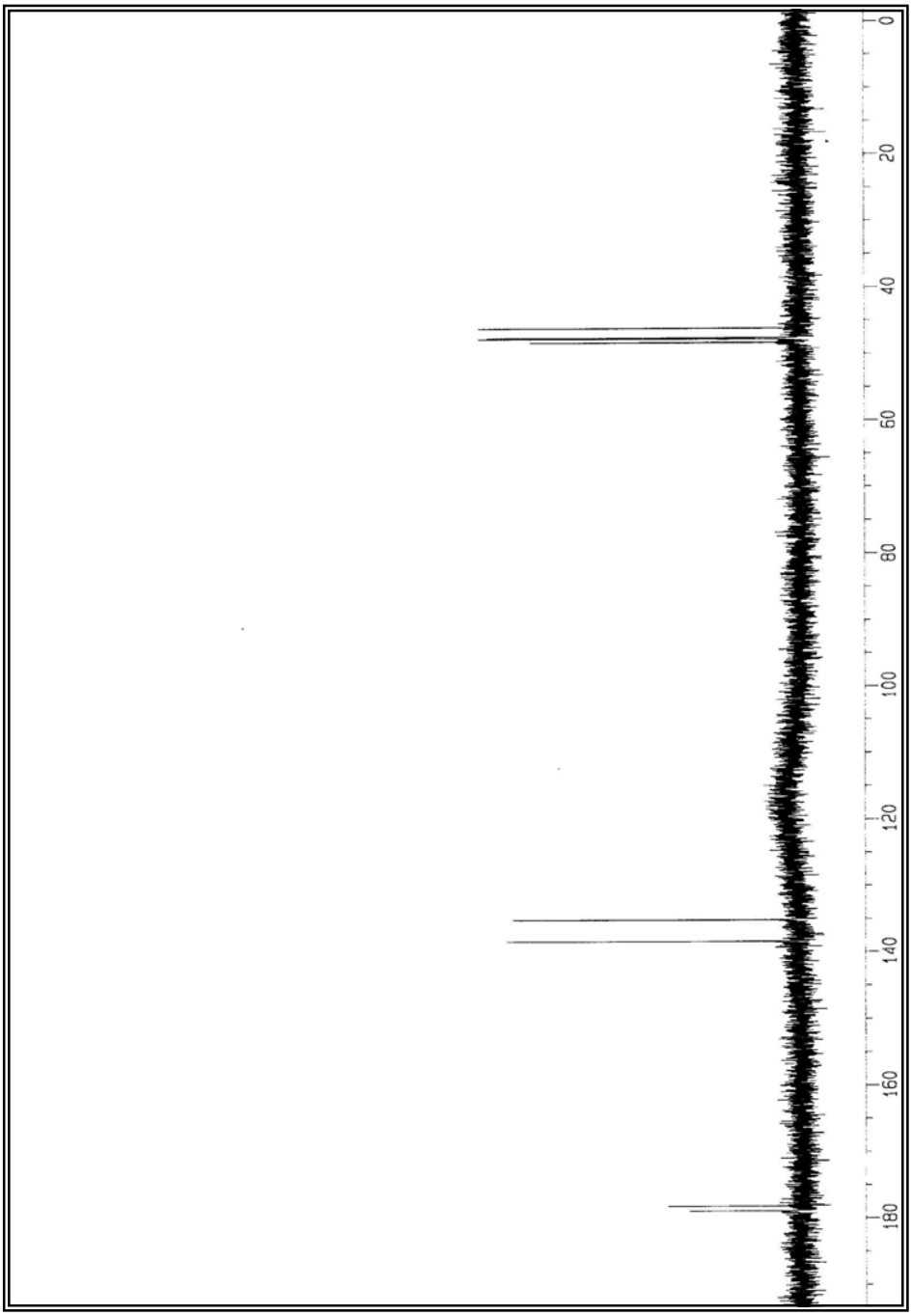

Figure 10. ^{13}C NMR spectrum of compound **156**

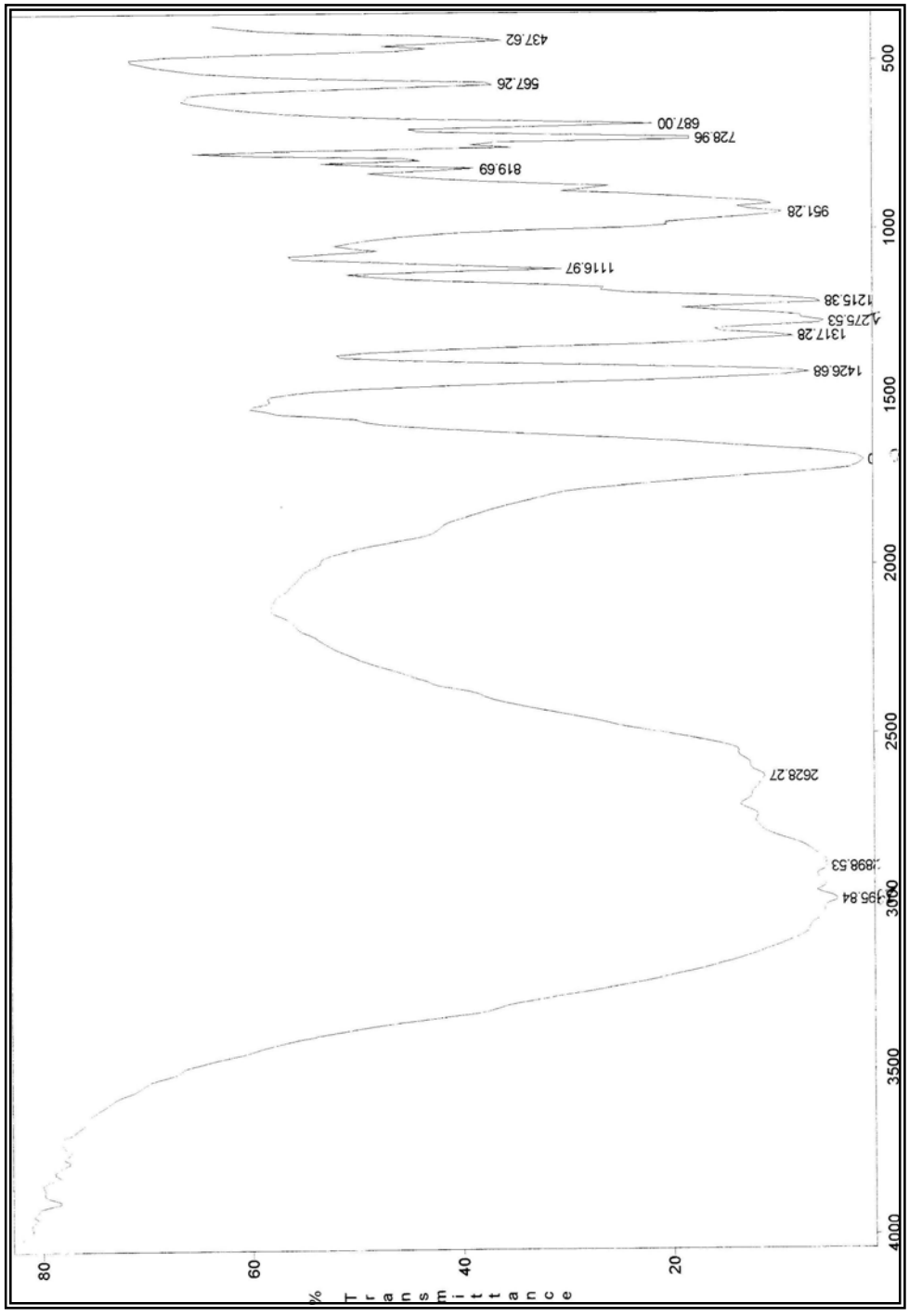

Figure 11. IR spectrum of compound **156**

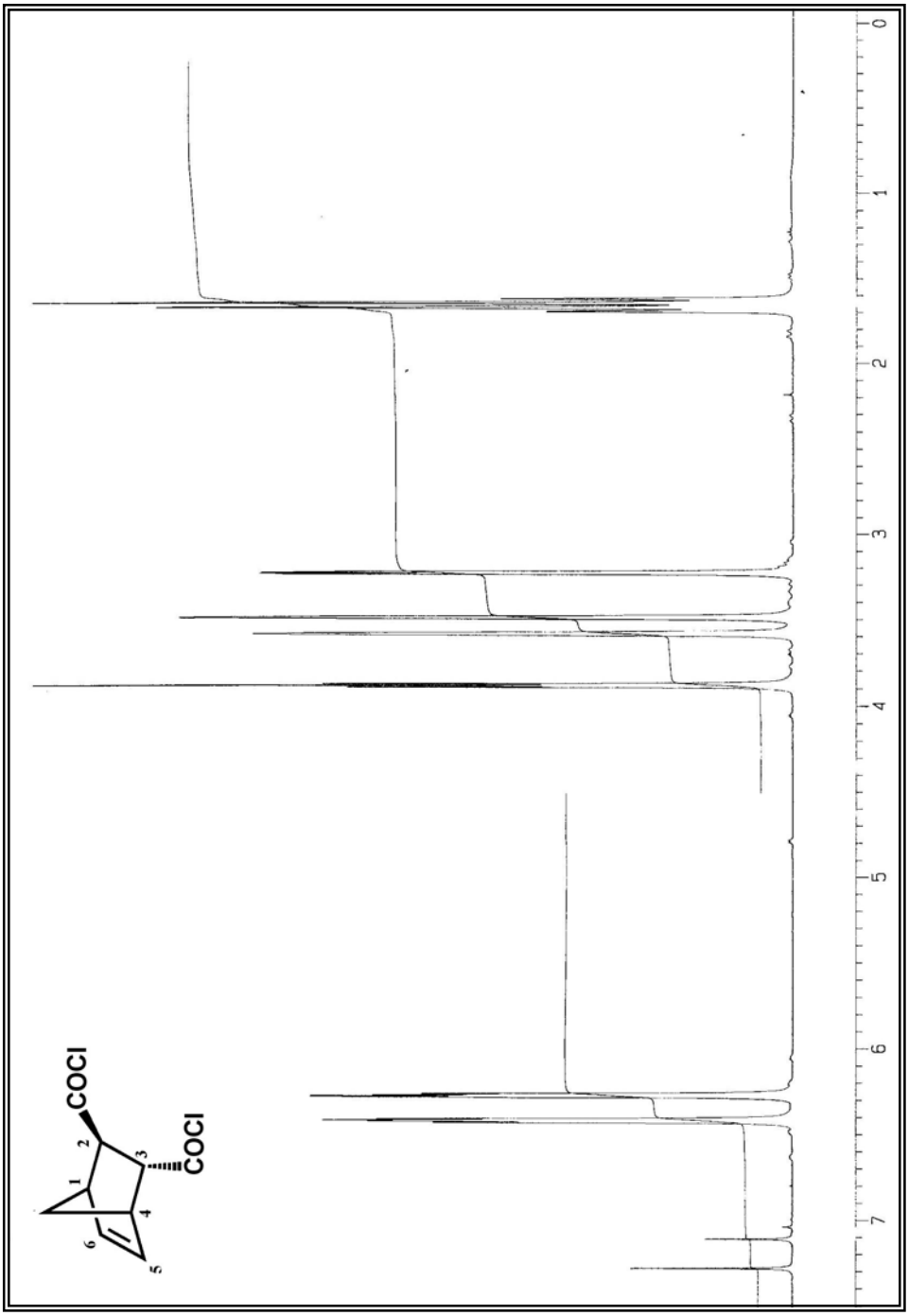

Figure 12. Structure and ^{1}H NMR spectrum of compound **158**

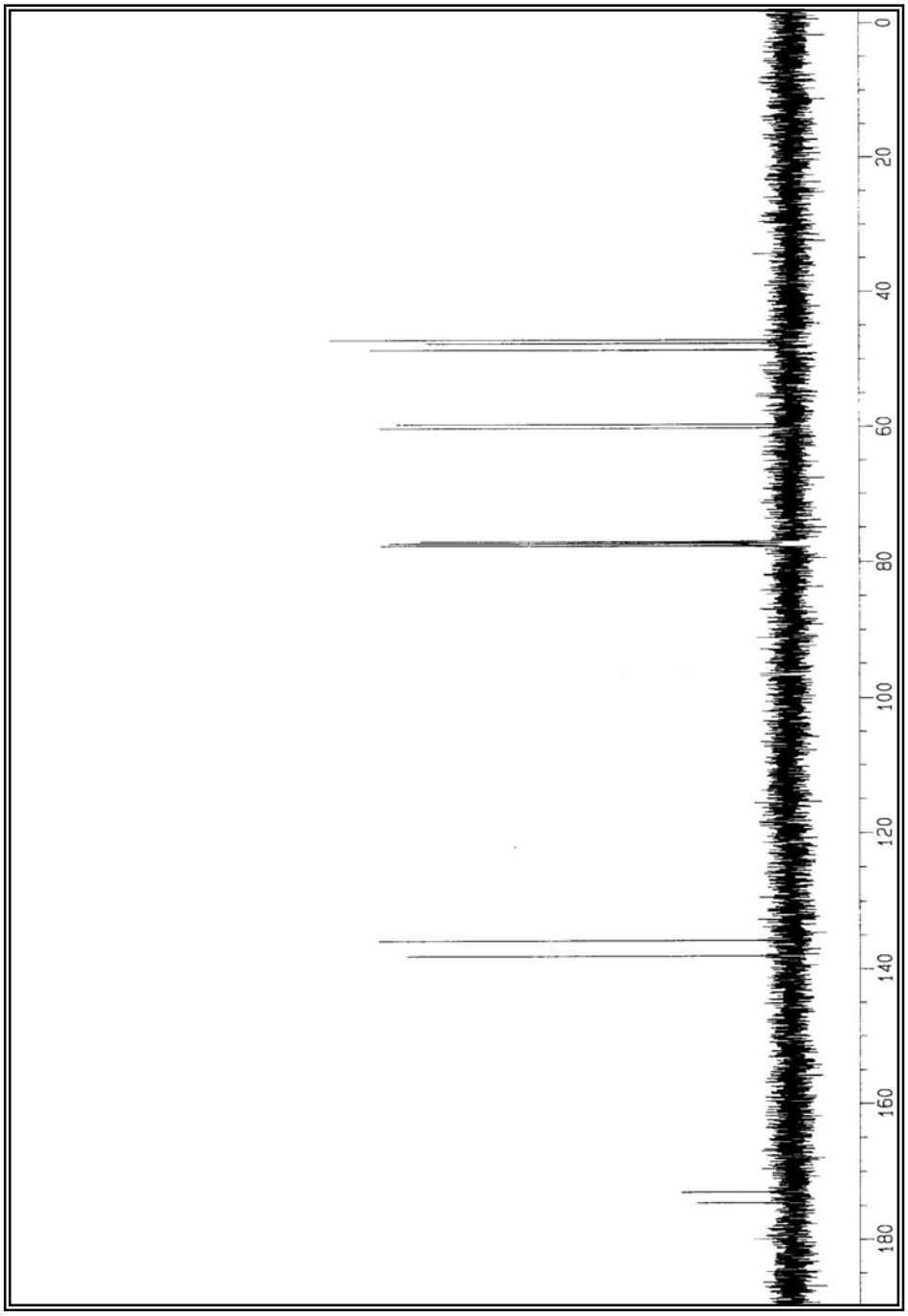

Figure 13. ^{13}C NMR spectrum of compound **158**

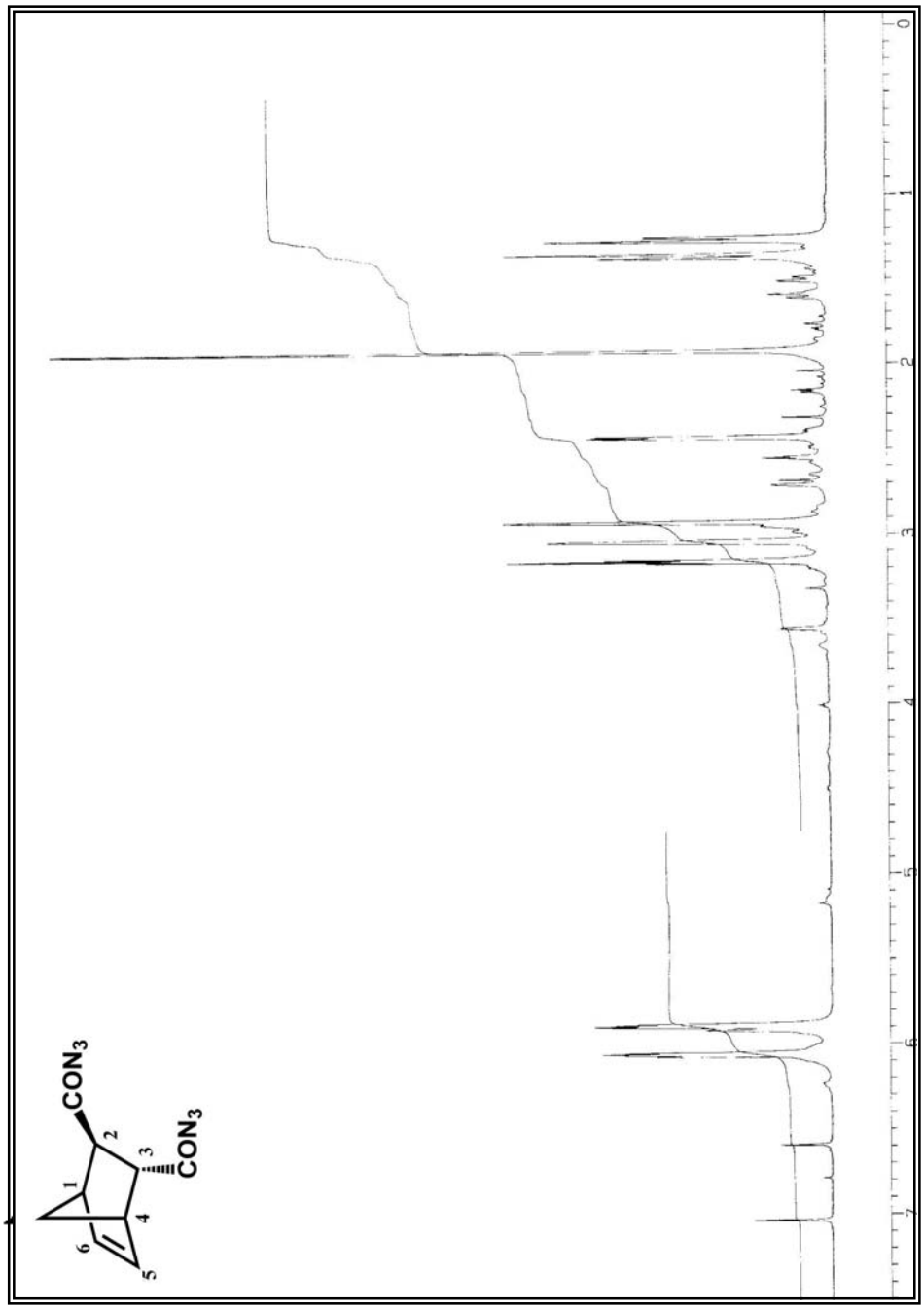

Figure 14. ^{1}H NMR spectrum of compound **159**

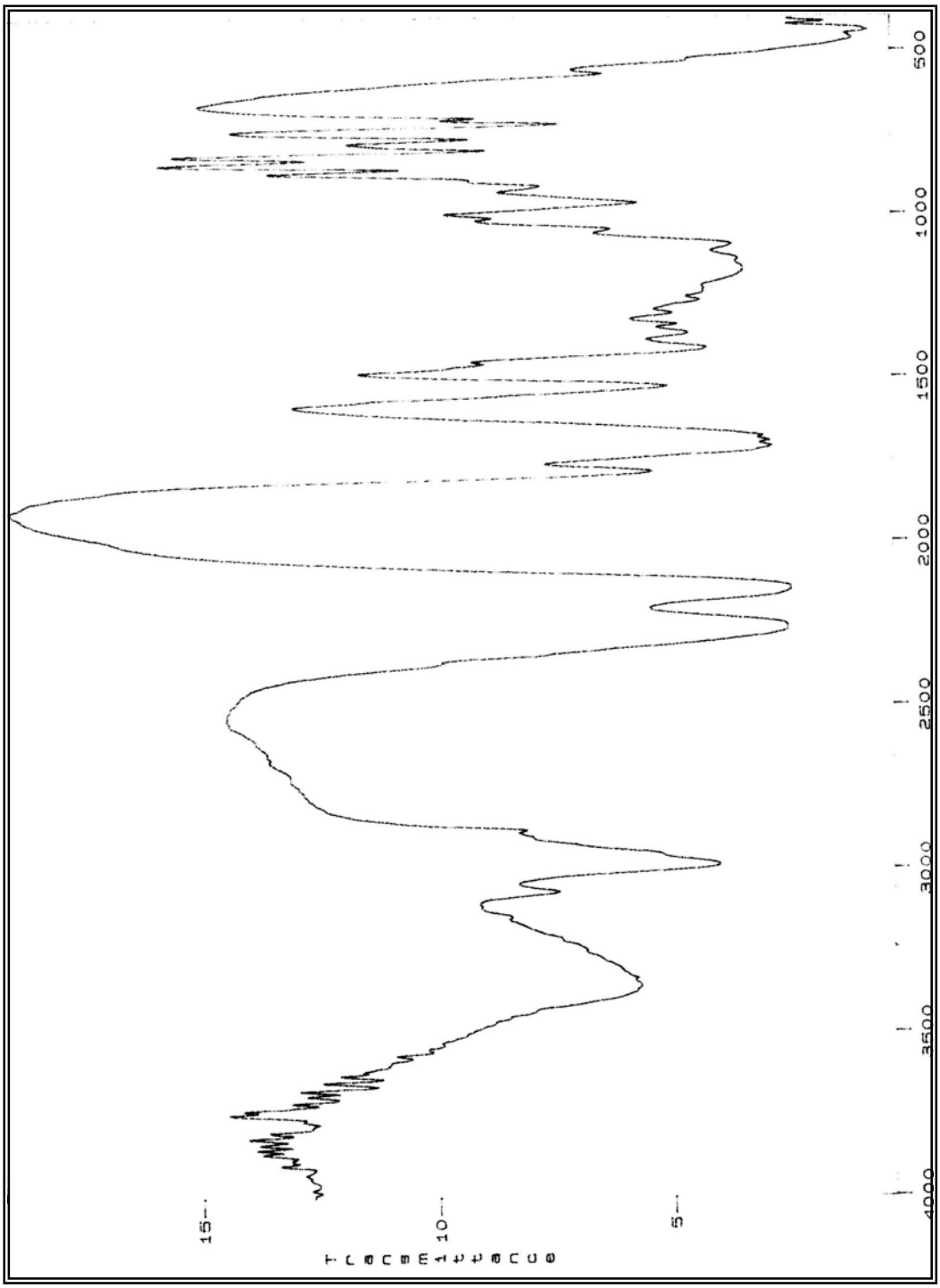

Figure 15. IR spectrum of compound **159**

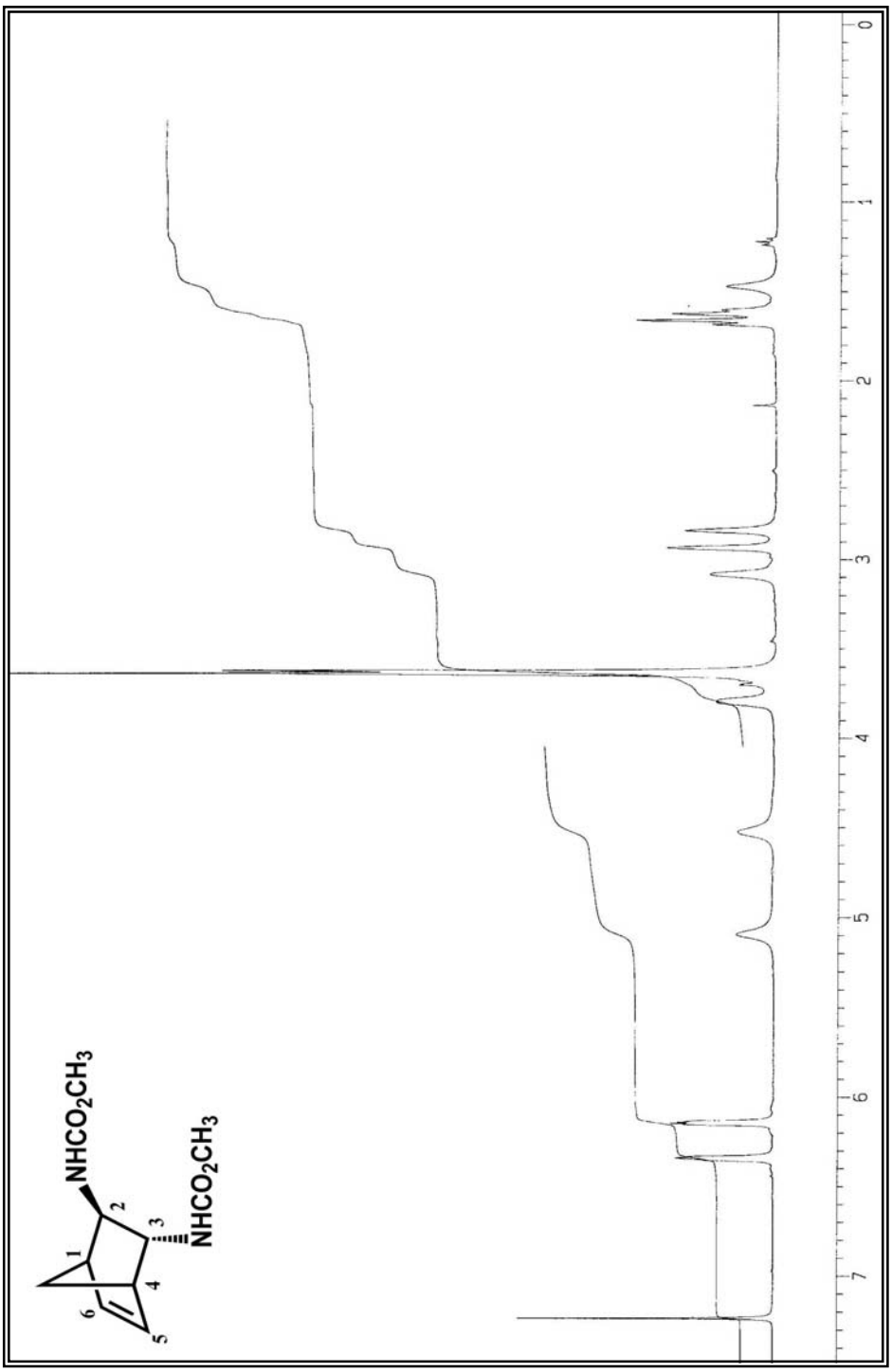

Figure 16. Structure and ^{1}H NMR spectrum of compound **157**

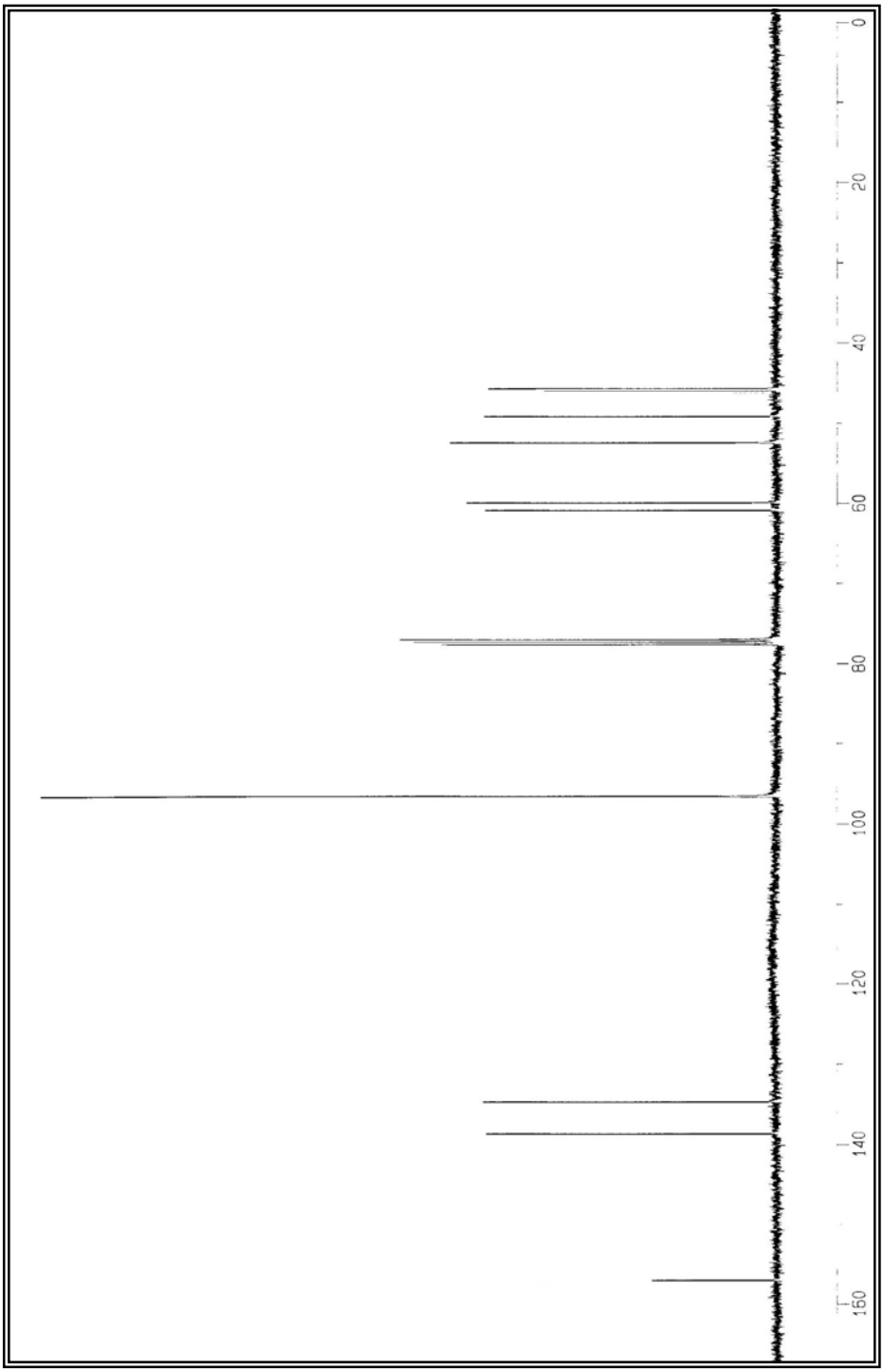

Figure 17. ^{13}C NMR spectrum of compound **157**

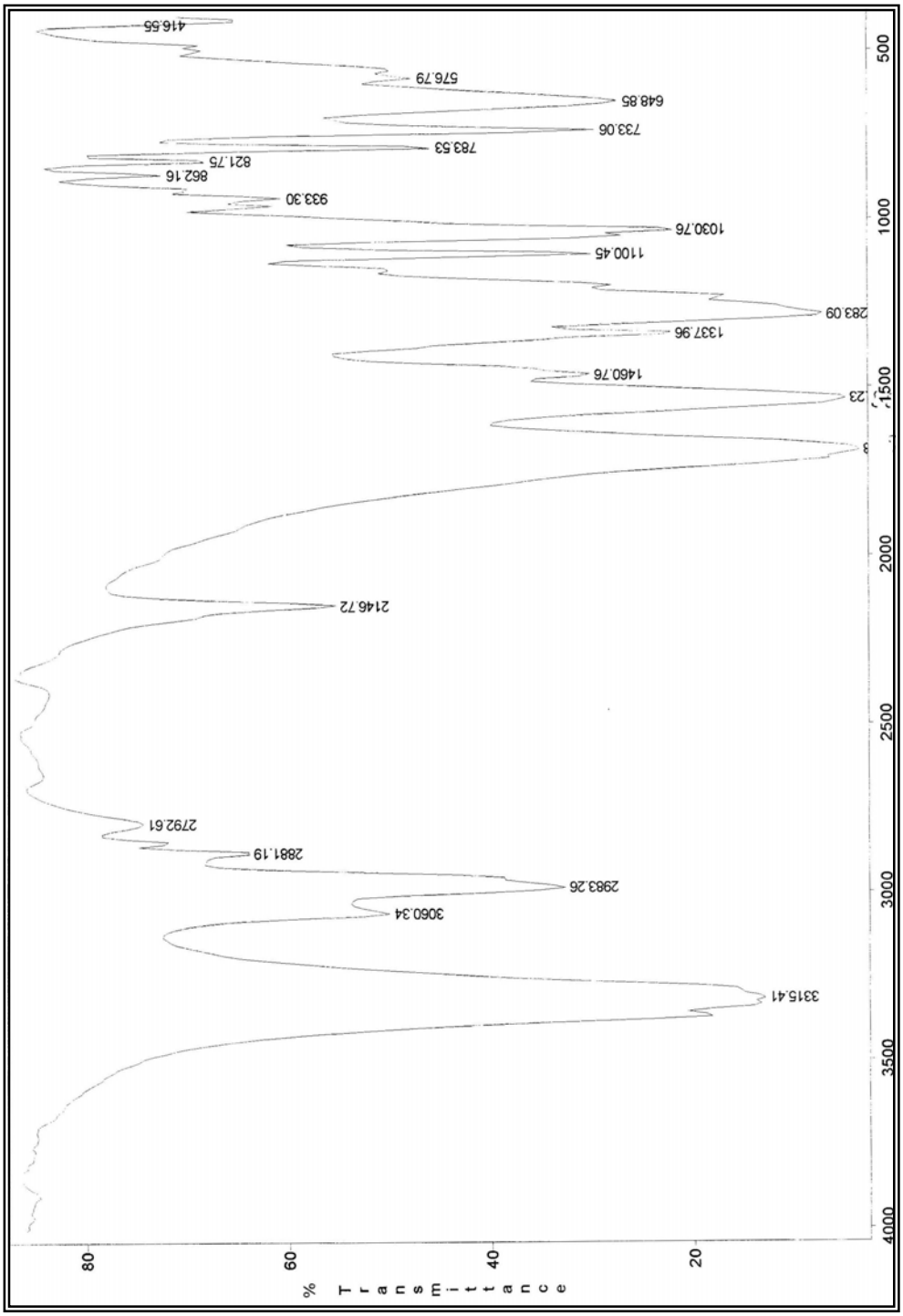

Figure 18. IR spectrum of compound **157**

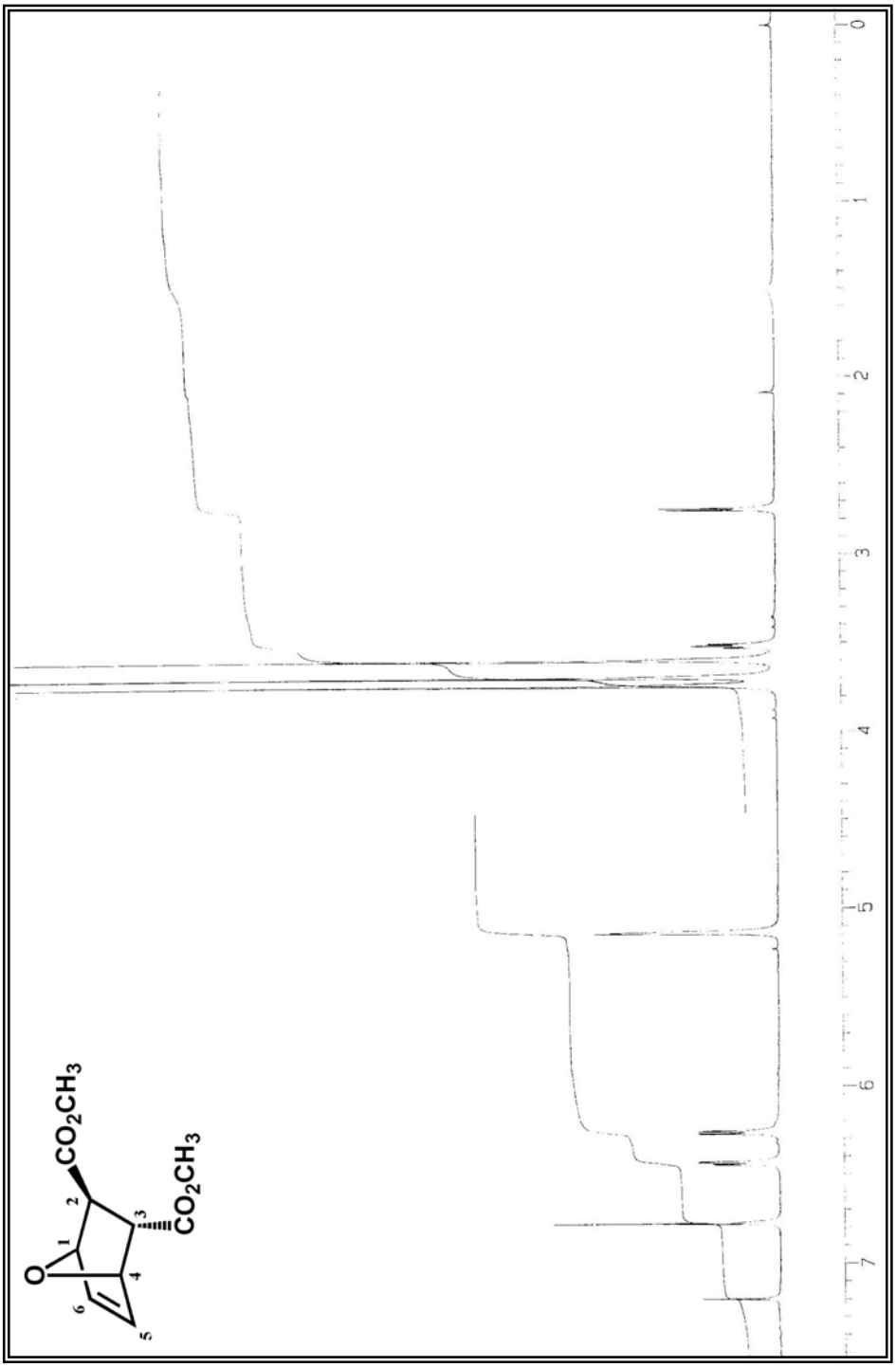

Figure 19. Structure and ^{1}H NMR spectrum of compound **163**

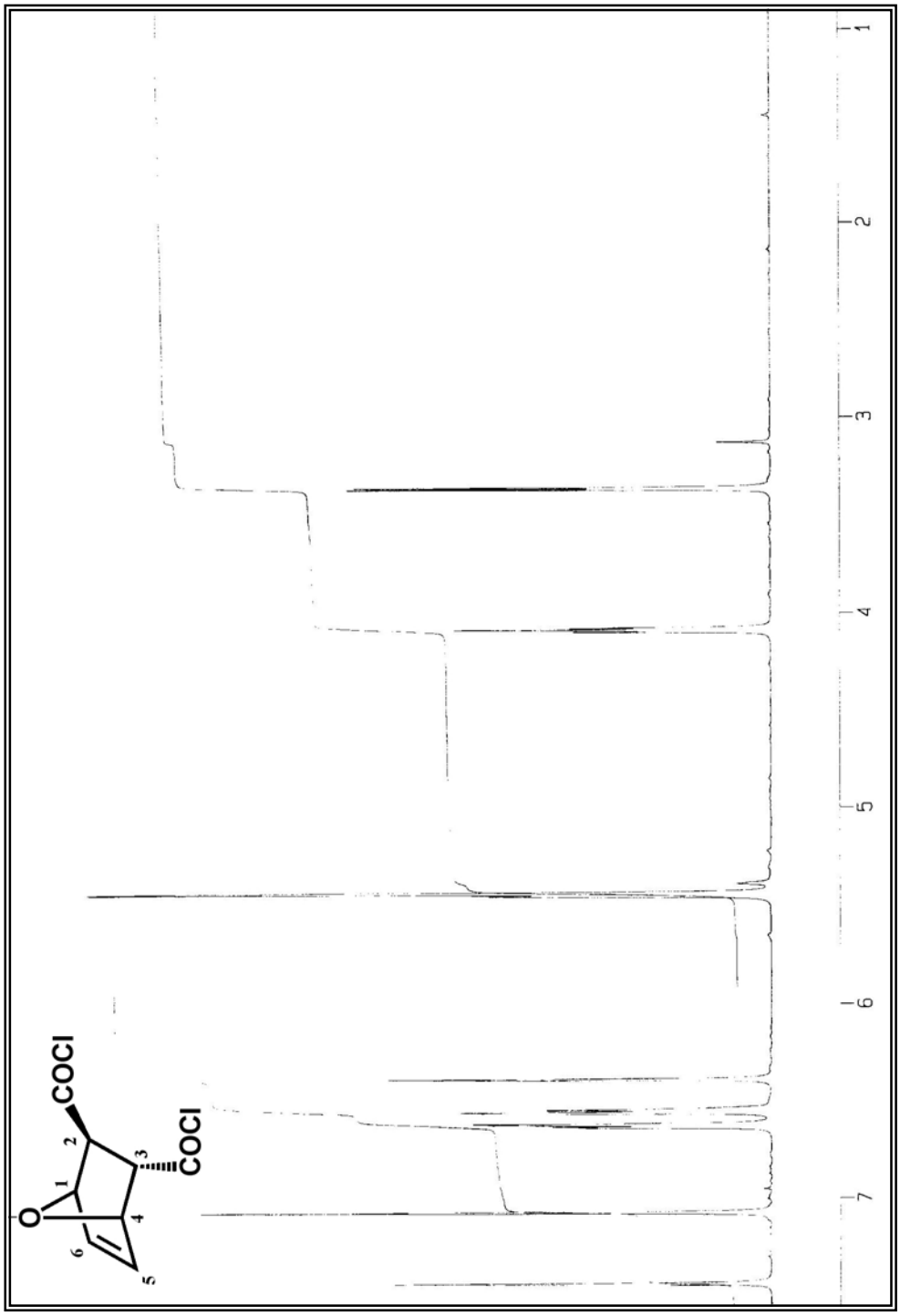

Figure 20. Structure and ^{1}H NMR spectrum of compound **164**

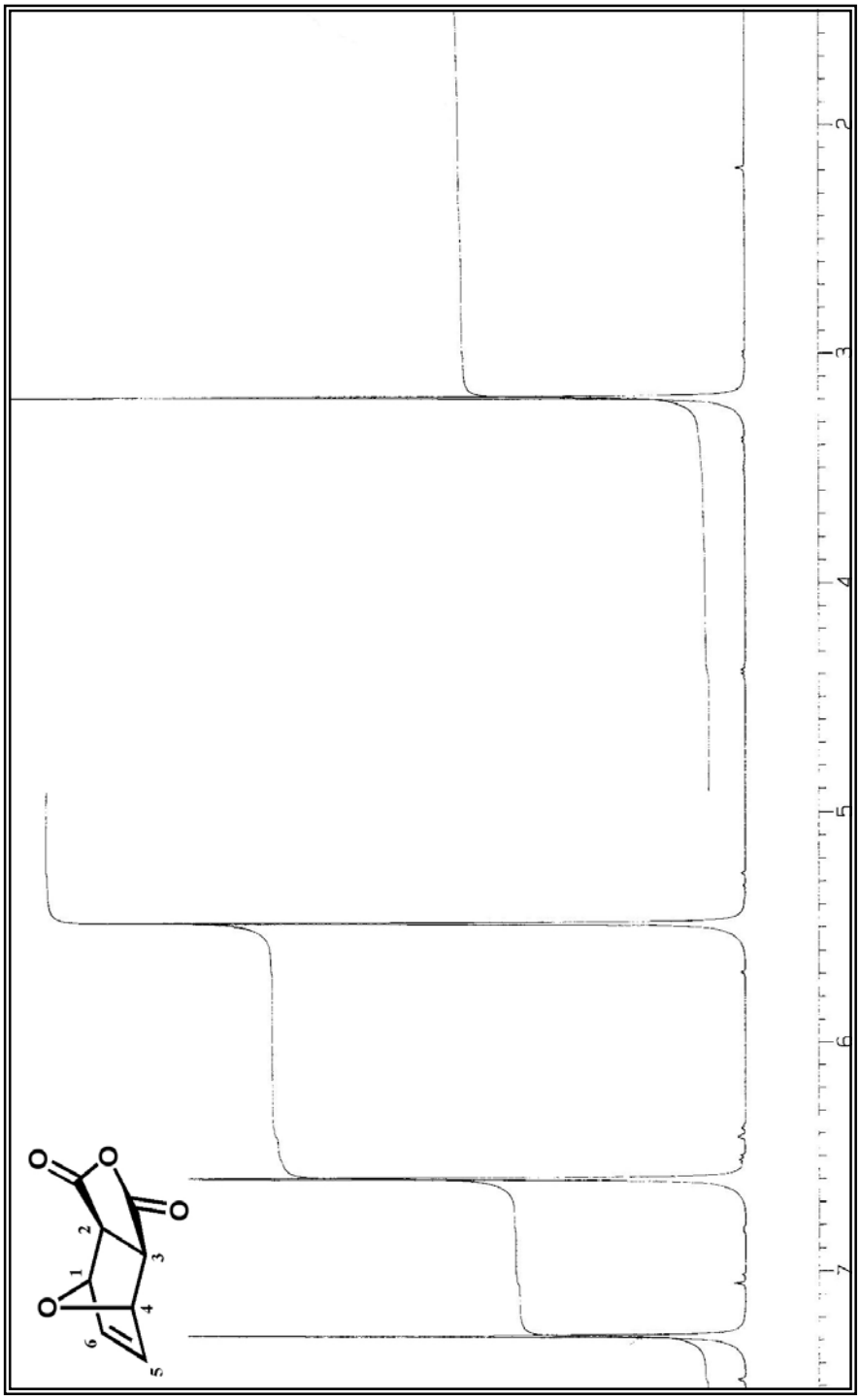

Figure 21. Structure and ^{1}H NMR spectrum of compound **166**

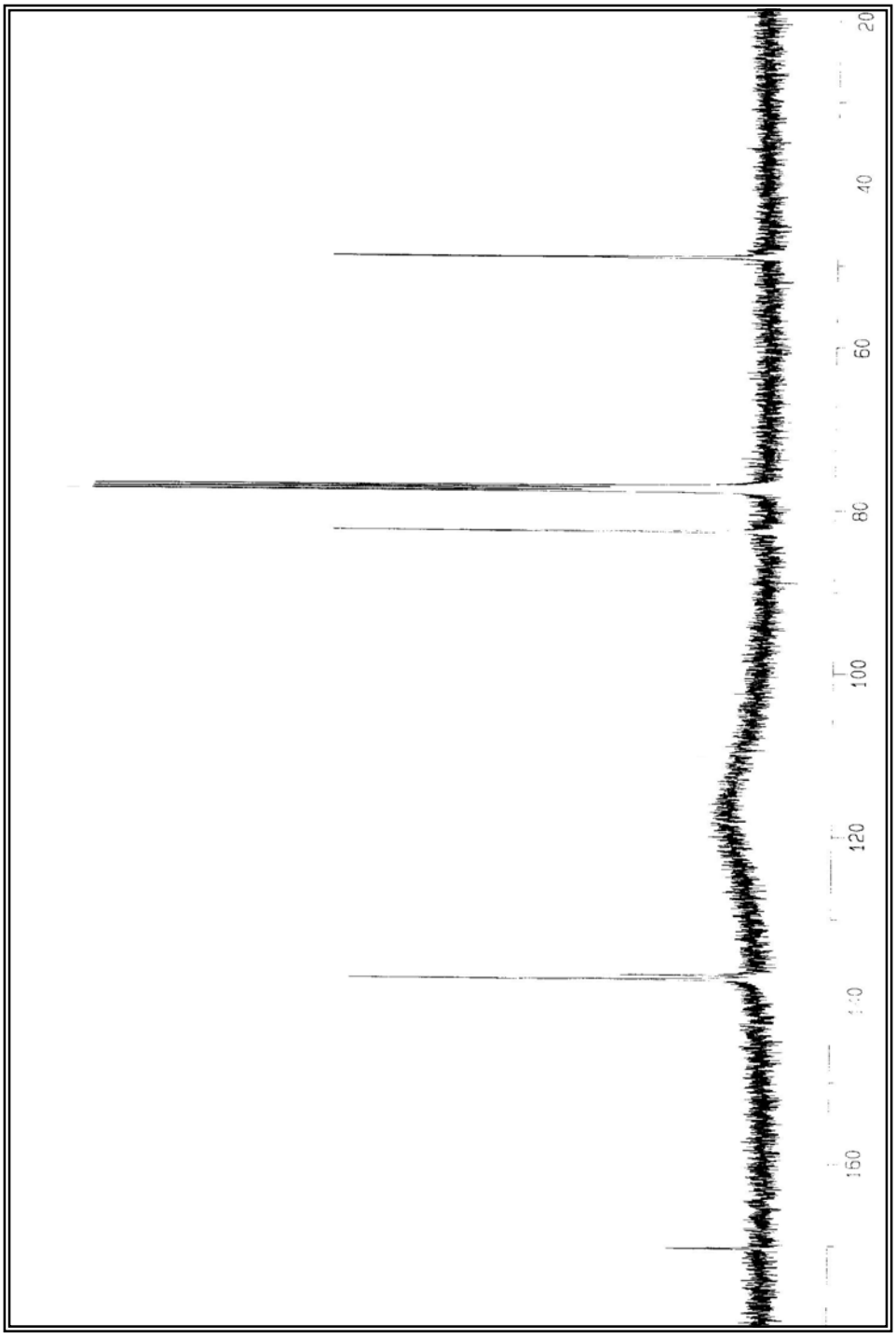

Figure 22. ^{13}C NMR spectrum of compound **166**

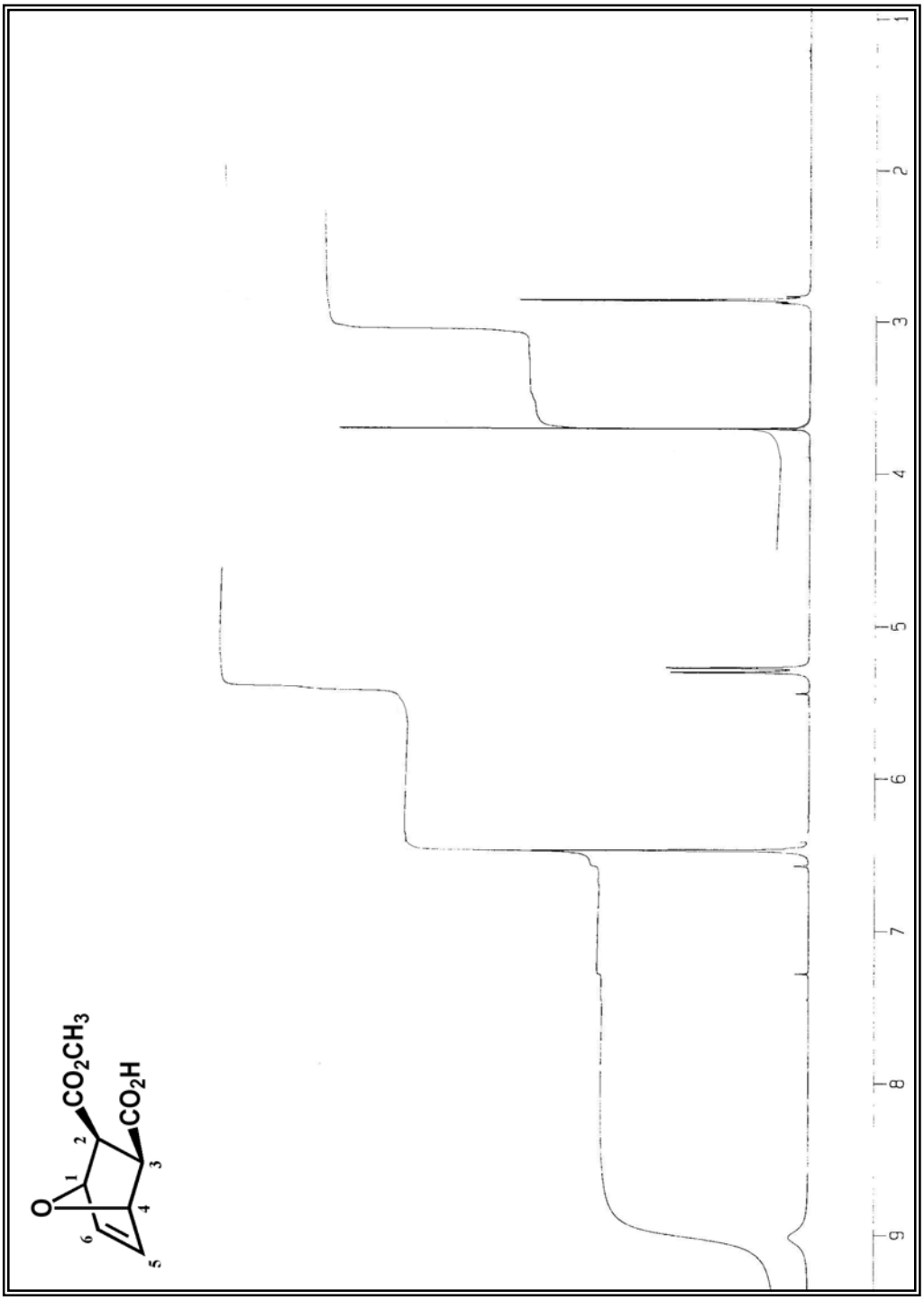

Figure 23. Structure and ^{1}H NMR spectrum of compound **169**

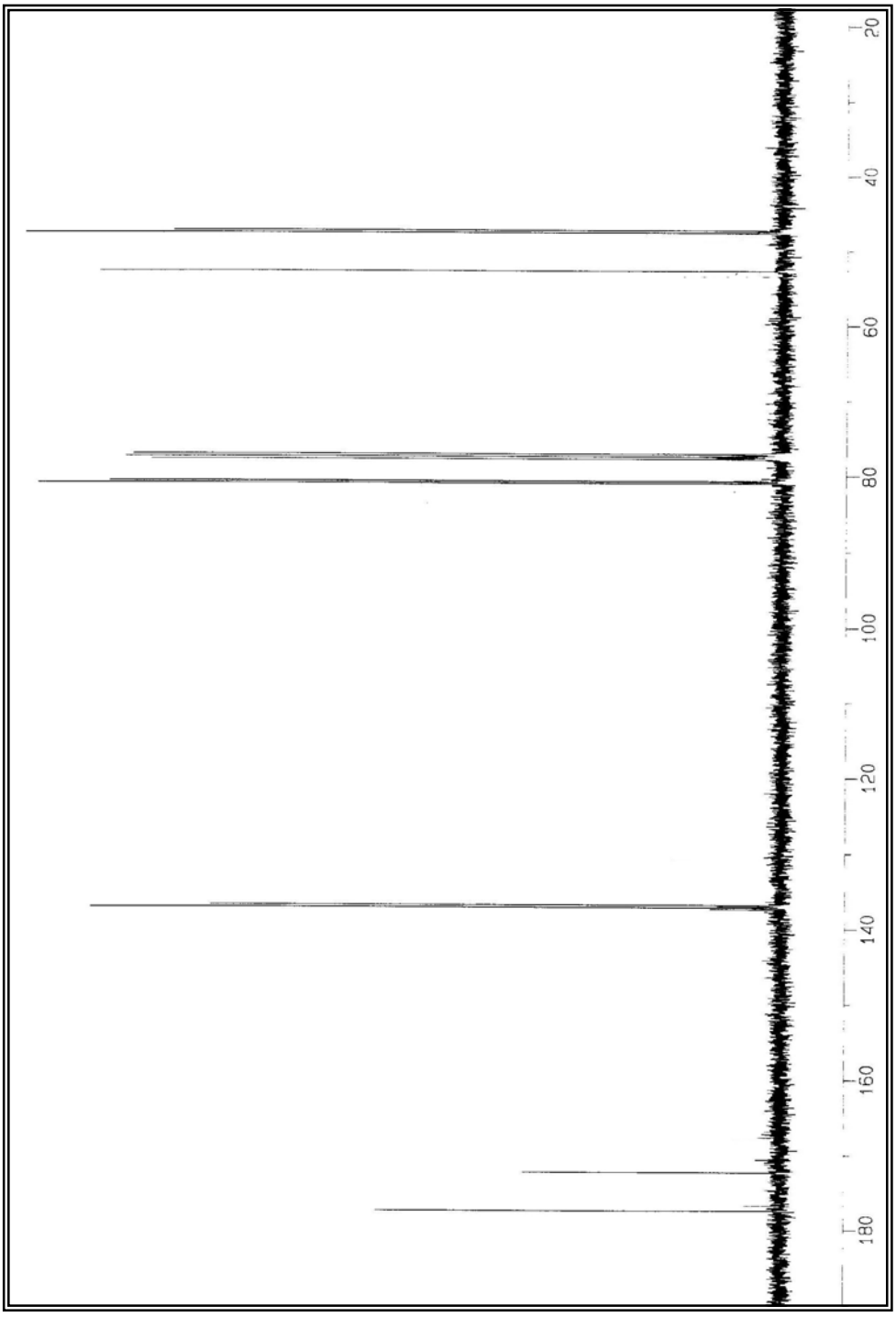

Figure 24. ^{13}C NMR spectrum of compound **169**

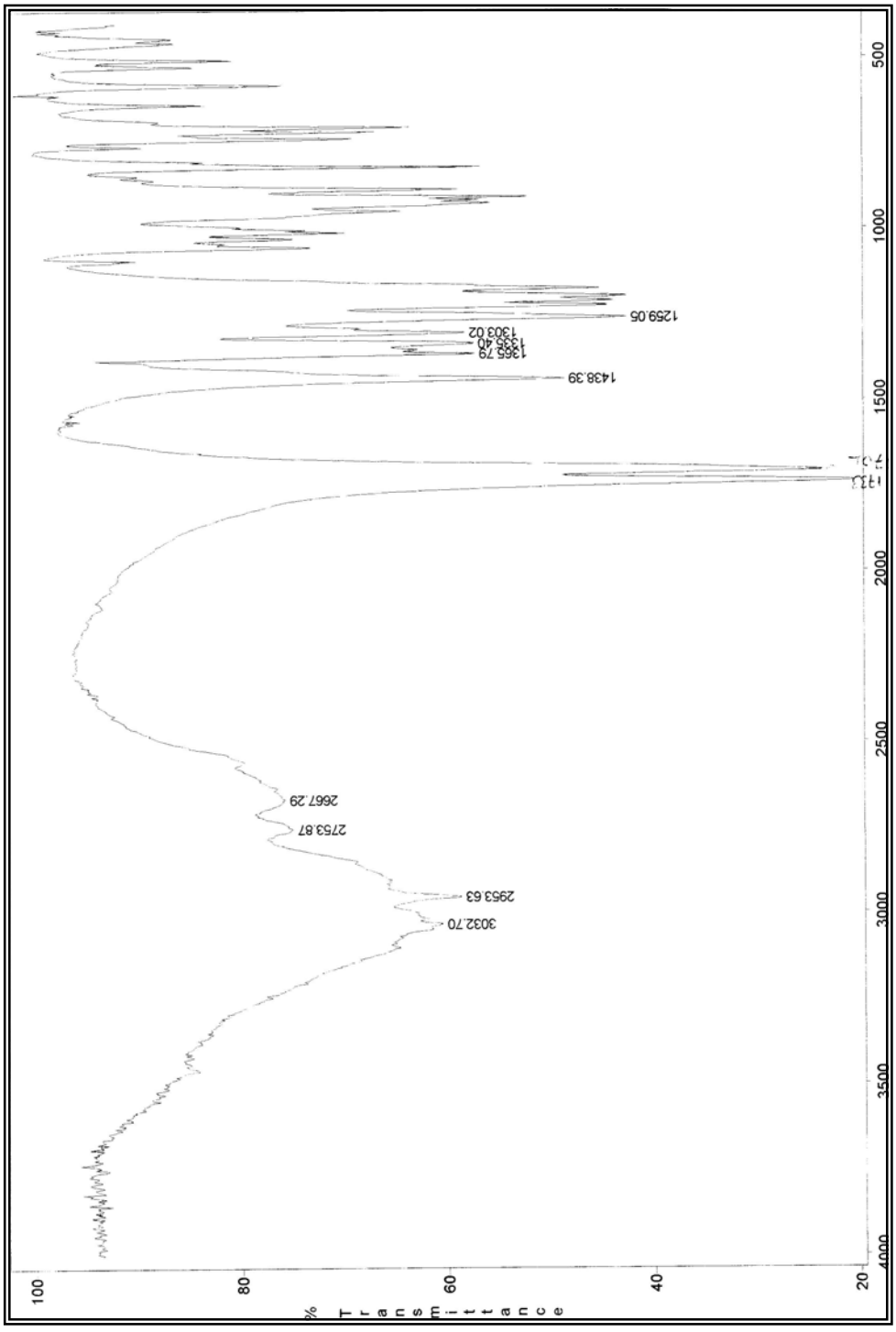

Figure 25. IR spectrum of compound **169**

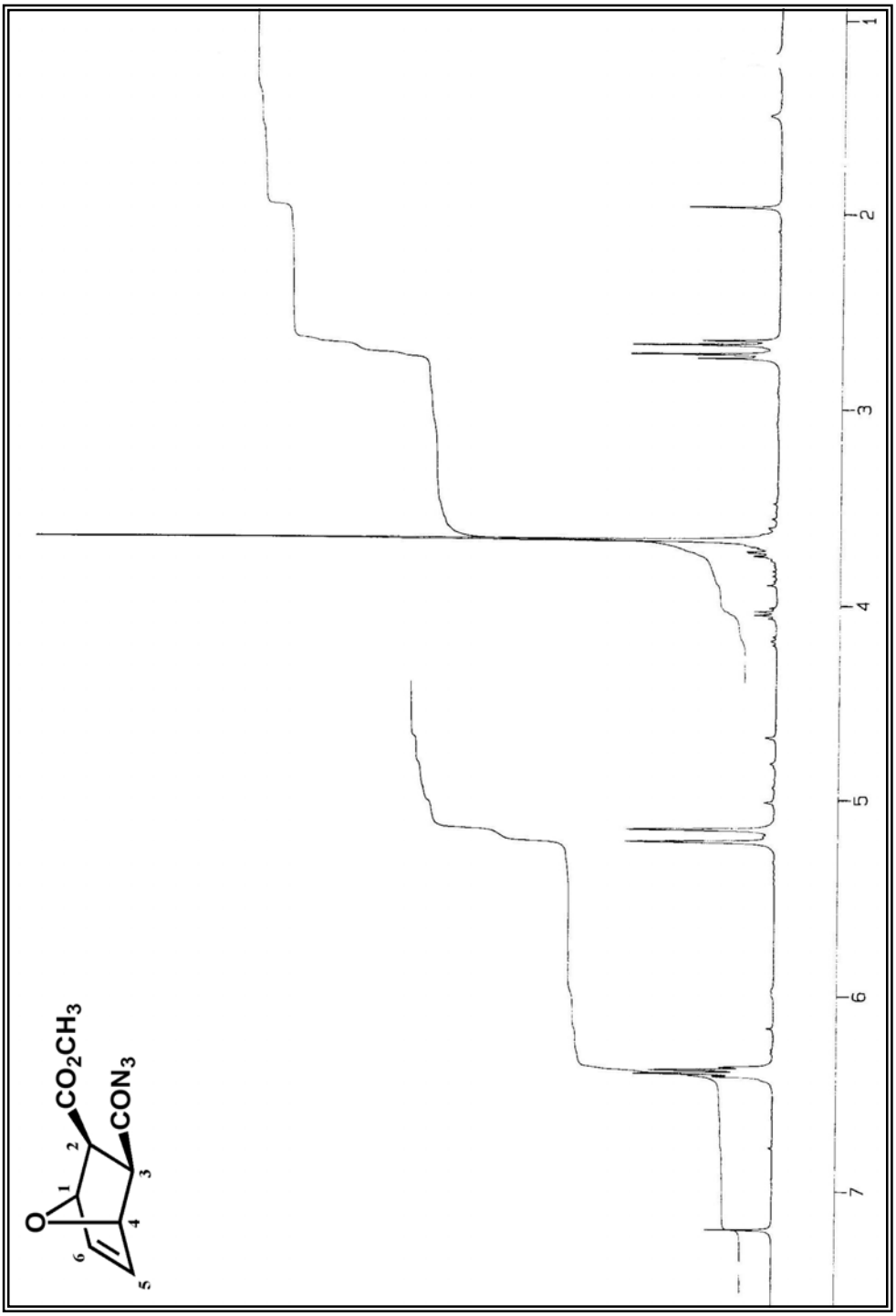

Figure 26. Structure and ^{1}H NMR spectrum of compound **171**

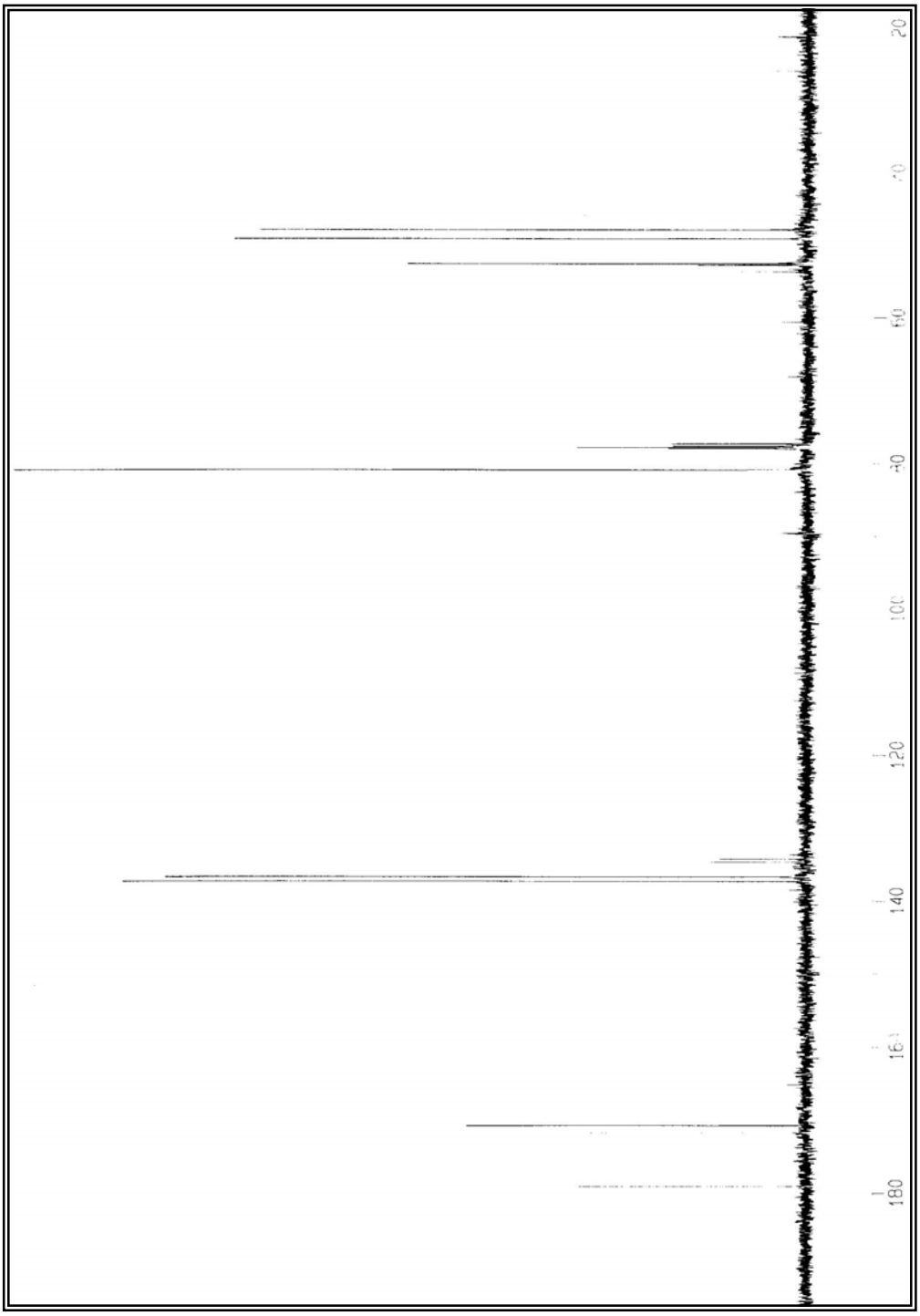

Figure 27. ^{13}C NMR spectrum of compound **171**

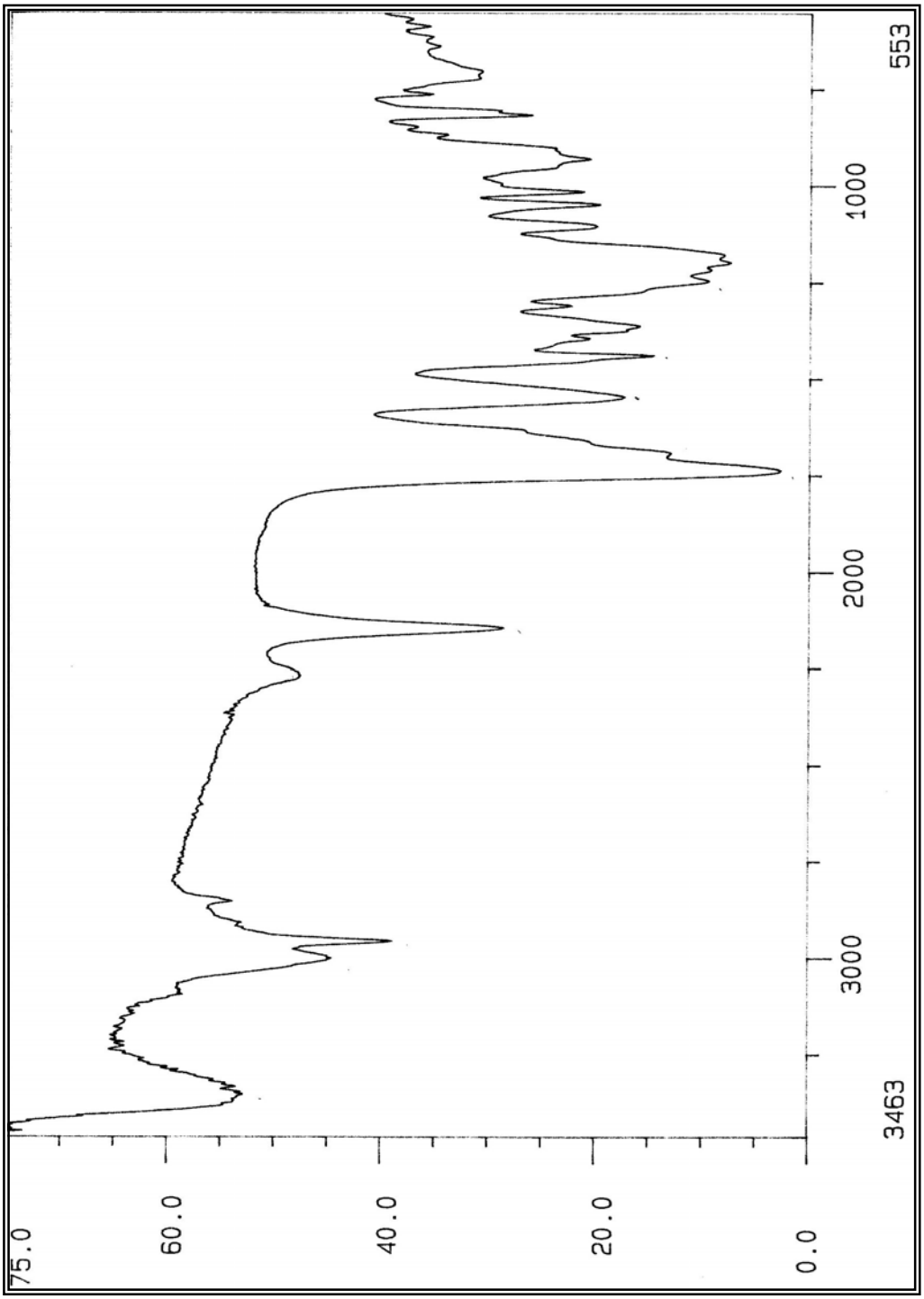

Figure 28. IR spectrum of compound **171**

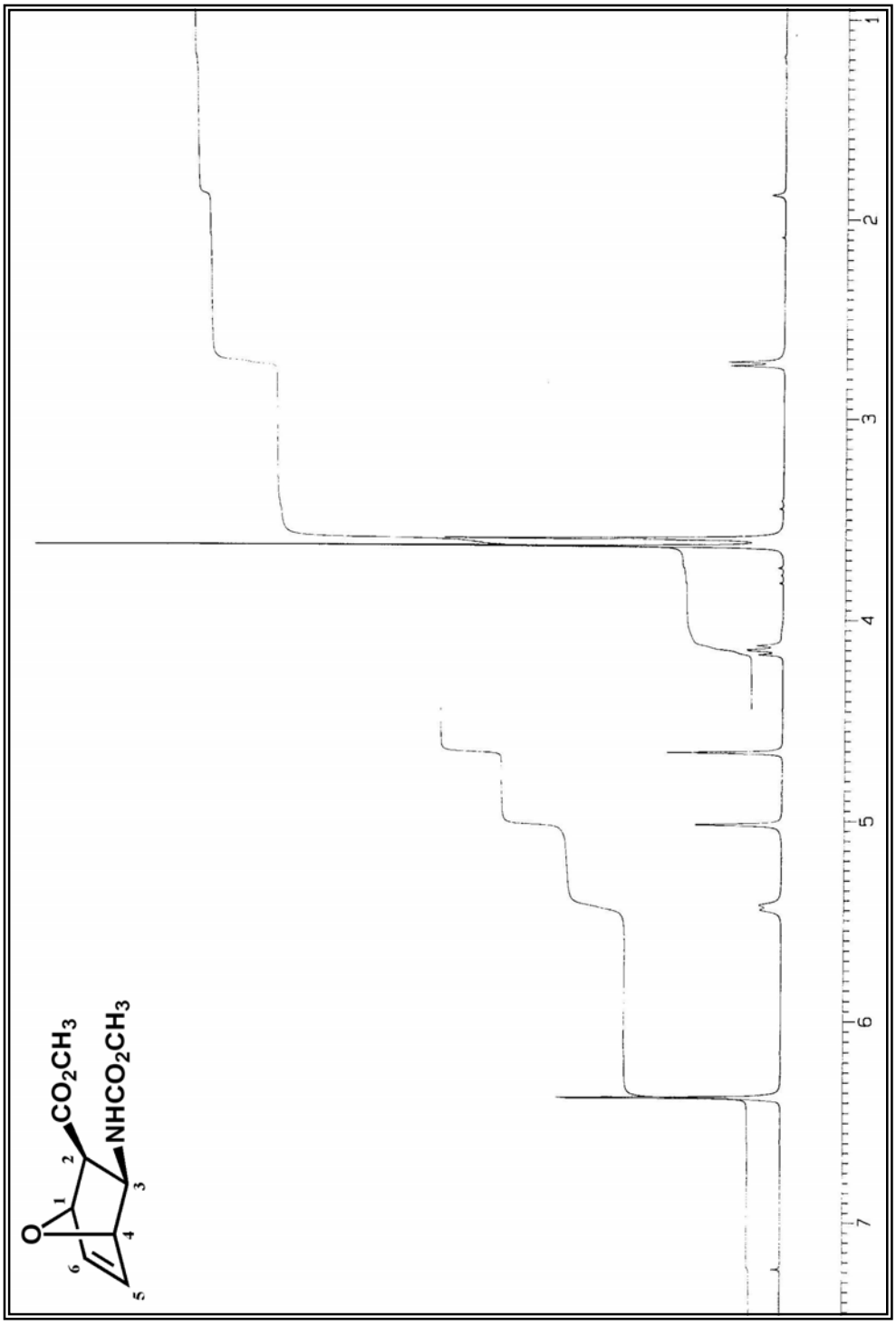

Figure 29. Structure and ^{1}H NMR spectrum of compound **152**

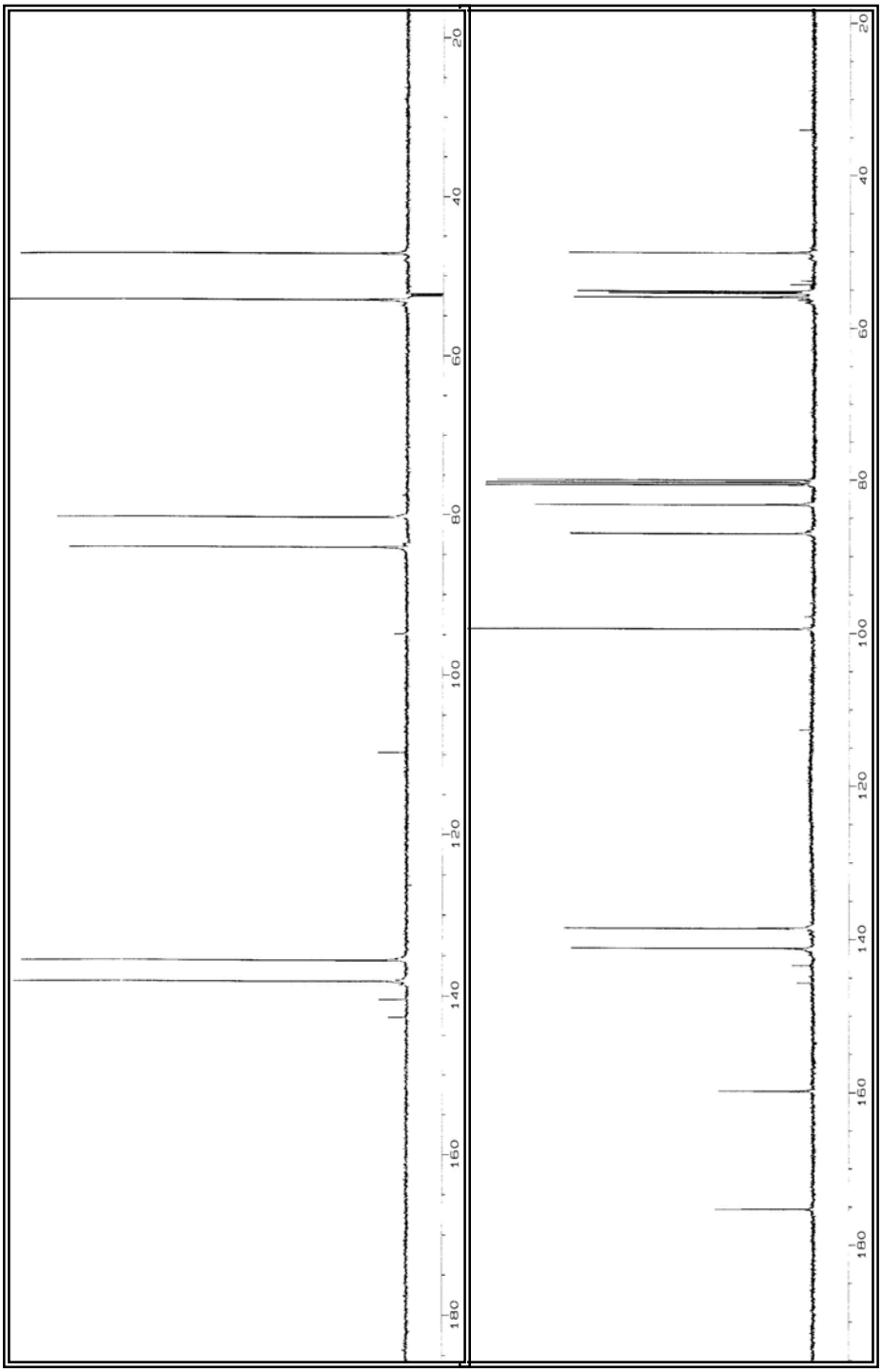

Figure 30. DEPT-90 and ^{13}C NMR spectra of compound **152**

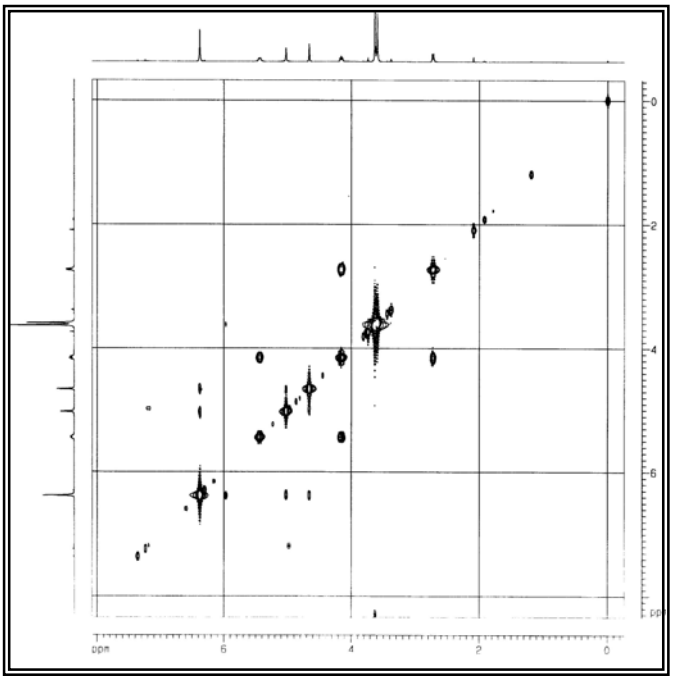

Figure 31. COSY spectrum of compound **152**

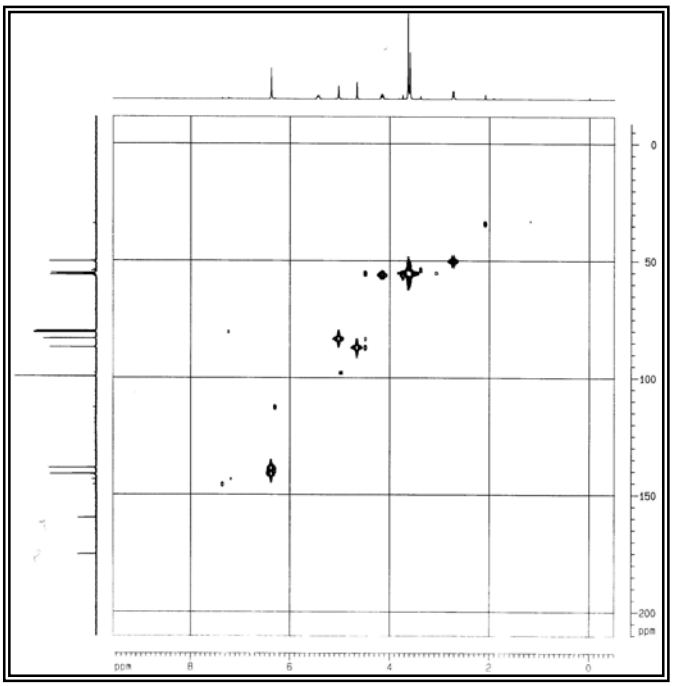

Figure 32. HMQC spectrum of compound **152**

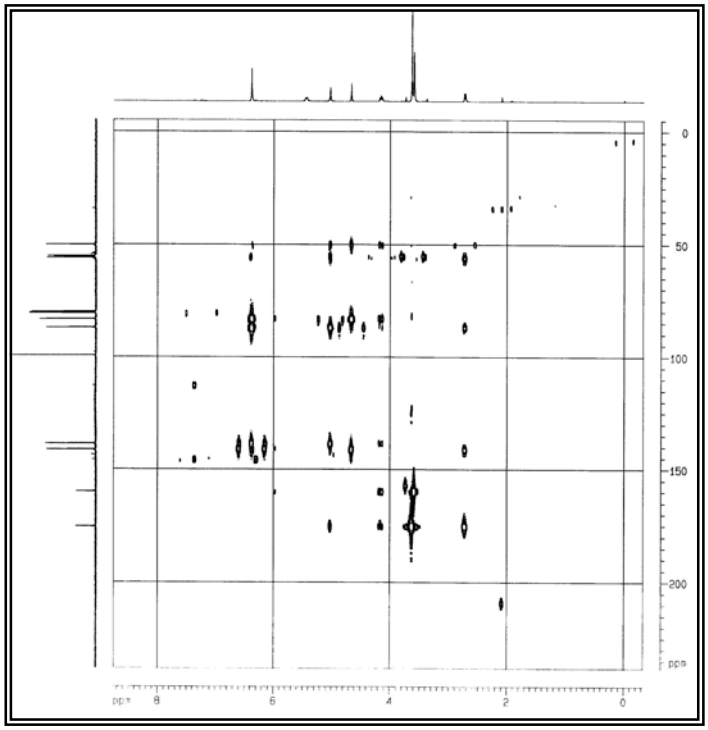

Figure 33. HMBC spectrum of compound **152**

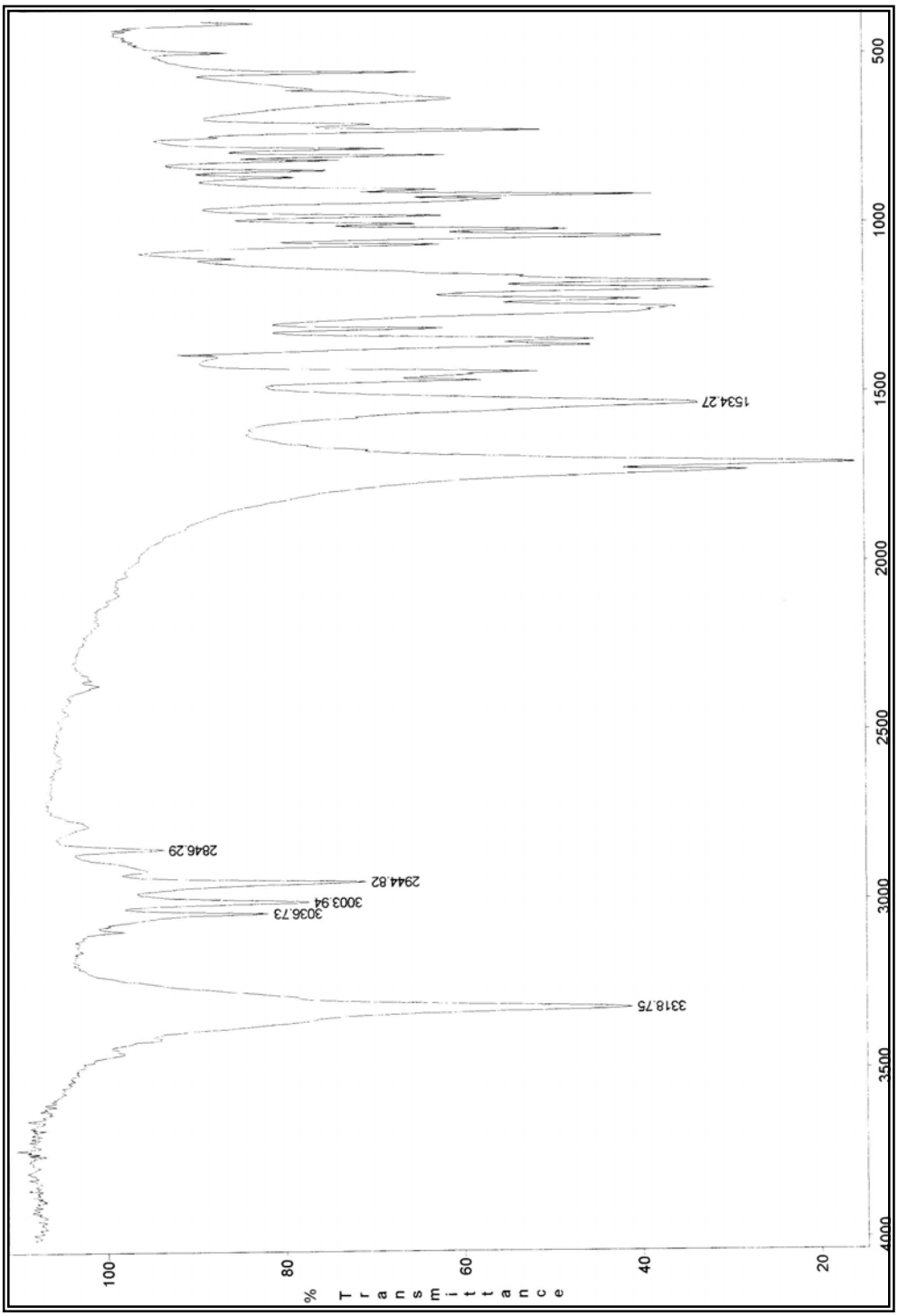

Figure 34. IR spectrum of compound **152**

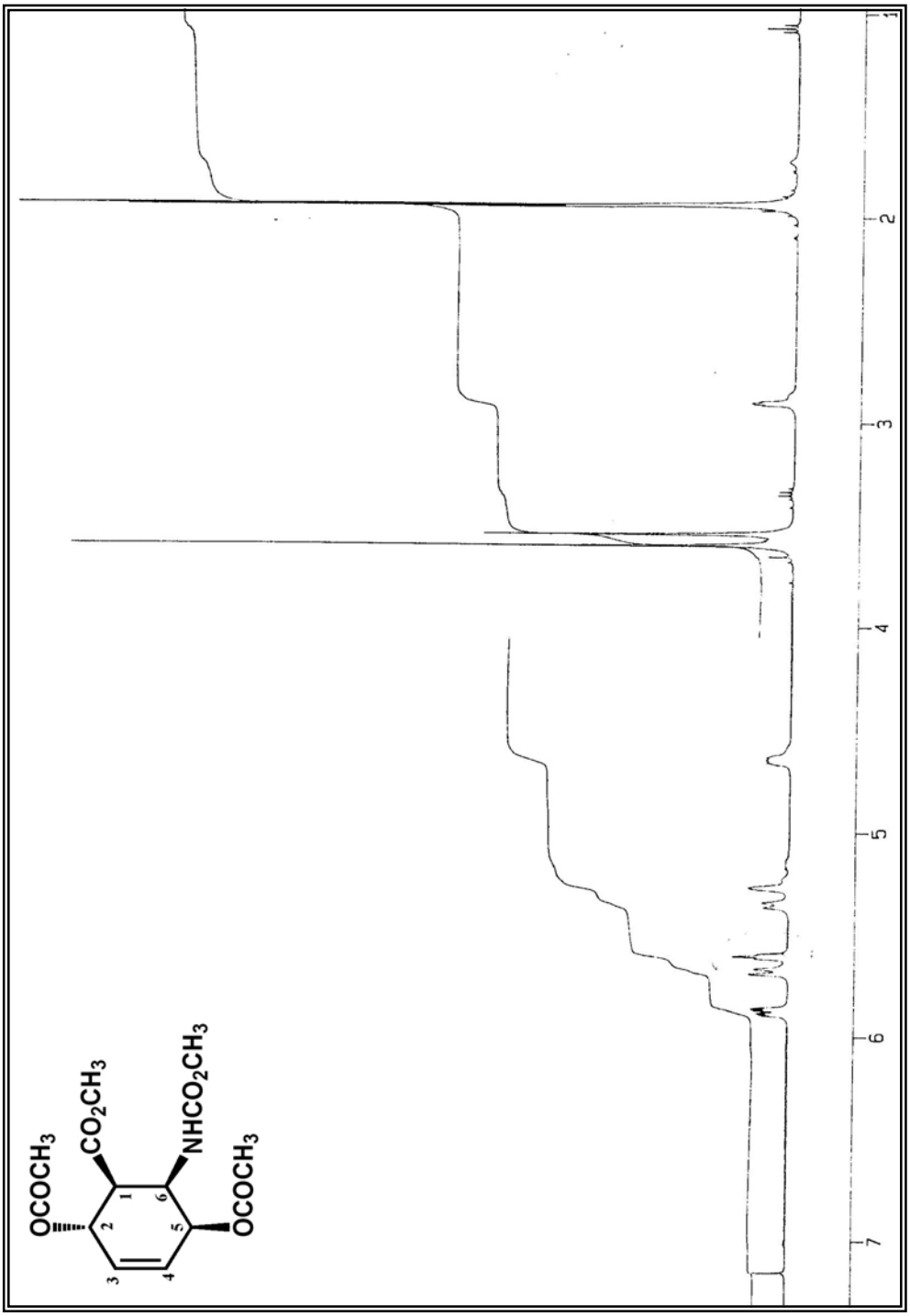

Figure 35. Structure and ^{1}H NMR spectrum of compound **173**

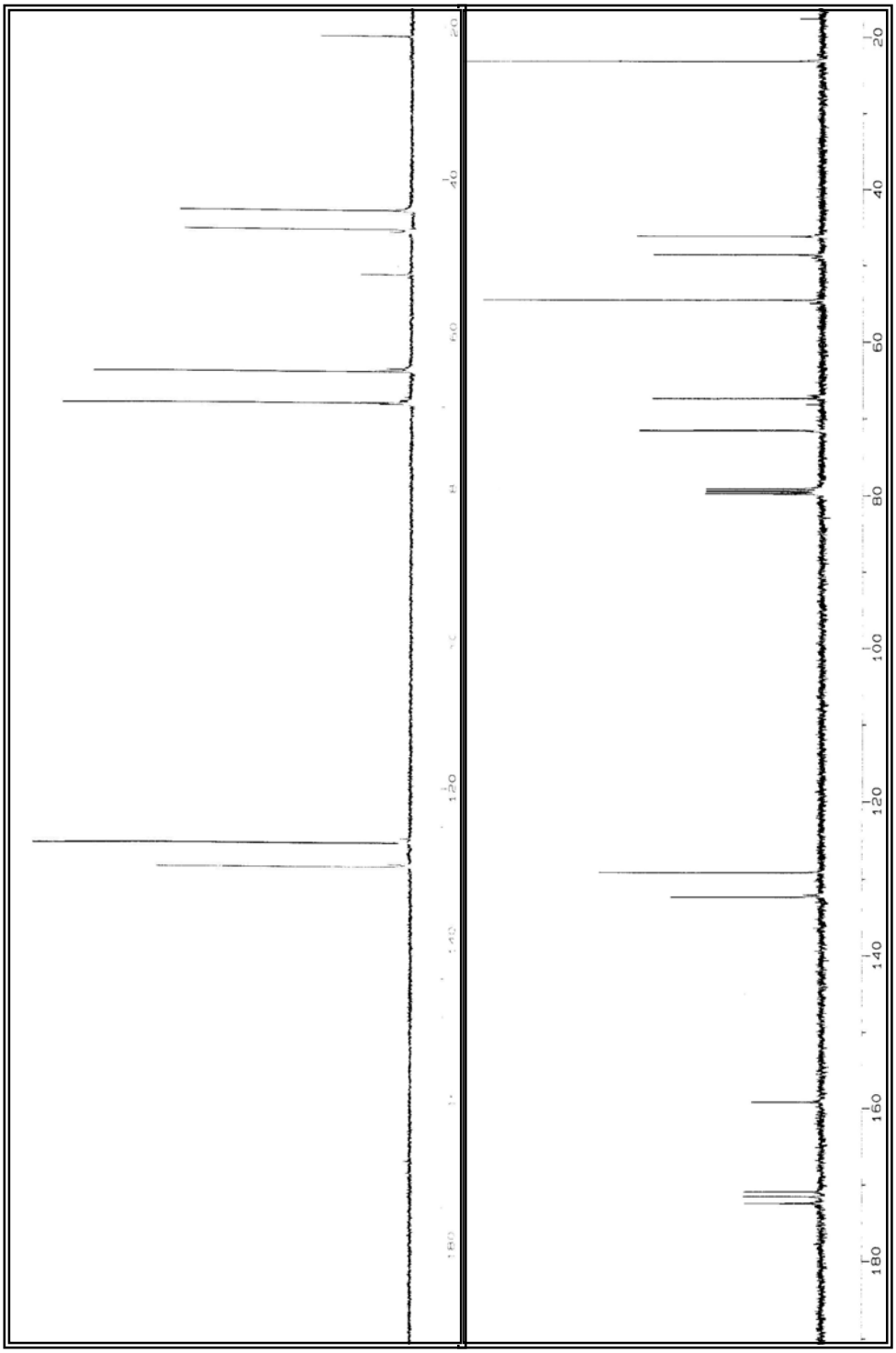

Figure 36. DEPT-90 and ^{13}C NMR spectra of compound **173**

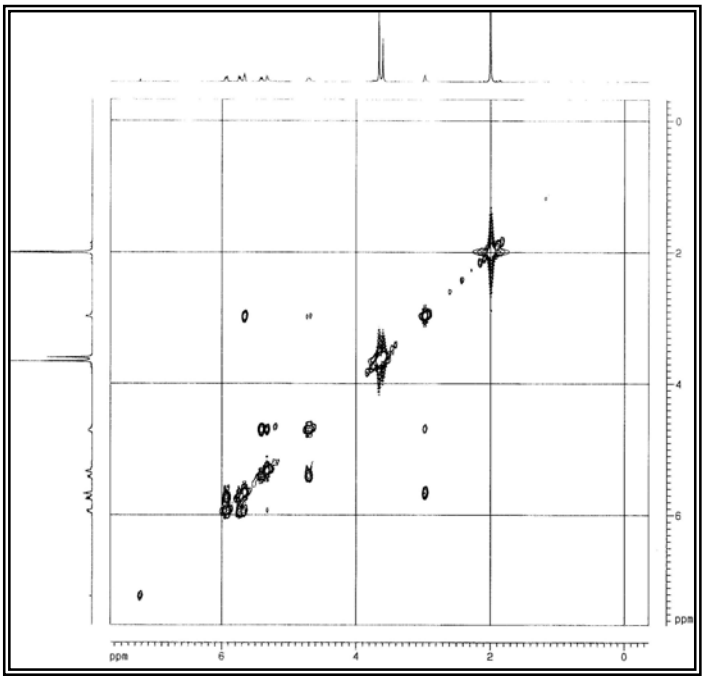

Figure 37. COSY spectrum of compound **173**

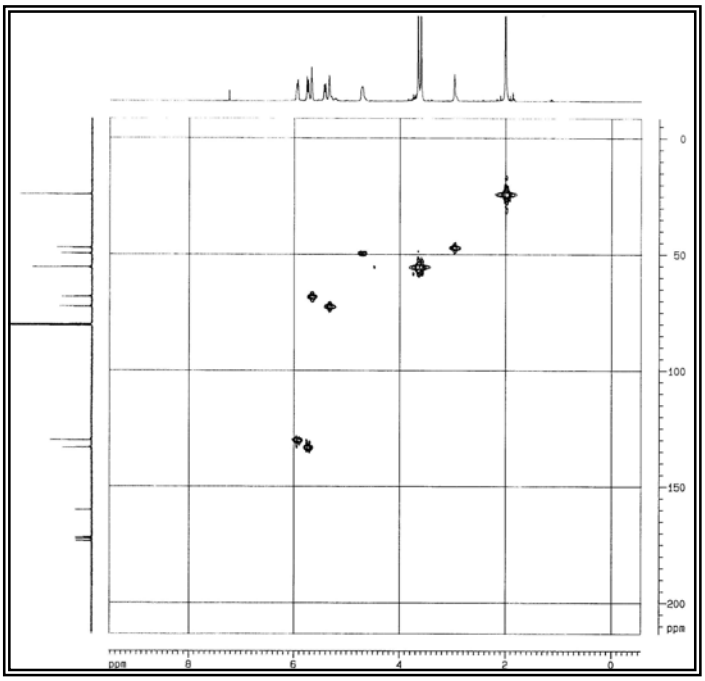

Figure 38. HMQC spectrum of compound **173**

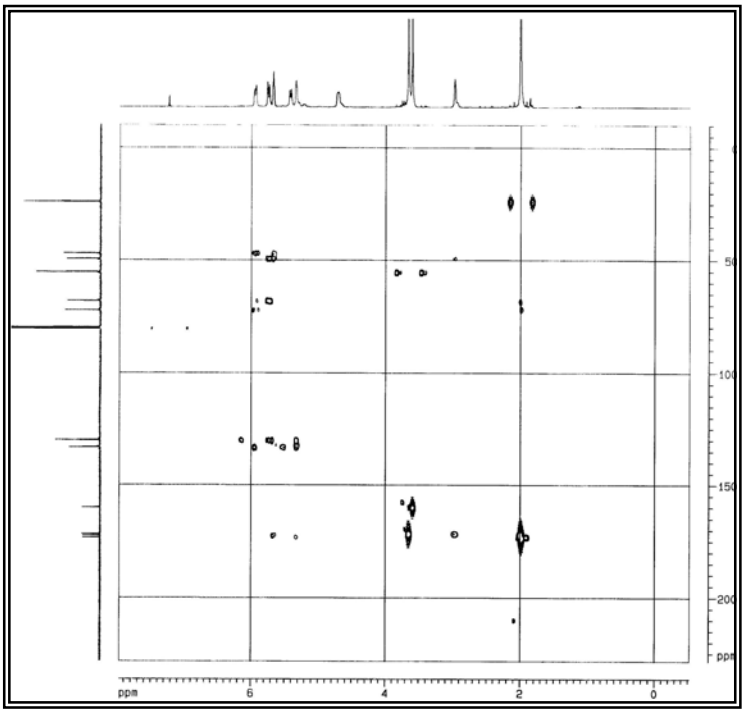

Figure 39. HMBC spectrum of compound **173**

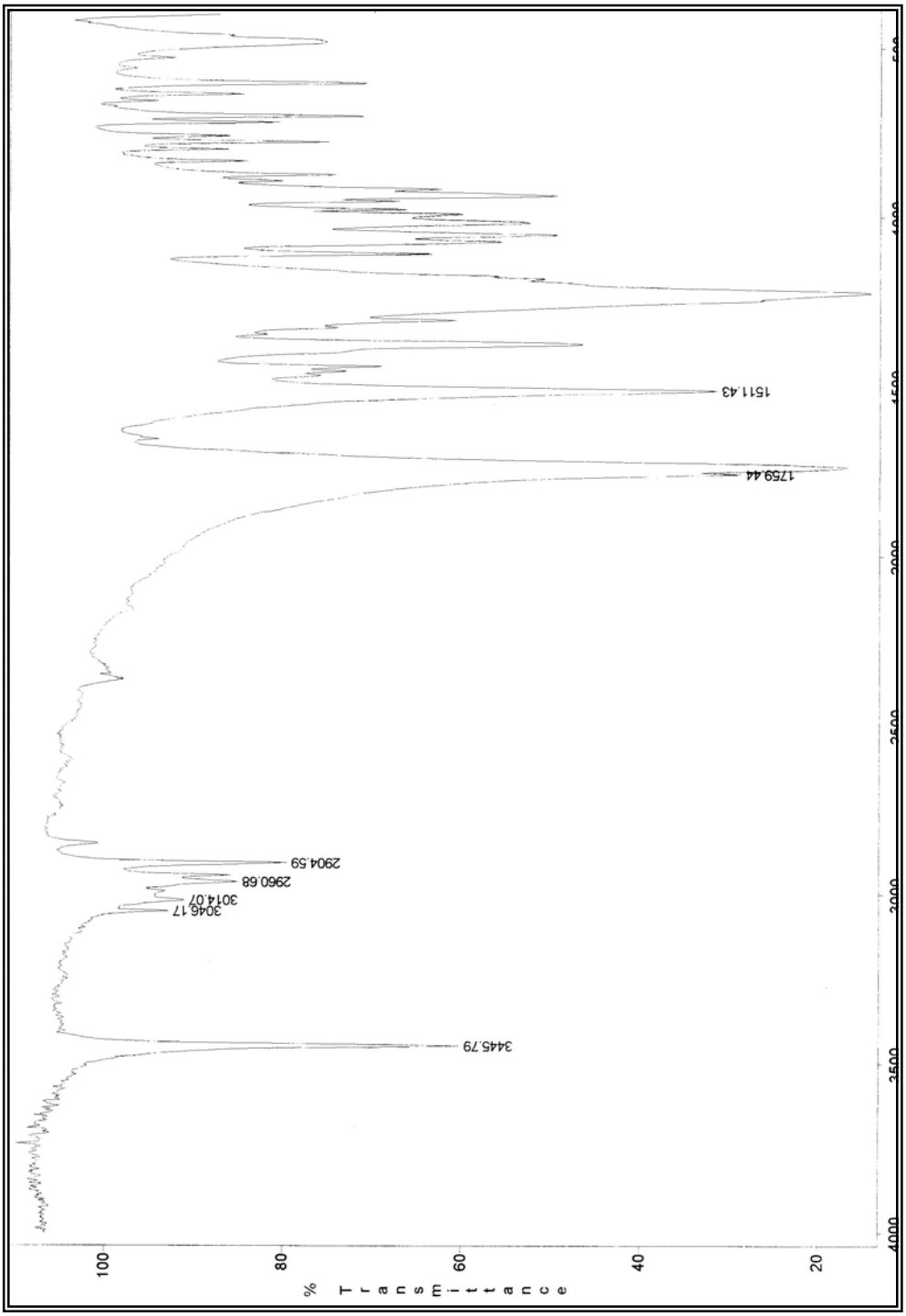

Figure 40. IR spectrum of compound **173**

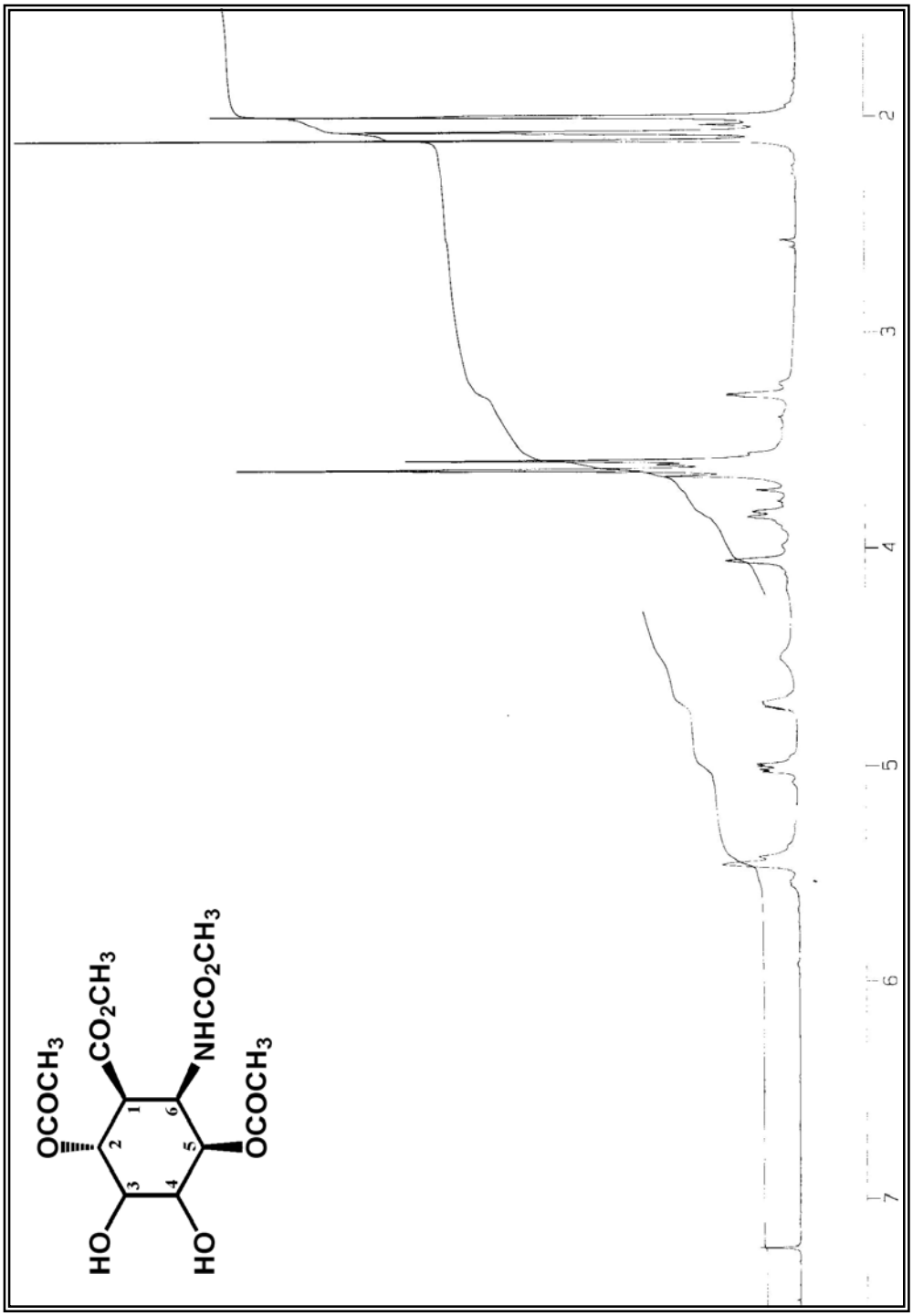

Figure 41. Structure and ^{1}H NMR spectrum of compound **174**

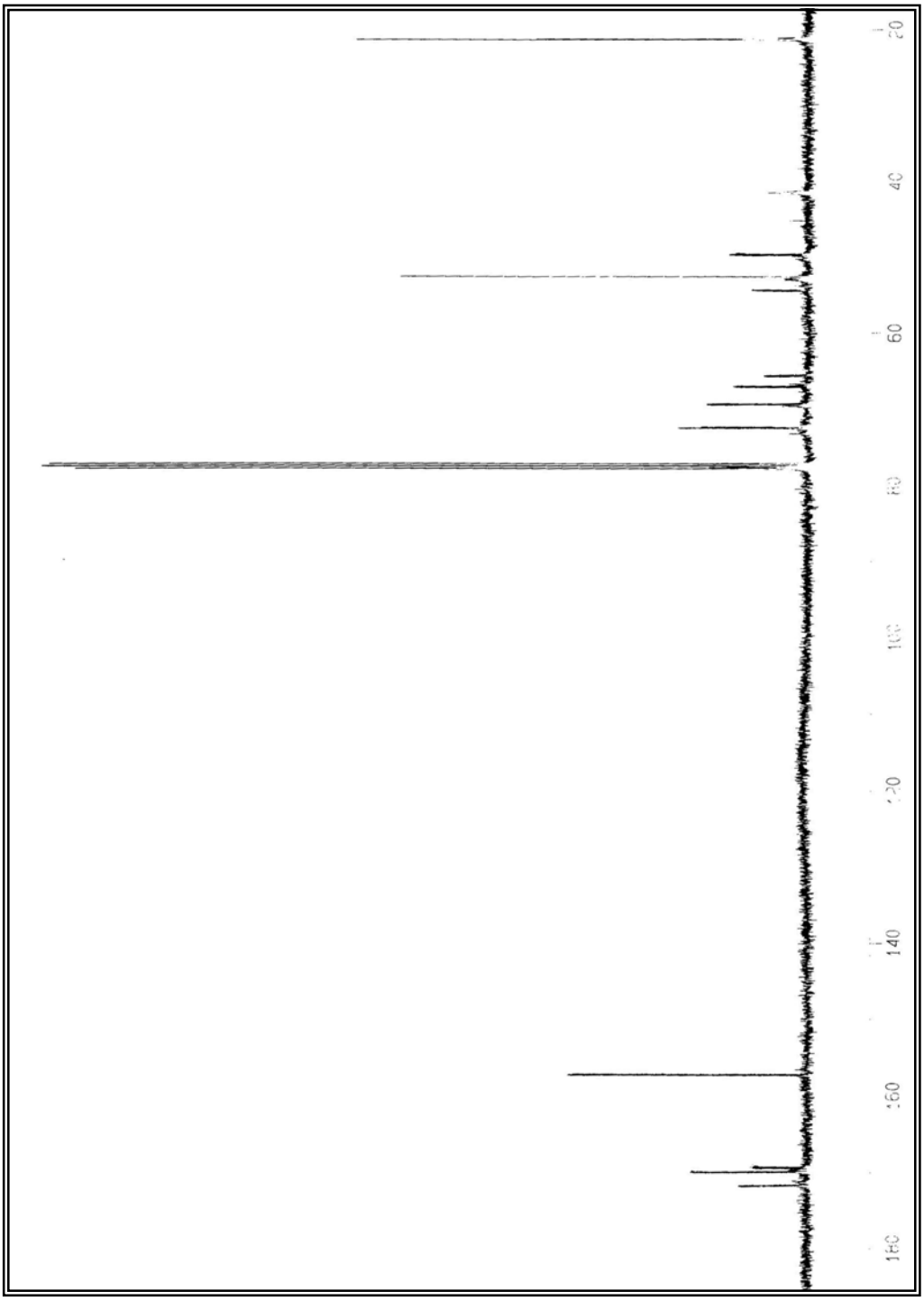

Figure 41. Structure and ^{1}H NMR spectrum of compound **174**