THE DEVELOPMENT OF THE NOVEL SYNTHESIS FOR CONDURITOLS

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

BY

SEDA CANTEKİN

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

SEPTEMBER 2006

Approval of the Graduate School of Natural and Applied Sciences

Prof. Dr. Canan Özgen
Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Prof. Dr. Hüseyin İşçi
Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

Prof. Dr. Metin Balcı
Supervisor

Examining Committee Members

Prof. Dr. Basri Atasoy (GAZİ UNV., CHEM EDUC.) _____
Prof. Dr. Metin Balcı (METU, CHEM) _____
Prof. Dr. Metin Zora (METU, CHEM) _____
Prof. Dr. İdris M. Akhmedov (METU, CHEM) _____
Assoc. Prof. Dr. Özdemir Doğan (METU, CHEM) _____

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

Name, Last Name: SEDA CANTEKİN

Signature :

ABSTRACT

THE DEVELOPMENT OF THE NOVEL SYNTHESIS FOR CONDURITOLS

CANTEKİN, Seda

M.S., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

September 2006, 120 pages

Conduritols have attracted a great deal of attention in recent years owing to biological activities exhibited by them and also their usefulness in the synthesis of other natural products and pharmaceuticals. Conduritols show interesting inhibitor activity for some glycosidases and serve as important intermediates in the synthesis of inositols. In this study, novel synthetic strategies leading to highly functionalized cyclohexene derivative containing an aromatic ring, namely phenyl-substituted conduritol was achieved successfully for the first time. As the starting material, substituted benzoquinone derivative, biphenyl-2-ol was used. Bromination of one double bond followed by the reduction of the carbonyl groups served the desired skeleton. Further substitution of the bromine atoms and functionalization of the remaining double bond opened up an entry for the synthesis of substituted conduritol and inositol derivatives. Moreover, by the use of hydroquinone as a starting material we developed new synthetic methodologies for the synthesis of another conduritol derivative, bromo-substituted conduritol for the first time. Oxidation of hydroquinone to the corresponding quinone followed by the bromination of one double bond gave the desired product. After the

reduction of the carbonyl groups and protection of the hydroxyl groups, the key compound for the synthesis of bromo-substituted conduritol was obtained. As a result, we enabled to synthesize new conduritol derivatives and we had considerable advance for the synthesis of other conduritol derivatives, inositols and quercitols.

Keywords: Inositol, Conduritol, Haloconduritol, Double Bond Substituted Conduritol, Tetrol.

ÖZ

KONDURİTOL TÜREVLERİNİN SENTEZLENMESİNDE
YENİ YÖNTEMLER

CANTEKİN, Seda
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2006, 120 sayfa

Konduritoller, çeşitli biyolojik aktivitelere sahip olmaları ve önemli doğal ürünlerin sentezinde çıkış bileşikleri olarak kullanılmaları nedeniyle, son yıllarda bilim adamlarının oldukça ilgisini çekmektedirler. Konduritoller glikozidaz enzimlerini inhibe etmekte ve inositol sentezinde önemli bir ara kademe olarak rol oynamaktadırlar. Bu çalışma çerçevesinde, aromatik halka içeren aşırı fonksiyonel grubun bağlı olduğu siklohekzen türevlerinden olan fenil sübstitüe konduritol'ün sentezi ilk kez gerçekleştirilmiştir. Çıkış bileşiği olarak sübstitüe benzokinon türevlerinden bifenil-2-ol kullanılmıştır. Çift bağlardan birinin brominasyonu ve karbonil gruplarının müteakip indirgenmesi ile arzu edilen iskelet oluşturulmuştur. Brom atomlarının sübstitüsyonu ve geri kalan çift bağın fonksiyonel hale getirilmesi sübstitüe konduritol ve inositol türevlerinin sentezi için yeni bir yöntem olmuştur. Daha sonra, hidrokinon çıkış bileşiği olarak kullanılmış ve bir diğer sübstitüe konduritol olan bromo-sübstitüe konduritol sentezlenmeye çalışılmıştır. Hidrokinon bileşiğinin kinona yükseltgenmesi ve kinon bileşiğindeki çift bağlardan birinin bromlanması ile arzu edilen bileşik elde

edilmiştir. Daha sonra karbonil gruplarının indirgenmesi ve hidroksil gruplarının korunması ile brom-sübstitüe konduritol'ün sentezinde önemli rol oynayan anahtar bileşik elde edilmiştir. Bu çalışma sonucunda yeni konduritol türevlerinin sentezi başarıyla gerçekleştirilmiş ve diğer konduritol türevlerinin, inositol ve kuersitollerin sentezlenmesinde aşamalar kaydedilmiştir.

Anahtar Kelimeler: İnositol, Konduritol, Halokonduritol, Sübstitüe-konduritol, Tetrol.

To a peaceful world…

ACKNOWLEDGEMENTS

I would like to present my feelings of gratitude to my supervisor Prof. Dr. Metin Balcı for his opening wide world of organic chemistry to me with a continuous guidance, endless support and patience. It was a great pleasure for me to learn many things about NMR spectroscopy, thus, to gain different aspects of the synthetic organic chemistry.

I wish to express my thanks to Dr. Raşit Çalışkan for his helps, encouragements and valuable critics throughout this study. It would be very difficult to achieve this hard work without feeling his being.

I deeply thank to NMR specialists Fatoş Polat Doğanel and Seda Karayılan for the NMR experiments. It was a great chance to work with those professional people.

I would like to thank to Seha Tirkeş who let me get all the IR spectra and I would like also thank to Asst. Prof. Dr. Ertan Şahin for the X-ray analysis.

I would like to express my special thanks to all the members of SYNTHOR® Research Group, especially to Nihal, Dilem and Sevil. It would not be possible to overcome difficulties without their close friendship and love.

The last but not the least, I would like to present my appreciation to my family, Ezgi, Selma and Orhan for their enduring a chemist at home with an endless love and support. I deeply thank to Umut Şekerdağ for his friendship, morale support and endless love.

TABLE OF CONTENTS

PLAGIARISM..... iii

ABSTRACT..... iv

ÖZ..... vi

ACKNOWLEDGEMENTS..... ix

TABLE OF CONTENTS..... x

LIST OF TABLES..... xiii

LIST OF FIGURES..... xiv

LIST OF ABBREVIATIONS..... xv

CHAPTER

1. INTRODUCTION..... 1

1.1. Cyclitols..... 1

1.2. Conduritols..... 1

1.3. Synthesis of Conduritols..... 2

1.3.1. Conduritol-A…..... 2

1.3.2. Conduritol-B…..... 6

1.3.3. Conduritol-C…..... 10

1.3.4. Conduritol-D…..... 14

1.3.5. Conduritol-E…..... 16

1.3.6. Conduritol-F…..... 19

1.3.7. Haloconduritols and Double Bond Substituted Conduritols..... 22

1.4. Biological Importance of Conduritols..... 24

1.5. Aim of the Study..... 27

2. RESULTS AND DISCUSSION

2.1. The Synthesis of 2-phenylbenzo-1,4-quinone **(138)**..... 28

2.2. The Synthesis f (5S(R),6S(R))-5,6-dibromo-2-phenylcyclo-hex-2-ene-1,4-dione **(139)**..... 29

2.3. The Synthesis of (1R(S),4R(S),5S(R),6S(R))-5,6-dibromo-2-phenylcyclohex-2-ene-1,4-diol **(140)**..... 30

2.4. The Synthesis of (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-5,6-dibromo-2- phenylcyclohex-2-en-1-yl acetate **(143)**..... 31
2.5. The Synthesis of (1S(R),4S(R),5R(S),6R(S))-4,5,6-tris-(acetyloxy)-2-phenylcyclohex-2-en-1-yl acetate **(144)**..... 35
2.6. The Synthesis of (1S(R),2R(S),3R(S), 4S(R))-5-phenylcyclo-hex-5-ene-1,2,3,4-tetrol (phenyl substituted conduritol-B) **(134)**..... 43
2.7. The Synthesis of 2-bromobenzene-1,4-diol **(150)**..... 44
2.8. The Synthesis of 2-bromobenzo-1,4-quinone **(151)**..... 45
2.9. The Synthesis of (5S(R),6S(R))-2,5,6-tribromocyclohex-2-ene-1,4-dione **(153)**..... 46
2.10. The Synthesis of (1R(S),4R(S),5S(R),6S(R))-2,5,6-tribromocyclohex-2-ene-1,4-diol **(154)**..... 47
2.11. The Synthesis of (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-2,5,6-tribromo-cyclohex-2-en-1-yl acetate **(155)**..... 47
3. EXPERIMENTAL
3.1. General Consideration..... 49
3.2. Synthesis of 2-phenylbenzo-1,4-quinone **(138)**..... 50
3.3. Synthesis of (5S(R), 6S(R))-5,6-dibromo-2-phenylcyclohex-2-ene-1,4-dione **(139)**..... 50
3.4. Synthesis of (1R(S),4R(S),5S(R),6S(R))-5,6-dibromo-2-phenylcyclohex-2- ene-1,4-diol **(140)**..... 51
3.5. Synthesis of (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-5,6-dibromo-3-phenyl-cyclohex-2-en-1-yl acetate **(143)**..... 51
3.6. Synthesis of (1S(R),4S(R),5R(S),6R(S))-4,5,6-tris-(acetyloxy)-2-phenylcyclohex-2-en-1-yl acetate **(144)**..... 52
3.7. Synthesis of (1S(R),2S(R),3R(S),4R(S))-5-phenylcyclohex-5-ene-1,2,3,4- tetrol (phenyl-substituted conduritol-B) **(134)**..... 53
3.8. Synthesis of 2-bromobenzene-1,4-diol **(150)**..... 53
3.9. Synthesis of 2-bromobenzo-1,4-quinone **(151)**..... 54

3.10. Synthesis of (5S(R),6S(R))-2,5,6-tribromocyclohex-2-ene-1,4-dione **(153)** 54
3.11. Synthesis of (1R(S),4R(S),5S(R),6S(R))-2,5,6-tribromocyclohex-2-ene-1,4-diol **(154)** 55
3.12. Synthesis of (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-2,5,6-tribromo-cyclohex-2-en-1-yl acetate **(155)** 56
4. CONCLUSION 57
REFERENCES 58
APPENDICES 61

LIST OF TABLES

TABLES

Table 1 Selected bond lengths, angles and torsion angles for **143**..... 34

Table 2 Selected bond lengths, angles and torsion angles for **144**..... 41

Table 3 Final Coordinates and Equivalent Isotropic Displacement for **144**..... 42

LIST OF FIGURES

FIGURES

Figure 1	Important Cyclitols……...	1
Figure 2	Conduritol Isomers ……..……...	2
Figure 3	Reduction mechanism of compound **139**…….....	31
Figure 4	Ortep structure of compound **143**…….	33
Figure 5	Molecular packing of the compound **143**…….	34
Figure 6	Ortep structure of compound **144**…….	40
Figure 7	Molecular packing of the compound **144**…….	40

LIST OF ABBREVIATIONS

COSY	: Correlation spectroscopy
DEPT	: Distortionless enhancement by polarization transfer
DMSO	: Dimethylsulfoxide
E. Coli	: Escherichia Coli
GC/MS	: Gas chromatography and mass spectrum
HMBC	: Heteronuclear multi-bond coherence
HMQC	: Heteronuclear multiple quantum coherence
Hz	: Hertz
IR	: Infrared
J	: Coupling constant
NIS	: N-iodo succinimide
NMR	: Nuclear magnetic resonance
p-putida	: Pseudomonas-putida
ppm	: Parts per million

CHAPTER 1

INTRODUCTION

1.1 CYCLITOLS

The word cyclitol refers to cyclic polyalcohols with a cyclohexane skeleton. Cyclitols can be analyzed in three main parts; conduritols **(1)**, quercitols **(2)**, and inositols **(3)** (Fig. 1). During the last decade, cyclitols have been very interesting molecules among chemists as well as biologists owing to their synthetic diversity and biological activity [1].

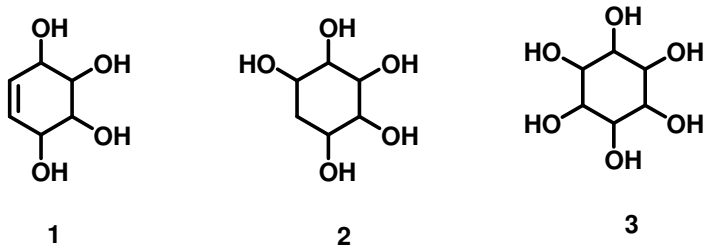


Figure 1. Important Cyclitols

Inositols play an important role in signal transduction in living organisms. They act as cell mediators. Quercitols constitute a large group of stereoisomeric family, some of which were isolated as natural products. Conduritols and their derivatives is of great deal of interest due to their glycosidase inhibitory activity and antibiotic effects [2].

1.2 CONDURITOLS

In 1908, a new alcohol was isolated from a bark of a vine, *Marsdenia condurango* and it was named as *conduritol* by Kübler. Kübler's conduritol was optically inactive and it had unsaturated cyclic constution. Its constution and configuration were later established by Dangschat and Fischer as conduritol-A **(4)** [3].

Theoretically there are six diastereomers of conduritols. To avoid confusion, they are named as A, B, C, D, E and F (Fig. 2). Conduritol A and D are meso compounds whereas other conduritols B, C, E and F are found as enantiomeric pairs. Within this group, only conduritol-A and conduritol-F are abundant in nature. Inspite of the fact that conduritol-F is abundant in almost all green plants, conduritol-A is only found in trace amonts [4].

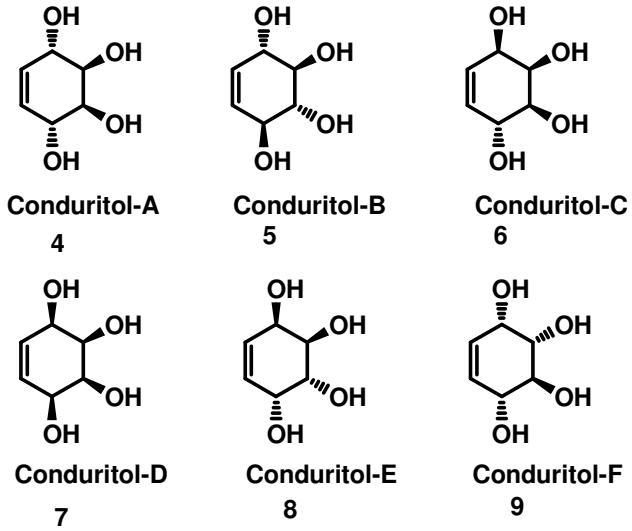


Figure 2. Conduritol Isomers

In 1962, another conduritol isomer was discovered by Plouver from *Crysanthemum Leucanthemum* and it was named as L-Leucanthemitol, Conduritol F **(9)** [3].

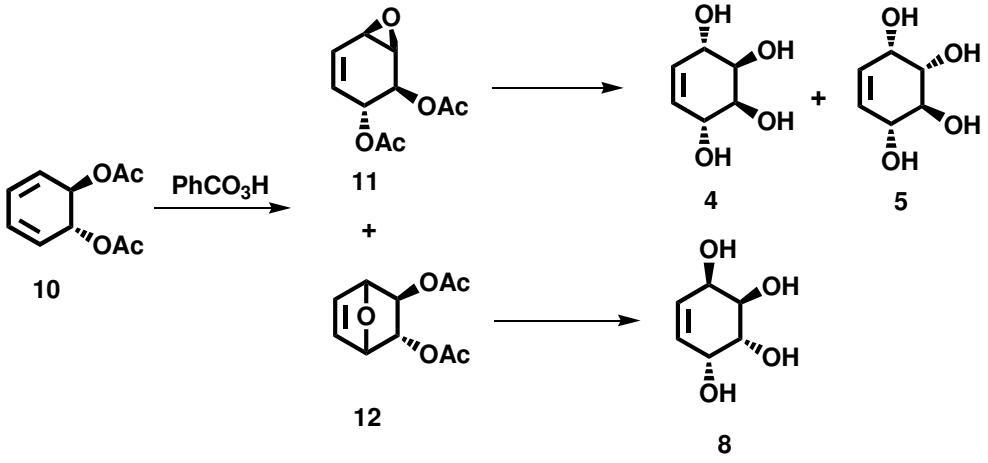
Conduritols have many biological properties and they are valuable precursors of many biologically important molecules [5].

1.3 SYNTHESIS OF CONDURITOLS

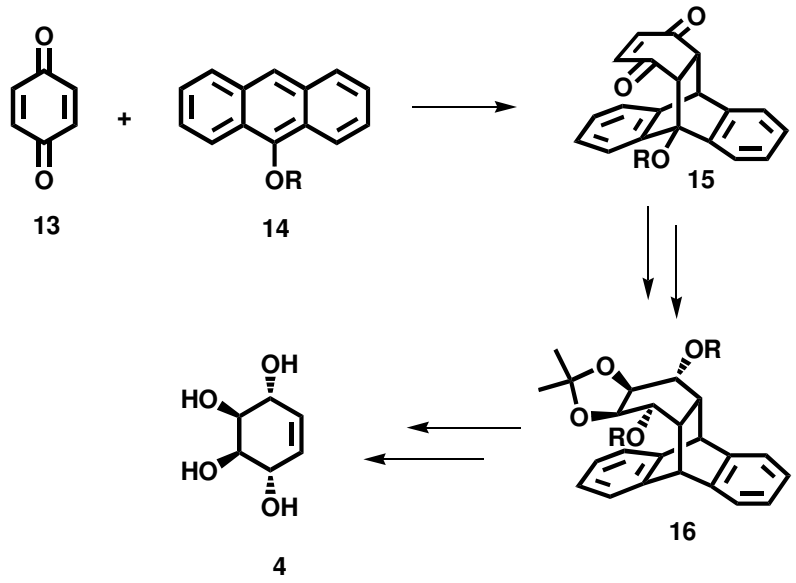
1.3.1 CONDURITOL-A

As mentioned before conduritol-A is a natural product and it was first isolated by Kübler in 1908. The first succesful and non-stereospecific synthesis of conduritol-A was carried out by Nakajima *et al*. [6]. Nakajima used *trans*-diacetate **10** for the

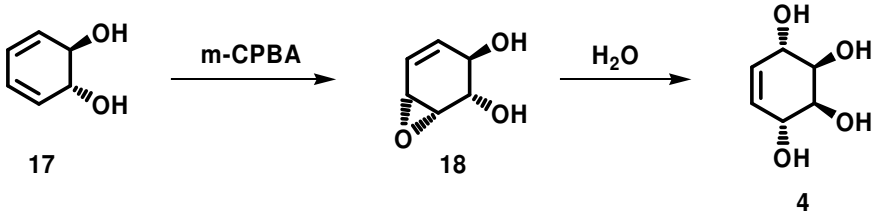
synthesis of conduritol isomers for the first time. Oxidation of diacetate **10** with perbenzoic acid gave a mixture of compounds **11** and **12**. Without separation, this mixture was hydrolized and three isomeric conduritols; A, B and E, **4**, **5**, **8** were obtained.



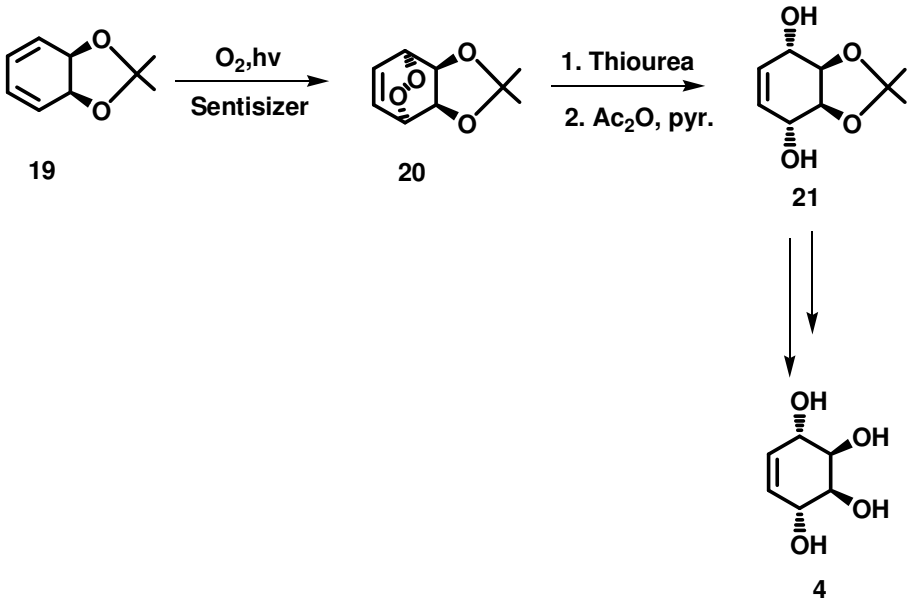
Knapp and coworkers reported a stereoselective synthesis for conduritol-A starting from *p*-benzoquinone **(13)** and an anthracene derivative **14** [7]. The reduction of Diels-Alder adduct **15** is followed by the oxidation of the double bond by osmium tetroxide to form **16**. Deprotection followed by retro-Diels-Alder reaction of **16** resulted in the formation of conduritol-A **(4)**. By using anthracene derivative as a protecting group, they also blocked one face of *p*-benzoquinone in order to direct *cis* reduction of two carbonyl carbons and *cis* functionalisation of the remaining double bond.



Aleksejczyk and Berchtold described a new synthesis of conduritol-A from *trans*-benzenediol **17** [8]. Epoxidation of **17** with *m*-chloroperbenzoic acid provided **18** and solvolysis of **18** in water at room temperature for several days gave conduritol-A **(4)**.

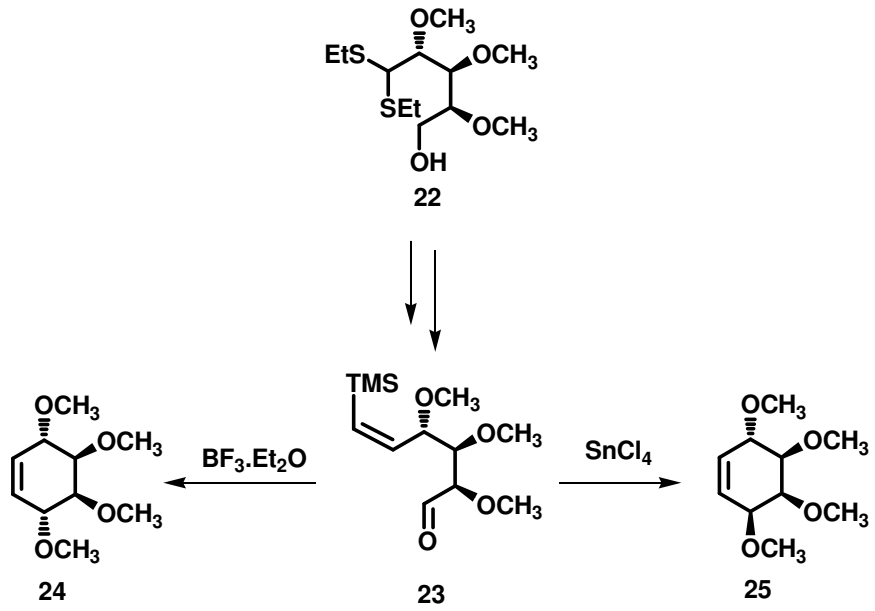


Balcı *et al.* developed a new, efficient and stereospecific synthesis of conduritol-A [9]. They added singlet oxygen to the protected *cis*-benzenediol **19** and obtained only one *endo*-peroxide **20** in high yield. The selective cleavage of peroxide was achieved by thiourea. After hydrolysis of the ketal **21**, conduritol-A **(4)** was isolated.

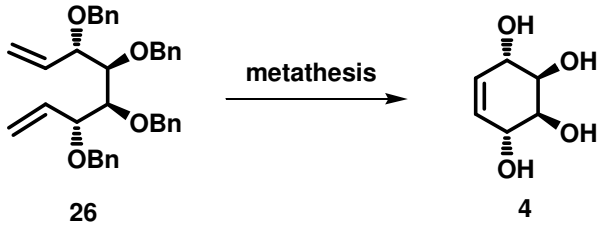


19 20 21 4

A novel method was reported by McIntosh and Weinreb for the synthesis of conduritol-A and C derivatives from the same key compound which was derived from dithioacetal trimethyl ether **22** [10]. Treatment of vinylsilane-aldehyde **23** with $BF_3.Et_2O$ gave tetraacetate of conduritol-A **(24)**. On the other hand, when vinylsilane-aldehyde **23** was reacted with $SnCl_4$, tetraacetate of conduritol-C **(25)** became the only product.



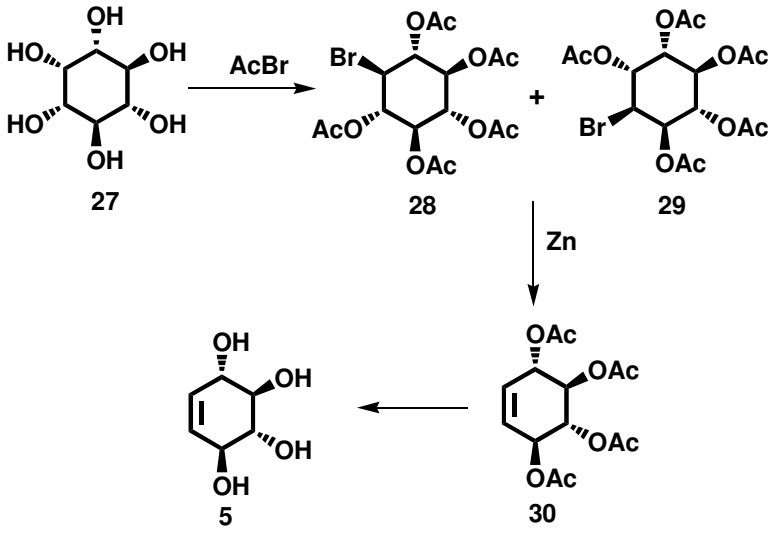
Recently, ring-closing olefin metathesis (RCM) has become a powerful technique for the asymmetric conduritol synthesis. Gallos *et al.* and Fürstner *et al.* synthesized independently conduritol-A, E and F by using this method [11,12] The diene **26** was synthesized starting from galactitol, D-mannitol and D-glucitol respectively. Conduritol-A **(4)** was obtained with a yield of 99% by this method.



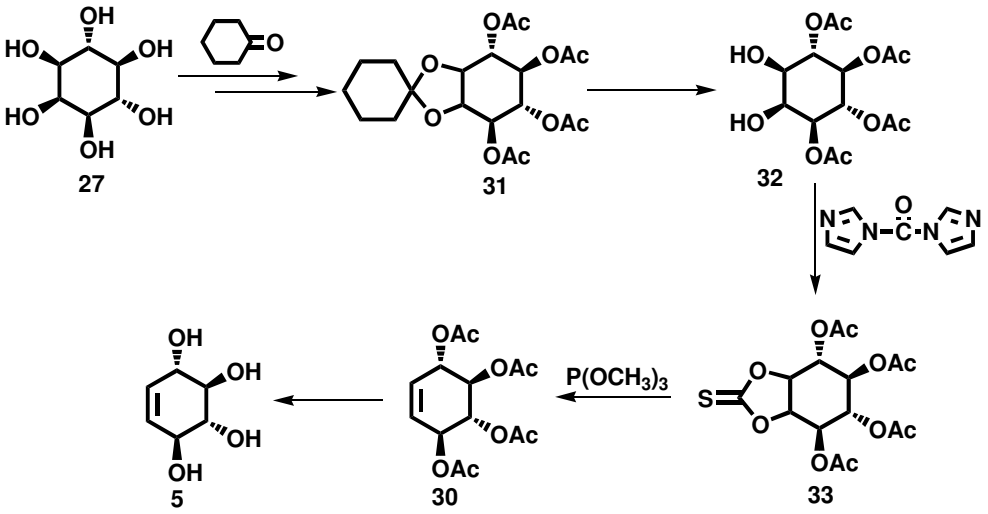
1.3.2 CONDURITOL-B

There are numerous studies on the synthesis of conduritol and its derivatives starting from a suitably substituted cyclitols like inositol and quercitol. For example, Müller synthesized conduritol-B from pentaacetate of 6-bromoquercitol **(28)** on treatment with zinc in acetic acid [13]. The results were reinvestigated by McCasland and Horswill [14]. They prepared two different bromoquercitols **28** and **29** by the reaction of *myo*-inositol **(27)** with acetyl bromide. The elimination

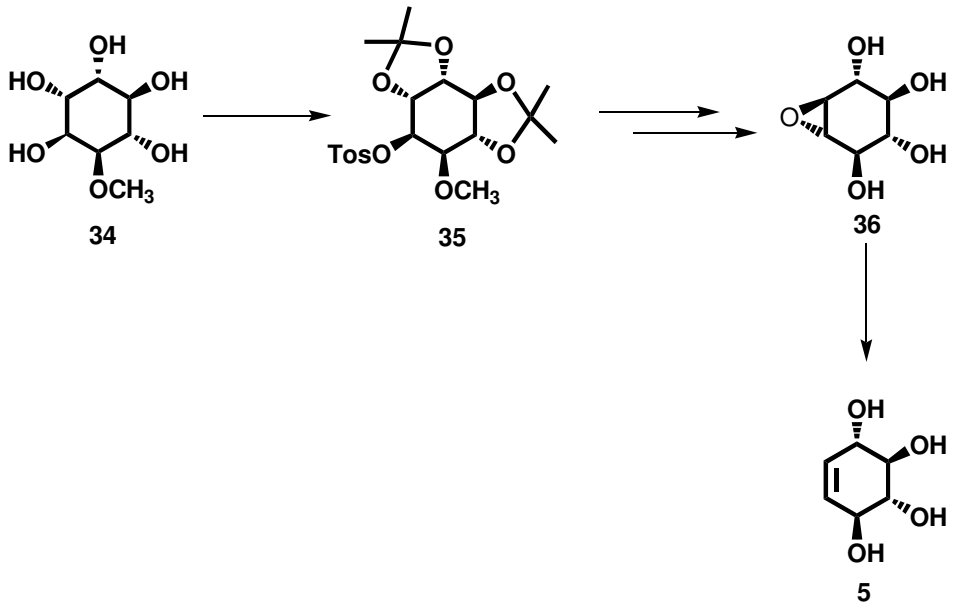
of bromine atoms gave the tetraacetate of conduritol-B **(30)** After the hydrolysis of acetyl groups, conduritol-B **(5)** was synthesized in a high yield.



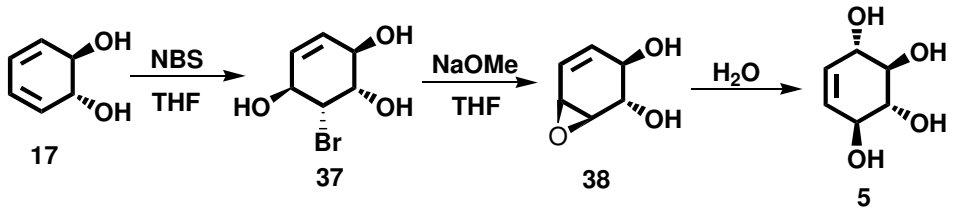
As mentioned in previous section, conduritol-A, B and E were synthesized as a mixture by Nakajima *et al*. After that, Nagabhushan developed another method for the synthesis of conduritol-B by using 1,4,5,6-tetra-O-acetylmyoinositol **(31)** [15]. Condensation of *myo*-inositol **(27)** with cyclohexanone gave 1,2-O-cyclohexylidene *myo*-inositol **(31)**. By acetylation and subsequent deketalisation, intermediate **32** was obtained. Application of Corey and Winter method on **32** with N,N'-thiocarbonyldiimidazole resulted in the formation of thiocarbonate **33**. Treatment of **33** with trimethylphosphite gave tetraacetate of conduritol-B **(30)** which was then converted to conduritol-B **(5)** *via* hydrolysis.



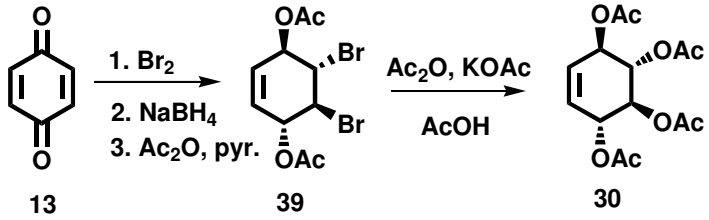
All synthesis leading to conduritol-B yielded a racemic mixture. An enantioselective synthesis of conduritol-B was described by Paulsen *et al* [16]. They also made use of an inositol derivative, quebrachitol **34** for the synthesis of the target molecule. The key intermediate **35** was first reduced by 3-methyl-2-(selenoxo)benzothiazole and oxidized to obtain epoxide **36** followed by several steps giving conduritol-B **(5)** in high yield. Akiyama and Ozaki reported the synthesis of conduritol-B and F by using the same starting material quebrachitol **34** and a similar pathway [17].



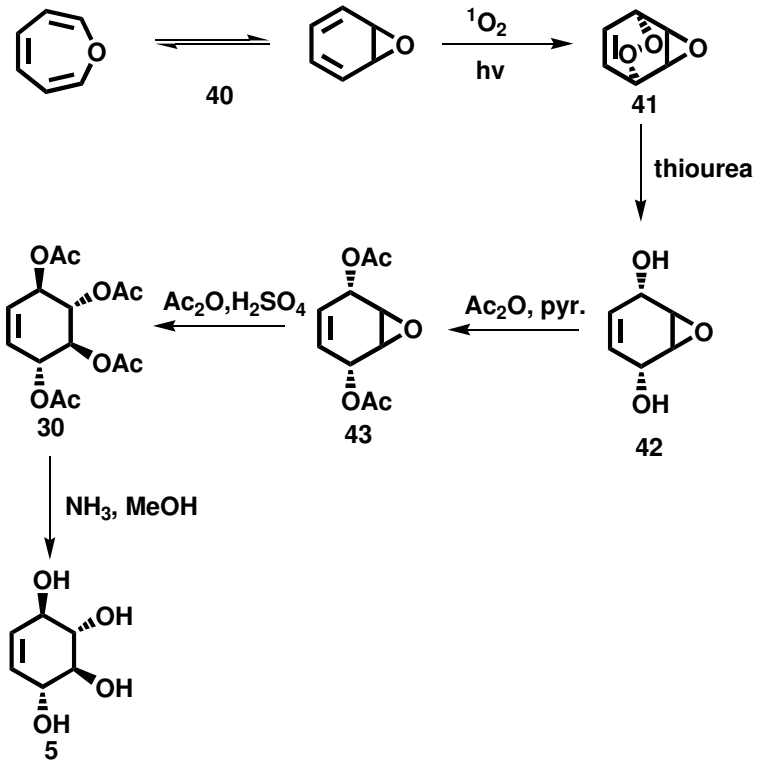
In addition to inositol derivatives, dihydrobenzene diol **17** was also used as a starting material for the synthesis of conduritol-B. Berchtold prepared bromide **37** by treating **17** with N-bromosuccinimide in aqueous THF [8]. The configuration of product **37** was established by X-ray crystal structure determination. Dehydrobromination of **37** gave compound **38** which was then converted into conduritol-B **(5)** in water.



Taylor *et al*. developed a simple synthetic pathway leading to the synthesis of racemic (±)-conduritol-B tetraacetate **(30)** starting from *p*-benzoquinone **(13)** [18]. Bromination of **13** at low temperature gave a dibromo compound. Carbonyl groups in this compound were reduced and hydroxyl groups were protected to form diacetoxybromide **39.** Substitution of bromine atoms in **39** by heating with potassium acetate and acetic anhydride in refluxing acetic acid gave (±)-conduritol-B tetraacetate **(30)**.

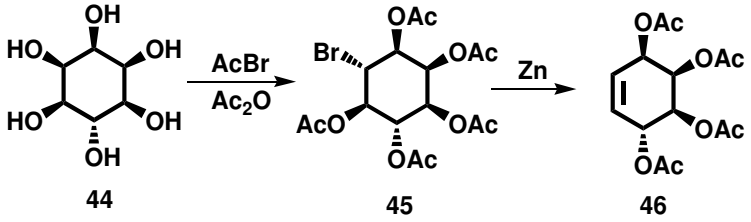


Recently, Balcı and coworkers reported simple and stereospecific synthesis of conduriol-B starting from oxepine-benzeneoxide **(40)** [19]. The addition of the oxygen functionality to the molecule **40** and reduction of **41** with thiourea gave epoxy diol **42**. Then, epoxy diol **42** was converted into epoxy diacetate **43**. Submission of **43** to acid-catalyzed ring-opening reaction gave tetraacetate of conduritol-B **(30)** which was then hydrolyzed to conduritol-B **(5)**.



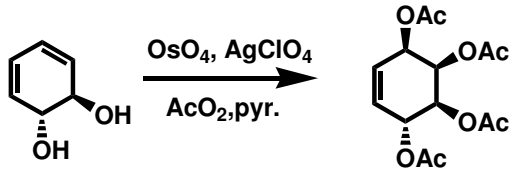
1.3.3 CONDURITOL-C

The first synthesis of conduritol-C was carried out by McCasland and Reeves starting from *epi*-inositol **(44)** [20]. They obtained a new 6-bromoquercitol pentaacetate **(45)** by heating *epi*-inositol **(44)** with acetyl bromide and acetic anhydride. This pentaacetate **45** was treated with zinc-acetic acid to give tetraacetate of conduritol-C **(46)**.



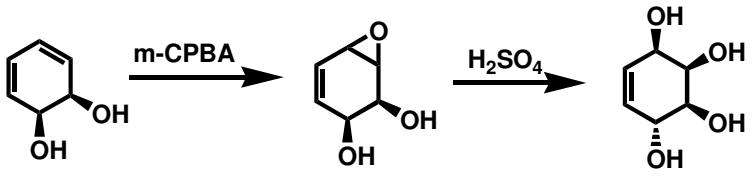
Nakajima *et al*. have synthesized conduritol-C starting from *trans*-benzenediol **17** [6]. *Trans*-benzenediol **17** was treated with osmium tetraoxide in presence of

silver perchlorate. The product was acetylated and teraacetate of conduritol-C **(46)** was synthesized.



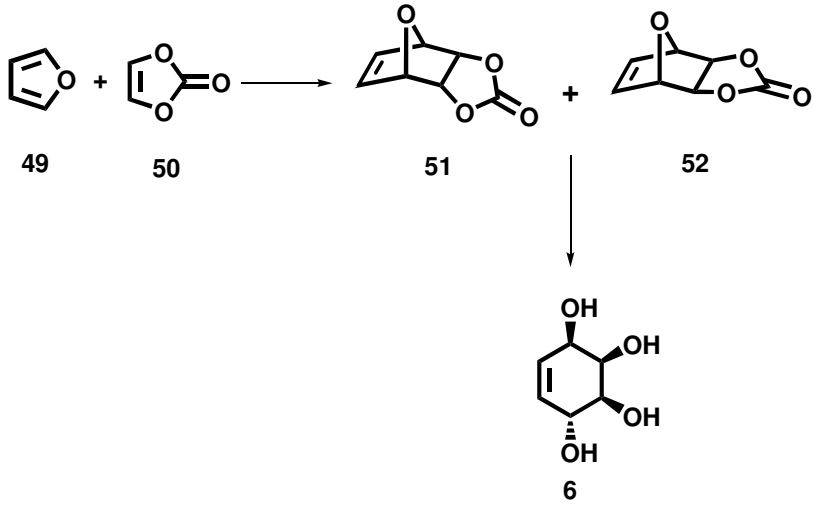
17 46

Conduritol-C **(6)** was also obtained from *cis*-benzenediol **(47)** by *trans*-hydroxylation by Nakajima and coworkers [6].



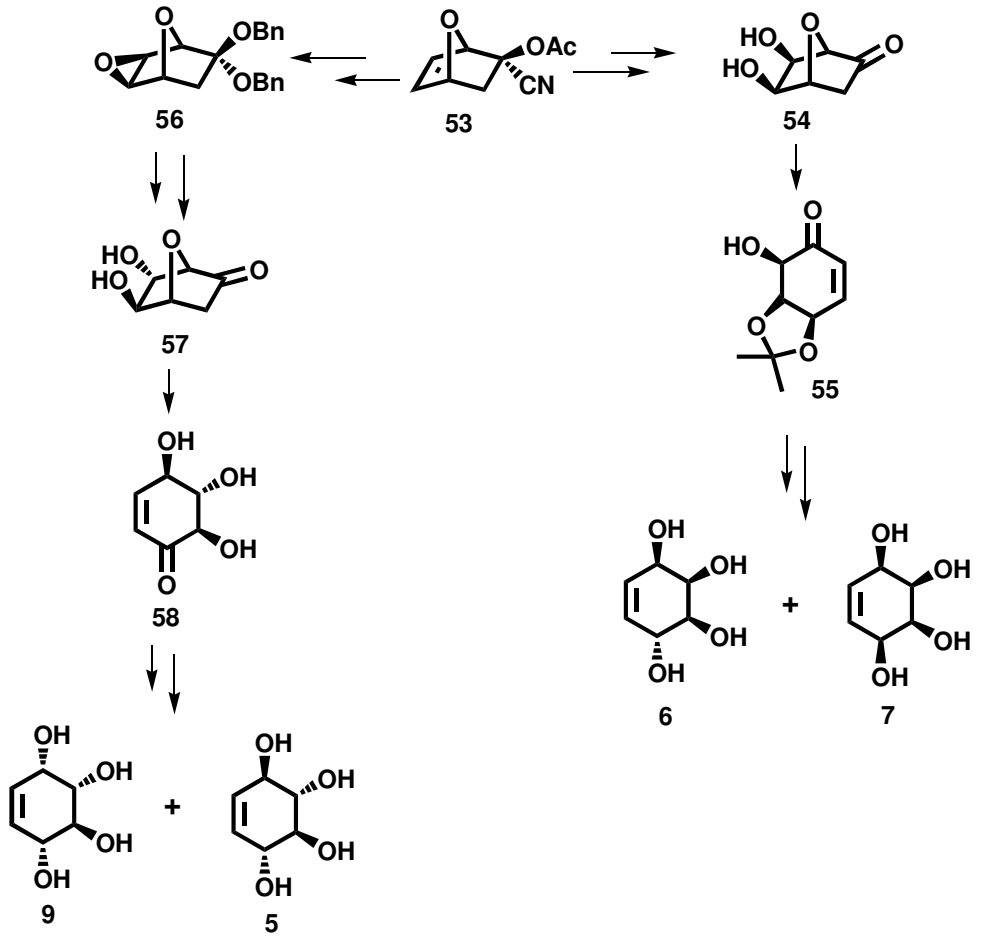
47 48 6

Yurev and Zefirov achieved a short and efficient synthesis of conduritol-C by using furan **(49)** and vinylene carbonate **(50)** [21]. Diels-Alder adducts **51** and **52** were first acidified and then treated with barium hydroxide to obtain conduritol-C **(6)**.



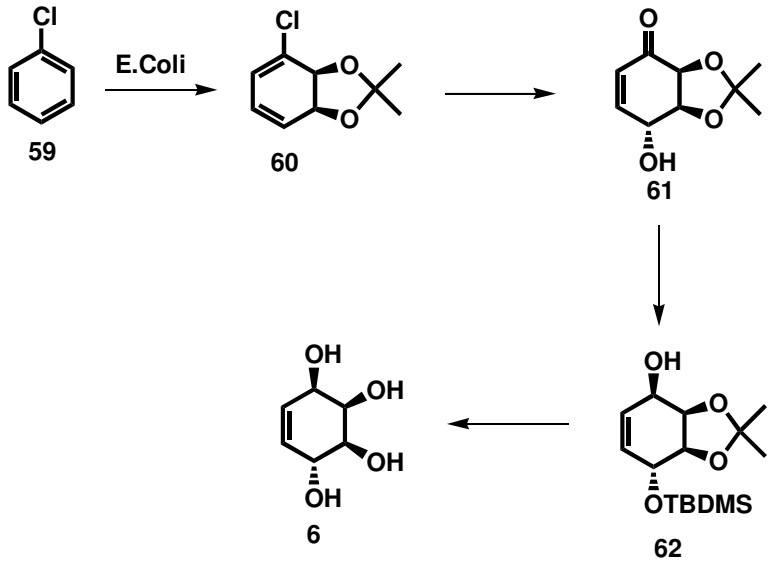
49 50 51 52 6

Vogel developed a different approach for the synthesis of conduritol-C starting from naked sugar **53** [22]. *Cis*-diydroxylation of the double bond in **53** was performed with H_2O_2 followed by protection and saponification steps to yield ketone **54**. Opening of the oxa-bridge in **54** was achieved by triethylamine in the presence of trimethylsilyl triflate and then several steps gave conduritol-C **(6)** and D **(7)**. In addition, they used similar pathway for the synthesis of conduritol-B **(5)** and conduritol-F **(9)**.

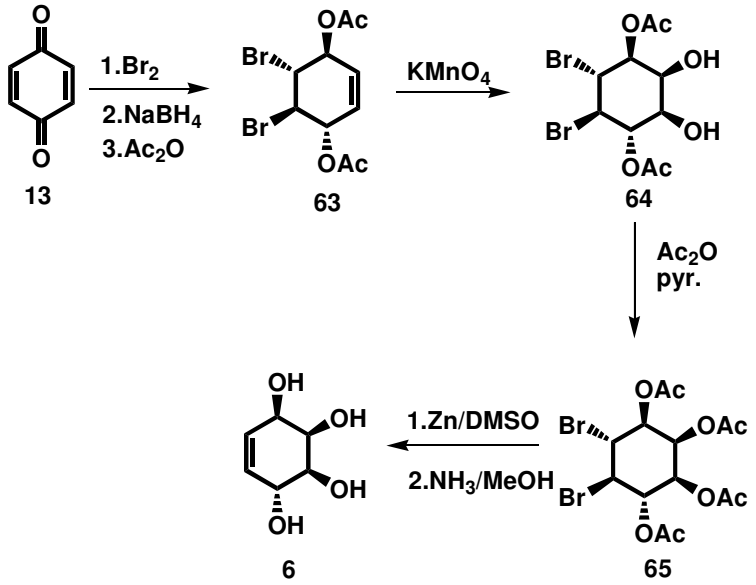


Hudlicky *et al*. reported a short synthesis *via* the enantiospecific conversion of chlorobenzene **(59)** to the protected *cis*-diol **60** [23]. Photooxygenation of **60** resulted in the formation of bicyclic endoperoxide **61**. This was followed by

thiourea reduction of bicyclic endoperoxide to form **62** which was then converted to conduritol-C **(6)** by hydrolysis.

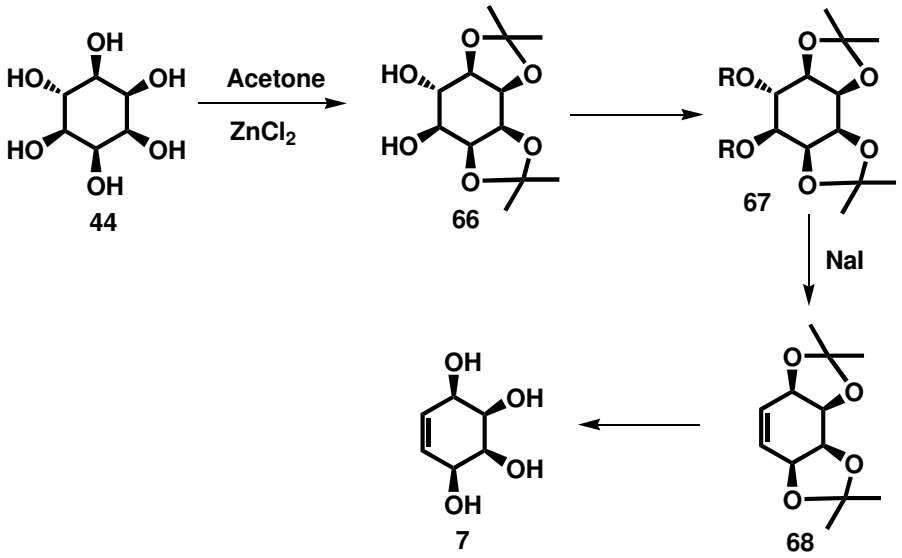


Recently, a different synthetic way leading to the synthesis of conduritol-C was reported by Balcı and coworkers [24]. *Cis*-hydroxylation of compound **63** led to the only isomer **64**. Reaction of **65** with zinc-DMSO followed by aminolysis provided conduritol-C **(6)**.

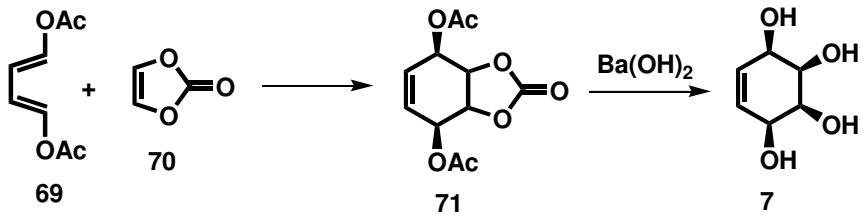


1.3.4 CONDURITOL-D

The first synthesis of conduritol-D was achieved from di-O-isopropylidene derivative of *epi*-inositol **(44)** by Angyal and Gilham [25]. In this method, two vicinal leaving groups in **67** were eliminated by iodide ion. After the hydrolysis of isopropylidene groups, conduritol-D **(7)** was obtained.

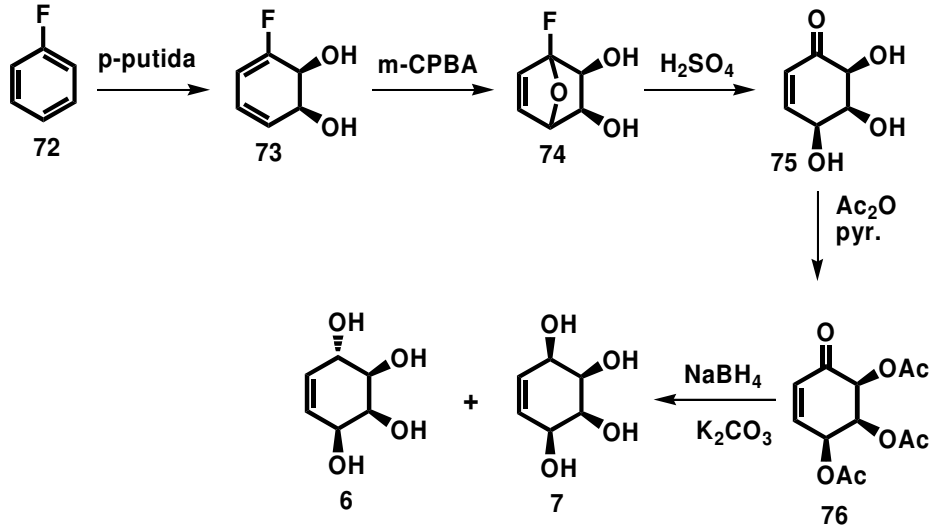


Criegee and Becher prepared the Diels-Alder adduct of *trans-trans*-diacetoxybutadiene **(69)** and vinylenecarbonate **(70)** at high temperature and high pressure [26]. The saponification of **71** with $Ba(OH)_2$ gave the desired conduritol **7**. The configuration of the product was established by the oxidation of the double bond with osmium tetroxide.

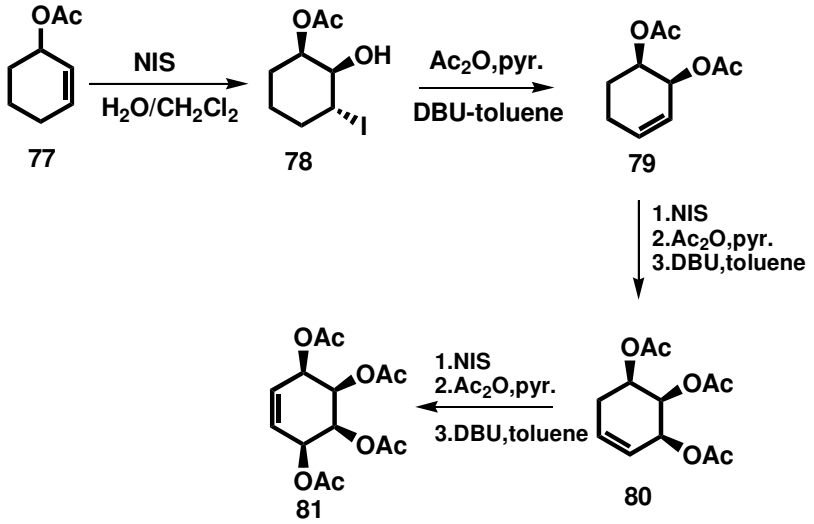


Recently, Oak and Carless reported another method starting from fluorobenzene **(72)** to synthesize conduritol-D [27]. Compound **72** was treated with a bacteria

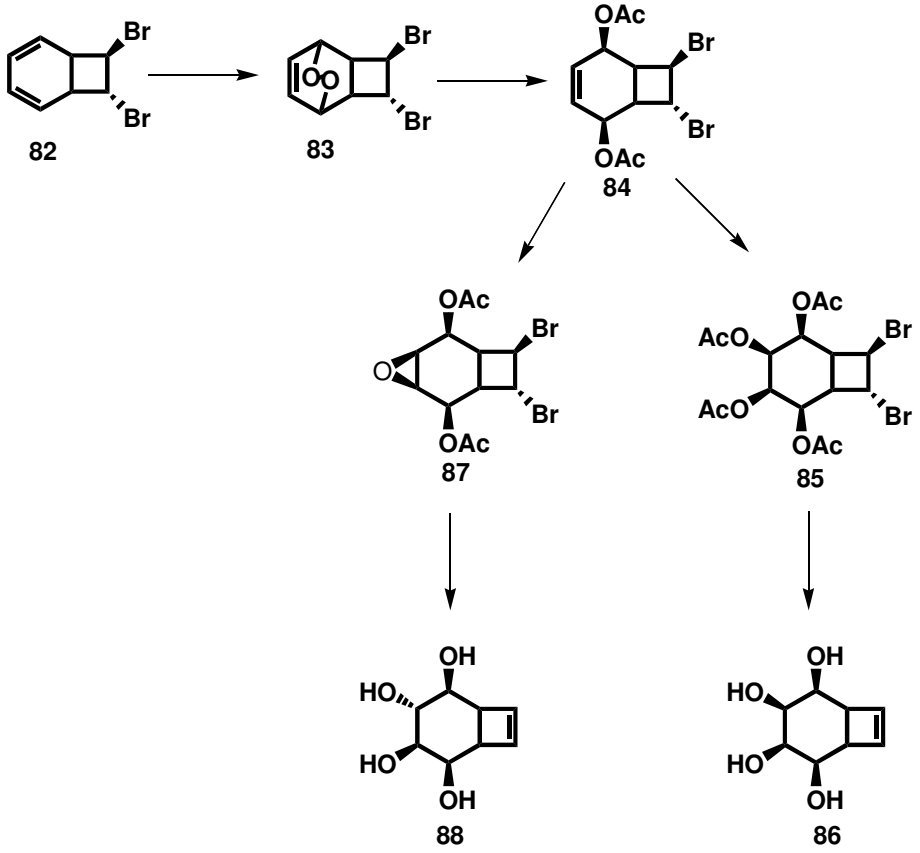
called p-putida to obtain fluorobenzenediol **73**. Epoxidation of **73** with *m*-chloroperbenzoic acid followed by hydrolysis in acidic medium gave hydroxy ketone **75**. After the acetylation and subsequent reduction of **75**, conduritol-C **(6)** and D **(7)** were obtained.



Knight and Sweeney used acyloxycyclohexene derivatives for the synthesis of conduritol-D [28]. The reaction of **77** with N-iodosuccinimide and water provided *trans*-1,2-hydroxyiodide **(78)**. Subsequent hydroxyiodinations of **79** and **80** both produced with similar diastereoselectivity conduritol-D tetraacetate **(81)**.



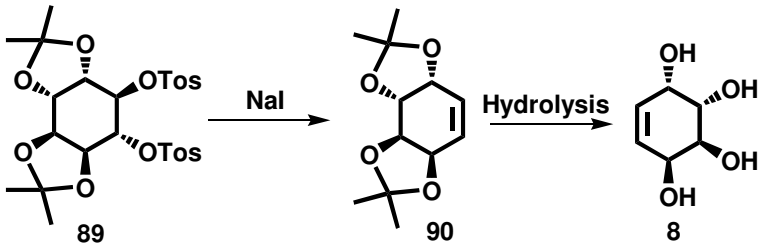
Balcı and coworkers synthesized a new class of compounds, *bis*-homoconduritol-D **(86)** and *bis*-homoconduritol-F **(88)**, starting from **82** [29]. Photooxygenation of the diene **82** followed by the thiourea reduction and acetylation with acetic anhydride gave diacetate **84**. $KMnO_4$ oxidation and acetylation of hydroxyl groups gave **85**. Elimination of bromine atoms with zinc dust provided the *bis*-homoconduritol-D **(86)**. Epoxidation of the double bond in **84** followed by elimination and epoxide-opening gave the corresponding conduritol-F analogue **88** [30].



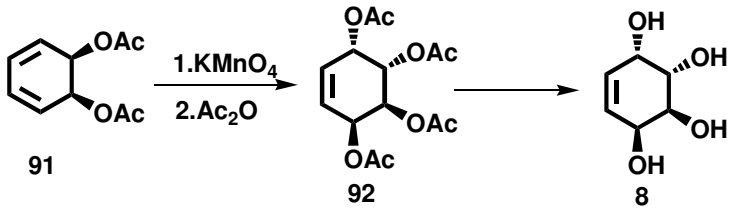
1.3.5 CONDURITOL-E

The first synthesis of conduritol-E performed by Nakajima *et al*. was not stereospecific and useful [6]. As mentioned, Angyal *et al.* used inositols as

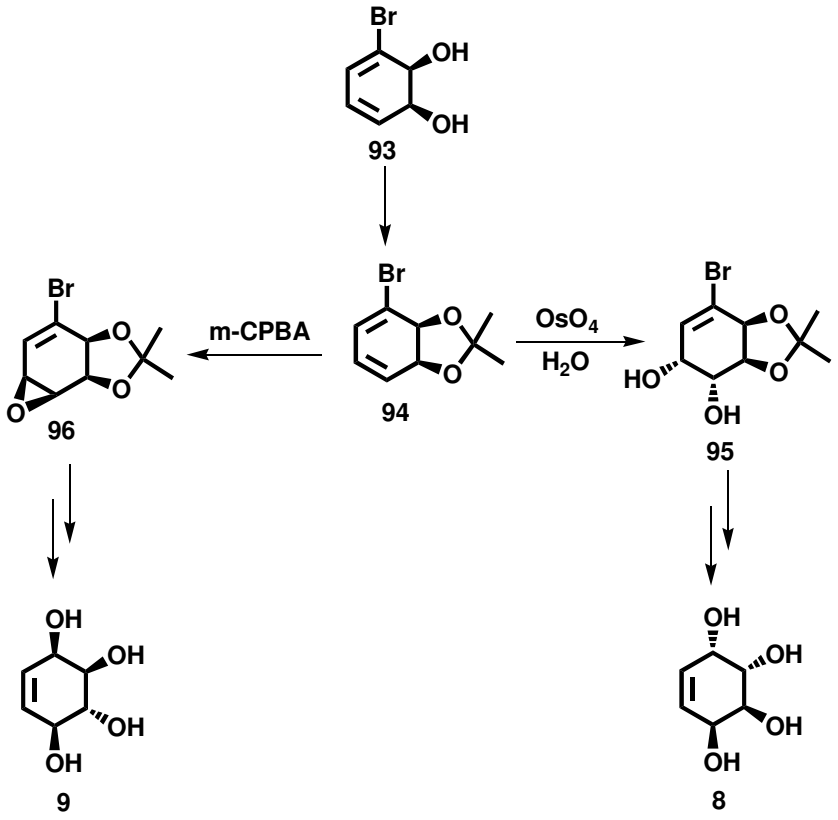
starting materials for the synthesis of conduritol-D [25]. They used a similar method to achieve the synthesis of conduritol-E **(8)**.



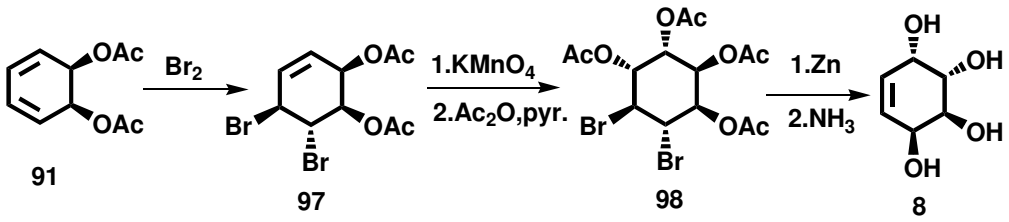
Moreover, conduritol-E was also synthesized starting from *cis*-diacetate **91** by Nakajima *et al* [6]. Oxidation of diacetate **91** with $KMnO_4$ followed by acetylation of resultant compound gave tetraacetate of conduritol-E **(92)** which was converted to conduritol-E **(8)** upon hydrolysis.



Hudlicky *et al*. synthesized both conduritol-E and F starting from the protected form of bromo-*cis*-benzenediol **(93)** [31]. The treatment of **93** with osmium tetroxide gave a single diol **95**. After the reduction of bromine atom with tributyl tinhydride, and deprotection, conduritol-E **(8)** was obtained in enantiomerically pure form. On the other hand, a single epoxide **96** was obtained by the reaction of **94** with *m*-chloroperbenzoic acid. Opening of epoxide under basic conditions led to the bromo-*trans*-diol, which was reduced by trimethyl tinhydride to give conduritol-F **(9)**.

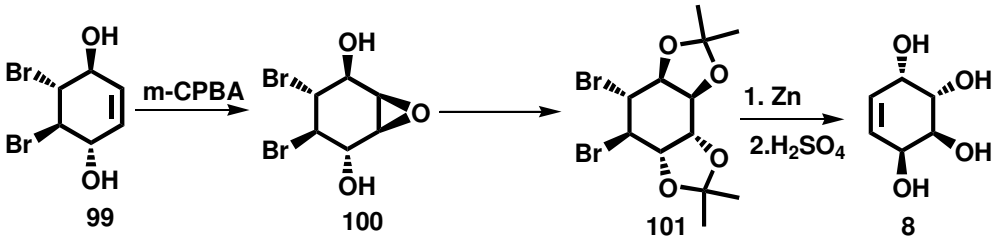


Recently Balcı et al. described a short and convenient method to obtain conduritol-E starting from diacetate **91** [32]. Bromination of **91** gave product **97**. After the oxidation of **97** with permanganate and protection of hydroxyl groups with acetoxy groups, **98** was obtained. By elimination of vicinal bromides in **98** followed by hydrolysis, conduritol-E **(8)** was isolated.

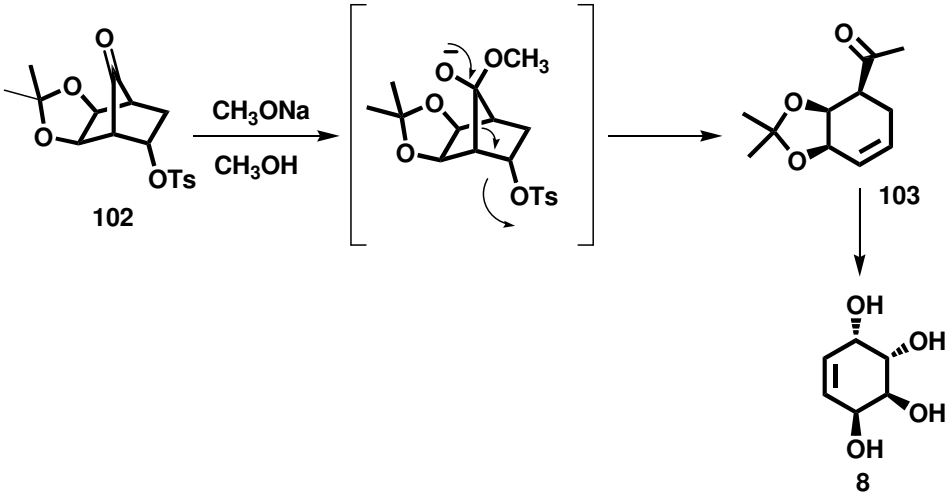


They also synthesized conduritol-E starting from epoxydiol **100** [24]. Acid-catalysed ring opening reaction of **100** provided a tetrol which was readily

converted into di-O-isopropylidene derivative **101**. The cyclic ketal **101** was treated with zinc and hydrolyzed to give conduriol-E **(8)**.

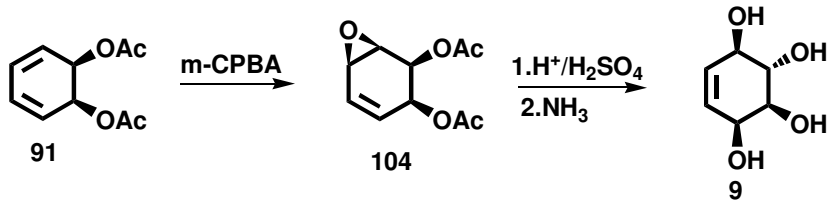


Mehta and coworkers developed a novel Grob like 'top to bottom' sequence in a norbornyl derivative **102** to furnish a building block **103** for the synthesis of conduritol-E and other carbasugars [33].

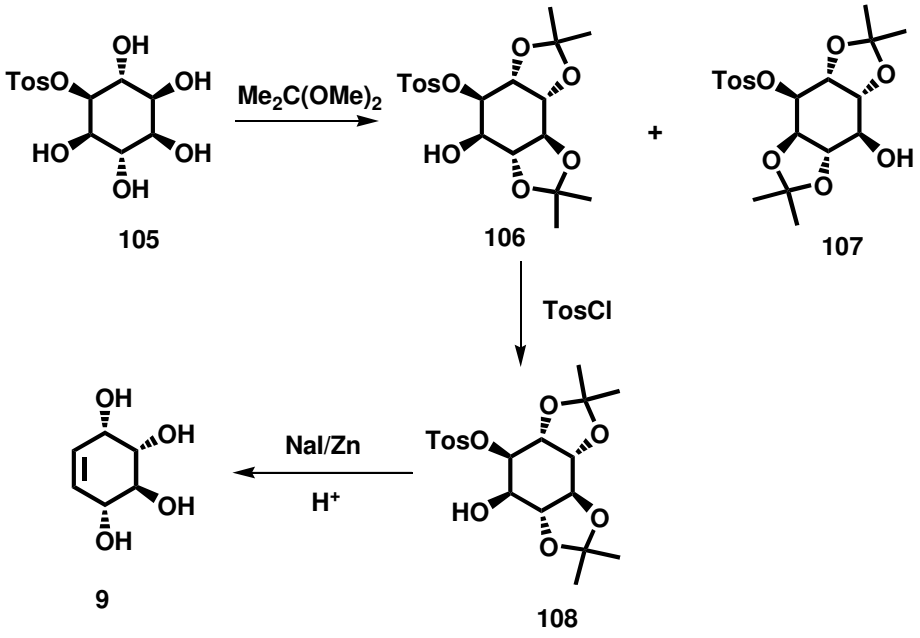


1.3.6 CONDURITOL-F

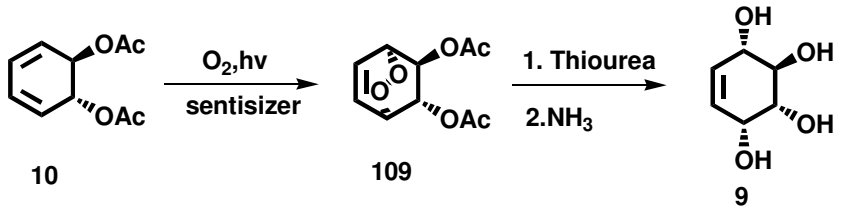
Conduritol-F was first synthesized by Nakajima *et al.* in 1959 before its discovery in nature [6]. Firstly, diacetate **91** was obtained from tetrachlorocyclohexene. Epoxidation of **91** with *m*-chloroperbenzoic acid yielded epoxide **104**. The hydrolysis of **104** in acidic medium gave the only product conduritol-F **(9)**.



Paulsen *et al*. used another method for the enantioselective synthesis of conduritol-F which was also used for the synthesis of conduritol-B and -E [16]. 1-O-Tosylate of quebrachitol (L-chiro-inositol) **105** was converted into its isopropylidene derivatives **106** and **107** which were then separated by column chromatography. Treatment of **106** with tosyl chloride followed by elimination with sodium iodide and zinc provided conduritol-F **(9)**.

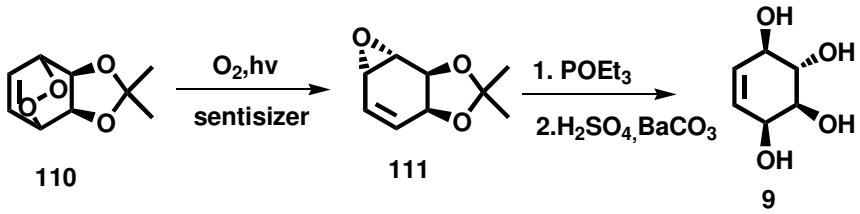


Balcı and *et al*. developed a new and stereospecific synthesis for racemic conduritol-F [19]. By means of the photooxygenation of *trans*-benzenediacetate **(10)**, the bicyclic endoperoxide **109** was obtained as a single isomer. The endoperoxide **109** was treated with thiourea for selective reduction of the peroxide linkage. After deacetylation of the former product, conduritol-F **(9)** was obtained.



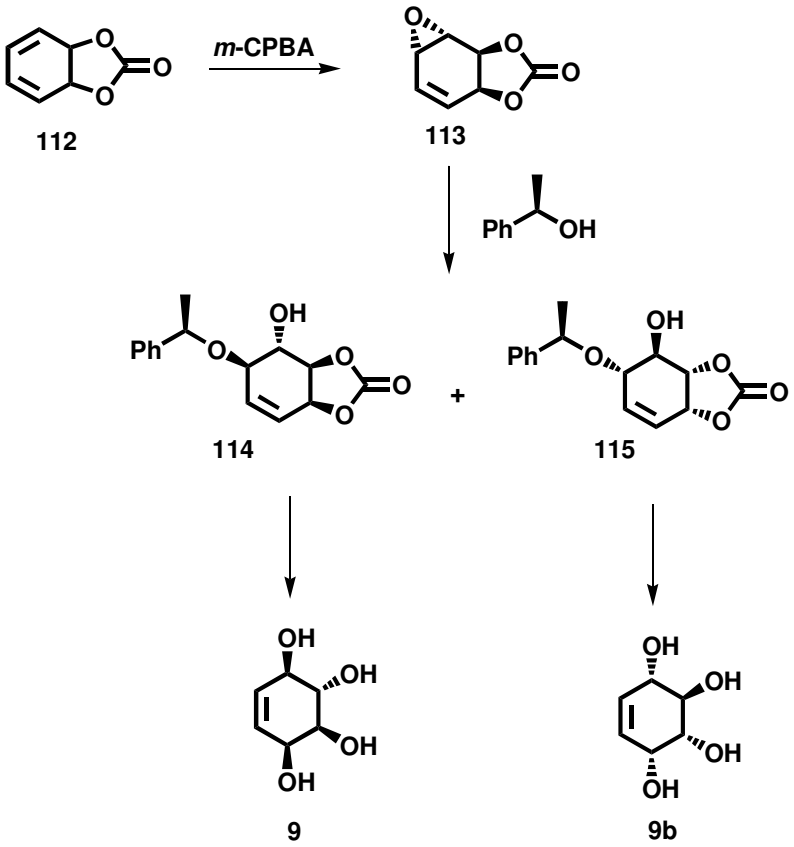
10 109 9

Furthermore, Balcı and his group reported that conduritol-F was also obtained by the cycloadditon of singlet oxygen to cyclohexadiene ketal **110** followed by reductive extrusion of one of oxygen atoms to obtain allylic monoepoxide **111** [34]. Epoxide ring in **111** was opened and ketal was hydrolysed to give conduritol-F **(9)**.



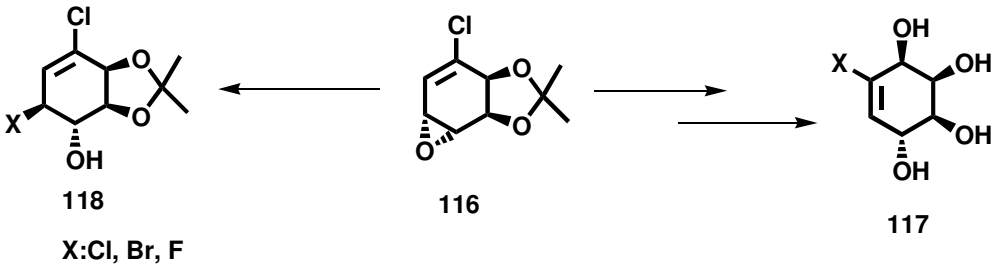
110 111 9

Ley and Redgrave used the carbonate **112** for the synthesis of (±)-conduriol-F [35]. Stereoselective epoxidation of **112** with *m*-chloroperbenzoic acid provided epoxide **113**. Then, regioselective opening of the epoxide ring gave diastereomeric separable alcohols **114** and **115** respectively. The reduction of these two alcohols with sodium in liquid ammonia gave natural (+)-conduritol-F **(9)** and unnatural product (-)-conduritol-F **(9b)**.

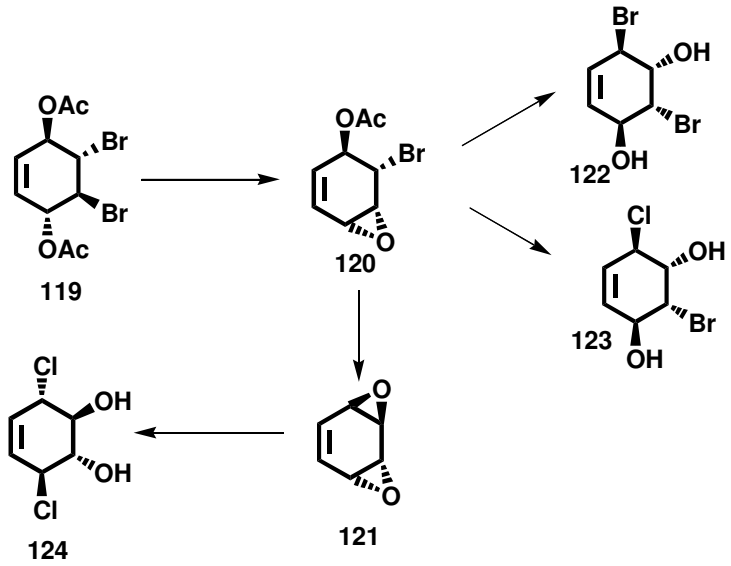


1.3.7 HALOCONDURITOLS and DOUBLE BOND SUBSTITUTED CONDUTIROLS

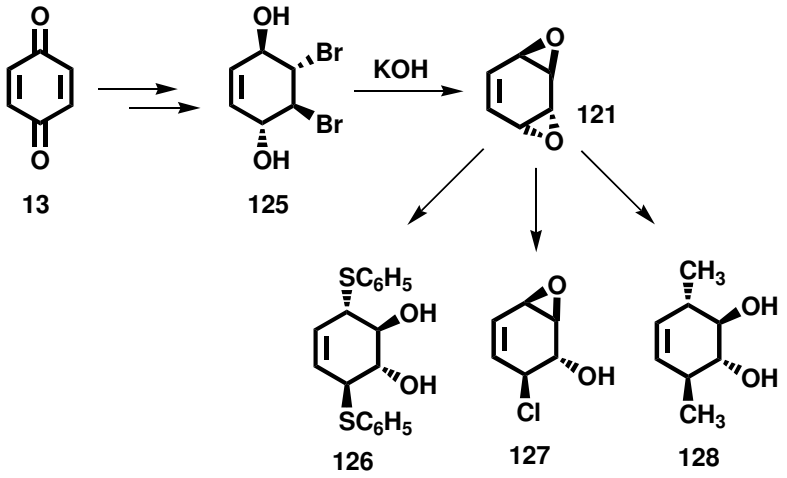
In connection with the conduritols, haloconduritols and double bond substituted conduritols have also gained importance in the last decade [36]. For example, bromoconduritols are interesting molecules in AIDS research because they are active site directed, covalent inhibitor of α–glucosidases. Hudlicky *et al*. and Carless reported the synthesis of double bond subsituted conduritols starting from halobenzenes [31,37]. Microbial oxidation of halobenzene followed by epoxidation of unhalogenated double bond gave product **116**. Acid-catalyzed ring opening reaction of **116** gave double bond substituted conduritol **117** where X can be chlorine, fluorine and bromine atoms. Moreover, nucleophilic attack at the allylic epoxide carbon atom of **116** resulted in the formation of **118**.



Taylor *et al*. started from bis-acetate **119,** converted it into monoepoxide **120** and *anti*-benzene dioxide **121** [38]. Ring-opening reaction of **120** and **121** gave corresponding haloconduritols **122**, **123** and **124**.



Ring-opening reaction of *anti*-benzene dioxide **121** with various sulphur, oxygen and carbon nucleophiles was also studied by Sequin *et al*. [39]. This led them to synthesize various conduritol and chloroconduritol derivatives.



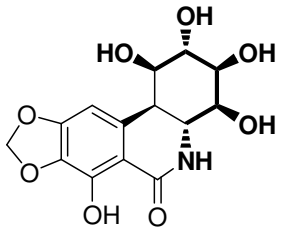
1.4 BIOLOGICAL IMPORTANCE OF CONDURITOLS

The main reason why conduritol and its derivatives have been of great interest among scientists is that they have many biological activities ranging from herbicidal and anti-microbial on the hand to glycosidase inhibition and mediation of cellular communication on the other [33].

Inhibitors of glycosidase enzymes have potential for the treatment of various disorders and diseases such as diabetes, cancer and AIDS. Their usefulness in the investigation of metabolic disorders such as Gaucher's disease have been also proved [40].

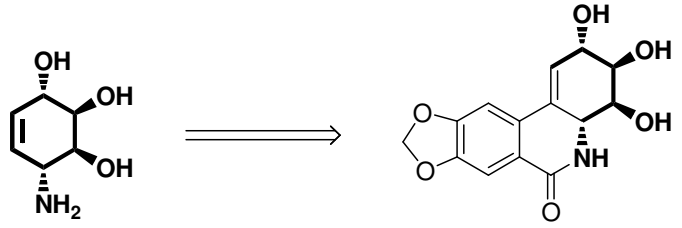
Conduritol and its derivatives show inhibitory activities for glycosidases and they posses antifeedant, antibiotic, anti-leukemic and growth-regulating activity. For example, conduritol-A is present in the leaves of *Gymnema Sylvestre*, a shrub which was used as a remedy for diabetes.

In addition, conduritols are building blocks of some biologically important molecules. For example pancratistatine **(128)**, a member of *Amaryllidacene* group of alkaloids, contains an aminoconduritol skeleton. Pancratistatine was isolated from the root of the Hawaiian plant *Pancratium littorale* and it has been used in herbal folk medicine since ancient Greek times. Pancratistatine is an important molecule because its biological activities include inhibition of protein synthesis, antineoplastic activities in ovarian sarcoma and lymphotic leukemia [41].



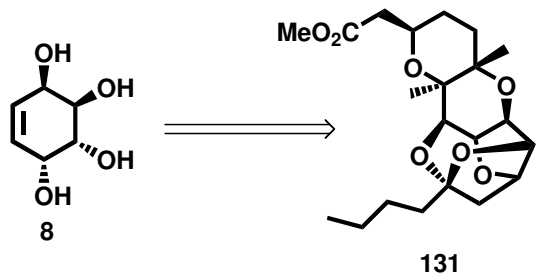
128

Lycoricidine **(129)** was synthesized from the key compound conduramine-A **(130)** in nine steps [42]. Ability of lycoricidine to inhibit oligosaccharide-processing enzymes provides a wide range of possible applications in chemotherapy for this compound. Lycoricidine and pancratistatine are both glycosidase enzyme inhibitors. Thus, they have a potential for the treatment of various disorders and diseases such as diabetes, cancer, and AIDS.



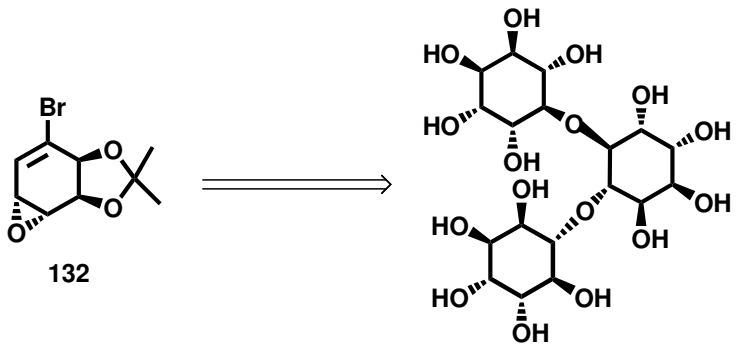
130 **129**

As mentioned, many of the syntheses of some natural products originate from conduritol intermediates. Halichondron, a potent member of a family of cytotoxic polyether macrolides. A model C1-C14 segment **131** of halichondron B was synthesized recently from conduritol-E **(8)** in 18 steps [43].



8 **131**

Oligosaccarides have received much attention because of their physiological roles and therefore therapeutic potential. Some of the unnatural derivatives of carbohydrates inhibit some metabolic functions such as glycolysis, enzyme inhibition and mediate insulin release. For the synthesis of these sugars, vinyl epoxide **132** and vinylaziridine were condensed with protected cyclitols to generate dimeric, trimeric and tetrameric conduritol derivatives **133** [44].



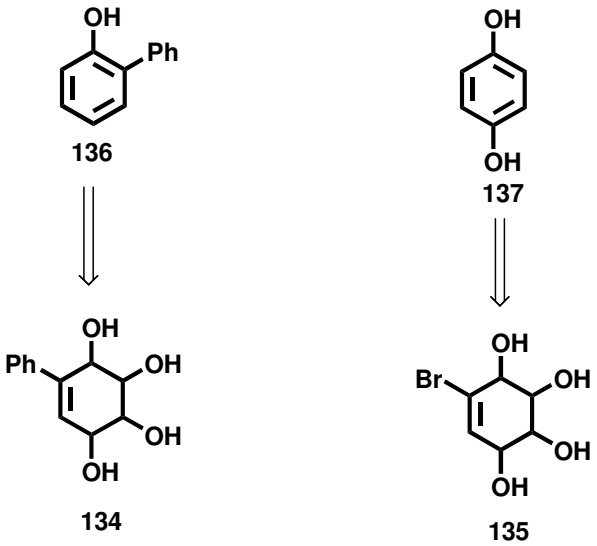
132 **133**

1.5 AIM OF THE STUDY

Owing to their diverse biological activities, to develop short, efficient and stereospesific synthetic methodologies for the synthesis of conduritols and their derivatives has an importance. In connection with the conduritols, double bond substituted conduritols gain much importance since there are not much work on the synthesis of them. The aim of our study was to develop a new and efficient strategy for the synthesis of these interesting molecules.

Our methodology based on the total synthesis of phenyl-substituted conduritol **(134)** and bromo-substituted conduritol **(135)**, starting from commercially available compounds 1,1'-biphenyl-2-ol **(136)** and hydroquinone **(137)**, respectively.

.

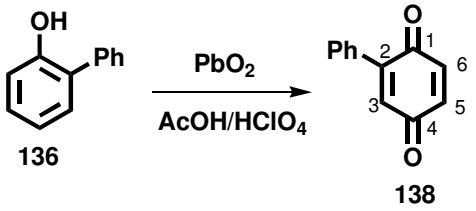


CHAPTER 2

RESULTS AND DISSCUSSION

2.1 THE SYNTHESIS OF 2-PHENYLBENZO-1,4-QUINONE (138)

In order to synthesize phenyl-substituted conduritol, a commercially available product, 1,1'-biphenyl-2-ol **(136)** was first oxidized with lead dioxide (PbO_2) in the presence of acetic acid and perchloric acid to form 2-phenylbenzo-1,4-quinone **(138).** This oxidation method is general and useful for the synthesis of *p*-benzoquinones from phenols. Lead dioxide works as a good oxidant in the presence of a strong acid [45]. Pure quinone **138** was obtained after crystallization from methanol in a yield of 84%.

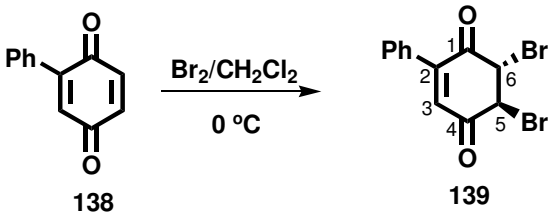


NMR data were in good agreement with the structure of **138**. The ^{1}H-NMR spectrum indicated two sets of proton signals; a multiplet at 7.35-7.50 ppm for the aromatic protons and a multiplet at 6.76-6.85 ppm for the olefinic protons H_3, H_5 and H_6.

The ^{13}C-NMR spectrum revealed carbonyl carbon resonances appear at 187.0 and 186.1 ppm along with the olefinic carbons at 145.8, 137.0, 136.1, 132.6 ppm and aromatic carbons at 132.7, 130.0, 129.2 and 128.4 ppm.

2.2 THE SYNTHESIS OF (5S(R),6S(R))-5,6-DIBROMO-2-PHENYLCYCLO HEX-2-ENE-1,4-DIONE (139)

In this step, it was aimed to brominate only one double bond of **138**. The molecule has two double bonds whose reactivities are inequal. One double bond is substituted with an aromatic ring which decrease the electron density on this double bond. Thus, bromine atoms prefer more reactive double bond. Moreover, in order to increase the selectivity, the reaction was carried out at low temperature as mentioned in the literature [46]. Since bromination reactions occur *via* the formation of a bromonium cation, bromine atoms in the resultant product **139** are in trans position [47]. Addition of one mole of bromine to quinone **138** provided compound **139** in a yield of 94%.



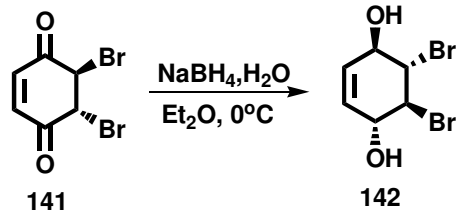
138 **139**

The structure of compound **139** was elucidated on the basis of ^{1}H and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum, the aromatic protons resonate as multiplet at 7.26-7.49 ppm. The olefinic proton H_3 resonates at 6.68 ppm as a doublet due to the allylic coupling between H_3 and H_5. The tertiary protons H_5 and H_6 have an AB system between 4.76 and 4.83 ppm. A part of the system belongs to H_6 and is split into a doublet with a coupling constant of 2.71 Hz whereas B part gives doublet of doublets due to the allylic coupling between H_5 and H_3. Coupling constant between H_5 and H_6 is 2.71 Hz which proves the *trans*-diaxial configuration of those protons.

In the ^{13}C-NMR spectrum, carbonyl carbons resonate at 187.1 and 187.5 ppm, olefinic carbon resonances appear at 131.3 and 146.7 ppm. The tertiary carbons C_5 and C_6 resonate at 45.1 and 47.1 ppm, respectively. Aromatic carbon resonances are in between 128.8 and 132.4 ppm.

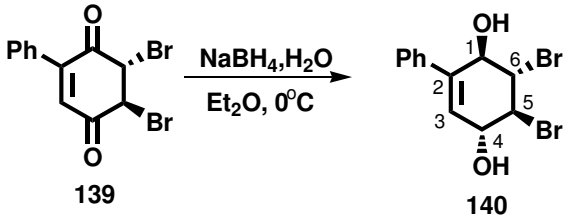
2.3 THE SYNTHESIS OF (1R(S),4R(S),5S(R),6S(R))-5,6-DIBROMO-2-PHENYLCYCLOHEX-2-ENE-1,4-DIOL (140)

Carbonyl groups can be reduced in the presence of metal hydrides like sodium or lithium borohydride. However, if a molecule has an α,ß-unsaturated system, reduction should be performed in certain conditions in order to prevent the reduction of the double bond together with the carbonyl groups. Vogel and Altenbach reported that double bonds were not reduced upon treatment of quinone **141** with sodium borohydride in presence of water and ether at 0 ºC. The reduction product diol **142** was formed as the sole product [46].



141 **142**

By using the same method, quinone **139** was reduced to give **140** in three hours in a yield of 75%.



139 **140**

Here only one isomer was obtained since bromine atoms in compound **139** have *trans*-diaxial configuration. The attack of hydride ions resulted in the formation of the more stable equatorial alcohol **140** as shown in the Figure 3.

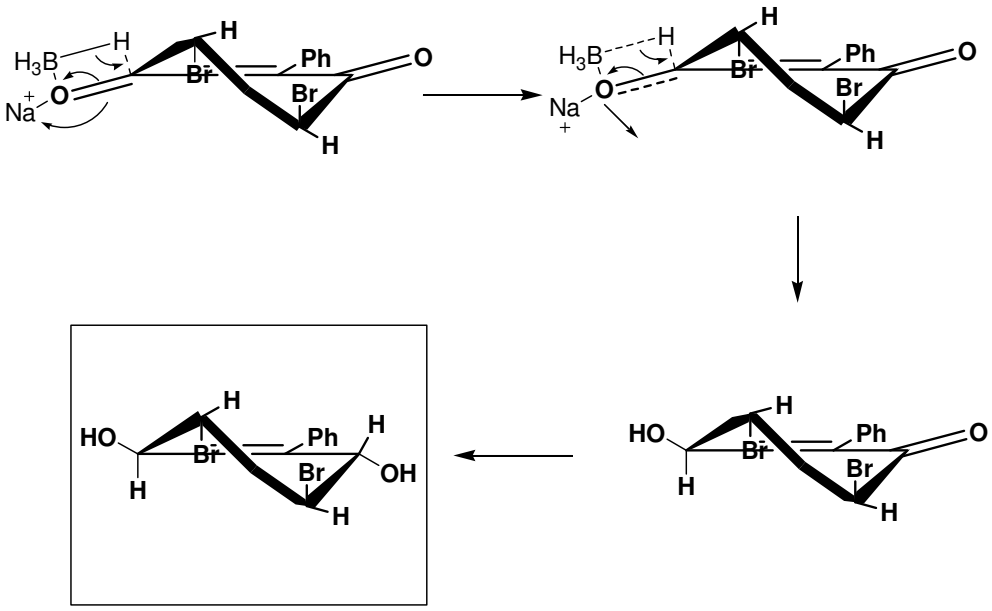
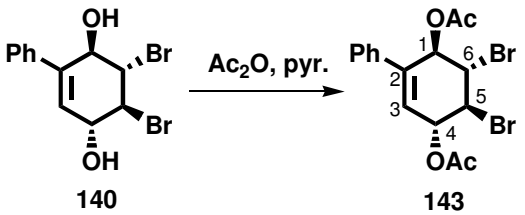


Figure 3. Reduction mechanism of compound **139**.

In order to characterize product **140** more accurately, the crude product was readily converted into its protected form **143**.

2.4 THE SYNTHESIS OF (1R(S),4R(S),5S(R),6S(R))-4-(ACETYLOXY)-5,6-DIBROMO-2- PHENYLCYCLOHEX-2-EN-1-YL ACETATE (143)

In order to protect hydroxyl groups in former substitution reaction and make an accurate characterization of the product, **140** was converted into (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-5,6-dibromo-2-phenylcyclohex-2-en-1-yl acetate **(143)** in the presence of acetic anhydride and pyridine at room temperature in 8 hours.



The sole product **143** was isolated after column chromatography and crystallization from EtOAc-hexane in a yield of 75%.

The configuration of **143** was determined by ^{1}H and ^{13}C-NMR spectra in conjunction with 2D-NMR (DEPT-90, HMQC, HMBC, and COSY) experiments as well as later by X-ray analysis. The data was consistent with the structure of **143**. In DEPT-90 spectrum, there are six carbon resonances in sp^2-region and four carbon resonances in aliphatic region. Comparing DEPT-90 to HMQC, it is observed that one of the carbon signals in aromatic region is an olefinic carbon because it correlates with the olefinic proton H_2. Other five carbon signals are aromatic ones. As for the other tertiary carbons in DEPT-90 spectrum, two of them resonate at lower field relative to the other two carbons. C_1 and C_4 which are attached to oxygen atoms are at lower field than C_5 and C_6 because the electronegativity of oxygen is much higher than that of bromine. In order to distinguish C_1 and C_4, the correlations in HMBC, were analyzed. Strong correlation between H_3 and C_4 shows that C_4 is attached to C_3, and C_1 is the carbon which is closer to the phenyl ring. Moreover, by the interaction between C_4 and H_5, it is possible to differentiate between C_5 and C_6. As for the quaternary carbon C_2, it correlates with H_1.

In the ^{1}H-NMR, five aromatic protons resonate as a multiplet at 7.15-7.27 ppm. The olefinic proton H_3 gives rise to a doublet of doublets at 5.86 ppm. The tertiary proton H_4 resonates at 5.80 ppm as a doublet of doublets whereas other tertiary proton H_1 gives a doublet of triplets at 6.33 ppm. H_1 is split into doublet due to the coupling between H_6 and triplets due to the W-coupling between H_3 and the long range coupling with H_4. H_5 and H_6 resonate as an AB system between 4.41-4.39 ppm. Methyl protons resonate at 2.10 and 1.90 ppm.

The ^{13}C-NMR revealed two carbonyl carbon resonances at 169.2 and 169.3 ppm along with eight carbon signals between 125.8 and 140.3 ppm and saturated carbon resonances at 51.4, 52.7, 72.3, and 73.7 ppm. Methyl carbon resonances appear at 20.7 and 20.5 ppm.

In addition to NMR spectroscopy, X-ray analysis was performed for the characterization of the product **143.** As shown in the Figure 4, acetoxy groups and bromine atoms are in trans configuration. In the Figure 5, the moleculer packing of compound **143** is displayed. Table 1 shows some selected bond lengths (Å) and angles (deg) in compound **143**.

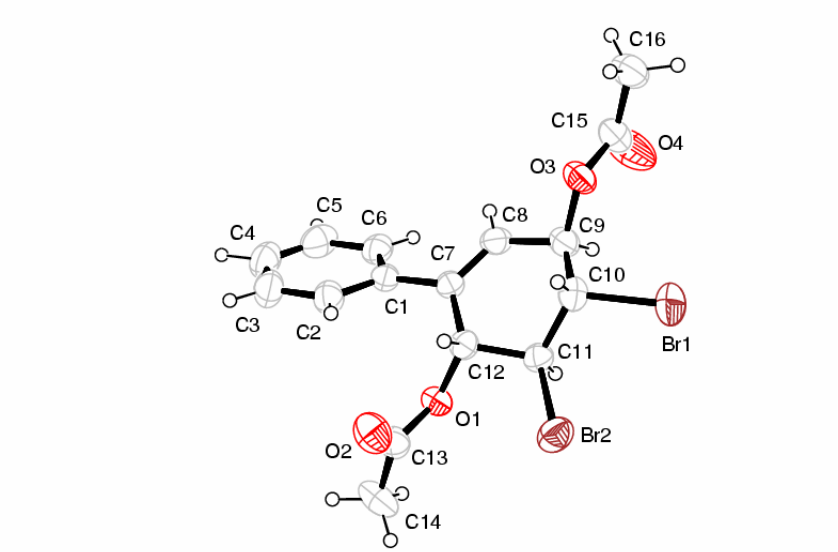


Figure 4. Ortep structure of compound **143** along with the labeling atoms. Thermal ellipsoids of non-hydrogen atoms are drawn at the 50% probability level.

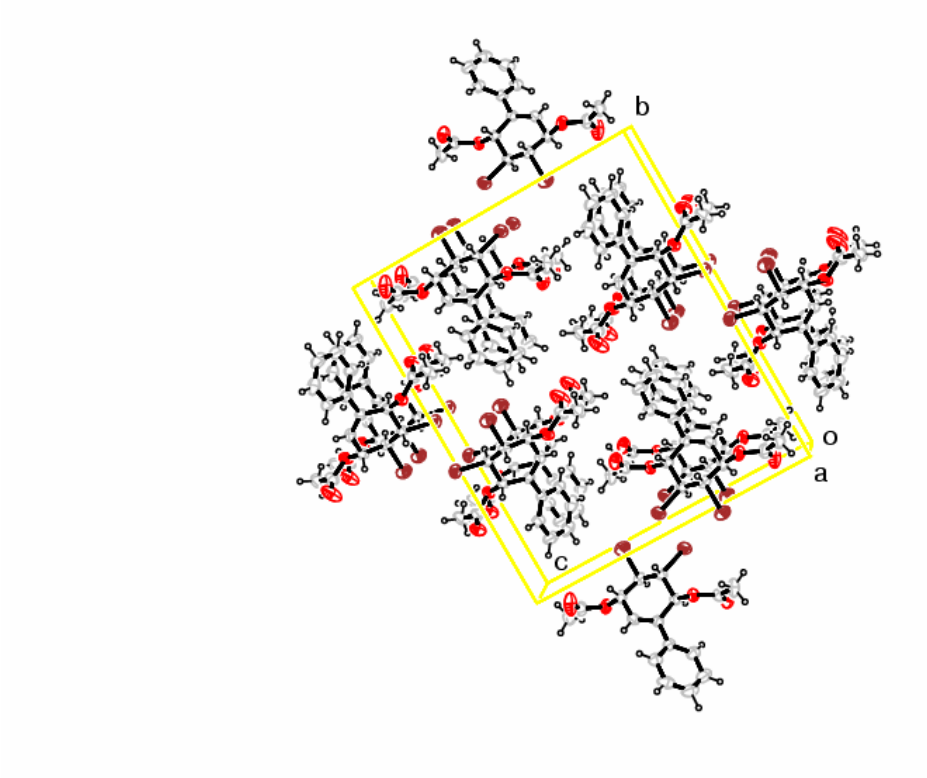


Figure 5. Molecular packing of the compound **143**

Table 1. Selected bond lengths (Å), angles (deg) and torsion angles (deg) for **143**

Br1-C(10)	1.951(3)	Br2-C(11)	1.948(3)
O(1)-C(13)	1.359(4)	C(7)- C(8)	1.318(4)
C(7)-C(1)	1.476(4)	C(7)- C(12)	1.514(3)
C(12)-C(11)	1.519(4)	O(4)-C(15)	1.186(5)
C(9)-C(10)	1.504(4)	C(11)-C(10)	1.508(3)
C(16)-C(15)	1.488(5)	C(13)-C(14)	1.486(5)
C(8)-C(7)-C(1)	122.4(6)	C(8)-C(7)-C(12)	119.3(6)
C(1)-C(7)-C(12)	118.2(5)	C(10)-C(11)-Br2	111.9(5)
C(7)-C(8)-C(9)	126.1(7)	C(9)-C(10)-Br1	108.7(4)

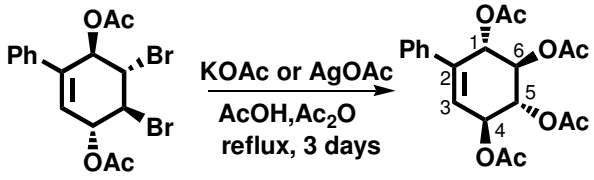
Table 1. (Continued)

C(7)-C(1)-C(2)	121.6(6)	C(7)-C(12)-C(11)	112.0(5)
O(1)-C(13)-C(14)	109.9(6)	O(2)-C(13)-C(14)	126.6(7)
C(9)-C(10)-C(11)	110.0(6)	O(3)-C(15)-O(4)	122.5(7)
O(3)-C(15)-C(16)	110.7(7)	O(4)-C(15)-C(16)	126.8(7)

C(8)-C(7)-C(1)-C(6)	34.2	C(1)-C(7)-C(8)-C(9)	177.0
C(8)-C(7)-C(1)-C(2)	-143.4	C(12)-C(7)-C(8)-C(9)	-0.5
C(8)-C(7)-C(12)-C(11)	-20.0	C(12)-C(7)-C(1)- C(6)	-148.2
C(12)-C(7)-C(1)-C(2)	34.2	C(1)-C(7)-C(12)-C(11)	162.3
C(5)-C(6)-C(1)-C(7)	-177.6	C(7)-C(8)-C(9)-C(10)	-11.6
C(8)-C(9)-C(10)-C(11)	43.6	C(12)-C(11)-C(10)-C(9)	-64.6
C(10)-C(11)-Br2-Br1	-28.5		

2.5 THE SYNTHESIS OF (1S(R),4S(R),5R(S),6R(S))-4,5,6-TRIS(ACETYL-OXY)-2-PHENYLCYCLOHEX-2-EN-1-YL ACETATE (144)

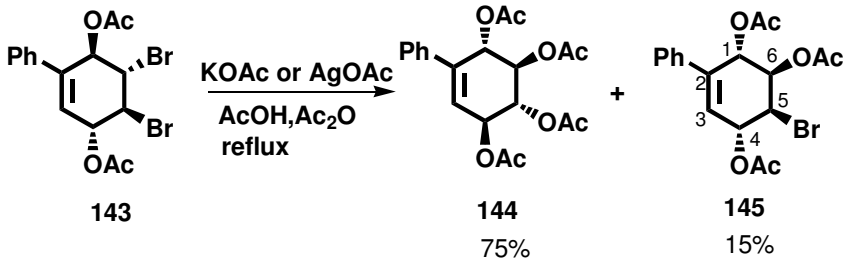
In this step, bromine atoms were substituted with acetoxy groups in the presence of potassium or silver acetate and acetic anhydride in refluxing acetic acid in three days. Pure tetraacetate **144** was obtained in a yield of 75% after thin layer chromatography of the crude product and crystallization from EtOAc-hexane.



143 **144**

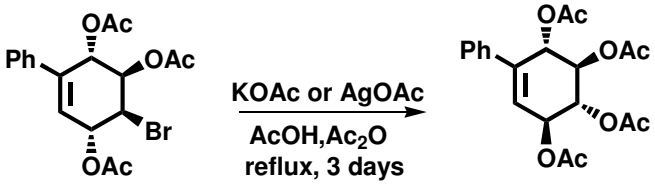
Actually, product **144** was not the only product throughout the reaction. A second compound, (1S(R),4R(S),5S(R),6R(S))-4,6-bis(acetyloxy)-5-bromo-phenylcyclo-

hex - 2-en-1-yl acetate **(145)** was isolated in a yield of 15% and characterized. The yield of **145** was decreased to nearly 5% when the reaction time was elongated up to 10 days, however, its formation was never be eliminated.



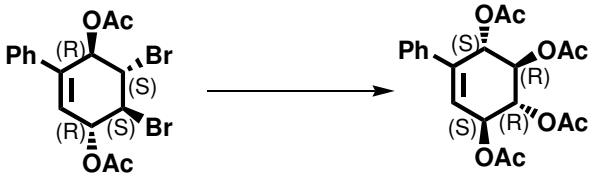
143 **144** 75% **145** 15%

Moreover, compound **145** gave tetraacetate **144** when it was treated with potassium or silver acetate in the presence of acetic anhydride in refluxing acetic acid in three days.



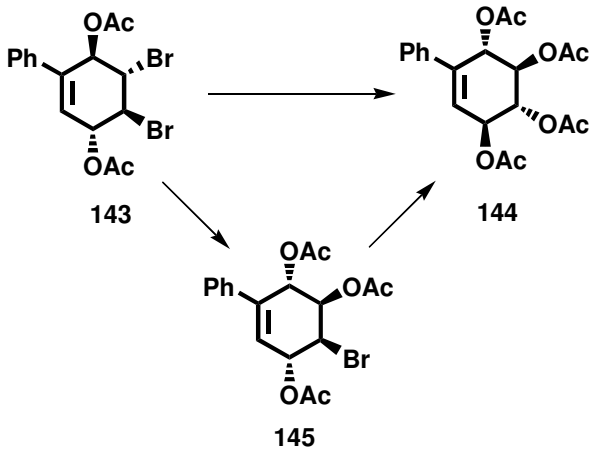
145 **144**

The isolation and characterization of compound **145** was not only important in view of synthetic goals. Its formation was also important for mechanistic point. First of all, the configuration of product **143** changed when it was converted into molecule **144**, as mentioned below. The change in the configuration was proved by NMR spectroscopy and X-ray analysis which will be discussed in following sections.

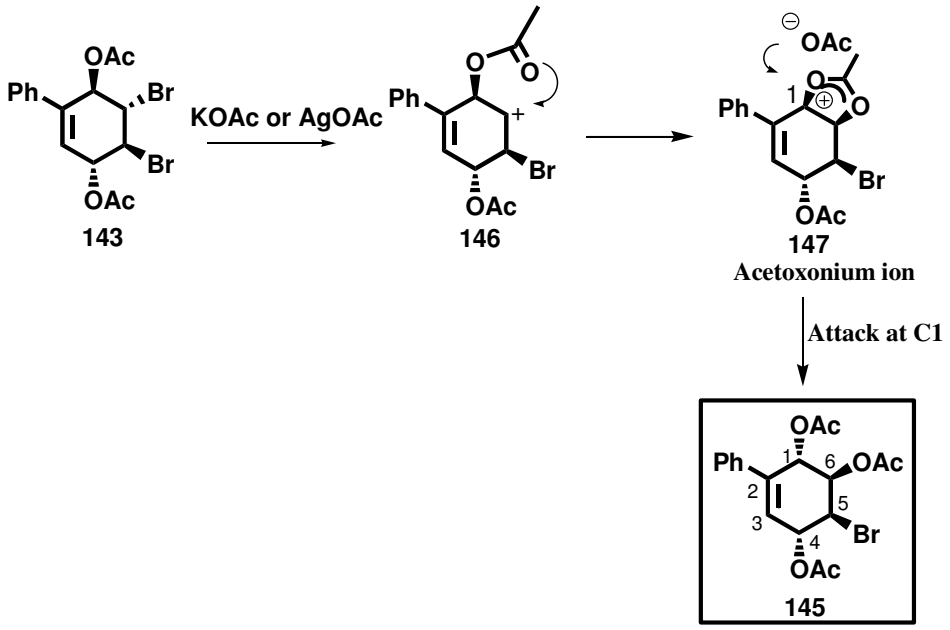


143 **144**

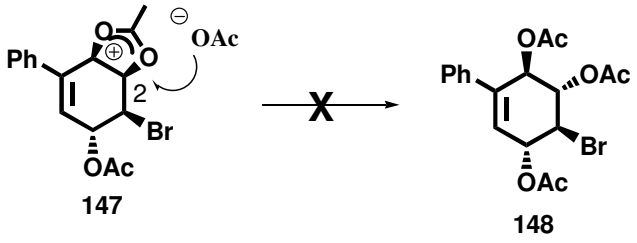
The change in configuration of the molecules **143** and **144,** and the synthesis of **144** *via* the formation of the product **145** proves that neighbouring group effect is the dominant factor in the reaction.



Firstly, one of the bromine atoms is abstracted by silver ions to form silver bromide, as a pale yellow precipitate. Due to the neighbouring group effect, carbonyl oxygen at the adjacent acetoxy group attacks the positive center at the equatorial position to give acetoxonium ion **147**. After that, the cation may undergo nucleophilic displacement by acetate ion from two sides. Actually, side **1** is much more favorable because it is closer to the double bond and more reactive towards a nucleophilic attack.



The acetate anion attacks the formed acetoxonium ion **147** exclusively at the allylic position to give **145**, so that **148** has not be formed.

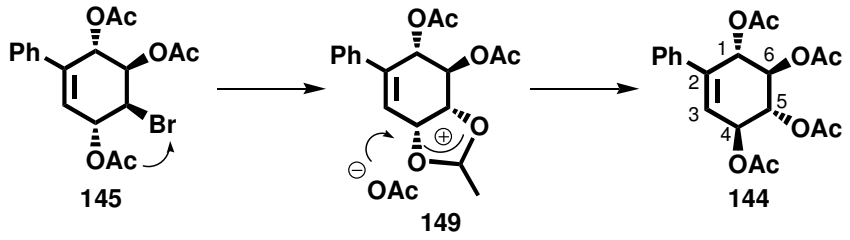


The structure of molecule **145** was elucidated on the basis of the NMR spectroscopy. The clue about which bromine atom was abstracted and substituted with acetoxy group first, was determined by the COSY experiment. The correlation between H_3, H_4 and H_5 shows that bromine atom is attached to C_5.

The ^{1}H-NMR indicates that H_1 and H_3 are overlapping at 6.20 ppm. The tertiary proton H_4 resonates at 5.50 ppm and H_6 appears at 5.80 ppm. H_5 gives a doublet of doublets at 4.50 ppm. Methyl protons appear at 2.00-2.30 ppm and aromatic protons resonate at 7.35-7.45 ppm as a multiplet.

The ^{13}C-NMR spectrum of 144 also revealed three carbonyl carbons at 169.3, 169.0 and 168.9 ppm, two olefinic carbons at 124.7 and 136.5 ppm and aromatic carbons at 138.9, 128.6, 128.5 and 126.2 ppm along with seven saturated carbon signals at 71.4, 71.3, 68.3, 47.2 and 20.8-20.5 ppm.

The reaction continues with the abstraction of the remaining bromine atom from the molecule **145** and the formation of a second acetoxonium ion **149**. Back side attack of the acetate ion from more reactive side leads to the formation of phenyl-substituted tetraacetate of conduritol-B **(144)**.



The structure of the molecule **144** was determined by NMR spectroscopy and X-ray analysis.

In the ^{1}H-NMR, aromatic protons give rise to a multiplet between 7.20 and 7.28 ppm. H_1 resonates at 5.73 ppm as a doublet of triplets. The olefinic proton H_3 appears at 5,83 ppm as a triplet and H_4 gives a doublet of triplets at 6.29 ppm. H_5 and H_6 set an AB system between 5,40-5,47 ppm. Methyl protons are oberved at 2.04-1.84 ppm.

The ^{13}C-NMR revealed three sets of signals. Carbonyl carbon resonances appear between 170.1 and 170.6 ppm. Eight signals are observed at sp^2-region. Tertiary carbons resonate at aliphatic region between 71.9 and 72.5 ppm and methyl carbon resonances appear at 20.7-21.1 ppm.

The X-ray data was also in good agreement with the proposed structure of **144**. Figure 6 shows the Ortep structure of compound **144** and molecular packing of that compound is displayed in the Figure 7.

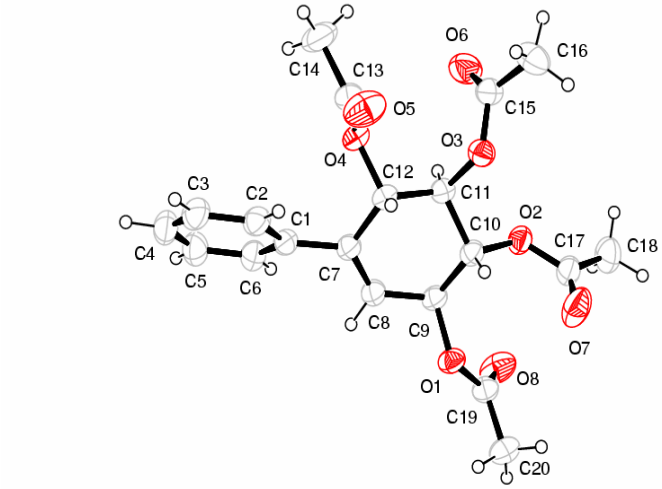


Figure 6. Ortep structure of compound **144** along with the labeling atoms. Thermal ellipsoids of non-hydrogen atoms are drawn at the 50% probability level.

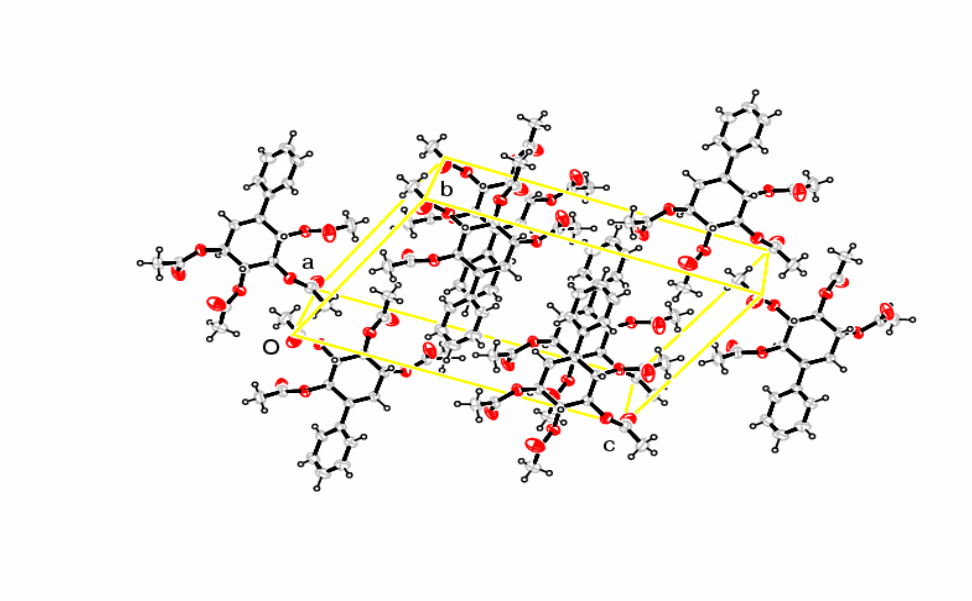


Figure 7. Molecular packing of the compound **144**

Table 2. Selected bond lengths (Å), angles (deg) and torsion angles (deg) for **144**

O(1)-C(19)	1.348(3)	O(4)-C(13)	1.342(3)
O(3)-C(15)	1.352(3)	O(6)-C(15)	1.191(4)
C(12)-C(7)	1.509(3)	C(1)-C(7)	1.485(3)
C(11)-C(10)	1.515(3)	C(7)-C(8)	1.332(3)
C(9)-C(8)	1.494(3)	C(6)-C(5)	1.387(4)
C(20)-C(19)	1.489(4)	C(17)-C(18)	1.487(4)
C(11)-C(12)-C(7)	112.2(4)	C(7)-C(1)-C(6)	120.2(3)
C(7)-C(1)-C(2)	121.7(5)	C(12)-C(11)-C(10)	111.8(2)
C(12)-C(7)-C(1)	117.7(4)	C(12)-C(7)-C(8)	120.2(2)
C(1)-C(6)-C(5)	120.9(4)	O(4)-C(13)-O(5)	123.7(3)
O(4)-C(13)-C(14)	110.5(4)	O(5)-C(13)-C(14)	125.9(3)
O(2)-C(17)-C(18)	110.4(5)	O(7)-C(17)-C(18)	126.2(4)
O(8)-C(19)-C(20)	125.3(3)	O(3)-C(15)-O(6)	124.1(2)
O(3)-C(15)-C(16)	109.9(5)	O(6)-C(15)-C(16)	126.0(4)
C(11)-C(12)-C(7)-C(1)	-155.2	C(7)-C(12)-C(11)-C(10)	-50.1
C(11)-C(12)-C(7)-C(8)	24.8	C(6)-C(1)-C(7)-C(12)	140.4
C(2)-C(1)-C(7)-C(8)	142.4	C(12)-C(11)-C(10)-C(9)	55.7
C(12)-C(7)-C(8)-C(9)	-4.6	C(1)-C(7)-C(8)-C(9)	175.4
C(11)-C(10)-C(9)-C(8)	-34.7	C(10)-C(9)-C(8)-C(7)	9.6

Table 3. Final Coordinates and Equivalent Isotropic Displacement for **144**

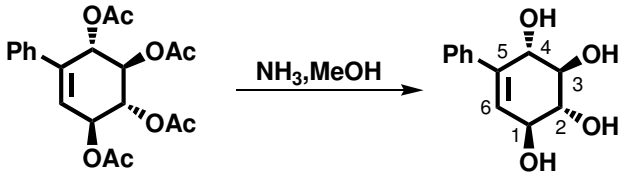
Atom	x	y	z	U(eq) [Ang^2]
O1	0.5695(3)	0.78029(13)	0.38650(8)	0.0478(4)
O2	0.5779(3)	0.95531(13)	0.20738(9)	0.0498(4)
O3	0.6295(3)	0.78435(14)	0.11727(8)	0.0497(4)
O4	0.2474(2)	0.59409(13)	0.17200(8)	0.0468(4)
O5	0.5513(3)	0.4782(2)	0.12330(12)	0.0820(8)
O6	0.3442(3)	0.8555(2)	0.03333(10)	0.0776(7)
O7	0.9453(3)	0.95648(19)	0.24496(14)	0.0819(7)
O8	0.4609(4)	0.98470(17)	0.38778(12)	0.0767(7)
C1	0.1141(4)	0.47314(18)	0.33603(11)	0.0449(5)
C2	0.1916(4)	0.3592(2)	0.31669(13)	0.0521(6)
C3	0.0453(5)	0.2529(2)	0.34138(15)	0.0633(8)
C4	-0.1808(5)	0.2584(2)	0.38531(16)	0.0675(8)
C5	-0.2582(4)	0.3691(2)	0.40617(16)	0.0641(8)
C6	-0.1131(4)	0.4761(2)	0.38157(13)	0.0535(6)
C7	0.2629(3)	0.59042(18)	0.30727(11)	0.0424(5)
C8	0.2775(4)	0.66591(19)	0.35290(12)	0.0465(6)
C9	0.4085(4)	0.79027(18)	0.32621(11)	0.0438(5)
C10	0.5641(3)	0.81590(17)	0.24494(11)	0.0426(5)
C11	0.4504(3)	0.76684(18)	0.18777(11)	0.0424(5)
C12	0.3997(3)	0.62252(18)	0.22337(11)	0.0420(5)
C13	0.3459(4)	0.5229(2)	0.12422(12)	0.0542(7)

Table 3. (Continued)

Atom	x	y	z	U(eq) [Ang^2]
C14	0.1640(6)	0.5074(3)	0.07461(18)	0.0812(11)
C15	0.5523(4)	0.8301(2)	0.04388(12)	0.0540(7)
C16	0.7660(5)	0.8415(3)	-0.02049(14)	0.0732(9)
C17	0.7742(4)	1.0143(2)	0.21335(13)	0.0535(7)
C18	0.7419(5)	1.1584(2)	0.17754(18)	0.0759(10)
C19	0.5845(4)	0.8863(2)	0.40971(12)	0.0493(6)
C20	0.7762(4)	0.8652(3)	0.46379(14)	0.0614(8)

2.6 THE SYNTHESIS OF (1S(R),2R(S),3R(S), 4S(R))-5-PHENYLCYCLO-HEX-5-ENE-1,2,3,4-TETROL (PHENYL SUBSTITUTED CONDURITOL-B) (134)

Acetoxy groups in molecule **144** was readily converted into hydroxyl groups through an aminolysis reaction in the presence of ammonia and methanol. Phenyl-substituted conduritol-B **(134)** was obtained in quantitative yield in three hours.



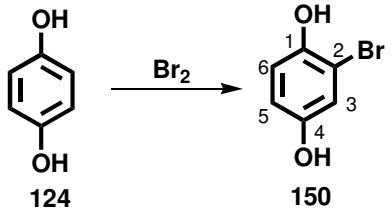
144 **134**

^{1}H-NMR indicated that five aromatic protons resonate at 7.33 ppm as a broad singlet. The olefinic proton H_6 gives a singlet at 5.71 ppm, H_1 resonates at 4.27 ppm. H_2 and H_3 give rise to an AB system at 3.52-3.64 ppm in which both parts are split into doublets. The remaining tertiary proton H_4 overlaps with hydroxyl protons at 4.70 ppm.

In the ^{13}C-NMR, there are six carbon signals at 127.1-139.6 ppm and four saturated carbons between 72.1 and 75.0 ppm.

2.7 THE SYNTHESIS OF 2-BROMOBENZENE-1,4-DIOL (150)

After the synthesis of phenyl-substituted conduritol, we were interested in the synthesis of a bromo-substituted conduritol. In order to do that a commercially available product, hydroquinone **(137)** was first brominated to obtain 2-bromobenzene-1,4-diol **(150)** [48].



Bromination was performed at low temperature in the presence of diehtyl ether in three hours. Column chromatography in ether-hexane was applied to separate **150** from the higher bromination products. Monobromination product **150** was obtained in a yield of 85% after purification.

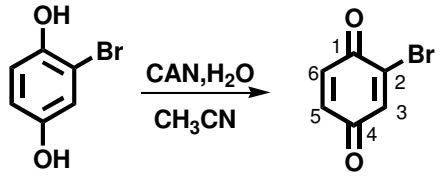
The structure of the compound **150** was elucidated on the basis of NMR spectroscopy. In the ^{1}H-NMR spectrum, the proton H_3 resonates at 6.11 ppm as a doublet due to the meta coupling between H_3 and H_5. Coupling constant between H_3 and H_5 is 2.8 Hz which is consistent wih the usual meta coupling constant. Protons H_5 and H_6 give rise to an AB system between 5.79-5.92 ppm. A part of the system belongs to H_6 and is split into doublet due to the ortho coupling between H_6 and H_5. B part of the system belongs to H_5 and it gives rise to a doublet of doublets, with a large coupling, 8.7 Hz and small coupling, 2.8 Hz. Two hydroxyl protons give a broad singlet at 6.00 ppm.

In the ^{13}C-NMR spectrum indicated six carbon signals at 149.0, 145.3, 117.9, 115.3, 114.1 and 108.4 ppm.

2.8 THE SYNTHESIS OF 2-BROMOBENZO-1,4-QUINONE (151)

Hydroquinones are oxidized to corresponding quinones in the presence of ceric ammonium nitrate (CAN) and acetonitrile. Recently, CAN has emerged as the reagent of choice in such transformations. The mechanism is believed to occur *via* two successive electron transfer processes from the electron-rich hydroquinone to cerium(IV) species [49].

Hydroquinone **150** was oxidized to quinone **151** in 30 minutes by using aqueous solution of CAN. Quinone **151** was obtained after crystallization from methanol in a yield of 87%.



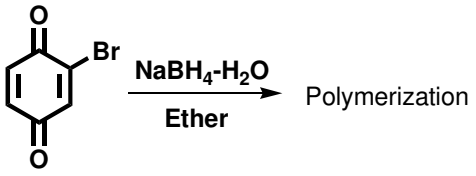
150 **151**

The ^{1}H-NMR and the ^{13}C-NMR spectra were in good agreement with the structure of the product **151**. The ^{1}H-NMR revealed that the olefinic proton H_3 resonates at 7.22 ppm as a doublet due to the allylic coupling with the olefinic proton H_5 with a coupling constant 2.3 Hz. H_5 and H_6 give rise to an AB system between 6.73-6.87 ppm. A part of the system belongs to H_6 and it gives a doublet due to the interaction with H_5 with a coupling constant 10.0 Hz which confirms the existence of a localized double bond between H_5 and H_6.

The ^{13}C-NMR indicated that carbonyl carbon resonances appear at 183.7 and 178.3 ppm. Olefinic carbons resonate at 137.9, 136.4, 135.6 ppm. Quaternary carbon C_2 resonates at 137.5 ppm.

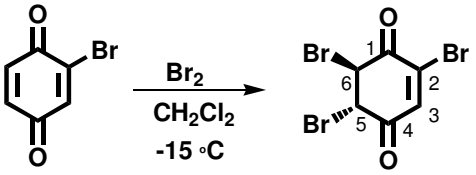
2.9 THE SYNTHESIS OF (5S(R),6S(R))-2,5,6-TRIBROMOCYCLOHEX-2-ENE-1,4-DIONE (153)

The next step was the reduction of the carbonyl groups in **151**. To achieve this process, compound **151** was treated with $NaBH_4$-H_2O in diethyl ether at 0 ºC. However, due to the unstability of **151** and its tendency to form the aromatic structure **150,** this step failed.



151

In order to overcome this problem, the strategy was changed. Before the reduction step, a bromination reaction was performed. As discussed before, molecule **151** was brominated in CH_2Cl_2 at low temperature in order to increase the selectivity of the reaction and to obtain tribromo compound **153**. The selectively bromination product **153** was found in quantitative yield.



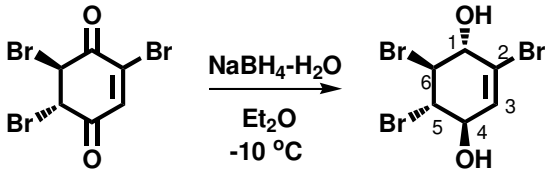
151 **153**

The NMR data of the molecule was consistent with the proposed structure. The olefinic proton H_3 resonates at 7.24 ppm as a doublet. The tertiary protons H_5 and H_6 give rise to an AB system between 4.81-4.97 ppm.

In the ^{13}C-NMR spectrum, there are three sets of carbon signals; carbonyl carbon resonances appear at 184.6 and 180.6 ppm, olefinic carbons resonate at 137.6 and 137.2 ppm and tertiary carbons C_5 and C_6 resonate at 44.7 and 43.4 ppm.

2.10 THE SYNTHESIS OF (1R(S),4R(S),5S(R),6S(R))-2,5,6-TRIBROMO-CYCLOHEX-2-ENE-1,4-DIOL (154)

Carbonyl groups in compound **153** were reduced upon treatment with aqueous $NaBH_4$ in dietylether at -10 ºC in three hours. The reaction should be performed at low temperatures to prevent the aromatization of compound **153** to form monobromo product **150**. The diol **154** was obtained in a yield of 80% after crystallization from methanol-hexane.

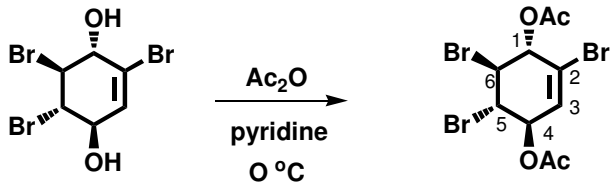


153 **154**

The ^{1}H-NMR spectral studies on **154** revealed the presence of the olefinic proton at 6.17 ppm as a singlet along with a doublet (H_1, J=7.4 Hz) at 4.44 ppm and doublet (H_4, J=6.7) at 4.38 ppm and an AB system at 4.16-4.21 ppm (H_5 and H_6). The ^{13}C-NMR spectrum also indicated two olefinic carbons at 134.5 (C_3) and 126.7 ppm (C_2) along with four saturated carbon signals at 76.8 (C_6), 74.4 (C_5), 60.0 (C_1), 59.2 ppm (C_4).

2.11 THE SYNTHESIS OF (1R(S),4R(S),5S(R),6S(R))-4-(ACETYLOXY)-2,5,6-TRIBROMOCYCLOHEX-2-EN-1-YL ACETATE (155)

Tribromo diol **154** was converted into diacetate **155** in the presence of acetic anhydride and pyridine at 0 ºC in 6 hours in order to protect hydroxyl groups. Compound **154** was obtained in quantitative yield.



154 **155**

The structure of the molecule was elucidated on the basis of ^{1}H-NMR and ^{13}C-NMR spectra. The ^{1}H-NMR indicated that the olefinic proton H_3 resonates at 6.18 ppm as a doublet and the tertiary proton H_1 gives a doublet at 5.88 ppm whereas H_4 gives rise to a doublet of doublets at 5.58 ppm. Protons H_5 and H_6 set up an AB system between 4.29 and 4.31 ppm.

^{13}C-NMR spectrum of **155** also revealed two carbonyl carbons at 168.9 and 168.4 ppm, two olefinic carbons at 130.3, 122.7 ppm along with six saturated carbon signals at 73.7, 73.3, 51.0, 50.3, 20.6, 20.5 ppm.

CHAPTER 3

EXPERIMENTAL

3.1 General Considerations

Nuclear Magnetic Resonance (^{1}H, ^{13}C, 2D) spectra were recorded on a Bruker Instrument, Avance Series-Spectrospin DPX-400 Bruker, 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. Deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) and deuterium oxide (D_2O) were used as solvents. Coupling constants (J values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols; s: singlet, d: doublet, t: triplet, q: quartet and m: multiplet. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}).

Column chromatographic separations were performed by using Fluka Silicagel 60 plates with 0,063-0,200 mm particle size. The relative proportions of solvents refer to volume:volume ratio. Thin layer chromatography (TLC) was effected by using precoated 0,25 mm silica gel plates purchased from Fluka.

All solvent purifications were done a stated in the literature [50].

3.2 Synthesis of 2-phenylbenzo-1,4-quinone (138)

A solution of 1,1'-biphenyl-2-ol **(136)** (10g, 59 mmol) in AcOH (40 mL) was added dropwise over a period of 10 min to a magnetically stirred, heterogeneous mixture of PbO_2 (35 g, 147 mmol), 70% $HClO_4$ (20 mL) and AcOH (60 mL). The resulting mixture was stirred for 15 min and filtered into a flask containing water (150 mL). The filter cake was washed with CH_2Cl_2 into the same flask. Black powder collected on the filter paper consisted of unreacted PbO_2. The contents of the flask were extracted with CH_2Cl_2. The organic extract was washed with water, dried over $MgSO_4$ and evaporated to dryness [45]. The residue was crystallized from methanol to give deep yellow crystals (9.0 g, 84%), m.p. 108-111 °C in good agreement with the literature data.

^{1}H-NMR (400 MHz, $CDCl_3/CCl_4$) δ 7.50-7.35 (5H, m, H_8-H_{12}), 6.85-6.76 (3H, m, H_3, H_5, or H_6); **^{13}C-NMR** (100 MHz, $CDCl_3/CCl_4$) δ 187.0, 186.1, 145.8, 137.0, 136.1, 132.7, 132.6, 130.0, 129.2, 128.4; **IR** (cm^{-1}) 3254 (br.), 1644 (s), 1591 (m), 1445 (w), 1105 (s), 977 (m), 897 (m), 747 (m), 692 (s).

3.3 Synthesis of (5S(R), 6S(R))-5,6-dibromo-2-phenylcyclohex-2-ene-1,4-dione (139)

To a solution of **138** (9.0 g, 49 mmol) in CH_2Cl_2, was added dropwise a solution of bromine (7.8 g, 49 mmol) in CH_2Cl_2 at -10 °C during 1 h. The mixture was stirred at -10 °C for 1 h and then it was allowed to warm to room temperature. The solvent was removed under reduced pressure to afford **139** (15.8 g, 94%) as a yellow solid, m.p.103-105 ºC.

^{1}H-NMR (400 MHz, $CDCl_3/CCl_4$) δ 7.49-7.26 (5H, m, H_8-H_{12}), 6.68 (1H, d, $J_{3,5}$=2.0 Hz, H_3), 4.83 (1H, d, A part of AB-system, $J_{6,5}$=2.7 Hz, H_6), 4.76 (1H, dd, B part of AB-system, $J_{5,6}$=2.7 Hz and $J_{5,3}$=2.0 Hz, H_5); **^{13}C-NMR** (100 MHz, $CDCl_3/CCl_4$) δ 187.5, 187.1, 146.7, 132.4, 131.3, 131.0, 129.1, 128.8, 47.1, 45.1; **IR** (cm^{-1}) 2934 (w), 1673 (s), 1592 (m), 1445 (w), 1348 (m), 1254 (m), 1227 (m),

1162 (m), 1016 (m), 961 (w), 928 (w), 913 (w), 768 (m), 709 (s), 687 (m), 638 (m). Anal. Calcd. for $C_{12}H_8Br_2O_2$: C, 41.00; H, 2.34. Found: C, 41.05; H, 2.56.

3.4 Synthesis of (1R(S),4R(S),5S(R),6S(R))-5,6-dibromo-2-phenylcyclohex-2-ene-1,4-diol (140)

Dibromo compound **139** (15 g, 44 mmol) was dissolved in 45 mL of ether and cooled down to 0 °C with an ice bath. To this mixture, an aqueous solution of $NaBH_4$ at 0 °C (4.1 g, 109 mmol) was added dropwisely. The reaction was monitored on TLC. After completion of the reaction, the organic phase was separated and aqueous phase was extracted with ether (3x50 mL). The combined organic extracts were dried over Na_2SO_4. Removal of the solvent gave oily product **140** (12.0 g, 80%) which was readily converted to compound **143**.

3.5 Synthesis of (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-5,6-dibromo-2-phenylcyclohex-2-en-1-yl acetate (143)

To a stirred solution of **140** (12 g, 35.0 mmol) in 20 mL of pyridine was added acetic anhydride (11.0 g, 105 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. The mixture was poured into 50 mL of HCl solution in ice and extracted with ether (3x50 mL). The combined organic extracts were washed with $NaHCO_3$ and water and then dried over $MgSO_4$. The removal of the solvent under reduced pressure followed by the column chromatography over SiO_2 of the residue with 9:0.5 EtOAc-hexane and crystallization from EtOAc-hexane (3:1) afforded pure white crystalline product **143** (11.0 g, 75%), m.p. 114-116 ºC.

^{1}H-NMR (400 MHz, $CDCl_3/CCl_4$) δ 7.32-7.22 (5H, m, aromatic protons), 6.33 (1H, dt, $J_{1,6}$=6.9 Hz and $J_{1,3}$=$J_{1,4}$=1.9 Hz, H_1), 5.86 (1H, dd, J_{34}=2.5 and J_{31}=1.9 Hz, H_3), 5.80 (1H, ddd, $J_{4,5}$=7.2 Hz, $J_{4,3}$=2.5 and $J_{4,1}$=1.9, H_4), 4.41 (1H, dd, A part of AB-system, $J_{6,5}$=10.8 Hz and $J_{6,1}$=6.9, H_6), 4.39 (1H, dd, B part of AB-system, $J_{5,6}$=10.8 Hz and $J_{5,4}$=7.2 Hz, H_5), 2.10 (3H, s, -CH_3), 1.90 (3H, s, -CH_3); **^{13}C-**

NMR (100 MHz, $CDCl_3/CCl_4$) δ 169.3, 169.2, 140.3, 136.7, 128.5, 128.4, 126.6, 125.8, 73.7, 72.3, 52.7, 51.4, 20.7, 20.5; **IR** (cm^{-1}) 2924 (m), 1853 (w), 1772 (s), 1758 (m), 1497 (m), 1474 (w), 1371 (s), 1194 (s), 1154 (s), 1081 (m), 920 (s), 875 (m), 850 (s), 716 (s); MS (m/z, relative intensity): 432, (M+), 188 (45), 171 (100), 170 (80), 153 (35), 143 (50), 142 (65), 116 (55), 103 (20), 92 (15), 77 (40), 63 (30). Anal. Calcd. for $C_{16}H_{16}Br_2O_4$; C, 44.47; H, 3.73. Found: C, 44.44; H, 3.62.

3.6 Synthesis of (1S(R),4S(R),5R(S),6R(S))-4,5,6-tris(acetyloxy)-2-phenyl-cyclohex-2-en-1-yl acetate (144)

A vigorously stirred mixture of **143** (10 g, 23 mmol) glacial AcOH (150 mL), Ac_2O (30 mL) and anhydrous KOAc (13.8 g, 140 mmol) was heated under reflux for 3 days under a nitrogen atmosphere. The solvent was removed under reduced pressure. Methanol (20 mL) was added to the residue and stirred for 10 min. The solution was concentrated and the residue was partitioned between ether (50 mL) and water (75 mL). The organic layer was washed with aqueous $NaHCO_3$, dried over MgSO4 and concentrated to yield a solid. The solid was chromatographed on silica gel by elution with EtOAc-Hexane (1:9) to afford colorless crystalline product **144** from EtOAc-Hexane (3:1) (6.0 g, 75%), m.p. 114-116 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (5H, m, aromatic protons), 6.29 (1H, dt, $J_{1,6}$=6.6 Hz and $J_{1,3}$=2.0 Hz, H_1), 5.83 (1H, t, $J_{3,1}$=$J_{3,4}$=2.0 Hz, H_3), 5.73 (1H, dt, $J_{4,5}$=7.1 Hz and $J_{4,3}$=$J_{4,1}$=2.0 Hz, H_4), 5.47 (1H, dd, A part of AB-system, $J_{5,6}$=10.2 Hz and $J_{5,4}$=7.1 Hz, H_5), 5.40 (1H, dd, B part of AB-system, $J_{6,5}$=10.2 Hz and $J_{6,1}$=6.6 Hz, H_6), 2.09 (3H, s, -CH_3), 2.07 (3H, s, -CH_3), 2.05 (3H, s, -CH_3), 1.80 (3H, s, -CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.2, 170.1, 139.4, 136.6, 128.7, 128.6, 126.6, 125.5, 72.5, 71.9, 71.1, 71.0, 21.1, 20.9, 20.8, 20.7; **IR** (cm^{-1}) 2995 (w), 1734 (s), 1363 (m), 1217 (s), 1018 (m), 964 (m), 927 (m), 766 (m), 705 (m); MS (m/z, relative intensity): 390 (M^+), 229 (10), 228 (50), 187 (30), 186 (100), 158 (25), 157 (20). Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.55; H, 6.00.

(1R(S),4R(S),5S(R),6R(S))-4,6-bis(acetyloxy)-5-bromo-2-phenylcyclohex-2-en-1-yl acetate (145), ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20-7.35 (5H, m, aromatic protons), 6.20 (2H, quasi t, H_1 or H_3), 5.80 (1H, dd, $J_{6,5}$=6.3 Hz and $J_{6,1}$=3.7 Hz, H_6), 5.50 (1H, dd, $J_{4,3}$=5.0 Hz and $J_{4,5}$=2.6 Hz, H_4), 4.50 (1H, dd, $J_{5,6}$=6.3 Hz and $J_{5,4}$=2.6 Hz, H_5), 2.20 (3H, s, -CH_3), 2.10 (3H, s, -CH_3), 1.90 (3H, s, -CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.3, 169.0, 168.9, 138.9, 136.6, 128.6, 128.5, 126.2, 124.7, 71.4, 71.3, 68.3, 47.2, 20.8, 20.6, 20.5; Anal. Calcd. for $C_{19}H_{21}BrO_5$: C, 55.76; H, 5.17. Found: C, 55.71; H, 5.14.

3.7 Synthesis of (1S(R),2R(S),3R(S),4S(R))-5-phenylcyclohex-5-ene-1,2,3,4-tetrol (phenyl-substituted conduritol-B) (134)

5.0 g (13 mmol) of tetraacetate **144** was dissolved in 40 mL of absolute methanol. While being passed dry NH_3 through the solution, the mixture was stirred for 2 h at room temperature. Evaporation of methanol and formed acetamide gave a viscous, colorless, oily **134** (2.5 g, 89%).

^{1}H-NMR (400 MHz, D_2O) δ 7.33 (5H, br. s, H_8-H_{12}), 5.71 (1H, s, H_6), 4.70 (5H, br. s, -OH and H_1), 4.27 (1H, br.d, J=7.0 Hz, H_4), 3.64 (1H, d, A part of AB-system, $J_{3,2}$=10.5 Hz, H_3), 3.52 (1H, d, B part of AB-system, $J_{2,3}$=10.5 Hz, H_2); **^{13}C-NMR** (100 MHz, D_2O) δ 139.6, 138.3, 128.6, 128.1, 127.8, 127.1, 75.8, 75.0, 72.3, 72.1; **IR** (cm^{-1}) 3352 (br.), 2990 (br.), 2214 (w), 2071 (m), 1121 (m), 972 (s), 822 (w).

3.8 Synthesis of 2-bromobenzene-1,4-diol (150)

To a solution of hydroquinone **(135)** (10 g, 90.6 mmol) in diethyl ether was added bromine (10.3 g, 64.3 mmol) in 2 h dropwise at 0 ºC. The reaction mixture was stirred at the same temperature for 2 h. The solvent was removed under reduced pressure. The residue was purified with column chromatograpy by elution with Et_2O-Hexane (1:1). Compound **150** (13.0 g, 75%) was obtained as a white solid,

m.p. 118-120 ºC. The physical properties of the compound is in agreement with the literature data [51].

^{1}H-NMR (400 MHz, DMSO-d_6/CCl_4) δ 6.60 (2H, s, -OH), 6.11 (1H, d, $J_{3,5}$=2.8 Hz, H_3), 5.92 (1H, d, A part of AB-system, $J_{6,5}$=8.7 Hz, H_6), 5.79 (1H, dd, B part of AB-system, $J_{5,6}$=8.7 Hz and $J_{5,3}$=2.8 Hz, H_5); **^{13}C-NMR** (100 MHz, DMSO-d_6/CCl_4) δ 149.0, 145.3, 117.9, 115.3, 114.1, 108.4; **IR** (cm^{-1}) 3175 (br.), 1597 (m), 1518 (w), 1448 (s), 1362 (m), 1274 (m), 1228 (s), 1035 (s), 891 (m), 855 (s), 772 (s).

3.9 Synthesis of 2-bromobenzo-1,4-quinone (151)

Monobromo compound **149** (7 g, 37 mmol) was dissolved in CH_3CN (30 mL). While stirring at room temperature, an aqueous solution of CAN (51 g, 92.6 mmol) was added to the mixture dropwise in 15 min. A transient orange-black colour was observed. After stirring for 30 min at room temperature, the reaction mixture was extracted with $CHCl_3$ (3x50 mL) and the organic phase was washed with water and dried over $MgSO_4$ [49]. The solvent was removed, and **150** (6.0 g, 85%) was obtained from methanol as a yellow crystal, m.p. 60-62 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, d, $J_{3,5}$=2.4 Hz, H_3), 6.87 (1H, d, A part of AB-system, $J_{6,5}$=10.0 Hz, H_6), 6.73 (1H, dd, B part of AB-system, $J_{5,6}$=10.0 Hz and $J_{5,3}$=2.4 Hz, H_5); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 183.7, 178.3, 137.9, 137.5, 136.4, 135.6; **IR** (cm^{-1}) 3054 (w), 1656 (s), 1577 (s), 1371 (w), 1314 (m), 1277 (s), 1095 (m), 1011 (w), 972 (s), 919 (s), 833 (s), 779 (w), 626 (m).

3.10 Synthesis of (5S(R),6S(R))-2,5,6-tribromocyclohex-2-ene-1,4-dione (153)

To a solution of **151** (6.0 g, 32 mmol) in CH_2Cl_2, was added dropwise at -20 °C a solution of bromine (7.5 g, 47 mmol) in CH_2Cl_2 in 2 h. The mixture was stirred at the same temperature for 2.5 h and then it was allowed to warm to room

temperature. The solvent was removed under reduced pressure to afford **153** (10 g, 94%) from EtOAc-hexane as a yellow crystal, m.p.63-65 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, d, $J_{3,5}$=1.8 Hz, H_3), 4.97 (1H, d, $J_{6,5}$=2.7 Hz, H_6), 4.81 (1H, dd, $J_{5,6}$=2.7 Hz and $J_{5,3}$=1.8 Hz, H_5); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 184.6, 180.6, 137.6, 137.2, 44.7, 43.4; **IR** (cm^{-1}) 3048 (w), 3000 (w), 1685 (s), 1577 (m), 1327 (m), 1303 (m), 1269 (s), 1224 (s), 1166 (w), 1126 (w),1023 (m), 951 (s), 906 (m), 791 (w), 768 (w), 708 (w), 632 (m),617 (m).

3.11 Synthesis of (1R(S),4R(S),5S(R),6S(R))-2,5,6-tribromocyclohex-2-ene-1,4-diol (154)

Tribromo quinone **153** (8 g, 23 mmol) was dissolved in 25 mL of ether and cooled down to -10 °C. To this mixture, an aqueous solution of $NaBH_4$ at 0 °C (2.2 g, 58 mmol) was added dropwisely. The reaction was monitored on TLC. After the completion of the reaction, the organic phase was separated and aqueous phase was extracted with ether (3x50 mL). The combined organic extracts were dried over Na_2SO_4. Removal of the solvent gave the crude product which was crystallized from MeOH-Hexane (4:1) to obtain white solid **154** (6.6 g, 82%), m.p. 160-162 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, s, H_3), 4.82 (2H, br. s, -OH), 4.44 (1H, d, $J_{1,6}$=7.4 Hz, H_1), 4.38 (1H, d, $J_{4,5}$=6.7 Hz, H_4), 4.21 (1H, dd, A part of AB-system, $J_{6,5}$=12.2 Hz and $J_{6,1}$=7.4 Hz, H_6), 4.16 (1H, dd, B part of AB-system, $J_{5,6}$=12.2 Hz and $J_{5,4}$=6.7 Hz, H_5); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 134.5, 126.7, 76.8, 74.4, 60.0, 59.2; **IR** (cm^{-1}) 3357 (br.), 2887 (w), 1648 (w), 1588 (w), 1448 (m), 1299 (m), 1260 (m), 1230 (s), 1194 (m), 1058 (s), 892 (m), 819 (m).

3.12 Synthesis of (1R(S),4R(S),5S(R),6S(R))-4-(acetyloxy)-2,5,6-tribromo-cyclohex-2-en-1-yl acetate (155)

To a stirred solution of **154** (6 g, 17 mmol) in 10 mL of pyridine was added acetic anhydride (5.2 g, 51 mmol) dropwisely at -5 °C. The reaction mixture was stirred at room temperature for 8 hours. The mixture was poured into 40 mL of HCl solution in ice and extracted with ether (3x50 mL) . The combined organic extracts were washed with $NaHCO_3$ and water and then dried over $MgSO_4$. The removal of the solvent under reduced pressure followed by crystallization from EtOAc-hexane (3:1) afforded pure white solid product **155** (6.0 g, 80%), m.p.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.18 (1H, d, $J_{3,4}$=3.0 Hz, H_3), 5.88 (1H, d, $J_{1,6}$=6.6 Hz, H_1), 5.58 (1H, dd, $J_{4,5}$=6.7 Hz and $J_{4,3}$=3.0 Hz, H_4), 4.31 (1H, dd, A part of AB-system, $J_{6,5}$=10.2 Hz and $J_{6,1}$=6.6 Hz, H_6), 4.29 (1H, dd, B part of AB-system, $J_{5,6}$=10.2 Hz and $J_{5,4}$=6.7 Hz, H_5), 2.19 (3H, s, -CH_3), 2.13 (3H, s, -CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 168.9, 168.4, 130.3, 122.7, 73.7, 73.3, 51.0, 50.3, 20.6, 20.5; **IR** (cm^{-1}) 2934 (w), 1751 (s), 1429 (w), 1371 (m), 1289 (w), 1205 (s), 1031 (s), 913 (m), 873 (m), 729 (w), 682 (m), 634 (m).

CHAPTER 4

CONCLUSION

Conduritols 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 conduritols and their derivatives is a field of interest.

In this study, double bond substituted conduritols, **134** and **135** were planned to be synthesized starting from **136** and **137**.

The synthesis of phenyl-substituted conduritol **(134)** was achieved succesfully. Moreover, a considerable advance in the synthesis of bromo-substituted conduritol **(135)** was obtained. All of the key compounds were synthesized for the first time throughout this work. **134** and **135** are believed to have some important biological activities. In future, studies on the investigation of biological activities of those molecules will be completed. In addition, those molecules will be the key compounds for the synthesis of other cyclitol derivatives like, inositols and quercitols. The synhetic methodology which was developped in this work will also be used for the synthesis of other double bond substituted conduritols in future.

REFERENCES

1. Posternak, T., *The Cyclitols*, Hermann, Paris, **1965**.

2. Jotterand, N.; Vogel, P. *Helv. Chim. Acta* **1999**, *82*, 821.

3. Balcı, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715.

4. Balcı, M. *Pure Appl. Chem*. **1997**, *69*, 97.

5. Hudlicky, T.; Luna, H.; Olivo, H. F.; Anderson, C.; Nugent, T.; Price, J. D. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2907.

6. Nakajima, M.; Tomida, I.; Takei, S. *Chem. Ber*. **1957**, *90*, 246.

7. Knapp, S.; Ornaf, R. M.; Rodriquez, K. E. *J. Am. Chem. Soc*. **1983**, *105*, 5494.

8. Aleksejczyk, R. A.; Berchtold, G. A. *J. Am. Chem. Soc*. **1985**, *107*, 2554.

9. Sütbeyaz, Y.; Seçen, H.; Balcı, M. *J. Chem. Soc. Chem. Commun*. **1988**, 1331.

10. McIntosh, M.C., Weinreb, S. M., *J. Org. Chem*., **1991**, *56*, 5010.

11. Gallos, J. K.; Koftis, T. V.; Sarli, V. C.; Litinas, K. E. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3705.

12. Ackermann, L.; Tom, D. E.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195.

13. Müller, H. *J. Chem. Soc*. **1912**, *101*, 2383.

14. Casland, G. E.; Horswill, E. C. *J. Am. Chem. Soc*. **1953**, *75*, 4020.

15. Nagabhushan,T., L. *Can. J. Chem*. **1970**, *48*, 383.

16. Paulsen, H.; Röben, W.; Heiker, F. R. *Chem. Ber*. **1981**, *114*, 3242.

17. Akiyama, T.; Shima, H.; Ozaki, S. *Tetrahedron Lett*. **1991**, *32*, 5593.

18. Guo, Z. X.; Haines, A. H.; Pyke, S. M.; Pyke, S. G.; Taylor, R. J. K. *Carbohyd. Res*. **1994**, *264*, 147.

19. Seçen, H.; Sütbeyaz, Y.; Balcı, M. *Tetrahedron Lett*. **1990**, *31*, 1323.

20. McCasland, G. E.; Reeves, J. M. *J. Am. Chem. Soc*. **1955**, *77*, 1812.

21. Yurev, Y. K.; Zefirov, N. S. *Zh. Obshchei Khim*. **1961**, *31*, 685.

22. Drian, Le C.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 338

23. Hudlicky, T.; Fan, R.; Tsunoda, T.; Luna, H. *J. Isr. Chem*. **1991**, *31*, 229.

24. Seçen, H.; Maraş, A.; Sütbeyaz, Y.; Balcı, M. *Synth. Commun*. **1992**, *22*, 2613.

25. Angyal, S. J.; Gilham, P. T. *J. Chem. Soc*. **1955**, 375.

26. Criegee, R.; Becher, P. *Chem. Ber*. **1957**, *90*, 2516.

27. Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc. Chem. Commun*. **1991**, 61.

28. Knight, J.; Sweeney, J. B. *Tetrahedron Lett*. **1996**, *37*, 6579.

29. Kara, Y.; Balcı, M., Bourne, S. A.; Watson, W. H. *Tetrahedron Lett*. **1994**, *35*, 3349.

30. Kara, Y.; Balcı, M. *Tetrahedron* **2003**, *59*, 2063.

31. Hudlicky, T.; Price, J. D.; Olivo, H. F. *Synlett* **1991**, 645.

32. Maraş, A.; Seçen, H.; Sütbeyaz, Y.; Balcı, M. *Turk. J. Chem*. **1996**, *20*, 341.

33. Mehta, G.; Lakshminath, S. *Tetrahedron Lett*. **2000**, *41*, 3509.

34. Seçen, H.; Gültekin, S.; Sütbeyaz, Y.; Balcı, M. *Synth. Commun*. **1994**, *24*, 2103.

35. Ley, S. V.; Redgrave, A. J. *Synlett* **1990**, 393.

36. Schulz, J.; Gani, D. *J. Chem. Soc. Perkin Trans. 1* **1997**, 657.

37. Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc. Chem. Commun*. **1992**, 234.

38. Guo, Z. X.; Haines, A. H.; Taylor, R. J. K. *Synlett* **1993**, 607.

39. Esser, T.; Farkas, F.; Mangholz, S.; Sequin, U. *Tetrahedron* **1994**, *50*, 3709.

40. Falshaw, A.; Hart, J. B.; Tyler, P. C. *Carbohyd. Res*. **2000**, *329*, 301.

41. Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc*. **1995**, *117*, 3643.

42. .Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc*. **1992**, *114*, 9694.

43. Lambert, W., Burke, S. D. *Org. Lett*. **2005**, *5*, 515.

44. Hudlicky, T.; Abbound, K. A.; Entwistle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J.; Bolonick, J.; Myers, B. *Synlett* **1996,** 897.

45. Omura, K. *Synthesis* **1998**, 1145.

46. Altenbach, H., J.; Stegelmeier, H.; Vogel, E. *Tetrahedron Lett*. **1978**, 3333.

47. De la Mare; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, Elsevier, New York, **1982**.

48. Barrero, A., F.; Alvarez-Manzaneda E., J.; Chahboun, R., Diaz, C., G. *Synlett* **2000**, 1561.

49. Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. Jr. *J. Org. Chem.* **1976**, 3627.

50. Furniss B. S.; Hannoford, A., J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Organic Chemistry, London*, Longman Group, **1989**.

51. Rajagopal, R.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Journal of Molecular Catalysis* **2003**, 165.

APPENDIX A

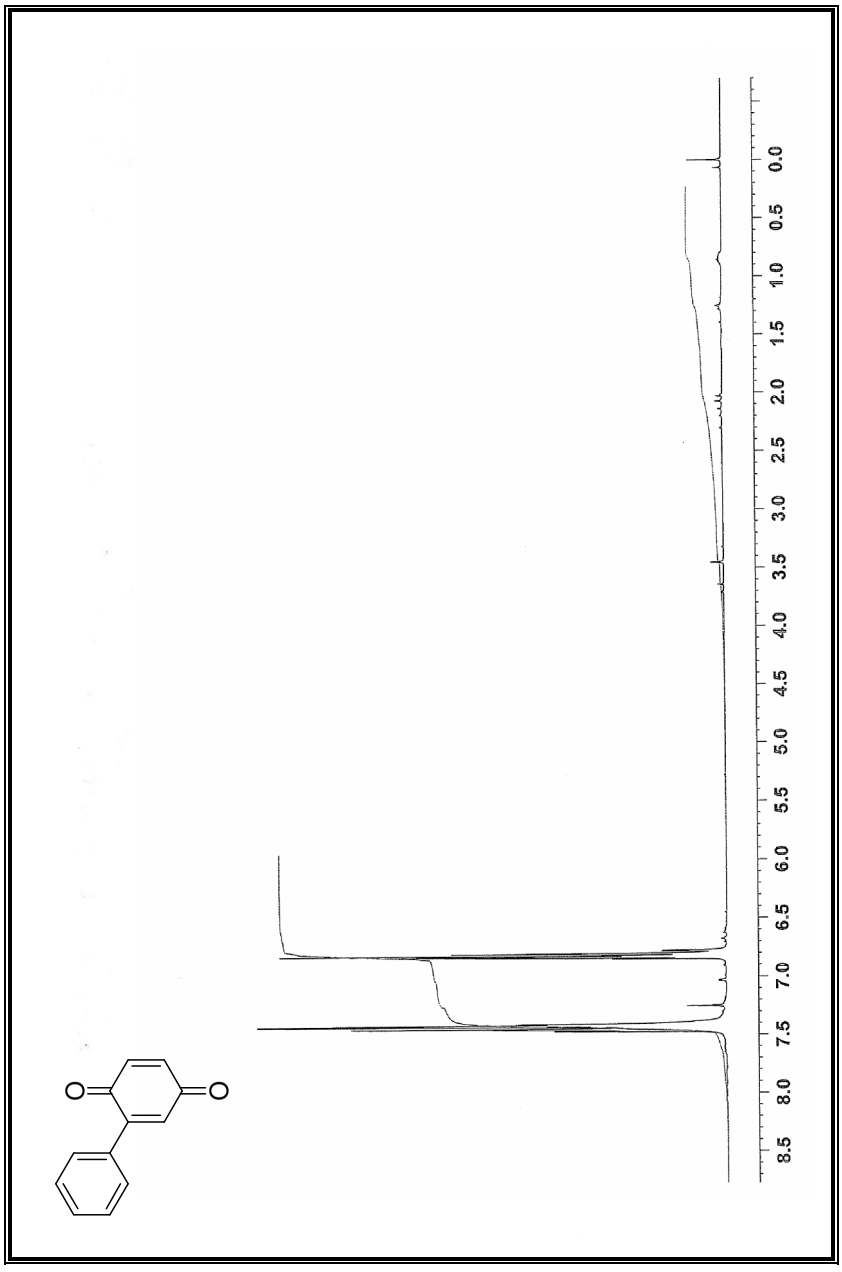


Figure A1 ^{1}H-NMR Spectrum of Compound **138**.

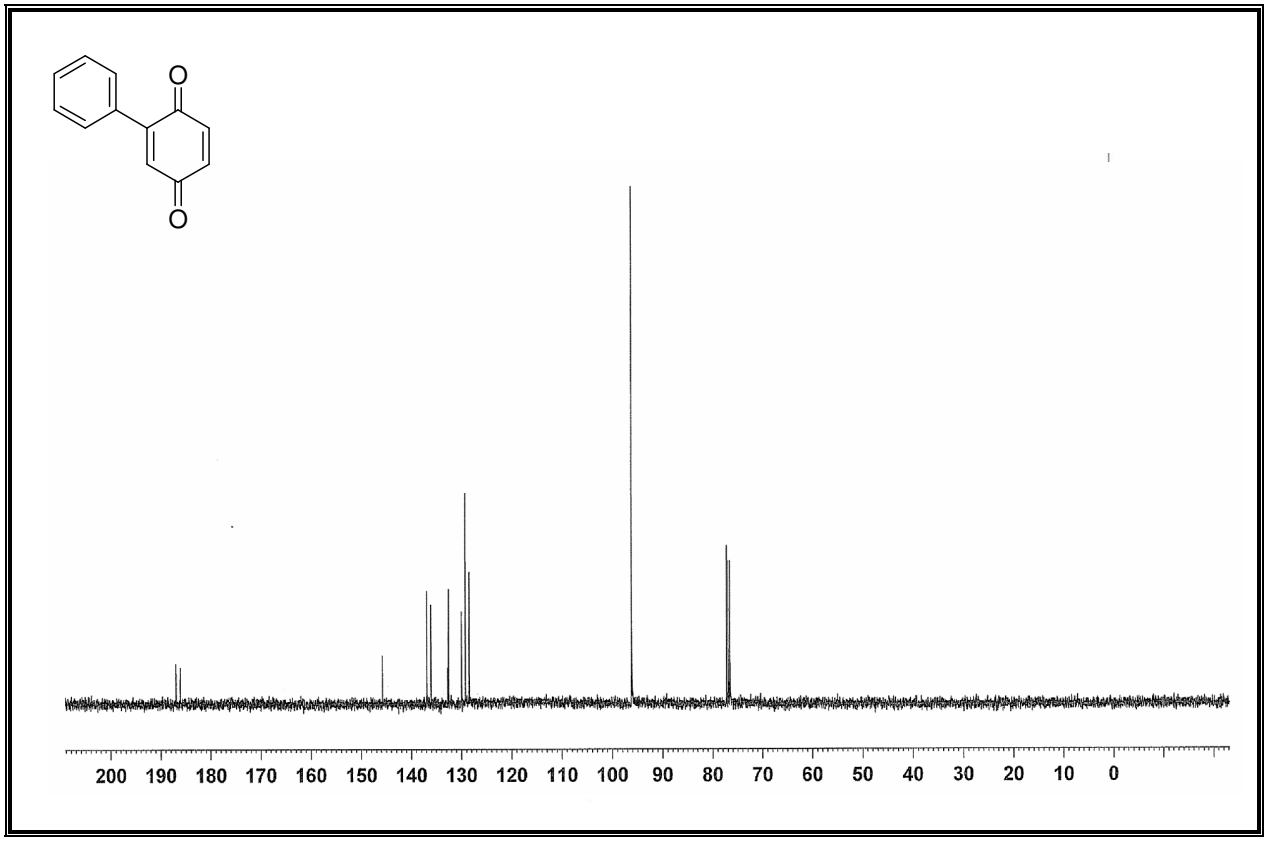


Figure A2 ^{13}C-NMR Spectrum of Compound **138**.

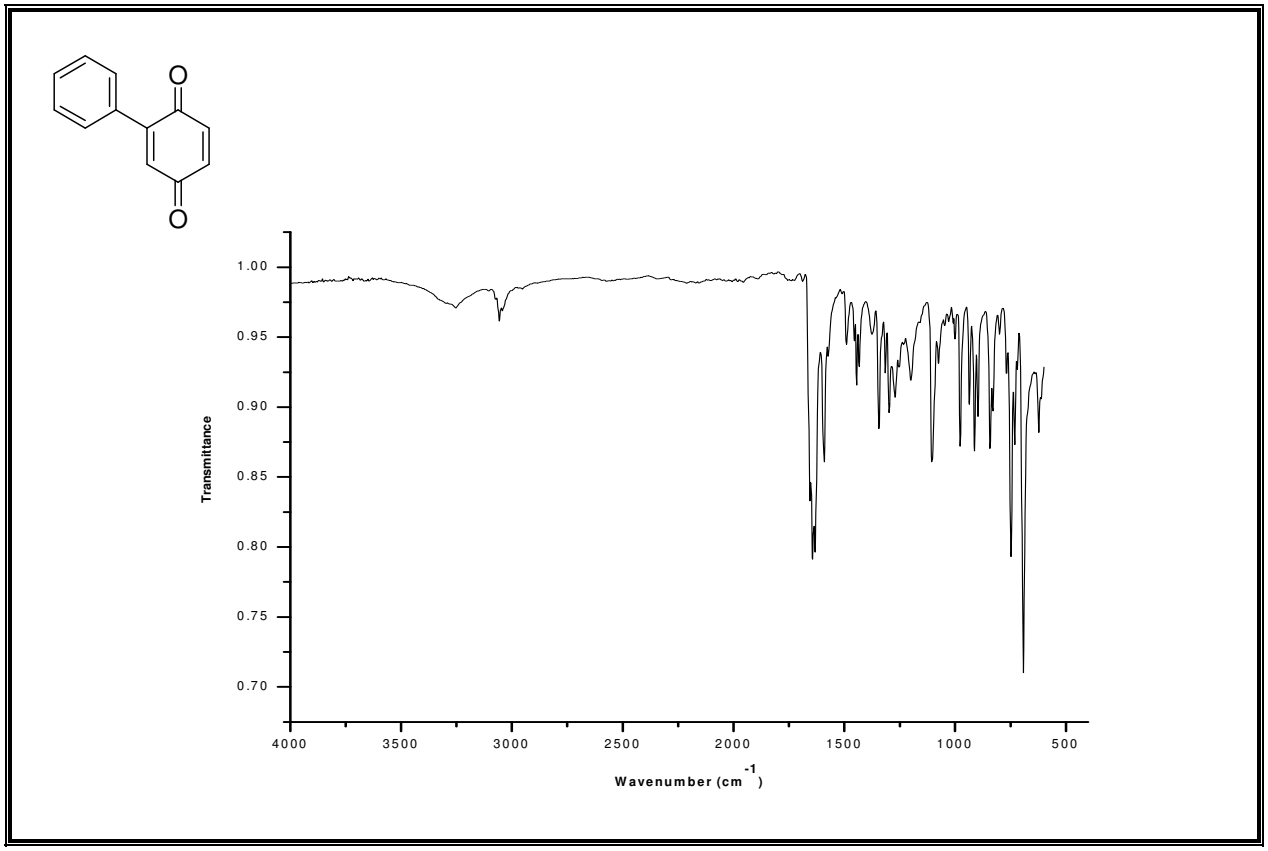


Figure A3 IR Spectrum of Compound **138**.

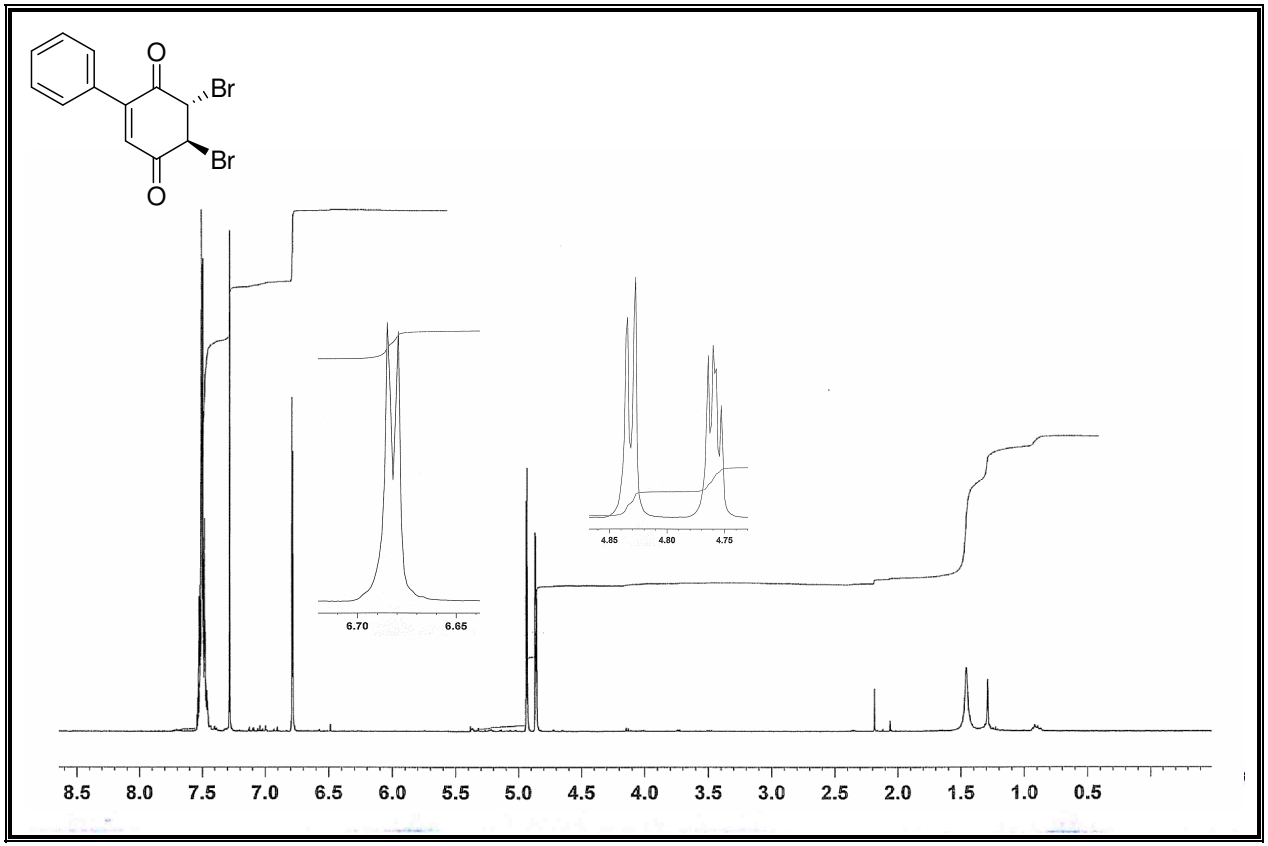


Figure A4 ^{1}H-NMR Spectrum of Compound **139**.

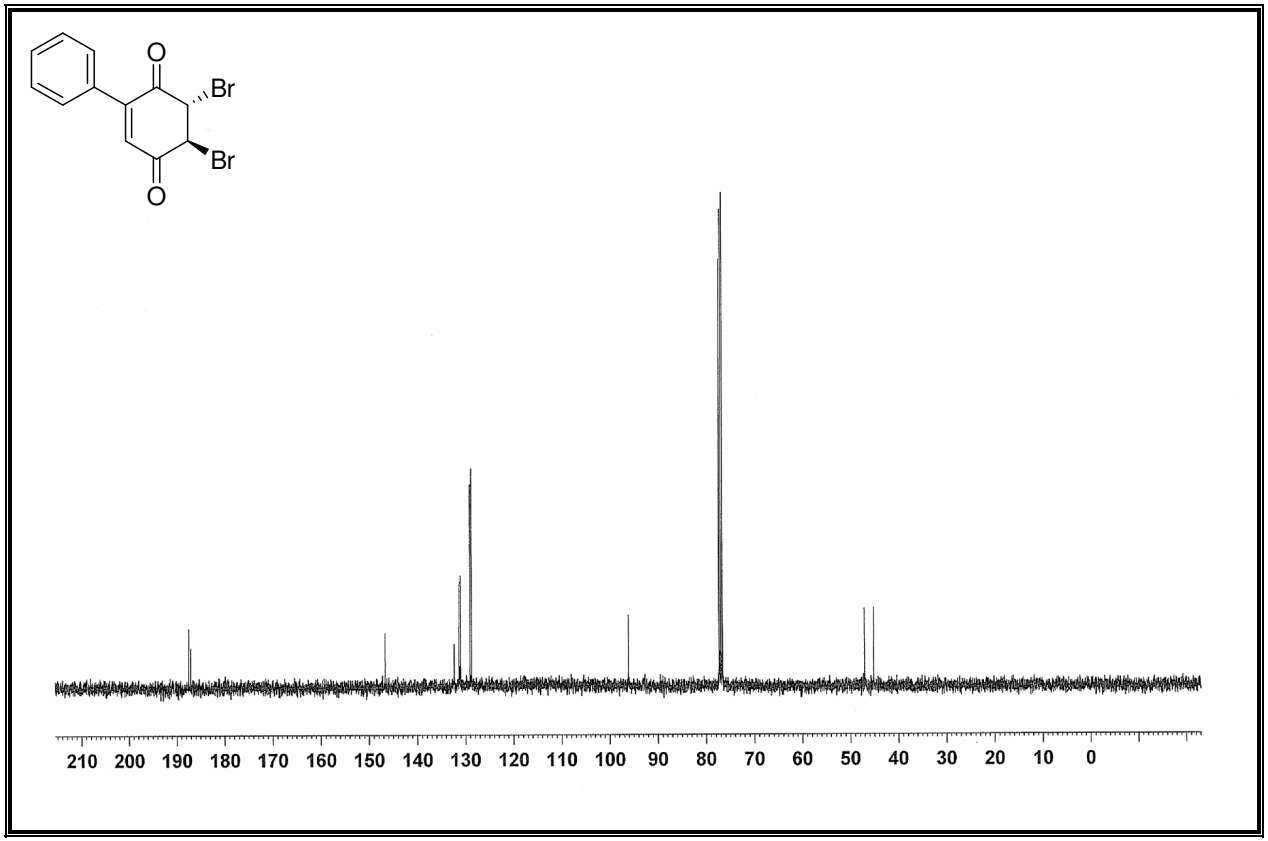


Figure A5 ^{1}C-NMR Spectrum of Compound **139**.

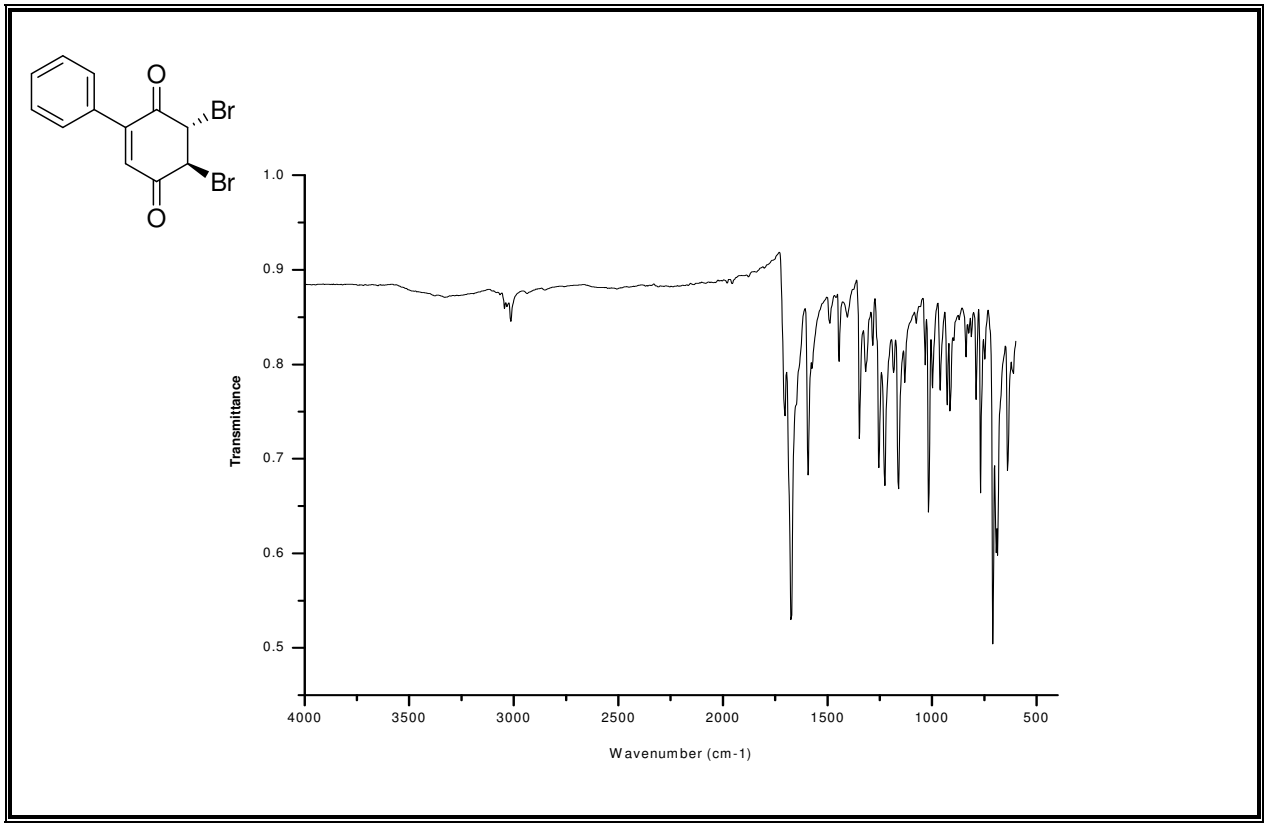


Figure A6 IR Spectrum of Compound **139**.

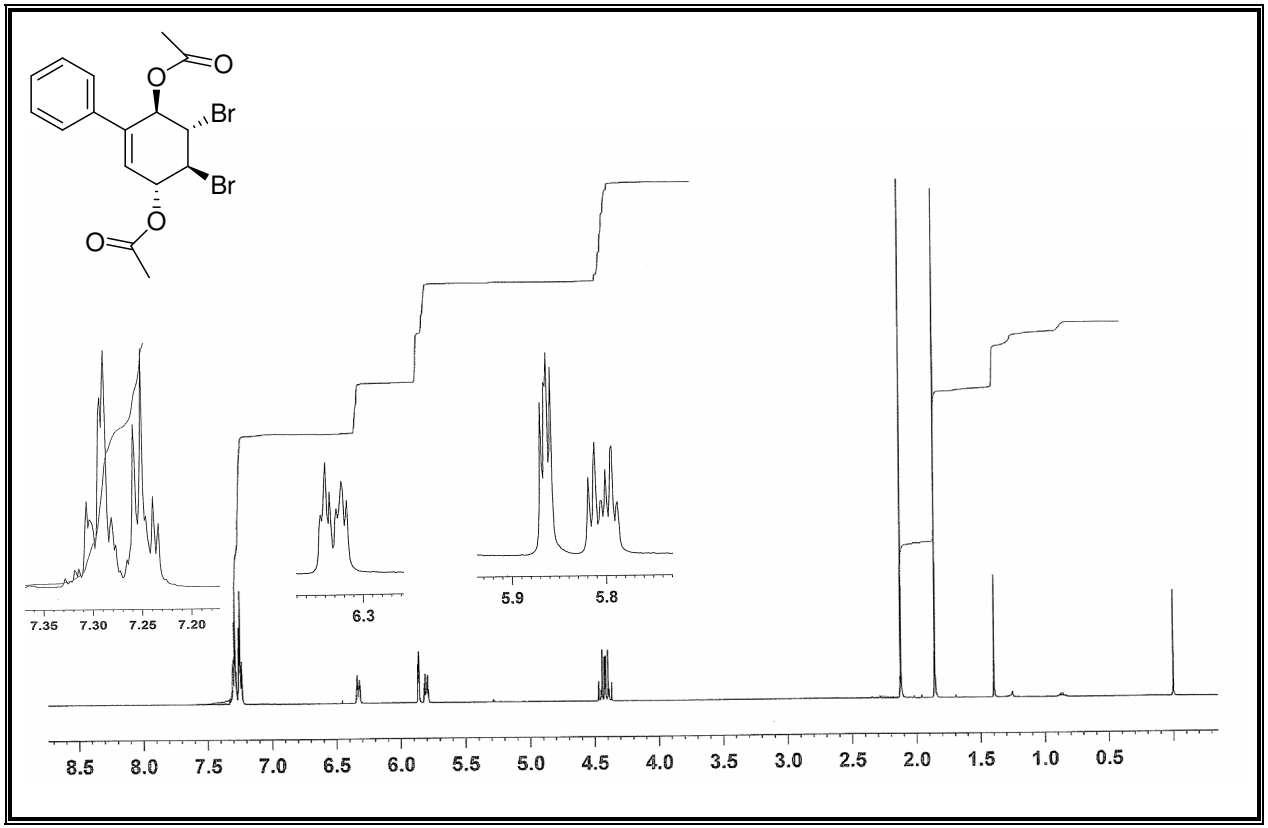


Figure A7 ^{1}H-NMR Spectrum of Compound **143**.

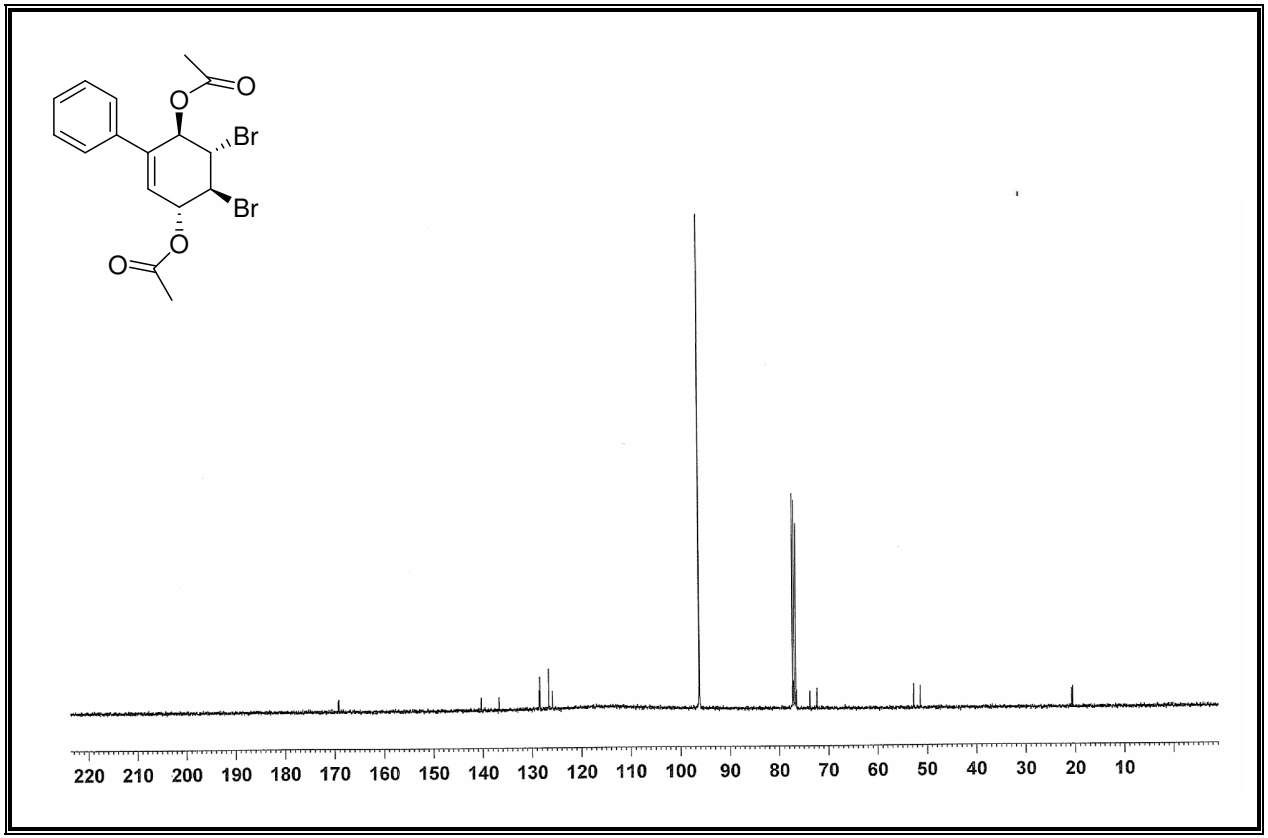


Figure A8 ^{13}C-NMR Spectrum of Compound **143**.

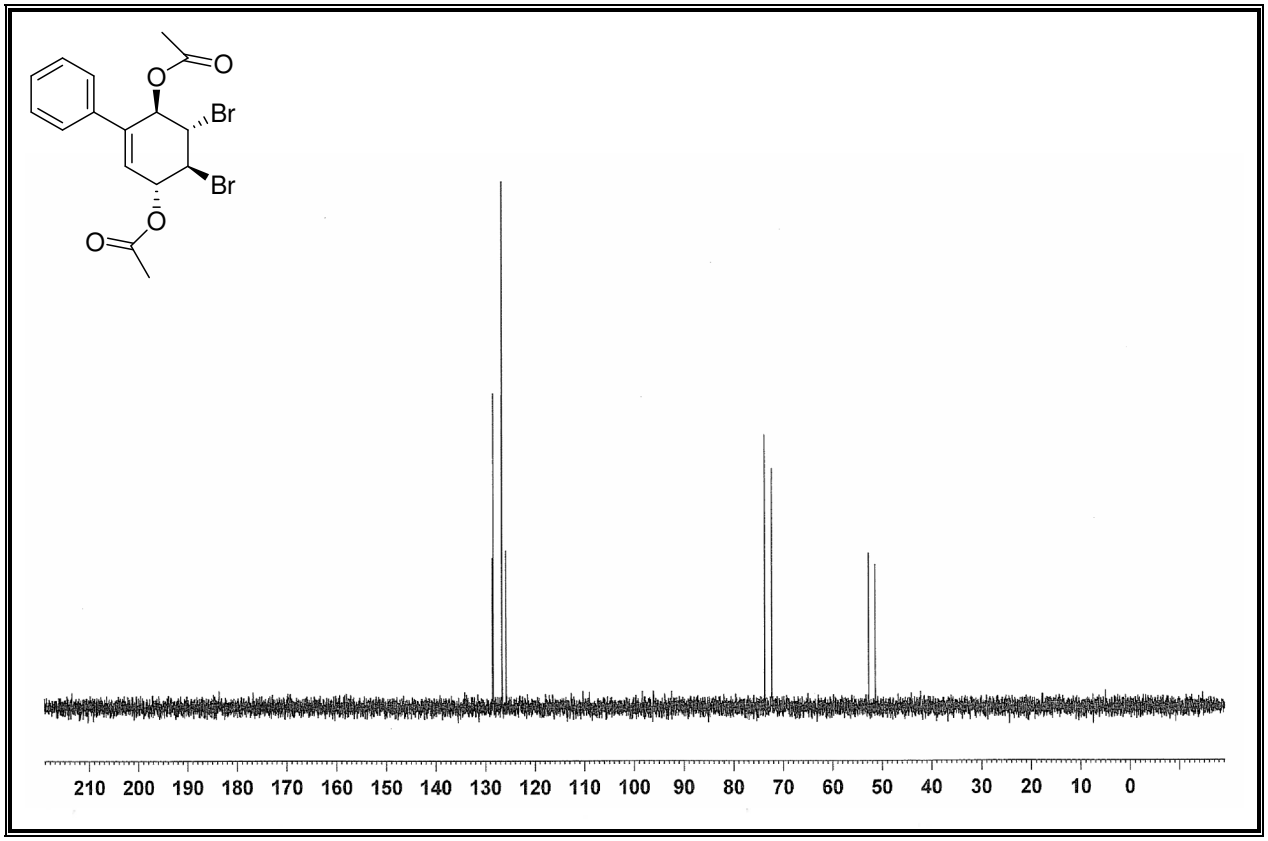


Figure A9 DEPT-90 Spectrum of Compound **143**.

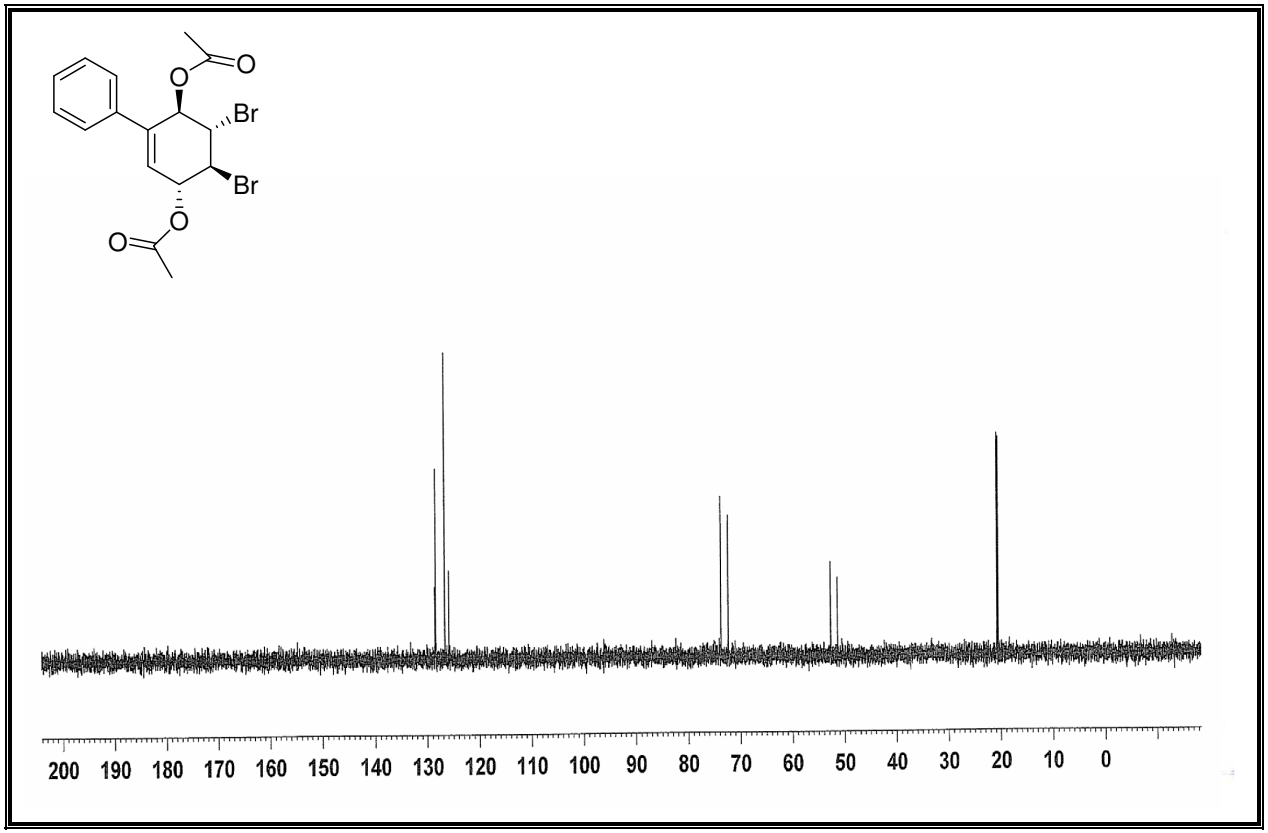


Figure A10 DEPT-135 Spectrum of Compound **143**.

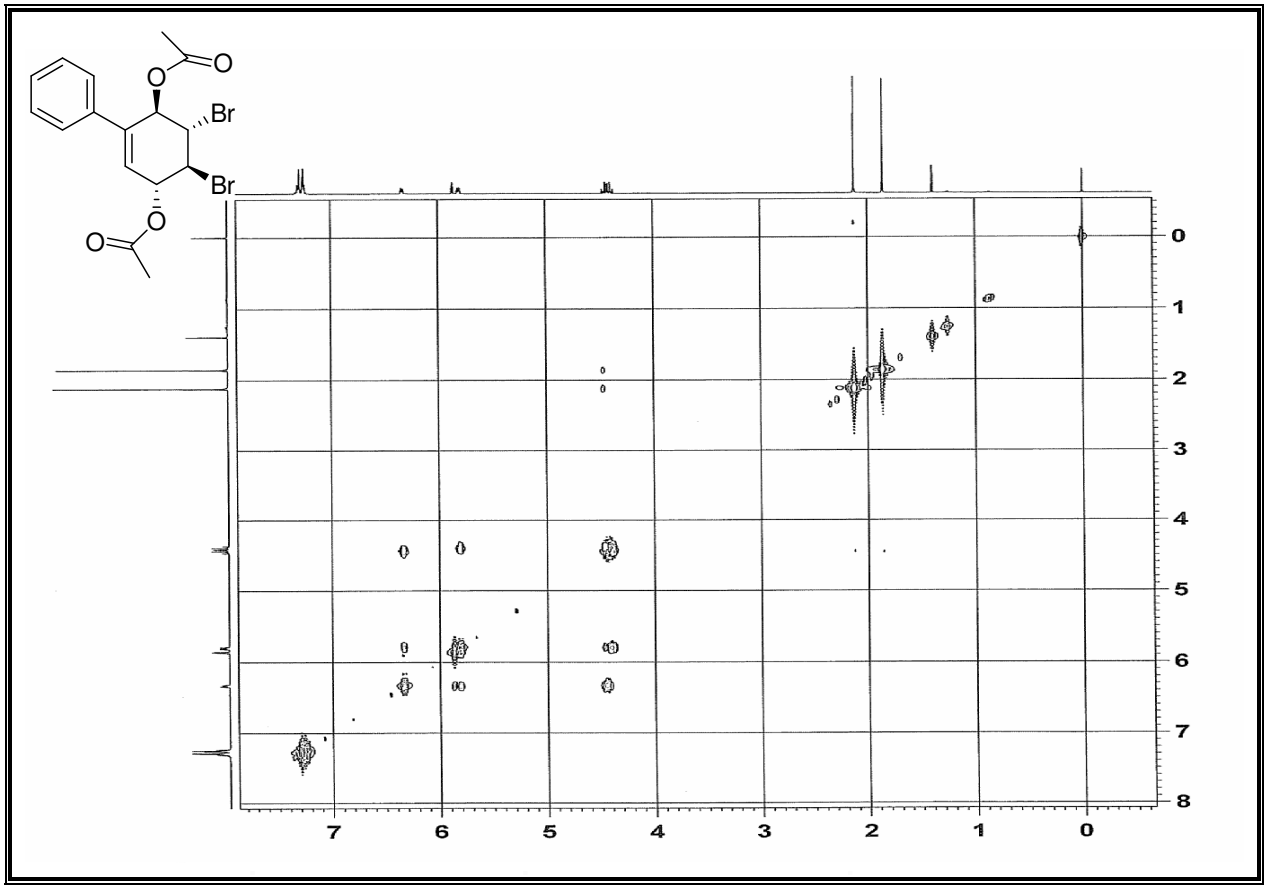


Figure A11 COSY Spectrum of Compound **143**.

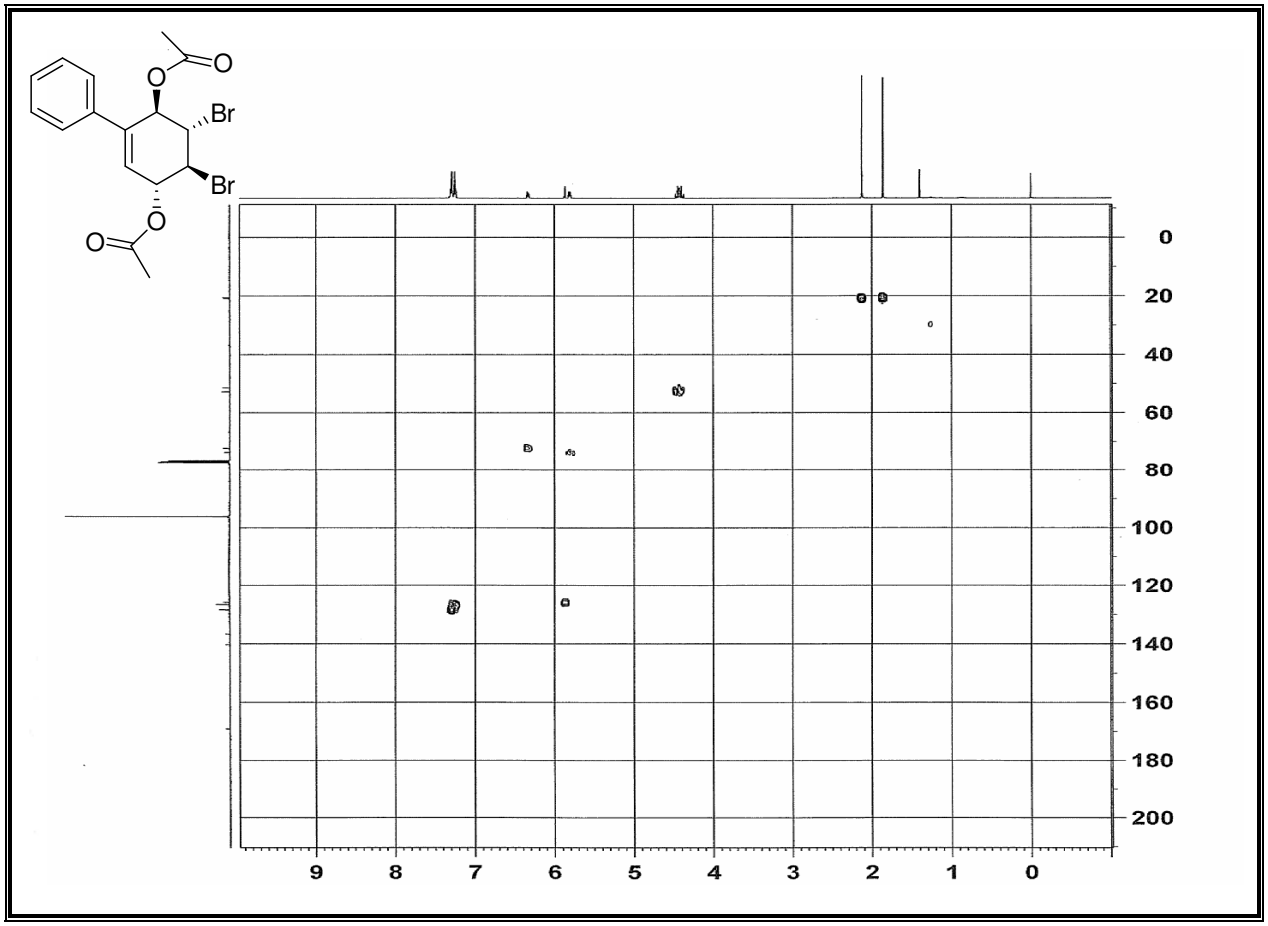


Figure A12 HMQC Spectrum of Compound **143**.

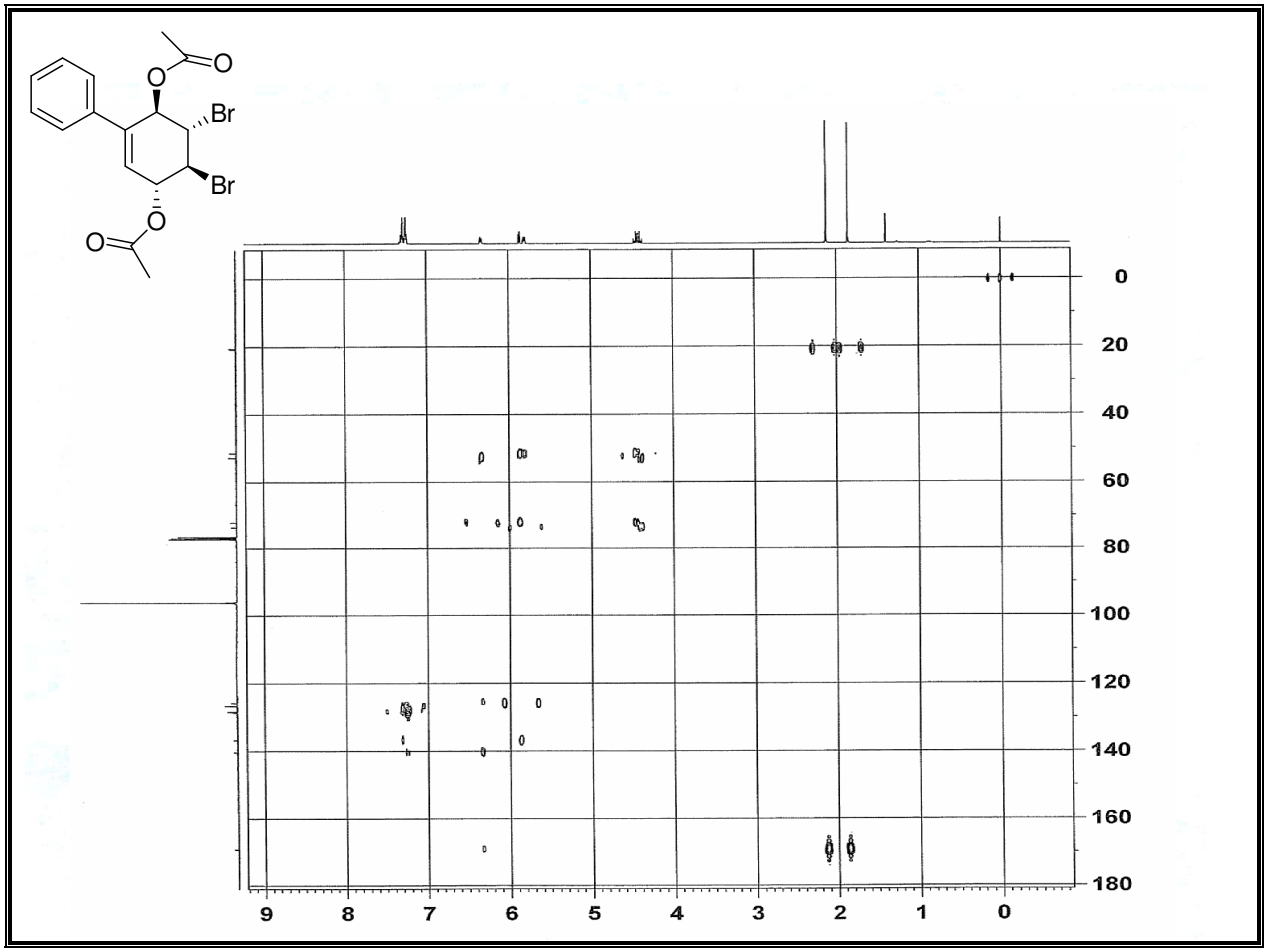


Figure A13 HMBC Spectrum of Compound **143**.

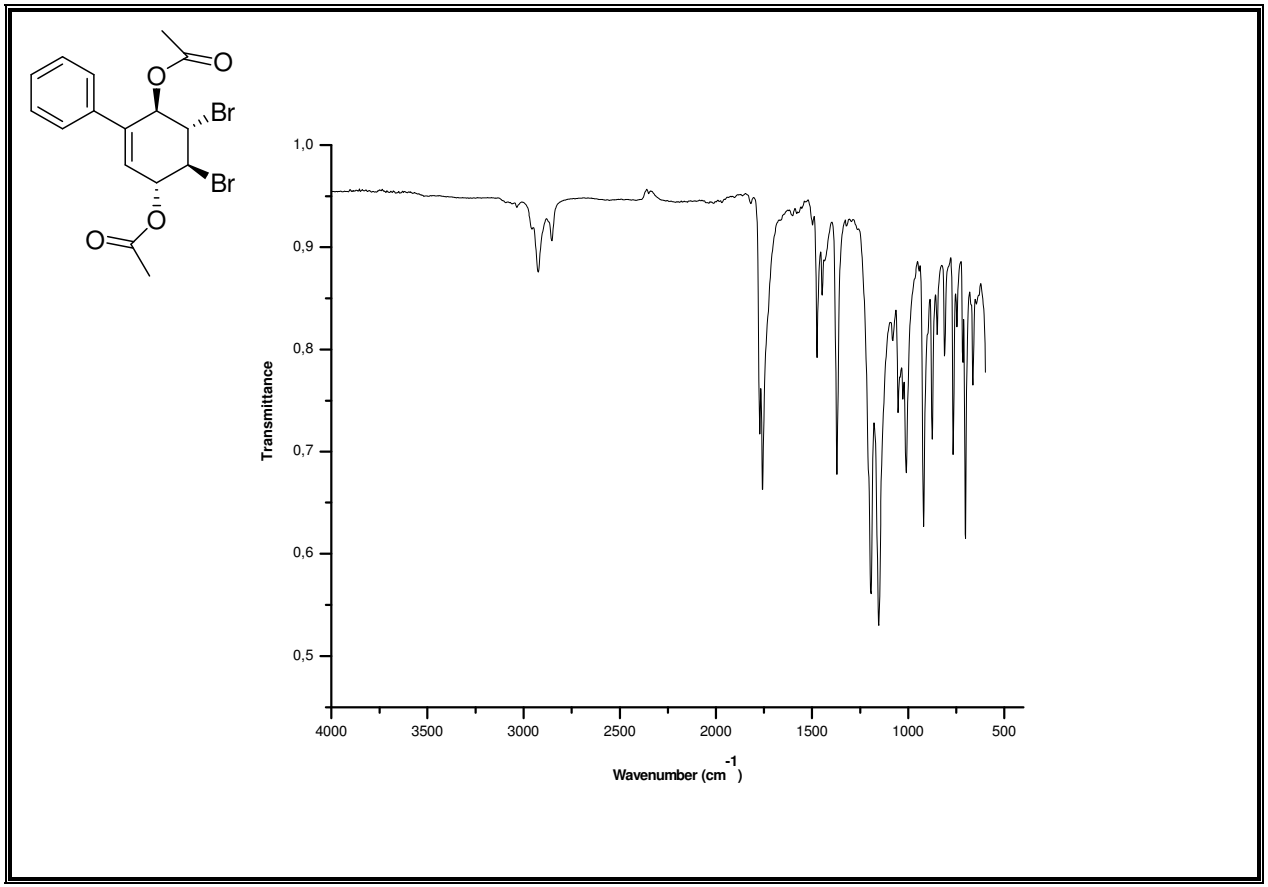


Figure A14 IR Spectrum of Compound **143**.

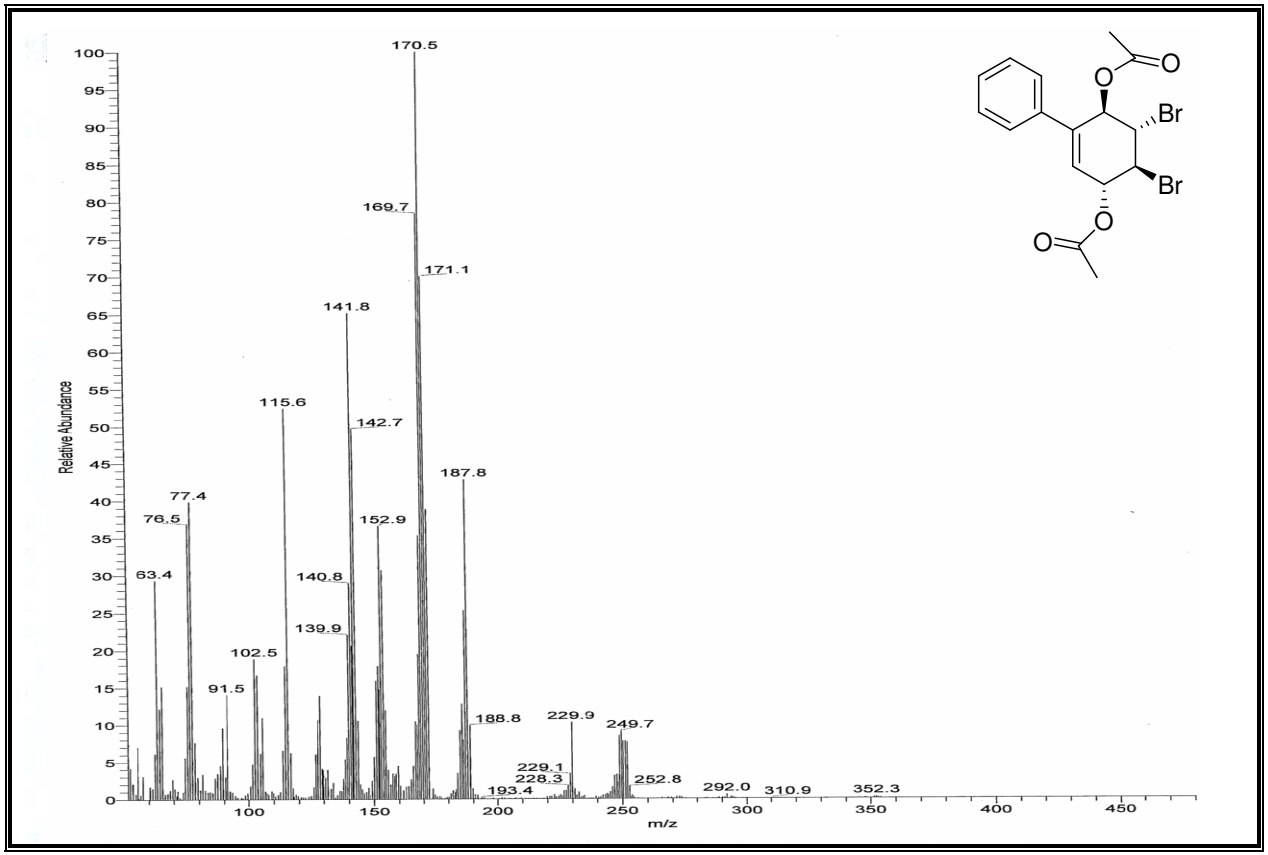


Figure A15 GC-MS Spectrum of Compound **143**.

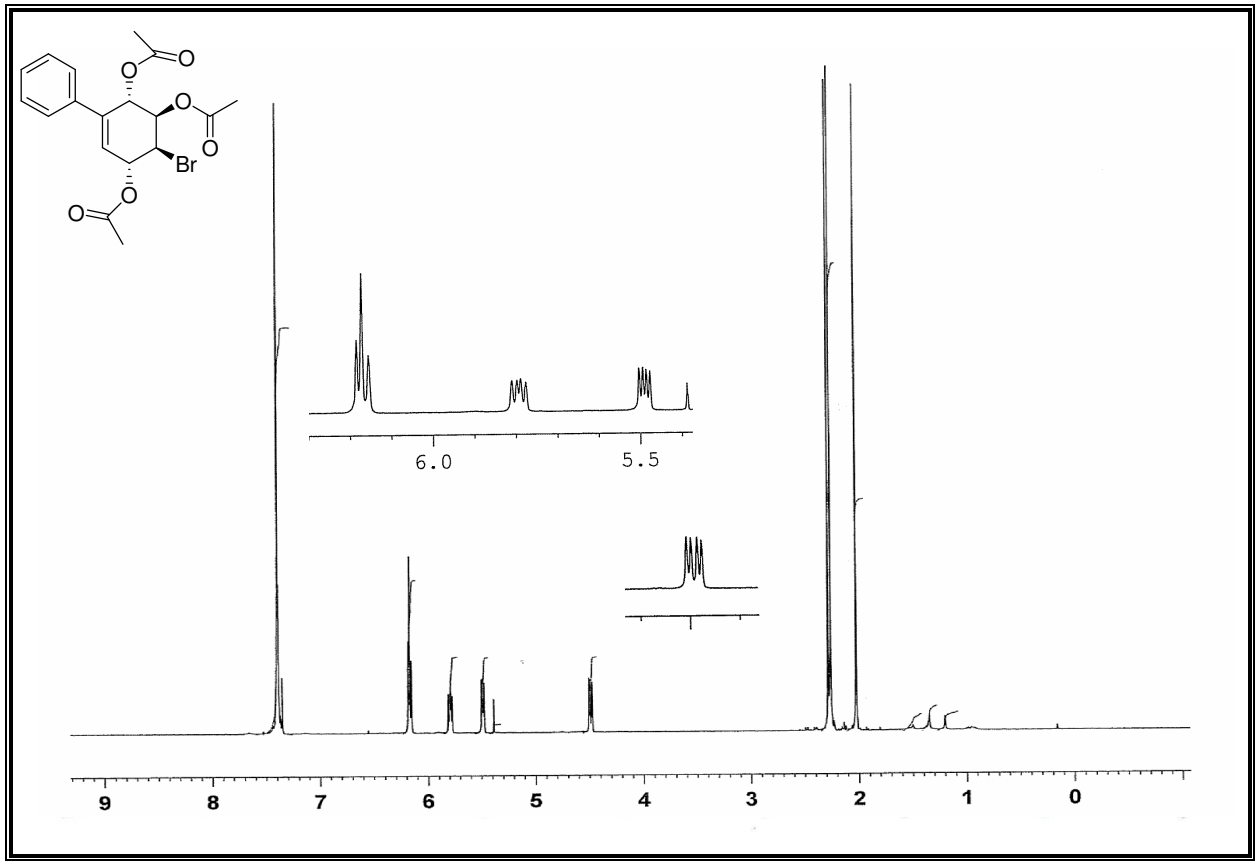


Figure A16 ^{1}H-NMR Spectrum of Compound **145**.

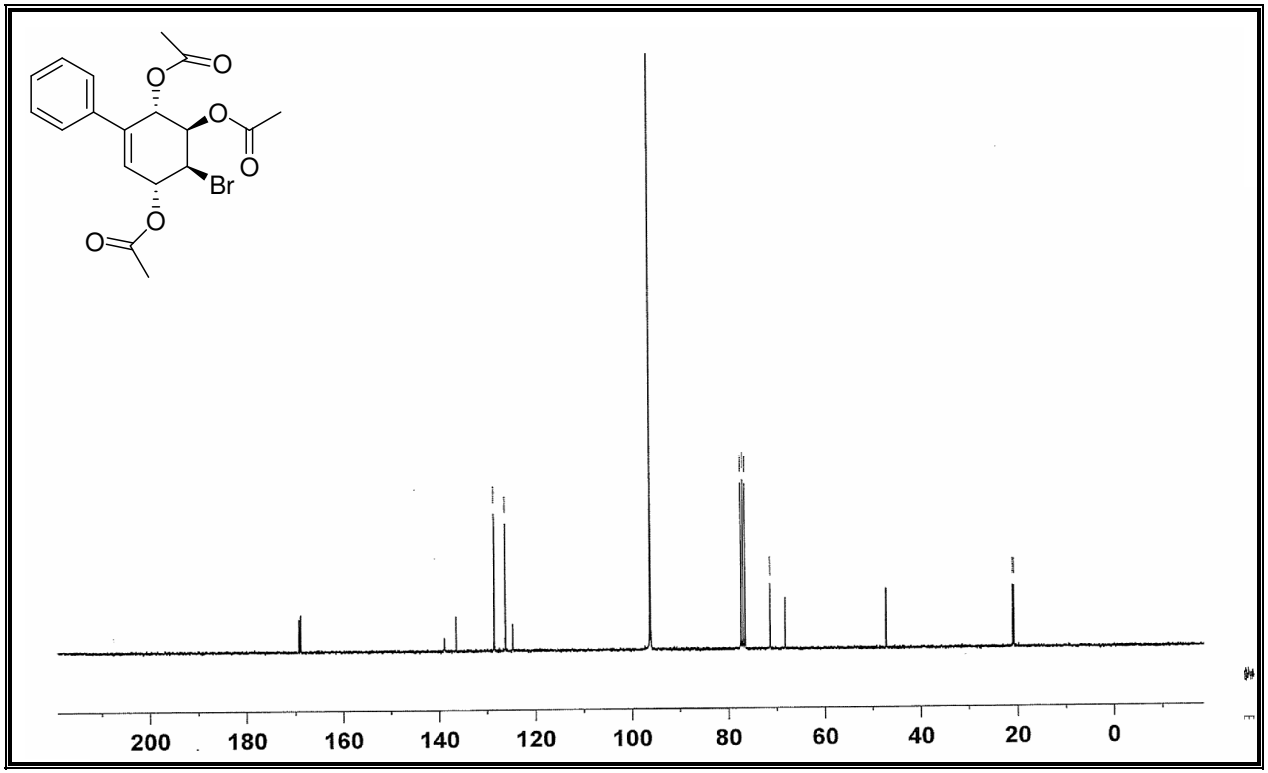


Figure A1. ^{13}C- NMR Spectrum of Compound **145**.

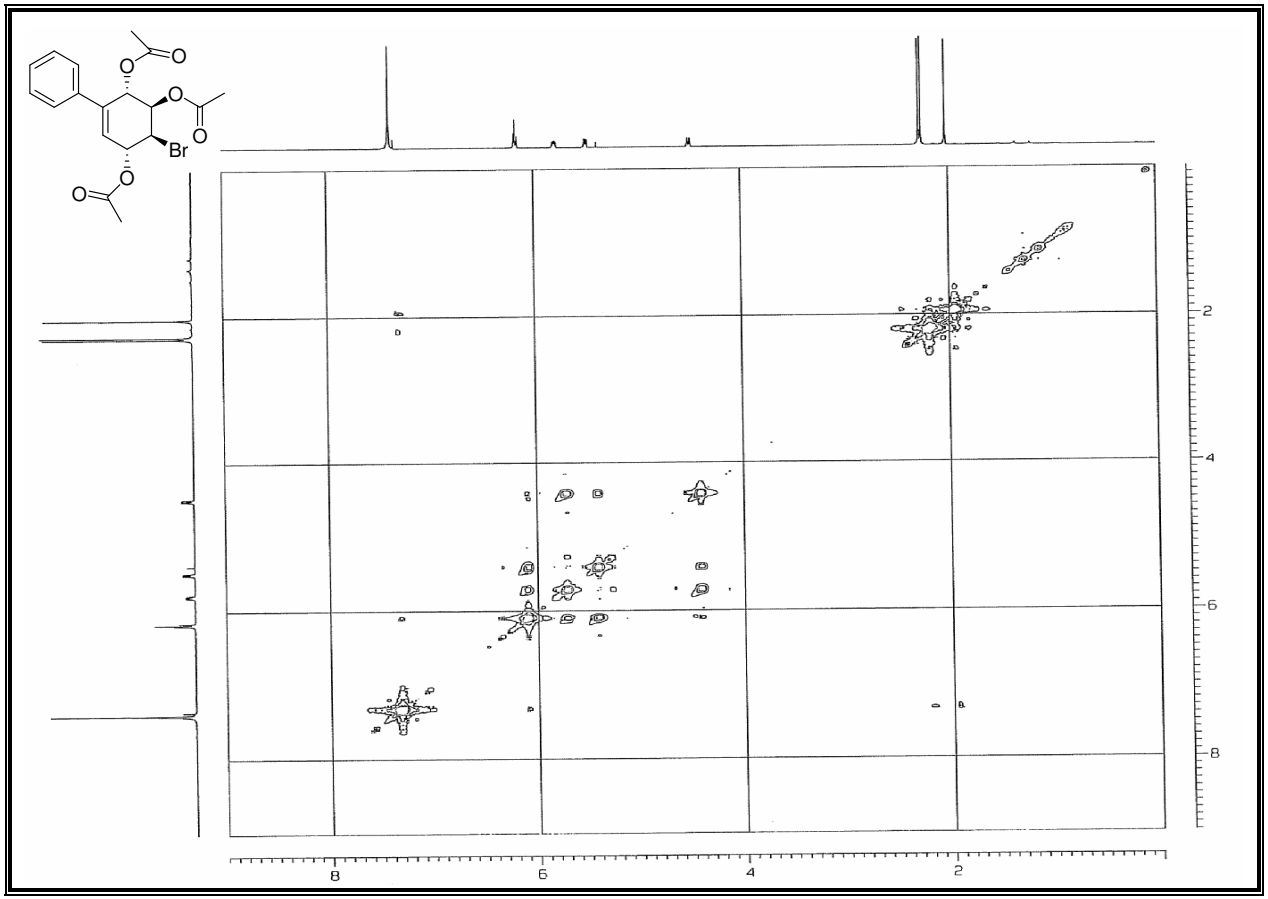


Figure A18 COSY Spectrum of Compound **145**.

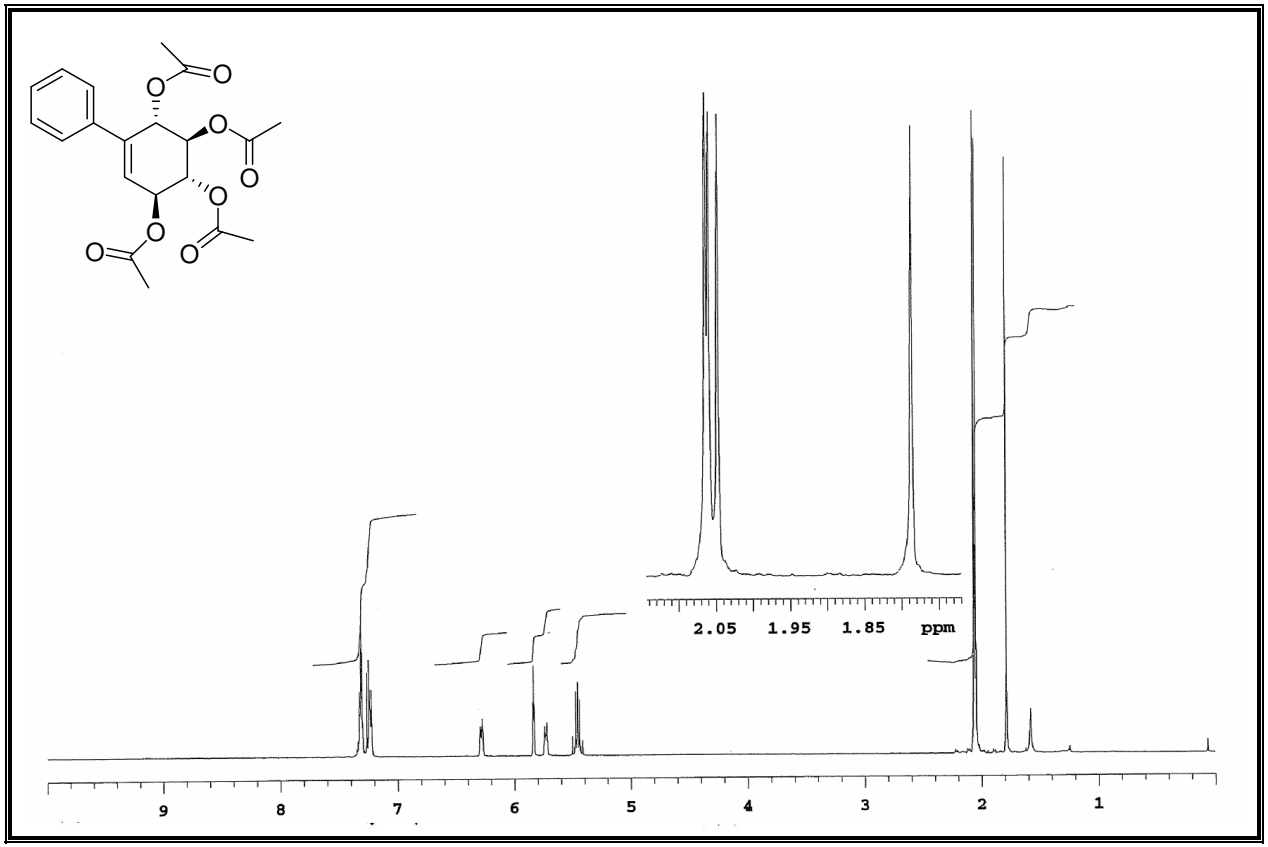


Figure A19 ^{1}H-NMR Spectrum of Compound **144**.

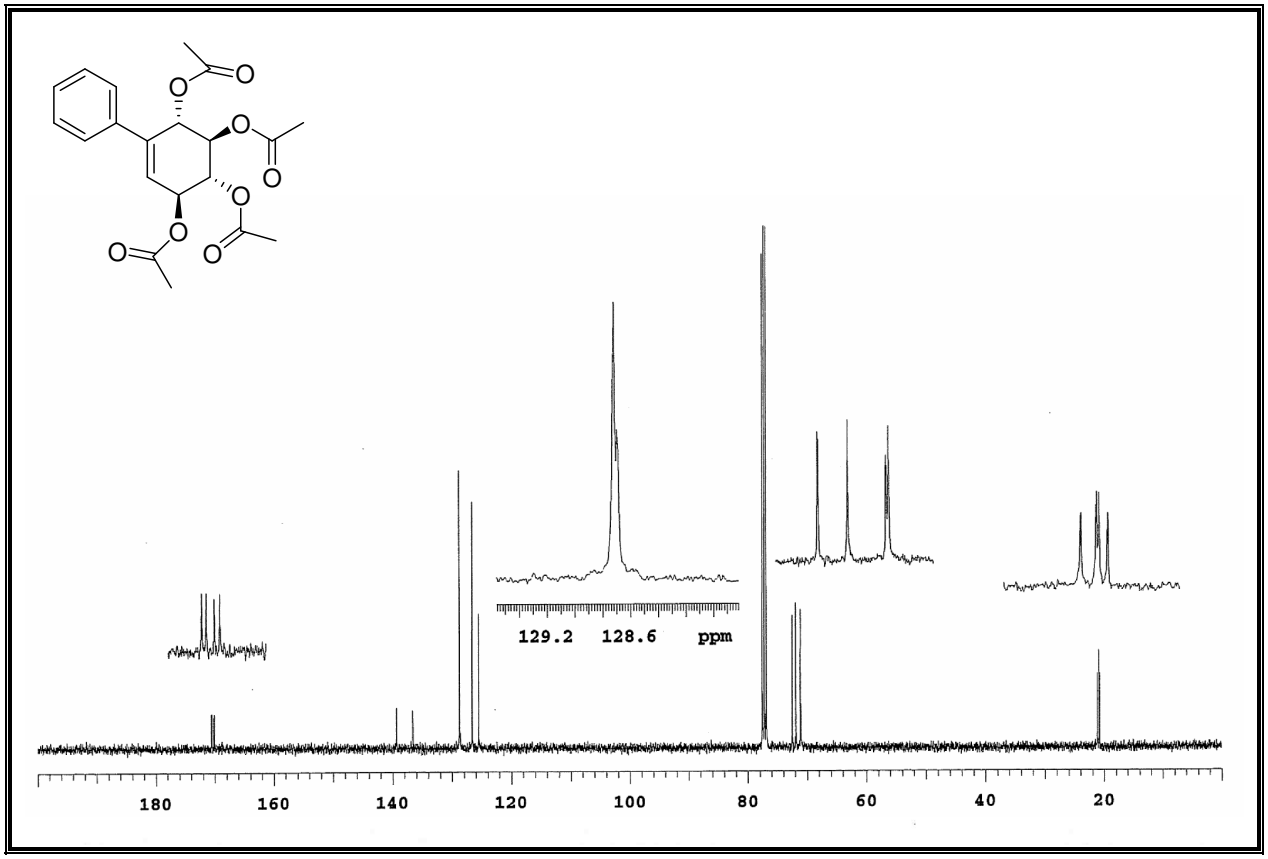


Figure A20 ^{1}C-NMR Spectrum of Compound **144**.

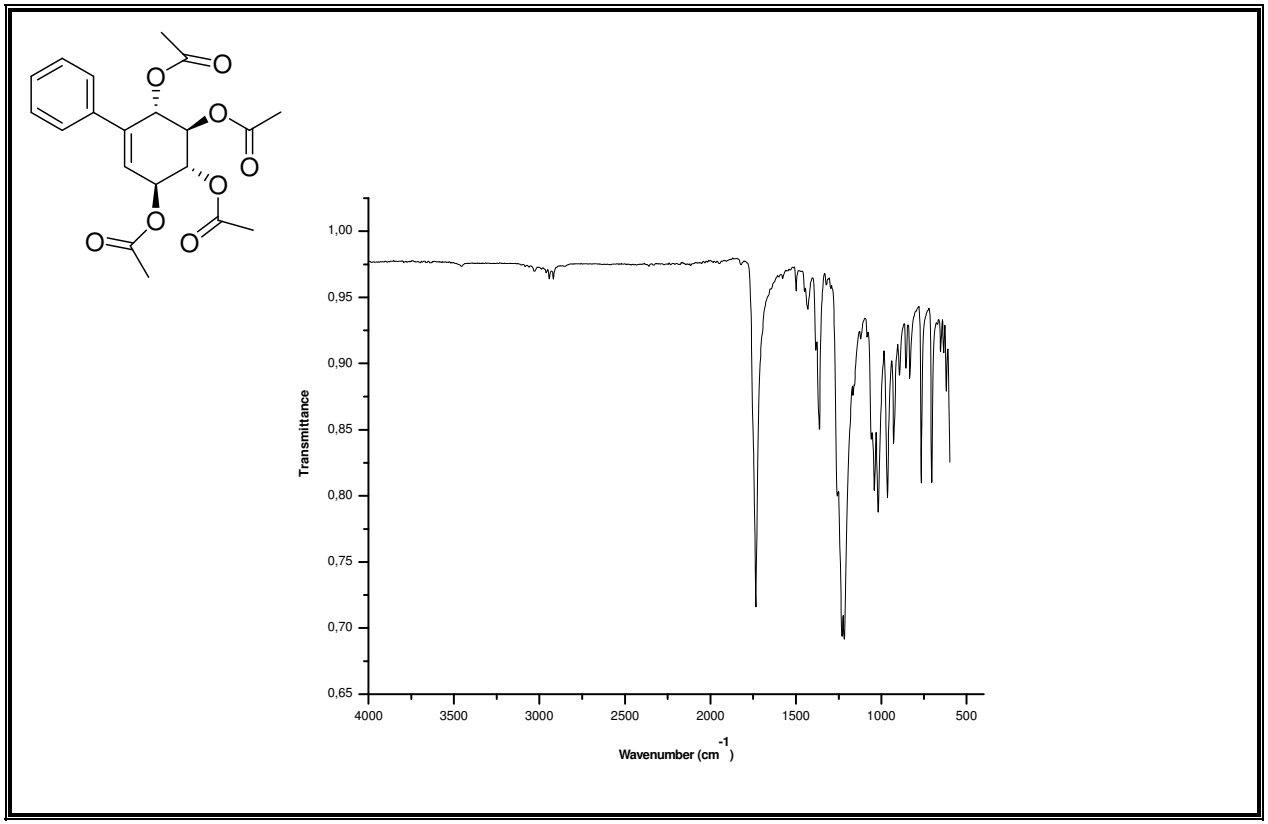


Figure A21 IR Spectrum of Compound **144**.

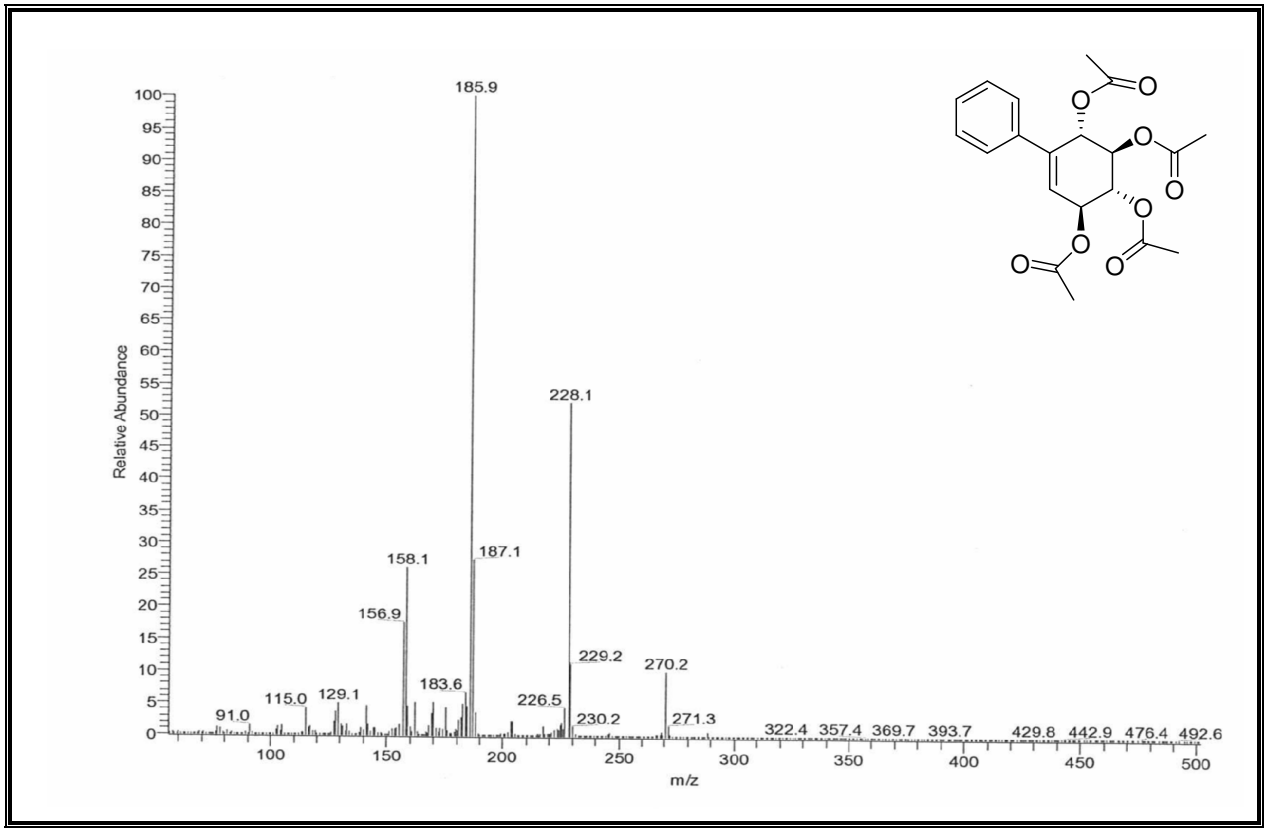


Figure A22 GC-MS Spectrum of Compound **144**.

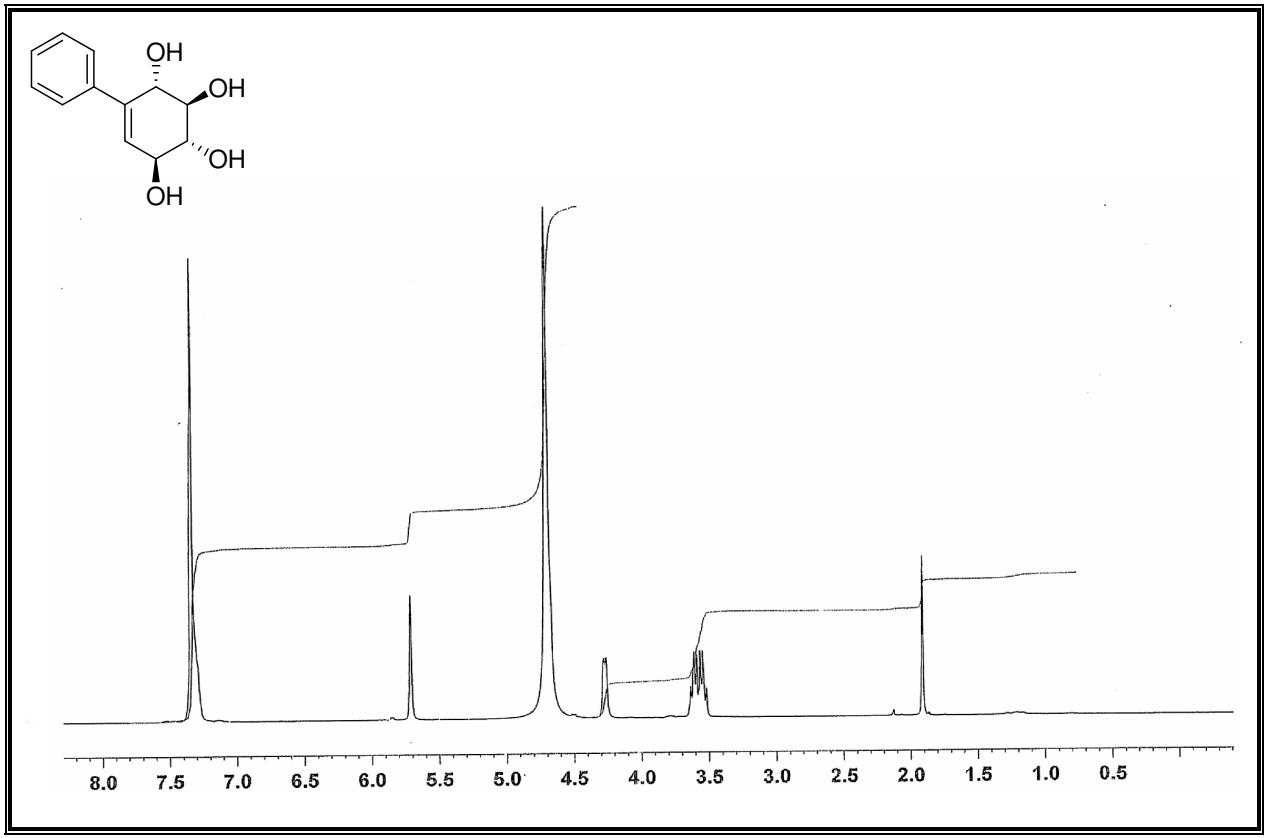


Figure A23 ^{1}H-NMR Spectrum of Compound **134**.

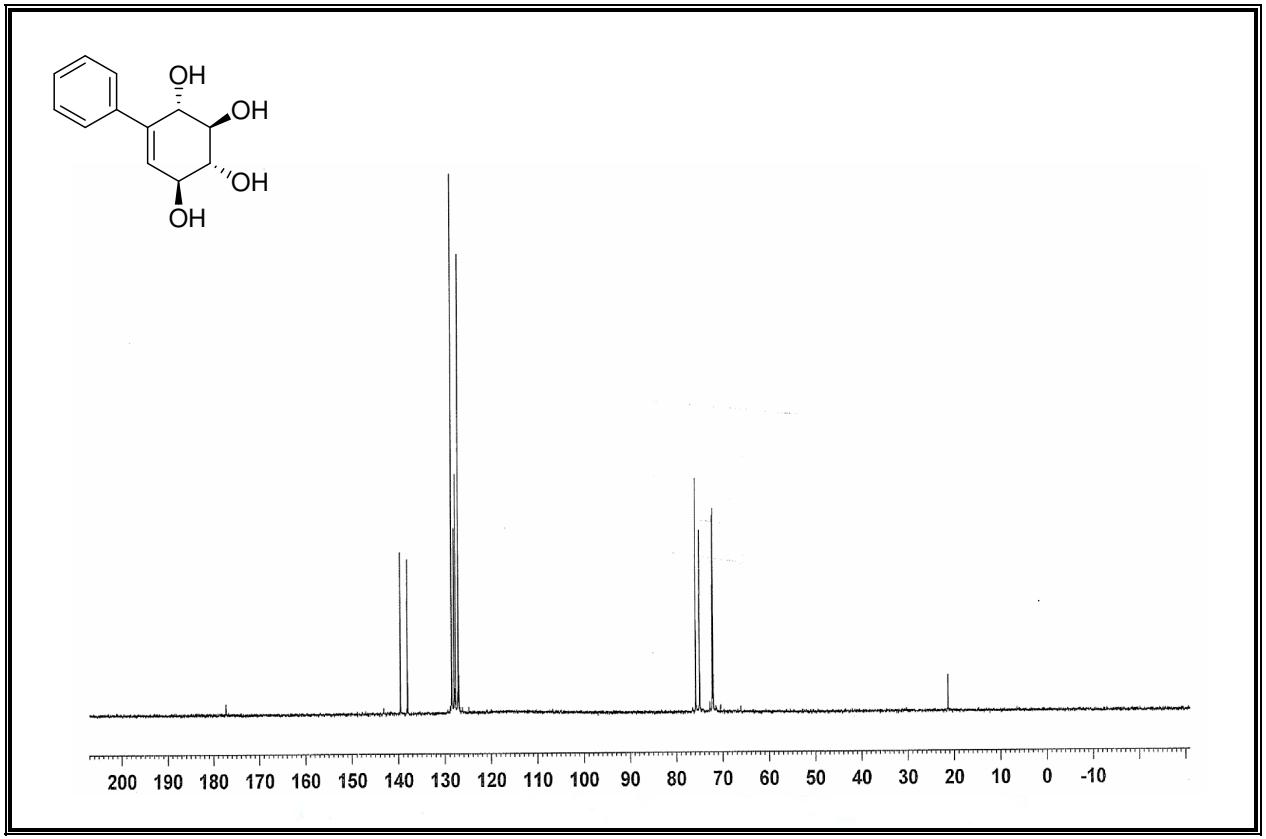


Figure A24 ^{13}C-NMR Spectrum of Compound **134**.

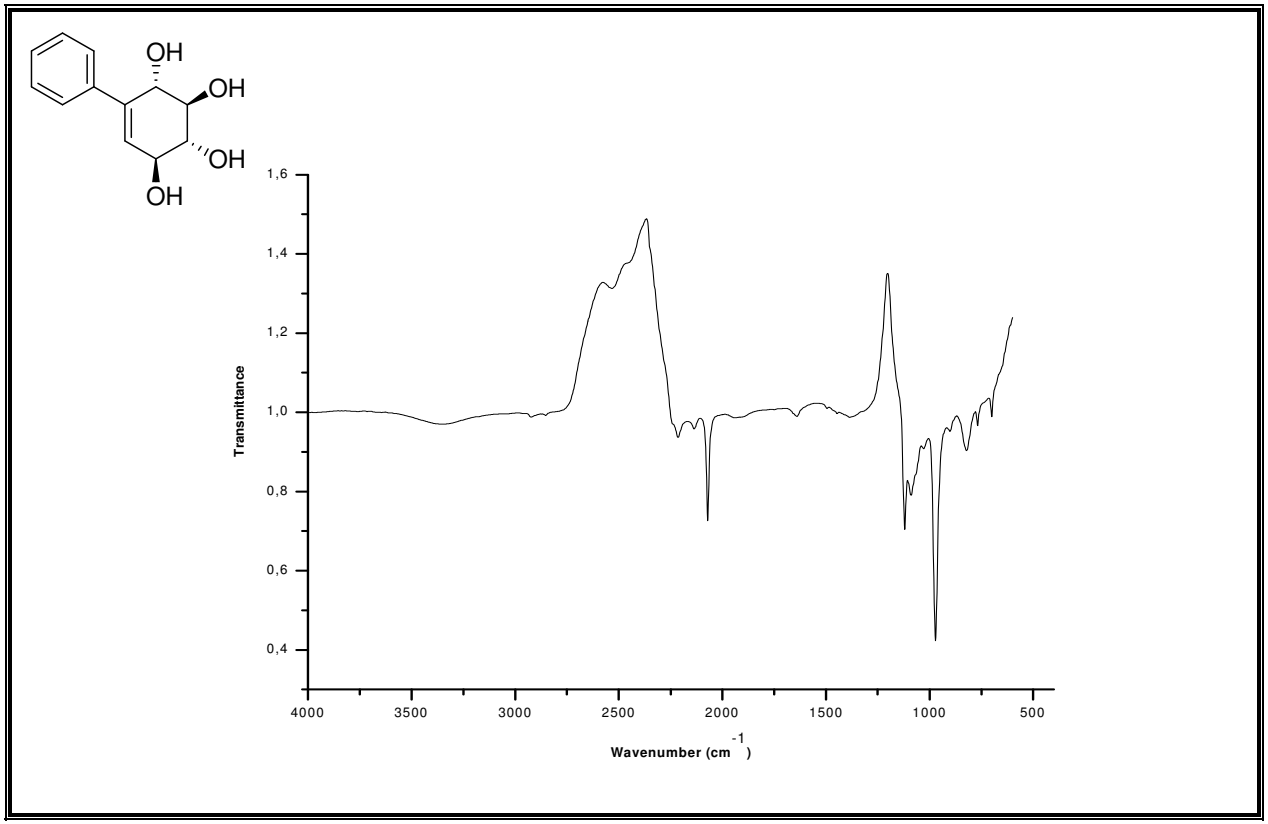


Figure A25 IR Spectrum of Compound **134**.

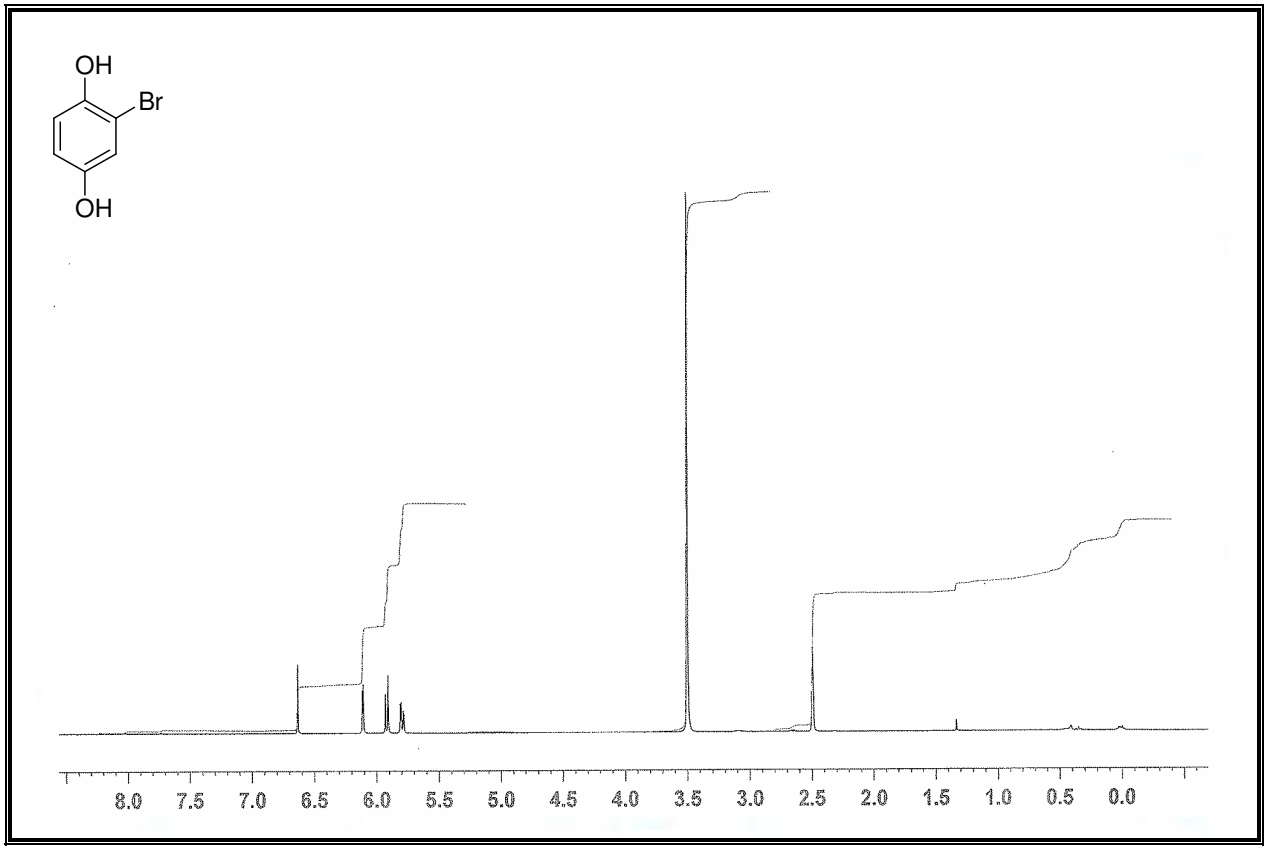


Figure A26 ^{1}H-NMR Spectrum of Compound **150**.

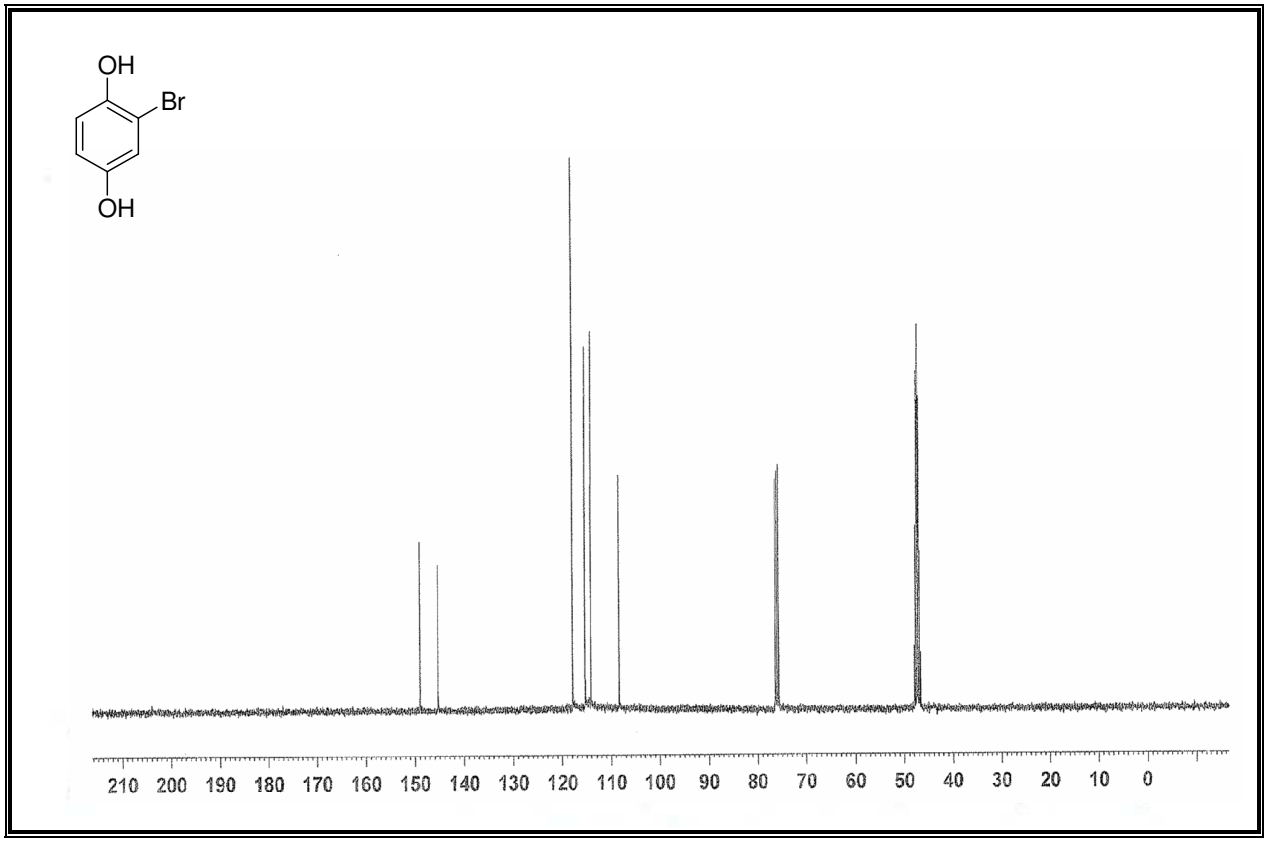


Figure A27 ^{13}C-NMR Spectrum of Compound **150**.

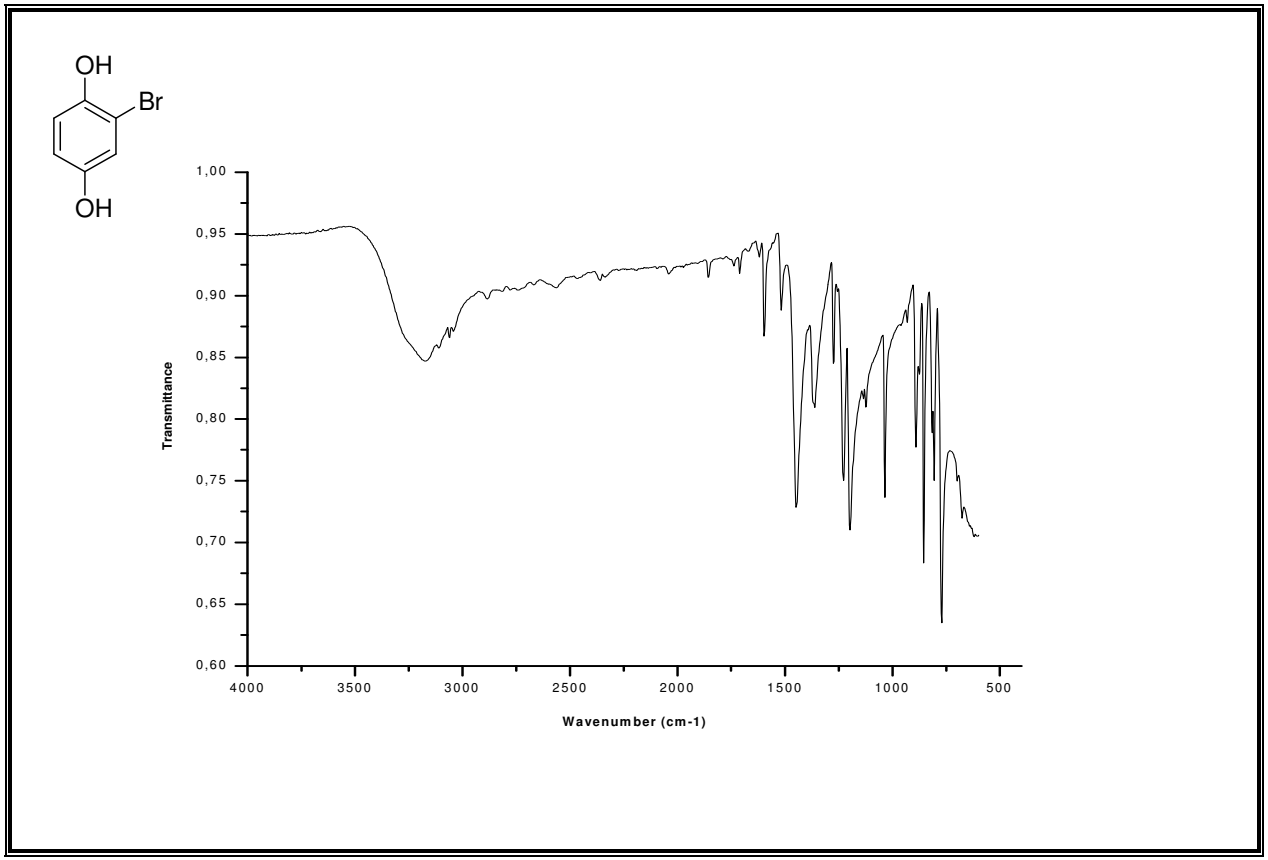


Figure A28 IR Spectrum of Compound **150**.

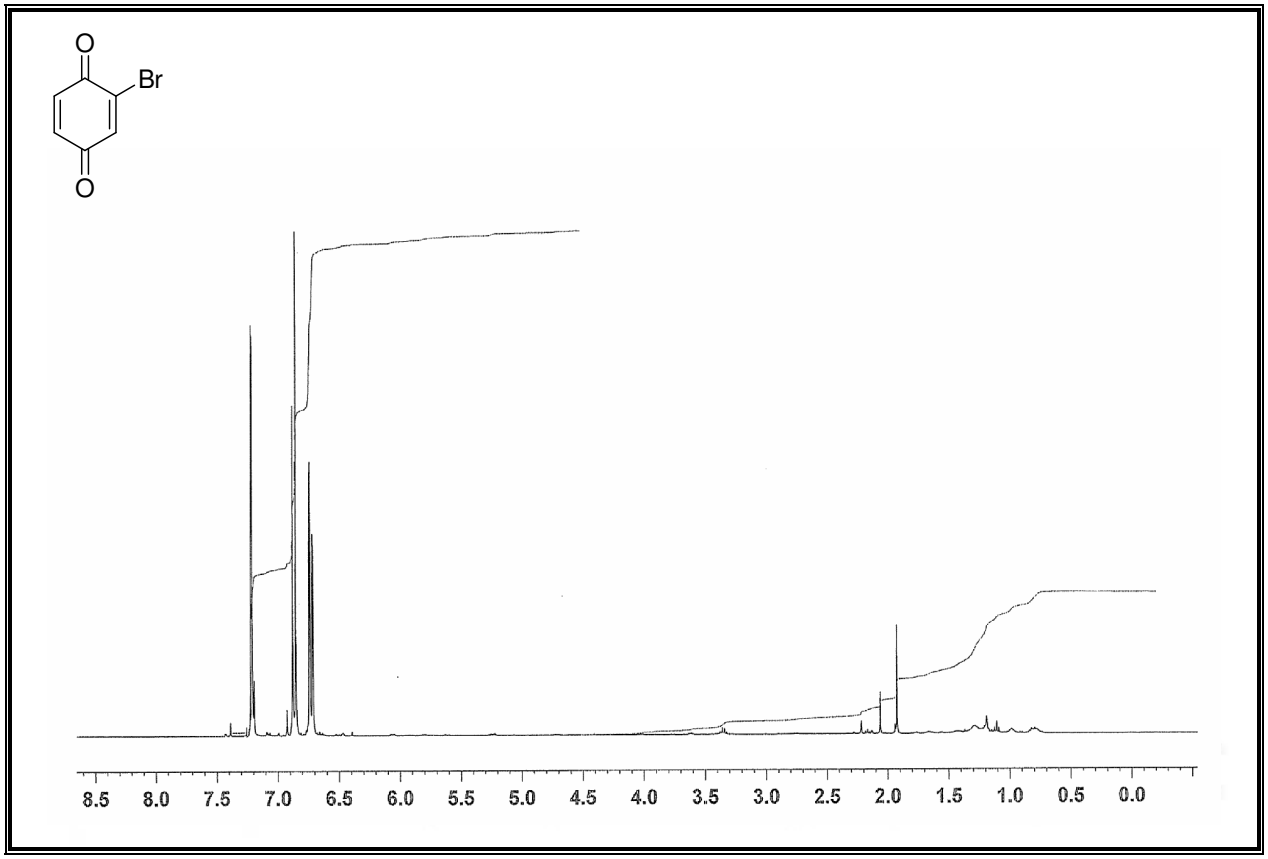


Figure A29 ^{1}H-NMR Spectrum of Compound **151**.

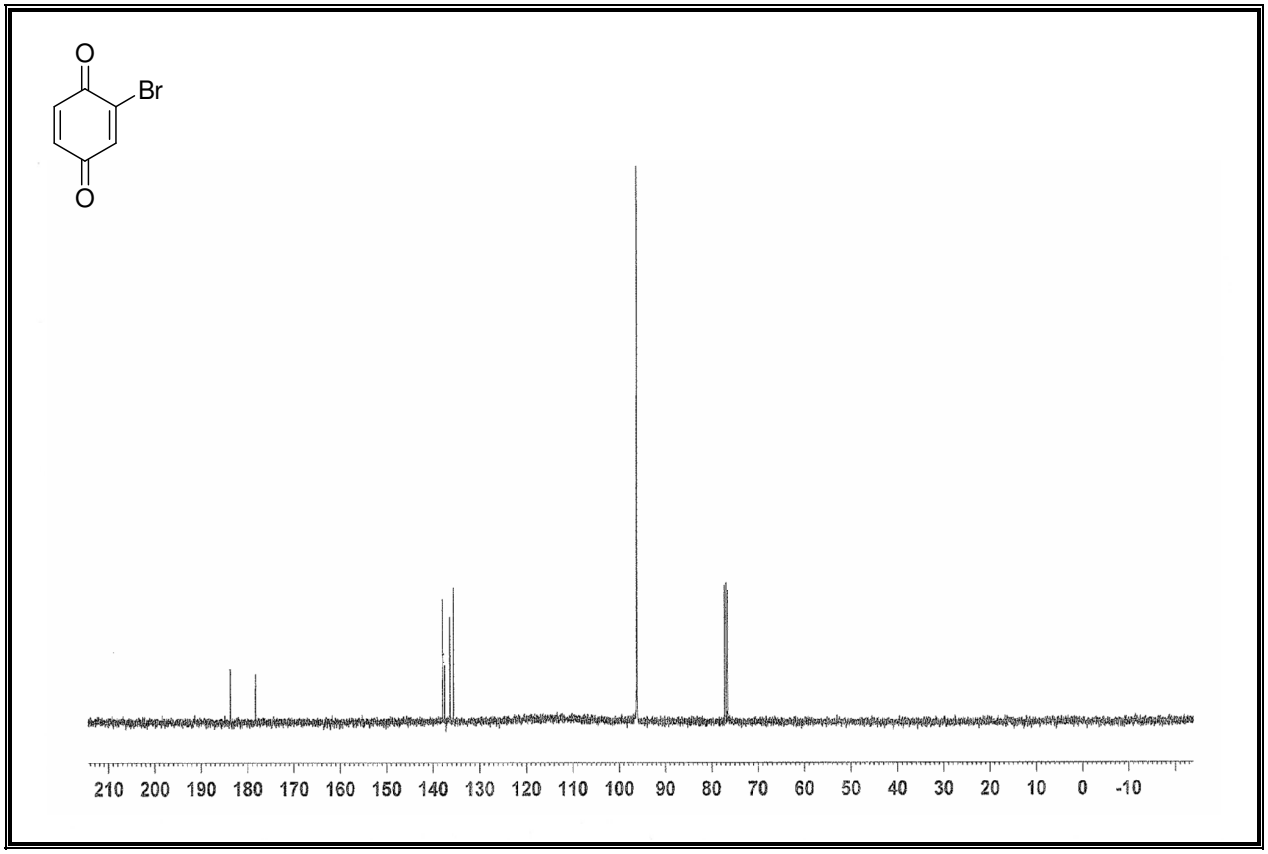


Figure A30 ^{13}C-NMR Spectrum of Compound **151**.

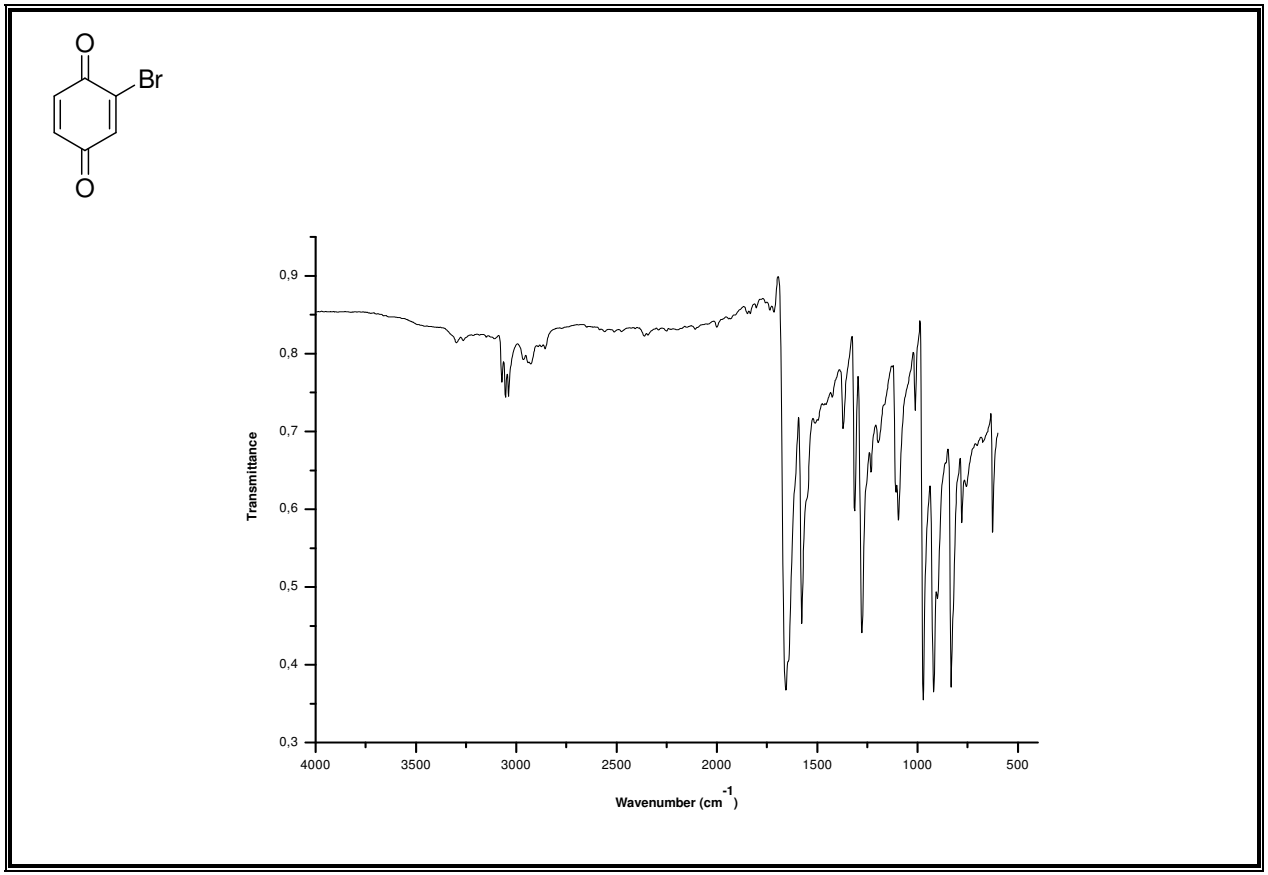


Figure A31 IR Spectrum of Compound **151**.

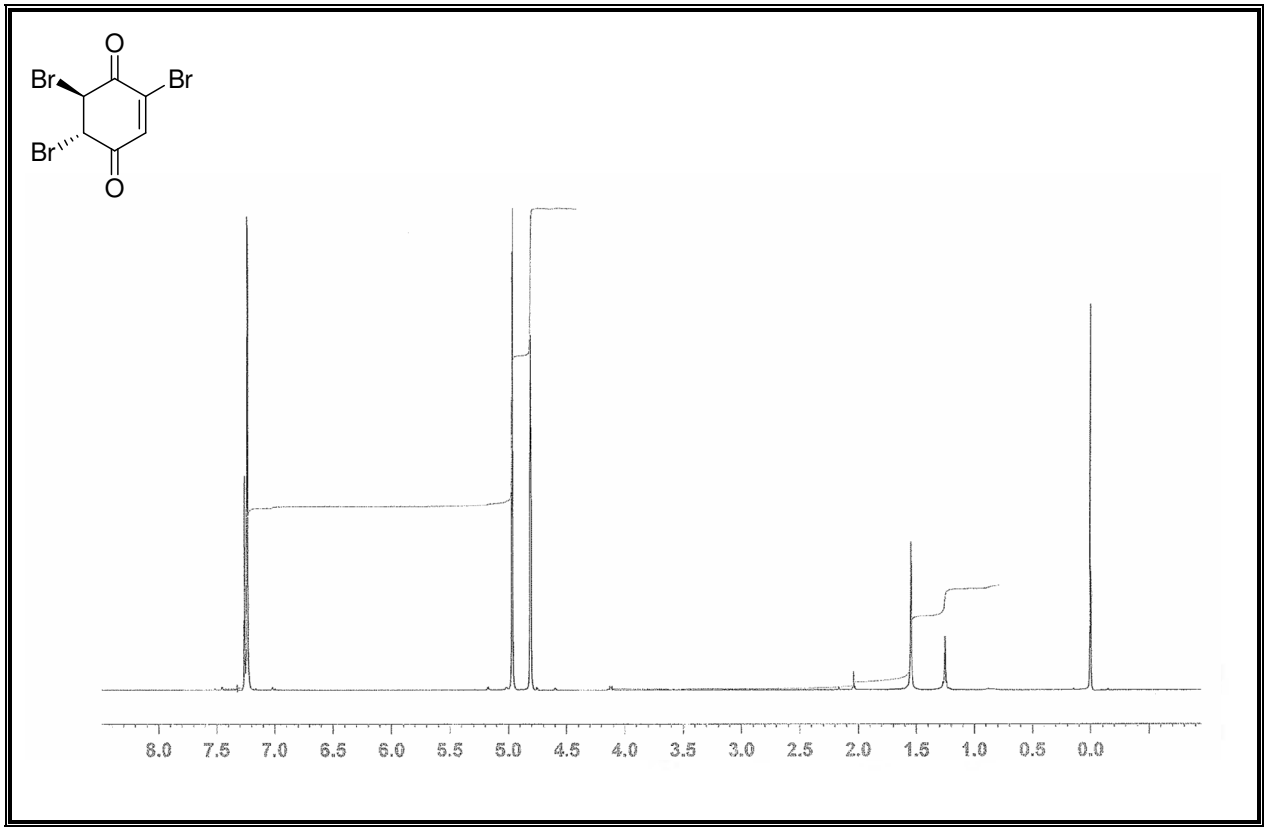


Figure A32 ^{1}H-NMR Spectrum of Compound **153**.

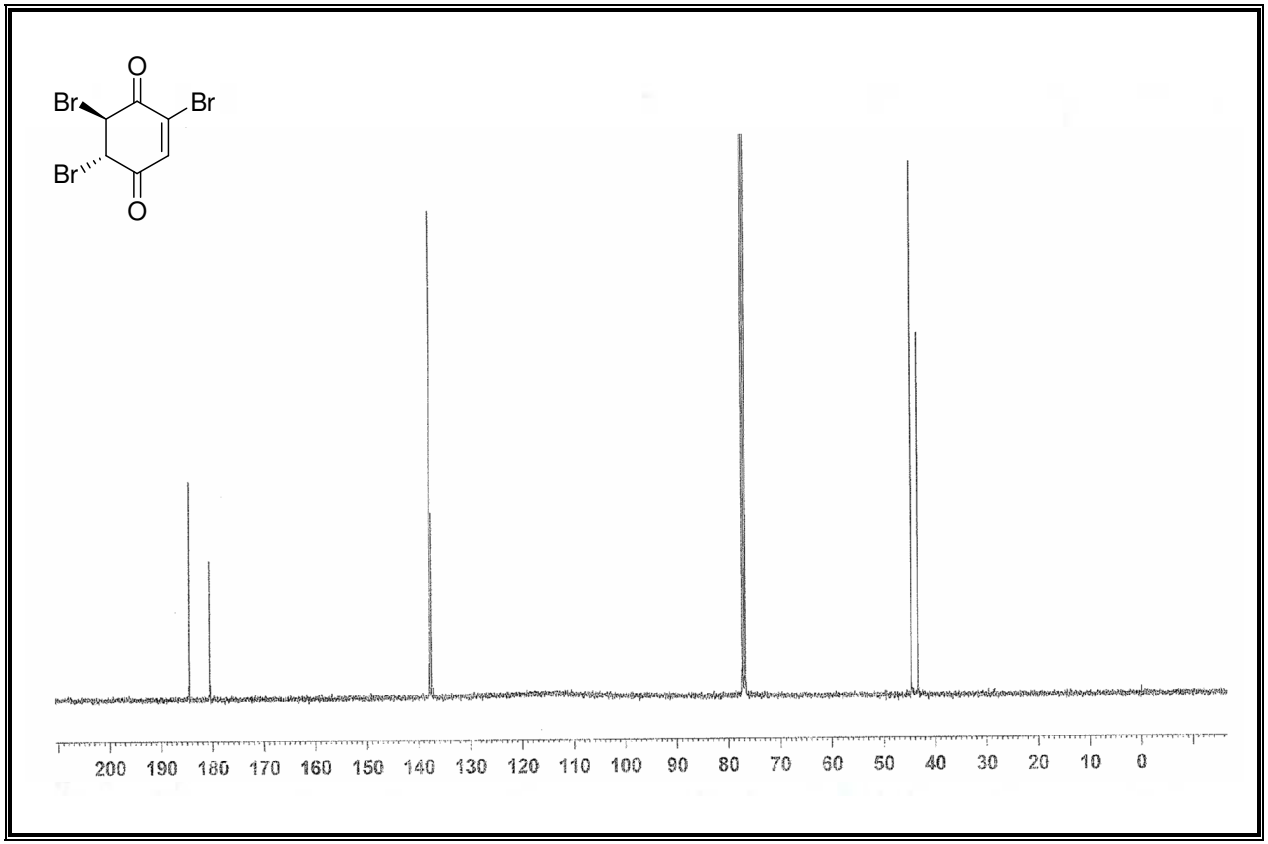


Figure A33 ^{13}C-NMR Spectrum of Compound **153**.

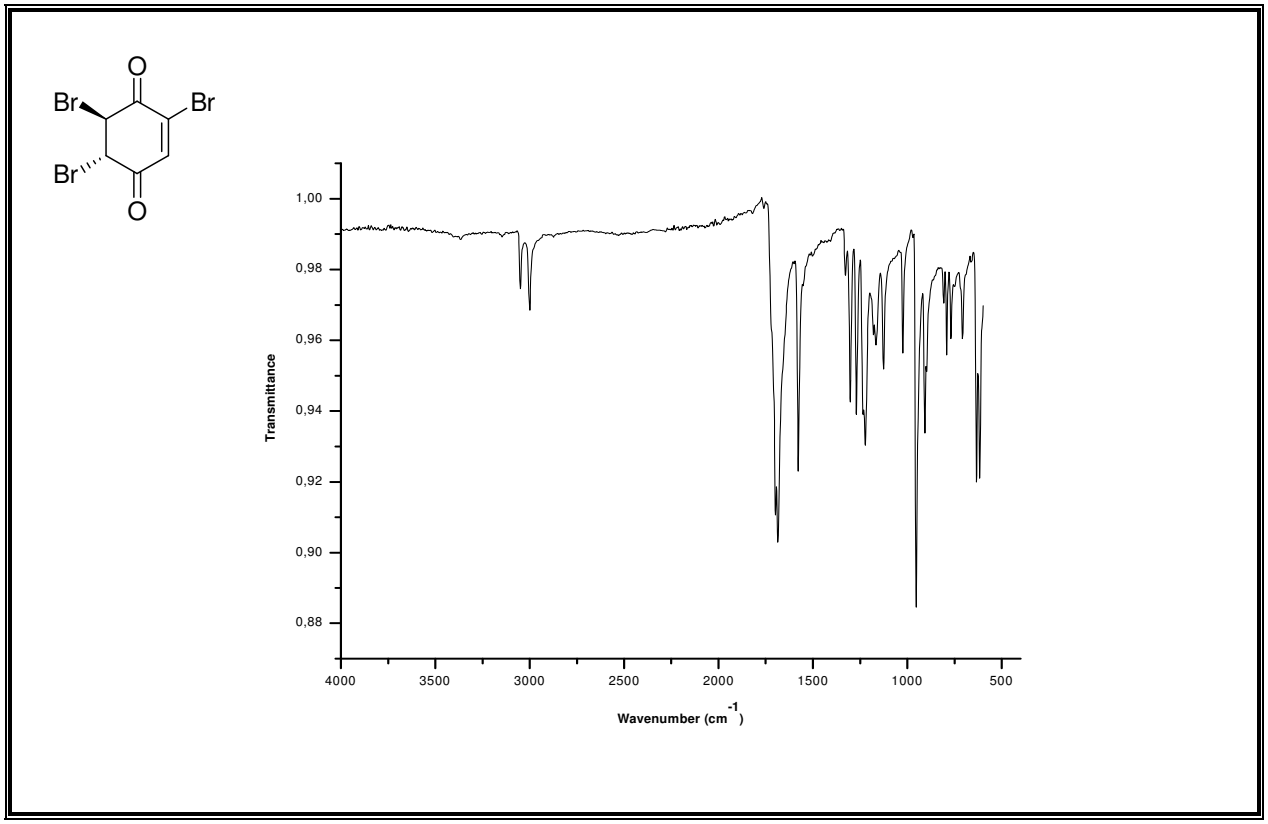


Figure A34 IR spectrum of Compound **153**.

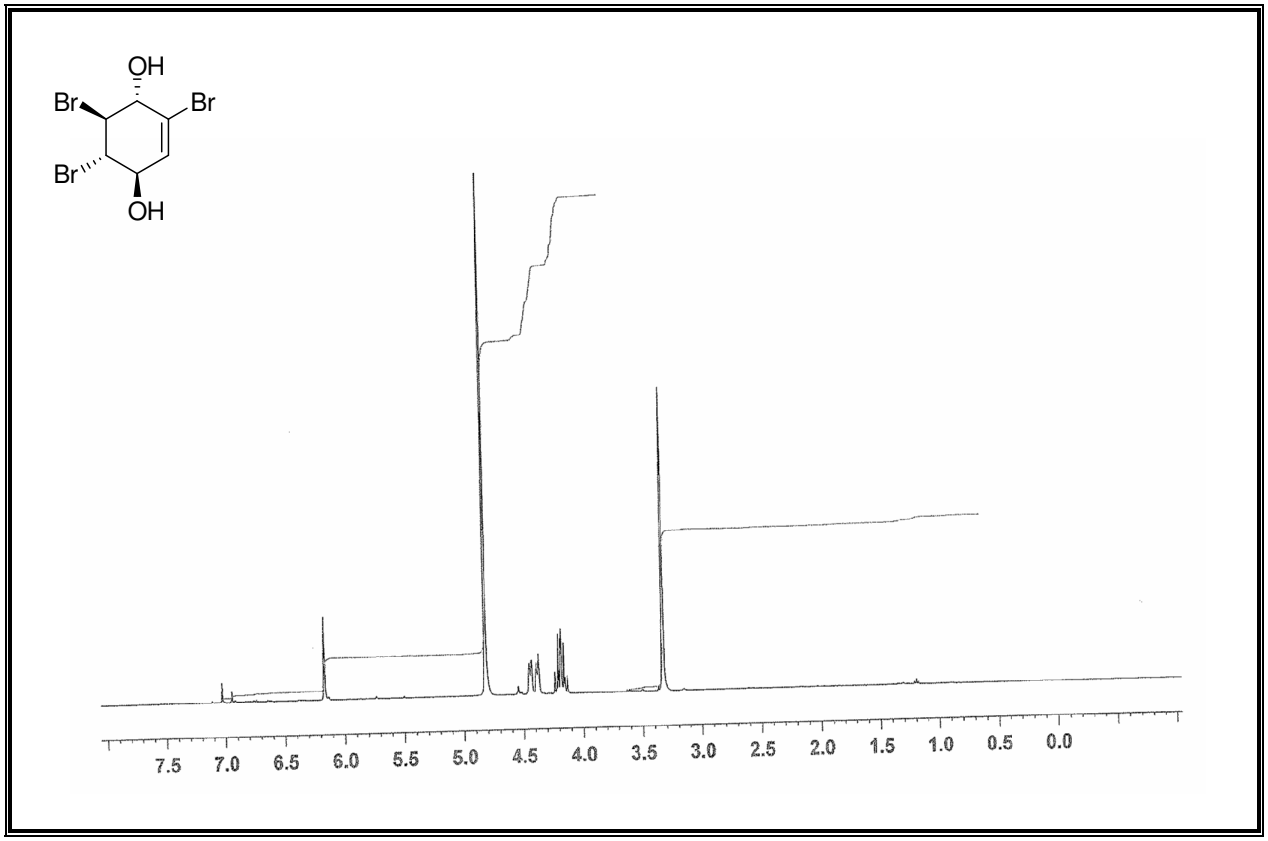


Figure A35 ^{1}H-NMR Spectrum of Compound **154**.

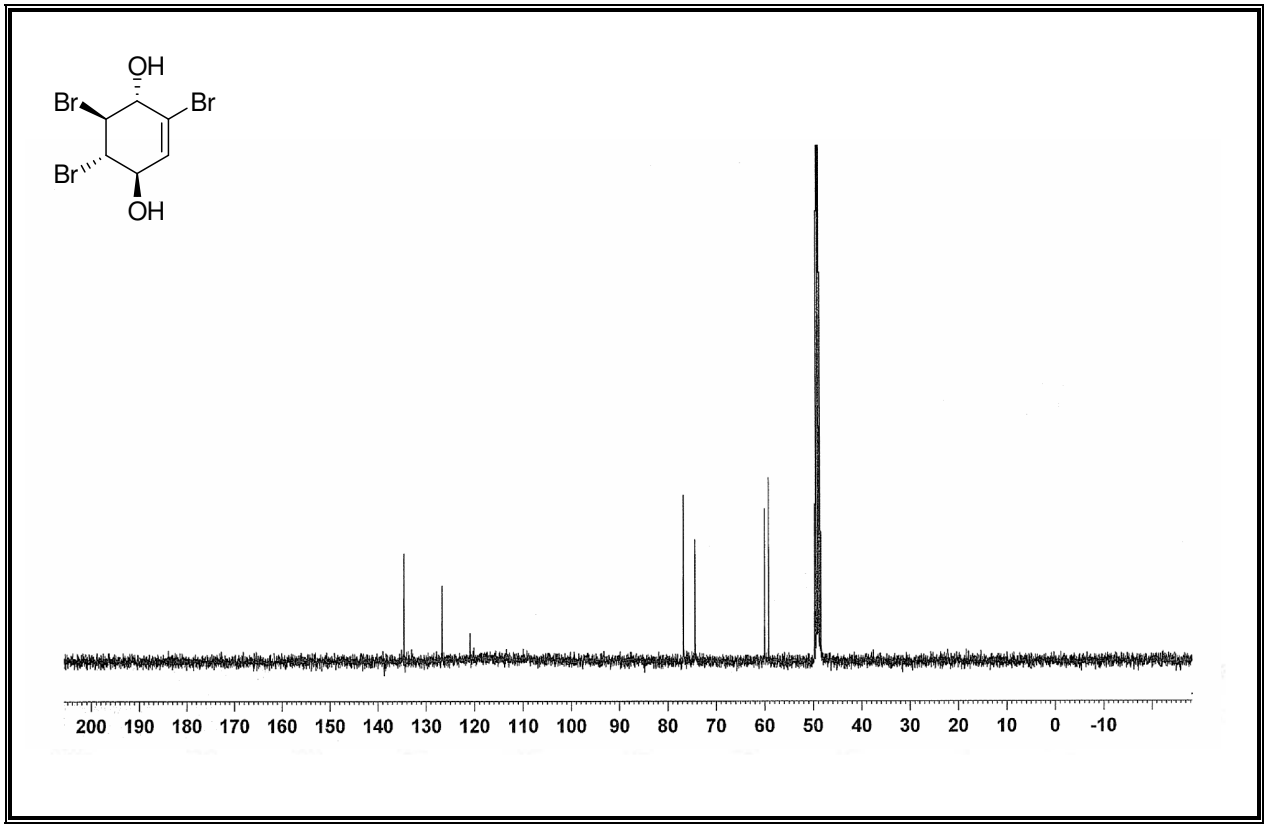


Figure A36 ^{13}C-NMR Spectrum of Compound **154**.

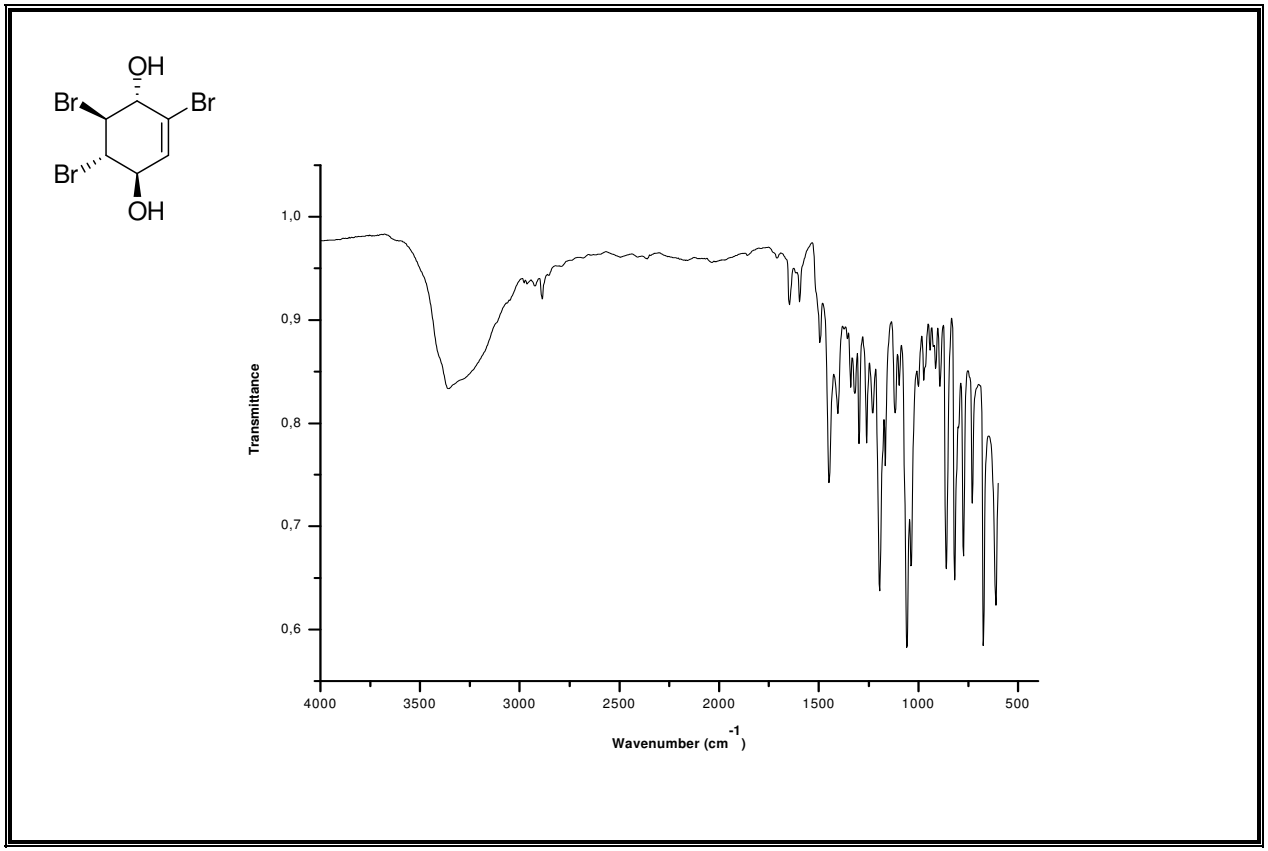


Figure A37 IR Spectrum of Compound **154**.

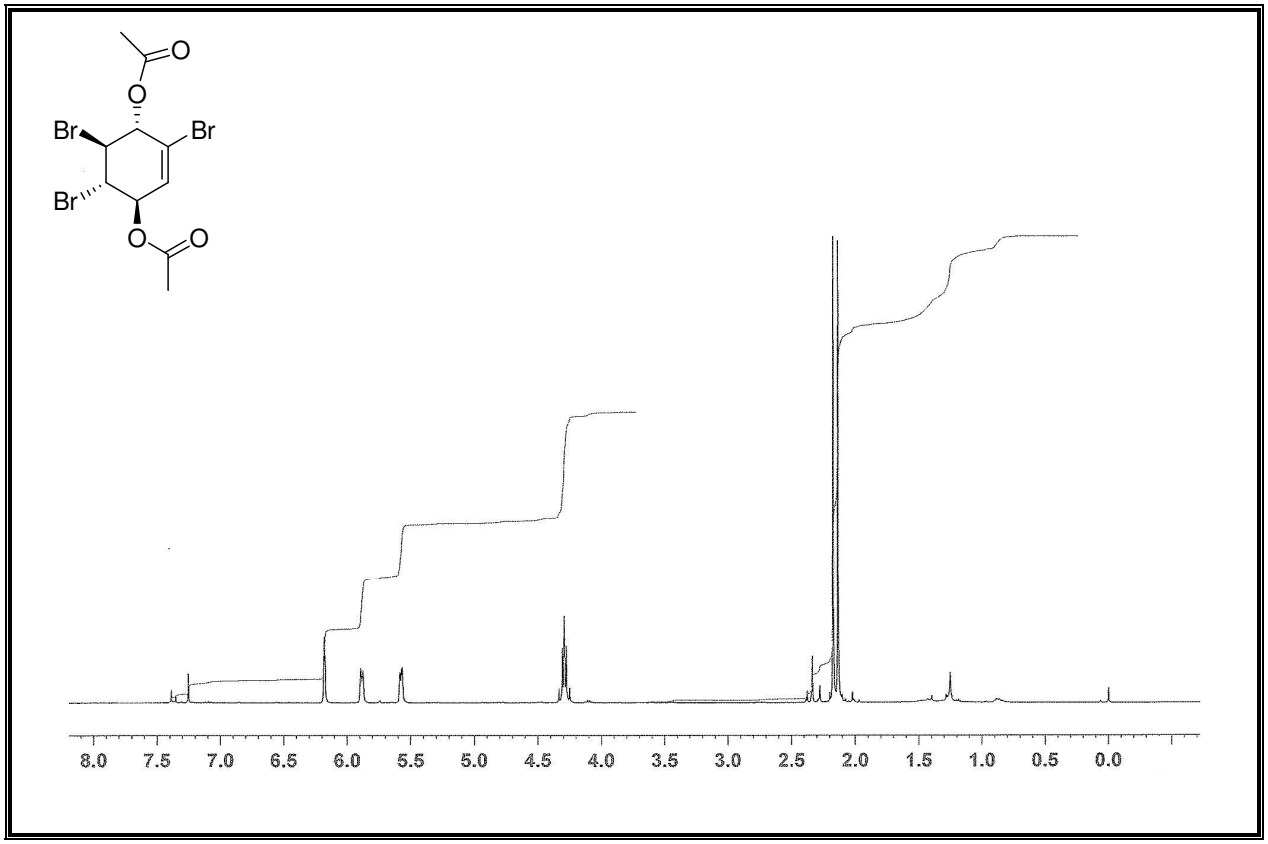


Figure A38 ^{1}H-NMR Spectrum of Compound **155**.

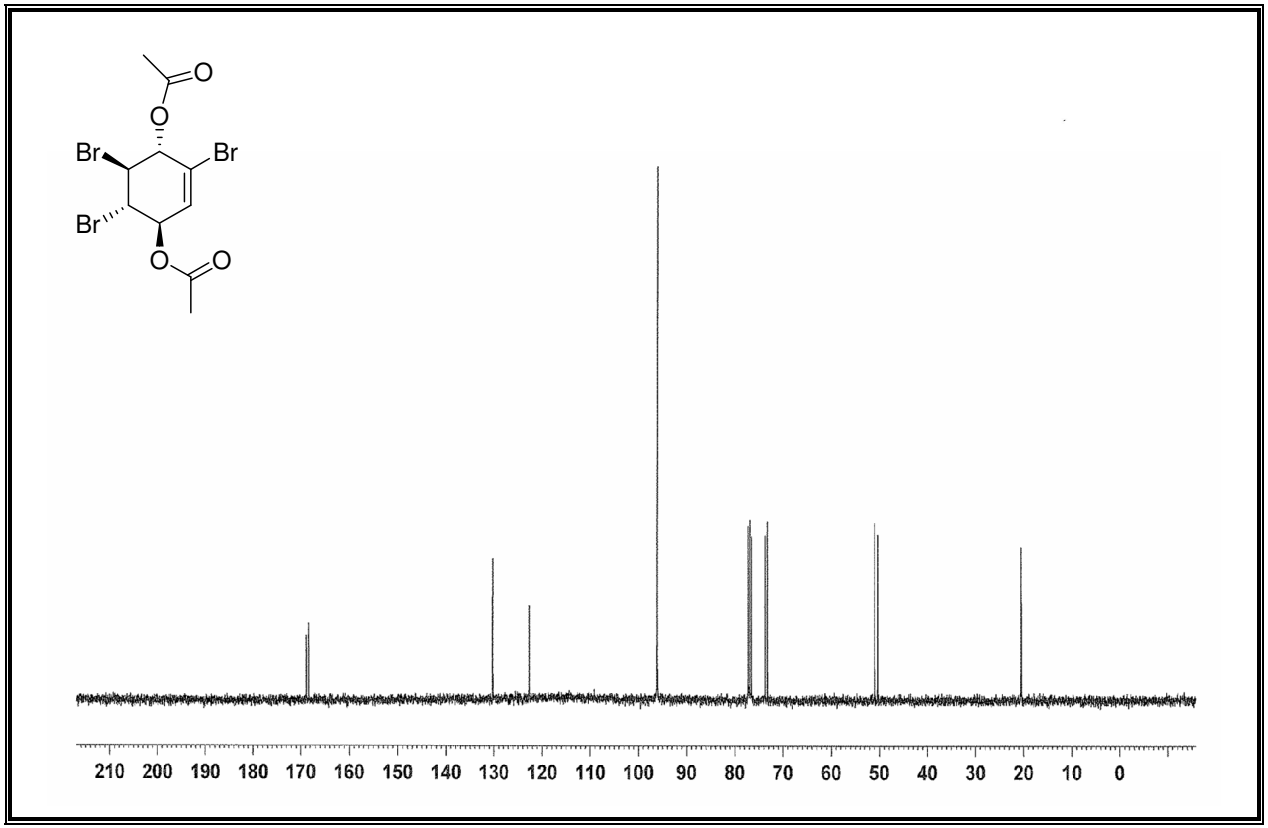


Figure A39 ^{13}C-NMR Spectrum of Compound **155**.

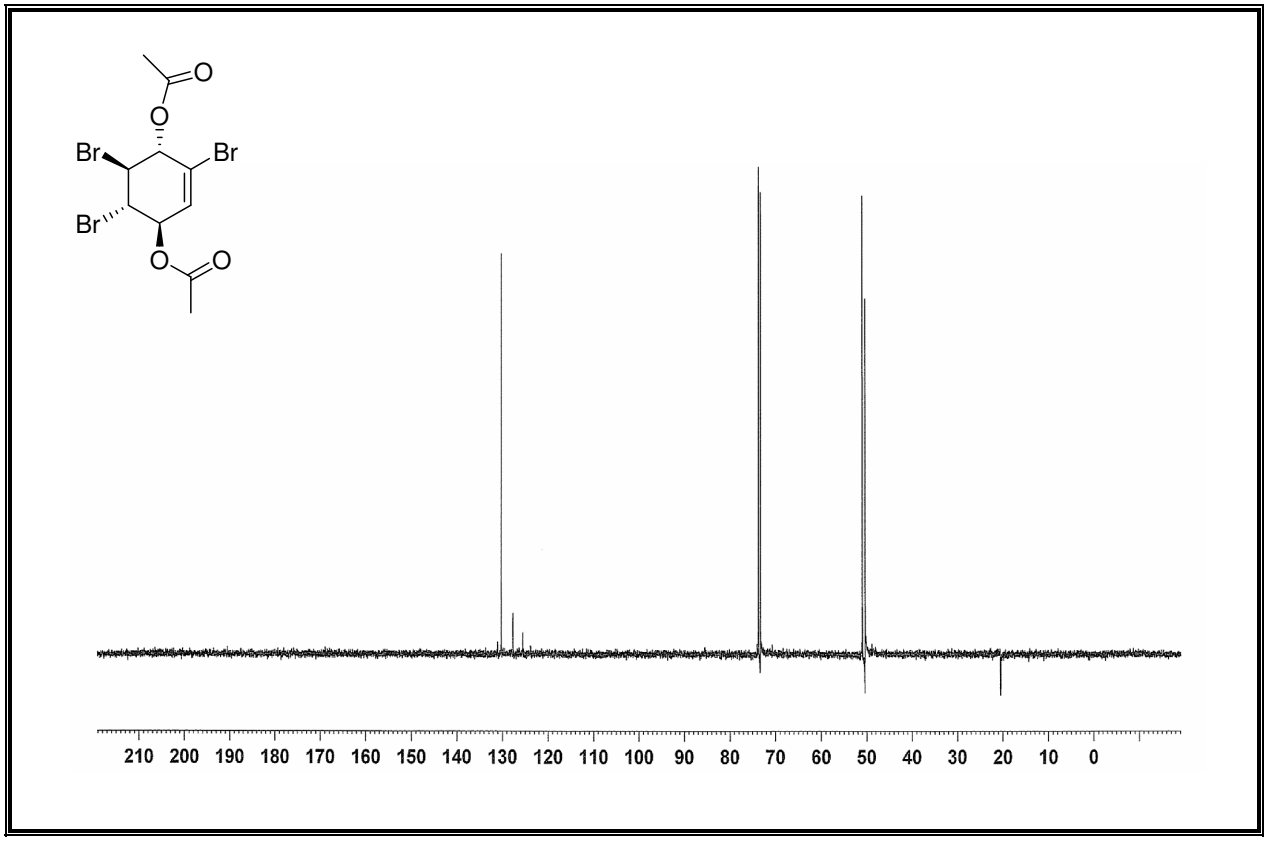


Figure A40 DEPT-90 Spectrum of Compound **155**.

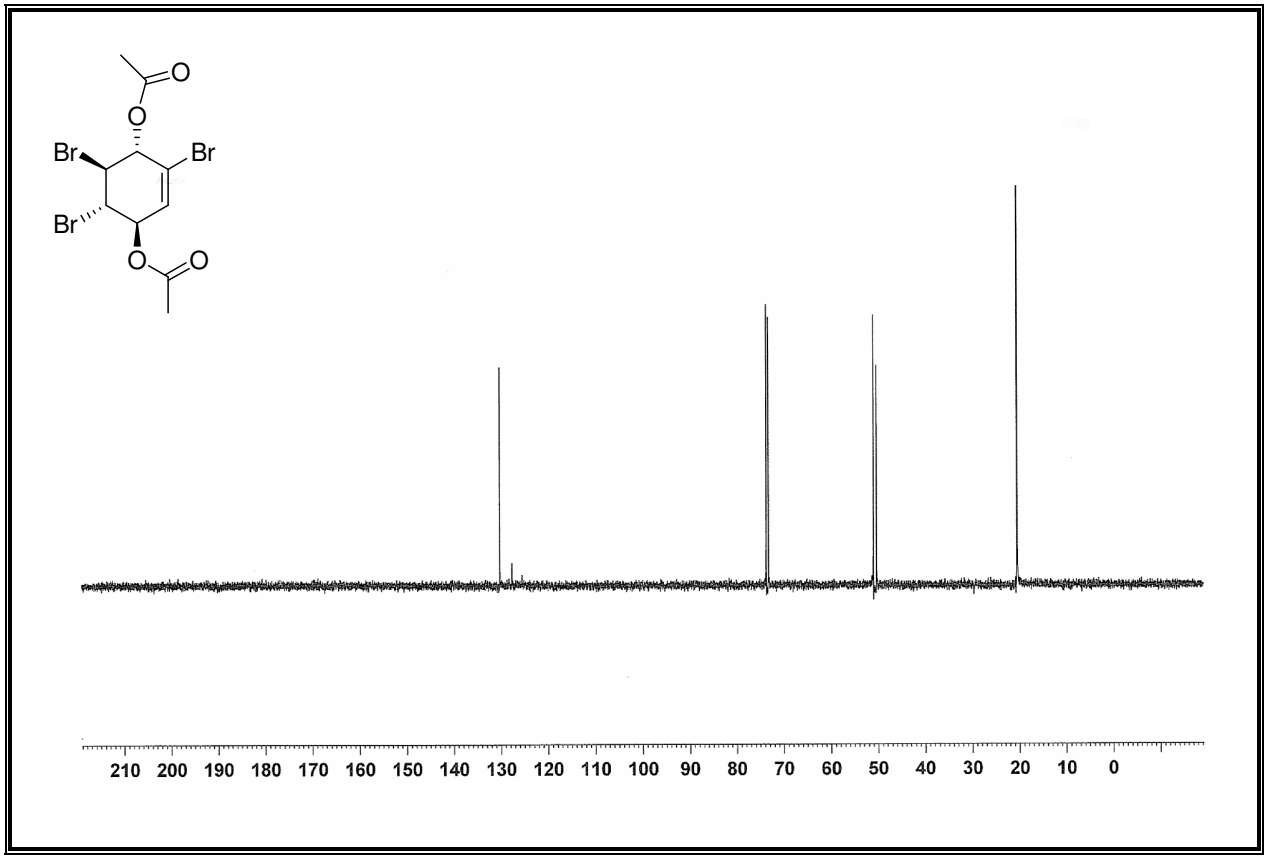


Figure A41 DEPT-135 Spectrum of Compound **155**.

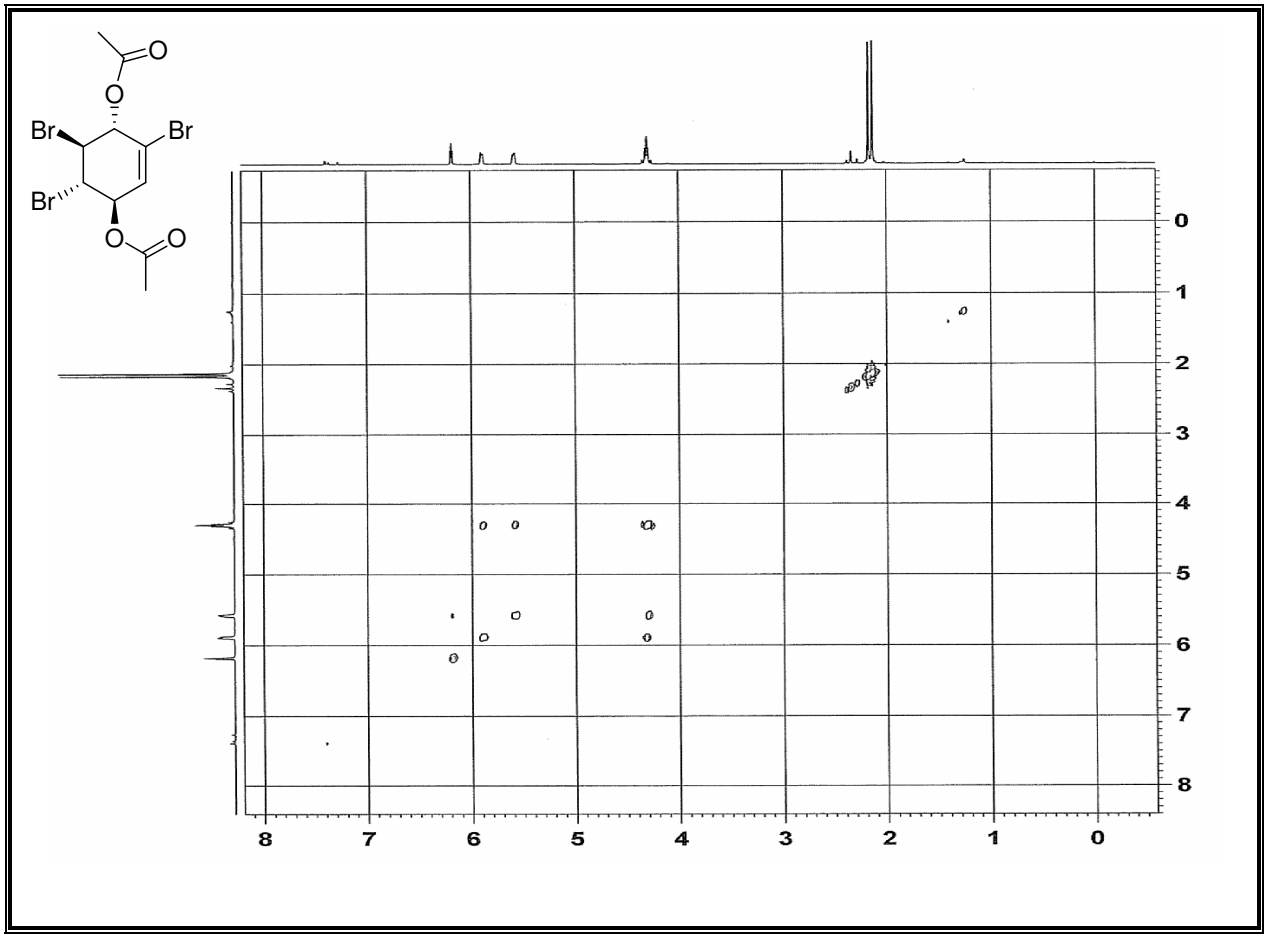


Figure A42 COSY Spectrum of Compound **155**.

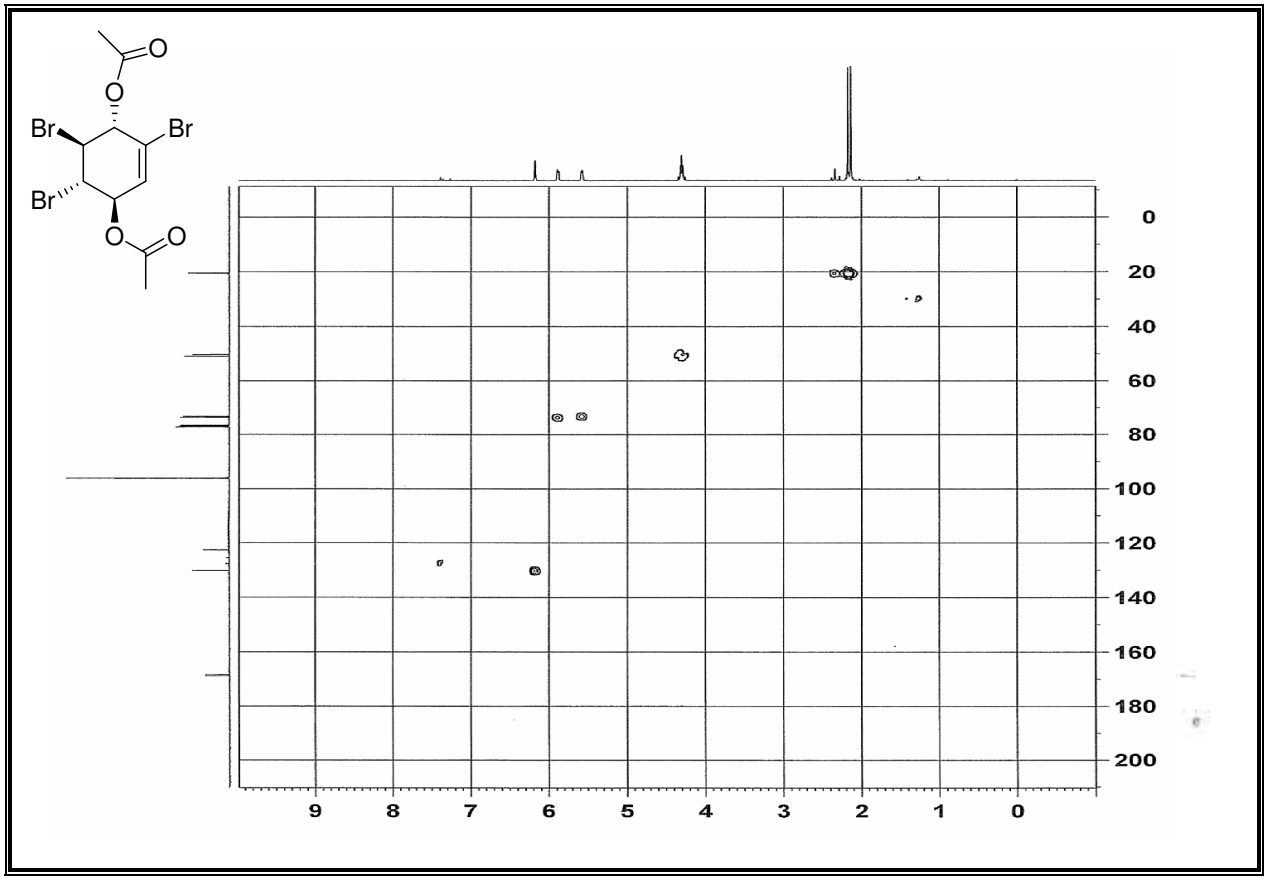


Figure A43 HMQC Spectrum of Compound **155**

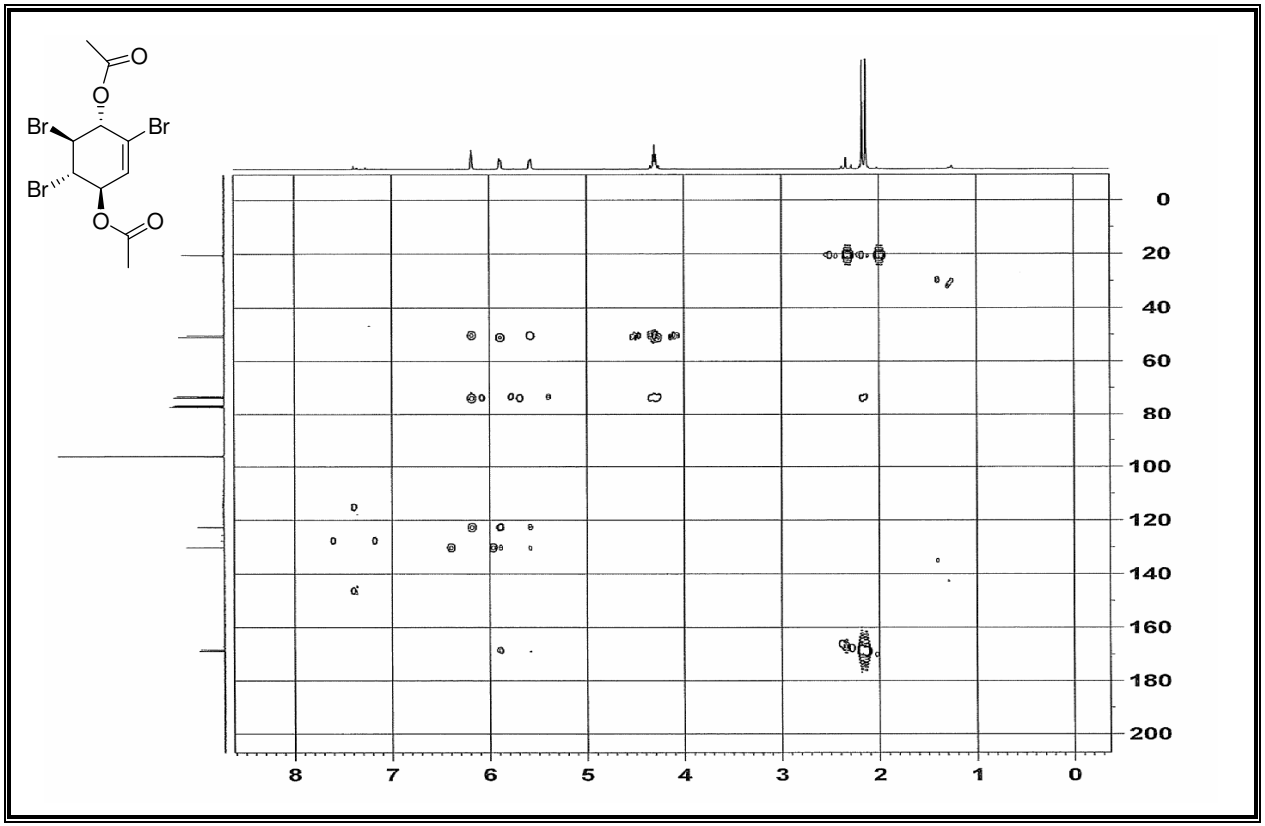


Figure A44 HMBC Spectrum of Compound **155**.

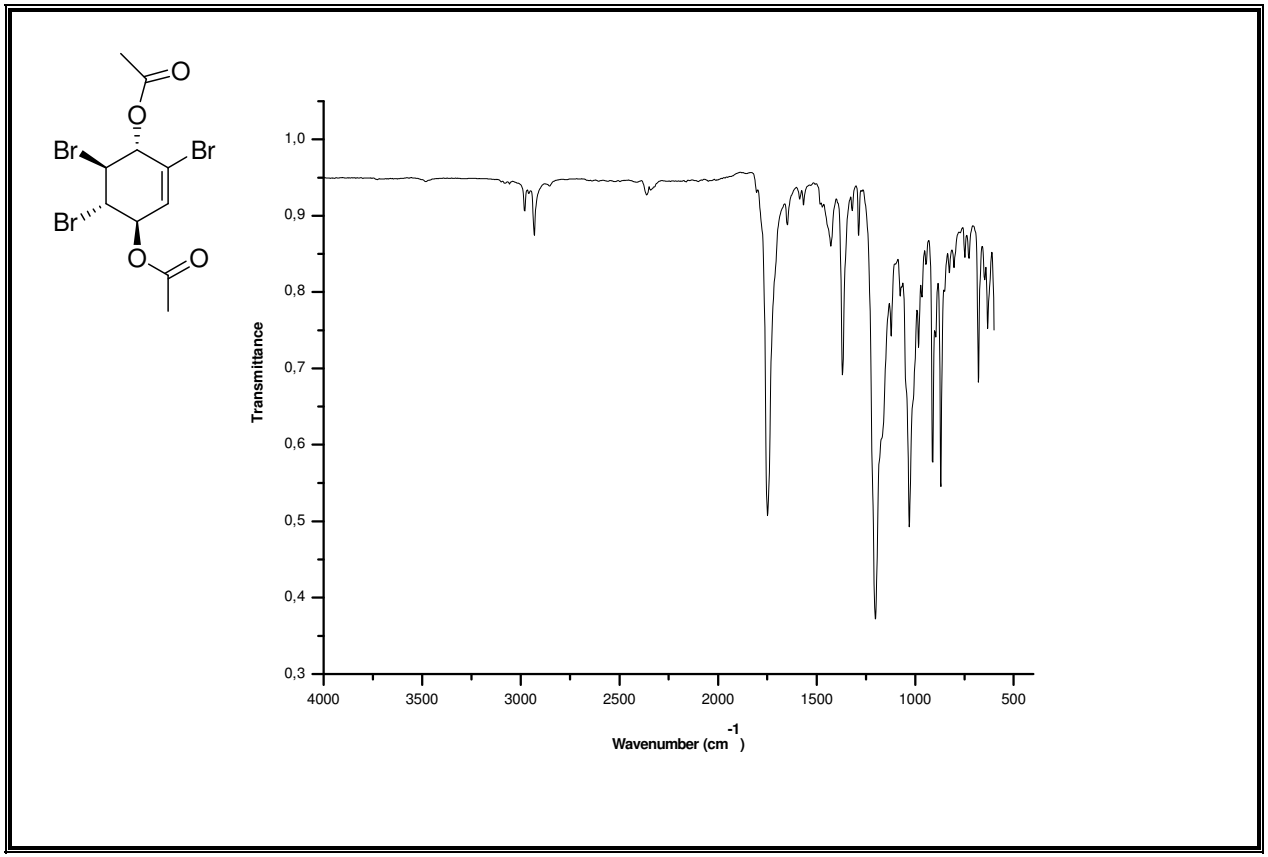


Figure A45 IR Spectrum of Compound **155**.