FUNCTIONALIZATION OF SATURATED BICYCLIC HYDROCARBONS: HIGH TEMPERATURE BROMINATION

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

BY

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

JANUARY 2011

Approval of the thesis:

FUNCTIONALIZATION OF SATURATED BICYCLIC HYDROCARBONS: HIGH TEMPERATURE BROMINATION

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ABSTRACT

FUNCTIONALIZATION OF SATURATED BICYCLIC HYDROCARBONS: HIGH TEMPERATURE BROMINATION

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January 2011, 139 pages

Although hydrocarbons are readily available and extremely cheap starting materials, they cannot be used in synthetic chemistry without prior activation. The selective functionalization of saturated hydrocarbons under mild conditions is of both biochemical and industrial importance.

Initially, saturated hydrocarbons such as octahydro-1*H*-indene **80**, octahydro-1*H*-4,7-methanoindene **81** and bicyclo[4.2.0]octan-7-one **82** were synthesized as starting materials. Then high temperature bromination reactions of these saturated hydrocarbons as a method for C-H bond activation have been investigated and the synthetic application of the formed intermediates has been searched. Furthermore, the role of the alkyl substituents in tricyclic systems and the effect of carbonyl group in bicyclo[4.2.0] octan-7-one **82** have been studied and the mechanism for the formation of the products have been discussed. Finally, whole products were conscientiously purified and characterized.

Keywords: Bromination, hydrocarbons, substitution, octahydro-1*H*-indene, pyramidalization, octahydro-1*H*-metahanoindene, bicyclo[4.2.0]octan-7-one.

ÖZ

DOYMUŞ BİSİKLİK HİDROKARBONLARIN FONKSİYONELLENDİRİLMESİ: YÜKSEK SICAKLIK BROMİNASYONU

Özer, Melek Sermin
Yüksek Lisans, Kimya Bölümü
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Ocak 2011, 139 sayfa

Doymuş hidrokarbonlar oldukça kolay ve bol bulunabilen ucuz maddeler olmasına rağmen, aktif hale getirilmeden sentetik kimyada kullanılamazlar. Ilımlı koşullar altında, doymuş hidrokarbonların seçici olarak fonksiyonel hale getirilmesi endüstriyel ve biyokimyasal açıdan önemlidir.

İlk olarak, oktahidro-1*H*-inden **80**, oktahidro-1*H*-4,7-methanoinden **81** ve bisiklo[4.2.0]oktan-7-on **82** gibi doymuş hidrokarbonlar başlangıç maddesi olarak sentezlendi. Daha sonra, bu hidrokarbonların C-H bağlarını aktif hale getirmek amacıyla yüksek sıcaklık brominasyon reaksiyonları oluşan ara ürünlerin sentetik uygulamaları incelendi. Buna ilaveten, trisiklik sistemlerde alkil sübstitüelerinin rolü ve bisiklo[4.2.0] oktan-7-on **82** karbonil grubunun etkisi araştırıldı ve oluşan ürünlerin oluşum mekanizmaları tartışıldı. Son olarak, bütün ürünler özenle saflaştırıldı ve karakterize edildi.

Anahtar Kelimeler: Brominasyon, hidrokarbon, sübstitüsyon, oktahidro-1*H*-inden, piramitleşme, oktahidro-1*H*-metahanoinden, bisiklo[4.2.0]oktan-7-on.

To my father

ACKNOWLEDGEMENTS

I would like to express my special thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, continuous interest, supports and encouragements. It was a great chance for me to be a student of Prof. Balcı.

My extensive thanks are offered to Dr. Benan Kılbaş for his endless help, comments and close interest as a friend. Thanks are also Assist. Prof. Dr. Gani Koza and Dr. Dilem Doğan for their help and comments.

I wish to express my thanks to my great friend: Merve Bekarlar for her friendship and encouragements throughout my master study. We had some difficulties in doing this task and experiments, but she was always with me as a labmate and a close friend.

I also give my thanks to the members of our research group; SYNTHOR especially to Alper Kılıklı, Berk Müjde, Emrah Karahan, Selbi Keskin, Yasemin Altun, Serdal Kaya, Zeynep Ekmekçi and my clever sister Merve Sinem Özer for their friendships and helpfulness.

I would like to thank to my friends; Hayri Apak, Can Nebigil, Tamer Tezel, and so on for their invaluable friendship and supports.

Thanks are also extended to Scientific and Technical Research Council of Turkey (TUBITAK) and The Turkish Academy of Sciences (TUBA) for the scholarship.

Finally, my special appreciation and great gratitude is devoted to my family for their endless love, patience, moral support and encouregement in every moment of my life.

TABLE OF CONTENTS

LIST OF FIGURES

FIGURES

LIST OF SCHEMES

SCHEMES

LIST OF TABLES

TABLES

LIST OF ABBREVIATIONS

GC/MS	: Gas chromatography and mass spectrum
HBr	: Hydrogen bromide
HMBC	: Heteronuclear multi-bond coherence
HMQC	: Heteronuclear multiple quantum coherence
Hz	: Hertz
IR	: Infrared
IUPAC	: International union of pure and applied chemistry
J	: Coupling constant
k	: Rate constant
NMR	: Nuclear Magnetic Resonance
ppm	: parts per million
RE	: Relative energy
T	: Temperature

CHAPTER 1

INTRODUCTION

1.1 Electrophilic Bromination of Alkenes

Electrophilic addition of bromine to olefins is very common reaction in organic chemistry.[1] Bromination of carbon-carbon double bonds has been studied extensively for many years and it has been generally believed that reaction always gives only the racemic *trans* product via an intermediate bromonium ion. In 1937, Roberts and Kimball first proposed that a three-membered cyclic bromonium ion as an intermediate which is formed during bromination reaction.[2] The NMR studies of Olah and co-workers[3] confirmed that the occurrence of bromonium ion had existence as an intermediate during the bromination reaction. However, there was no conclusive evidence to prove their existence because the reaction is too fast. There have been many experimental studies and spectroscopic observations to confirm the existence of bromonium ion. Subsequently, a bromonium ion tribromide was produced as a yellow crystalline material in the laboratory by the treatment of bromine with adamantylideneadamantane in CCl_4 by Wynberg.[4] After that, Slebocka-Tilk *et al*.[5] obtained for the first time the X-ray structure of adamantylideneadamantane bromonium ion as its tribromide salt as shown in Figure 1.

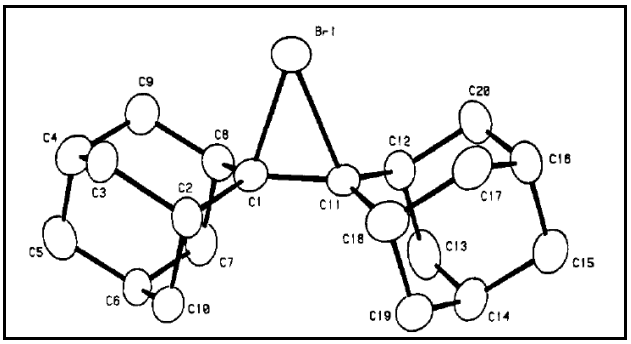
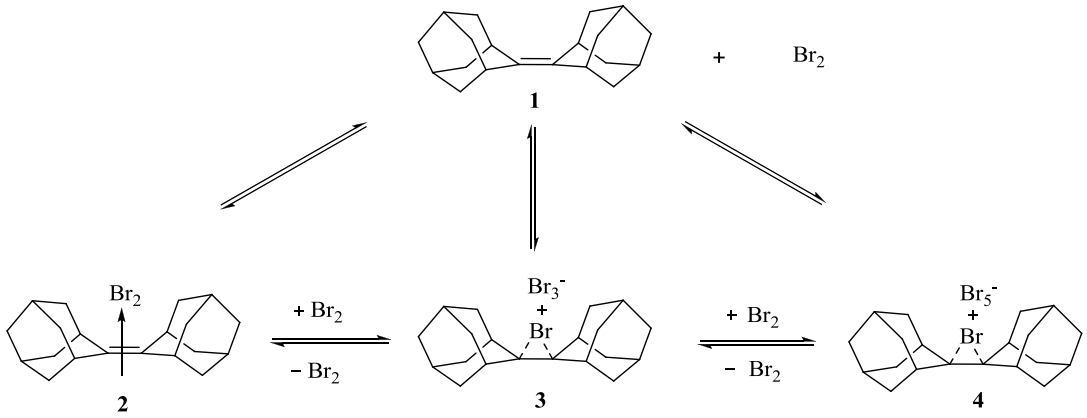


Figure 1. Crystal structure of bromonium ion from adamantylideneadamantane

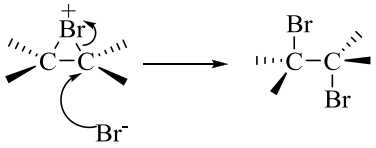
Because of the steric hindrance to back-side nucleophilic attack by Br^-, it is unable to give the *trans* dibromide product. In addition to that, Adamantylideneadamantane is very stable compound and its melting point is 160-162 ^oC.[5] Nevertheless, when this salt dissolved in chlorinated solvents like 1,2-dichloroethane, a complex equilibrium occurs consisting of Ad=Ad **1** and free Br_2, a charge-transfer complex **2**, adamantylideneadamantane bromonium ion tribromide **3**, and a fourth partner believed to be adamantylideneadamantane bromonium ion pentabromide **4** as shown Scheme 1.[6]



Scheme 1. Bromination of adamantylideneadamantane

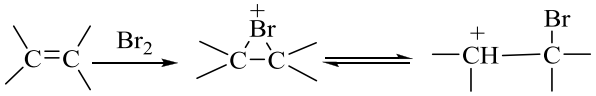
Thus, the stereoselectivity of the bromine addition to alkenes can be explained by three-membered cyclic bromonium ion. It is believed that the reaction mechanism for electrophilic bromination follows these steps: (1) complex equilibrium of olefin-

bromine charge-transfer complex, (2) ionization of π-complex into a σ-complex and,(3) the formation of product by nucleophilic attack (Scheme 2).[7]



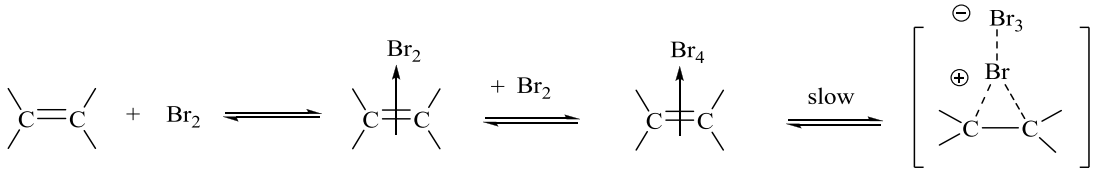
Scheme 2. The formation of product by nucleophilic attack

Theoretical calculations demonstrated that the cyclic bromonium ion is 6.3 kJmol^{-1} more stable than the acyclic carbocation. The activation barrier for the conversion is about 104.5 kJmol^{-1} and bromination undergoes zwitterionic three-center transition states (Scheme 3).[7]



Scheme 3. The conversion of cyclic bromonium ion to acyclic carbocation

On the other hand, if there is a free rotation about carbon-carbon single bond, it would lead to a mixture of *cis*- and *trans*-dibromides. Recently, it has been shown that there are two possible mechanisms for the bromination reaction. Sidewise attack of one equivalence Br_2 to double bond results in the formation of bromonium ion and followed by formation of a *trans* product. The reaction with two equivalences of Br_2 leads to a bromonium/Br_3^- ion pair where the second Br_2 assists in the ionization of the complex (Scheme 4).[7]

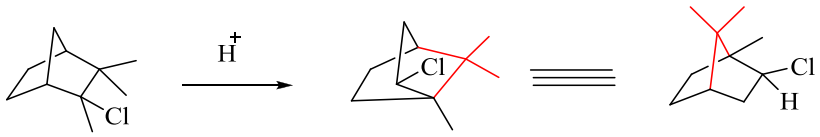


S

Scheme 4. Bromination reaction with two equivalences of Br_2

1.2 Wagner-Meerwein Rearrangements

The migration of an alkyl group to a cationic centre is known as a Wagner-Meerwein rearrangement. The original example is the acid-catalyzed rearrangement of camphene hydrochloride **5** to isonorbornyl chloride **6** (Scheme 5).[8]



5 **6**

Scheme 5. Acid-catalyzed rearrangement of camphene hydrochloride **5**

Wagner-Meerwein rearrangement is a rearrangement in which an alkyl or aryl group moves from a carbon atom to an adjacent carbon atom during a reaction. The carbocation which is formed as an intermediate is stabilized during this rearrangement.

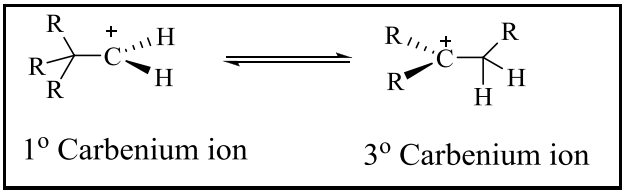
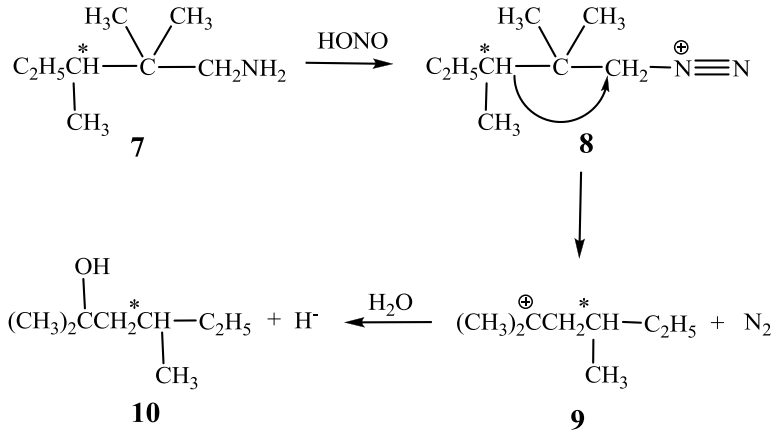


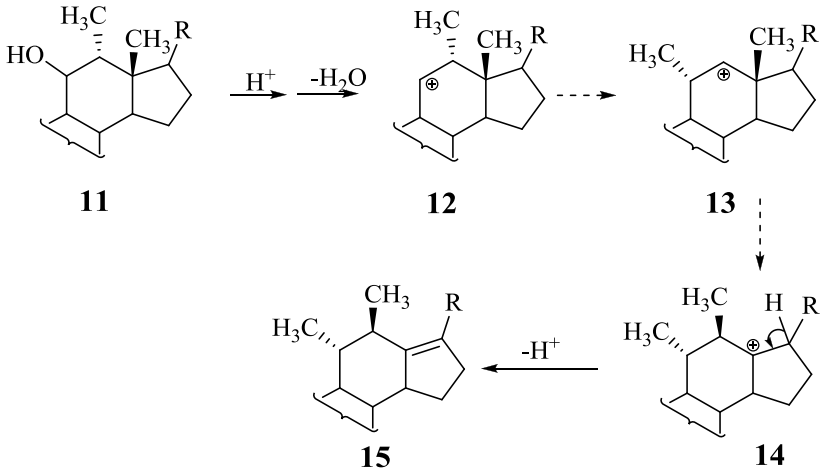
Figure 2. Rearrangement of a carbocation

Early investigators considered the possibility that Wagner-Meerwein rearrangements proceed by cleavage of the bonds joining the migrating groups to the remainder of the molecules, followed by formation of new bonds at different positions. However, it was found that migrating groups normally retain their configurations during Wagner-Meerwein rearrangements (Scheme 6).[9]



Scheme 6. Retention of configuration during Wagner-Meerwein rearrangements

Furthermore, during migrations of substituents on carbocyclic rings, the substituents inverably end up on the face of the ring from which they started (Scheme 7).[10]



Scheme 7. Wagner-Meerwein rearrangements on carbocyclic rings

These facts demonstrate that Wagner-Meerwein rearrangements are intramolecular reactions. They have transition states that resemble cyclic arrays of three atomic orbitals, each array containing two electrons from the migrating bond. (The transition states for Wagner-Meerwein rearrangements, in fact, have been decribed as “corner – protonated cyclopropanes”.) That description requires that there must be at least one proton on the migrating carbon.

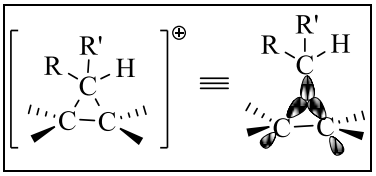
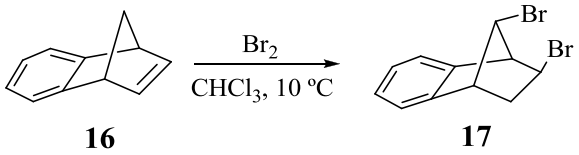


Figure 3. The transition state for Wagner-Meerwein

1.3 Bromination of Unsaturated Bicyclic Systems

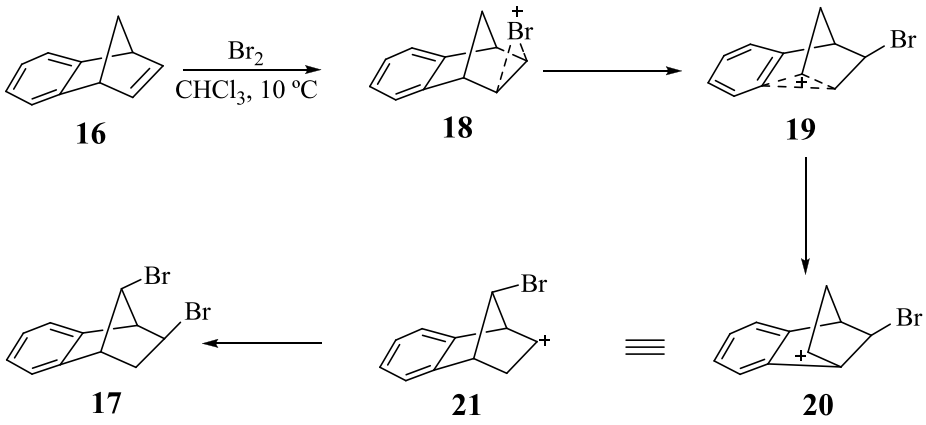
In acyclic case, an open ion pair can be stabilized by an electron donating group via neighbouring group participation such as a phenyl group so that *syn* addition can predominate. On the other hand, a freely rotating open carbocation cannot occur in the cyclic alkene which leads to only *anti* product. However, Wittig *et al*. noted that the bromination of benzonorbornadiene **16** in chloroform at low temperature gives only the rearranged product **17** in quantative yield (Scheme 8).[11]



16 **17**

Scheme 8. Bromination of benzonorbornadiene

The molecular bromine addition to unsaturated bicyclic systems rearranged the molecular skeleton via Wagner-Meerwein rearrangement. Winstein and Roberts suggested that *non*-classical carbocation **19** was formed during the reaction to explain the rearranged product.[12] Therefore, the mechanism of formation of the rearranged product can be almost certainly rationalized by the following mechanism (Scheme 9).

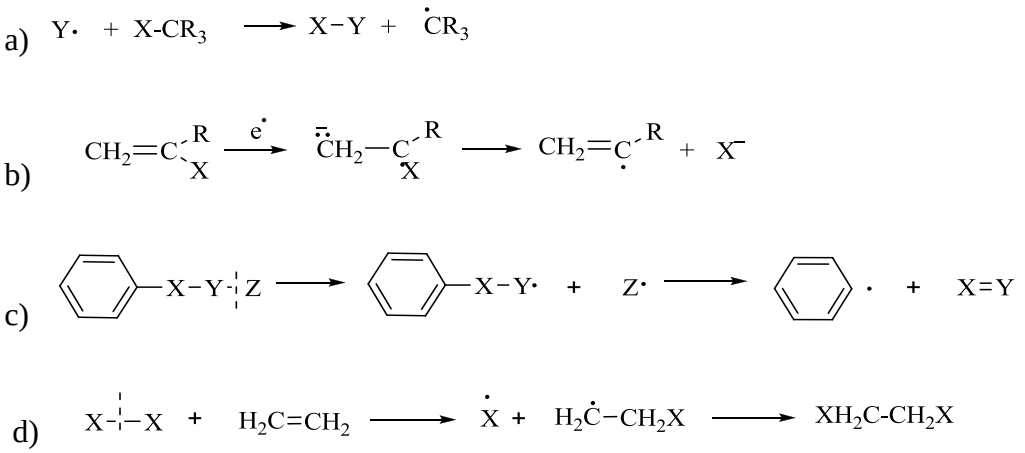


Scheme 9. The proposed mechanism of formation of rearranged products

Nevertheless, rearrangement of the molecular skeleton prevents the synthesis of non-rearranged products. In order to hinder the molecular arrangement, Balci and *co-workers*[13] developed "High Temperature Bromination Reactions, (HTBR)" and applied succesfully this methodology to bromination of various cyclic hydrocarbons.

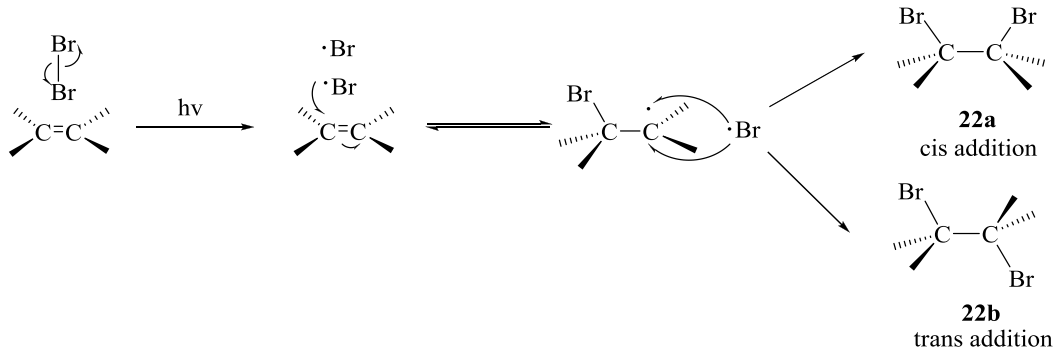
1.4 Free-Radical Bromination

Free radicals are atoms, higly reactive species, with an unpaired number of electrons. Pairs of electrically neutral "free" radicals are formed via homolytic bond breakage. There are several ways to generate free radicals from neutral molecules such as photolysis, thermolysis and redox reactions. In radical reactions, there are almost generally four type of reactions; **(a)** atom abstraction, **(b)** one-electron reduction and dissociation, **(c)** homolytic bond cleavage and fragmentation, and finally, **(d)** homolytic bond cleavage and addition (Scheme 10).[14]



Scheme 10. Examples for general radical reactions

The addition to carbon-carbon double bond is the most important group of reactions involving radicals. The reactivity of different halogens to alkenes are the same as electrophilic bromination, i.e. $F_2 > Cl_2 > Br_2 > I_2$. Bromination occurs easier and is usually reversible. The reversibility of addition of bromine is responsible for formation of *cis* and *trans* products as shown in Scheme 11.

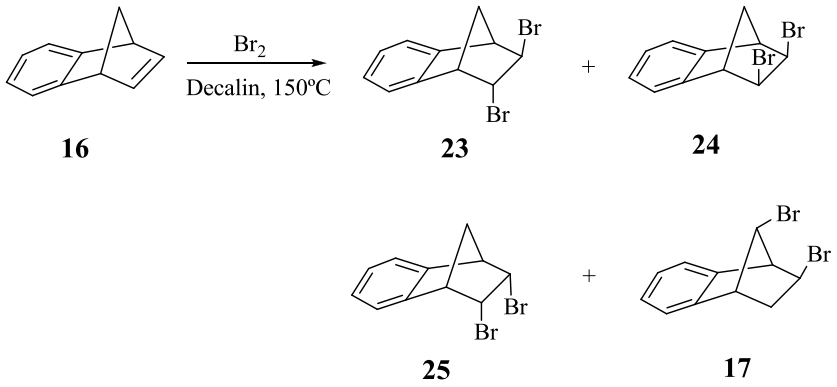


Scheme 11. Formation of *cis* and *trans* products

1.4.1 High Temperature Bromination of Benzobicyclic Systems

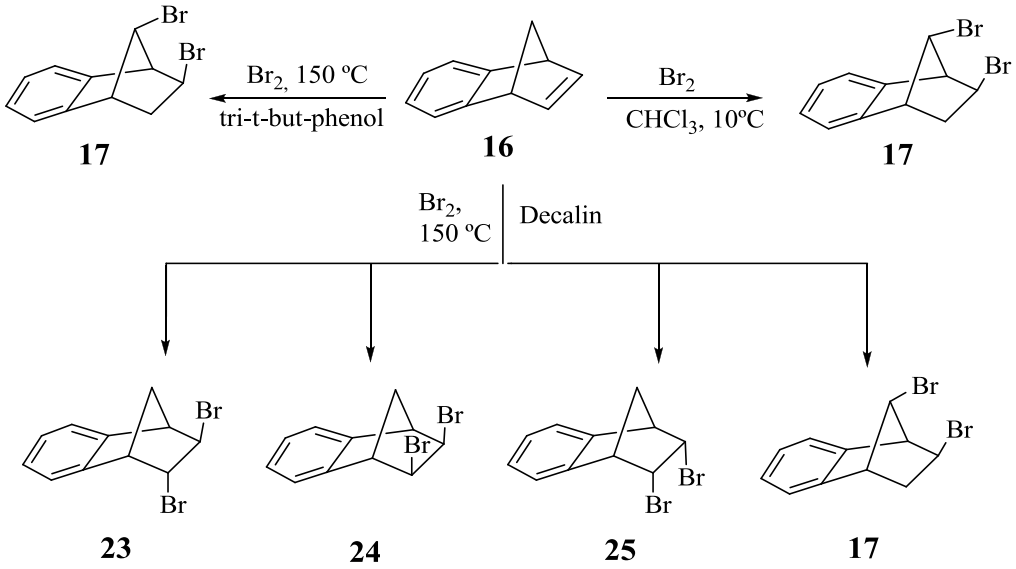
Balci and *co-workers* noted that the product distribution of bromine addition was significantly affected by the reaction temperature.[15] The bromination of benzonorbornadiene (**16)** at 0 ^{o}C was found to give only rearranged product.[12] However, high temperature bromination of **16** in decalin at 150 ^{o}C produced four

products, *non*-rearranged dibromides **23-25** besides the rearranged product **17** in the yield of 34, 35, 9, 18 and 2 %, respectively (Scheme 12).[16]



Scheme 12. High temperature bromination of benzonorbornadiene

Symmetrical *endo-cis*-isomer **25** was observed for the first time. In general, electrophilic bromination of olefins yields *trans*-1,2-dibromides. *Cis*-addition of bromine to double bound cannot be explained via bromonium ion. *Cis*-addition demonstrates that the *cis*-adduct can occur either from direct *syn*-collapse of an ion pair or from rotation followed by *anti*-collapse. Because of the rigid skeleton in **16**, the carbon-carbon single bond cannot rotate. In this case, it can be assumed that a free radical mechanism can explain the formation of *non*-rearranged products. Since radical intermediates are unable to rearrange, at higher temperatures, mostly *non*-rearranged products are formed. In order to find out the mechanism of formation of the *non*-rearranged products, bromination reaction was carried out in the presence of free radical inhibitors like 2,4,6-tri-tert-butylphenol (Scheme 13).[16] It was shown that radical and ionic reactions during the bromination at high temperature compete to give rearranged and *non*-rearranged products. This strongly supports the theory of free-radical mechanism.



Scheme 13. Bromination reaction in the presence of free radical inhibitor

Benzonorbornadiene **16** has a *non*-conjugated diene system. There can be two types of intermediates during bromination reaction. In *non*-classical type of intermediates, if Br_2 attacks the double bond, it forms a classical bromonium ion, which rearranges to the more stable *non*-classical carbocation **19**. So, rearranged products can be formed via Wagner-Meerwein rearrangement (Figure 4).

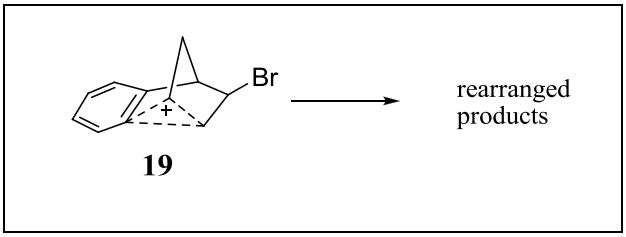


Figure 4. *Non*-classical carbocation as an intermediate

On the other hand, the radical **27** formed after addition of bromine radical to the double bond in benzonorbonadiene, it does not have great tendency for the rearrangement (Figure 5).

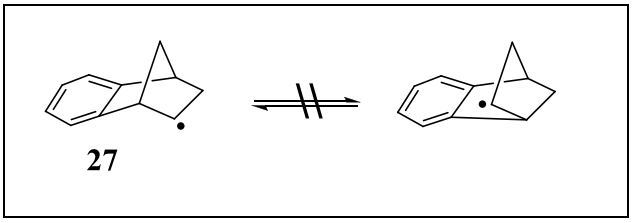
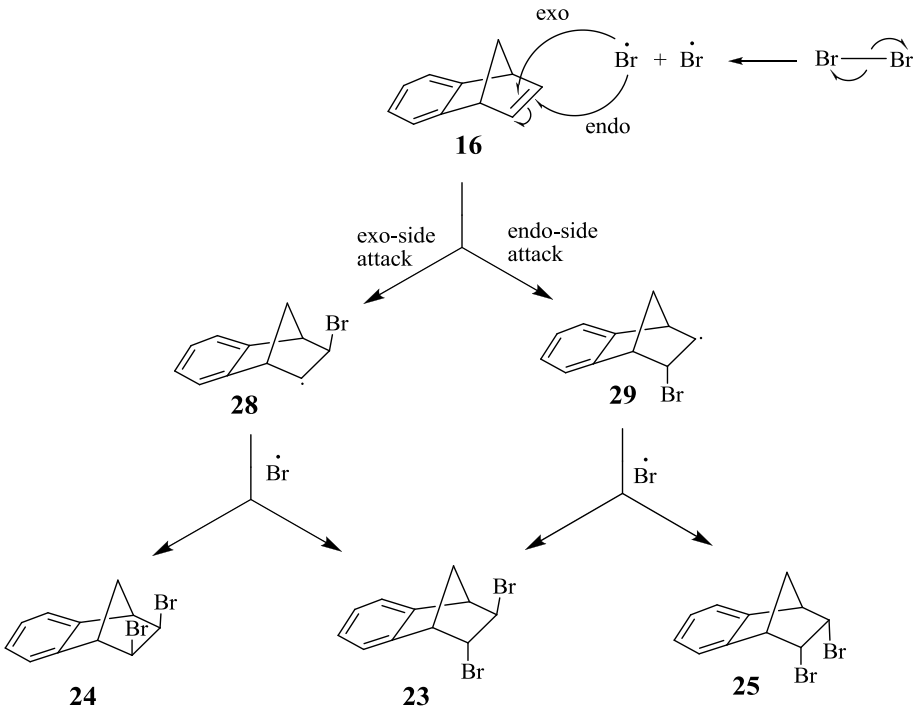


Figure 5. Radical intermediate

In the light of these observations, the following mechanism for the formation of the rearranged products can be suggested: After homolytic bond cleavage of bromine, bromine radical attacks the double from both *endo*- and *exo*-side of the molecule to give monobromides **28** and **29** followed by capture of second bromine radical to form the products **23-25** (Scheme 14).

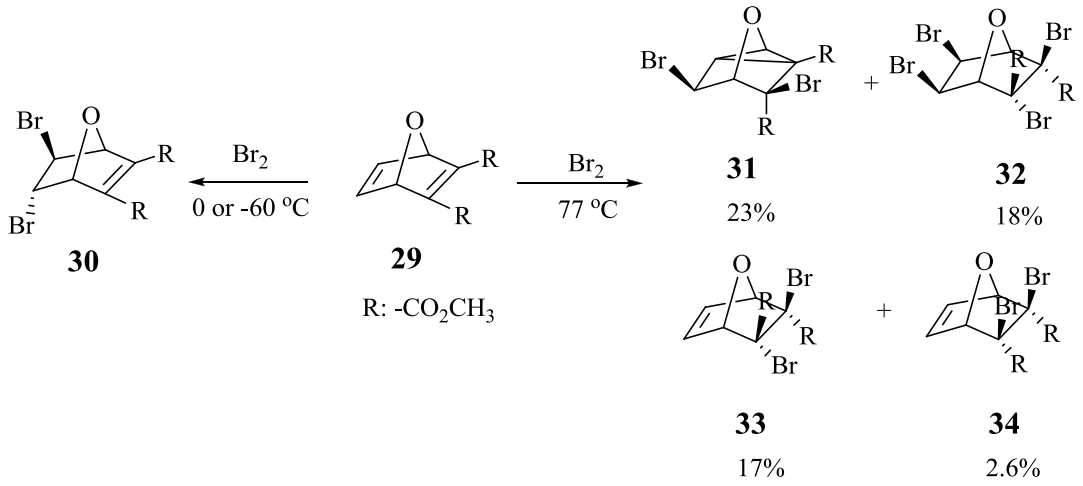


Scheme 14. The possible mechanism for high temperature bromination of **16**

1.4.2 Heteroatom Effect on Bromination of Bicyclic Systems

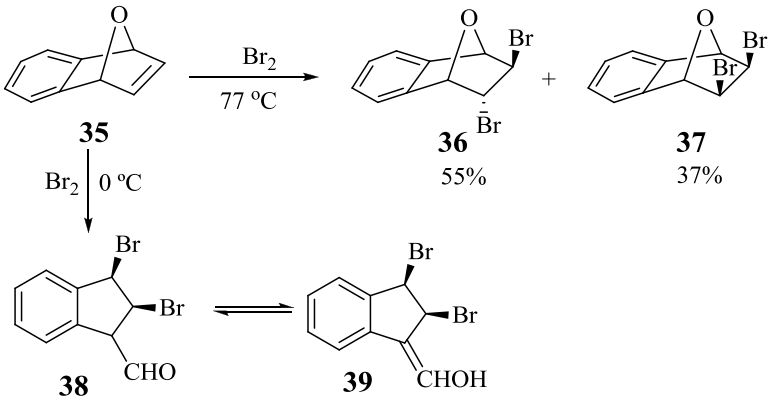
In high temperature bromination reactions, electronic or steric factors control the formation of products. For example, benzonorbornadiene **16** needs higher temperature (150 °C) to form *non*-rearranged products.[16] Even at this temperature, rearranged product **17** was also formed in 20% yield. In order to understand the effect of the bridge atoms (oxa, aza), Balcı *et al.* have studied the bromination reactions of some heteronorbornadiene derivatives.

For instance, low temperature bromination of oxanorbornadiene **29** at 0 or -60 ^{o}C did not reveal any trace of rearranged product, however the same molecule gave at 77 ^{o}C four products **31-33**, three of which have mainly the non-rearranged skeletons (Scheme 15).[17]



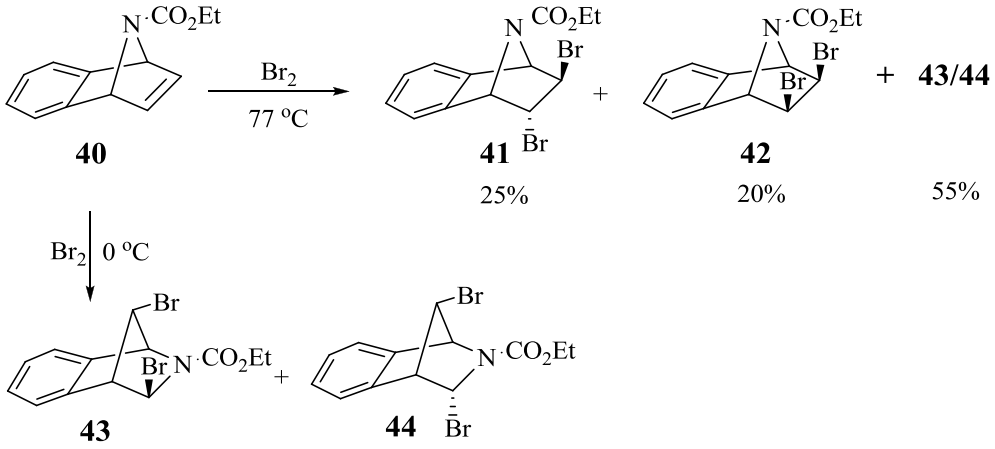
Scheme 15. High and low temperature bromination of oxanorbornadiene

Nevertheless, oxabenzonorbornadiene **35** afforded *non*-rearranged products **36**-**37** at 77 °C in high yield (Scheme 16).[18]



Scheme 16. High and low temperature bromination of oxabenzonorbornadiene

On the other hand, bromination of azacompound **40** at 77 °C resulted in the formation of the rearranged products **43-44** (55%) beside the *non*-rearranged products **41-42** in 25 and 20% yields (Scheme 17).[19]



Scheme 17. High and low temperature bromination of **40**

Studies show that high temperature bomination of brominated benzonorbornadiene and benzonorbarrelene such as **45** and **46** form easier products with the parent molecules of benzonorbornadiene and benzonorbarrelene. For example, bromination of benzonorbornadiene **16** at 77 °C leads to rearranged products. However, bromination of 2-bromobenzonorbornadiene **45** at the same temperature gives *non*-rearranged product in high yield.[20] In addition to that, the reaction of 2,3,5-

tribromobenzobarrelene **46** even at room temperature produced the *non*-rearranged product in quantitative yield.[21]

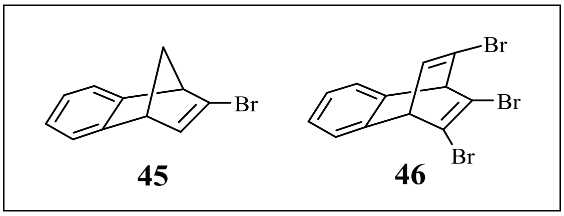


Figure 6. Substituted benzobicyclic systems

Finally, it was concluded that the heavy atoms attached to the double bond prevent the skeletal rearrangement.

1.5 Applications of High Temperature Bromination

Synthetic materials, usually halocarbons, are used as flame retartand compounds. These include organobromines such as polybrominated diphenyl ethers (PBDEs) **47**, hexabromocyclododecane (HBCD) **48,** and tetrabromobisphenol A (TBBPA) **49.**[22] The compound **50,** with benzonorbornadiene skeleton is also flame retardant which involves in brominated benzonorbornadiene derivative.[23]

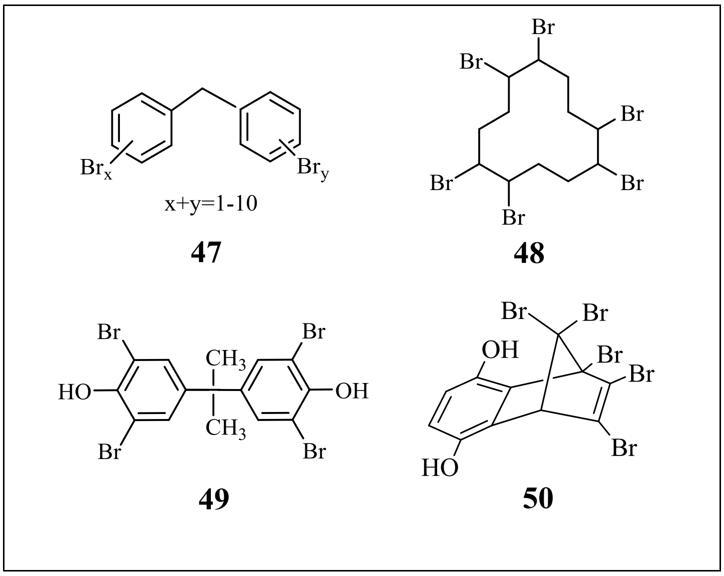


Figure 7. Polybrominated organic compounds

Beside the different types of industrial applications of this highly brominated compounds, such as pesticides, plastics, fire-retardants and pharmaceutical chemicals, they are also higly halogenated compounds which are used as the key intermediates for the synthesis of other derivatives. For example, *di-*, *tri-* and *tetra-*bromobenzobarrelenes (**46** and **51-53**) firstly have been synthesized[24] by the application of high temperature bromination reaction and were used for various purposes.[25]

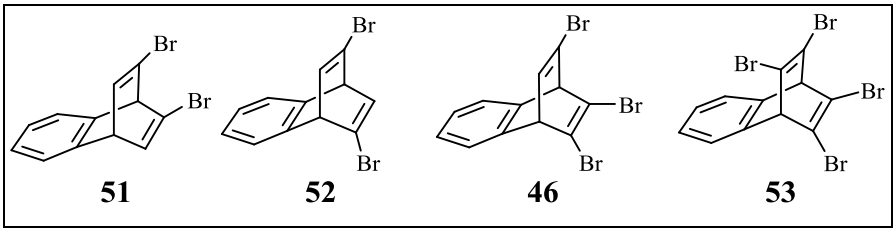


Figure 8. Di-, tri-, tetra-bromobenzobarralene derivatives

High temperature bromination of benzonorbornadiene **16** allowed the synthesis of 2-bromobenzonorborenadiene **45** and 2,3-dibromobenzonorbornadiene **54** which were used as a key compounds for synthesis of other derivatives.[21] The mono- and dibromo-oxabenzonorbornadienes **55-56** were only accessible via this method.[26] Vinylic monobromides or dibromides **55-56** are indispensable key compounds for cyclotrimers **58.**[23]

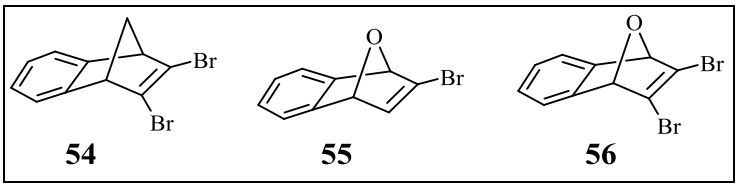


Figure 9. Bromobenzonorbornadiene derivatives

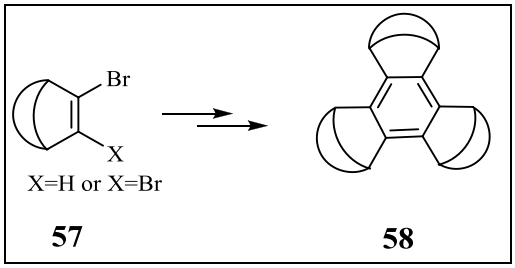


Figure 10. The synthesis of cyclotrimers

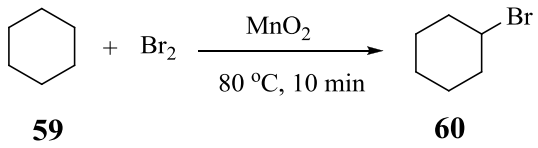
Schlosser and Castagnetti[27] used this method to obtain new naphthalene derivatives starting from dibromooxabenzonorbornadiene derivatives.

1.6 The Functionalization of Inactive C-H Bonds

If there is no electron releasing group attached to the carbon atom, the reactivity of C-H bonds is generally not enough to react. Many hydrocarbons are halogenated with elemental chlorine or bromine while being heated or irradiated together. However, the reaction usually cannot be controlled easily during halogenation. Radicals play an important role to functionalize the carbon-hydrogen bonds.

There are various methods that have been developed for the C-H bond activation of alkanes. Transition metal reagents such as Pd, Ru, Rh, Ir, or complex metal systems are used as a catalyst for this purpose. However, these transformations, either stoichiometric or catalytic, involve expensive metals and also the recovery and direct reuse of these catalysts are difficult.[28-31] Among the haloalkanes, alkylbromides are the most important synthetic intermediates in chemical industry.[32-35] For that reason, direct and selective bromination of alkanes would be of choice and it is certainly the ideal way to produce alkylbromides.

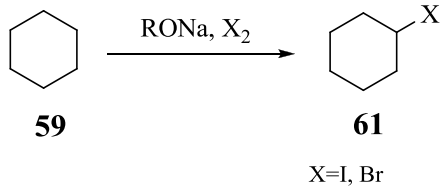
The selective halogenations of saturated hydrocarbons and various reagents have been investigated. For example, Li *et al.* reported a novel chemoselective bromination of alkanes promoted by unactivated MnO_2.[33] Cylohexane can be brominated by application of this method in a very short time to give cyclohexyl bromide (Scheme 18).



59 **60**

Scheme 18. Bromination of alkanes promoted by unactivated MnO_2

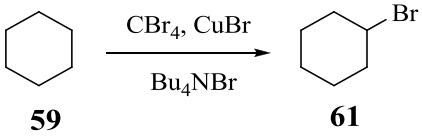
Wirth and Montoro reported that stechiometric mixtures of elemental halogen and sodium alkoxides leads to the formation of alkyl hypohalides which can activate the C-H bonds of alkanes to furnish haloalkanes as shown in Scheme 19.[34]



59 **61**

Scheme 19. Bromination reaction with elemental halogen and sodium alkoxides

Furthermore, catalytic bromination of alkanes, cycloalkanes and arylalkanes using CBr_4 as a brominating agent in the presence of copper bromide and tetrabutyl ammonium bromide was also reported (Scheme 20).[35]



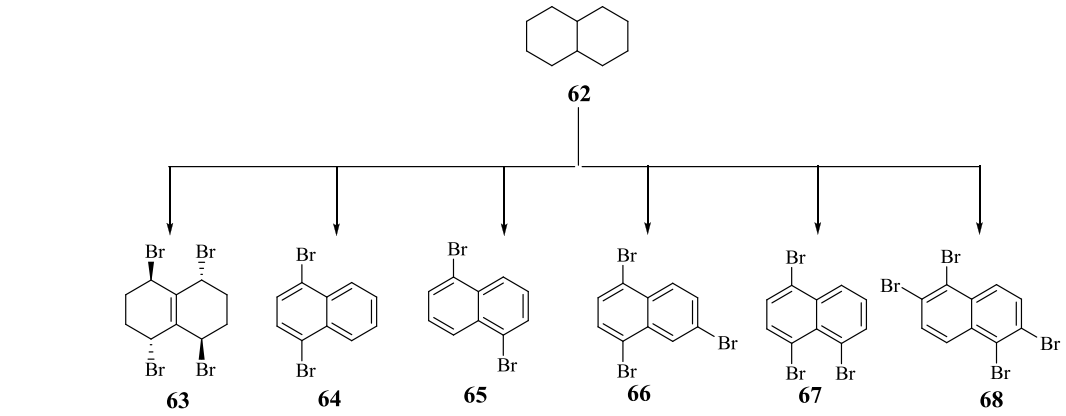
59 **61**

Scheme 20. Copper bromide as a brominating agent

1.6.1 High Temperature Bromination of Saturated Hydrocarbons

In this manner, Balci and Dastan have studied the high temperature bromination of decalin **62**, a saturated bicyclic hydrocarbon.[36] They have reported that thermal bromination of decalin **62** gave *trans*,*trans*,*trans*-2,5,7,9-tetrabromooctalin, **63**, as the major product with remarkable regio- and stereoselectivity along with smaller amounts of bromonaphthalene derivatives **64**-**68** (Scheme 21).[36]

Bromination reaction of decalin at temperatures of 10 and 50 ^{o}C was also investigated. The effect of temperature showed that decreasing the reaction temperature increased the yield of tetrabromo compound **63**. It was remarkable to note that the reaction proceeded with regio- and stereoselectivity.



Br_2/ hv/ 10^{o}C	68%	3%	4%	-	-	2%
Br_2/ hv/ 50^{o}C	48%	8%	5%	-	-	-
Br_2/ 150^{o}C	32%	14%	10%	5%	3%	-

Scheme 21. Bromination of decalin under different conditions

Theoretically, five different isomers **63**, **69**, **70, 71** and **72** can be formed during this reaction (Figure 11). The exclusive formation of **63** can be explained by thermodynamic control.

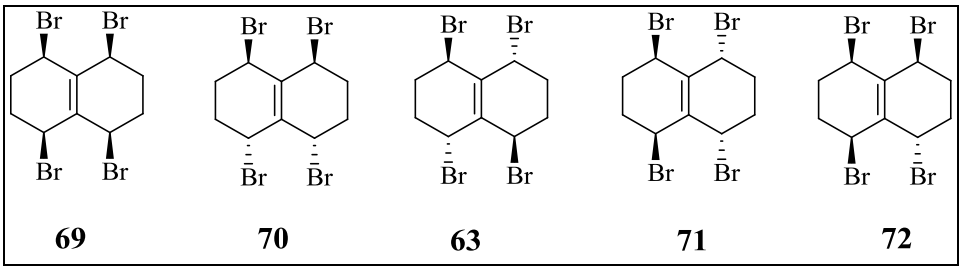
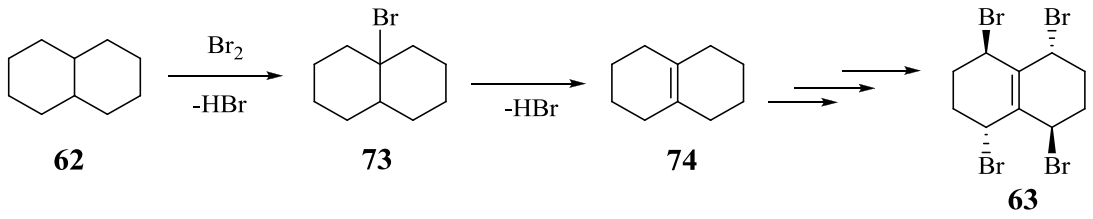


Figure 11. Possible isomers of formed tetrabromide compound

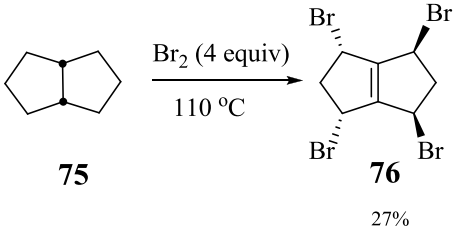
Theoretical calculations also showed that the most stable isomer is the isomer **63**. It was not surprising that this configuration is the most stable one because of dipole-dipole interactions between bromine atoms force bromine to be as far apart as possible. The formation of tetrabromide **63** was explained as follows: decalin **62** reacts with bromine radical to give a monobromide **73** from which HBr elimination affords octalin **74**. This alkene would undergo sequential allylic bromination reactions to furnish tetrabromide **63** (Scheme 22). When an allylic position initially brominated, it can direct the second bromine *trans* to it either three or four carbons removed.



Scheme 22. The proposed mechanism of formation of **63**

It is noteworthy that formation of tetrabromide **63** takes place with remarkable regio- and stereoselectivity in contrast to the fact that radical reactions have a bad reputation for being not particularly selective.

In order to evaluate the effect of size of the ring, high temperature bromination of octahydropentalene **75** was carried out. The treatment of octahydropentalene **75** with 4 equiv. of bromine at 110 ^{o}C afforded the tetrabromide **76** in a yield of 27% (Scheme 23).[37]



Scheme 23. High temperature bromination of octahydropentalene

The ^{13}C-NMR studies of the tetrabromide **76** shows the presence of three signals, which are also in agreement with the structures **77-79** (Figure 12).

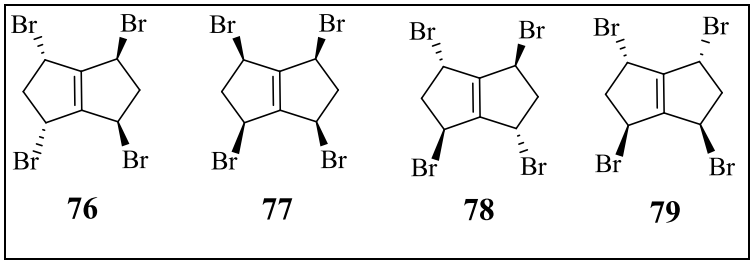


Figure 12. Possible isomers for tetrabromide compound **76**

AM1 and MMX molecular mechanics calculations showed that the energy of **76** and **78** are close each other and they are approximately 2–4 kcal/mol more stable than the other isomers. According to these values it was expected that the isomer **78** should also be formed. Careful examination of the reaction mixture did not reveal the formation of any trace of the isomer **78**, to where they assumed that **76** is favored kinetically.

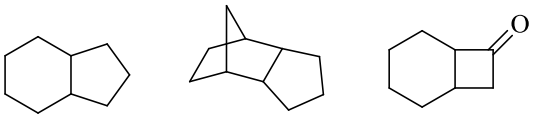
The appealing feature of high temperature bromination reaction is that it takes place with remarkable regio- and stereoselectivity in the case of saturated bicyclic hydrocarbons. It may be recalled that decalin **62**, an unsaturated bicyclo[4.4.0] system, affords *trans,trans,trans*-2,5,7,9-tetrabromooctalin **63** with remarkable regio- and stereoselectivity. On the other hand, octahydropentalene **75**, bicyclo[3.3.0]octane provides *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene **76**. These results suggest, perhaps counterintutively, that the configurations of bromines are not related to the size of the ring. When the steric factors predominate in the six-membered ring (decalin, **62**) bromines prefer all *trans*- arrangement, steric affects are less effective in the case of a five-membered ring (octahydropentalene, **75**) so that bromine atoms prefer *cis,trans,cis*- arrangement.

1.7 Aim of Thesis

Although hydrocarbons are readily available and extremely cheap starting materials, they cannot be used in synthetic chemistry without prior activation. The selective functionalization of saturated hydrocarbons under mild conditions is of both biochemical and industrial importance.

The activation of carbon-hydrogen bonds in aliphatic hydrocarbons is difficult to achieve and a challenging process in organic synthesis. Therefore, a new chemical process for direct and selective funtionalization of alkanes to upgrade products such as alcohols, aldehydes ketones, carbocylic acids, etc. under mild conditions is one of the most promising methods for future organic synthesis. Despite the fact that radical reactions have a bad reputation for being not particularly selective, novel halogenation methods have been changing this picture dramatically over the last decade. Our contribution to this field exemplified with a series of high temperature bromination of the saturated bicyclic hydrocarbons having tertiary hydrogen. Balci and Dastan have studied the effect of size of the ring in the case of six- and five-membered ring such as decalin **62**, octahydropentalene **75**. The results were conflicting but demonstrated a way to understand whether the formation of mechanism related to the size of the ring or not.

In this work, we are interested in searching of high temperature bromination of the octahydro-1*H*-indene **80**, octahydro-1*H*-4,7-methanoindene **81** and bicyclo[4.2.0] octan-7-one **82** and the synthetic application of the formed intermediates will be searched. Furthermore, the role of the alkyl substituents in tricyclic systems such as **81** and the effect of carbonyl group in bicyclo[4.2.0]octan-7-one **82** will be studied and the mechanism for the formation of the products will be discussed.



80 **81** **82**

CHAPTER 2

RESULTS AND DISCUSSION

Selective halogenation of saturated hydrocarbons is a very important method for the synthesis of useful intermediates in synthetic organic chemistry. Firstly, we focused on the synthesis of two different types of saturated hydrocarbons **80-81** for the functionalization of them via high temperature bromination reaction. In addition to that, we examined the effect of functional groups such as carbonyl group in **82** on the bromination reaction (Scheme 27).

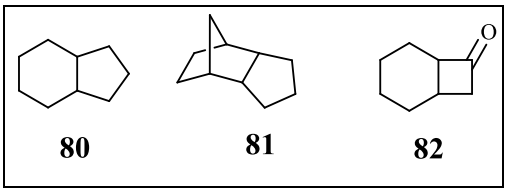
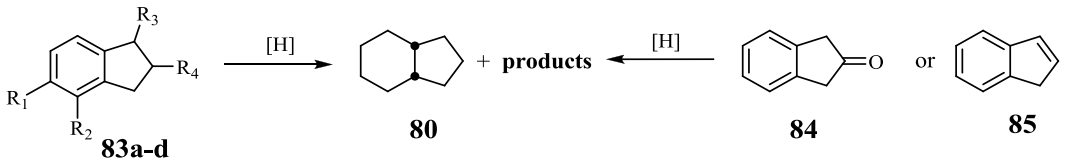


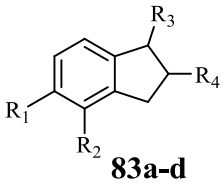
Figure 13. Saturated bicyclic and tricyclic hydrocarbons

2.1 Octahydro-1*H*-indene 80

There are numerous routes for the synthesis of bicyclo[4.3.0] skeleton **80**. Most of these methods were based on the reduction of the aromatic compounds (alcohol derivatives **83a-d**, ketone **84**, indene (**85**) with an appropriate metal catalyst under a variety of reaction conditions, i.e. high temperature and pressure (Scheme 24).[38]



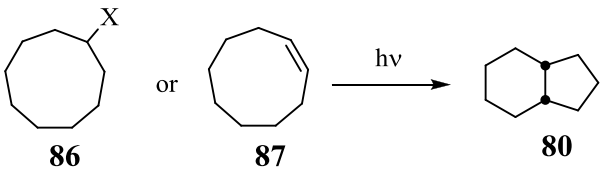
Scheme 24. Reduction of the aromatic compounds



R_1	R_2	R_2	R_4
OH	H	H	H
H	OH	H	H
H	H	OH	H
H	H	H	OH

Table 1. Indane derivatives

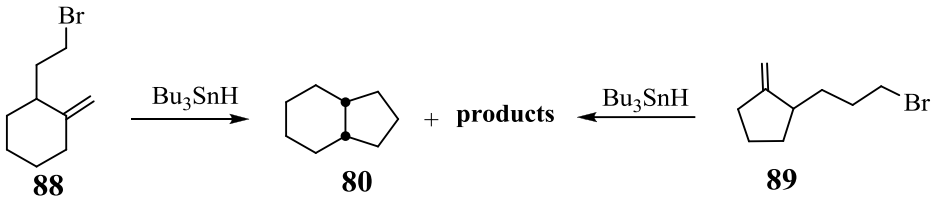
The irradiation of the nine-membered ring analogues such as **86** and **87** were also reported to give the same hydrocarbon **80** (Scheme 25).[39]



X: H, $-N_2SO_2C_6H_4CH_3$

Scheme 25. The irradiation of **86** and **87**

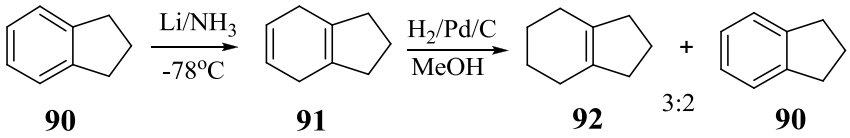
Radical cyclizations of bromo compounds such as **88** or **89** provide bicyclic hydrocarbon **80** albeit in low yields (Scheme 26).[40]



Scheme 26. Radical cyclizations of bromo compounds

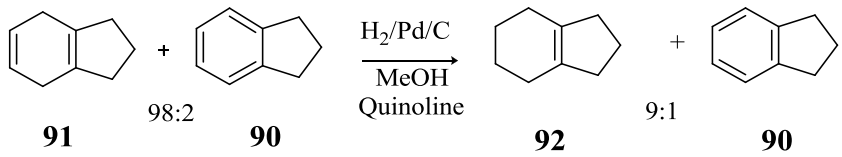
2.1.1 The Synthesis of Octahydro-1*H*-indene 80

In order to obtain the saturated hydrocarbon **80**, indane (**90**) was used as the starting material. Birch reduction of indane **90** gave the 2,3,4,7-tetrahydro-1*H*-indene **91** with small amount of starting material in 92% yield.[41] The ratio of this mixture was determined by using ^{1}H-NMR spectrum. The second step was the catalytic hydrogenation[46] of this mixture **90-91** with Pd/C in MeOH which did not give the only desired saturated hydrocarbon but also large amount of indane (**90**) as shown in Scheme 27.



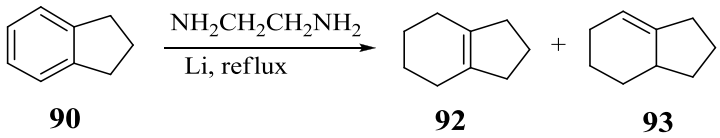
Scheme 27. Reduction of (**90**)

During this reaction, the reduction and oxidation occured at the same time. Since Pd/C is highly active catalyst, we added quinoline during the hydrogenation reaction to prevent the oxidation of 2,3,4,7-tetrahydro-1*H*-indene **91**. Because quinoline decreased the activity of catalyst, the reduction of **91** was also decreased. The reaction resulted in the formation of 2,3,4,5,6,7-hexahydro-1*H*-indene **92** in 80% yield (Scheme 28).



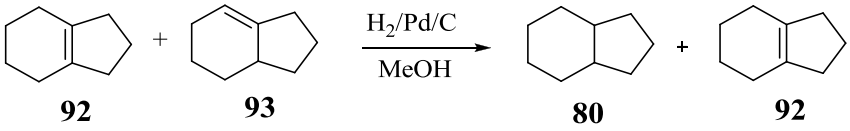
Scheme 28. Catalytic hydrogenation of the mixture of (**90**) and **91**

Due to the problems related with reduction of (**90)**, we changed our strategy. Benkeser reduction is another way to synthesize the target saturated hydrocarbon **80**. The treatment of indane **90** with lithium in ethylenediamine distilled over Na provided the mixture of mono-olefins 2,3,4,7-tetrahydro-1*H*-indene **92** and 2,3,3a,4,5,6-hexahydro-1*H*-indene **93** with a ratio of 76:24 in 59.6% yield (Scheme 29).[43]



Scheme 29. Benkeser reduction of (**90**)

After Benkeser reduction of indane (**90)**, the obtained mixture consisting of **92** and **93** was submitted to catalytic hydrogenation[42] and the desired bicyclic saturated hydrocarbon **80** was obtained with large amount of compound **92** with a ratio of 68:32 (Scheme 30).

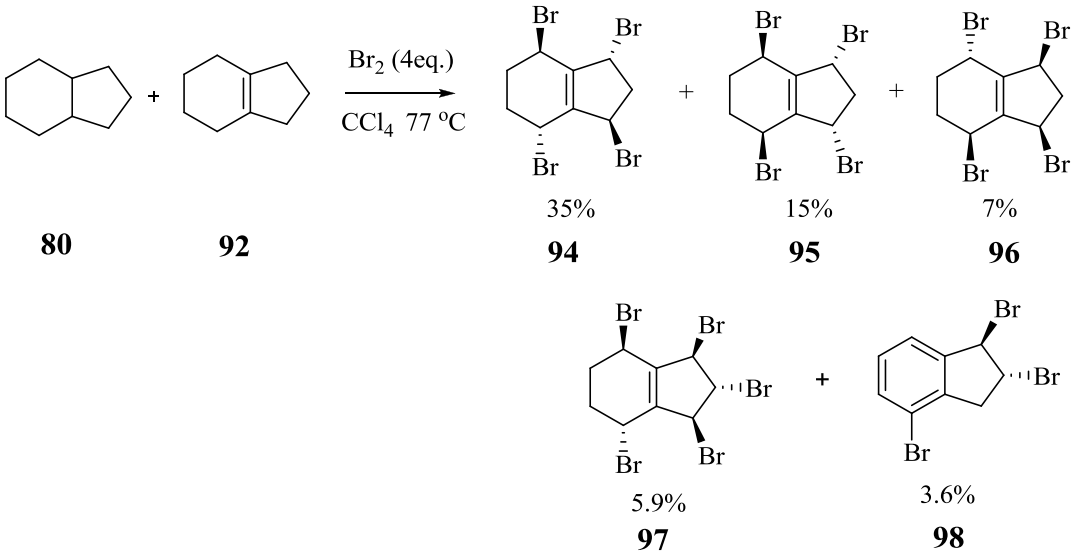


Scheme 30. Catalytic hydrogenation of the mixture of **92** and **93**

The ^{1}H-NMR spectrum showed that the signals in the olefinic region were disappeared and the quaternary carbon resonance on olefinic region in the ^{13}C-NMR spectrum demonstrated that the compound **92** was still remained.

2.1.2 High Temperature Bromination of 80 and 92 with 4 equiv Br_2

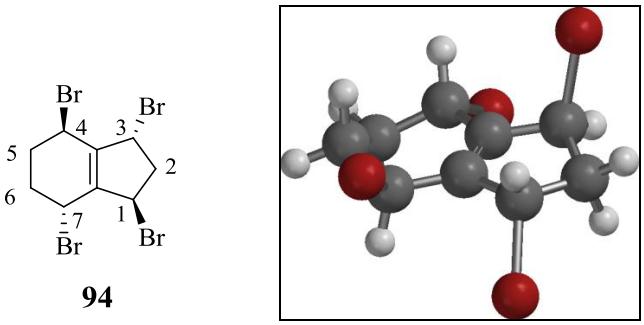
The treatment of octahydro-1*H*-indene **80** and **92** with 4 equivalence of bromine at 77 ^{o}C in CCl_4 over a period of 20 min provided a mixture consisting of five products rel-(1*S*,3*S*,4*S*,7*S*)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-*1H*-indene **94**, rel-(1*R*,3*S*,4*S*,7*R*)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1*H*-indene **95,** rel-(1*R*,3*S*,4*S*,7*S*)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1*H*-indene **96**, rel-(1*R*,2*R*,3*S*,4*R*,7*R*)-1,2,3,4,7-penta bromo-2,3,4,5,6,7-hexahydro-1*H*-indene **97** and rel-(1*S*,3*R*)-1,3,4-tribromo-2,3-dihydro-1*H*-indene **98** in 35, 15, 7, 5.9 and 3.6% yields, respectively (Scheme 31). The products were seperated by column chromatography and their structures were determined by spectral data.



Scheme 31. High temperature bromination of compound **80** and **92**

The ^{1}H-NMR spectrum of compound **94** indicates that the methine protons (H_1 and H_3) in the five membered ring resonate at 5.15 ppm as triplet ($J_{12} = J_{23} = 5.6$ Hz) whereas the methane protons in the six-membered ring (H_4 and H_7) resonate at 5.08-5.07 ppm as multiplet. Nevertheless, dihedral angles between the methylenic protons of five-memebered ring and its neighboring protons can help us to define the configuration of bromine atoms. According to the Karplus-Conroy curve, if the

dihedral angle is about 90° between the relevant protons, the protons do not couple with each other.[44] We determined the dihedral angles by using SPARTAN '08 mechanics program and the most stable configuration for compound **94** was found as follows (Figure 14).



94

Figure 14. The most stable configuration for compound **94**

The results from this calculations show that the dihedral angle between *cis* protons H_1 and $H_{2'}$ is 29.4° whereas the measured angle between other *cis* protons H_2 and H_3 is 20.9°. The dihedral angle between the *trans* protons $H_{2'}$ and H_3 was calculated as 141.6°. Moreover, dihedral angle between H_1 and H_2 was found as 90.3° and these protons will not couple each other. The methylenic protons of the five-membered ring (H_2 and $H_{2'}$) give rise to a triplet ($J_{21} = J_{23} = 5.6$ Hz) at 3.04 ppm which is not in agreement with the calculations. We assume that the conformation of methylenic protons on the plane changes so fast, so does the angle. Therefore, the protons H_1 and H_3 are almost equivalent. However, methylenic protons (H_5, $H_{5'}$, H_6 and $H_{6'}$) resonate as an AA'BB'-system at 2.52-2.25 ppm. A five line ^{13}C-NMR spectrum is also consistent with the structure.

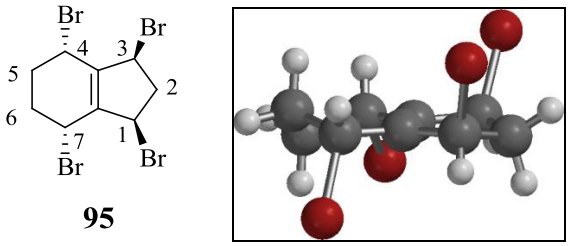


Figure 15. The most stable configuration for compound **95**

Notably, the ^{1}H-NMR spectrum of **95** is quite different from that of **94**. The methine protons (H_1 and H_3) of the five-membered ring give rise to a doublet at 5.21 ppm whereas the protons (H_4 and H_7) of the six-membered ring resonate as a multiplet at 4.95-4.93 ppm. Additionally, methylenic protons (H_2 and $H_{2'}$) of the five-membered ring setup an AB-system at 3.22 ppm (1H, dt, $J_{22'}$ = 16.7, J_{21} = 7.0 Hz, H_2) and 2.82 ppm (1H, d, $J_{22'}$ = 16.7 Hz, $H_{2'}$) which proves the *cis*- configuration of the bromine atoms. The dihedral angles between the protons $H_{2'}$ and H_3 for compound **95** were also calculated and found to be 95.6^{o}. The results clearly demonstrate the reason why B-part of AB-system resonates as doublet. The determined dihedral angle between *cis* protons H_1-$H_{2'}$ and $H_{2'}$-H_3 (24.3^{o}) is also agreement with doublet of triplets splitting of the proton $H_{2'}$. A similar ^{13}C-NMR spectrum as in the case of compound **94** was obtained.

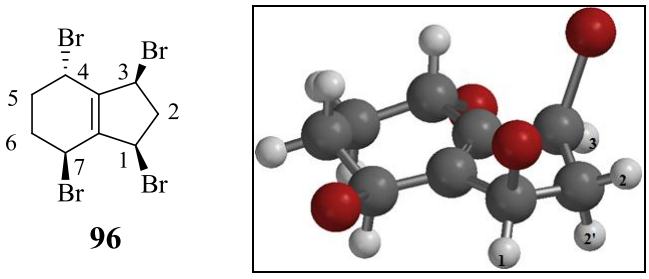


Figure 16. The most stable configuration for compound **96**

The ^{1}H-NMR and ^{13}C-NMR spectra of compound **96** indicate that there is an unsymmetrical compund which involves four different protons adjacent to bromine atoms and nine line carbon atom signals. The protons H_3 and H_1 in cyclopentane ring

resonate as broad singlet at 5.09 ppm and as broad doublet at 4.58 ppm ($J_{12(trans)}$ = 5.7 Hz H_4), respectively. Since the dihedral angle between the protons $H_{2'}$ and H_3 is 89.0°, the proton H_3 does not couple with $H_{2'}$ proton and gives broad singlet. In addition to that the methylenic protons (H_2 and $H_{2'}$) of the five-membered ring setup an AB-system. A part of AB-system ($H_{2'}$) at 3.48-3.42 ppm splits into doublet of doublets of doublets. First doublet splitting is arising from the geminal coupling with $H_{2'}$ ($J_{22'(gem)}$ = 18.3 Hz). The second doublet splitting is *cis* coupling between H_1 and H_2 ($J_{2'1(cis)}$ = 5.7 Hz) and their dihedral angle 31.2°, and finally, the last doublet is originated from H_3 proton which is also *cis* coupling ($J_{2'3(cis)}$ = 2.2 Hz) and the angle is 29.1°. Moreover, B part of AB-system (H_2) at 2.62 ppm splits into only doublet ($J_{2'2(gem)}$ = 18.3 Hz). The dihedral angle of H_2 proton with the protons H_1 and H_3 measured as 90° and 89.0°, which leads to loss of coupling constant and they do not couple.

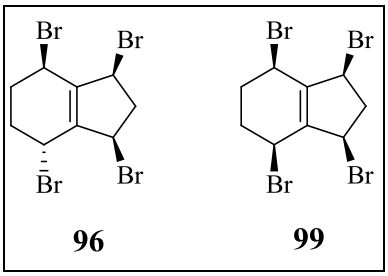


Figure 17. The possible configurations for compound **96**

On the basis of these results, the symmetrical compound **99** was excluded (Figure 17). The COSY spectrum also supports the relative configuration of protons in **96** as shown in Figure 18.

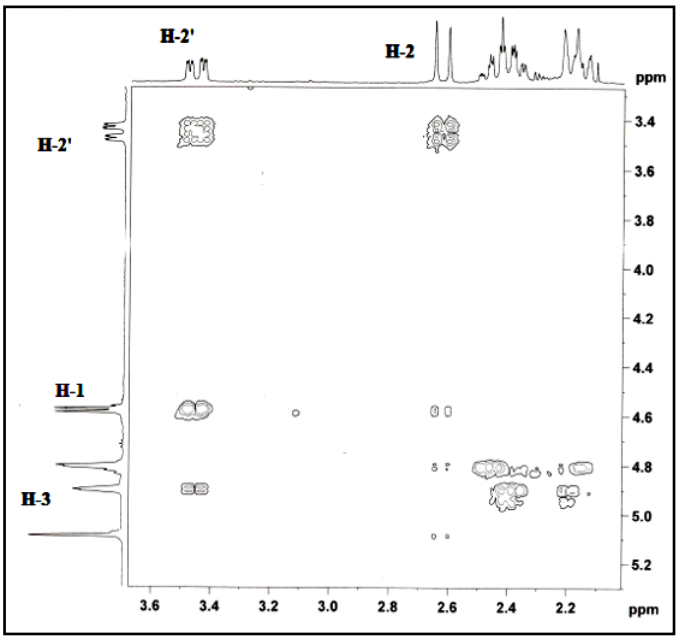
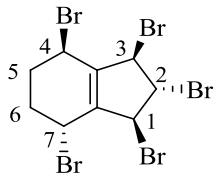


Figure 18. COSY spectrum of compound **96**



97

The ^{1}H-NMR spectrum of compound **97** exhibited eight sets of signals. Moreover, a nine line ^{13}C-NMR spectrum for compound **97** also indicates the presence of an unsymmetrical structure. The location of bromine atoms on the carbon skeleton was found by using 2D-NMR spectra. The protons (H_1, H_2 and H_3) adjacent to bromine atoms in the five membered ring resonate at 5.11 ppm (H_1) as broad singlet, 4.91 ppm (H_3) as singlet and at 4.77 ppm (H_2) as triplet ($J_{13} = J_{23} = 1.0$ Hz). Moreover, the dihedral angles θ_{12} and θ_{23} are 87.8^{o} and 90^{o}. The configuration of bromine atoms can be established by the comparison with similiar brominated compunds such as **75** and **100** (Figure 19).

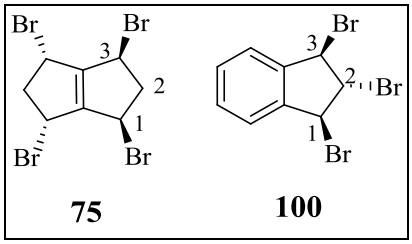
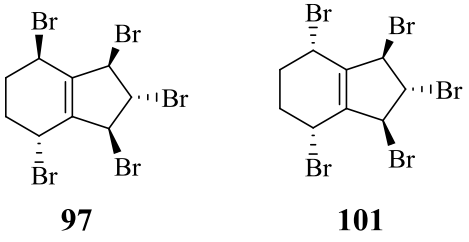


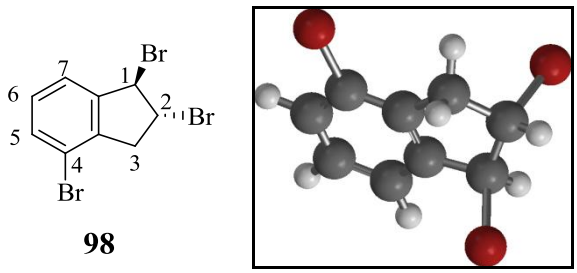
Figure 19. The similar configurations as compound **97**

The ^{1}H-NMR spectrum of **75**[37] shows that the methine protons (H_1 and H_3) appear as a doublet of doublets at 5.04 ppm (J_{13} = 1.5 Hz and J_{13} = J_{23} = 7.0 Hz). The *trans*-coupling constant J_{13} and J_{23} in **97** is 1.0 Hz. This value is comparable with the value J_{13} = J_{23} = 1.5 Hz found in **75**. Therefore, we assign the *trans*-configuration to the bromine atoms in the five-membered ring in **97**. In addition to that, the compound **100** was synthesized and analyzed by Balci and *co-workers*.[45] The ^{1}H-NMR spectrum of this indane derivative revealed that *trans,trans* configuration between H_1, H_2 and H_3 protons and they give a rise to doublet at 5.61 ppm (H_1 and H_3, J_{12} = J_{32} = 2.0 Hz) and triplet at 5.00 ppm (H_2, J_{23} = J_{21} = 2.0 Hz). Other methylenic protons (H_4 and H_7) in the six-membered ring resonate at 4.97 ppm (H_7, J_{76} = 1.5 Hz and $J_{76'}$ = 4.5 Hz) as doublet of doublets and at 4.73-4.74 ppm as multiplet. If the configuration of bromine atoms in the six-membered ring is *cis* to each other, the compound **97** would be symmetric as the compound **101**.



The methylenic protons (H_1, H_2, H_3, H_4 and H_7) reveal four different signals in the region between 5.11-4.73 ppm. The product **97** must be an unsymmetrical compound regardless of its ^{1}H-NMR spectrum. The signals of the methylnic protons (H_5, $H_{5'}$, H_6 and $H_{6'}$) appear as an AB-system. H_5 and H_6 protons resonates as a doublet of doublets of doublets at 2.63 ppm (H_6, $J_{66'(gem)}$ = 15 Hz, $J_{65'(trans)}$ = 13 Hz,

$J_{65(cis)}$ = 4.5 Hz and $J_{67(cis)}$ = 1.5 Hz) and 2.42 ppm (H_5, $J_{55'(gem)}$ = 14.9 Hz, $J_{56'(trans)}$ = 12.9 Hz, $J_{56(cis)}$ = 3.9 Hz and $J_{54(cis)}$ = 2.4 Hz), $H_{5'}$ and $H_{6'}$ resonate as multiplet at 2.18-2.12 ppm and at 2.26-2.21 ppm.



98

Figure 20. The most stable configuration for compound **98**

The ^{1}H-NMR spectrum of compound **98** consists of seven distinct signals three of which are in the region of aromatic protons and resonate at 7.48 (d, J_{56} = 7.8 Hz, H_5), 7.40 (d, J_{76} = 7.5 Hz, H_7) and 7.19 (t, J_{65} = 7.8 Hz, H_6) ppm. The position of bromine atom in benzene ring was found from HMBC spectrum by the correlations between C_4 atom and the methylenic protons H_3 and $H_{3'}$ as shown in Figure 21.

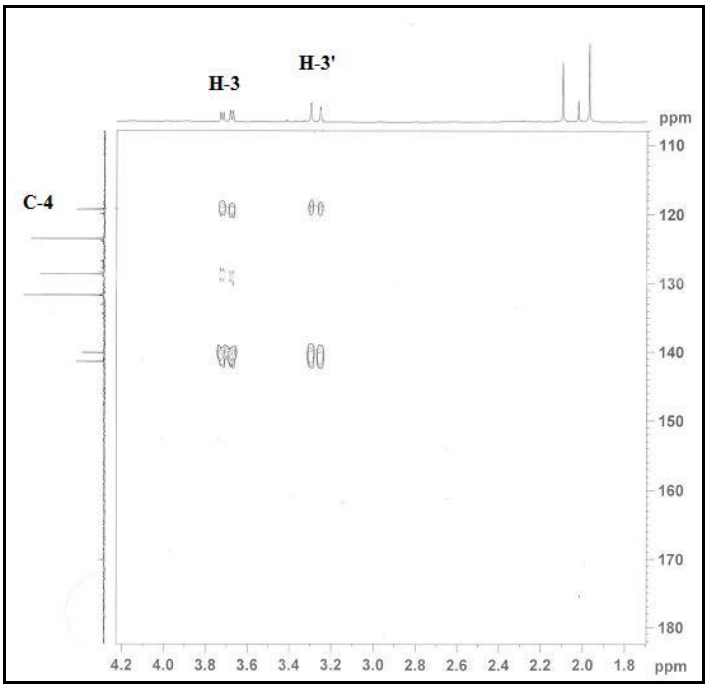
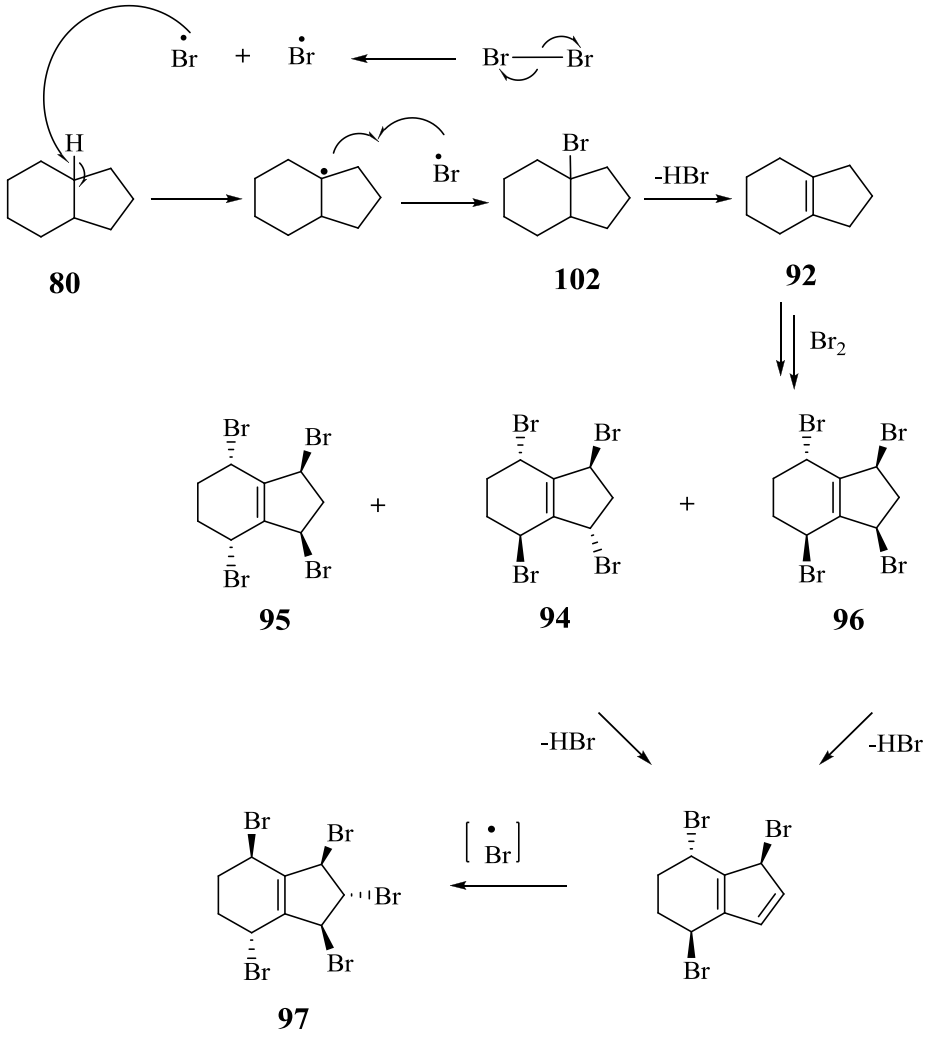


Figure 21. HMBC spectrum of the compound **98**

The H_2 and H_1 protons give rise to a singlet at 5.65 ppm and a broad doublet at 4.84 ppm, respectively. The dihedral angle between H_2 and H_1 protons was found to be 82.1°. The methylenic protons gives an AB-system at 3.77 (dd, A-part of AB-system, $J_{33'}$ = 18.0, J_{32} 5.3 Hz, H_3) and 3.35 (d, B-part of AB-system, $J_{3'3}$ = 18.0 Hz, $H_{3'}$) ppm. H_3 and $H_{2'}$ do not couple ecah other due to the measured dihedral angle 86.2°. However, the *cis*- protons H_2 and H_3 splits each other as doublet depending on the dihedral angle (33.7°). Moreover, a nine line ^{13}C-NMR spectrum for compound **98** indicates the presence of an unsymmetrical structure.

After the determination of the correct structures of the product, we propose the following mechanism for their bromination (Scheme 32). The first step is the formation of bromine radicals by homolytic bond cleavage of Br-Br under the thermal condition. The formed bromine radical abstracts exclusively the hydrogen atom from the tertiary carbon atoms to furnish a tertiary carbon-radical which can be stabilized by either combination with bromine radical or by abstracting bromine radical from bromine molecule to form the monobromide **102**. The monobromide **102** from which HBr elimination affords 2,3,4,5,6,7-hexahydro-1*H*-indene **92**. Sequential allylic bromination of intermediate **92** would result in the formation of compounds **94**, **95** and **96**.



Scheme 32. The possible mechanism for the bromination of **80** and **92**

According to SPARTAN geometry optimization calculation at 3G* level, it has been established that the compound **96** is higher energy molecules about 6.79 kcal/mol (Table 2) than the other molcules. Therefore, we assume that **96** undergoes further reactions such as elimination followed by bromine addition to give **97**. These findings was also supported by low yield of **96**.

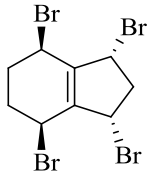
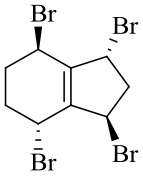
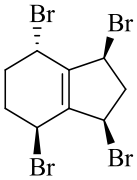
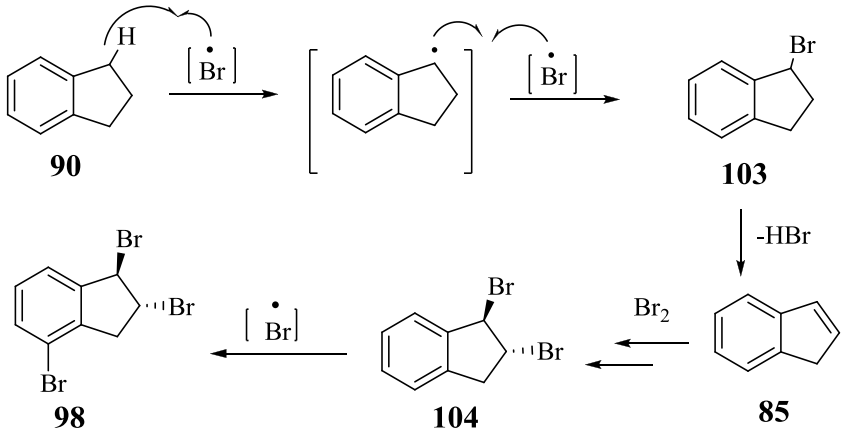
 **95**	 **94**	 **96**
0.00 kcal/mol	1.62 kcal/mol	6.79 kcal/mol

Table 2. Relative energy of tetrabromides

For the formation of compound **98,** the following mechanism is proposed (Scheme 33). The bromine radical attacks the methylenic proton of (**90**), to give the most stable benzylic radical which can be captured by bromine to give the monobromide **103**. HBr elimination of the compound **103** provides indene (**85**).



Scheme 33. The suggested mechanism for the formation of compound **98**

After *anti* addition of bromine to olefin in the five-membered ring (**85**) gave **104.** Further bromination of the benzene ring may result in the formation of **98**.

As a conclusion, high temperature bromination of saturated bicyclic[4.3.0]system results in the formation of three isomeric tetrabromides **94**, **95** and **96**. Some part of the compound **96** underwent elimination under the reaction conditions due to the steric repulsion among *cis* configurated bromine atoms. Significantly, the regioselectivity of the high temperature bromination reaction is still preserved when

the steroselectivity was diminished to lesser extent in contrast to bromination of decalin and octahydropentane. However, we can assume that allylic bromination changes its mechanism depending on the size of the ring.

2.1.3 Pyramidalization of Double Bonds

Mostly, the double bond between the olefin carbon atoms is in the same plane with the four atoms which are attached to the double bond.[46] Nevertheless, if there is pyramidalized alkene molecule, the carbon-carbon double bond is not coplanar with their substituents. This distortion from a trigonal geometry to a tetrahedral geometry is the result of angle strain induced in the molecule due to geometric constraints.[47] Extremely, in *syn* pyramidalization, rehybridaziton of carbon atoms make the geometry enviroment of the carbon nonplanar by additional p character into the original sp^2 σ bonds. The formation of new π bond is involved in two p-orbitals with some added s character; the alignment between the two orbitals is optimal, but their direction in the p-plane is nonparallel. Then, the increasing of distance between orbitals makes the net overlap smaller. The pyramidalization angle ψ **b** can be determined as the angle between two substituents attached to one of the doubly bonded carbons. The butterfly angle or folding angle Φ **c** is defined as dihedral angle between R_1CCR_2 and R_4CCR_3[47] (Figure 22).

The degree of pyramidalization was affected by the electron density of the alkenyl π-bond. The X-ray studies by Barlett[48] and Paquette[49] show that pyramidalization of π-bonded carbons in the *syn* isomer has folding angles ranging from 16 to 18°.

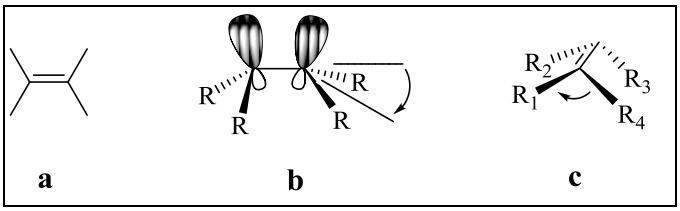
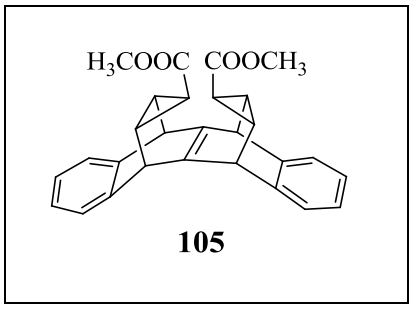


Figure 22. Modes of distortion of strained olefins

Balci and *co-workers*[50] have studied pyramidalized double bonds and have reported the synthesis of *syn*-1 **105** (Figure 23). In order to minimize interactions between

carboxylate groups, double bond have a tendency to pyramidalize. The X-ray analysis of structure confirmed that the pyramidalization angle is 16.8°. Although the pyramidal double bonds are mostly very reactive, the compund *syn*-1 **105** is unlikely to react with bromine, hydrogen and oxygen because of its steric shielding.



105

Figure 23. *Syn-1*

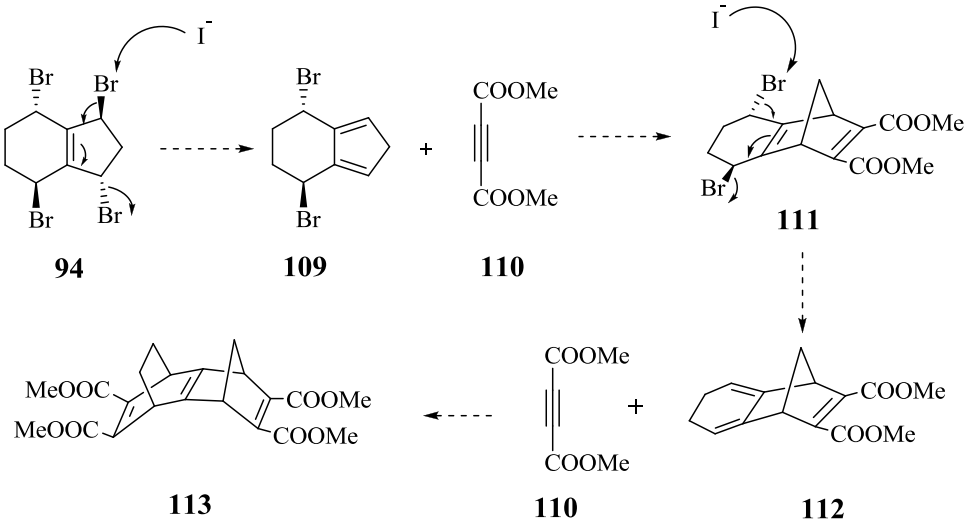
2.1.4 Attempted synthesis of a new pyramidalized double bond starting from tetrabromide compound 94

Finkelstein reaction[51] is used for the exchange of one halogen for another one. An alkyl chloride or an alkyl bromide can be converted to the alkyl iodide in the presence of acetone with sodium iodide. For example, starting with bromoethane in polar solvents results in the substitution of iodine with bromine (Scheme 34).

$$CH_3CH_2Br + NaI \xrightarrow{\text{Acetone}} CH_3CH_2I + NaBr$$

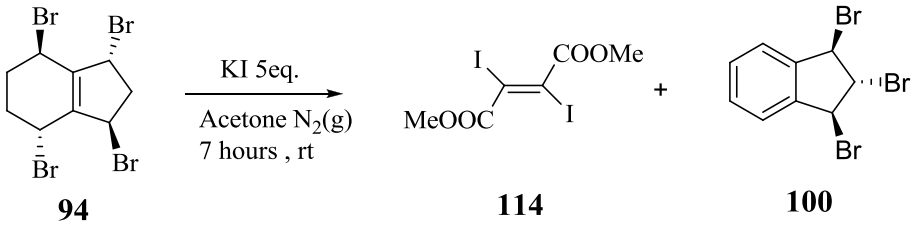
Scheme 34. Iodination of bromoethane

Therefore, we thought that if the bromine atoms in tetrabromide **94** are displaced by iodine, iodine will afford elimination to give an 1,3-dien system **109**, which can be captured by dimethylacetylendicarboxylate **110** to produce **111**. Progressively, tetrabromide **94** can be pyramidalized in one-pot reaction by forming **113** (Scheme 35).



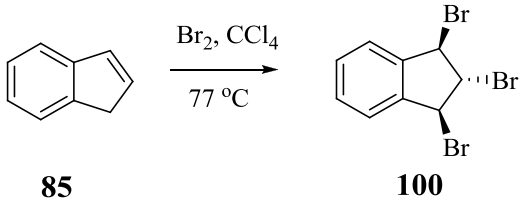
Scheme 35. The possible mechanism for compound **113**

In order to perform this reaction, the tetrabromide **94** was reacted with KI under the various reaction conditions. Unfortunately, instead of the expected 1,4-elimination product, aromatized product rel-(1*R*,2*r*,3*S*)-1,2,3-tribromo-2,3-dihydro-1*H*-indene (**100**) was isolated along with the iodine addition product **114** (Scheme 36). The structure compound **100** was assigned by comparison with those reported in the literature.[45]



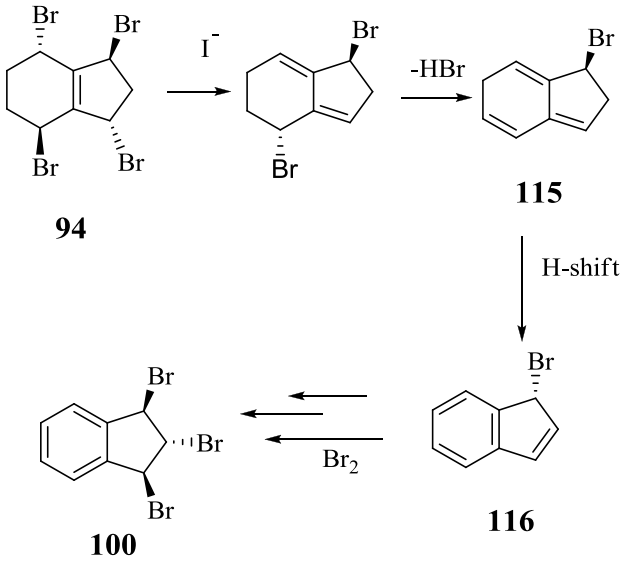
Scheme 36. Finkelstein reaction of compound **94**

The tribromide **100** was synthesized by treating of indene (**85)** with 3 equiv. of bromine in refluxing carbontetrachloride as reported in the literature (Scheme 37). [45]



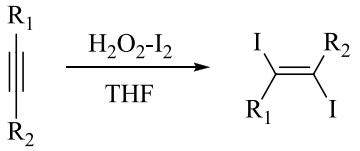
Scheme 37. Synthesis of compound **100**

For the formation of compound **100**, we suggest the following mechanism as shown in Scheme 38. In the first step, iodine attacks the bromine in the six-membered ring to create a 1,3-dien system (**115**). Then, abstraction of a proton by iodine followed by sequentially bromine elimination and H-shift provided **115**. Further bromine addition to double bond occurs to give the compound **100**.



Scheme 38. The proposed mechanism of formation of compound **100**

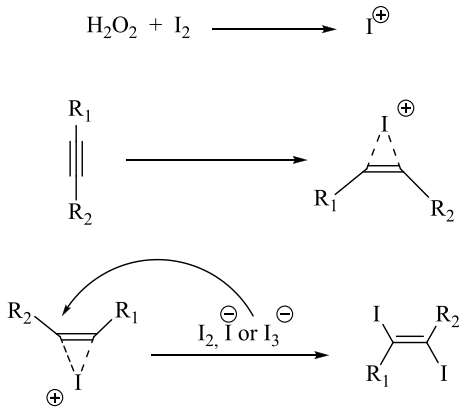
In literature, it is reported that the substituted alkynes can form diiodine addition products by reacting of alkynes with H_2O_2-I_2 in THF to give the *trans*- addition product **116** (Scheme 39).[52]



118 **119**

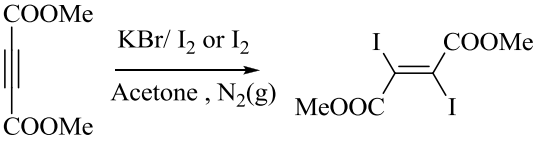
Scheme 39. Synthesis of *E*-diiodoalkene **119**

Hydrogen peroxide and iodine generate an iodonium ion, the formed electrophilic species attack the alkyne and affords a cyclic intermediate. The reaction ends up with *trans* addition of iodine donor to form an *E*-diiodoalkene as shown in Scheme 40.



Scheme 40. Proposed mechanism of iodination of alkynes with I_2-H_2O_2 system

E-diiodoalkene **114** was synthesized by reacting of iodine[53] or potasium bromide in acetone (Scheme 41). The ^{1}H NMR and ^{13}C NMR spectra of this compound **114** arein agreement with those reported in the literature.[53]



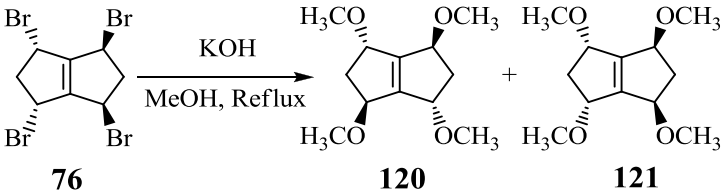
110 **114**

Scheme 41. Iodination of imethylacetylendicarboxylate **110**

Therefore, we assume that iodine ions catalyze the elimination of HBr from the molecule **94**. Futher elimination causes the aromatization of compound **94**.

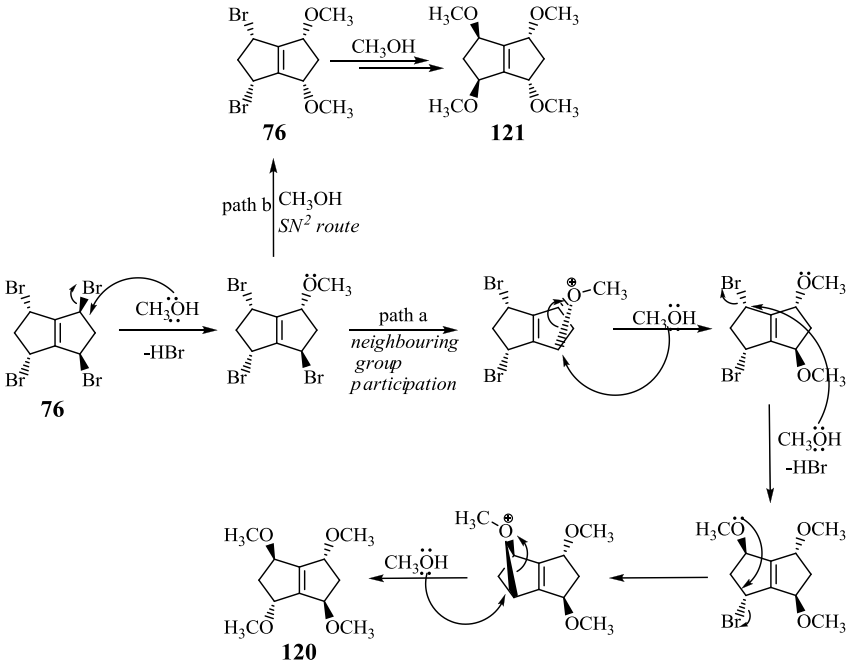
2.1.5 Attempted Substitution of Bromines

Recently, Balcı and *co-workers*[37] have studied the functionalization of the compound **76** and they reported that the bromines provide the substitution products **120** and **121** (Scheme 42).



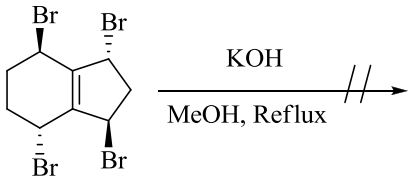
Scheme 42. Substitution of bromines in the compound **76**

The stereochemical result of the reaction was interesting. The following mechanism was postulated for the formation of the products Scheme 43.



Scheme 43. The possible mechanism for tetramethoxy compounds **120** and **121**

Since the substitution reaction of compound **76** has a great synthetic potential to pentalene derivatives, we applied the same conditions for the functionalization of tetrabromide **94** (Scheme 44).



94

Scheme 44. Attempted substitution of tetrabromide **94**

However, the elimination reaction took place instead of substitution of bromines. ^{1}H NMR spectrum of residue shows that the aromatization of compound **94** occured and a complex mixture of aromatic isomers were formed.

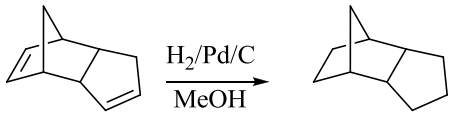
Finally, we assume that it can be easier to functionalize the octahydropentalene than the functionalization of bicyclic[4.3.0] system due to tendency of aromatization for compound **94**.

2.2. Tricyclic Sytems

2.2.1 The Sythesis of Octahydro-1*H*-4,7-methanoindene 81

The synthesis of octahydro-1*H*-4,7-methanoindene **81** generally was based on the hydrogenation of **122** in the presence of metal reagents such as Al, Ni, Pd etc. at high temperatures.[54]

Initially, the catalytic hydrogenation of dicyclodipentadiene **122** at room temperature gave the octahydro-1*H*-4,7-methanoindene **81** in 90% yield (Scheme 45). [42]



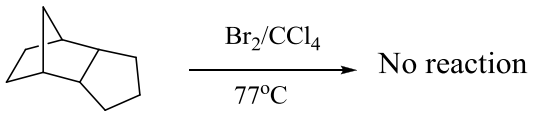
122 **81**

Scheme 45. Catalytic hydrogenation of dicyclodipentadiene

The ^{1}H-NMR and ^{13}C-NMR spectra clearly show that the olefinic proton and carbon resonances in the olefinic region are disappeared and the saturated tricyclic system **81** was formed.

2.2.2 High Temperature Bromination of Octahydro-1*H*-4,7-methanoindene 81

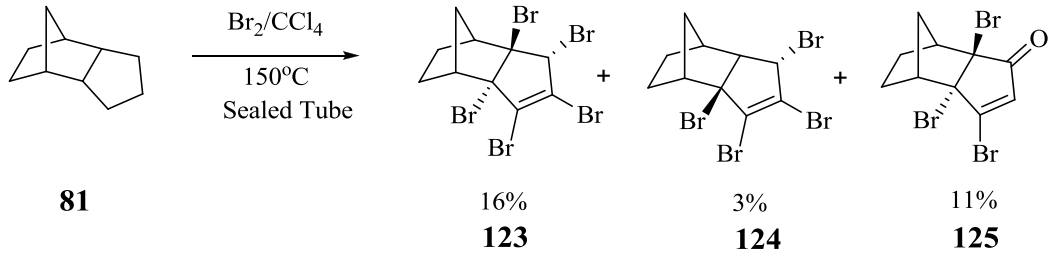
We applied the same procedure, high temperature bromination reaction of **80** to the bromination of octahydro-1*H*-4,7-methanoindene **81**. However, the unreacted starting material was recovered (Scheme 46).



81

Scheme 46. Bromination of compound **81** at 77 ^{o}C

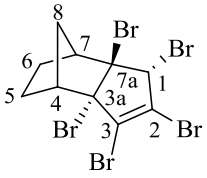
Since the structure **81** has a higly rigid skeleton, probably the reaction temperature is not enough to overcome the energy of transition state during bromination reaction. So, we decided to change temperature of reaction. Therefore, the reaction was carried out in a sealed tube. High temperature bromination of the compound **81** in a sealed tube at 150 ^{o}C provided the mixture of three brominated compounds rel-(1*R*,3a*R*,7a*S*) -1,2,3,3a,7a-pentabromo-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methanoindene **123**, rel-(1*S*,3a*R*)-1,2,3,3a-tetrabromo-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methanoindene **124**, and rel-(3a*S*,7a*S*)-3,3a,7a-tribromo-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methanoinden-1-one **125** in yield 16, 3 and 11% , respectively (Scheme 47).



Scheme 47. Bromination of compound **81** in a sealed tube

The products were seperated by column chromatograhy and their structures were characterized by spectroscopic methods such as 1D- and 2D-NMR.

First, we have determined from GC-MS and elemental analysis the presence of five bromine atoms in molecule **123**. The ^{1}H-NMR spectrum of compound **123** shows a proton which is resonating as singlet at 5.41 ppm. The presence of two carbon signals at 131.3 and 125.1 ppm clearly indicated the presence of a tetrasubstituded carbon-carbon double bond. We mainly used 2D-NMR to reveal the exact configuration.



123

The HMBC spectrum of compound **123** (Figure 24) indicates that there are correlations among H_1 proton and lower field carbon atoms such as the bridgehead carbon atom C_7, the quarternary carbon atoms C_{7a} and C_{3a} and finally the quarternary olefinic carbon atoms C_2 and C_3.

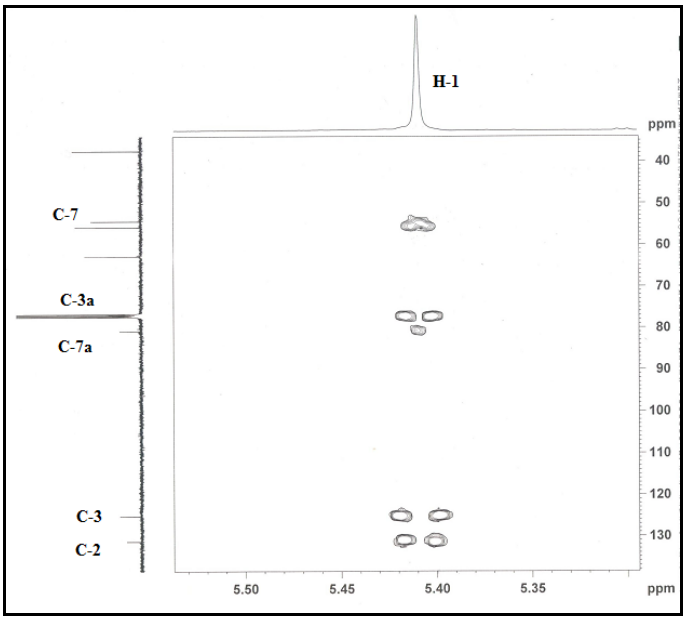


Figure 24. HMBC spectrum of compound **123**

The proton H_1 is shifted to lower field by neighboring bromine atoms and does not show any interaction with other protons in the COSY spectrum as shown in Figure 25.

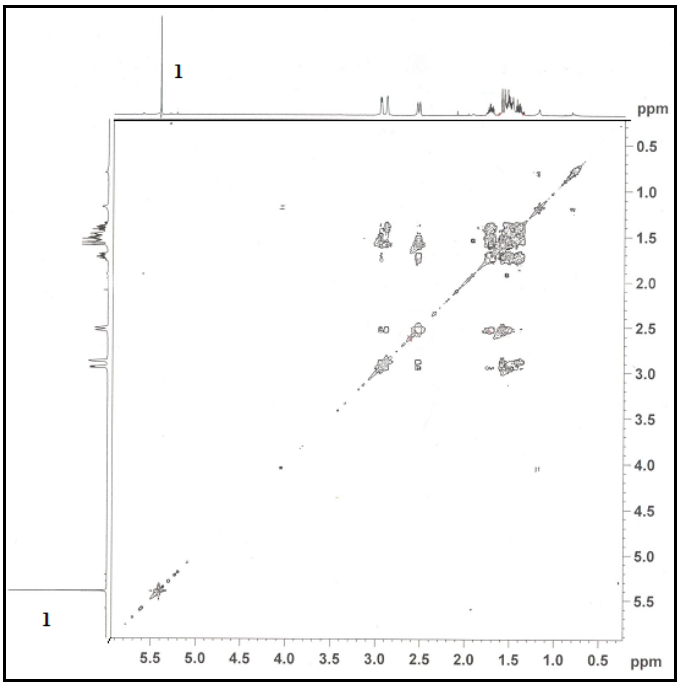
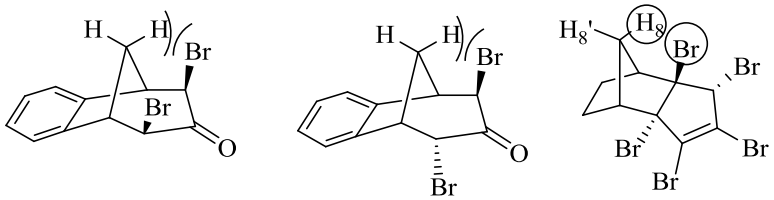


Figure 25. COSY spectrum of compound **123**

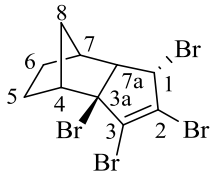
The bridging methylene protons H_8 and $H_{8'}$ are resonating as an AB-system at 2.53 and 1.59 ppm and the geminal coupling constant between H_8 and $H_{8'}$ $J_{88'(gem)}$ was found to be 10.8 Hz. The *endo*-proton H_8 resonance is shifted about, 1 ppm to lower field compared to the proton $H_{8'}$.



126 **127** **123**

Figure 26. Example structures for γ-gauche effect

Balci and *co-workers*[55] noted that the number of bromine atoms in *exo*-position in **126** affect the bridging proton resonance due to the γ-gauche effect (Figure 26). The electron density between C_8-H_8 proton becomes deformed related to the steric repulsion between neighboring bromine in *exo*-position and corresponding C-H proton. In addition to that, the carbon resonance of C_8 in **123** shifted about 4 ppm to high field compared with **81**.



124

The number of bromine atoms in compound **124** was estimated from the result of GC-MS spectroscopy. However, the exact configuration of bromine atoms was determined by 2D-NMR spectra.

In the ^{1}H NMR spectrum, the proton H_1 resonance is split into doublet with a small coupling (J_{17a} = 0.6 Hz) and resonates at 4.75 ppm. On the other hand, the proton H_{7a} gives rise to a broad doublet (3.60 ppm) with a larger coupling constant (J_{17} = 4

Hz). The correlations between the protons H_1 and H_{7a} is also determined by the COSY spectrum (Figure 27).

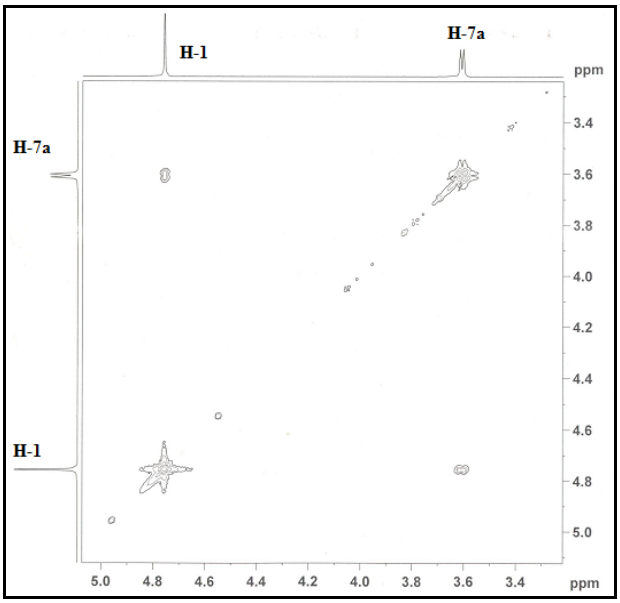


Figure 27. COSY spectrum of compound **124**

Like to compound **123**, the bridging methylene protons H_8 and $H_{8'}$ in **124** forms also an AB-system but their couplings becomes more complex. The proton $H_{8'}$ resonates at lower field due to the steric repulsion between the proton $H_{8'}$ and *exo*-bromine atom on the C_{3a}. The large splitting ($J_{88'}$ = 10.4 Hz) is originates from the geminal coupling.

Since there is no interaction such as 'M' or 'W' between the proton H_{7a} and the proton $H_{8'}$ in the COSY spectrum, we assume that the proton H_{7a} is in *exo*-position, not in the *endo*-position as in **124a** (Figure 28).

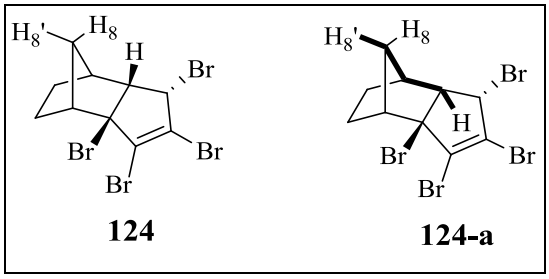
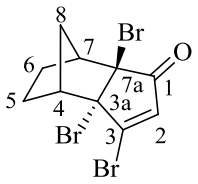


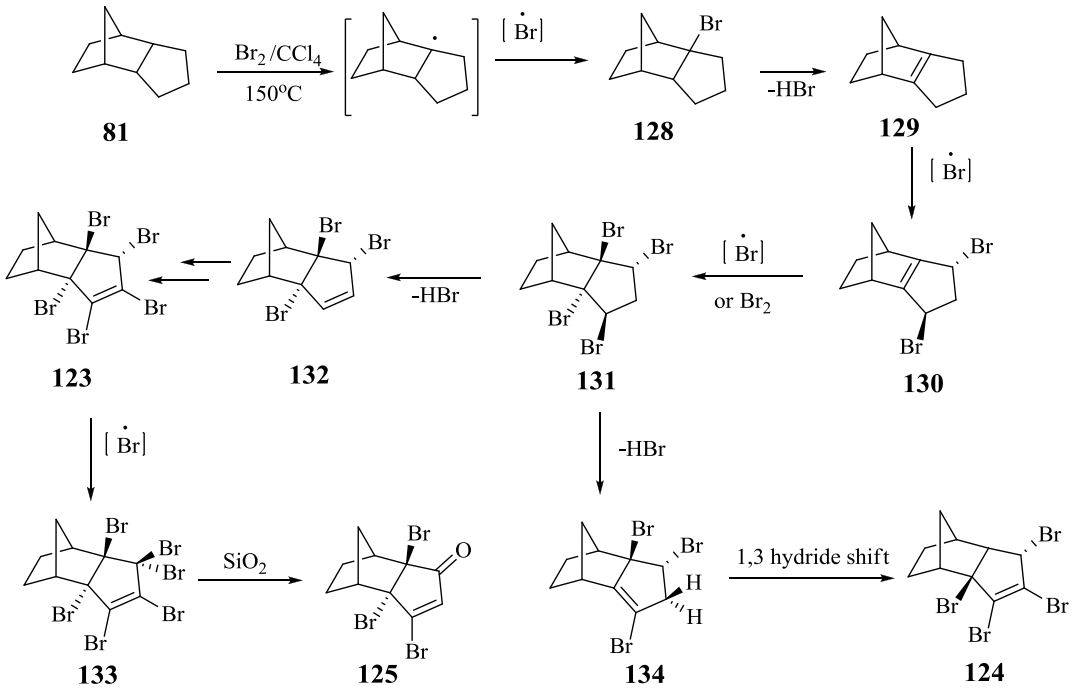
Figure 28. The possible configuration of the proton H_{7a}

The other correlations between aliphatic protons were detected also by the COSY spectrum and approved by the HMBC spectrum.



125

The ^{13}C NMR spectrum of compound **125** demonstrates that there is a carbonyl carbon atom in the molecule and this signal appears at 195.9 ppm. The carbonyl carbon resonances in α,β-unsaturated systems are shifted high field due to increasing of electron density at carbonyl carbon atom. Additionally, the proton H_2 resonates as a singlet at 6.48 ppm and this lower field proton resonance supports the presence of a α-β-unsaturated system. When the carbon atom C_3 moves to low field, the carbon atom C_2 is located on the high field as expected. The configuration of bromine atoms on the carbon C_{3a} and C_{7a} is based on the γ-gauche effect and founded from the COSY and HMBC spectra.

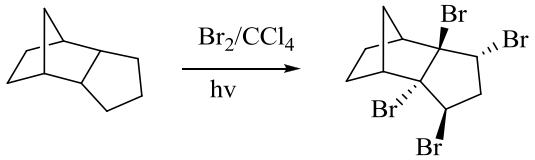


Scheme 48. The suggested mechanism of formation of compound **123**, **124** and **125**

In order to clarify the formation of those products, a mechanism was suggested as shown in Scheme 50. Formation of the compound **131** plays an important role at this point. A similar mechanism discussed for the bromination of **80** is postulated. After the allylic bromination of compound **129** is occurred, bromine addition to double bond takes places instead of allylic bromination at bridgehead positions. Since the bridgehead protons are unable to produce a radical form, the addition of bromine to double bond is favoured. Under the reaction conditions, the compound **131** can undergo two types of HBr elimination to create the compounds **132** and **134**. The formed product **132** gives the compound **123** by addition of bromine to double bond. Further bromination and hydrolysis of compound **123** on silica gel provide the compound **125**. We assume that the compound **124** is formed via 1,3-H shift of the compound **134**.

2.2.3 Photobromination of Octahydro-1*H*-4,7-methanoindene 81

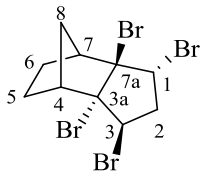
The irradiation of compound **81** with a 150 W projector lamp resulted in the formation of rel-(1*R*,3*R*,3a*S*,7a*S*)-1,3,3a,7a-tetrabromooctahydro-1*H*-4,7-methano indene **131** in yield of 23 (Scheme 49).



81 23% **131**

Scheme 49. Photochemical bromination of compound **81**

The product was purified by column chromatography and characterized on the basis of 1D-, 2D-NMR.



131

The protons H_3 and H_1 resonate as a doublet of doublets ($J_{32'}$ = 12.8 Hz and J_{32} = 7.6 Hz H_1) at 5.08 ppm and as a doublet ($J_{12'}$ = 6.0 Hz H_3) at 4.83 ppm, respectively. The methylenic H_2 and $H_{2'}$ protons give rise to an AB-system at 2.76 ppm (dd, A-part of AB-system $J_{22'(gem)}$ = 15.2 Hz, J_{23} = 7.6 Hz) and 2.60 ppm (ddd, B-part of AB-system $J_{2'2}$ = 15.2 Hz, $J_{2'3}$ = 13.2 Hz, $J_{2'1}$ = 6.0 Hz). The correlations between the methylenic protons and H_3 and H_1 clearly were observed from the COSY spectrum of the compound **131** as shown in Figure 29.

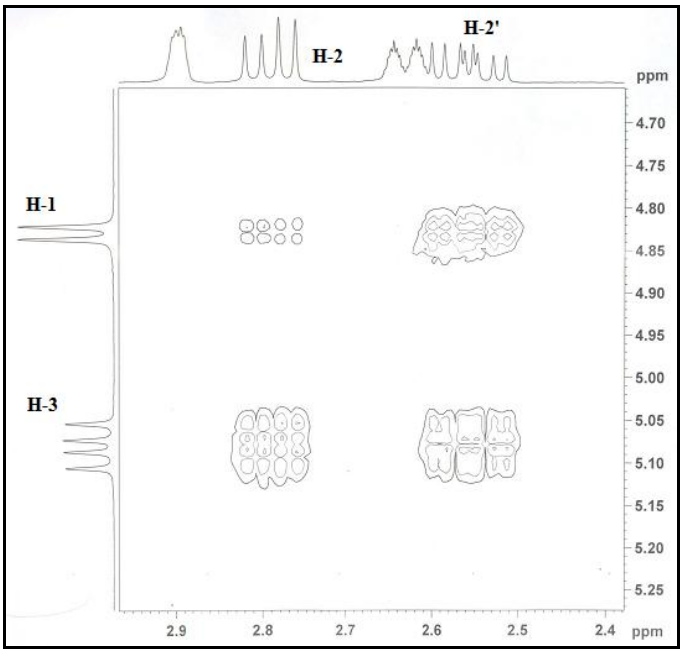


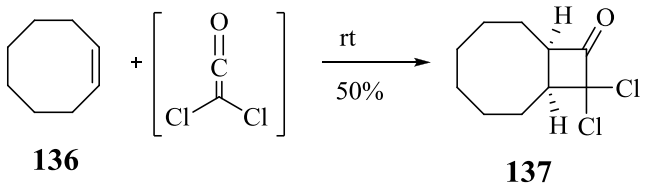
Figure 29. COSY spectrum of the compound **131**

The configuration of bromine atoms on the C_{3a} and C_{7a} was also determined on the basis of γ-gauche effect and founded from the COSY and HMBC spectra like the compounds **123**, **124** and **125**. Elemental analysis result of the compound **131** is consistent with the proposed structure.

High temperature bromination and photobromination of compound **81** results in the bromination of five-membered ring in the tricyclic system as expected. Because allylic bromination of tertiary bridghead protons is difficult, we could not observed any further brominated products.

2.4 The synthesis of Bicyclo[4.2.0]octan-7-one 82 and its Bromination

The synthesis of bicyclo[4.2.0]octan-7-one **82** is generally based on the [2+2] cycloaddition reaction.[56] The cycloaddition reaction involves halogenated ketenes which activates the relative unreactive nature of ketene towards [2+2] cycloaddition with non-activated alkenes. These reactions appear to have some of characteristic of pericyclic cycloadditions, such as being stereospecifically *syn* respect to the double bond as shown in Scheme 50.

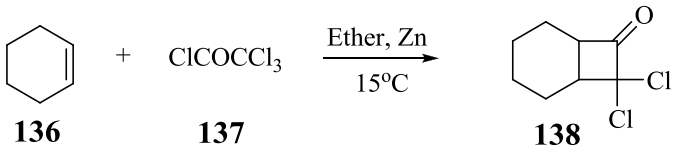


136 **137**

Scheme 50. Cycloaddition reaction of compound **136**

2.4.1 The synthesis of Bicyclo[4.2.0]octan-7-one 82

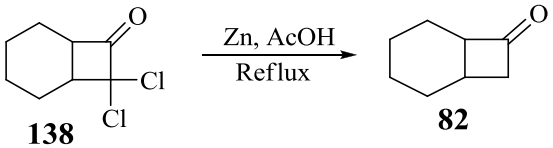
The treatment of cyclohexene with tricholoroacetylchloride **137** resulted in the addition of dichloroketene to cyclohexene (**129**) in 68% yield as shown in scheme 51.[57] After the purification by column chromatography, the compound 8,8-dichlorobicyclo[4.2.0] octan-7-one **138** was characterized by NMR spectroscopy as in the literature.



136 **137** **138**

Scheme 51. Ketene addition to cyclohexene **136**

Reduction of chlorides with zinc in refluxing acetic acid gave bicyclo[4.2.0]octan-7-one in 61% yield (Scheme 52). The ^{1}H NMR and ^{13}C NMR spectra were in agreement with those reported in the literature.[58]

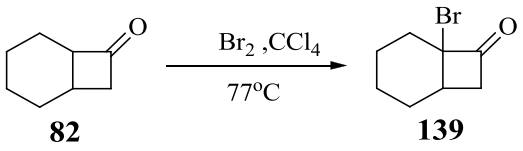


138 **82**

Scheme 52. Reduction of zinc in compound **138**

2.4.2 High Temperature Bromination of 82

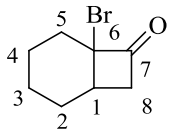
The compound **82** was submitted to high temperature bromination reaction with 4 equiv. of bromine in carbontetrachloride. The reaction resulted in the formation of the product, 6-bromobicyclo[4.2.0]octan-7-one **139** in 56% yield (Scheme 53).



82 **139**

Scheme 53. High temperature bromination of compound **82**

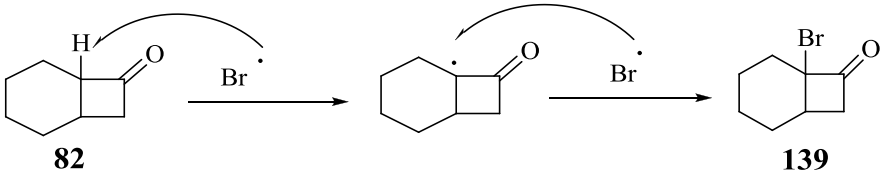
The ^{1}H-NMR spectrum of compound **139** is not quite diffrent from the The ^{1}H-NMR spectrum of compound **82**. Since the addition of bromine to tertiary carbon 6 made the structure more planar, the AB-system signals of the methylenic protons H_8 would be so clear in contrast to the methylenic protons of the compound **82**.



82

The ^{13}C-NMR spectrum of compound **139** clearly showed that the C_6 is shifted about 12 ppm to the lower field when bromine is attached to the carbon atom.

The formed product obtained as expected. For the formation mechanism of the compound **139** can be expected as shown in Scheme 54.



82 **139**

Scheme 54. The possible mechanism for the formation of compound **139**

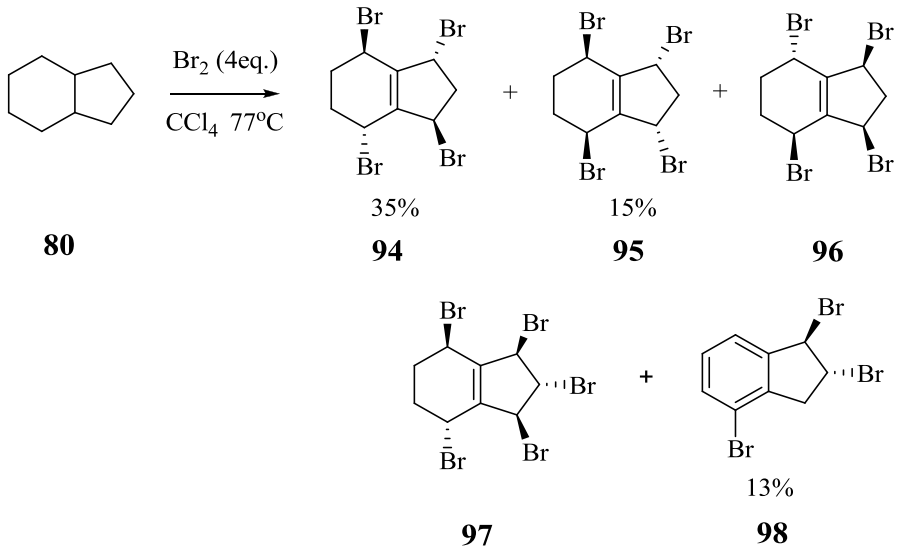
Although the bromination reaction was performed with four equiv. of bromine in different conditions such as 150 ^{o}C, the product proceeded from the most stable tertiary carbon and we did not observed any minor product.

At this point, since the quaternary double bond was not form, the allylic positions were not brominated.

CHAPTER 3

CONCLUSION

The selective functionalization of saturated hydrocarbons under mild conditions is of both biochemical and industrial importance. High temperature bromination reaction is very useful methodology in order to functionalize the saturated bicyclic hydrocarbons.

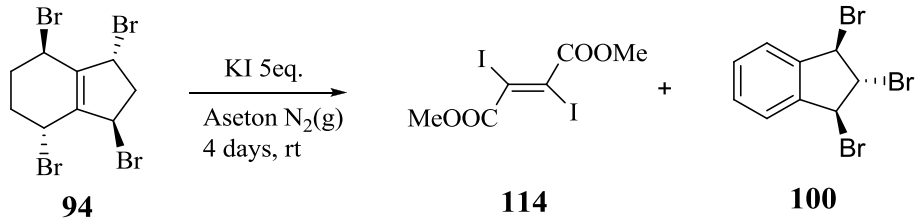


Scheme 55. High temperature bromination of **80** and **92**

In the first part of the study, the effect of the size of the ring on product distribution as well as on the formation mechanism was investigated. In contrast to both decalin (**62**) and octahydopentalene (**75**), octahydro-1*H*-indene (**80**) gave the both *trans,trans,trans*- (**94**) and *cis,trans,cis*- (**95**) products beside further brominated compounds. Significantly, the regioselectivity of the high temperature bromination reaction is still preserved albeit the stereoselectivity was diminished to lesser extent

in the case of an unsymmetrical hydrocarbon appendage. When the steric effects predominate in the six-membered ring bromines prefer *all trans*-arrangement, steric factors are less effective in the case of five-membered ring so that bromine atoms prefer *cis,trans,cis*-arrangement. When we examine the five-membered ring products, it could be also suggested that five-membered ring has a tendency to give *cis*- addition of bromine.

In the second episode, attempted functionalization of tetrabromide **94** via converting to the corresponding methyl esters was failed due to the tendency of aromatization of the compound **94**. In addition to that, attempted pyramidalization of the compound **94** resulted in the formation of aromatic tribromide derivative instead of the desired pyramidalized double bond as shown in scheme 56.



Scheme 56. Functionalization of tetrabromide **94**

In this view, the functionalization of octahydropentalene is easier than further functionalization of octahydro-1*H*-indene.

In the second and third part of the study, the substituents effect on the regioselectivity of bromination was studied. As expected, the regio- and stereo-selectivity and selectivity of resulting products kept reserved.

In summary, high temperature bromination of saturated hydrocarbons was investigated. The sheer number of exemplified saturated hydrocarbons discussed so far, i.e. bicyclo[4.4.0], bicyclo[3.3.0], bicyclo[4.3.0], bicyclo[4.2.0] systems and finally, tricyclic systems underscores the appealing feature of high temperature bromination reactions that take place with remarkable regio- and stereoselectivity.

Furthermore, high temperature bromination is a versatile tool for functionalization of saturated hydrocarbons en route to useful synthetic intermediates.

CHAPTER 4

EXPERIMENTAL

4.1 General Experimental Techniques

Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-$_{d6}$ and $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters ($cm^{-1).}$

Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ChemDraw Ultra 10.0.

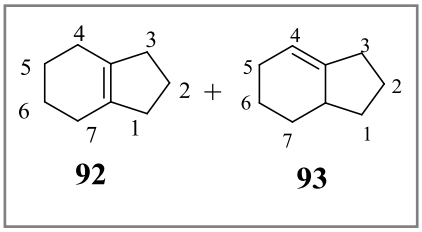
Solvents were purified as reported in the literature.[59]

4.2 Benkeser Reduction of 2,3-dihydro-1*H*-indene (90)

Anhydrous ethylene diamine was purified by heating with sodium for a few days then distilling. Indane (**90**) (23.6 g, 0.2 mol) and ethylene diamine (500 ml) was added into a three-necked round-bottom flask (1000 ml) equipped with a mechanical stirrer, a condenser and a dropping funnel. The mixture was heated to 100-110 °C. Lithium (11.2 g, 1.6 mol) was then introduced into the flask in small portions about an hour. The characteristic dark-blue color developed quickly. The solution was stirred for an additional 4 hours. The reaction was cooled in ice and water (150 ml)

was added carefully to react with excess lithium. The resulting white solution was extracted with pentane three times and combined pentane layers dried over $MgSO_4$. Evaporation of the pentane gave the mixture of 2,3,4,5,6,7-hexahydro-1*H*-indene **92** and 2,3,3a,4,5,6-hexahydro-1*H*-indene **93** as a light yellow liquid (14.6 g, 0.12 mol, 59.6%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.28 (t, $J_{1,2} = J_{3,2} = 8$ Hz, 4H, H-1 and H-3), 1.98 (br s, 4H, H-4, H-7), 1.85 (qui, $J_{1,2} = J_{3,2} = 8$ Hz, 1H, H-2), 1.67-1.64 (m, 4H, H-5, H-6).



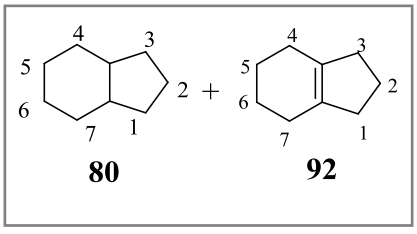
^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.2, 36.1, 25.8, 23.2 , 21.7.

IR (ATR) 2934, 2958, 1782, 1447, 1189, 1079.

4.3 Hydrogenation of 90:

Into a 50 ml, two-necked, round-bottomed flask were placed Pd/C (10%) (100 mg) catalyst and of 2,3,4,5,6,7-hexahydro-1*H*-indene **92** 1 g (8.3 mmol) in MeOH (20 ml). One of the necks was attached to hydrogen gas with a three-way stopcock, the other neck was capped with a rubber septum. The reactants were degassed and flushed with hydrogen gas, while stirring magnetically. After 24 h the solution was decanted from the catalyst and aqueous phase was extracted with three portions of 10 ml pentane. Organic extracts were dried over $MgSO_4$. Evaporation of the solvent provided octahydro-1*H*-indene **80** and unreacted 2,3,4,5,6,7-hexahydro-1*H*-indene **92** (0.79 g, 6.5 mmol, 78%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.87-1.83 (m, 4H, H-1, H-3), 1.75-1.69 (m, 2H, H-3a and H-7a), 1.59-1.55 (m 4H, H-4,H-7), 138-1.28 (m, 6H, H-2, H-5, H-6).



^{13}C-NMR (100 MHz, $CDCl_3$) δ 46.7, 31.9, 31.3, 26.6, 21.6.

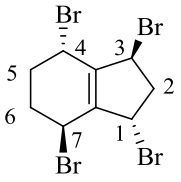
IR (ATR) 3022, 2916, 2850, 2659, 1446.

4.4 High Temperature Bromination of the mixture of 80 and 92 with 4 equiv Br_2

The mixture of octahydro-1*H*-indene (**80**) and 1.0 g (8.05 mmol) 2,3,4,5,6,7-hexahydro-1*H*-indene **92** were placed into a two-necked, round-bottom flask and the solution was heated until carbon tetrachloride began to reflux, while strirring magnetically. The solution of bromine (5.15 g, 32.2 mmol) in 20 ml of CCl_4 was added drop by drop to the refluxing solution over a period of 15 min. After the reaction mixture was heated for 5 min at reflux temperature, the mixture was allowed to cool to room temperature. The excess bromine was quenched with saturated $Na_2S_2O_5$ solution and organic layer was seperated and dried over Mg_2SO_4. After the evaporation of carbon tetrachloride, the residue was submitted to column chromatography on silica jel (80g). Elution with hexane gave five products: **94** (0.703 g, 2.06 mmol, 35 %), **95** (0.341 g, 1 mmol, 15%), **96** (0.141 g, 0.322 mmol, 7%), **97** (0.118 g, 0.228 mmol, 5.9%) and **98** (0.073 g, 0.205 mmol, 3.6%).

Rel-(1*S*,3*S*,4*S*,7*S*)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1*H*-indene (94):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.15 (t, $J_{12} = J_{32} = 5.6$ Hz, 2H, H-1, H-3); 5.08-5.07 (m, 2H, H-4, H-7); 3.04 (t, $J_{21} = J_{23} = 5.6$ Hz, 2H, H-2, H-2'); 2.52-2.25 (AA'BB'-system, 4H, H-5, H-5', H-6 and H-6').



94

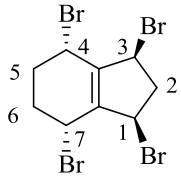
^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.1 (C-3a, C-7a), 51.0 (C-1, C-3), 46.0 (C-2), 42.5 (C-4, C-7), 27.9 (C-5, C-6).

IR (ATR): 2958, 2917, 2848, 2360, 2341, 1458, 1430, 1386, 1299, 1260, 1170, 1082, 961, 881, 764, 729, 607.

Anal. Calcd for $C_9H_{10}Br_4$: C, 24.69, H, 2.30. **Found:** C, 24.63, H, 2.36. White solid m.p. 79-81 ^oC

Rel-(1*R*,3*S*,4*S*,7*R*)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1*H*-indene (95):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.25 (d, $J_{12} = J_{32} = 7.0$ Hz, 2H, H-1, H-3); 4.98-4.95 (m, 2H, H-4, H-7); 3.24 (dt, A part of AB-system, $J_{12} = J_{32} = 7.0$ Hz, $J_{22'} = 16.8$ Hz, 1H, H-2); 2.85 (d, B part of AB-system, $J_{22'} = 16.8$ Hz, 1H, H-2'); 2.43-2.30 (m, 4H, H-5, H-6).



95

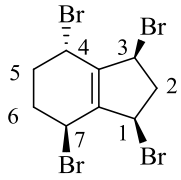
^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3 (C-3a, C-7a), 51.9 (C-1, C-3), 43.1 (C-2), 42.5 (C-4, C-7), 31.7 (C-5, C-6).

IR (ATR): 3004, 2955, 2918, 2849, 2351, 2339, 1866, 1770, 1714, 1682, 1651, 1634, 1556, 1504, 1424, 1275, 1204, 1149, 1093, 1009, 897, 826, 714, 619.

Anal. Calcd for $C_9H_{10}Br_4$: C, 24.69, H, 2.30. **Found:** C, 24.63, H, 2.36. White solid m.p. 148-150 ^{o}C

Rel-(1*R*,3*S*,4*S*,7*S*)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1*H*-indene (96):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.09 (br s, 1H, H-3); 4.90-4.89 (m, 1H, H-7); 4.80 (br s, 1H, H-1); 4.58 (br d, J_{12} = 5.7 Hz, H-1); 3.48-3.42 (ddd, A part of AB-system $J_{22'}$ = 18.3 Hz, $J_{2'1}$ = 5.7 Hz, $J_{2'3}$ = 2.2 Hz, 1H, H-2'); 2.62 (d, B part of AB-system, $J_{2'2}$ = 18.3 Hz, 1H, H-2); 2.50-2.35 (m, 1H, H-5, H-6); 2.22-2.13 (m, 1H, H-5', H-6').



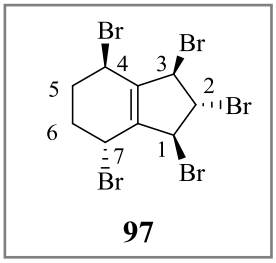
96

^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.1 (C-3a), 138.4 (C-7a), 60.3 (C-3), 49.9 (C-1), 44.6 (C-4), 44.1 (C-2), 42.3(C-7), 28.3 (C-5), 27.8 (C-6).

IR (ATR): 3002, 2945, 2818, 2809, 2321, 2329, 1766, 1710, 1704, 1602, 1601, 1546, 1514, 1428, 1265, 1214, 1149, 1083, 1019, 887, 836, 712, 615.

Rel-(1*R*,2*R*,3*S*,4*R*,7*R*)-1,2,3,4,7-pentabromo-2,3,4,5,6,7-hexahydro-1*H*-indene (97):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.11 (br s, 1H, H-3); 4.98 (dd, $J_{45'}$ = 4.5 Hz, J_{45} = 1.4 Hz, 1H, H-4); 4.91 (s, 1H, H-1); 4.77 (t, J_{13} = J_{23} = 1.0 Hz, H-2); 4.74-4.73 (m, 1H, H-7); 2.63 (dddd, A part of AB-system $J_{55'}$ = 15.0 Hz, $J_{56'}$ = 13.0 Hz, $J_{5'6'}$ = 4.5 Hz, J_{54} = 1.5 Hz, 1H, H-5); 2.42 (dddd, B part of AB-system, $J_{6'6}$ = 14.9 Hz, $J_{56'}$ = 12.9 Hz, $J_{6'5'}$ = 3.9 Hz, J_{67} = 2.4 Hz, 1H, H-6); 2.26-2.21 (m, 1H, H-5'); 2.18-2.12 (m, 1H, H-6').



97

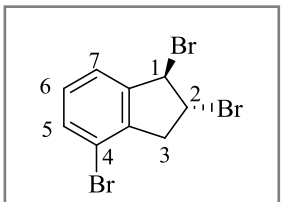
^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.7 (C-3a), 139.5 (C-7a), 55.3 (C-2), 54.5 (C-3), 54.2(C-1), 42.9 (C-4), 40.9 (C-7), 29.3 (C-5), 28.2 (C-6).

IR (ATR): 3003, 2970, 2953, 2841, 1738, 1770, 1428, 1365, 1229, 1216, 1199, 1140, 957, 712, 616.

Anal. Calcd for $C_9H_9Br_5$: C, 20.92; H, 1.76. **Found:** C, 20.50, H, 2.21. White solid m.p. 165-168 ^{o}C.

Rel-(1*R*,2*R*)-1,2,4-tribromo-2,3-dihydro-1*H*-indene (98):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J_{56} = 7.8 Hz, 1H, H-5); 7.40 (d, J_{76} = 7.5 Hz, 1H, H-7); 7.19 (t, J_{56} = J_{76} = 7.8 Hz, 1H, H-6); 5.65 (bs, 1H, H-1); 4.84 (bd, J=5.3 Hz, 1H, H-2); 3.77 (dd, A-part of AB-system, $J_{33'}$ = 18.0 Hz, J_2 = 5.3 Hz, 1H, H-3); 3.35 (d, B-part of AB-system, 1H, $J_{3'3}$ = 18.0 Hz, H-3')



98

^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.5 (C-4), 141.1 (C-5), 132.6 (C-7), 129.5 (C-6), 124.4 (C-3a), 120.0 (C-7a), 57.2 (C-1), 52.3 (C-2), 42.8 (C-3).

IR (ATR): 3005, 2918, 2849, 2352, 2318, 1732, 1644, 1571, 1556, 1456, 1376, 1275, 1212, 1111, 947, 885, 764, 750, 620.

Anal. Calcd for $C_9H_7Br_3$: C, 30.46, H, 1.99. **Found:** C, 30.38, H, 2.02. Light yellow liquid.

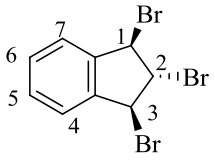
4.5 Treatment of 94 with KI

In a 100 ml three neck flask equipped with a dropping funnel, a efficient condenser and a mechanical stirrer were placed 1.9 g (11.45 mmol) of potassium iodide, the compound **94** (1 g, 2.28 mmol) and 40 ml of acetone. After the color of the mixture was yellow, dimethyl acetyl dicarboxylate (0.6 g, 1.51 mmol) in 20 ml of acetone was added dropwise to the solution over a period of 30 min. The mixture was stirred for an additional 5 hours. After the water was added, the mixture was extracted with with three 50 ml portions of chloroform. The chloroform layers were dried over magnesium sulfate. The chloroform was removed rotary-evaporator. The residue was

chromatographed on silica gel (50 g). Elution with hexane-ethyl acetate (9:1) afforded **100** (580 mg, 1.63 mmol, 71%), **114** (590 mg, 1.49 mmol, 98%).

Rel-(1*R*,2*r*,3*S*)-1,2,3-tribromo-2,3-dihydro-1*H*-indene (100):

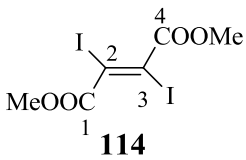
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (AA'BB'-system, 4H, H-4, H-5, H-6 and H-7); 5.61 (d, $J_{12} = J_{32} = 1.9$ Hz, 2H, H-1, H-3); 4.99 (t, $J_{23} = J_{21} = 1.9$ Hz, 1H, H-2).



100

^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.2 (C-3a, C-7a), 130.5 (C-4, C-7), 126.1 (C-6, C-5), 57.7 (C-1, C-3), 53.6 (C-2).

Dimethyl 2,3-diiodofumarate (114):



114

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 6H, methyl protons).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.2 (C-1, C-4), 88.1 (C-2, C-3), 53.7.

Colorless crystals m.p. 204-206 ^{o}C.

4.6 Iodination of Acetylene with KBr:

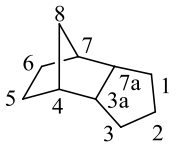
The synthesis of 2,3-diiodofumaric acid dimethyl ester (**114**) was performed according to the literature protocol. A solution of dimethyl acetylene dicarboxylate (10.0 mmol, 1.22 ml) and iodine (12.0 mmol, 3.04 g) in acetone (30 ml) was stirred at room temperature in 7 hours. The mixture was extracted with 50 ml of chloroform and dried over. Recrystallization from chloroform/hexane (4:1) furnished colourless crystals (10.0 mmol, 3.96 g, 80%). The spectroscopic data were in agreement with the literature.

4.7 Hydrogenation of dicyclodipentadiene (117):

Into a 50 ml, two-necked, round-bottomed flask were placed Pd/C (10%) (100 mg) catalyst and of dicyclodipentadiene **117** 1 g (7.56 mmol) in MeOH (20 ml). One of the necks was attached to hydrogen gas with a three-way stopcock, the other neck was capped with a rubber septum. The reactants were degassed and flushed with hydrogen gas, while stirring magnetically. After 24 h the solution was decanted from the catalyst and aqueous phase was extracted with three portions of 10 ml pentane. Organic extracts were dired over $MgSO_4$. Evaporation of the solvent provided octahydro-1*H*-4,7-methanoindene **81** (0.85 g, 6.23 mmol, 82%) as a colorless liquid.

Octahydro-1*H*-4,7-methanoindene (81):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27-2.22 (m, 1H), 2.01-2.00 (m, 1H), 1.56-1.48 (m, 1H), 1.45-1.39 (m, 2H), 1.38-1.32 (m, 2H), 1.31-1.15 (m, 3H), 0.83-0.79 (t, *J* = 8 Hz, 2H).



80

^{13}C-NMR (100 MHz, $CDCl_3$) δ 45.5, 43.2, 41.5, 28.7, 26.9, 24.7, 23.0.

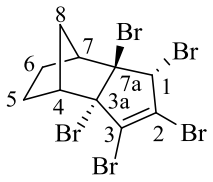
IR (ATR) 2941, 2874, 1483, 1454, 1263, 741.

4.8 High Temperature Bromination of 81:

2.0 g (14.68 mmol) of octahydro-1*H*-4,7-methanoindene **81** and 11.7 g (73.4 mmol) bromine were dissolved in 30 mL of carbon tetrachloride in a sealed tube. The mixture was stirred at 150 ^{o}C over a period of 4 hours. After being cooled to room temperature the solvent was evaporated. The residue was chromatographed on silica gel (100 g). Elution with hexane afforded **123** (650 mg, 1.22 mmol, 16%), **124** (122 mg, 0.27 mmol, 3%), **125** (446 mg, 1.45 mmol, 11%).

Rel-(1*R*,3a*R*,7a*S*)-1,2,3,3a,7a-pentabromo-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methano indene (123):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.47 (s, 1H, H-1); 3.02-3.01 (m, 1H, H-4); 2.95 (br d, 1H, H-7); 2.61 (dt, A part of AB-system, $J_{88'}$ = 12.0 Hz, 1H, H-8)1.84-1.76 (m, 1H, H-6); 1.67-1.64 (dt, B part of AB-system, $J_{88'}$ = 12.0 Hz, 1H, H-8'); 1.63-1.52 (m, 2H H-5' and H-6'); 1.51-1.42 (m, 1H, H-5).



123

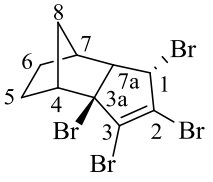
^{13}C-NMR (100 MHz, $CDCl_3$) δ 131.2 (C-2), 125.1 (C-3), 80.7 (C-3a), 77.2 (C-7a), 62.7 (C-1), 55.7 (C-7), 54.3 (C-4), 37.5 (C-8), 26.2 (C-6), 23.6 (C-5).

IR (ATR): 3566, 3420, 2986, 2956, 2878, 1731, 1591, 1450, 1308, 1189, 1166, 1092, 933, 848, 723.

Anal. Calcd for $C_{10}H_9Br_5$: C, 22.72, H, 1.72. **Found:** C, 22.67, H, 1.95. Colorless crystals m.p. 96-98 ^{o}C

Rel-(1*S*,3a*R*)-1,2,3,3a-tetrabromo-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methano indene (124):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.75 (d, J_{7a1} = 0.6 Hz, 1H, H-1); 3.61 (br d, J_{7a7} = 4.0 Hz 1H, H-7a); 2.73-2.72 (m, 1H, H-4); 2.65-2.63 (m, 1H, H-7); 2.12-2.07 (m, A part of AB-system, 1H, H-8'); 1.56 (dt, B part of AB-system, $J_{88'}$ = 10.4 Hz, 1H, H-8); 1.45-1.33 (m, 2H, H-5, H-6); 1.30-1.18 (m, 1H, H-6'); 1.02-0.93 (m, 1H, H-5').



124

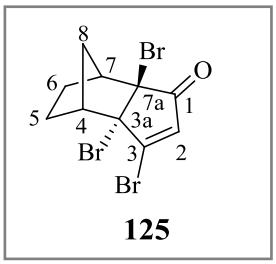
^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.3 (C-3), 132.6 (C-2), 77.2 (C-3a), 65.8 (C-7a), 54.0 (C-1), 51.1 (C-4), 41.8 (C-7), 38.7 (C-8), 22.6 (C-6), 20.8 (C-5).

IR (ATR): 2969, 2878, 2251, 1737, 1586, 1474, 1306, 1261, 1234, 1189, 1172, 905, 852, 729, 688.

Anal. Calcd for $C_{10}H_{10}Br_4$: C, 26.70, H, 2.24. **Found:** C, 26.52, H, 2.67. Colorless crystals m.p. 130-133 ^{o}C.

Rel-(3a*S*,7a*S*)-3,3a,7a-tribromo-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-methanoinden-1-one (125):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 1H, H-2); 2.89-2.88 (m, 1H, H-7, H-4); 2.63 (br d, A part of AB-system, 1H, $J_{88'}$ = 10.7 Hz, H-8); 1.70 (br d, B part of AB-system, $J_{88'}$ = 10.7 Hz, H-8'); 1.61-1.49 (m, 1H, H-5); 1.37-1.29 (m, 1H, H-6); 1.22-1.15 (m, 1H, H-6').



125

^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.9 (C-1), 161.5 (C-3), 132.8 (C-2), 81.3 (C-3a), 74.1 (C-7a), 51.8 (C-4), 51.5 (C-7), 40.8 (C-8), 25.3 (C-6), 24.5 (C-5).

IR (ATR): 3004, 2955, 2918, 2849, 2351, 2339, 1866, 1770, 1714, 1682, 1651, 1634, 1556, 1504, 1424, 1275, 1204, 1149, 1093, 1009, 897, 826, 714, 619.

Anal. Calcd for $C_{10}H_9Br_3$: C, 31.21, H, 2.36. **Found:** C, 31.37, H, 2.63. Colorless crystals 154-156 ^oC

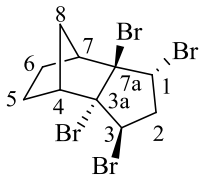
4.9 Photochemical Bromination of 81

2.0 g (14.68 mmol) of octahydro-1*H*-4,7-methanoindene **81** 11.7 g (73.4 mmol) bromine were dissolved in 30 mL of carbon tetrachloride in a flask with 150 W sun lamp. The resulting solution was photolyzed at room temperature for 7 hours while magnetcally stirring.stirred. After the excess bromine quenced with sodium meta bisulfate in water, the organic phase evaporated. The residue was chromatographed on silica gel (100 g). Elution with hexane gave **131** (935 mg, 2.07 mmol, 23%), **135** (399 mg, **x** mmol, 10%).

Rel-(1*R*,3*R*,3a*S*,7a*S*)-1,3,3a,7a-tetrabromooctahydro-1*H*-4,7-methanoindene (131):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.10 (dd, $J_{32'}$ = 12.8 Hz, J_{32} = 7.6 Hz, 1H, H-3); 4.83 (d, $J_{12'}$ = 6.0 Hz 1H, H-1); 3.15-3.14 (m, 1H, H-4); 2.90-2.89 (m, 1H, H-7); 2.76 (dd, A part of AB-system, $J_{22'}$ = 15.2 Hz, J_{23} = 7.6 Hz, 1H, H-2); 2.60 (ddd, B part of AB-system, $J_{22'}$ = 15.2 Hz, $J_{2'3}$ = 13.2 Hz, $J_{2'1}$ = 6.0 Hz, 1H, H-2'); 2.62 (dh, A part

of AB-system, $J_{88'}$ = 10.4 Hz, 1H, H-8); 1.69-1.64 (br d, B part of AB-system, $J_{88'}$ = 10.4 Hz, 1H, H-8'); 2.13-2.05 (m, 2H, H-5 an H-5'); 1.62-1.47 (m, 2H, H-6 and H-6').



131

^{13}C-NMR (100 MHz, $CDCl_3$) δ 82.4 (C-3a), 81.1 (C-7a), 58.2 (C-3), 57.9 (C-1), 56.5 (C-4), 55.6 (C-7), 45.8 (C-2), 42.3 (C-8), 24.9 (C-5), 24.0 (C-6).

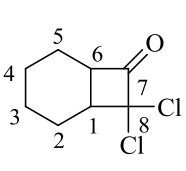
IR (ATR): 3566, 3420, 2986, 2956, 2878, 1731, 1591, 1450, 1308, 1189, 1166, 1092, 933, 848, 723.

Anal. Calcd for $C_{10}H_{12}Br_4$: C, 26.58, H, 2.68. **Found:** C, 26.53, H, 3.04. Colorless crystals m.p. 165-166 ^{o}C.

4.10 The synthesis of 8,8-dichlorobicyclo[4.2.0]octan-7-one (139):

Compound **139** was prepared according to the literature procedure. A 500 ml two-neck round bottom flask was equipped with a nitrogen inlet and pressure-regulated dropping funnel. The solution of 5 g (62.5 mmol) cylohexene and 8.15 g (125 mmol) powder Zn in 100 ml dry ether was replaced to flask. The water bath was cooled to 15 ^{o}C by adding pieces of ice periodically. A solution of 22.7 g (125 mmol) trichloroacetylechloride in 100 ml dry ether was given drop wise within 2 h. The reaction was continued extra 1 h while maintaining the water bath temperature at 15 ^{0}C. When the reaction was complete, the solids were removed by simple filtration. Then filtrate was extracted with first H_2O (2 x 100ml) and then saturated $NaHCO_3$ (2x100 ml). The solution was dried over Na_2SO_4 and solvent was evaporated. Finally the product was further purified by silica gel (30g, ethyl acetate: hexane (1:9)) as yellow liquid. (7.164 g, 68 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93-9.88 (m, 1H, H-1); 2.93 (q, $J_{65} = J_{61}$ = 8 Hz, 1H, H-6); 2.11-2.01 (m, 2H, H-2); 1.65-1.50 (m, 3H, H-5, H-3); 1.38 (m, 1H, H-3'); 1.17-1.11 (m, 2H, H-4).



139

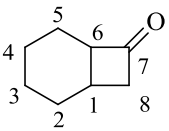
^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.9 (C-7), 89.2 (C-8), 51.82 (C-1), 42.3 (C-6), 24.4 (C-2), 20.6 (C-5), 20.3 (C-3), 19.7 (C-4).

IR (ATR): 3446, 2931, 2856, 1773, 1448, 1237, 1171, 0192, 1038, 871, 714, 651.

4.11 The synthesis of bicyclo[4.2.0]octan-7-one 82:

Bicyclo[4.2.0]oct-3-en-7-one was prepared according to the literature procedure. A 100 ml two-neck flask 5 g (76.9 mmol) Zn dust 50 ml glacial acetic acid was left to stir magnetically. To one neck a condenser was in connected. To the other nect a pressure regulated dropping funnel containing 7.5 g (39.3 mmol) dichloroketene cyloadduct and 25 ml of glacial acetic acid was plugged. This solution was given drop wise at room temperature. The reaction was then warmed to 70 ^{o}C for 1 h and then allowed to cool room temperature and stirred for 8 h. When the reaction was completed a few drops of distilled water was added to the system to dissolve the formed zinc salt. The product was then filtered ordinary filter paper. The solution was transferred to a separatory funnel and washed with H_2O (2x20 ml), with saturated $NaHCO_3$ until no HOAc remained. The solution was dried over $MgSO_4$ and product was concentrated under vacuum by rotary evaporator. The product was eluted with 2:98 ethyl acetate:hexane solvent system with silica gel column (30 g) chromatography to achieve the pale yellow liquid, pure ketone (2.75g, 61 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.20 (br t, 1H, H-8'); 3.10 (ddd, $J_{88'}$ = 17.8, J_{86} = 3.8 Hz, J_{81} = 9.2 Hz, 1H, H-8); 2.43-2.36 (m, 1H, H-6); 2.10-2.06 (m, 1H, H-1); 1.90-1.86 (m, 2H, H-5); 1.51-1.46 (m, 2H, H-4); 1.42-1.31 (m, 2H, H-3); 1.17-1.00 (m, 2H, H-2).



82

^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.7 (C-7), 56.4 (C-6), 51.92 (C-8), 29.3 (C-1), 22.4 (C-5), 22.3 (C-4), 22.1 (C-3), 21.0 (C-2).

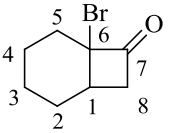
IR (ATR): 3446, 2931, 2856, 1773, 1448, 1237, 1171, 0192, 1038, 871, 714, 651.

4.12 High Temperature Bromination of 82:

1.0 g (8.05 mmol) of bicyclo[4.2.0]octan-7-one **82** was dissolved in 30 mL of carbon tetrachloride in a 100 mL fask, which was equipped with reflux condenser. The solution was heated until carbon tetrachloride started to refux while stirring

magnetically. To the refuxing solution was added dropwise a hot solution of bromine (6.44 g, 40.26 mmol) in 30 mL of carbon tetrachloride during 15 min. The resulting reaction mixture was heated for 5 min at reflux temperature. After being cooled to room temperature the solvent was evaporated. The residue was chromatographed on silica gel (30 g). Elution with hexane:ethyl acetate (98:2) afforded 6-bromo bicyclo[4.2.0]octan-7-one **139** (916 mg, 4.50 mmol, 56%) as a light yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.23 (dd, $J_{88'}$ = 16.8 Hz, $J_{18'}$ = 9.6, 1H, H-8'); 2.90 (dd, $J_{88'}$ = 16.4 Hz, J_{81} = 7.2 Hz, 1H, H-8); 2.71-2.64 (m, 1H, H-1); 2.11-1.94 (m, 3H); 1.54-1.42 (m, 5H).



139

^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.7 (C-7), 68.5 (C-6), 48.0 (C-8), 35.6 (C-1), 31.5 (C-5), 25.2 (C-4), 20.8 (C-3), 19.9 (C-2).

IR (ATR): 3441, 2911, 2843, 1771, 1452, 1218, 1166, 1092, 1042, 876.

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APPENDIX A

SPECTRAL DATA

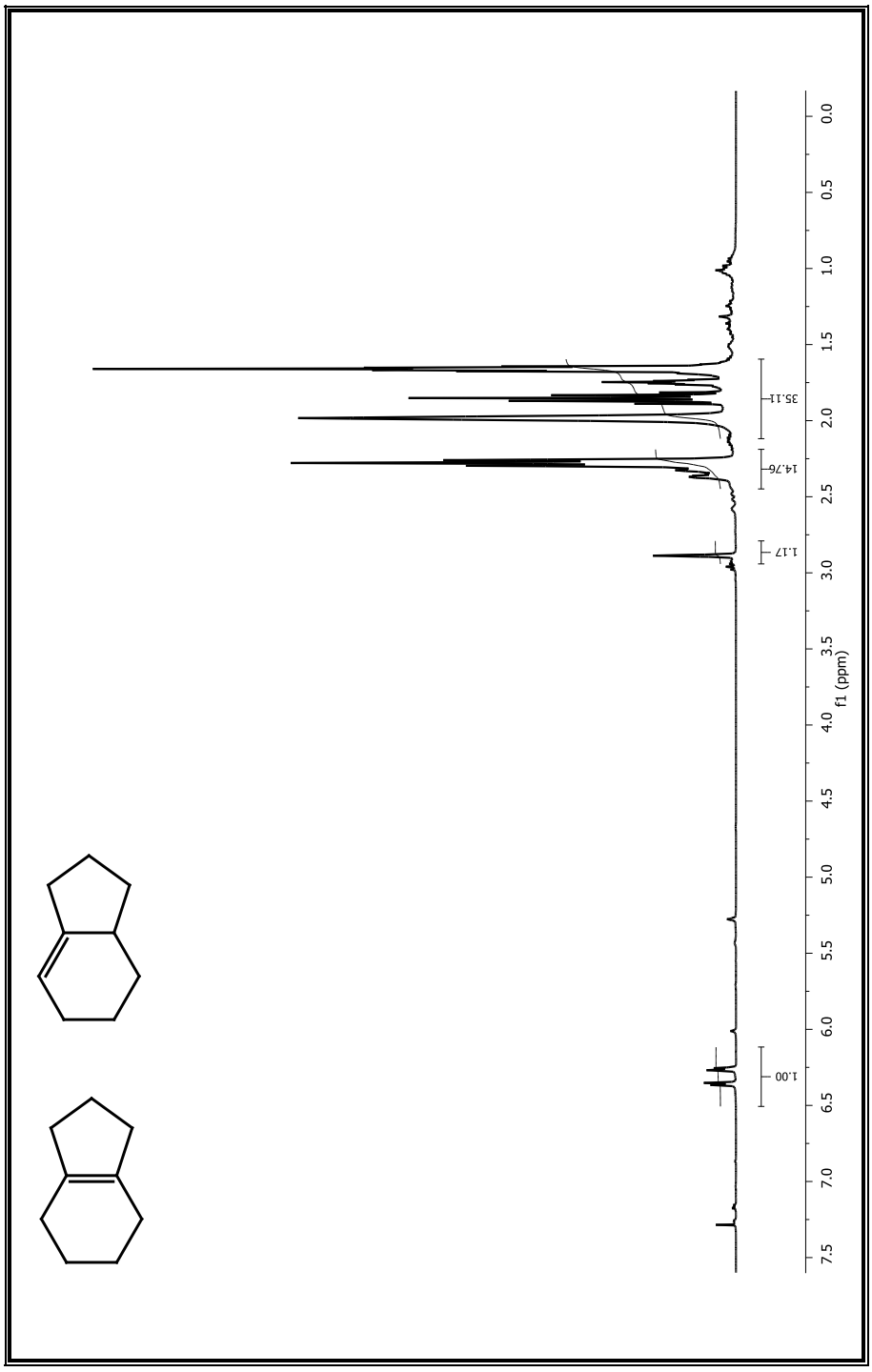

Figure A.1 ^{1}H-NMR spectrum of compound **92** and **93**.

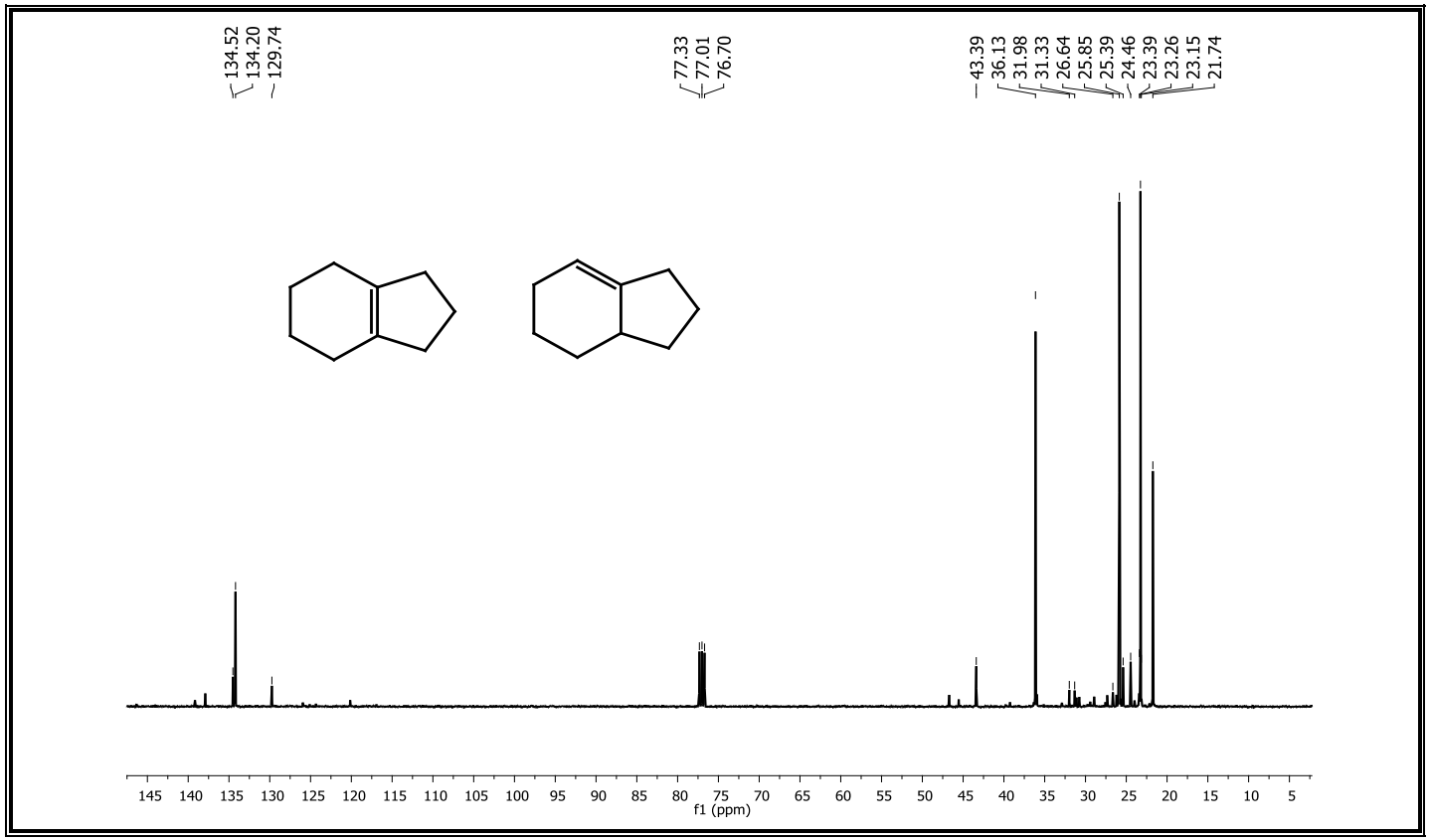

Figure A.2 ^{13}C-NMR Spectrum of Compound **92** and **93**.

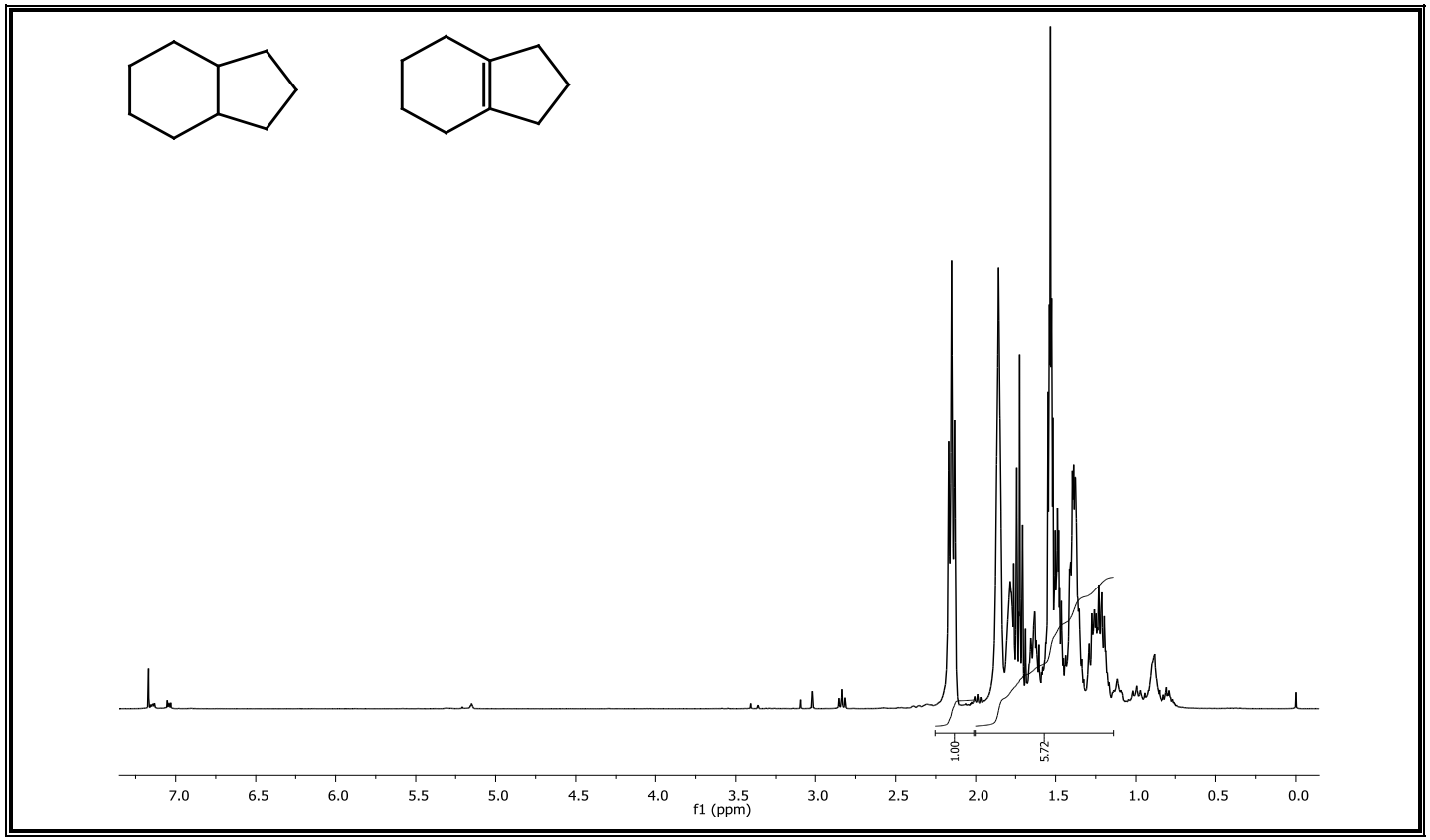

Figure A.3 ^{1}H-NMR spectrum of compound **92** and **80**.

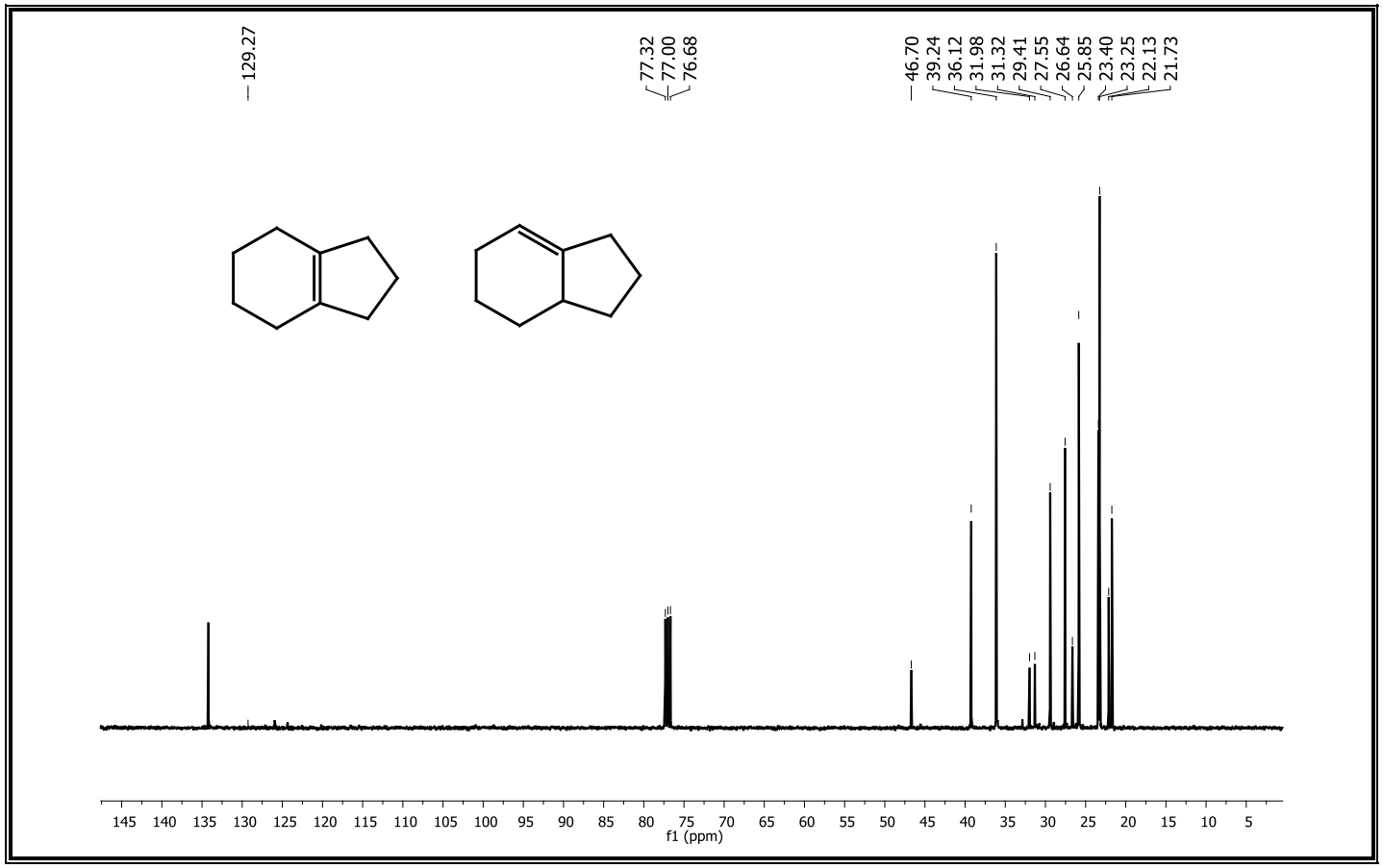

Figure A.4 ^{13}C-NMR spectrum of compound **92** and **80**.

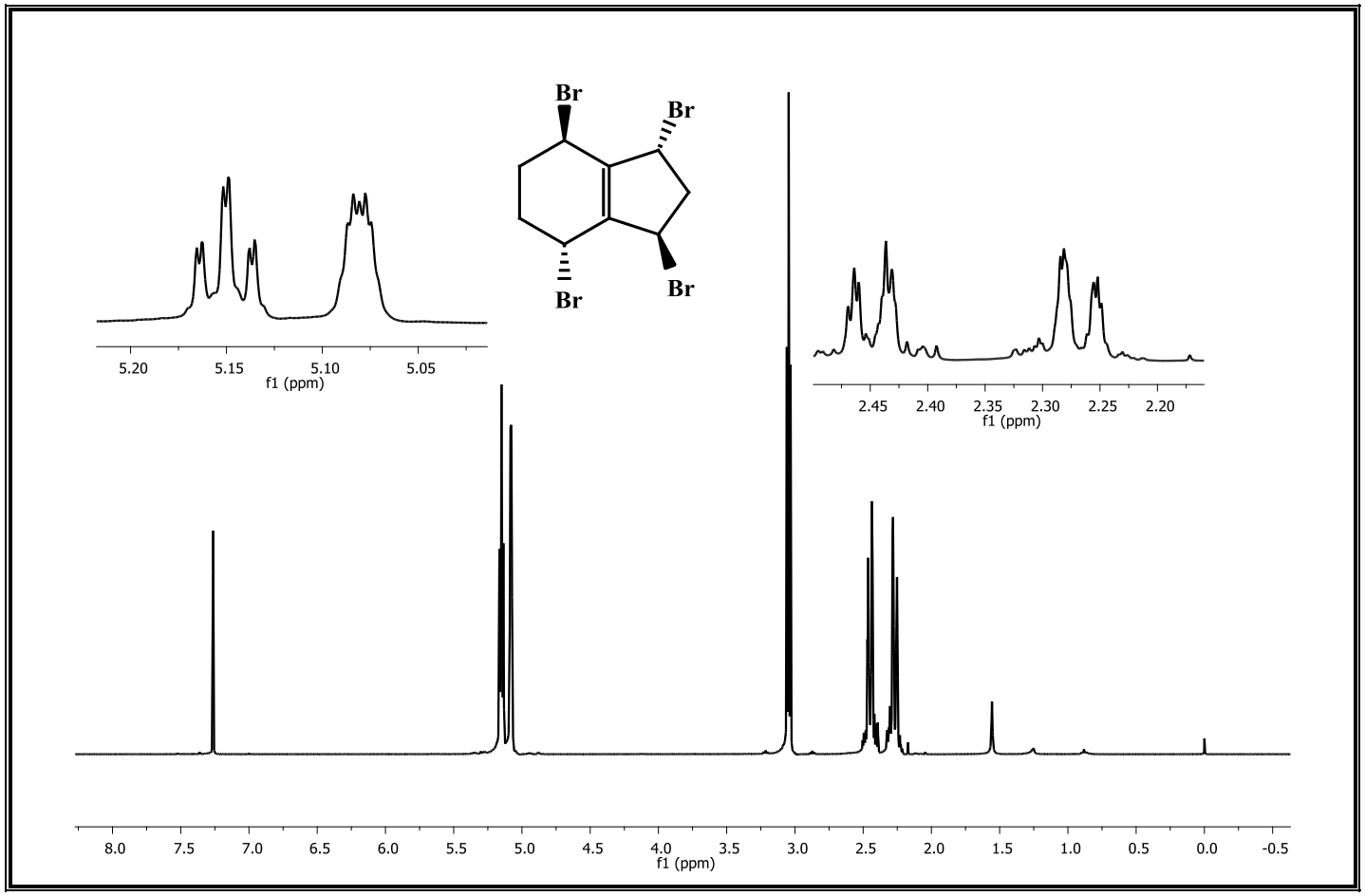

Figure A.5 ^{1}H-NMR spectrum of compound **94**.

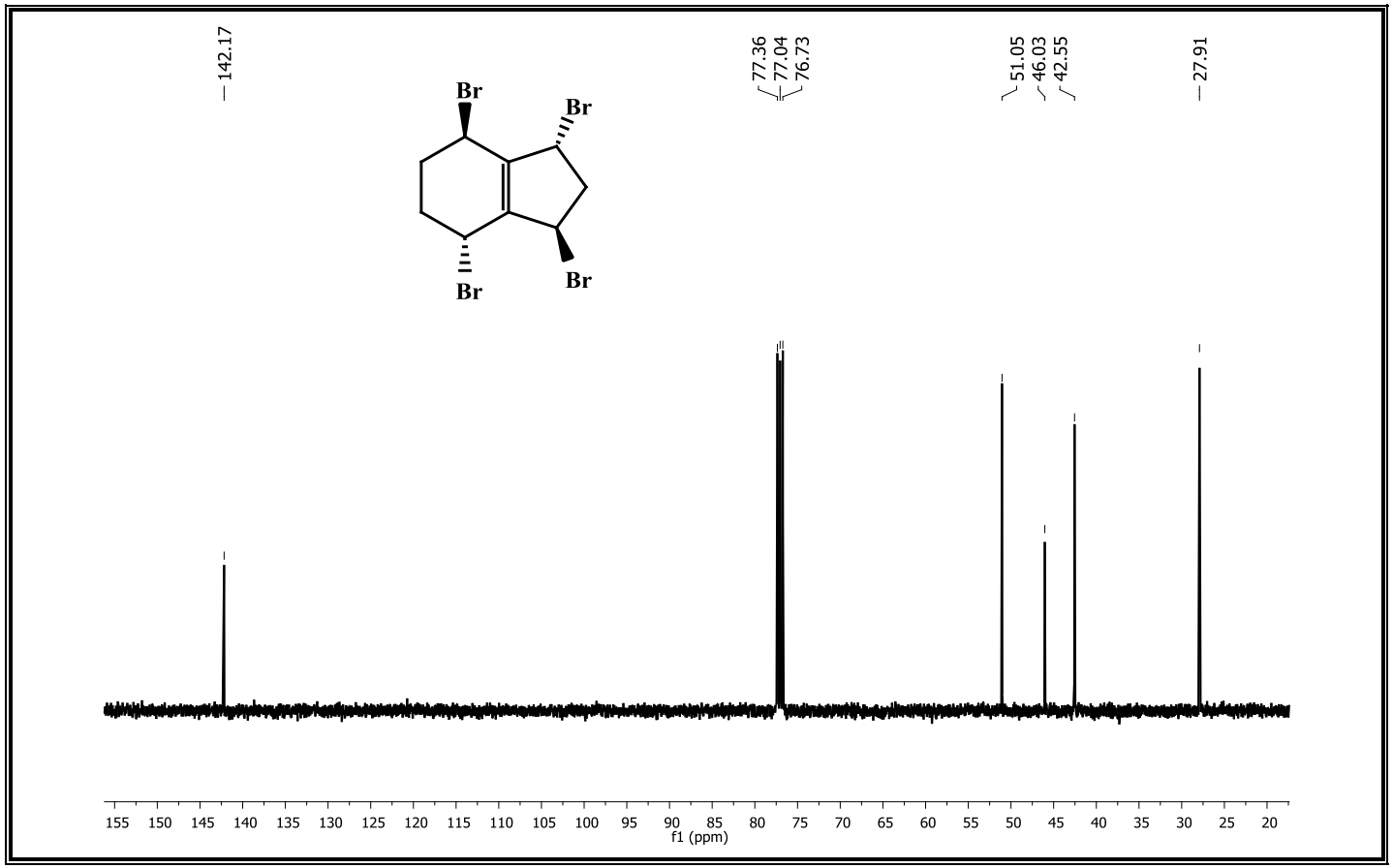

Figure A.6 ^{13}C-NMR spectrum of compound **94**.

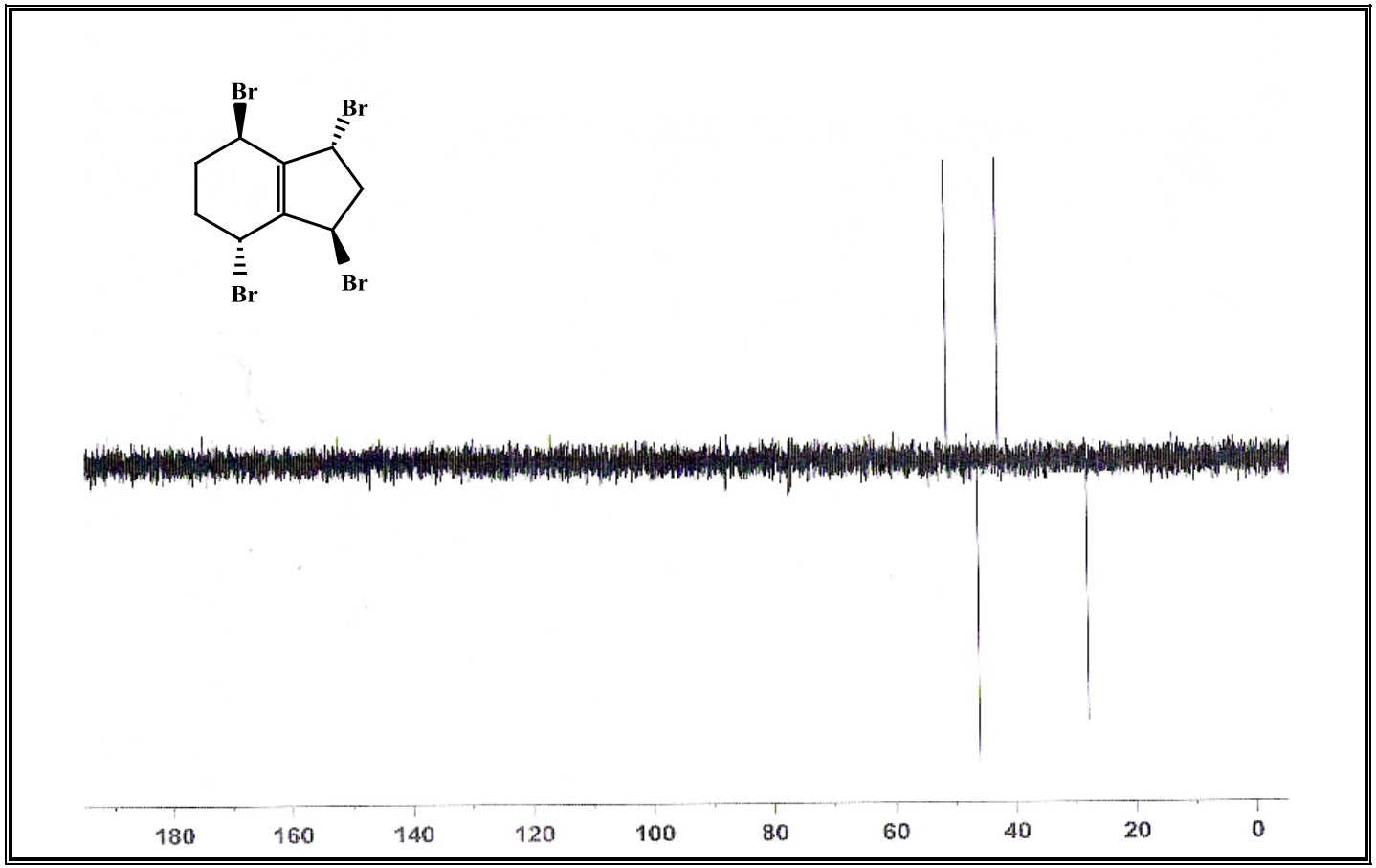

Figure A.7 DEPT-135 Spectrum of Compound **94**.

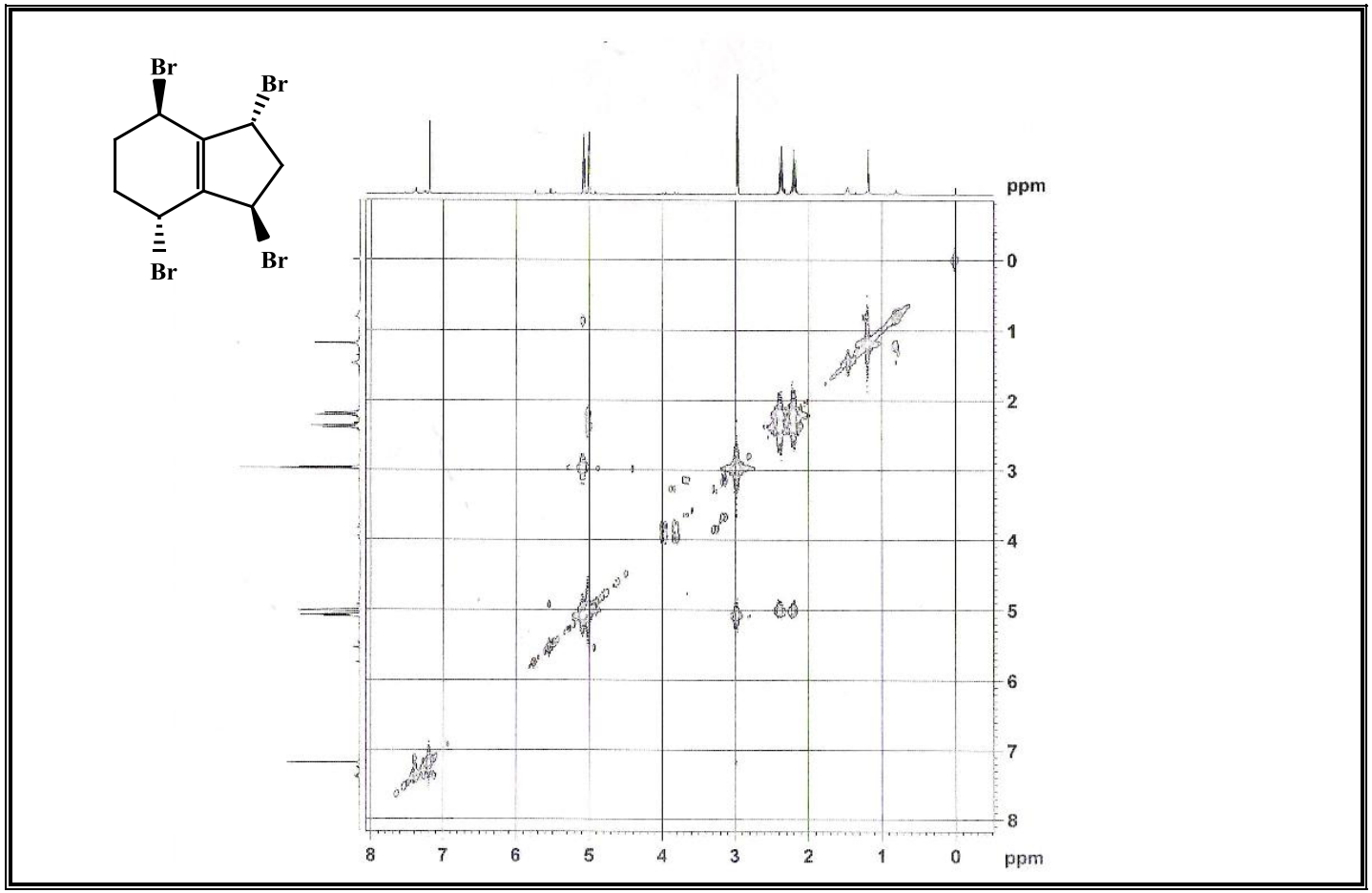

Figure A.8 COSY Spectrum of Compound **94**.

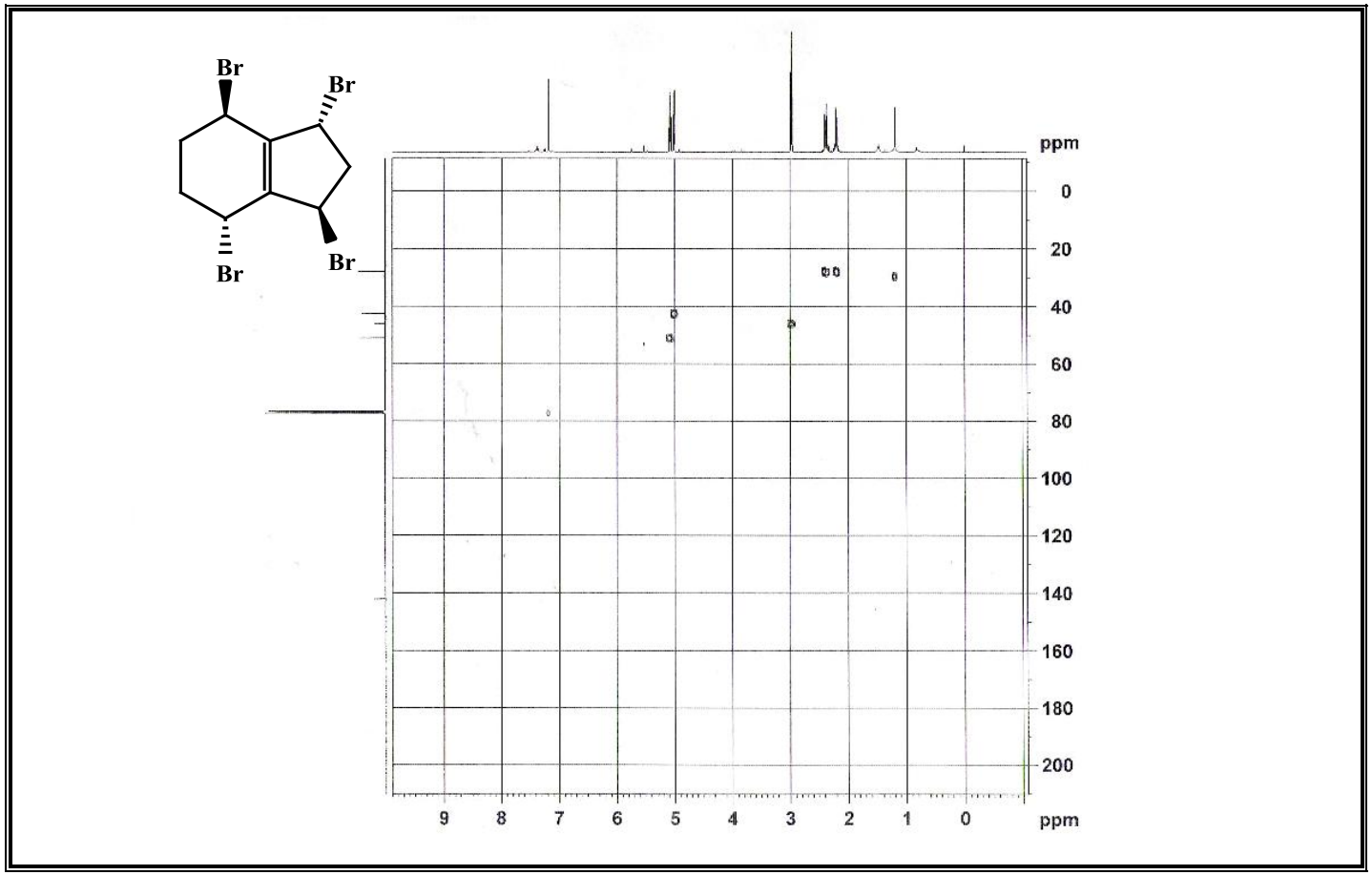

Figure A.9 HSQC Spectrum of Compound **94**.

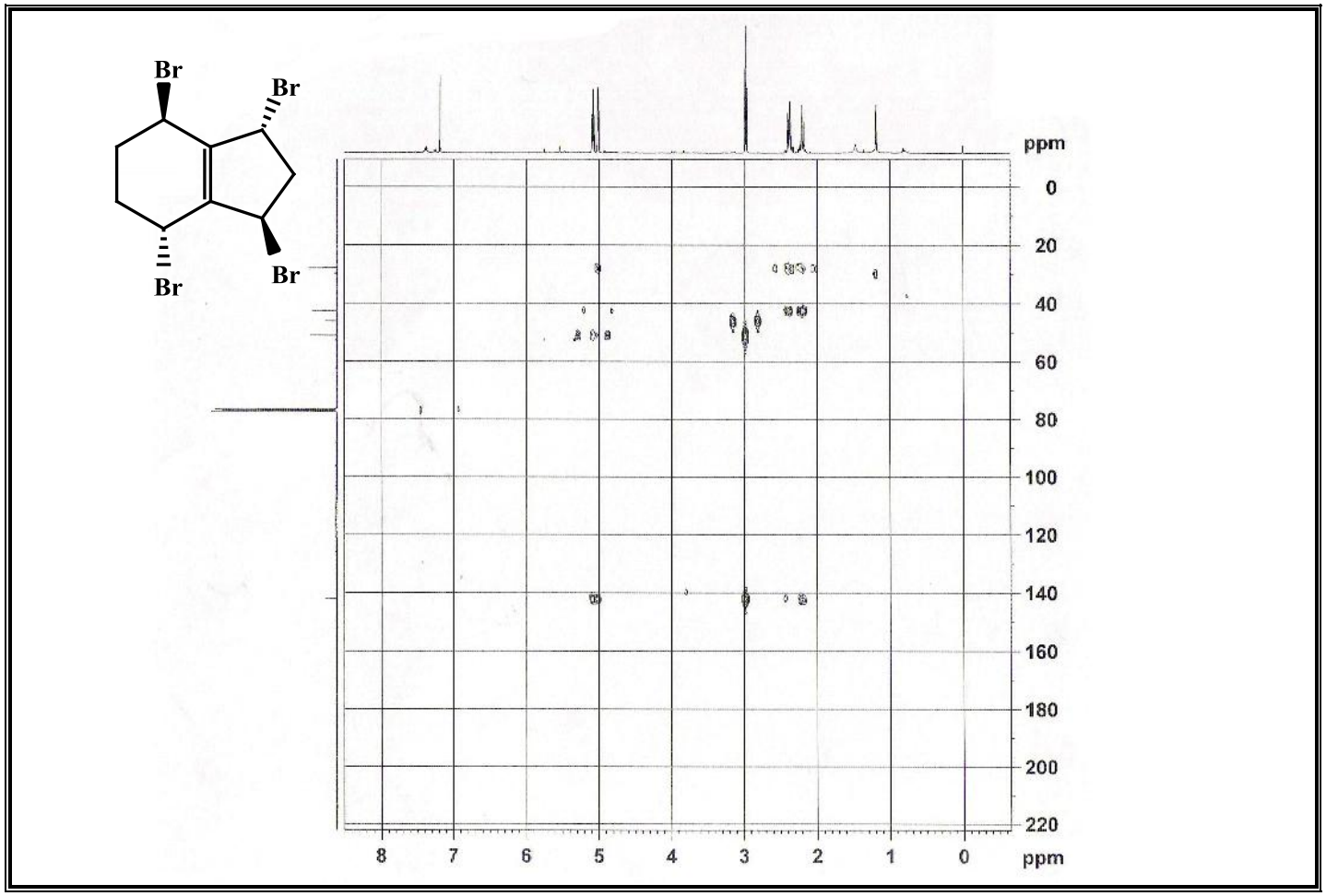

Figure A.10 HMBC Spectrum of Compound **94**.

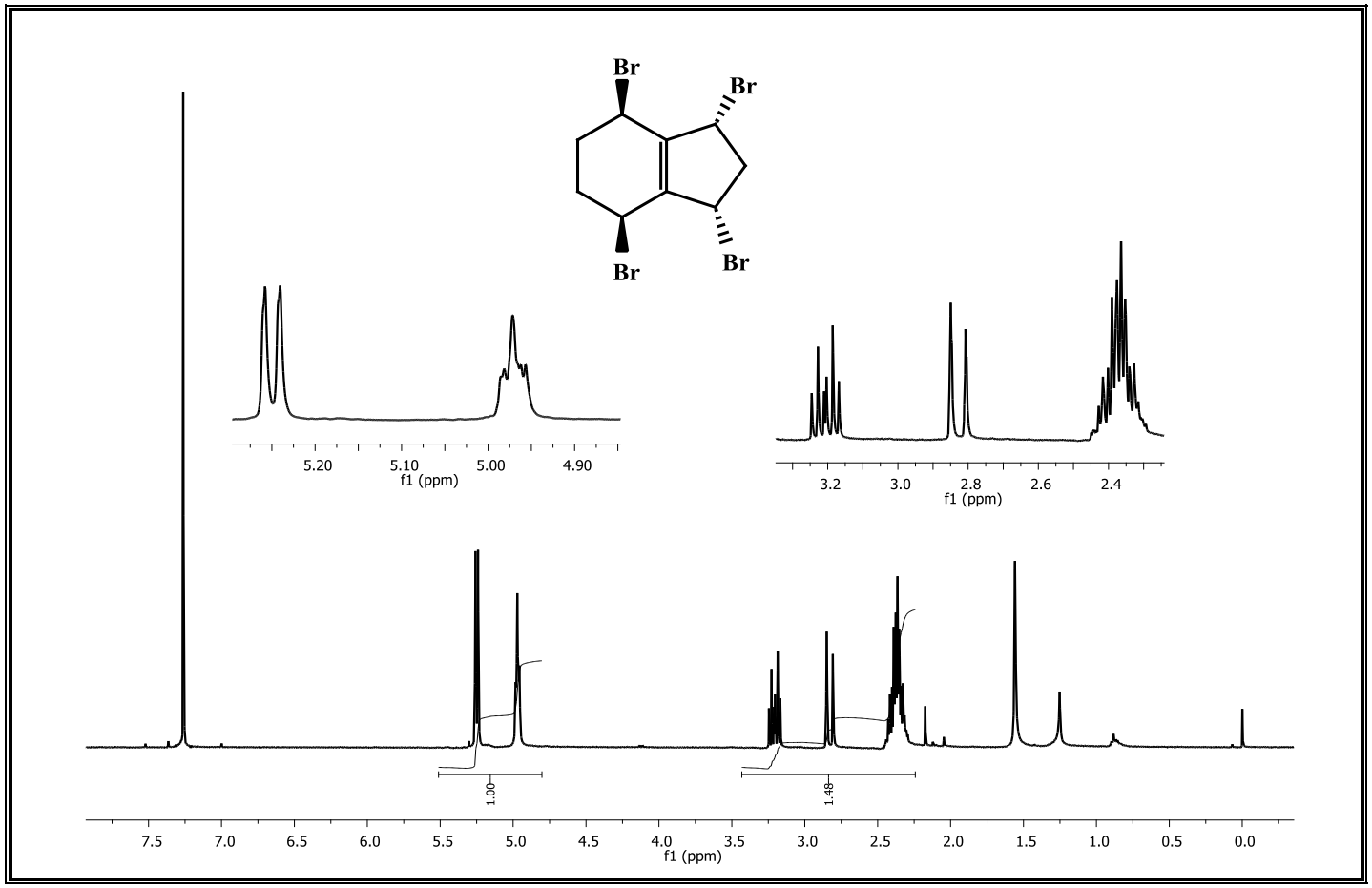

Figure A.11 ^{1}H-NMR spectrum of compound **95**.

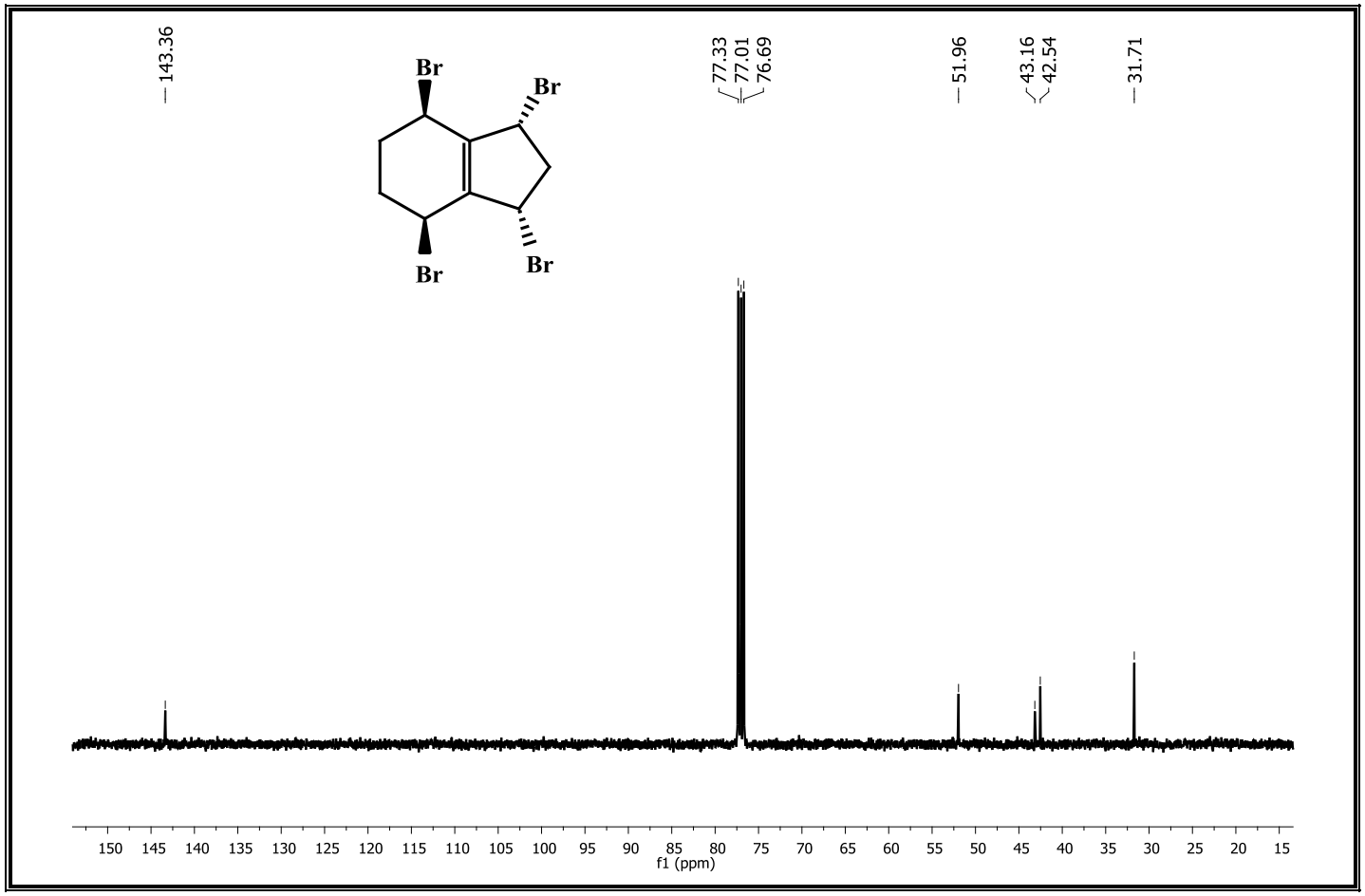

Figure A.12 ^{13}C-NMR spectrum of compound **95**.

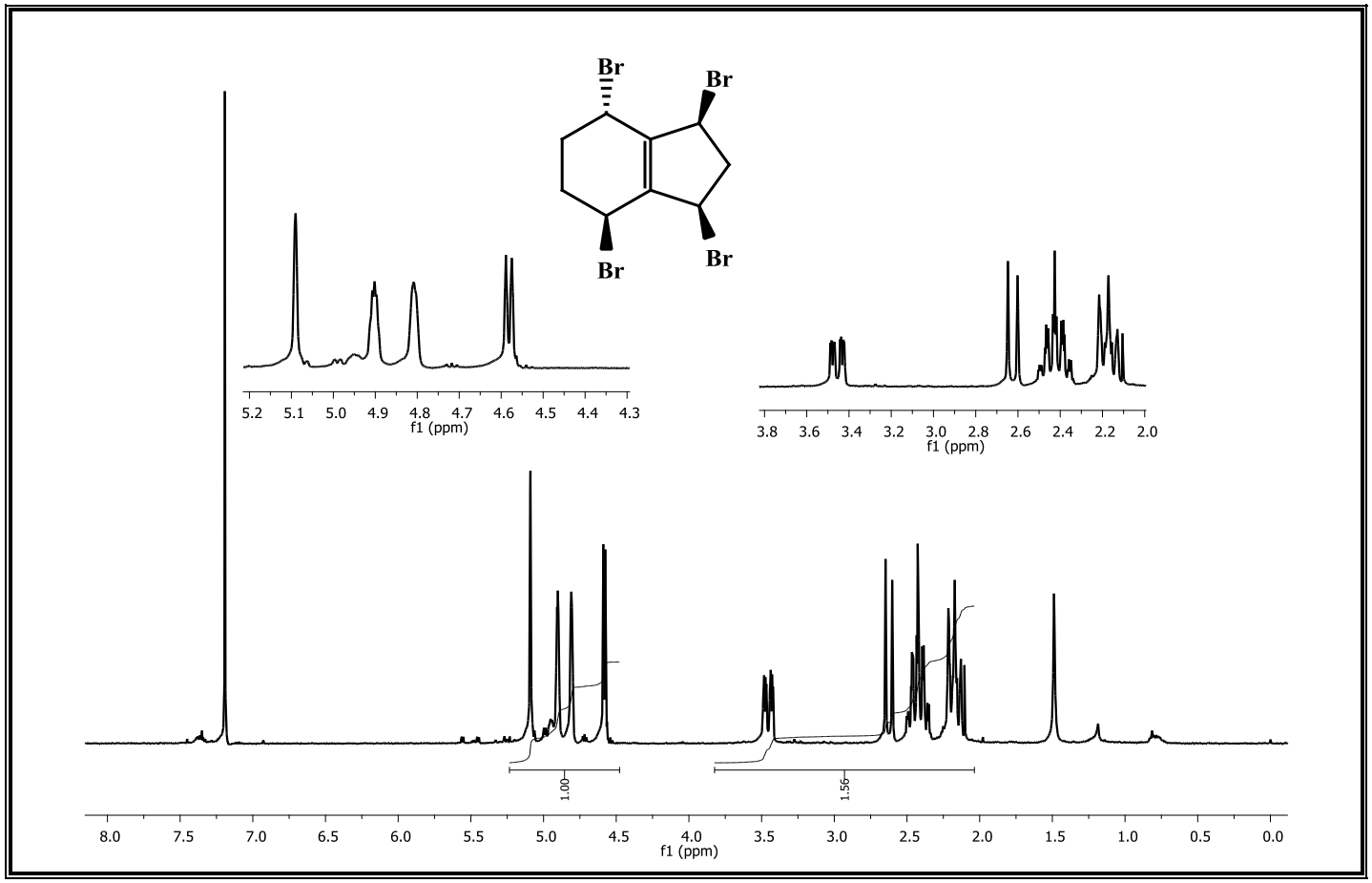

Figure A.13 ^{1}H-NMR spectrum of compound **96**.

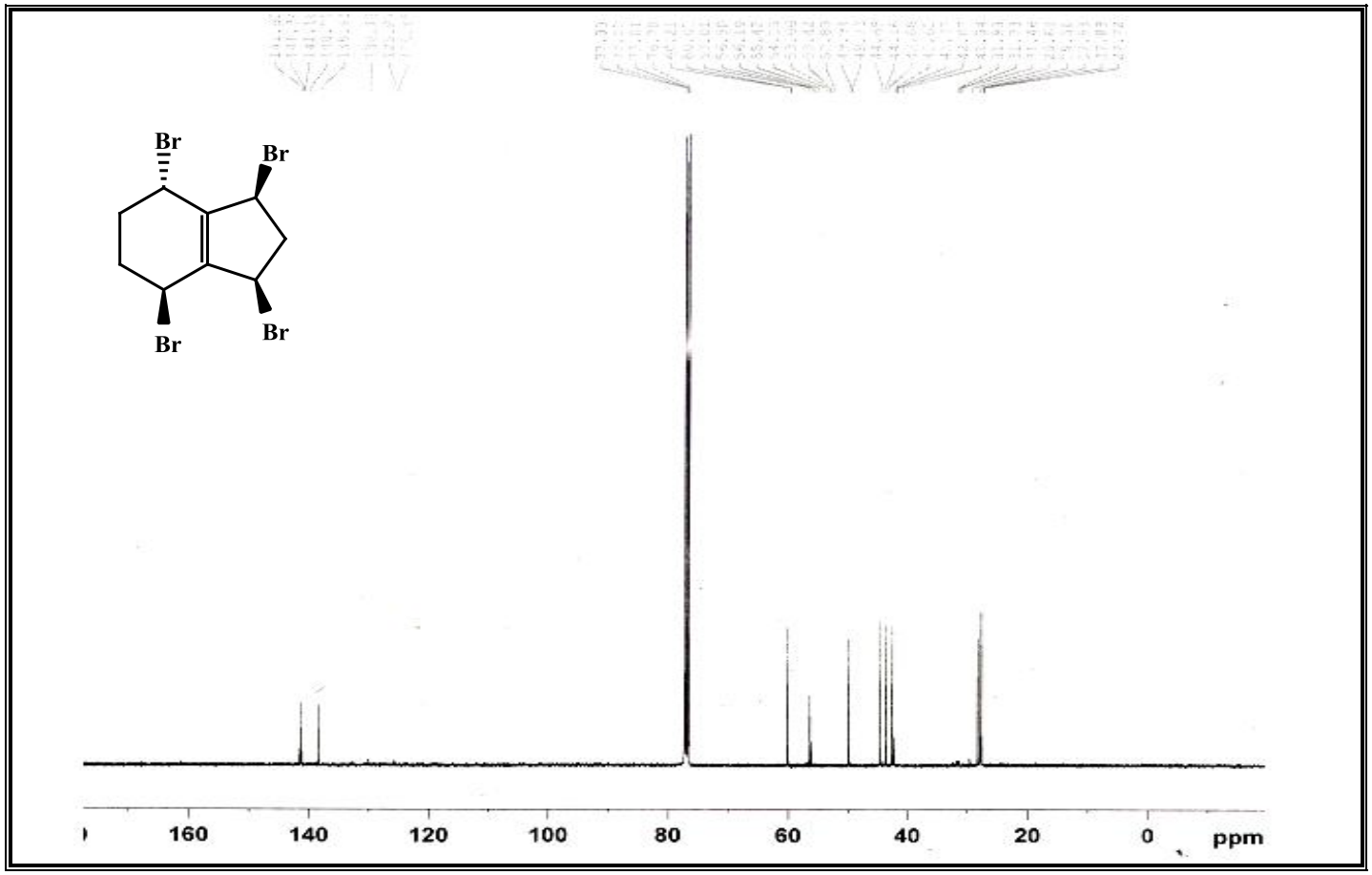

Figure A.14 ^{13}C-NMR spectrum of compound **96**.

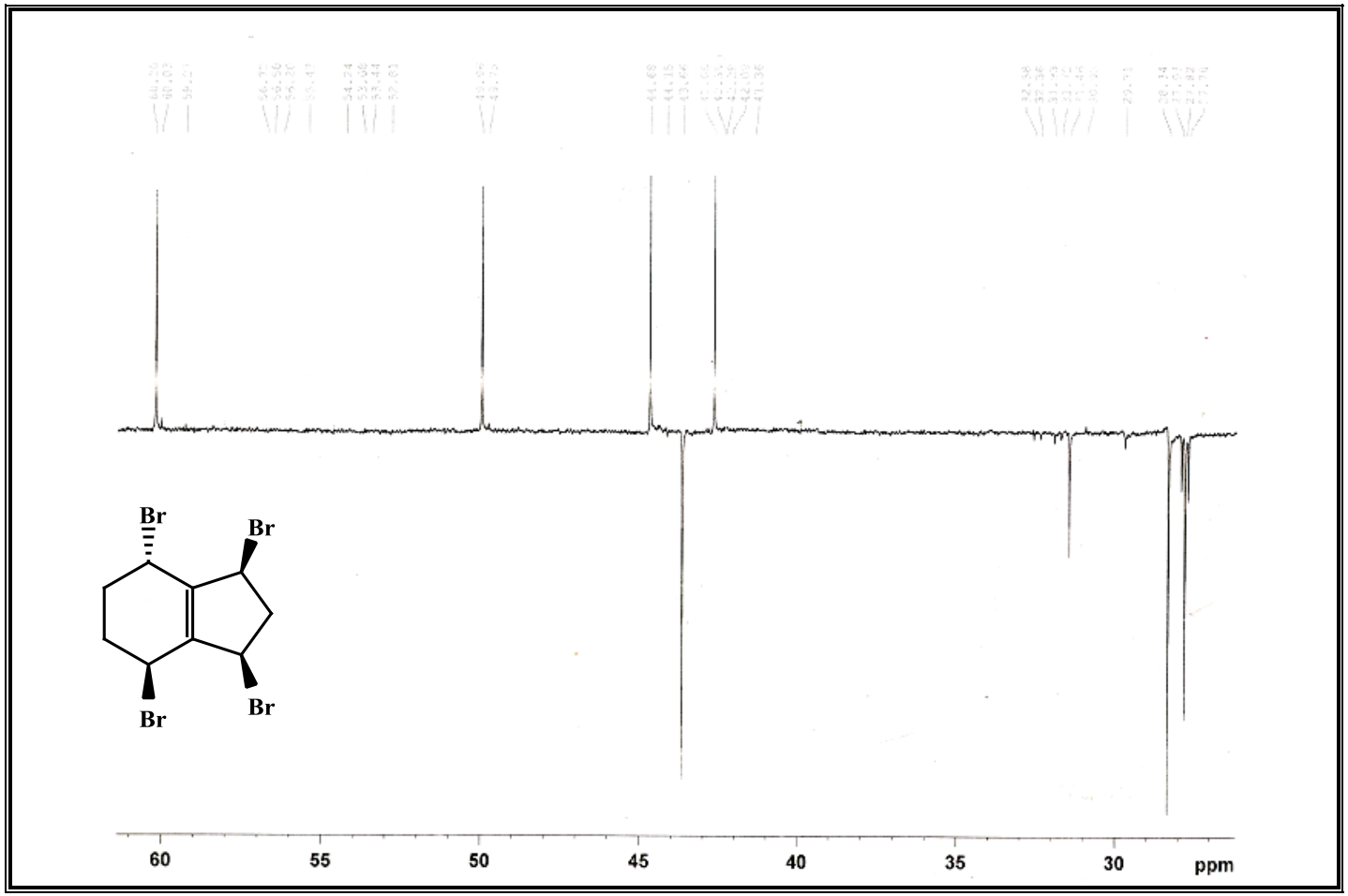

Figure A.15 DEPT-135 Spectrum of Compound **96**.

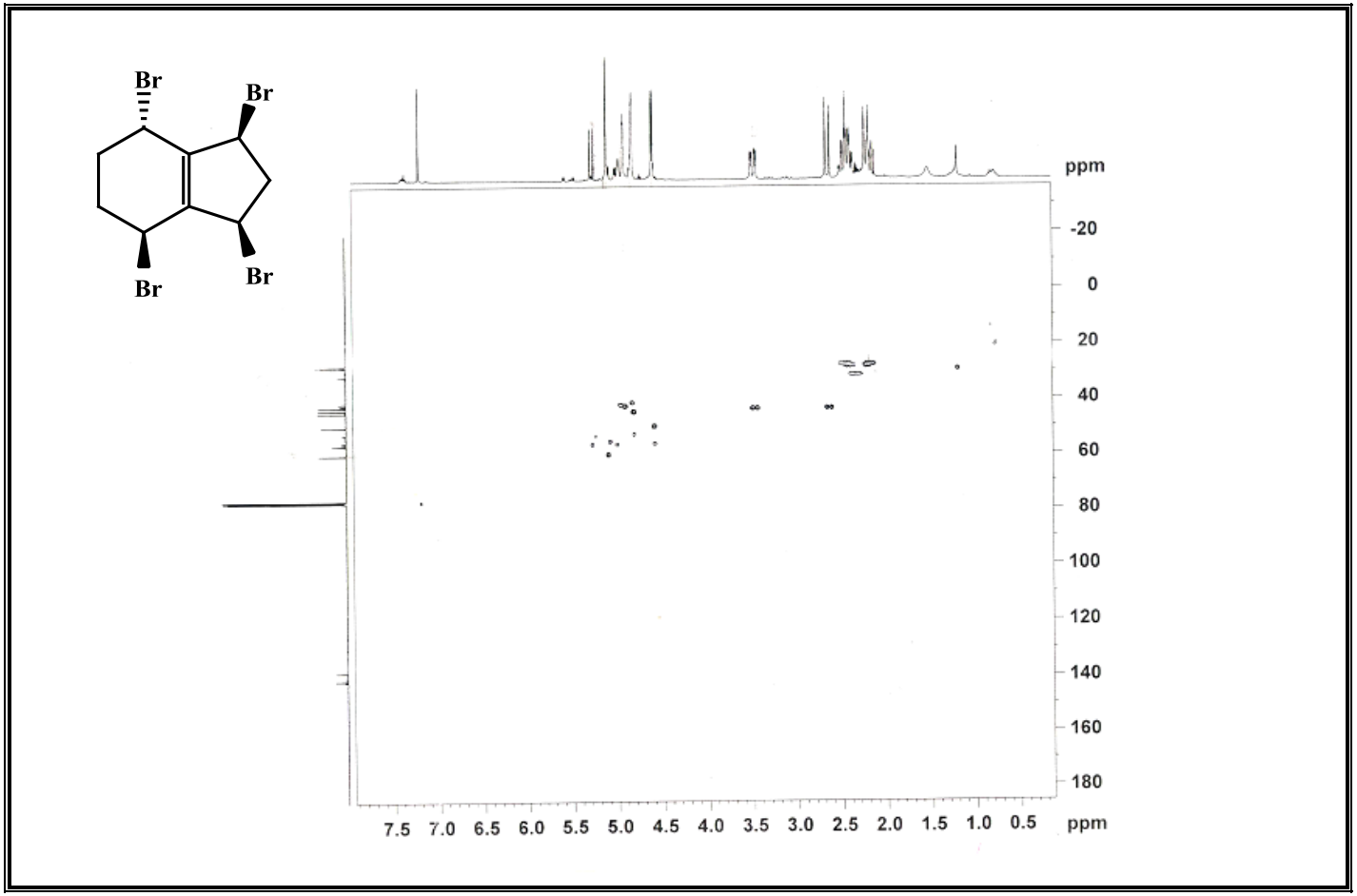

Figure A.16 HSQC Spectrum of Compound **96**.

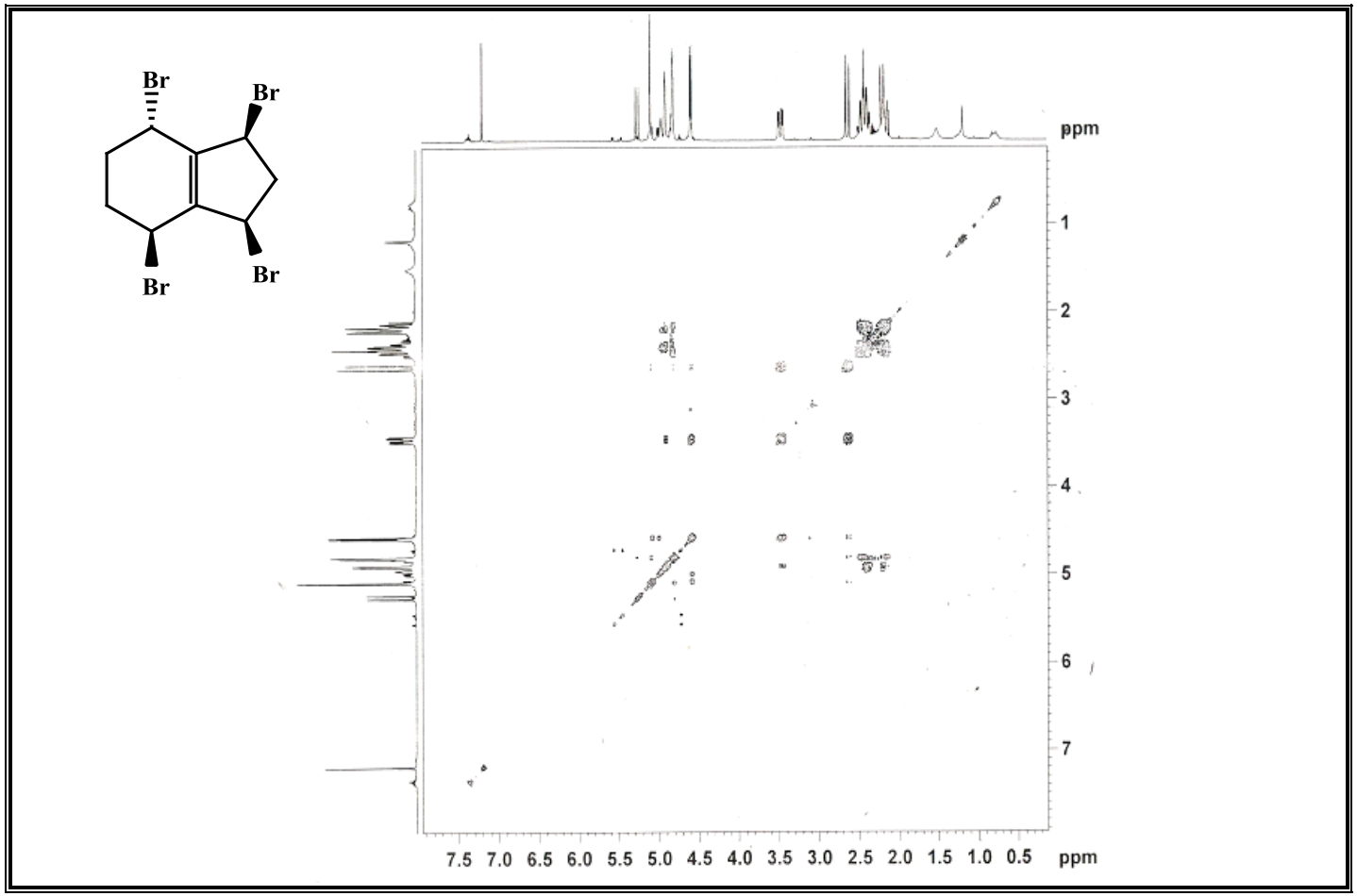

Figure A.17 COSY Spectrum of Compound **96**.

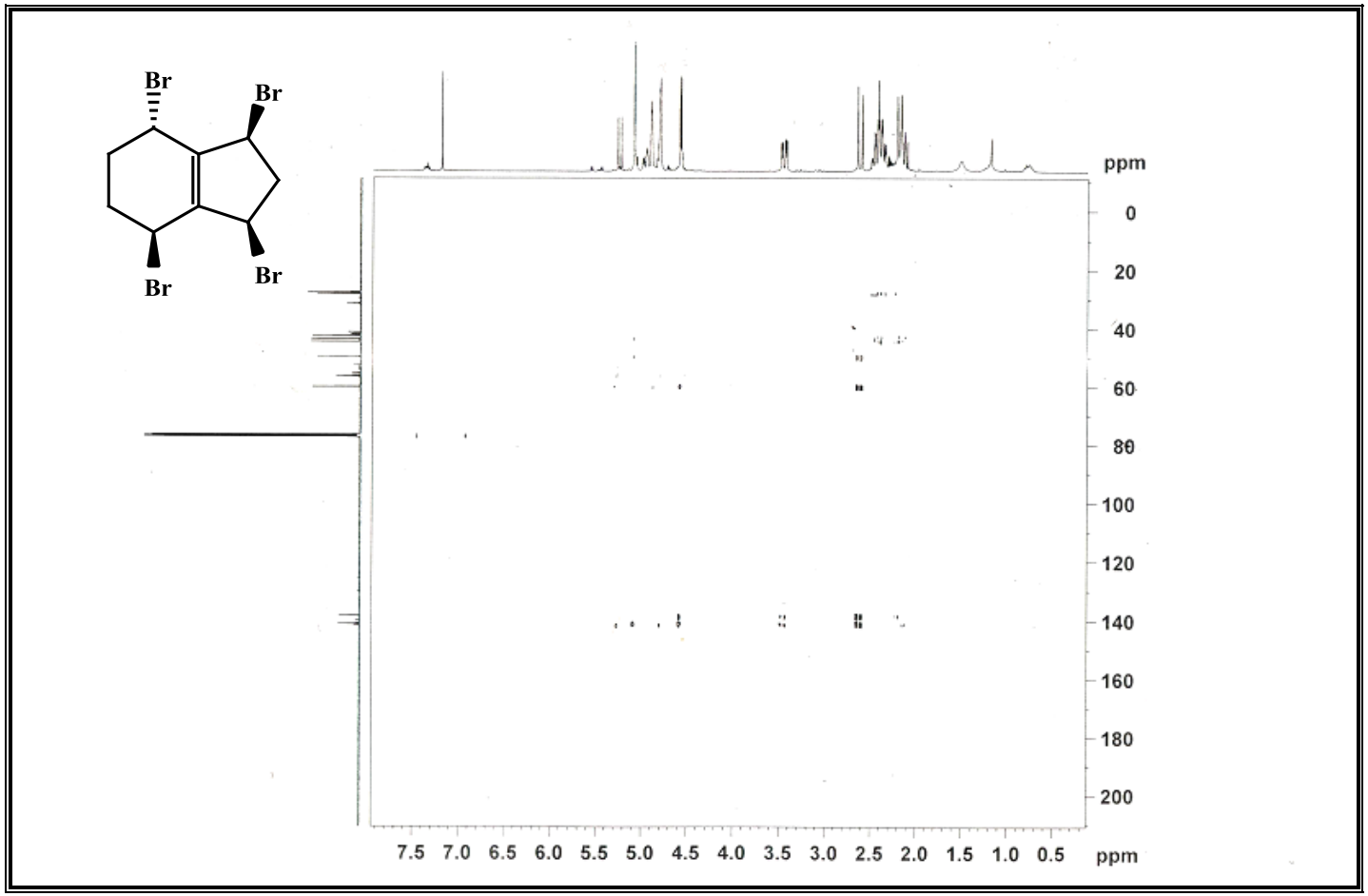

Figure A.18 HMBC Spectrum of Compound **96**.

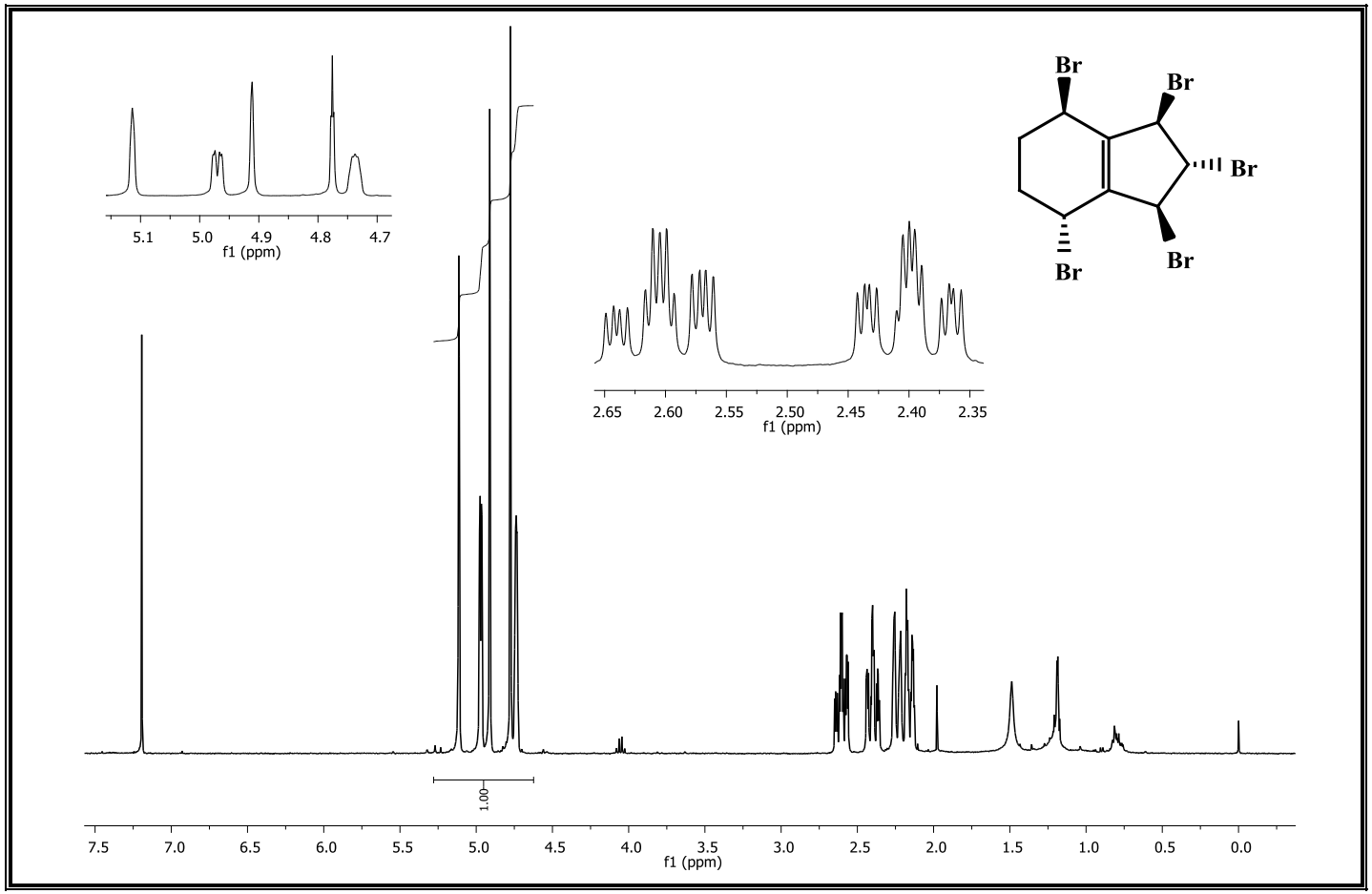

Figure A.19 ^{1}H-NMR spectrum of compound **97**.

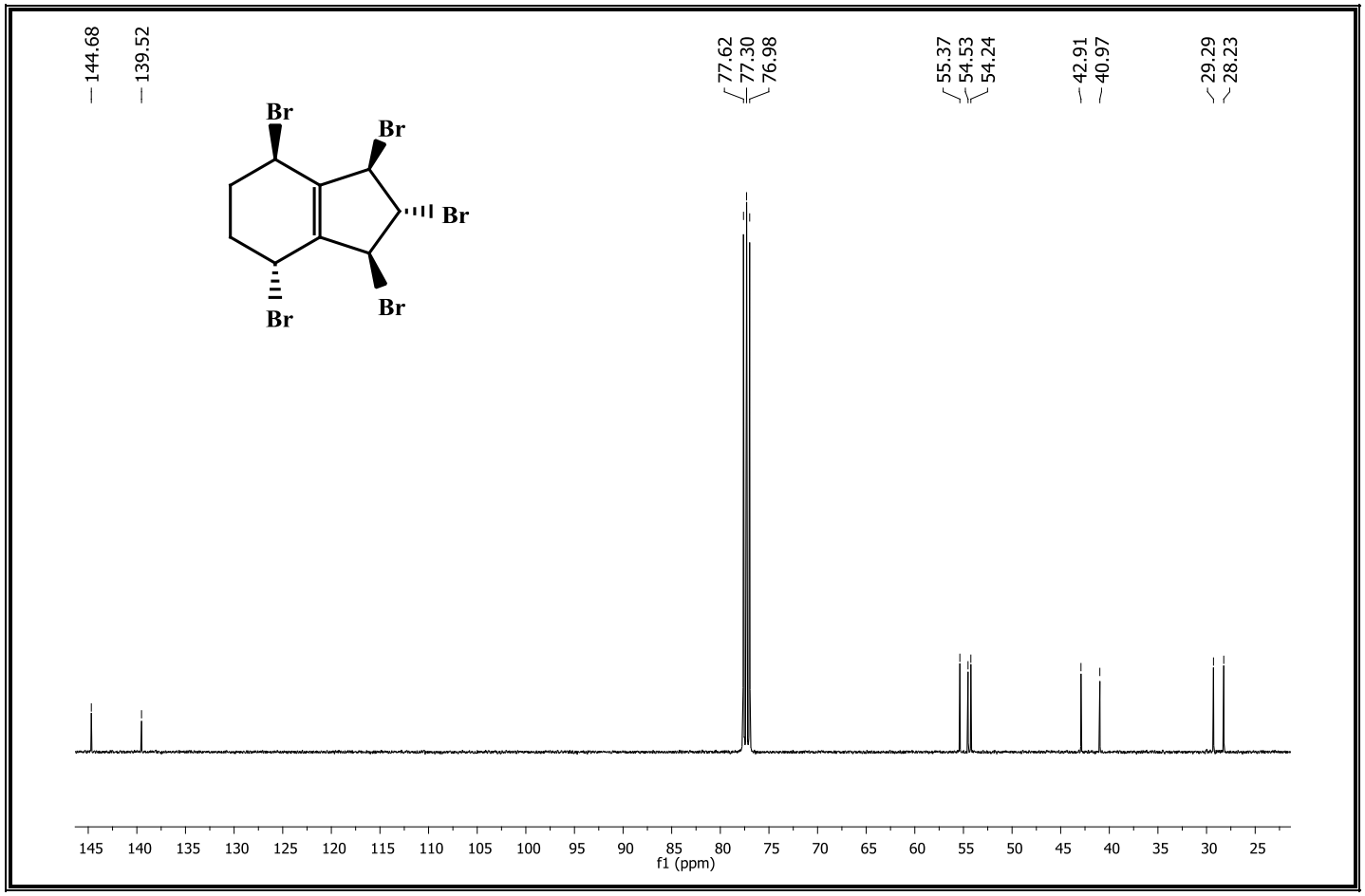

Figure A.20 ^{13}C-NMR spectrum of compound **97**.

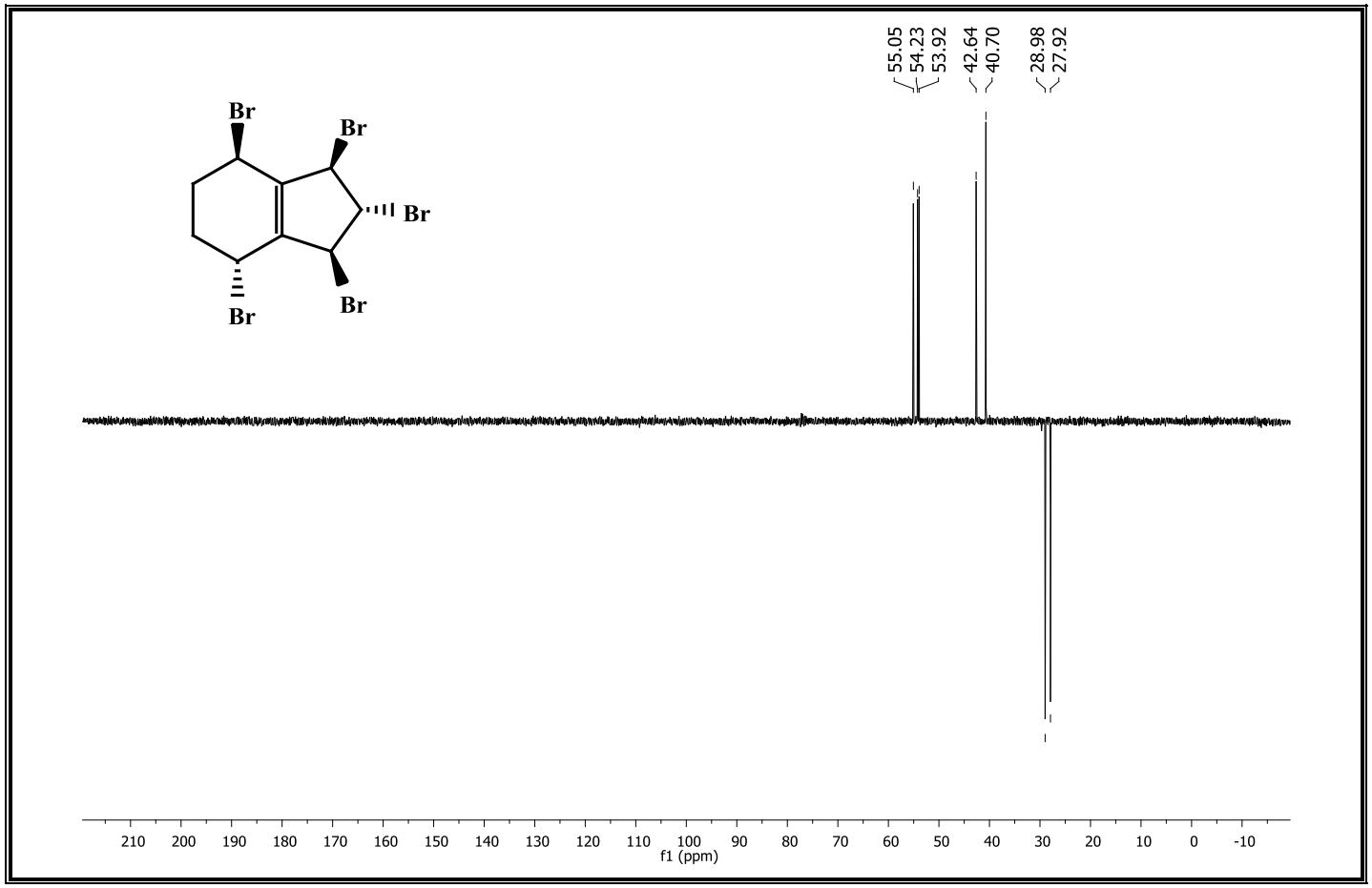

Figure A.21 DEPT-135 spectrum of compound **97**.

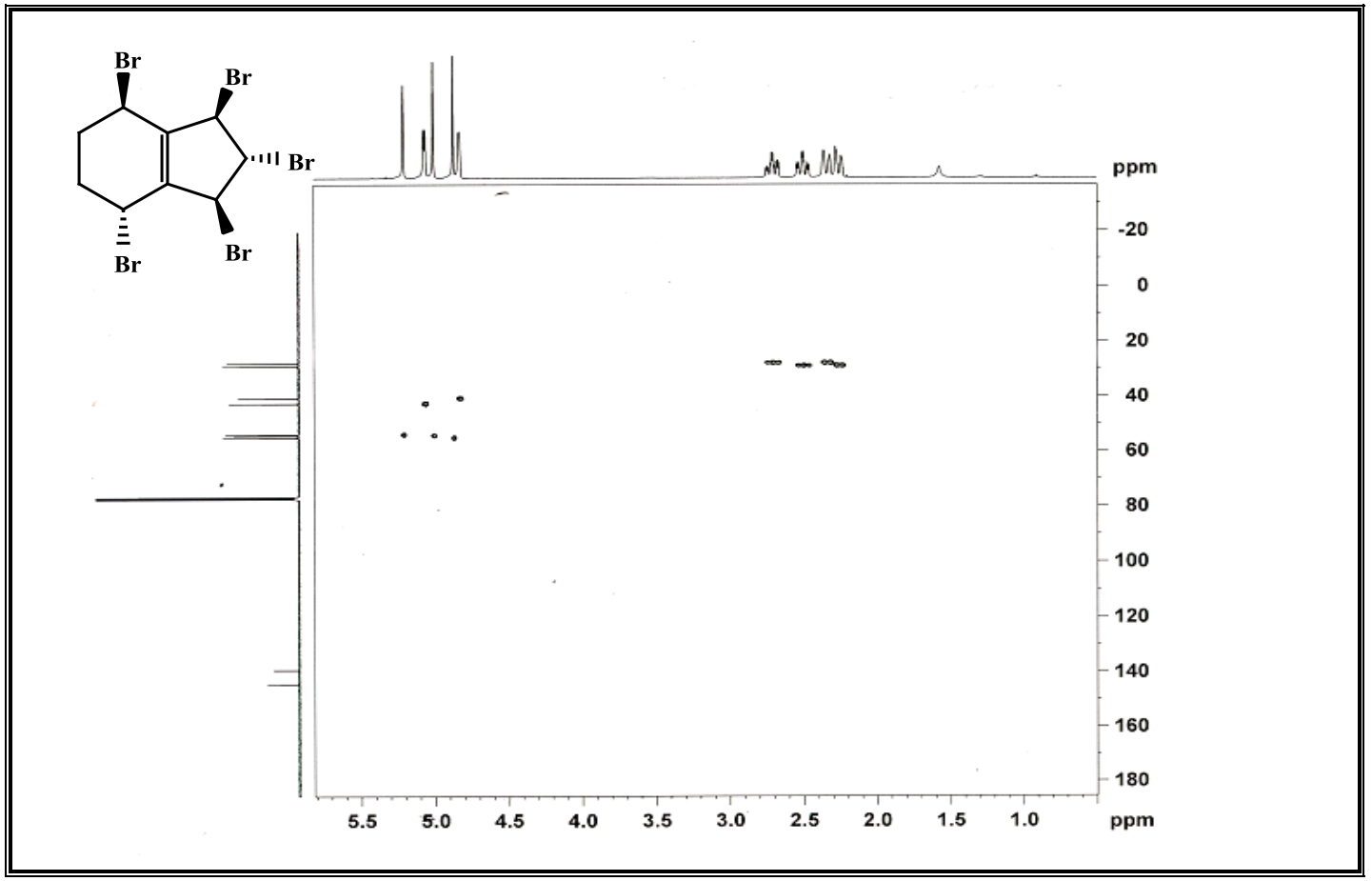

Figure A.22 HSQC spectrum of compound **97**.

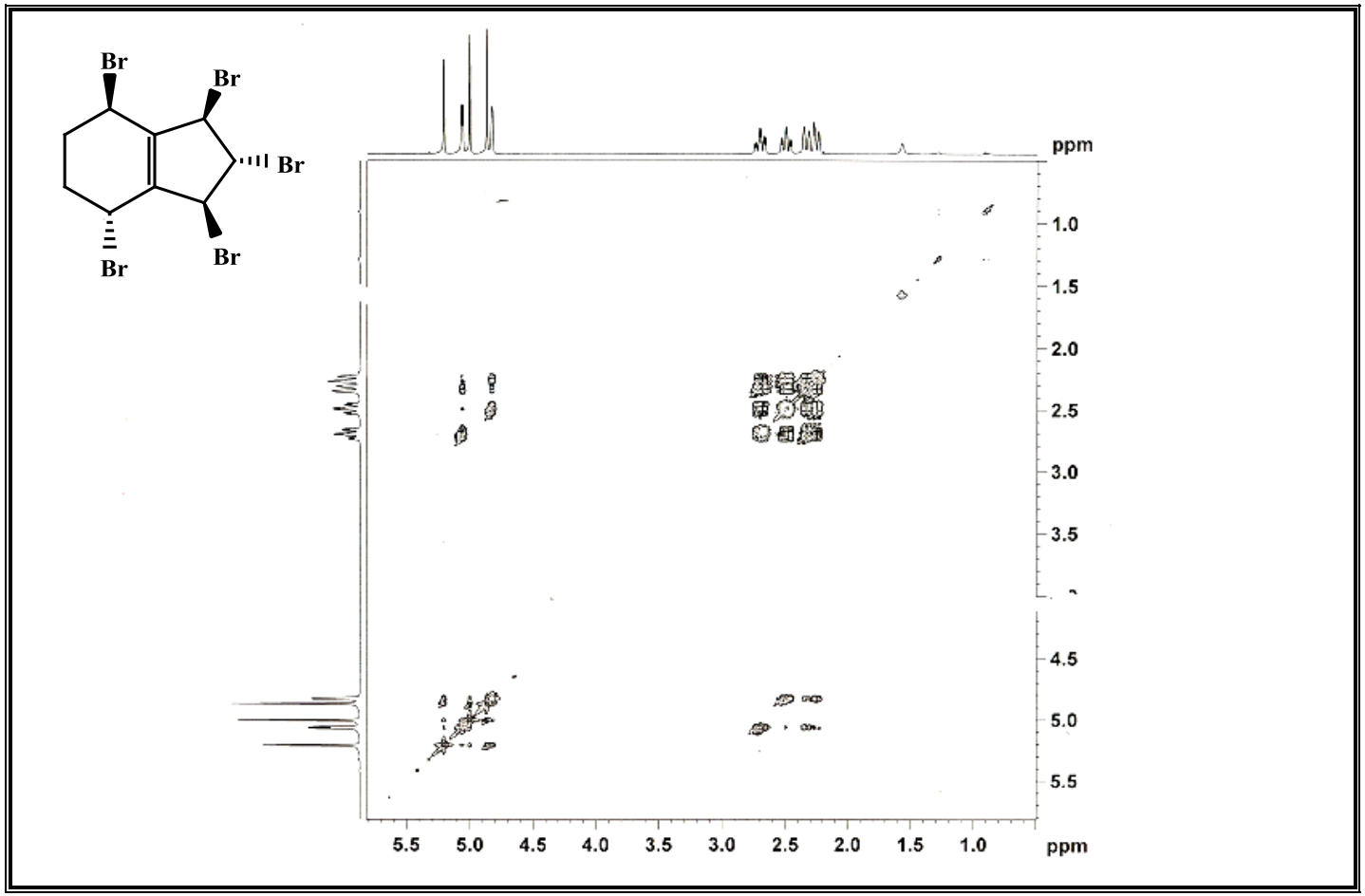

Figure A.23 COSYspectrum of compound **97**.

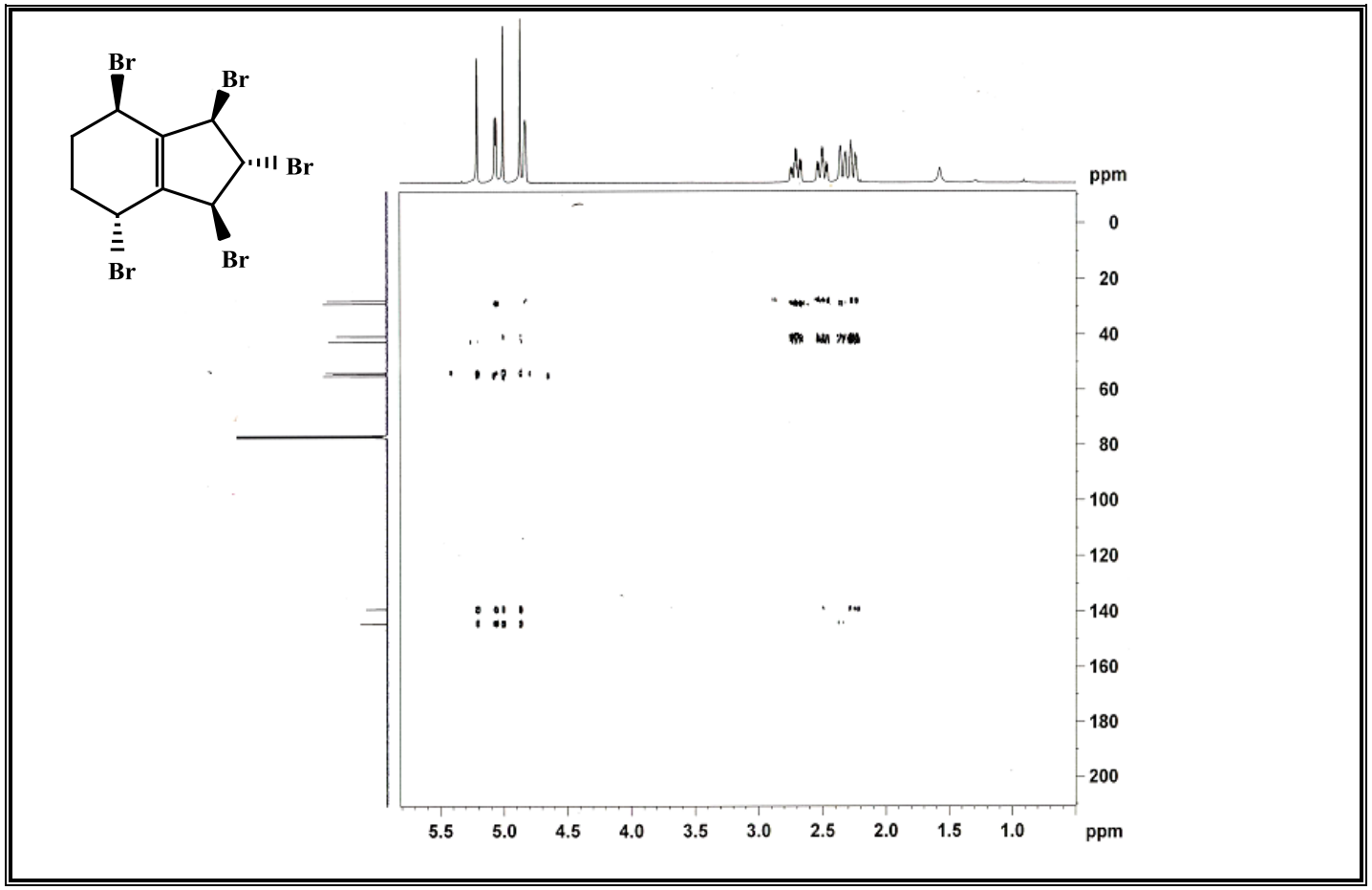

Figure A.24 HMBC spectrum of compound **97**.

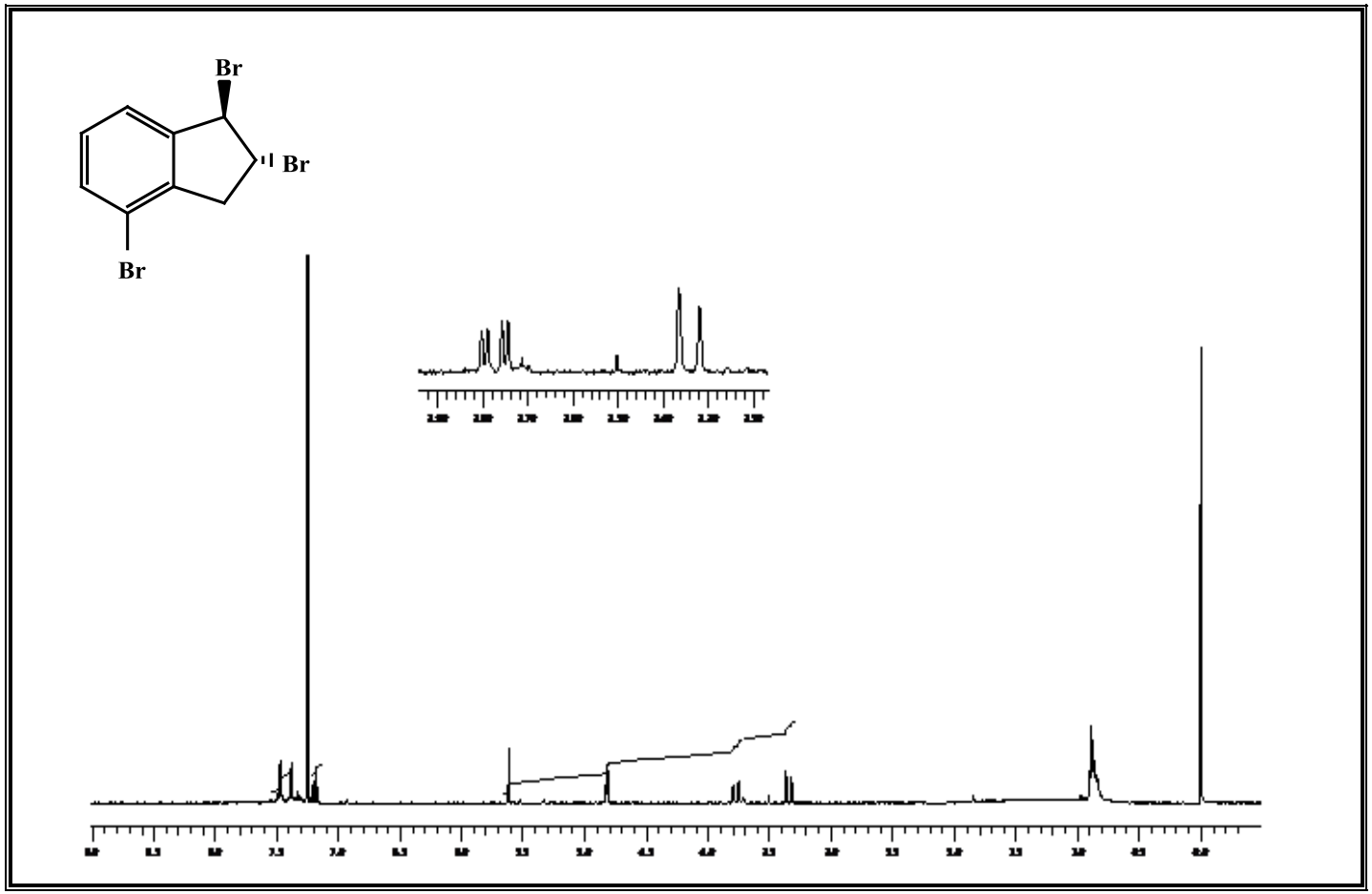

Figure A.25 ^{1}H-NMR spectrum of compound **98**.

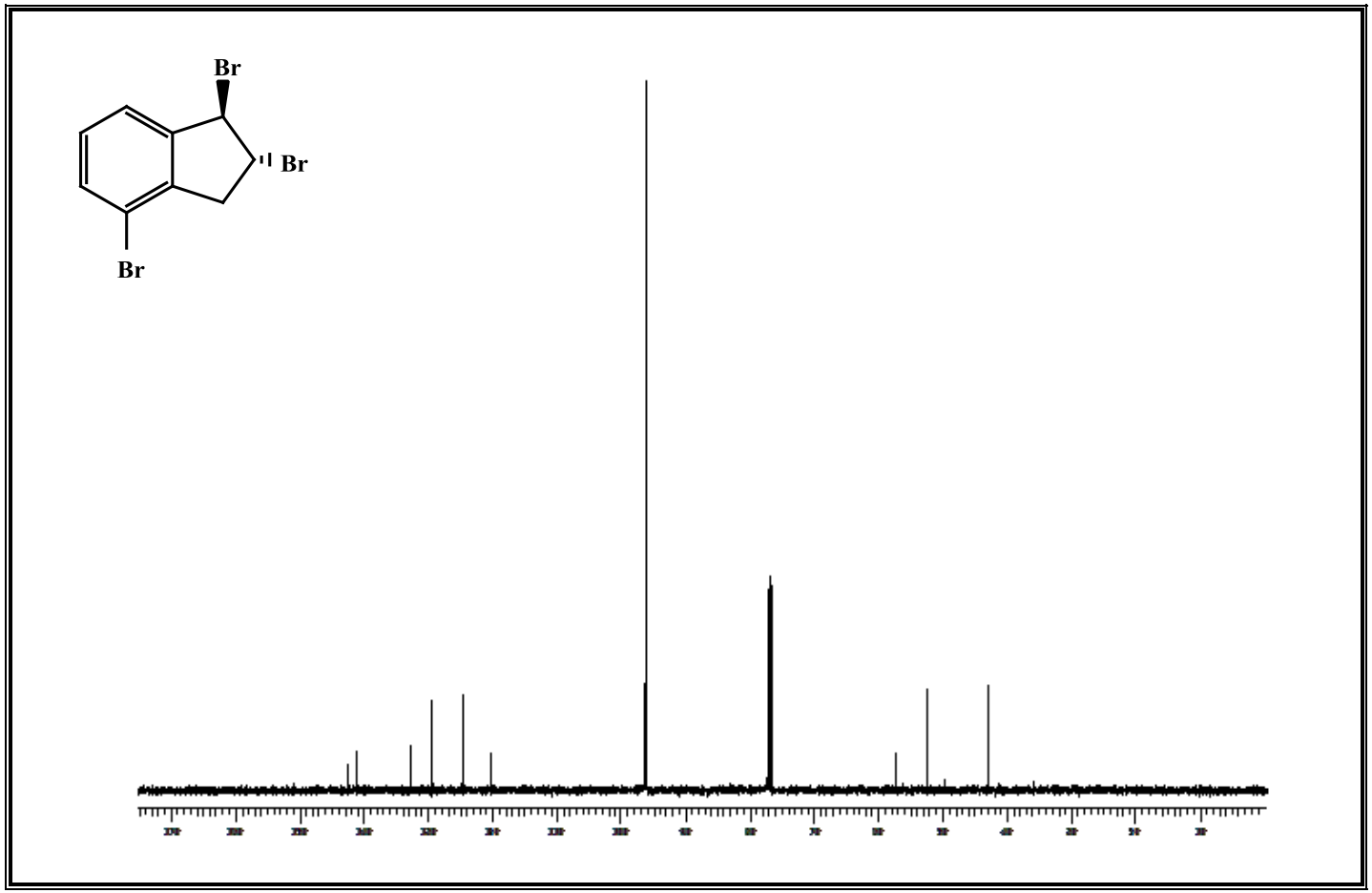

Figure A.26 ^{13}C-NMR spectrum of compound **98**.

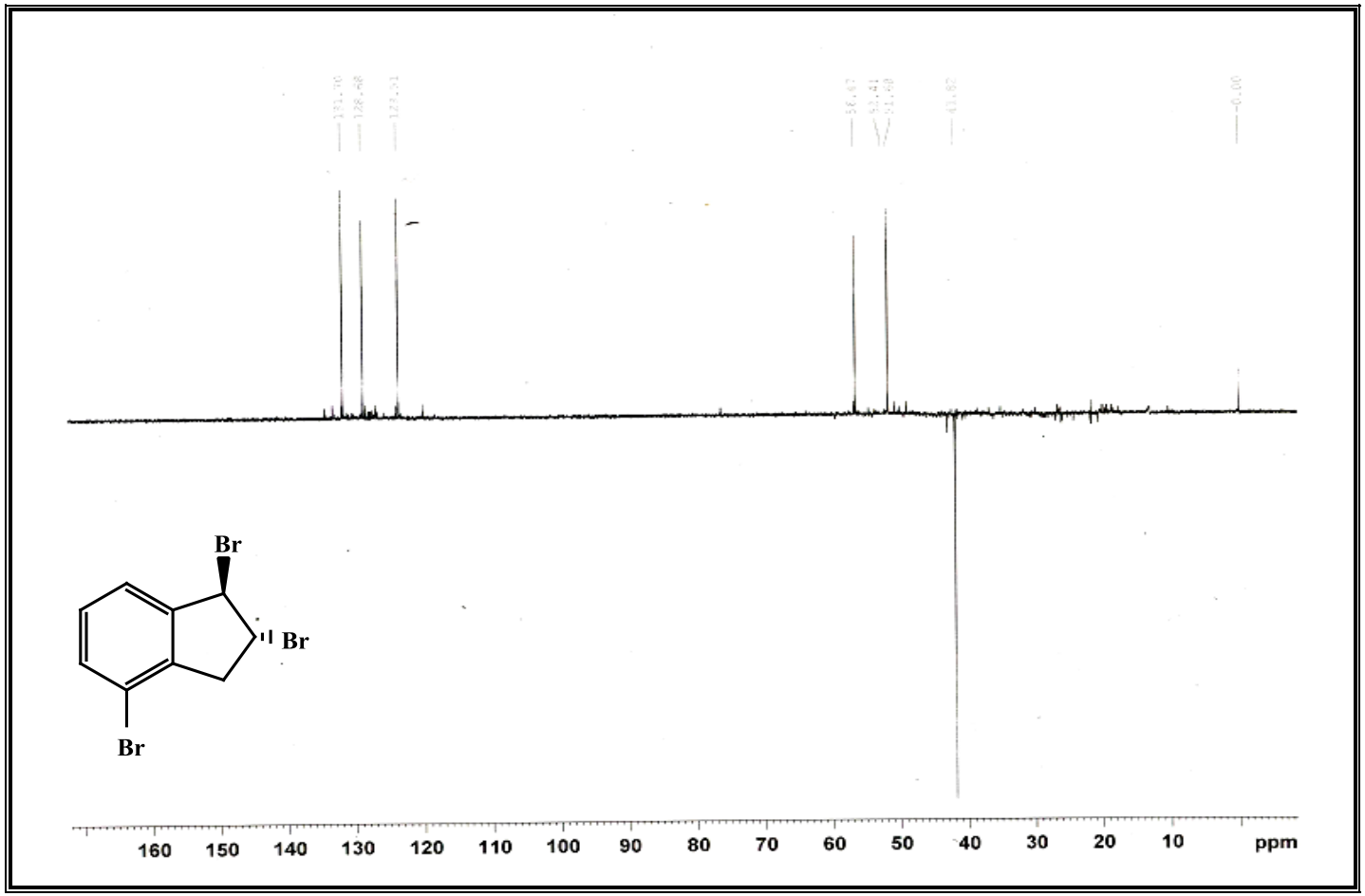

Figure A.27 DEPT-135 spectrum of compound **98**.

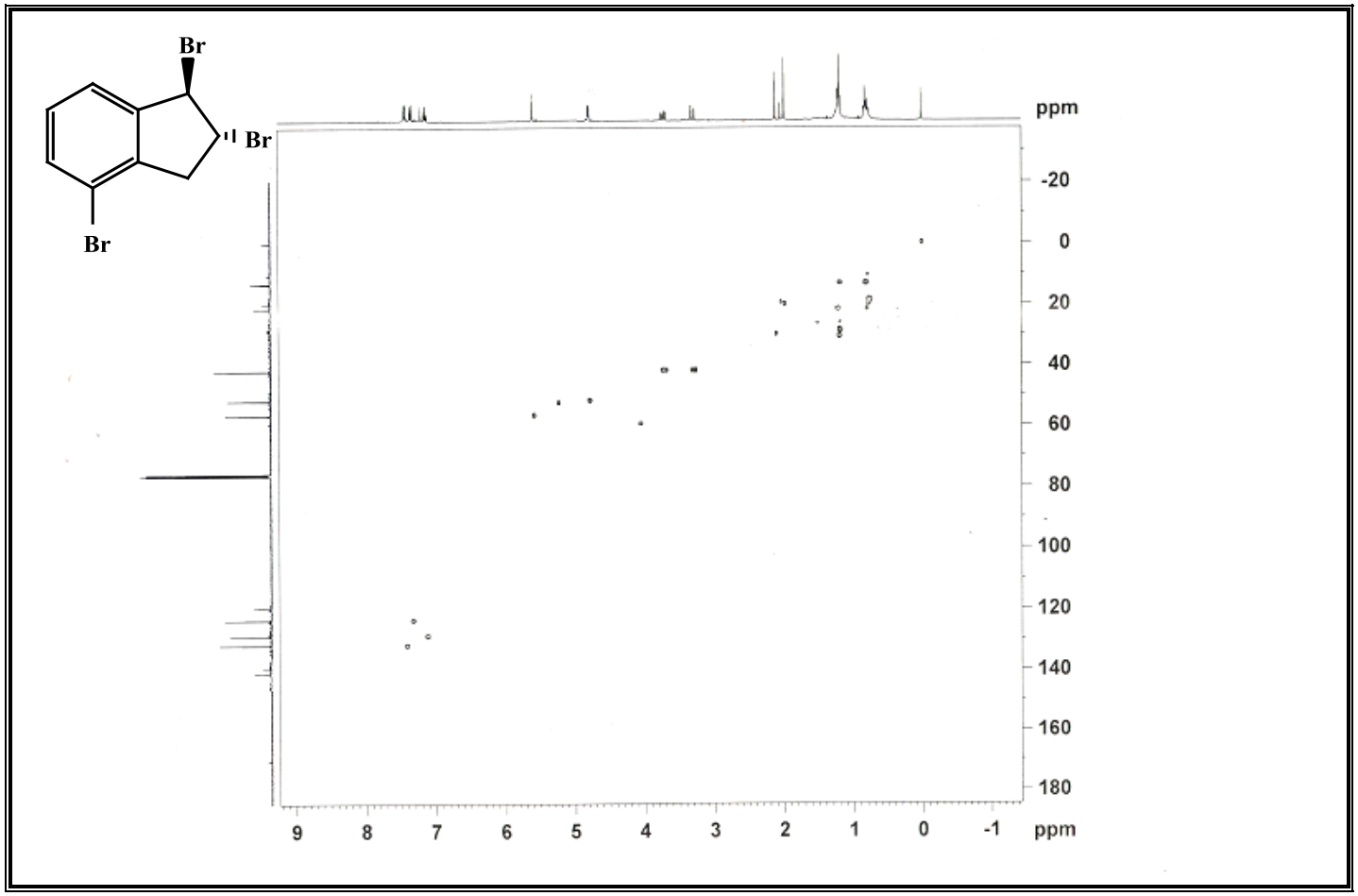

Figure A.28 HSQC spectrum of compound **98**.

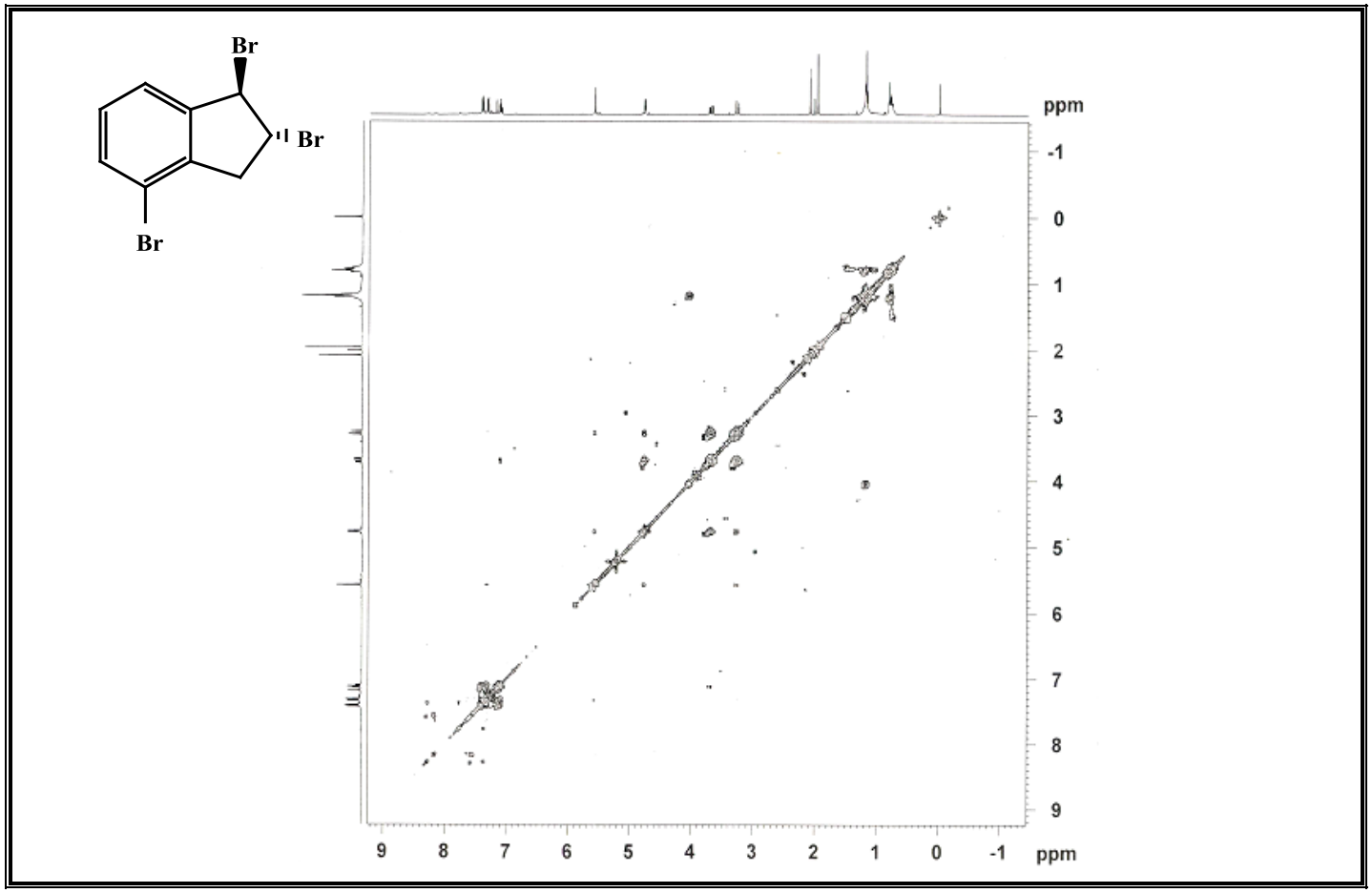

Figure A.29 COSY spectrum of compound **98**.

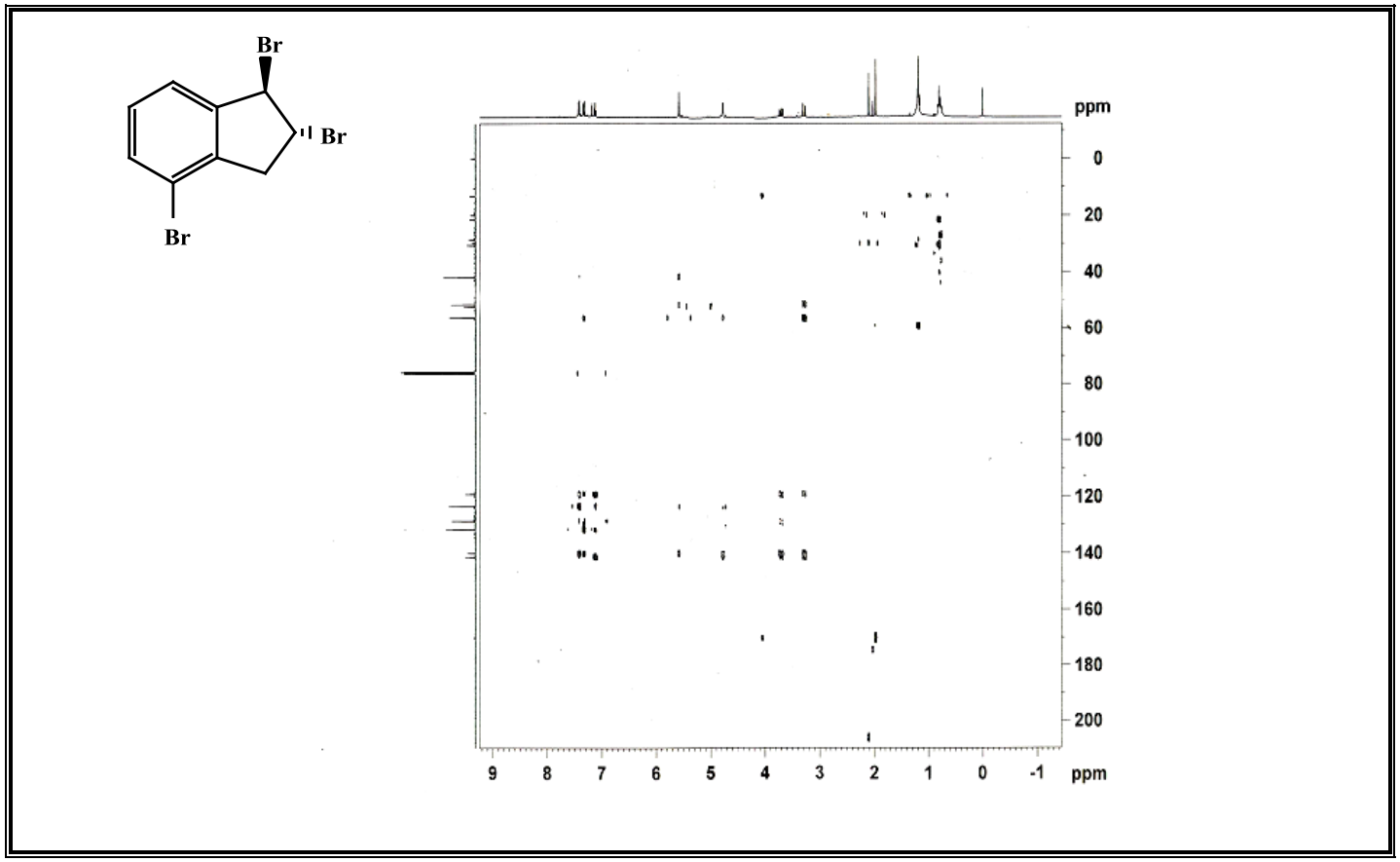

Figure A.30 HMBC spectrum of compound **98**.

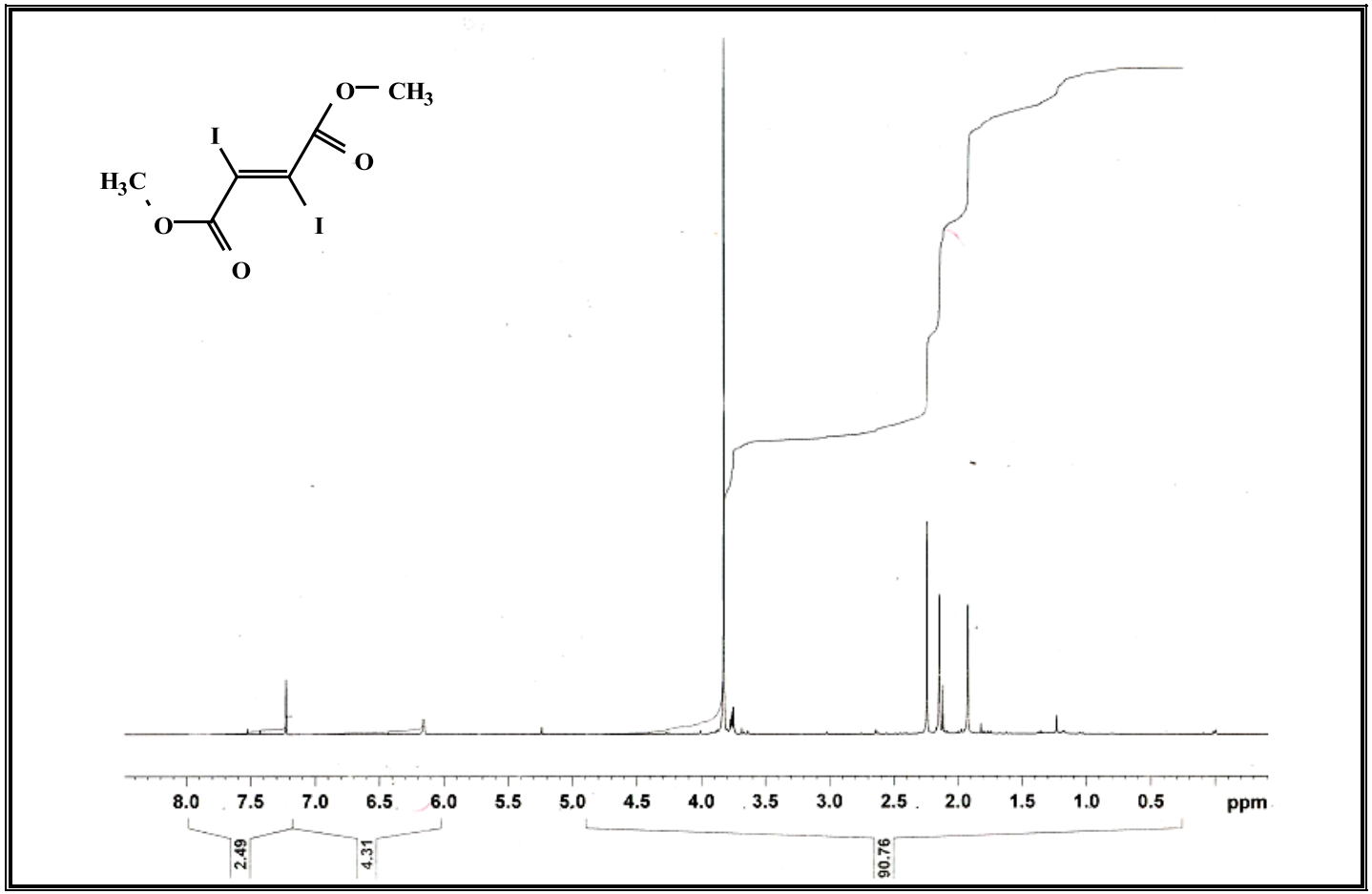

Figure A.31 ^{1}H-NMR spectrum of compound **114**.

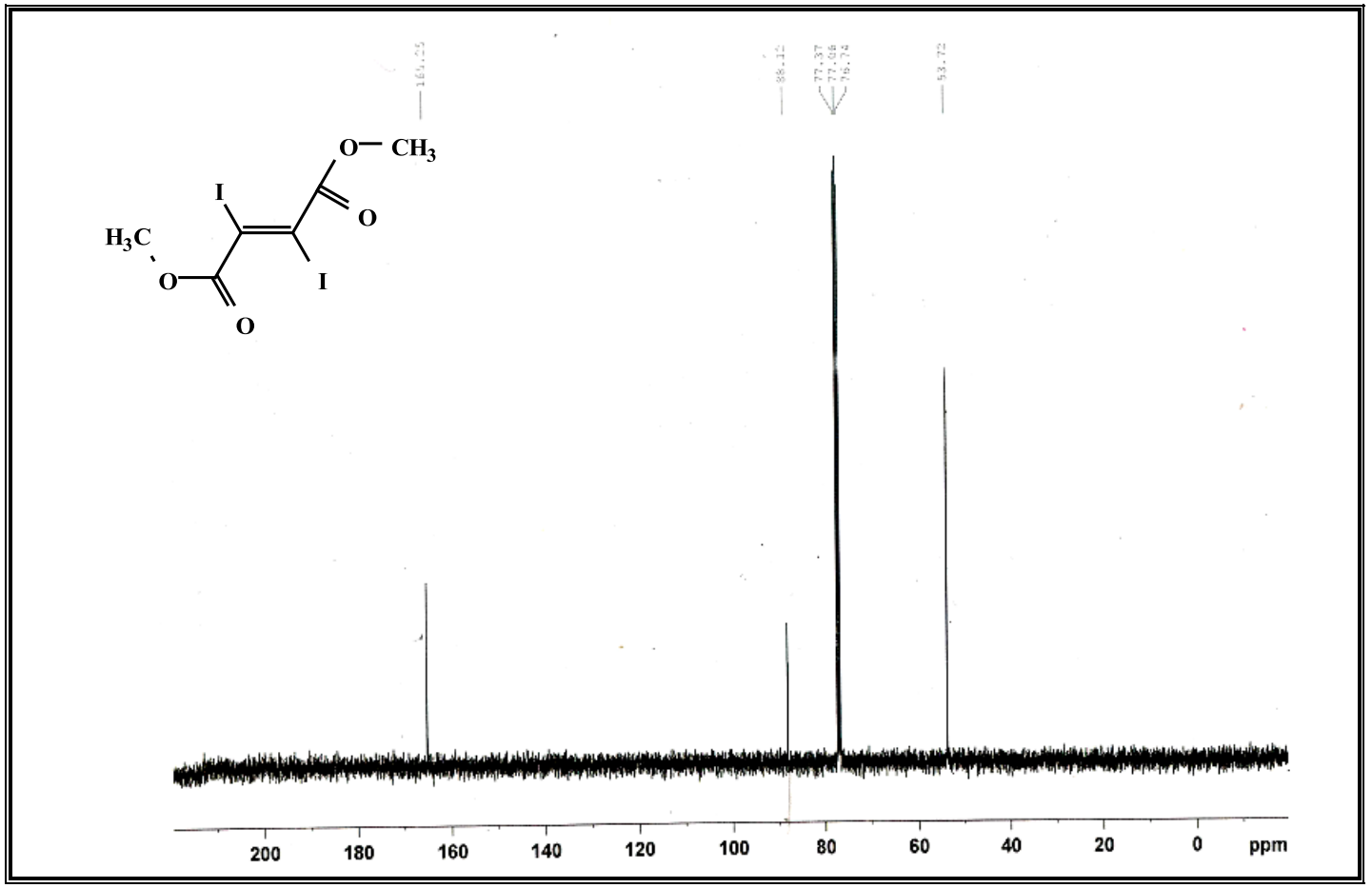

Figure A.32 ^{13}C-NMR spectrum of compound **114**.

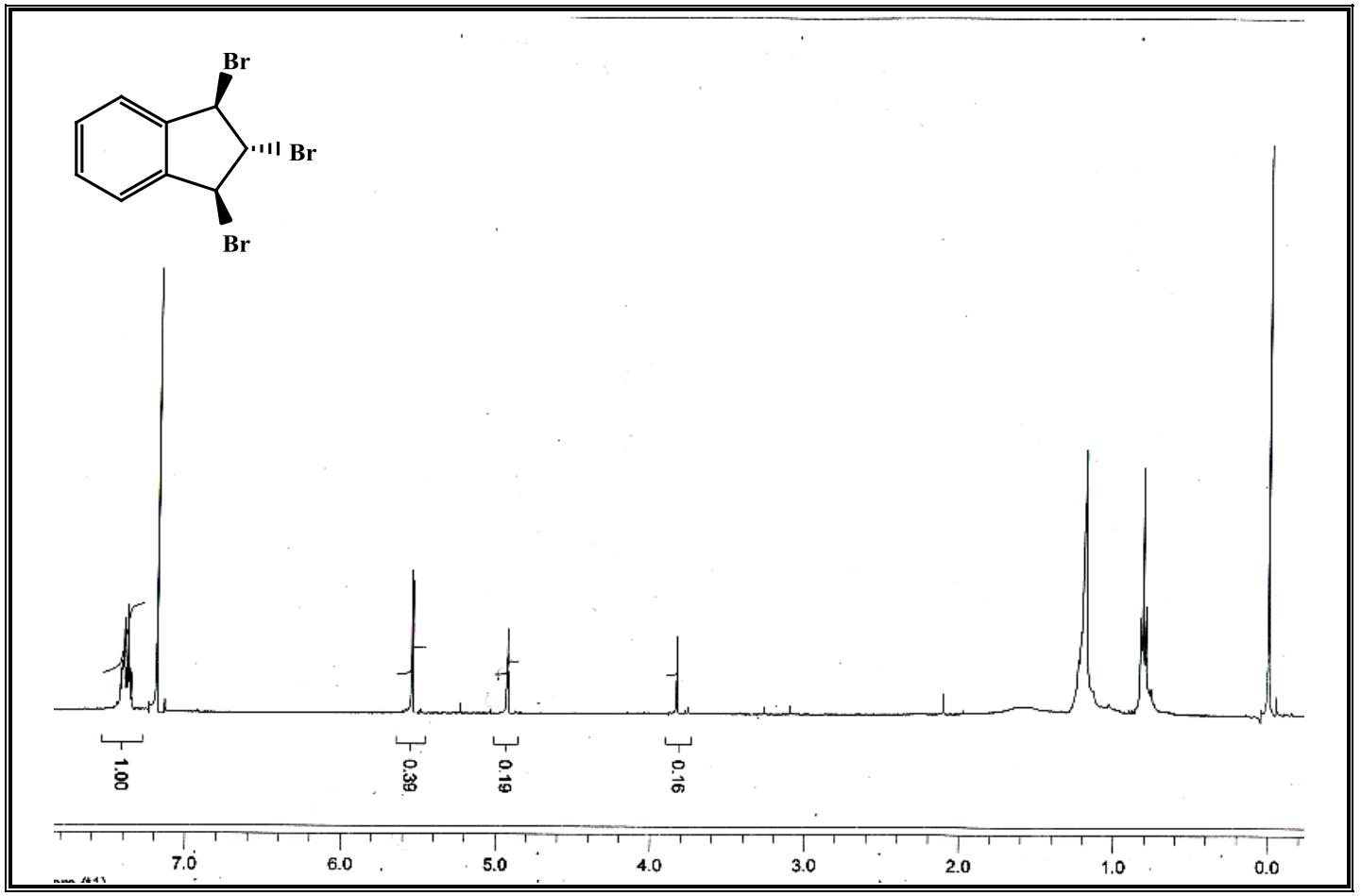

Figure A.33 ^{1}H-NMR spectrum of compound **100**.

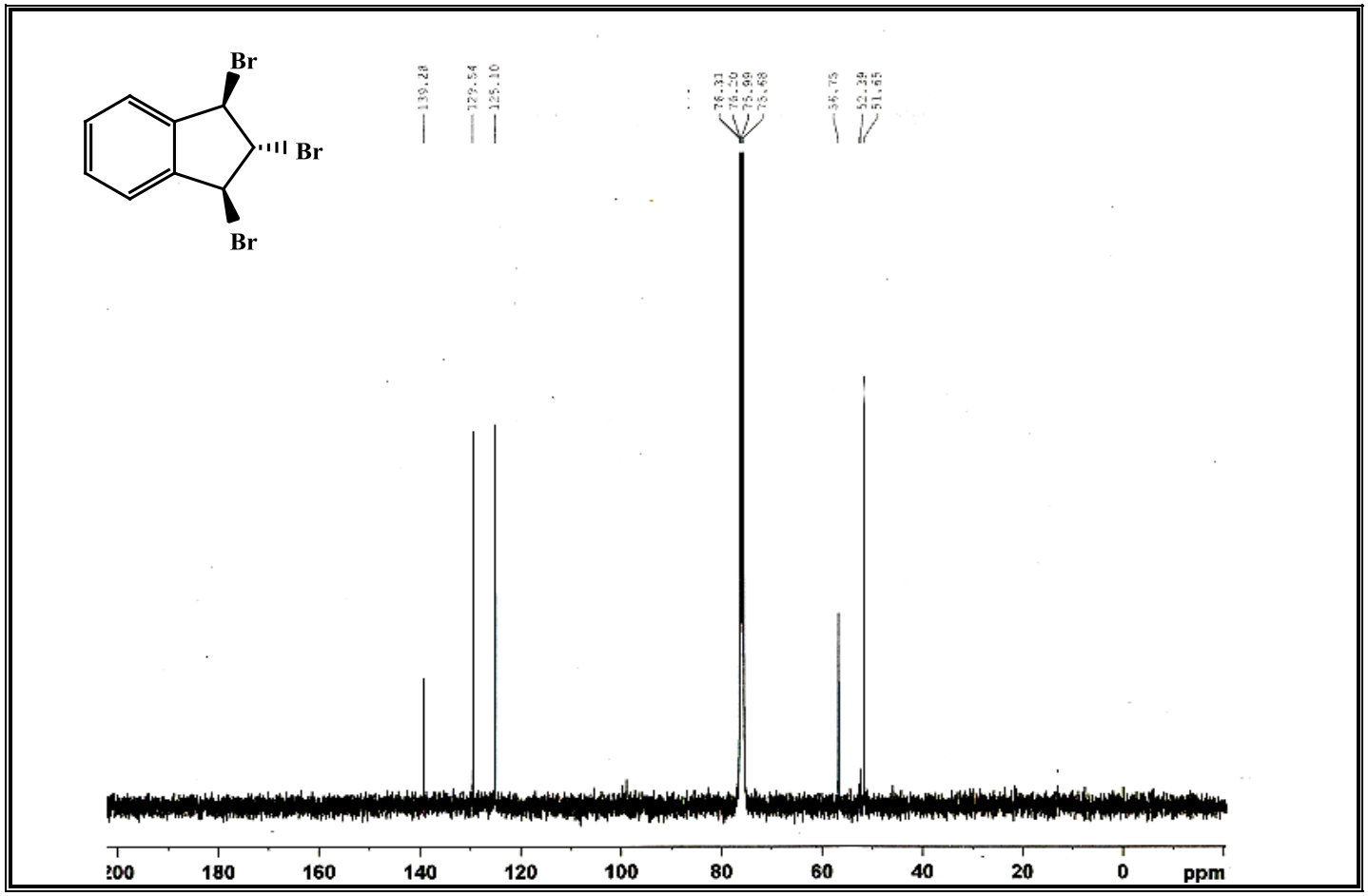

Figure A.34 ^{13}C-NMR spectrum of compound **100**.

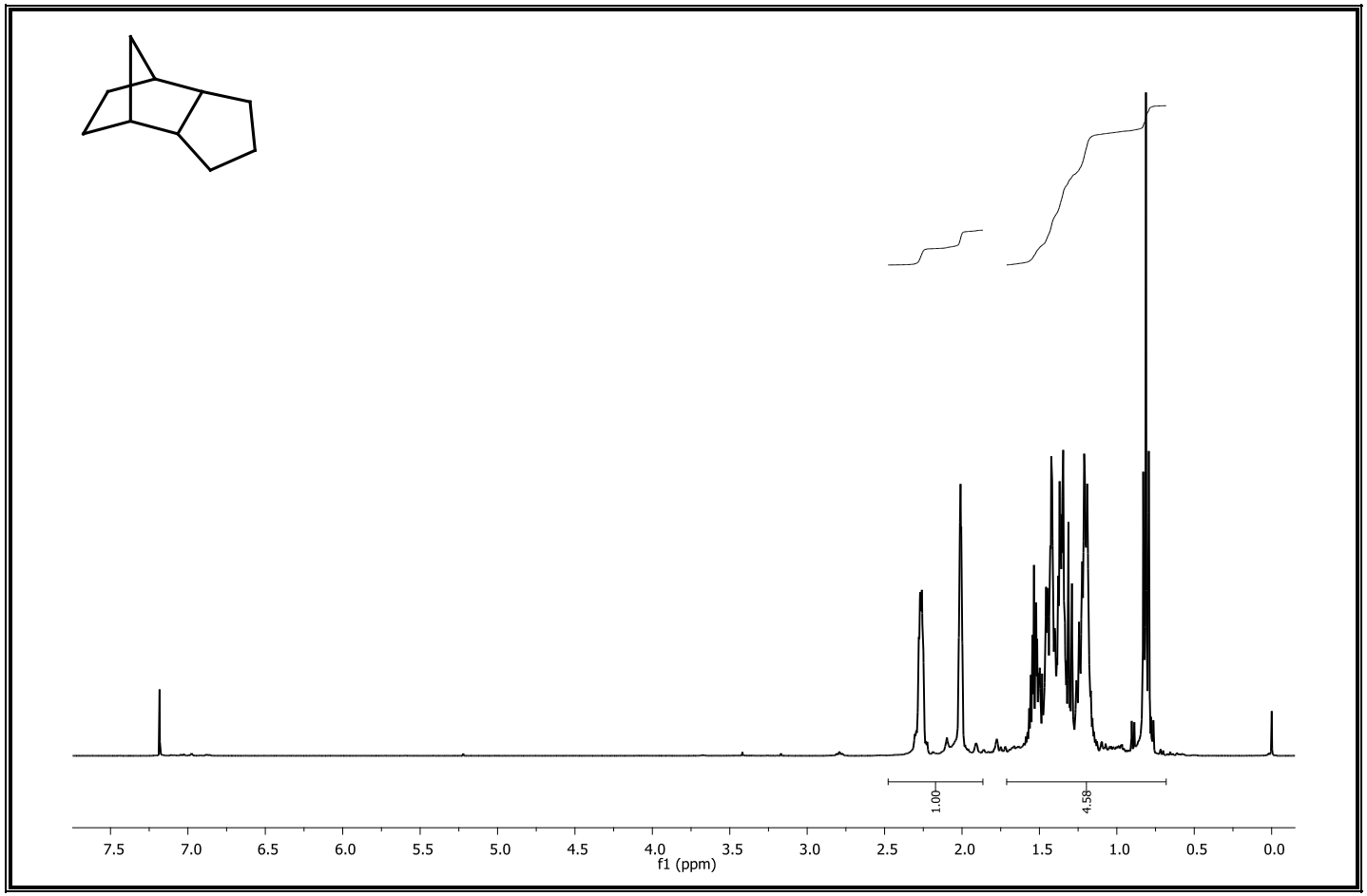

Figure A.35 ^{1}H-NMR spectrum of compound **81**.

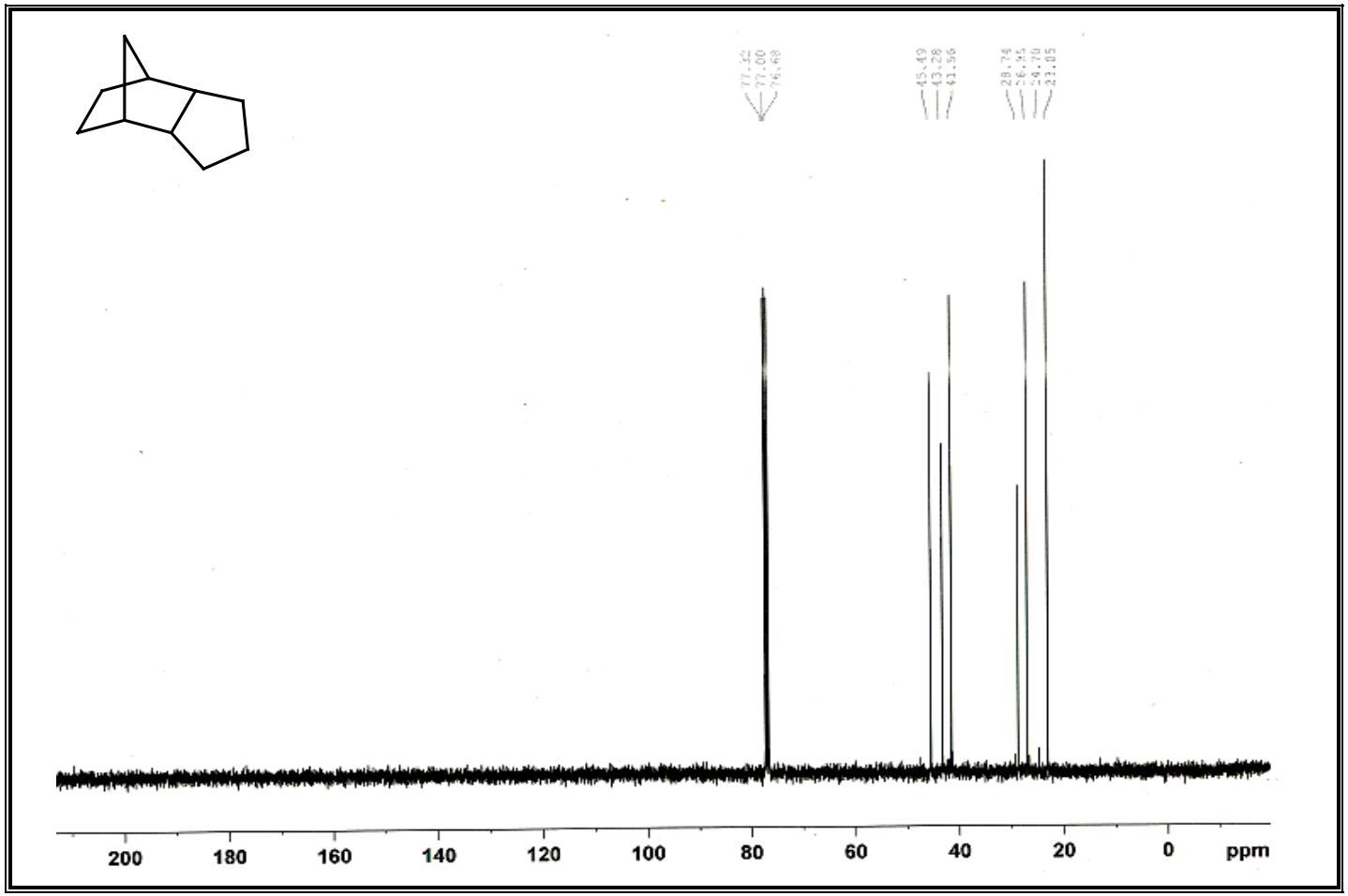

Figure A.36 ^{13}C-NMR spectrum of compound **81**.

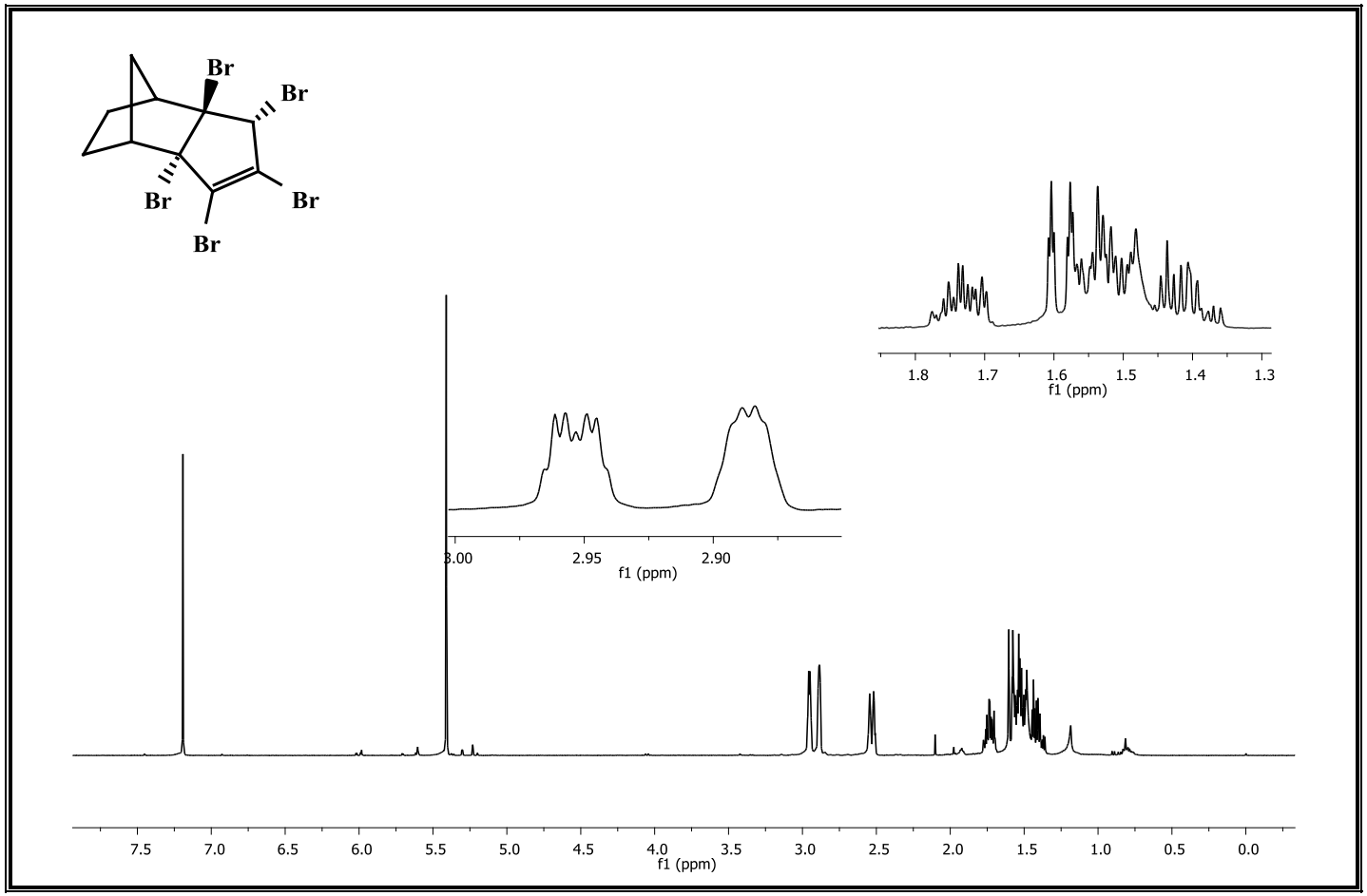

Figure A.37 ^{1}H-NMR spectrum of compound **123**.

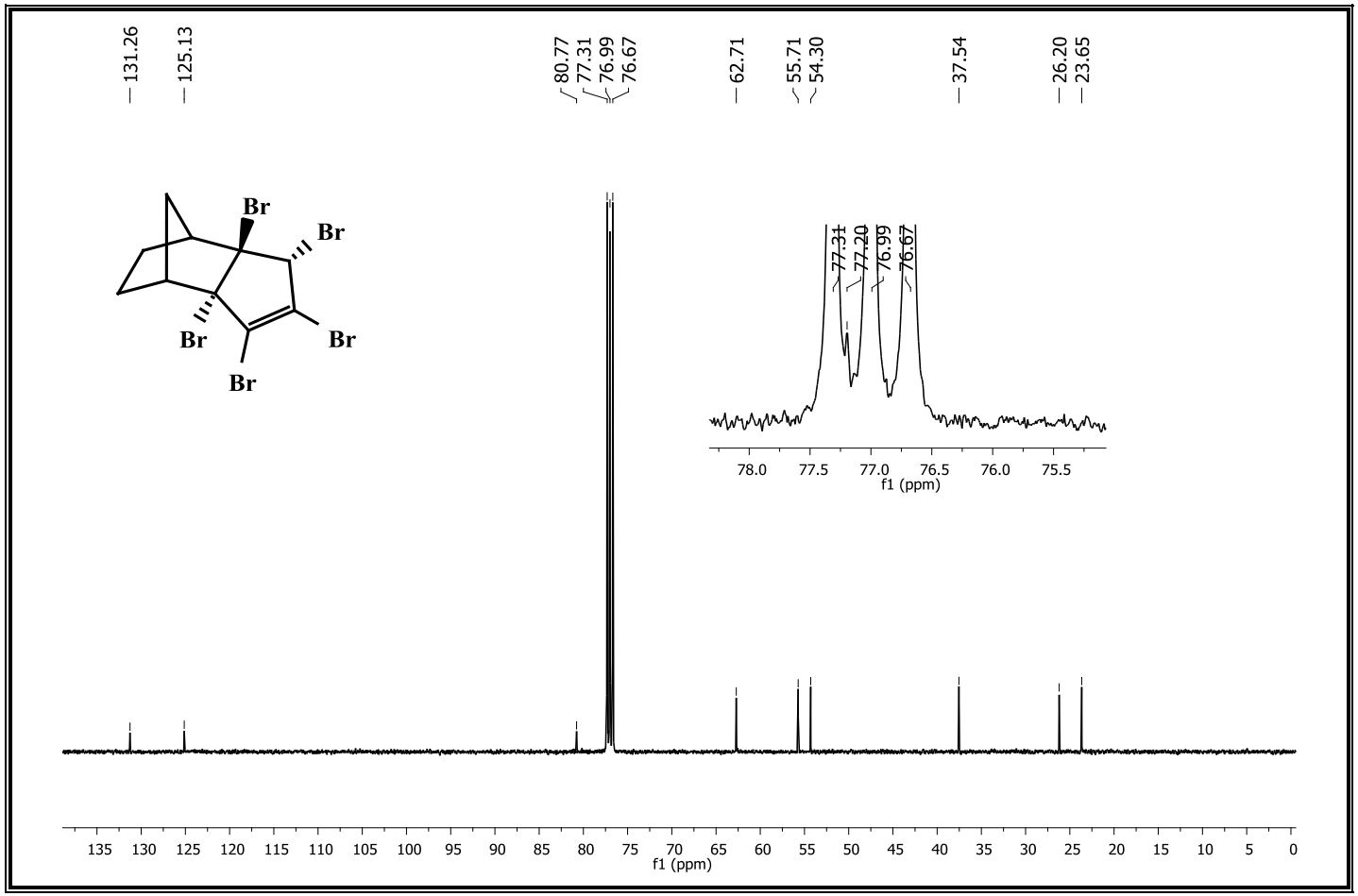

Figure A.38 ^{13}C-NMR spectrum of compound **123**.

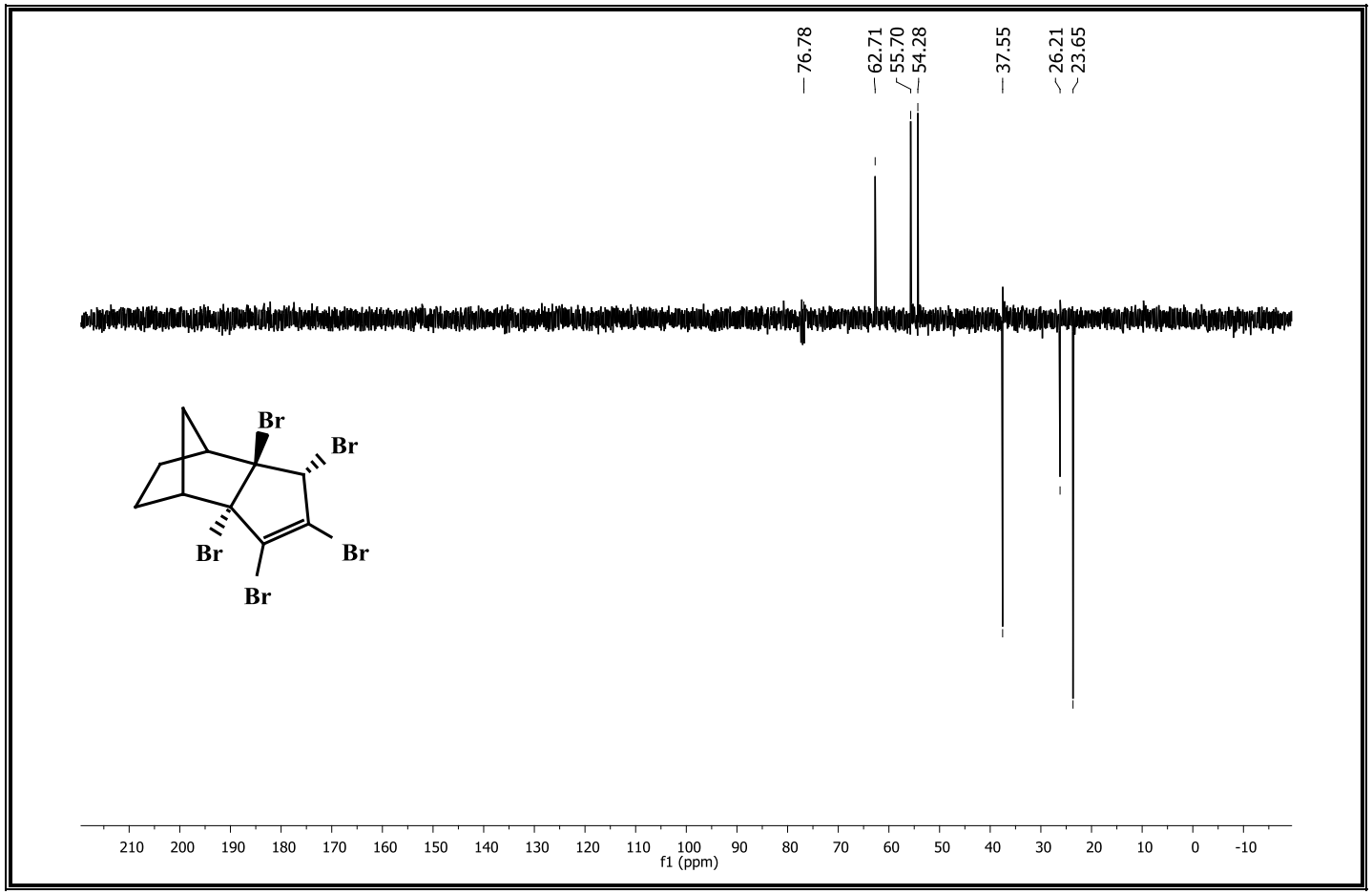

Figure A.39 DEPT-135 spectrum of compound **123**.

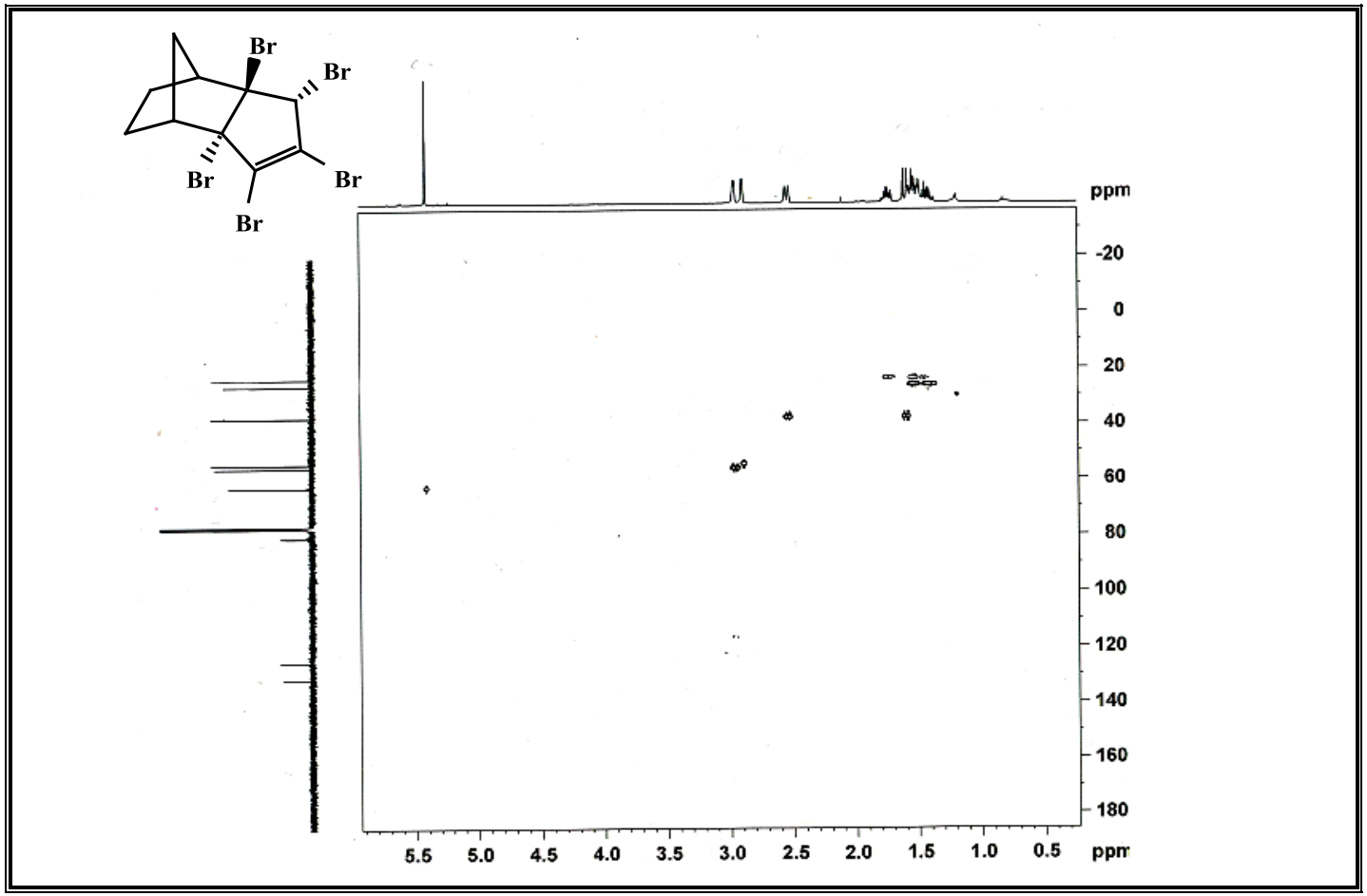

Figure A.40 HSQC spectrum of compound **123**.

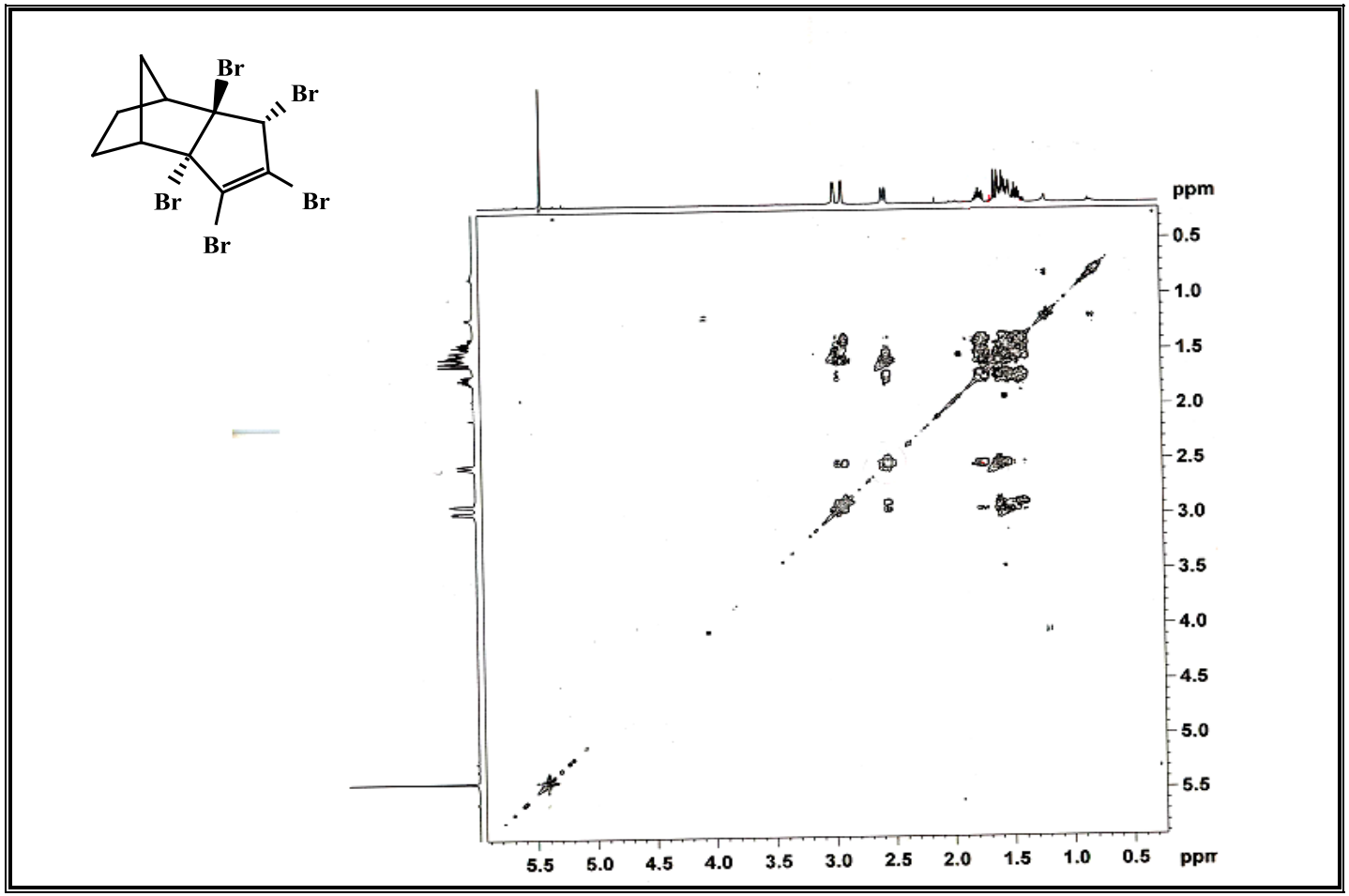

Figure A.41 COSY Spectrum of Compound **123**.

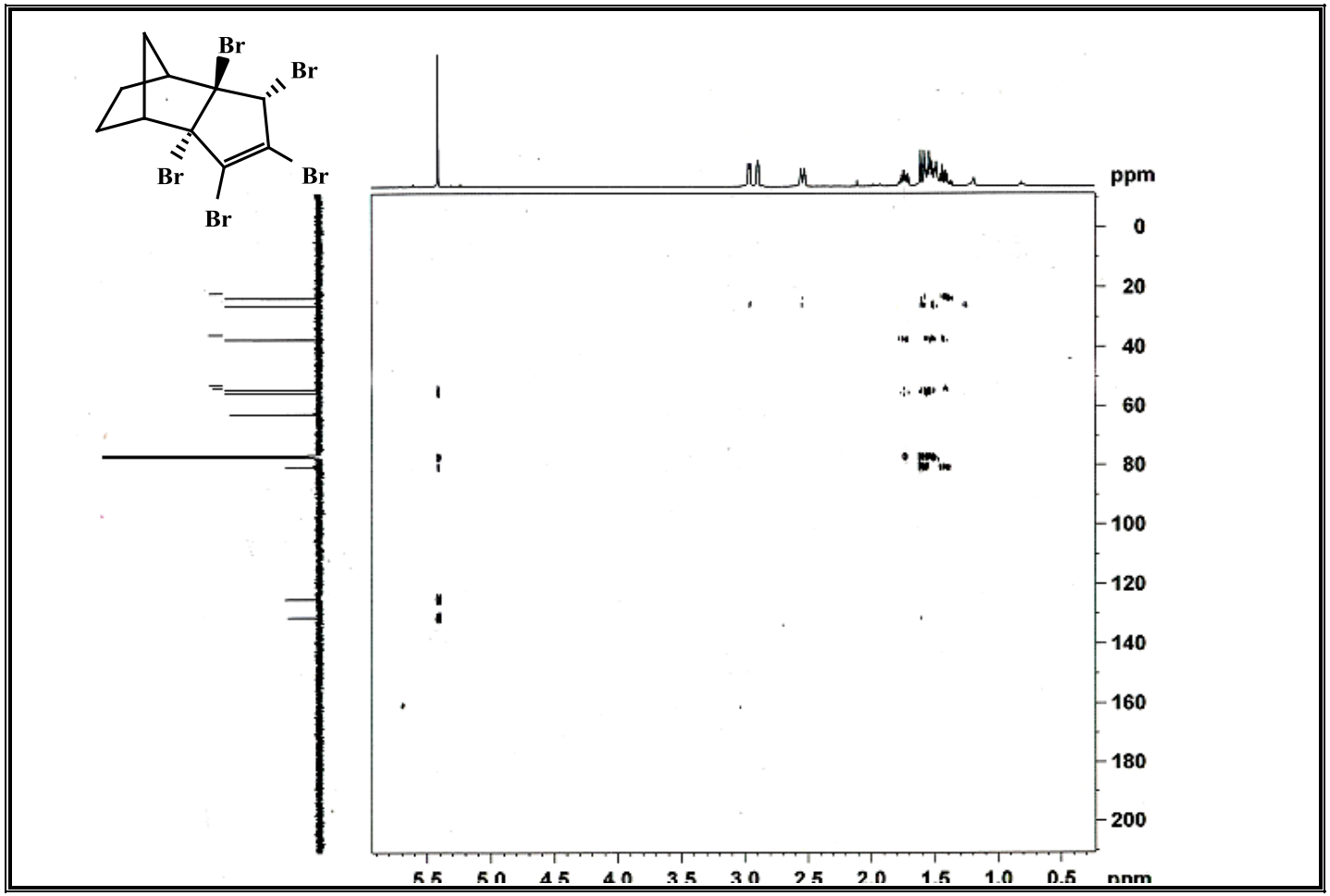

Figure A.42 HMQC Spectrum of Compound **123**.

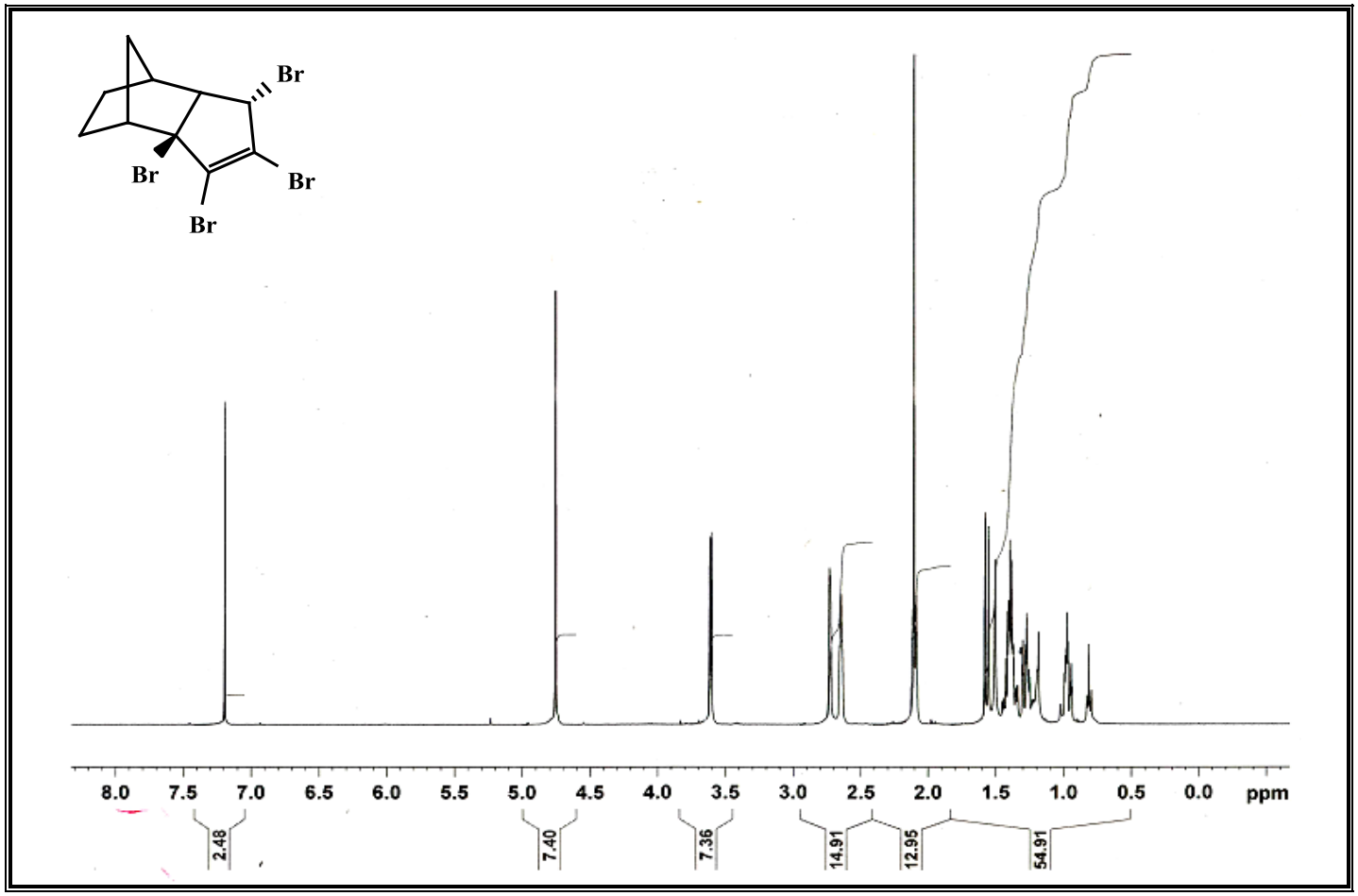

Figure A.43 ^{1}H-NMR spectrum of compound **124**.

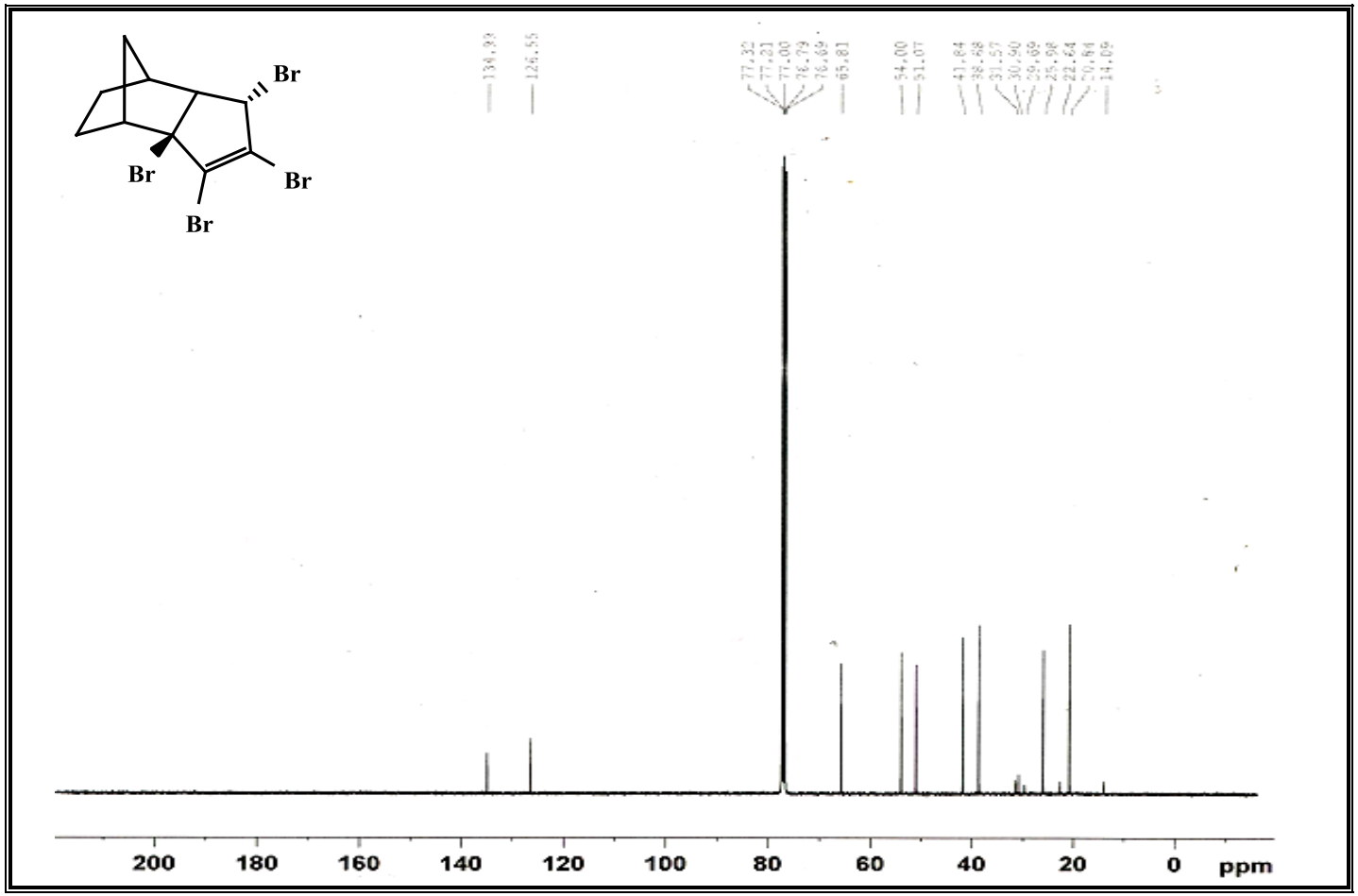

Figure A.44 ^{13}C-NMR spectrum of compound **124**.

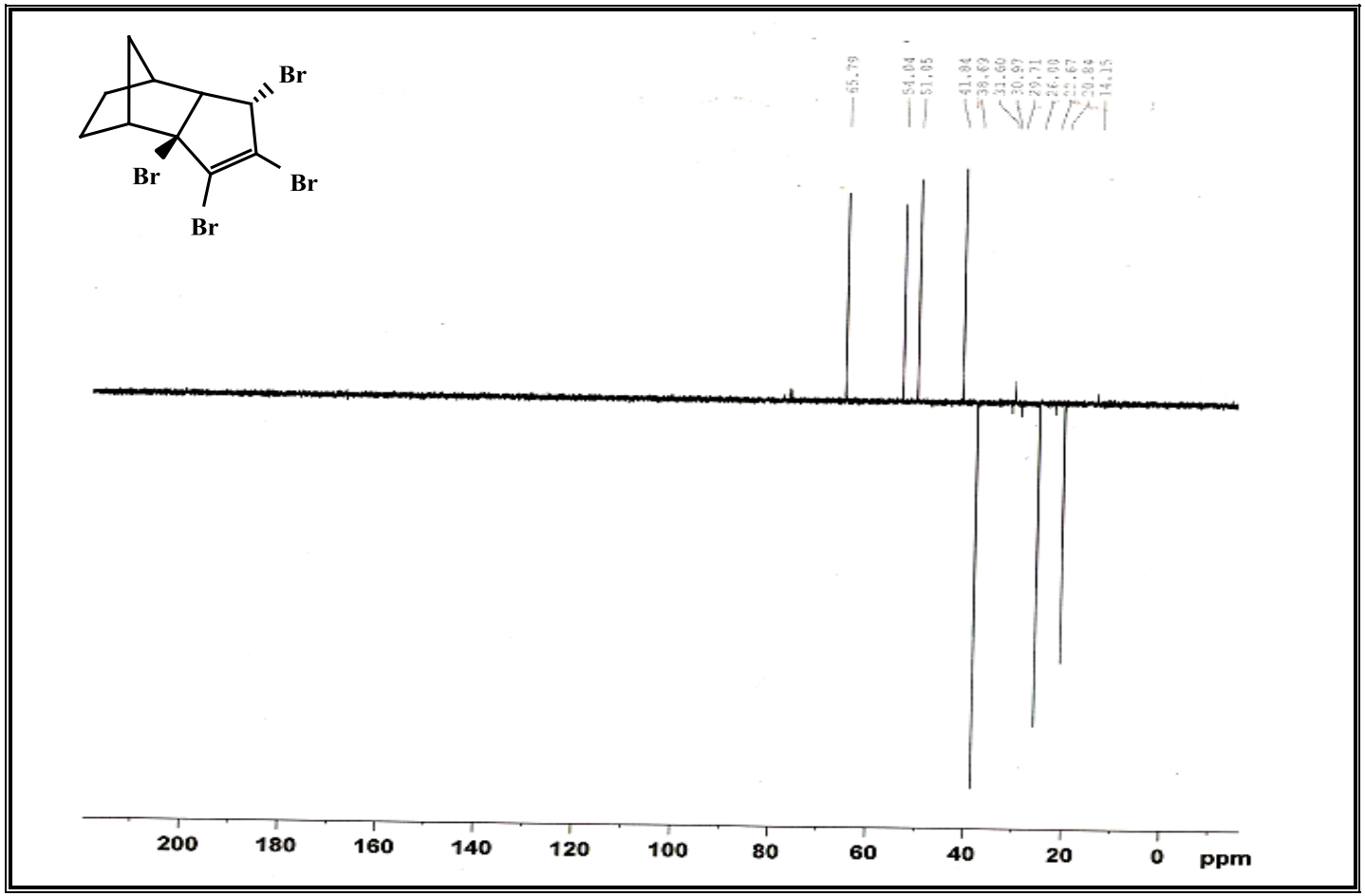

Figure A.45 DEPT-135 spectrum of compound **124**.

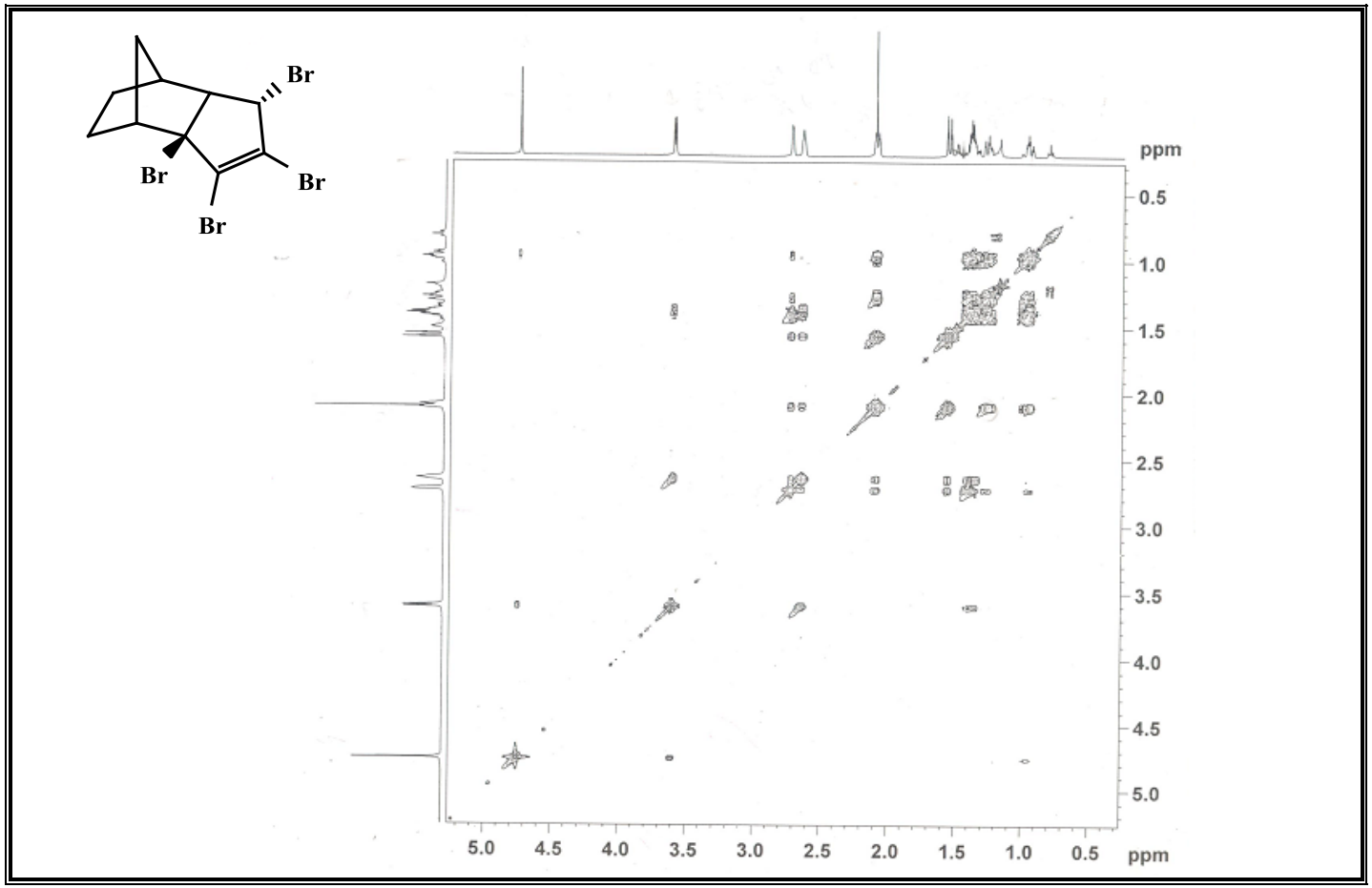

Figure A.46 COSY spectrum of compound **124**.

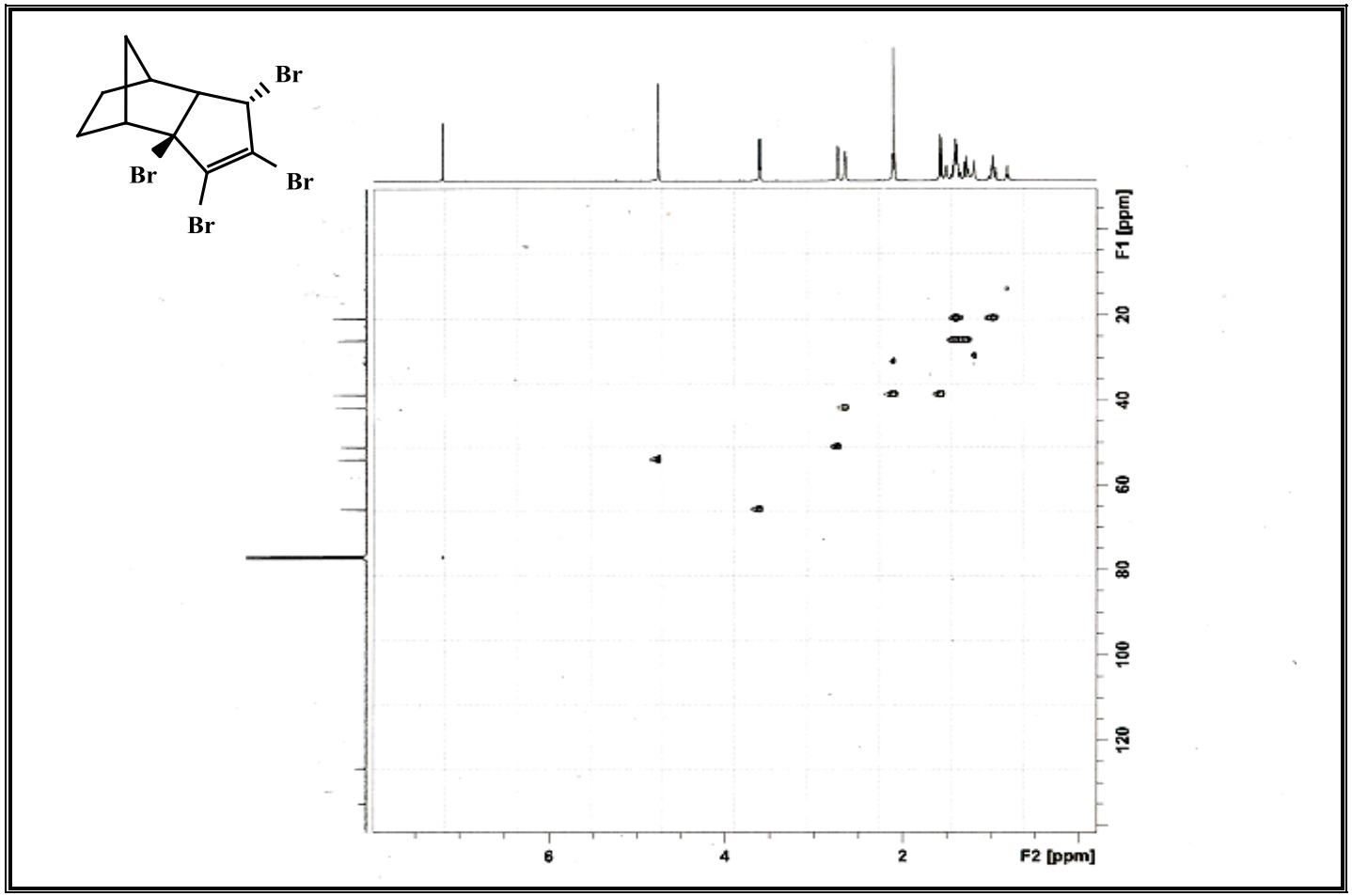

Figure A.47 HSQC spectrum of compound **124**.

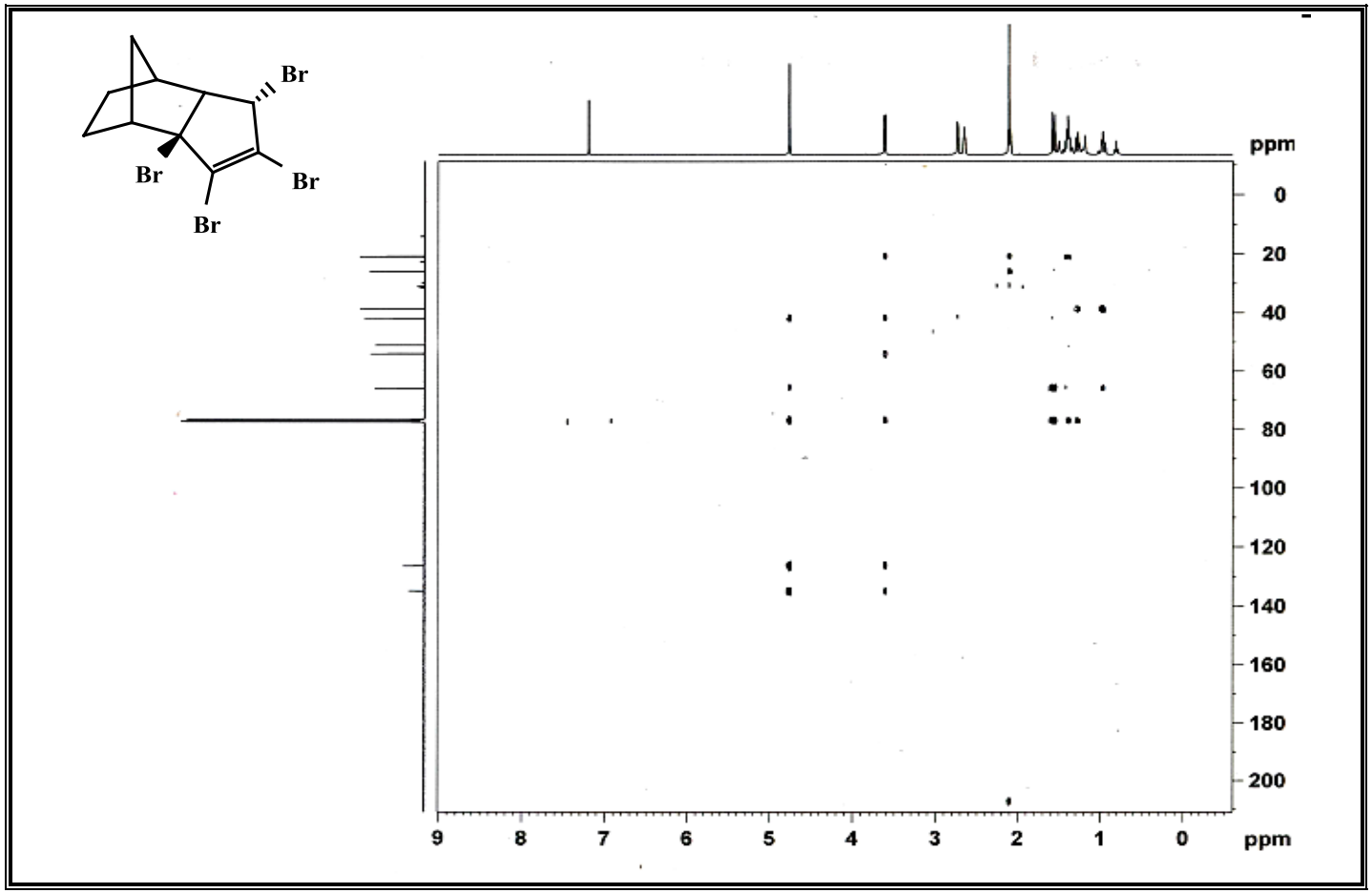

Figure A.48 HMBC spectrum of compound **124**.

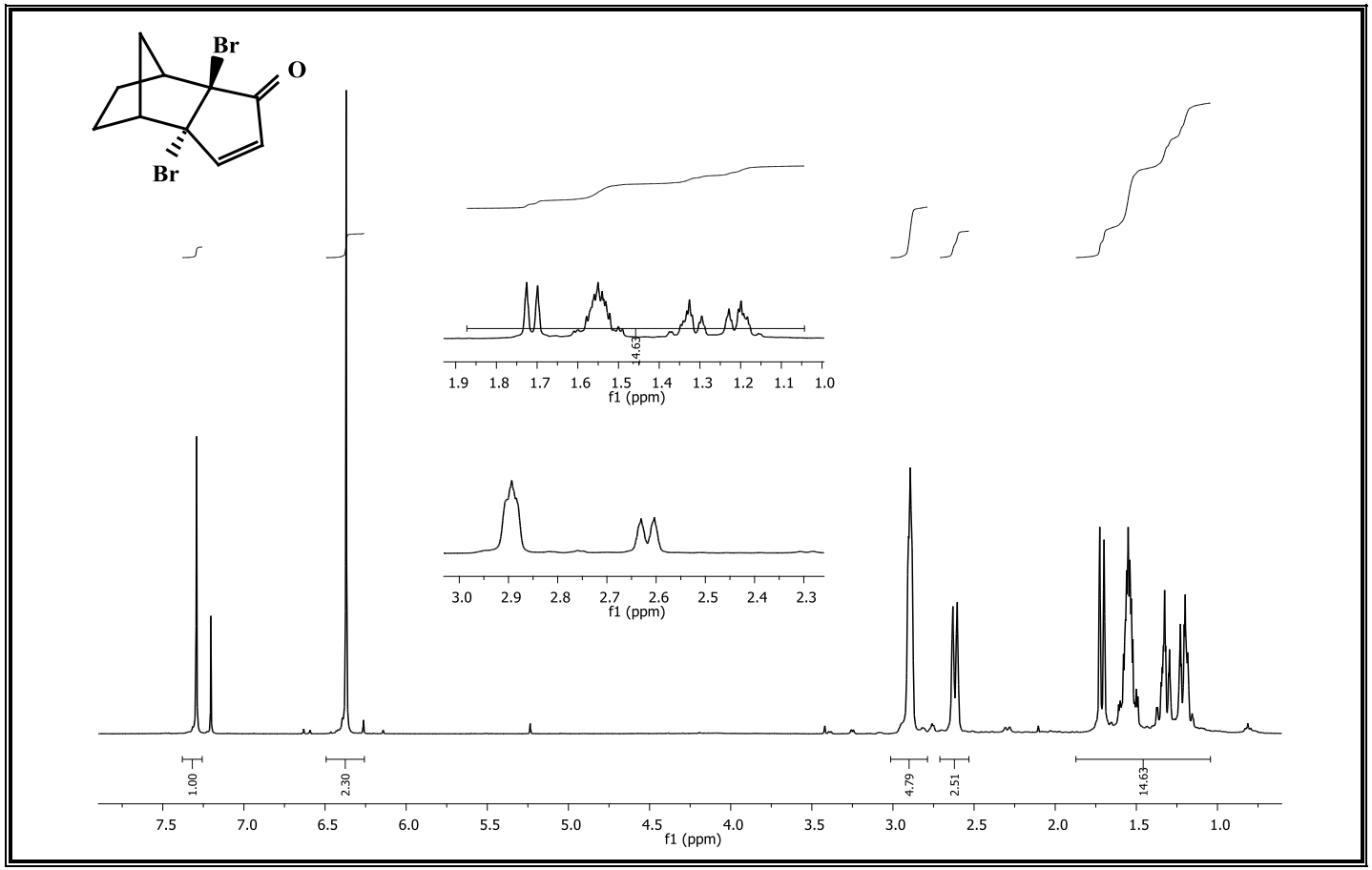

Figure A.49 ^{1}H-NMR spectrum of compound **125**.

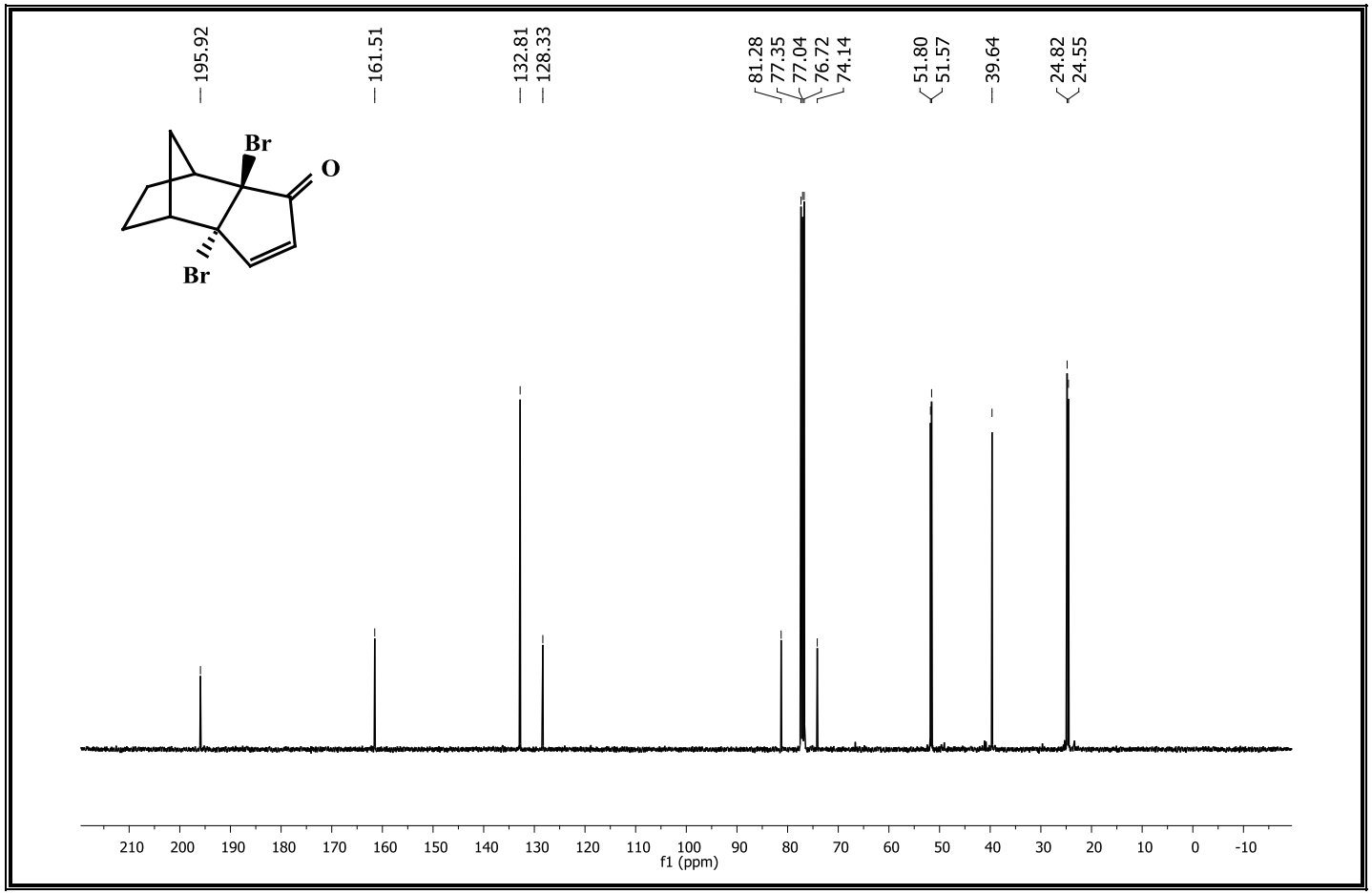

Figure A.50 ^{13}C-NMR spectrum of compound **125**.

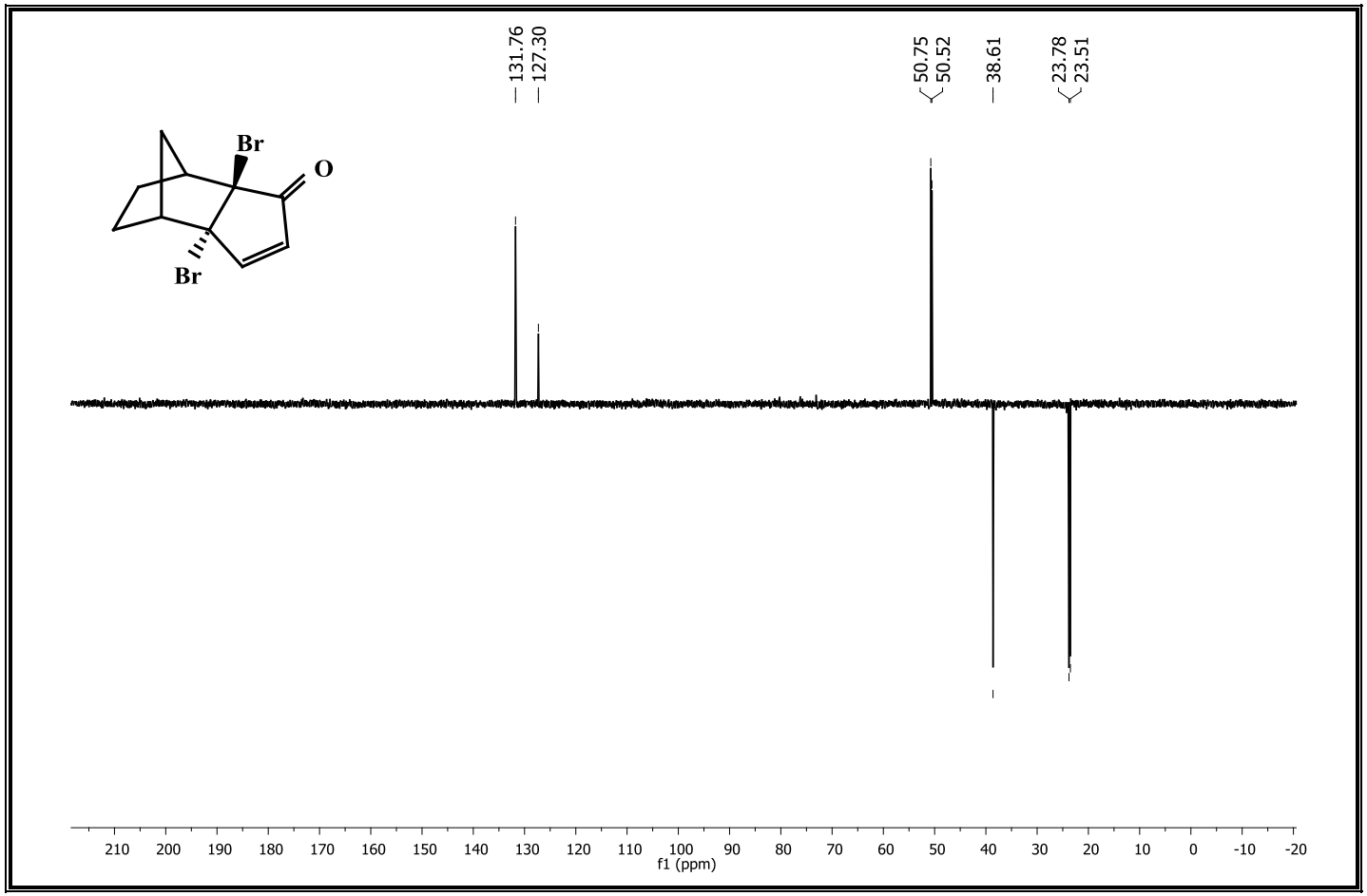

Figure A.51 DEPT-135 spectrum of compound **125**.

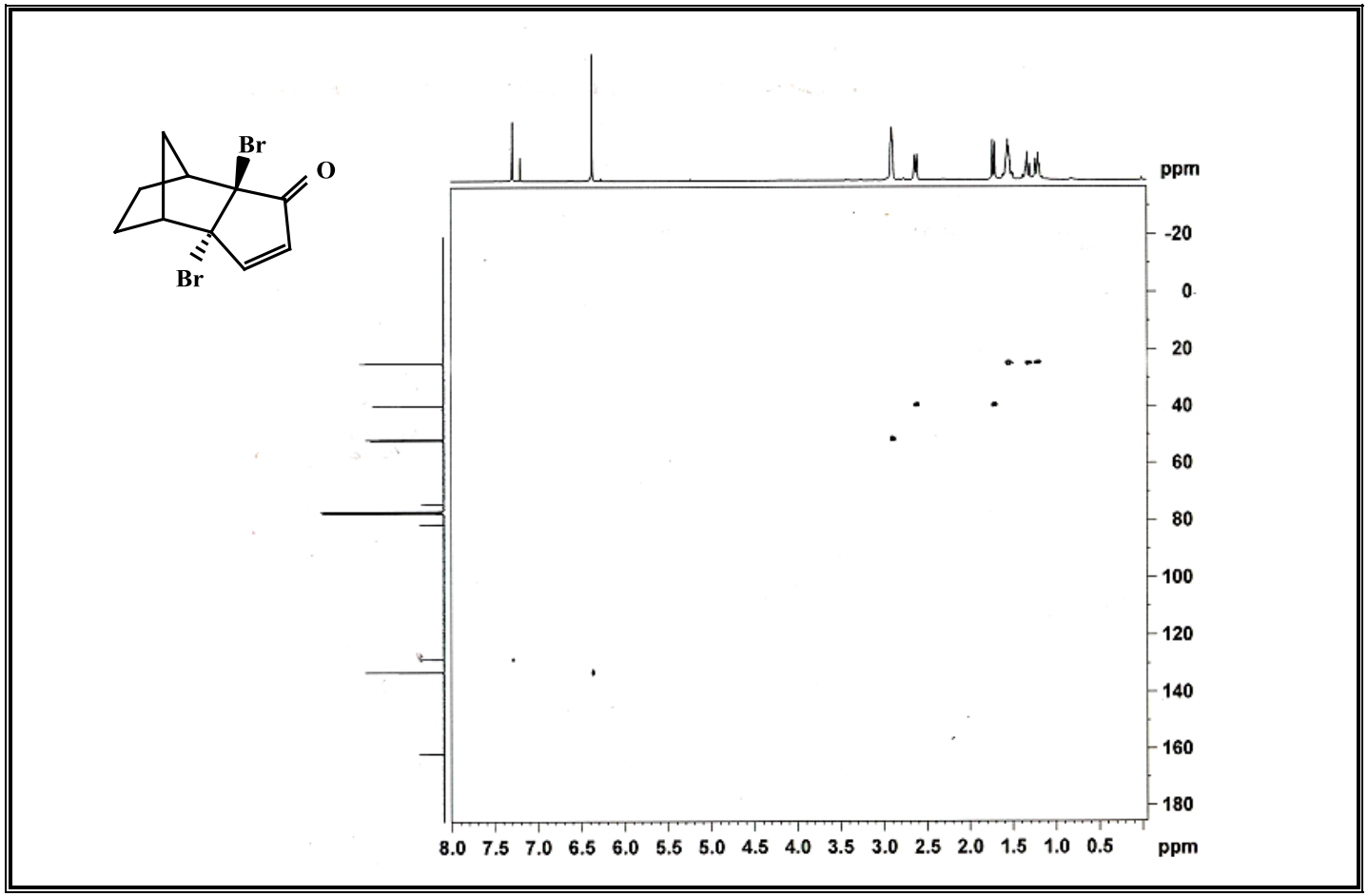

Figure A.52 HSQC spectrum of compound **125**.

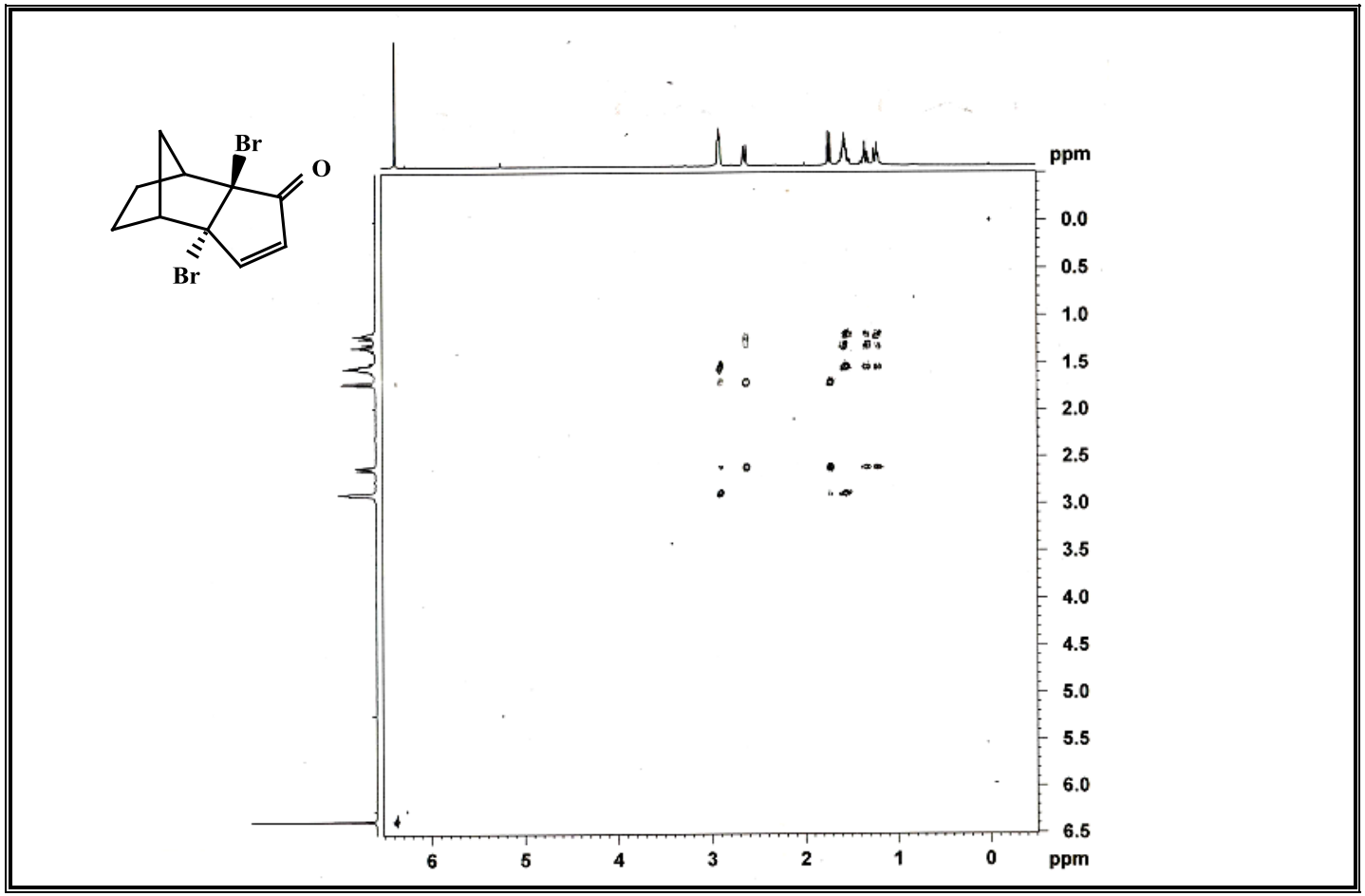

Figure A.53 COSY spectrum of compound **125**.

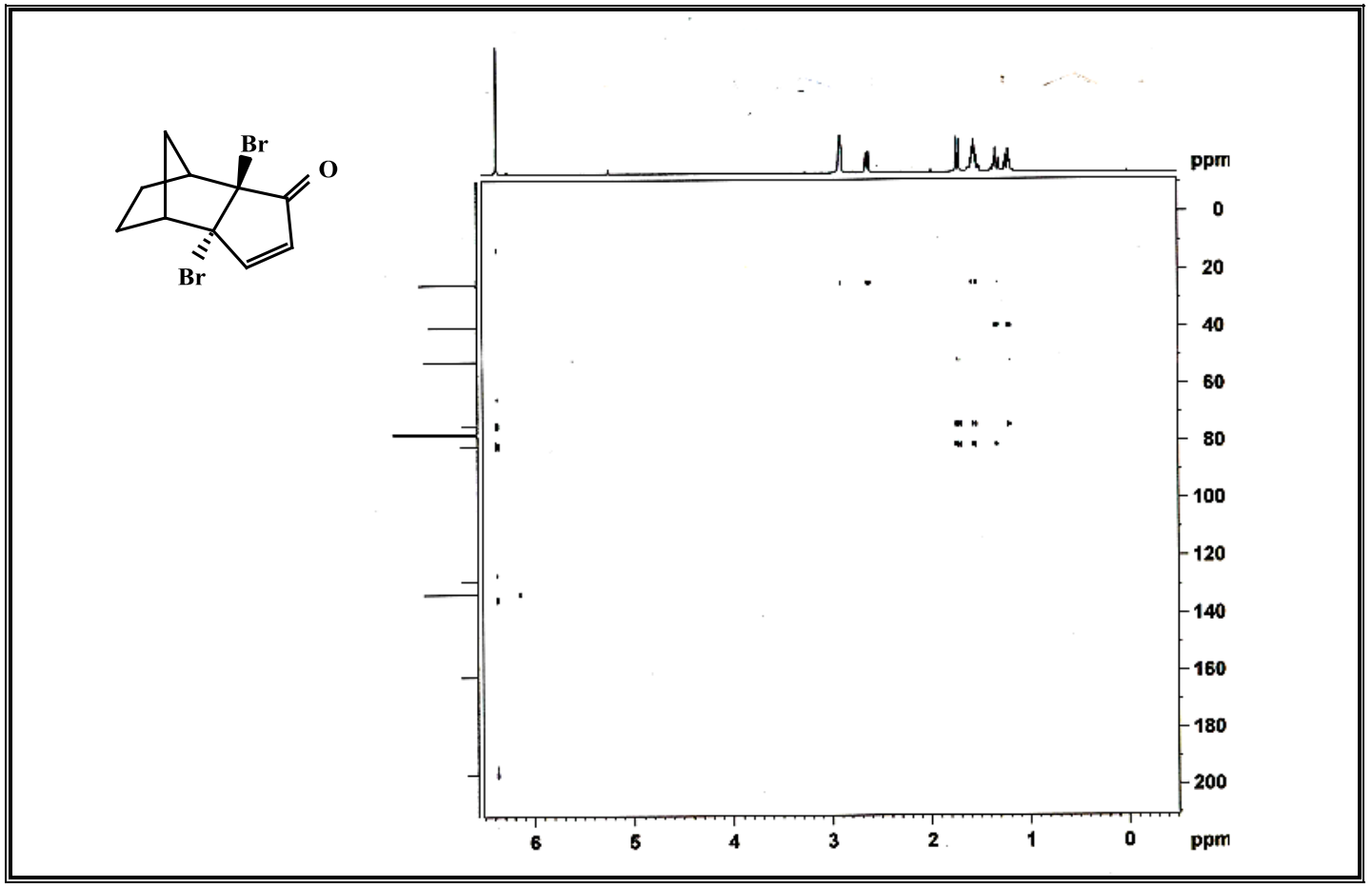

Figure A.54 HMBC spectrum of compound **125**.

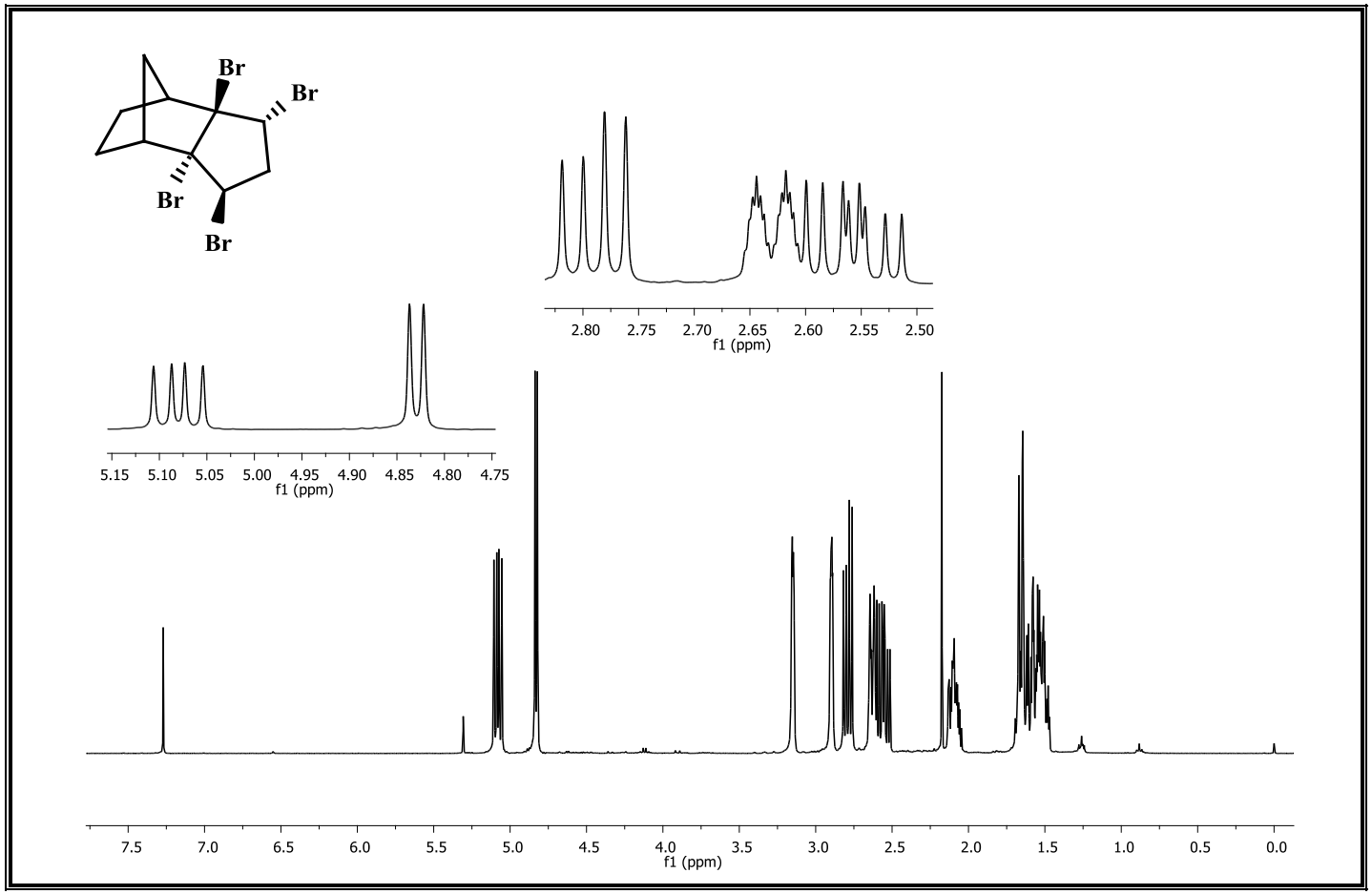

Figure A.55 ^{1}H-NMR spectrum of compound **135**.

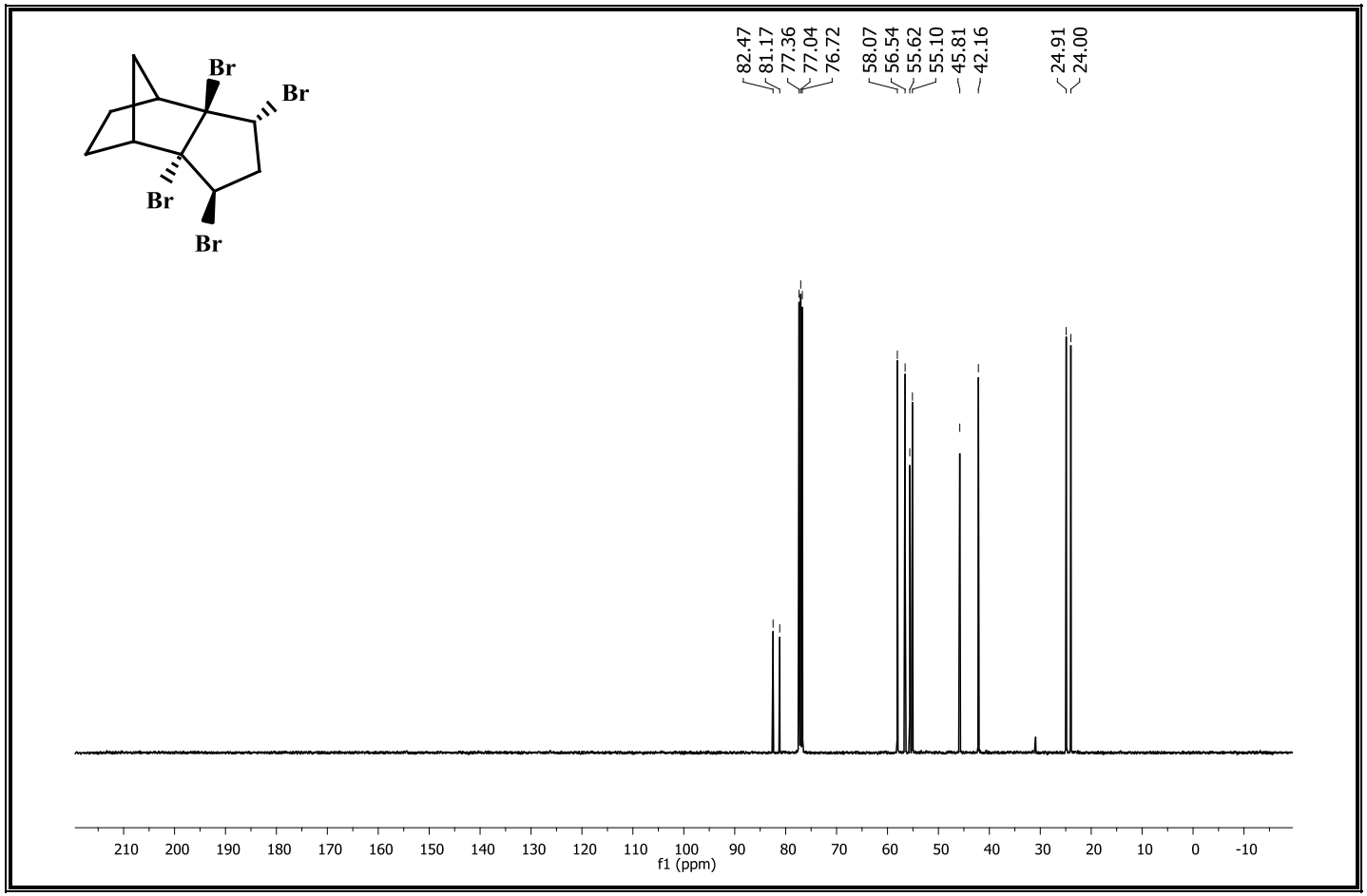

Figure A.56 ^{13}C-NMR spectrum of compound **135**.

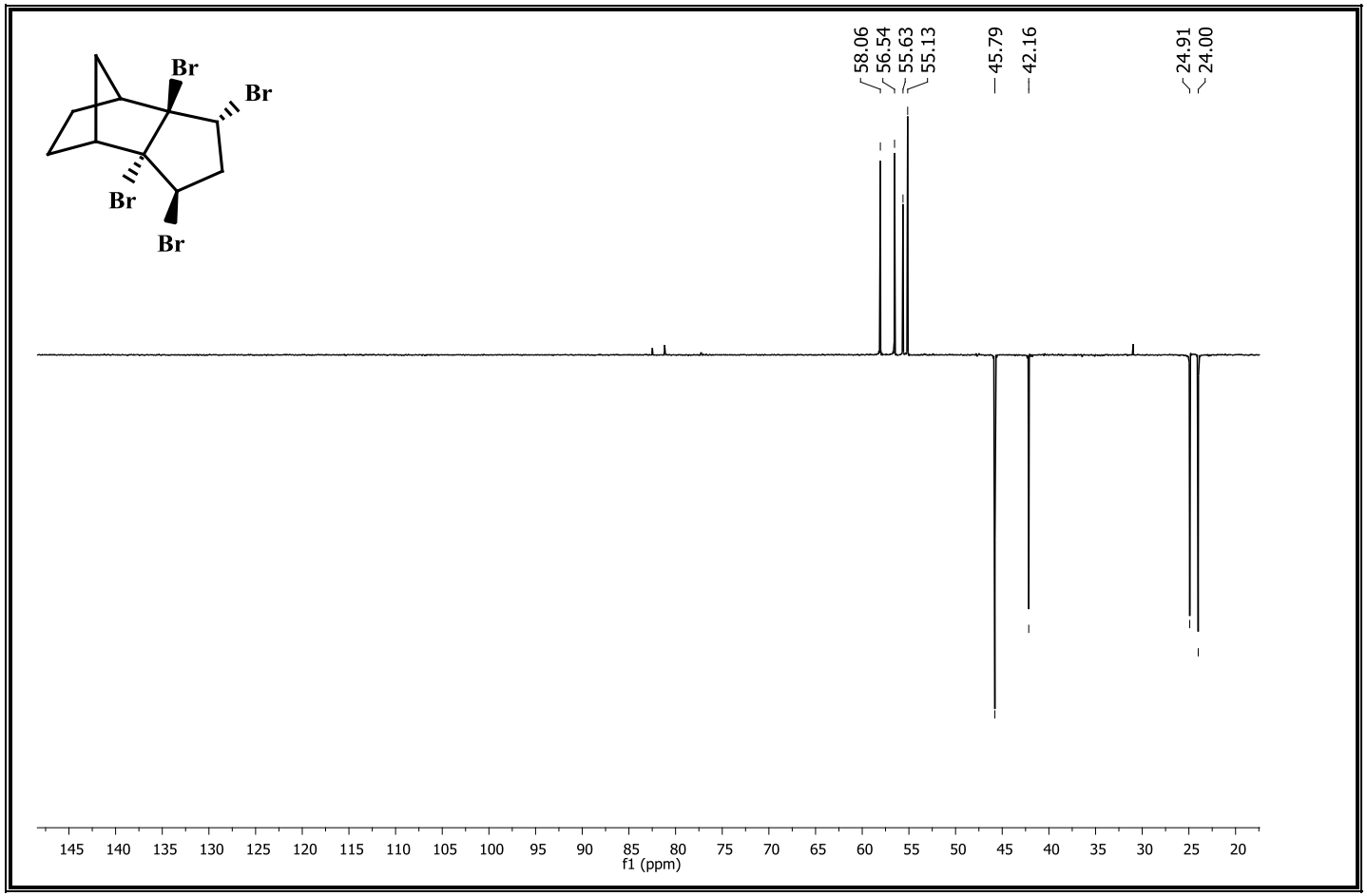

Figure A.57 DEPT-135 spectrum of compound **135**.

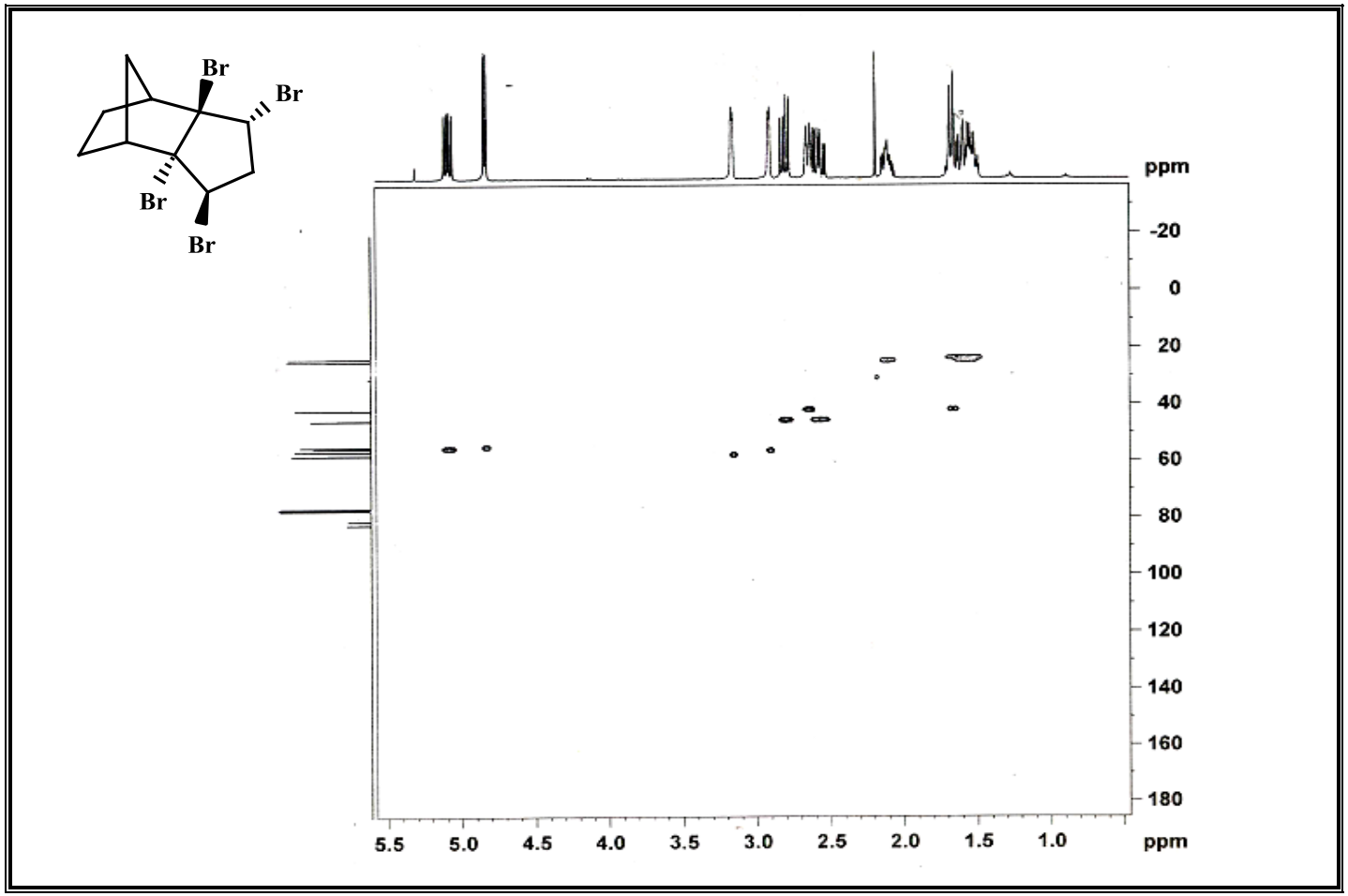

Figure A.58 HSQC spectrum of compound **135**.

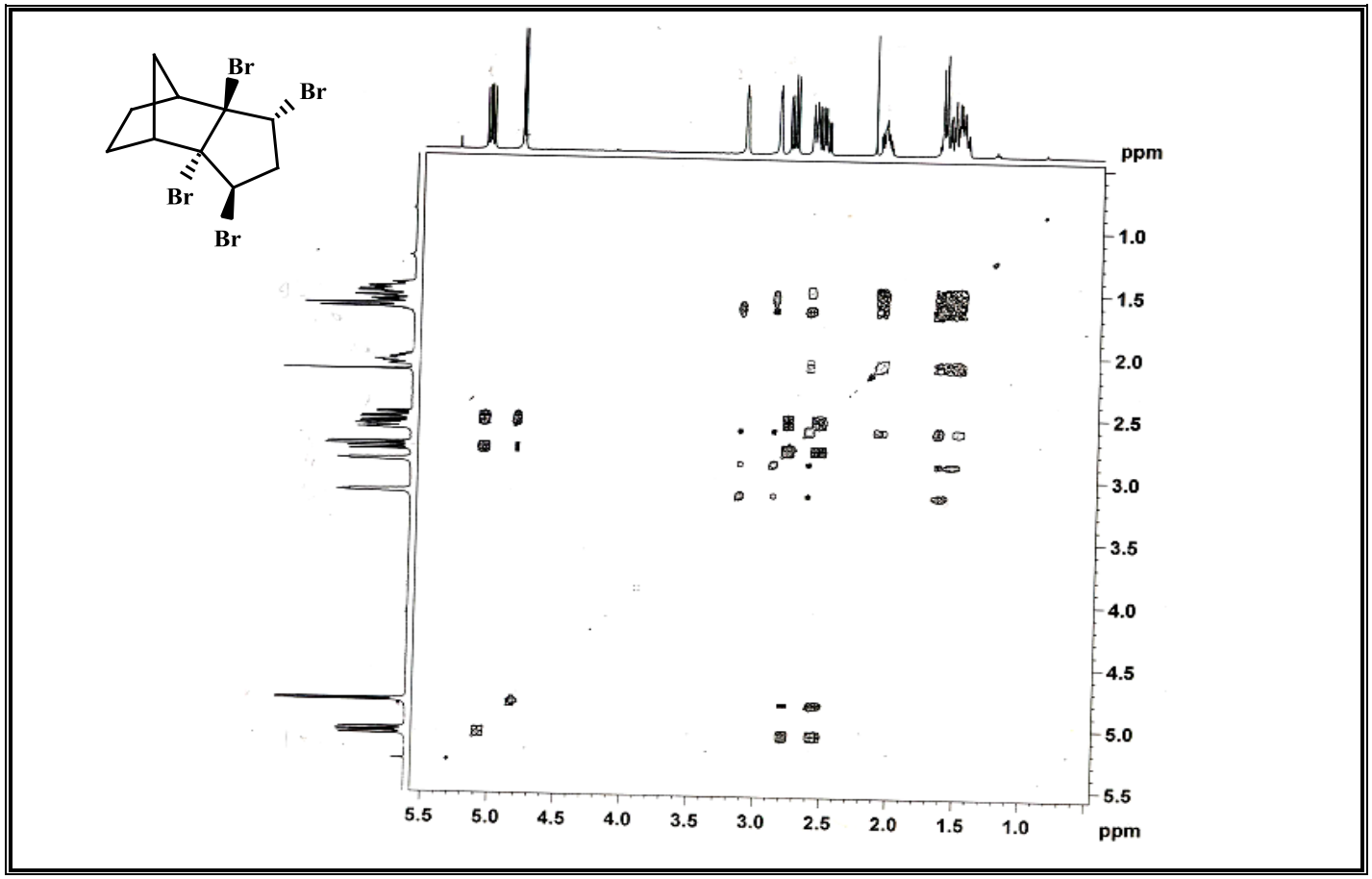

Figure A.59 COSY spectrum of compound **135**.

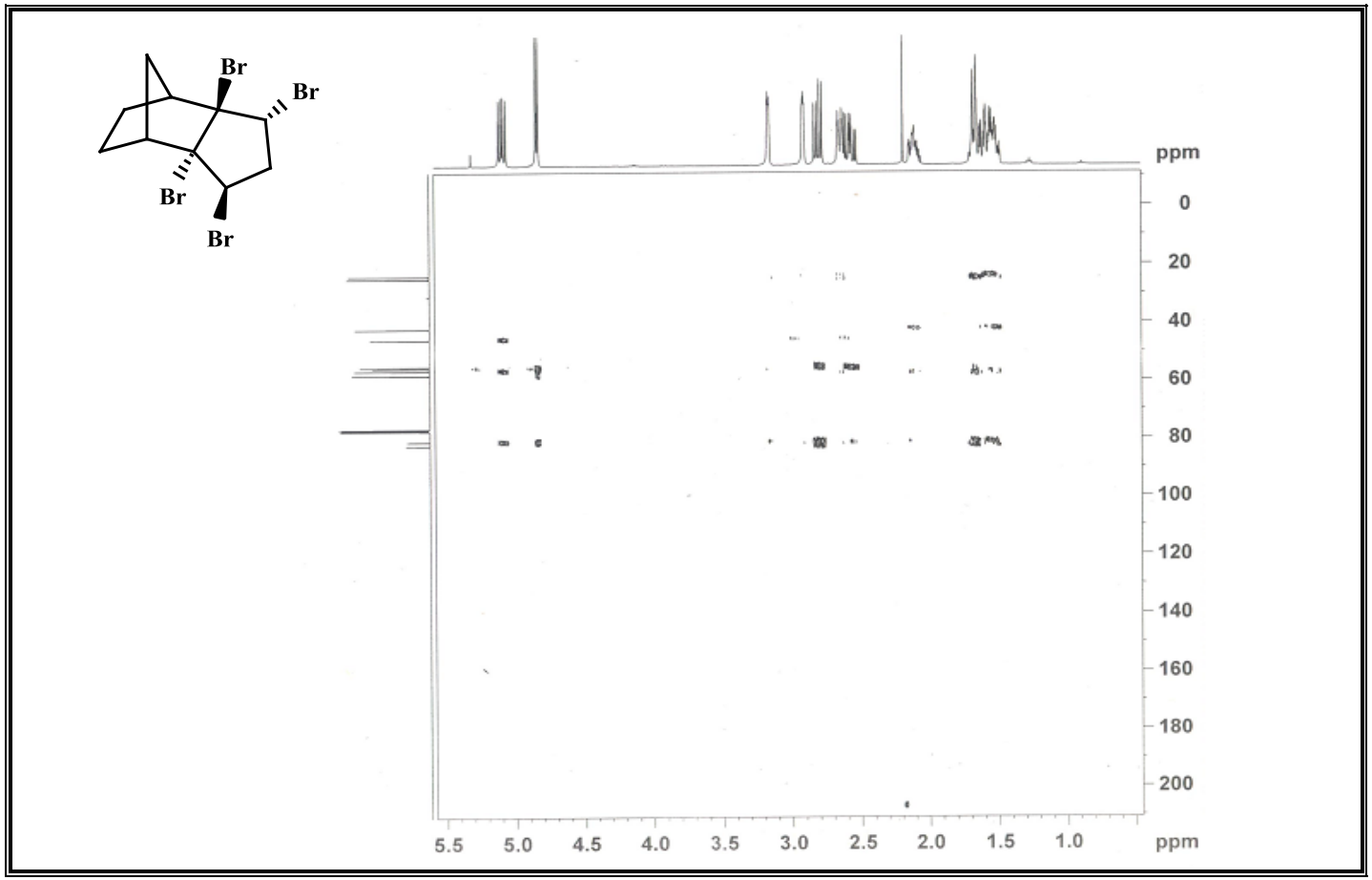

Figure A.60 HMBC spectrum of compound **135**.

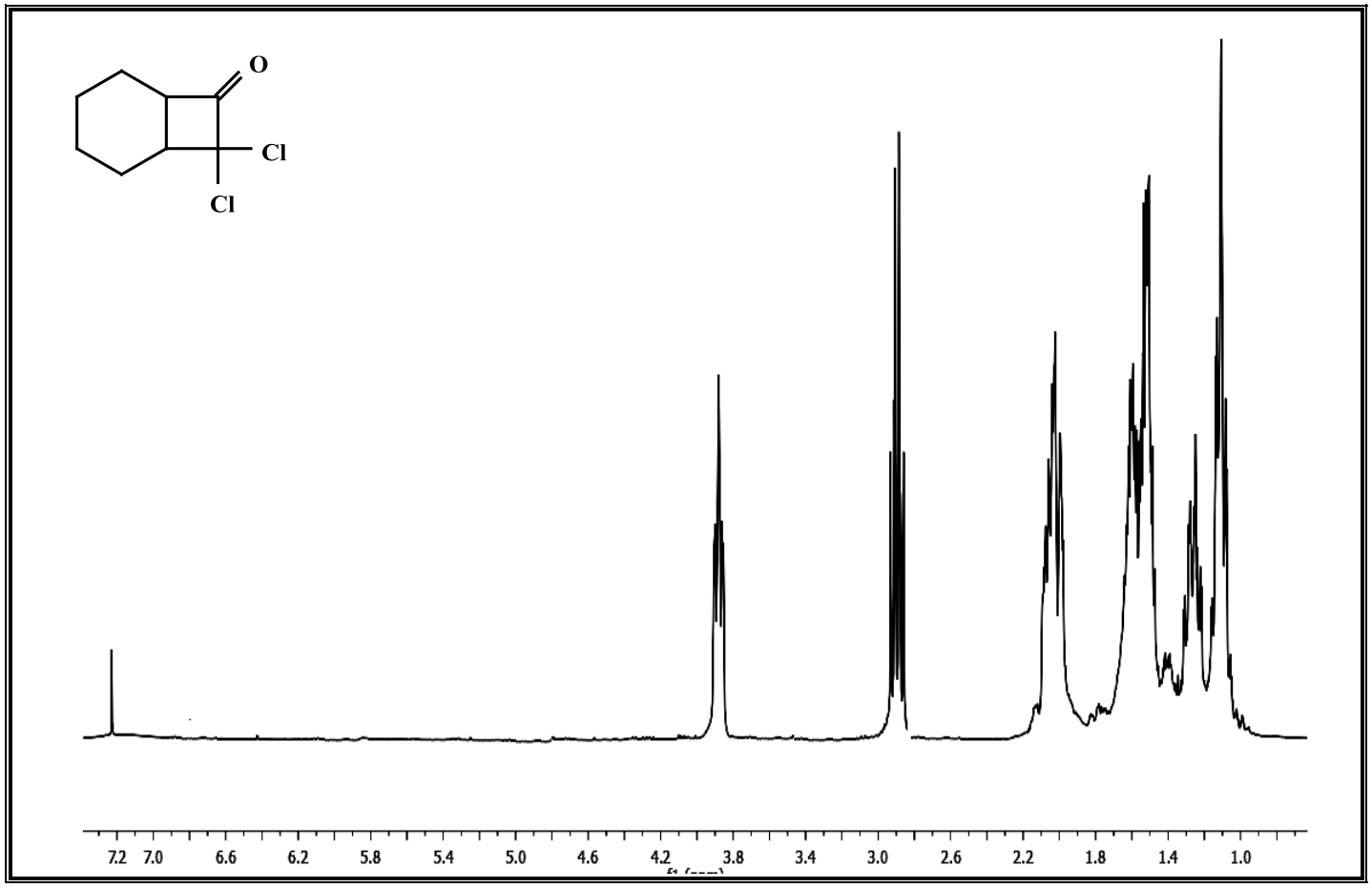

Figure A.61 ^{1}H-NMR spectrum of compound **138**.

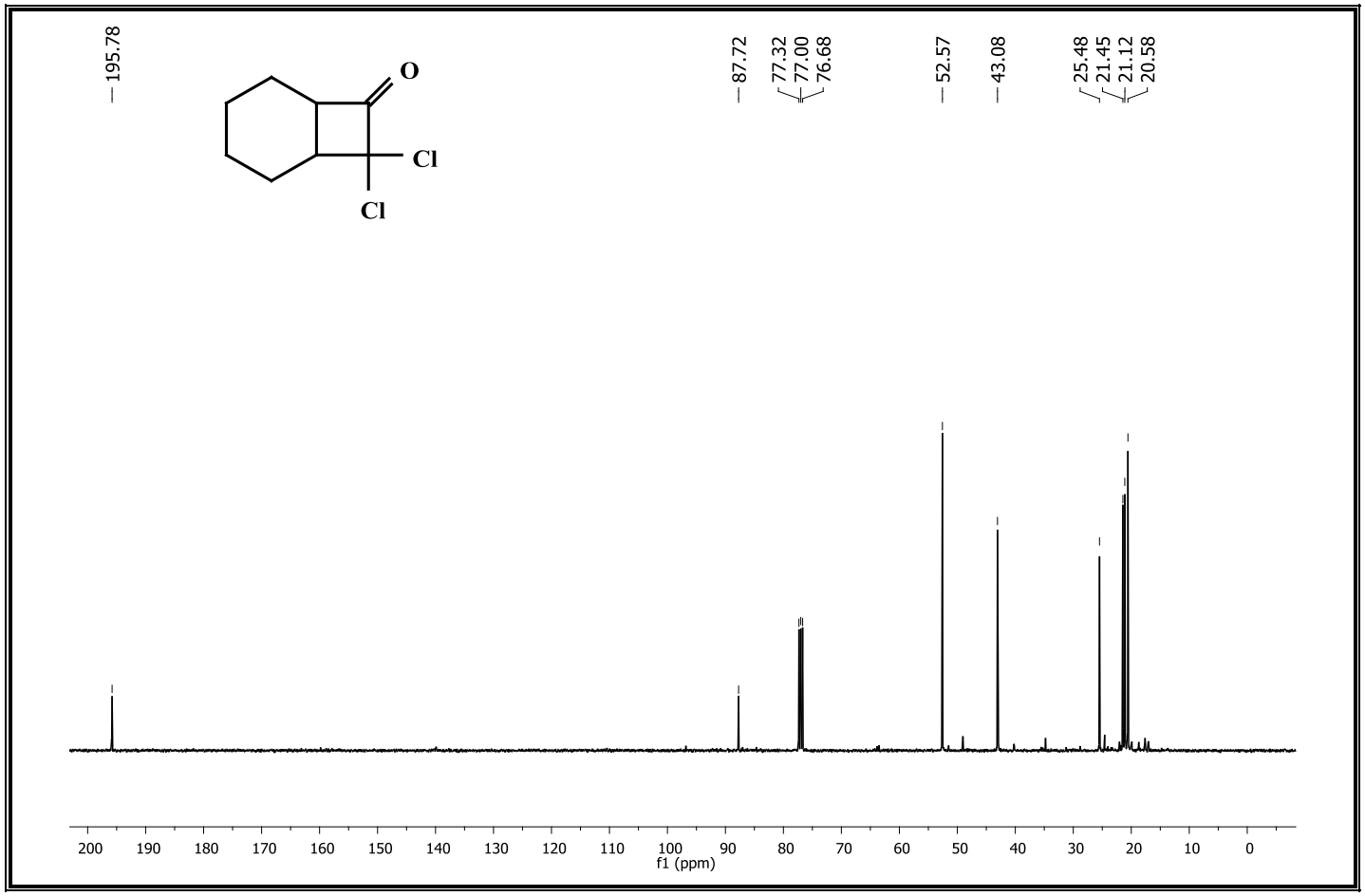

Figure A.62 ^{13}CNMR spectrum of compound **135**.

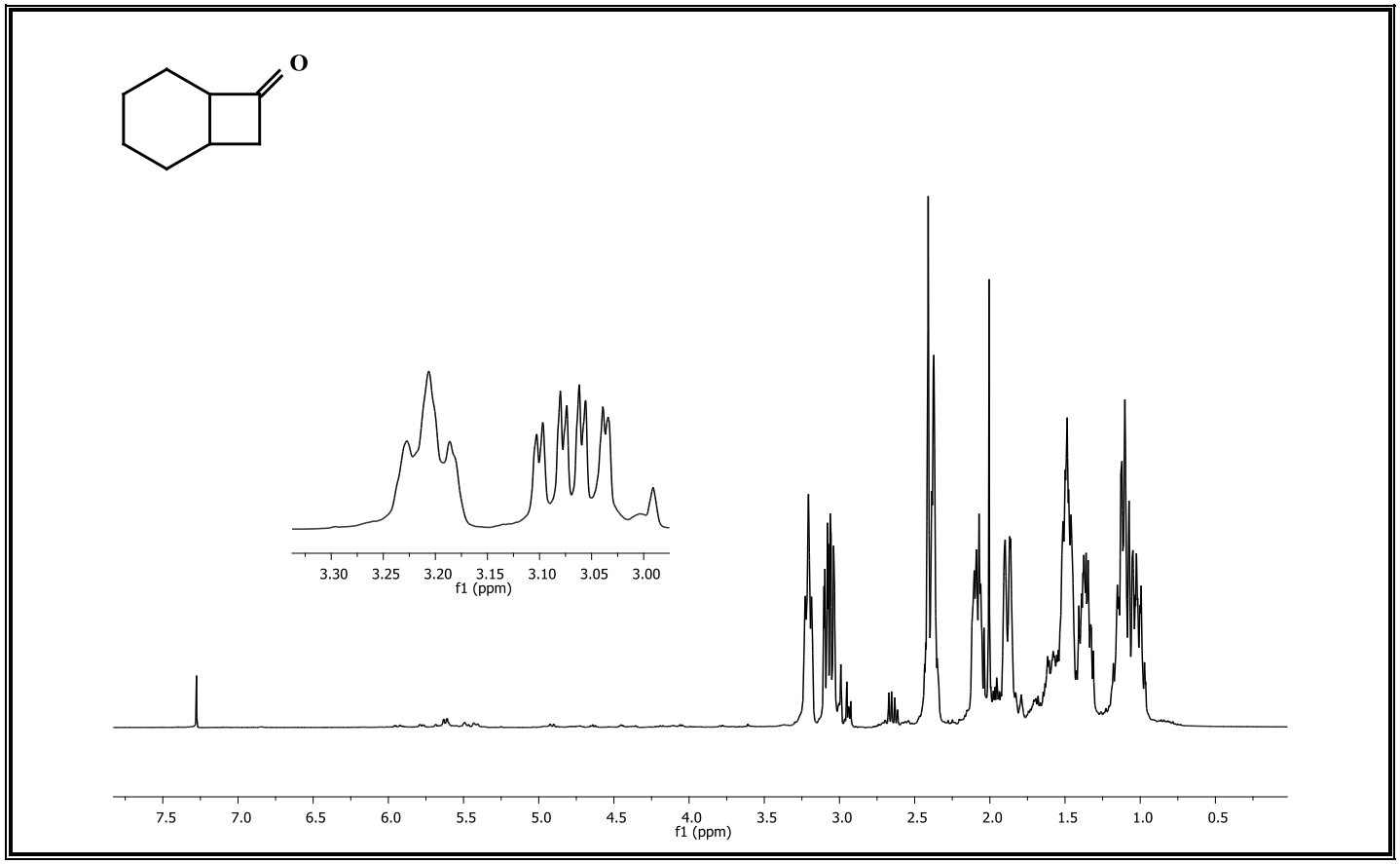

Figure A.63 ^{1}H-NMR Spectrum of Compound **82**.

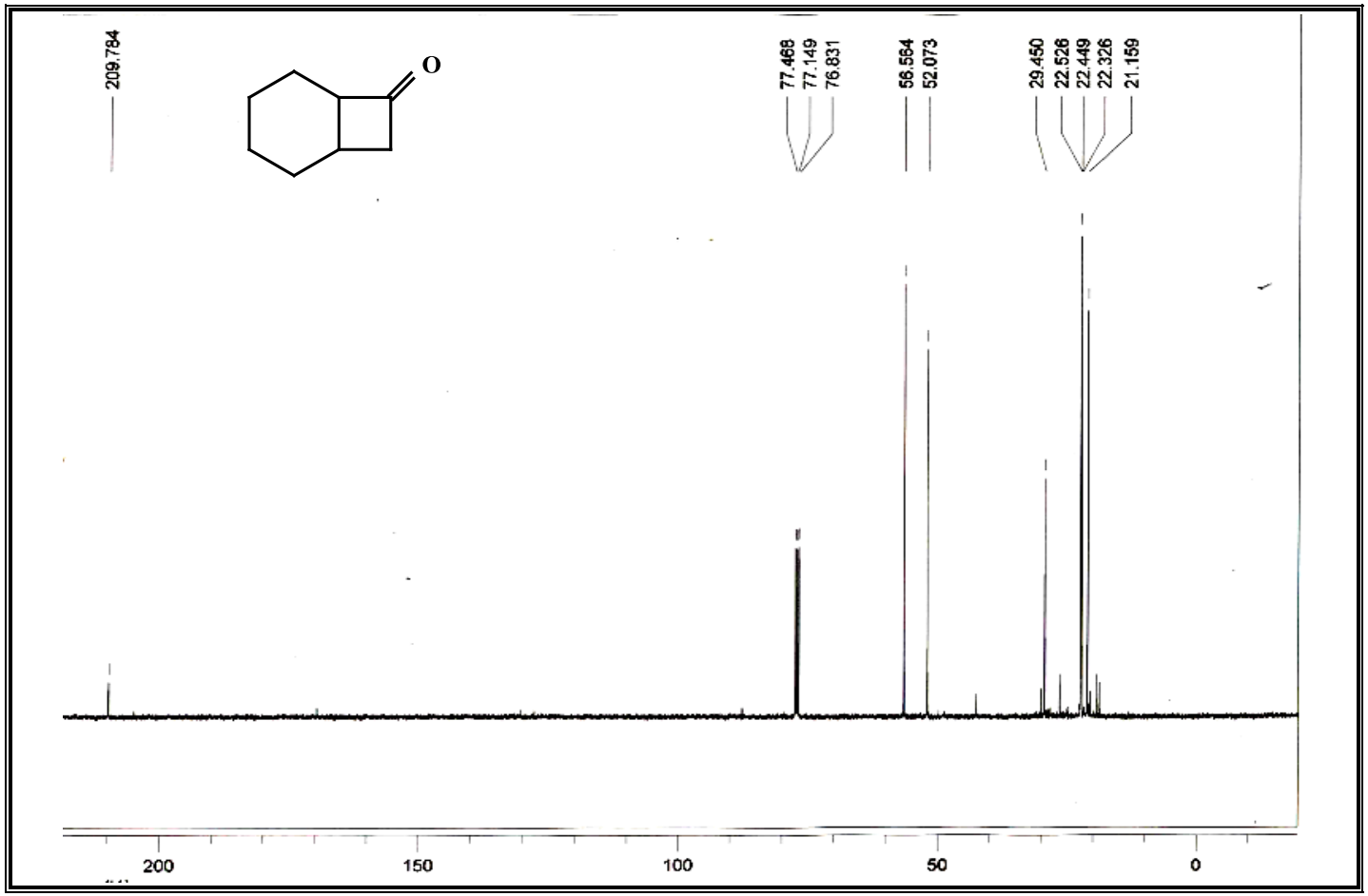

Figure A.64 ^{13}C-NMR Spectrum of Compound **82**.

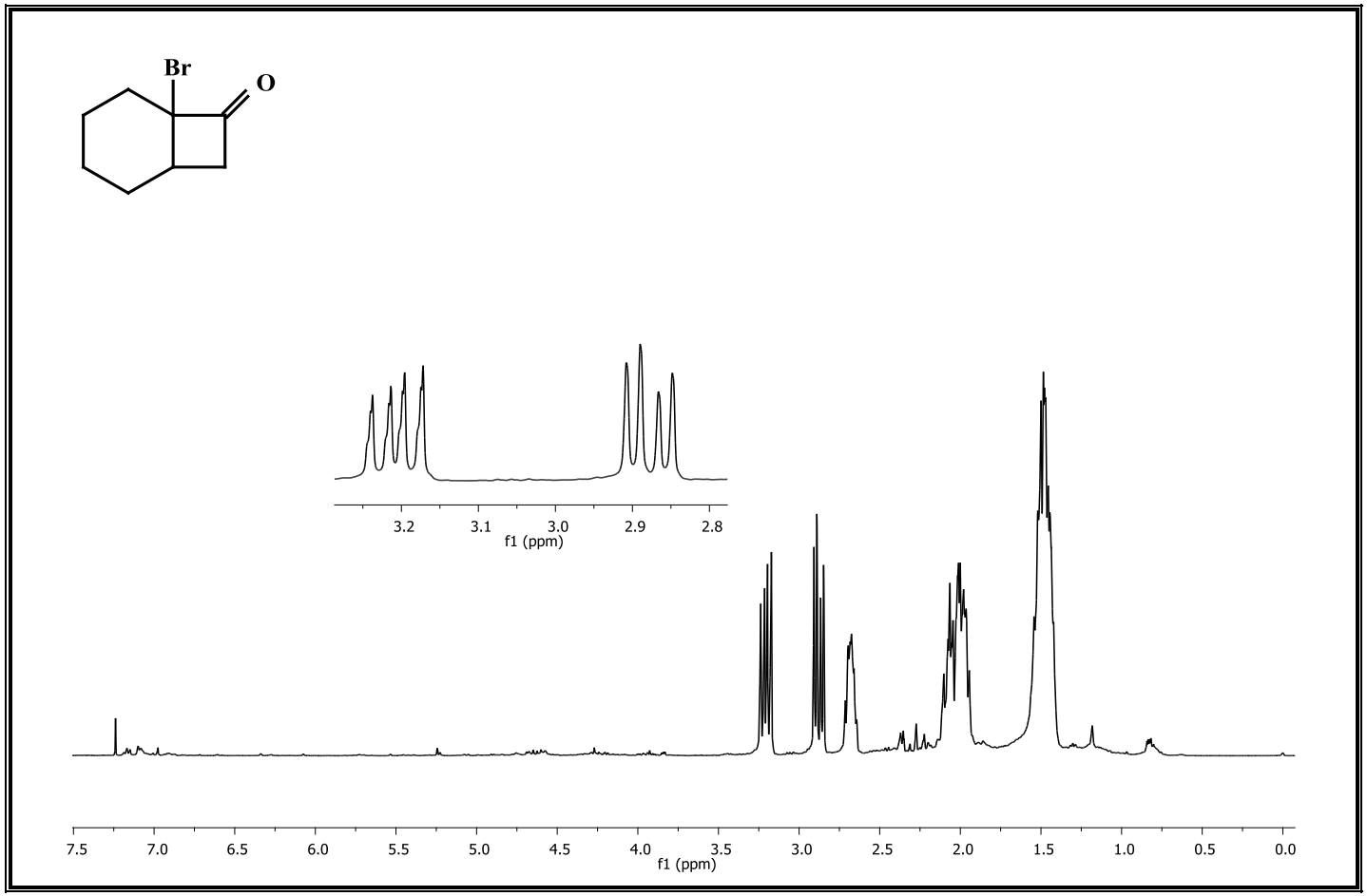

Figure A.65 ^{1}HNMR spectrum of compound **139**.

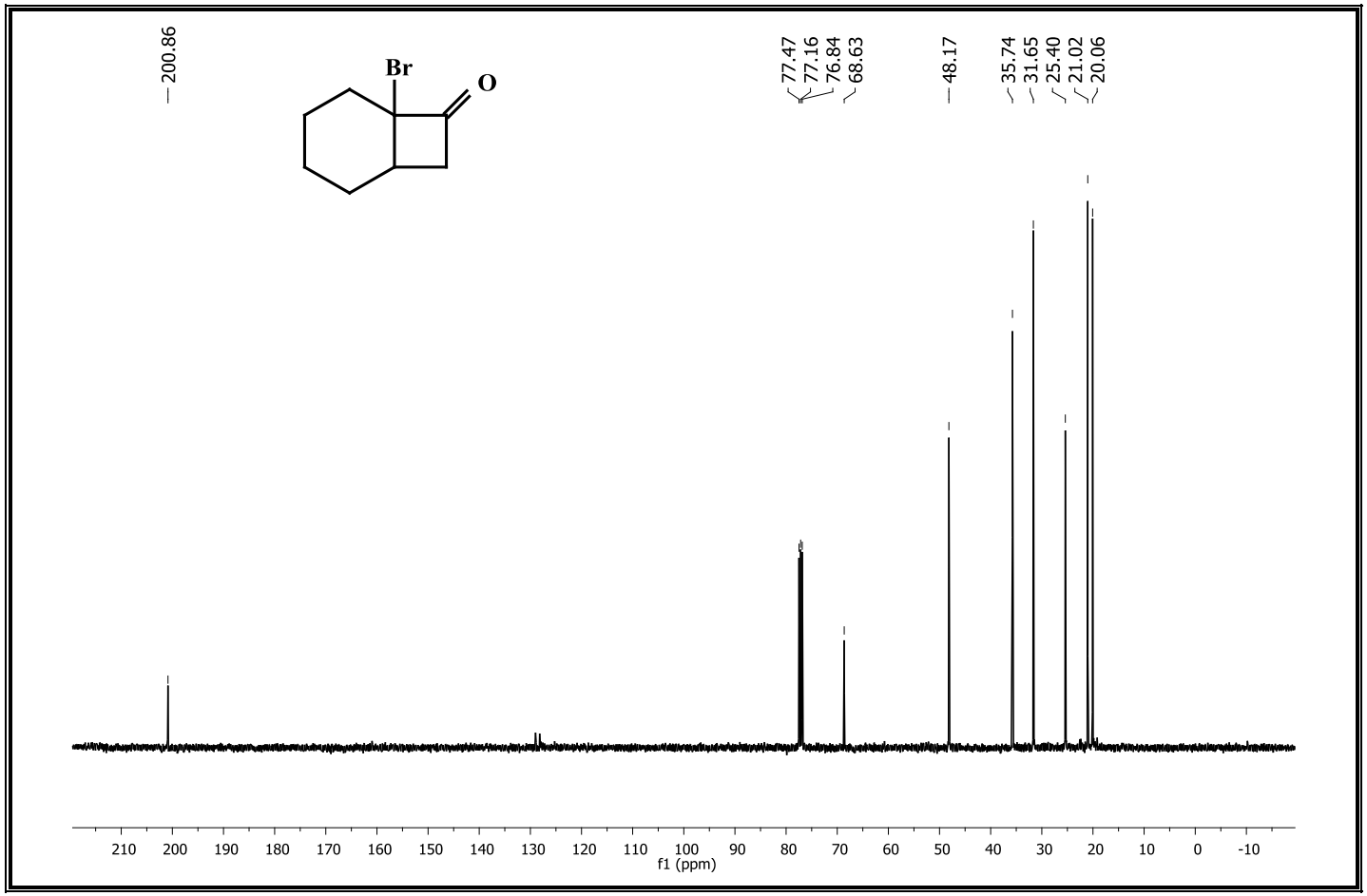

Figure A.66 ^{13}CNMR spectrum of compound **139**.