

FUNCTIONALIZATION OF SATURATED HYDROCARBONS:
HIGH TEMPERATURE BROMINATION

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ABSTRACT

FUNCTIONALIZATION OF SATURATED HYDROCARBONS: HIGH TEMPERATURE BROMINATION

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Although saturated hydrocarbons are readily available and extremely cheap starting materials, they can not be used in synthetic chemistry without prior activation. Efficient functionalization of alkanes leading to the production of useful organic chemicals in an industrial scale is of considerable interest for the chemical and pharmaceutical industries and remains a long-term challenge for chemists. In this respect, halogenations of hydrocarbons which leads to a variety of useful synthetic intermediates is an open avenue which deserves special attention.

It is also noteworthy to mention that efficient methods for selective functionalization of saturated bicyclic hydrocarbons still remains elusive, albeit a number of methods employing various reagents have been developed for the C–H bond activation of open chain and monocyclic alkanes.

Herein, we will investigate the high temperature bromination reactions as a method for functionalization of saturated bicyclic hydrocarbons such as octahydropentalene (**1**), octahydro-1H-indene (**2**) and 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (**3**). The scope and the limitations of the reaction will reveal the regio-and

stereoselectivity. Furthermore, formation mechanism of the products will be discussed and the chemistry of these compounds will be extended for further functionalization

Keywords: Bromination, Hydrocarbons, Substitution, Pentalene, Octahydro-1H-indene, 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene.

ÖZ

DOYMUŞ HİDROKARBONLARIN FONKSİYONELLENDİRİLMESİ: YÜKSEK SICAKLIK BROMİNASYONU

Günbaş, Duygu Deniz
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Haziran 2006, 174 sayfa

Doymuş hidrokarbonlar oldukça kolay ve bol bulunabilen ucuz maddeler olmasına rağmen, aktif hale getirilmeden sentetik kimyada kullanılamazlar. Alkanların endüstriyel düzeyde kullanışlı organik kimyasallara dönüştürülmesi sentetik kimyada oldukça önem arzetymekte olup kimyacıları uzun süre uğraştıracak gibi gözükmektedir. Bu vesile ile hidrokarbonların halojenlemek suretiyle kullanışlı sentetik ara ürünlere dönüştürülmesi özel ilgi ve uğraşı vermeye değerdir.

Ayrıca düz zincirli ve monosiklik alkanları halojenlemeye yönelik bir kaç metot bulunmasına rağmen, doymuş bisiklik hidrokarbonların etkin ve seçici bir şekilde fonksiyonel hale getirebilecek bir yöntem henüz bulunmamaktadır.

Bu çalışmada oktahidropentalen (1), oktahidro-1H-inden (2) ve 1a,2,7,7a-tetrahidro-1H-siklopropa[b]naftalin (3) gibi bazı doymuş bisiklik hidrokarbonları fonksiyonel hale getirmek amacıyla yüksek sıcaklık brominasyonu bir yöntem olarak incelenecektir. Yöntemin olanak ve sınırları regio- ve/veya stereo- seçiciliği de gözler önüne serilecektir. Ayrıca bileşiklerin oluşum mekanizmaları tartışılacak ve kimyaları da incelenecektir.

Anahtar Kelimeler: Brominasyon, Hidrokarbon, Sübstitüsyon, Pentalene, Oktahidro-1H-inden, 1a,2,7,7a-tetrahidro-1H-siklopropa[b]naftalin.

To the great memory of my father

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LIST OF ABBREVIATIONS

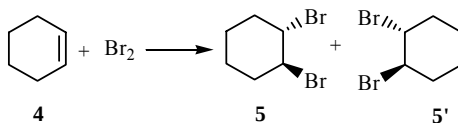
GC/MS	: Gas chromatography and mass spectrum
HBr	: Hydrogen bromide
HMBC	: Heteronuclear multi-bond coherence
HMQC	: Heteronuclear multiple quantum coherence
Hz	: Hertz
IR	: Infrared
IUPAC	: International union of pure and applied chemistry
J	: Coupling constant
k	: Rate constant
KOtBu	: Potassium <i>tert</i> -butoxide
<i>n</i> -BuLi	: <i>n</i> -Butyllithium
NBS	: N-Bromo Succinimide
NMR	: Nuclear Magnetic Resonance
ppm	: parts per million
RE	: Relative energy
T	: Temperature
THF	: Tetrahydrofuran
TS	: Transition structure

CHAPTER 1

INTRODUCTION

1.1 Simple Bromination of Alkenes

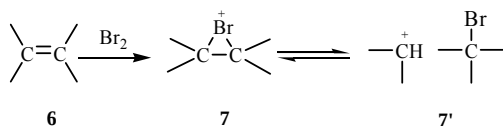
Alkene brominations are among the most general of organic reactions, and mechanistic study of these reactions has provided much detailed insights into the addition reactions of alkenes [1]. For example, addition of bromine to cyclohex-1-ene gives only the racemic *trans* product and none of the *cis*-meso product. A very intriguing aspect of the addition is that it is stereospecific.



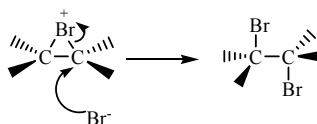
Two of the principal points at issue in the description of the mechanism for a given reaction are: (1) Is there a discrete positively charged intermediate, or is the addition concerted? (2) If there is a positively charged intermediate, is it a carbocation or a cyclic halonium ion?

The nature of the intermediates of the addition depends on temperature, steric factors, torsional effects, π - and σ -participation in the transition state and the formation of *non*-classical ions or a fast equilibrium of classical ions [2].

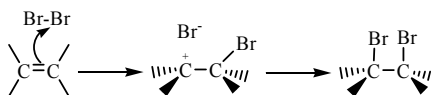
Interpretation of reaction stereochemistry has focused attention on the role played by cyclic bromonium ion.



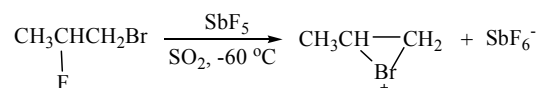
If the addition of Br^+ to the alkene results in a bromonium ion, the *anti* stereochemistry is readily explained. Nucleophilic ring opening by bromide ion would occur by back-side attack at carbon ($\text{S}_{\text{N}}2$), with rupture of one of the C-Br bonds, giving overall *anti* additions.



On the other hand, a freely rotating open carbocation would be expected to give both the *syn* and *anti* addition products. If the principal intermediate were an ion pair that collapsed faster than rotation about the C-C bond, *syn* addition could predominate.



There is direct evidence for the existence of bromonium ion. The bromonium ion related to propane can be observed by NMR spectroscopy when 1-bromo-2-fluoro propane is subjected to superacid conditions. The terminal bromine adopts a bridging position in the resulting cation [3].



The highly hindered alkene adamantylideneadamantane, forms a bromonium ion which crystallizes as a tribromide salt. An X-ray crystal structure has confirmed the cyclic nature of the bromonium ion species [4]. This particular bromonium ion does not react further because of extreme steric hindrance to back-side approach by bromide ion.

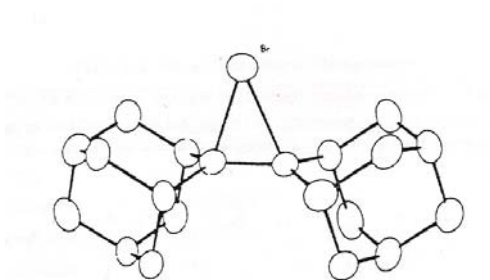


Figure 1 Crystal structure of bromonium ion from adamantylideneadamantane

An interpretation of activation parameters has led to the conclusion that the bromination transition states resemble a three-membered ring. It was found that for *cis*-*trans* pairs of alkenes the difference in the enthalpy at the transition state for bromination was greater than the enthalpy difference for the isomeric alkenes as shown in Figure 2. This finding indicates that the steric repulsions between *cis* groups increase on going from reactant to transition state. This would be consistent with a cyclic transition state in which the *cis* substituent was still eclipsed and somewhat closer together than in the alkene [5].

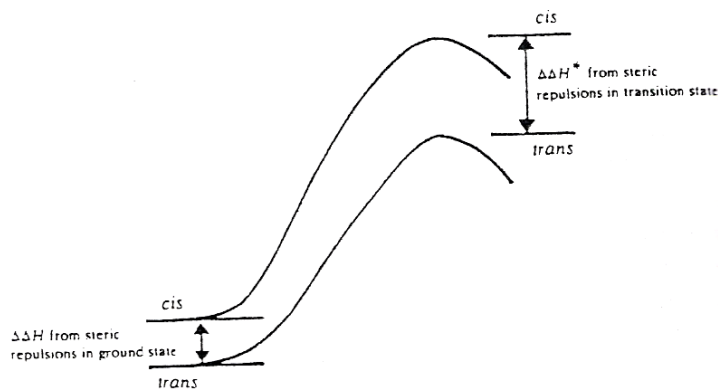


Figure 2 Enthalpy differences of starting alkenes and transition states in bromination.

The kinetics of brominations are often very complex, with at least three terms making contributions under given conditions [6].*

$$\text{Rate} = k_1[\text{alkene}][\text{Br}_2] + k_2[\text{alkene}][\text{Br}_2]^2 + k_3[\text{alkene}][\text{Br}_2][\text{Br}^-]$$

* For detailed discussion see ref. 5 and references therein.

1.2 Wagner-Meerwein Rearrangements

1,2-Shifts of migrating groups to empty orbitals in carbocations or toward partially empty orbitals in developing carbocations, are the most common rearrangements of organic molecules.

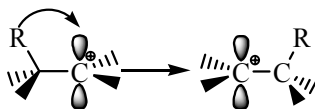
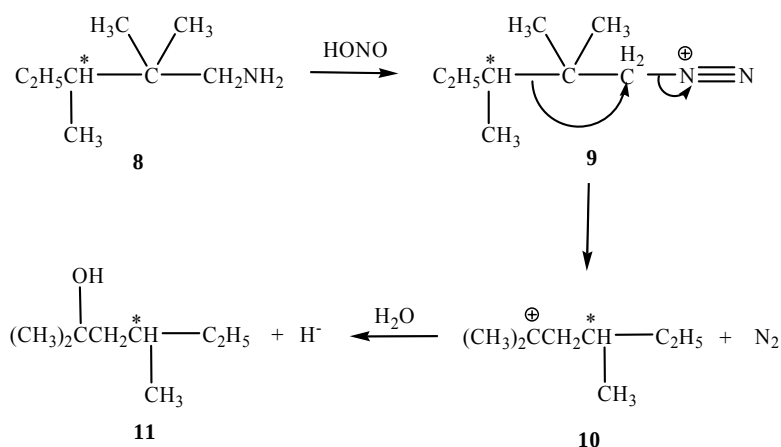


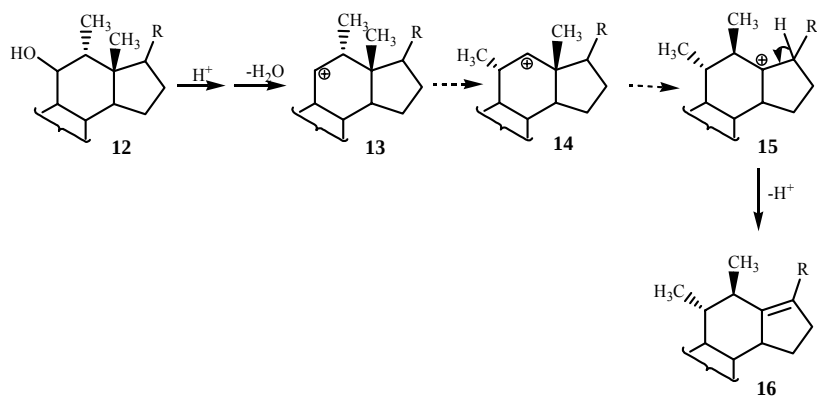
Figure 3 Rearrangement of a carbocation.

Migrations of hydrogen atom, alkyl or aryl groups in carbocations are often called Wagner-Meerwein rearrangements, in honor of the terpene chemists who first observed and studied the reactions [7].

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 [8].



Furthermore, in migrations of substituents on carbocyclic rings, the substituents invariably end up on the face of the ring from which they started [9].



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 described as “corner – protonated cyclopropanes”). That description requires that there be at least one proton on the migrating carbon.

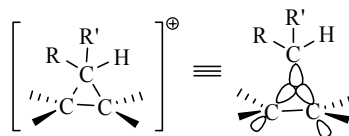


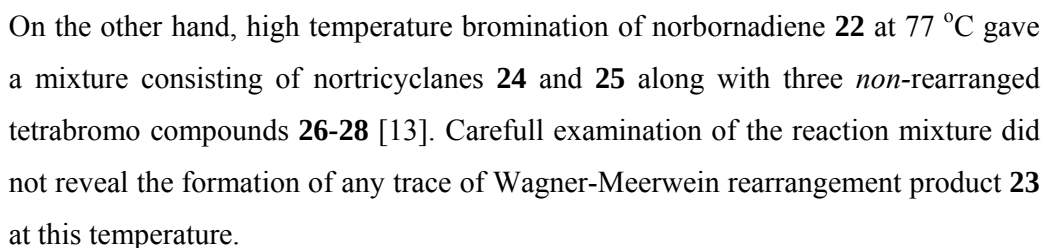
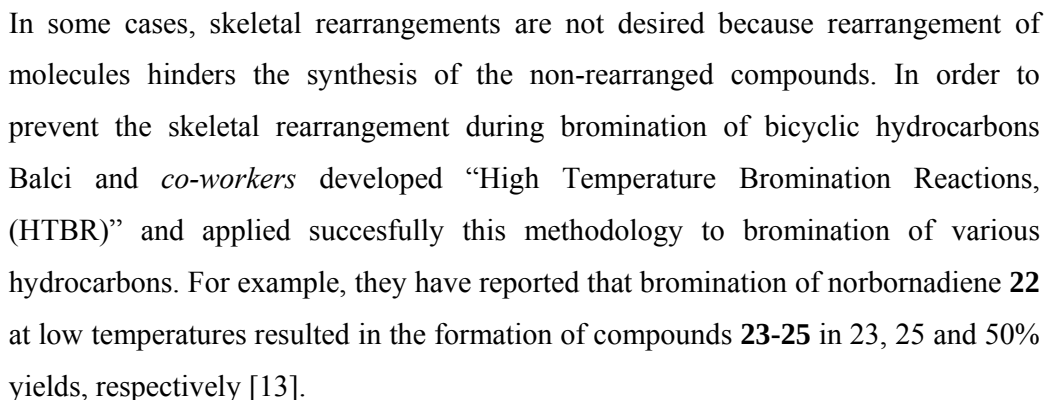
Figure 4 The transition state for Wagner-Meerwein rearrangement (a corner-protonated cyclopropane).

1.3 Bromination of Unsaturated Bicyclic Systems *

The bromination of unsaturated bicyclic systems with molecular bromine leads to rearrangements of the molecular skeleton [2,11]. Skeletal rearrangements in the reactions of bicyclic systems with various electrophiles have attracted a great deal of attention, particularly in relation to discussions about *non*-classical carbocations[11].

For example, bromination of norbornene **17** gives the rearranged product **21**, exclusively [12].

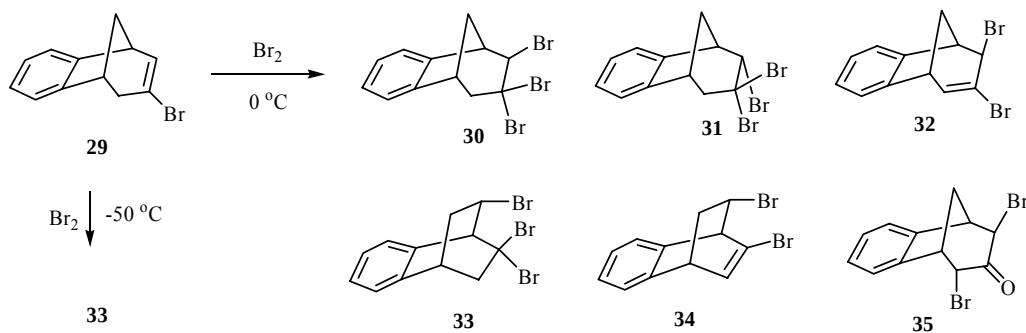
* For a detailed discussion see ref. 10.



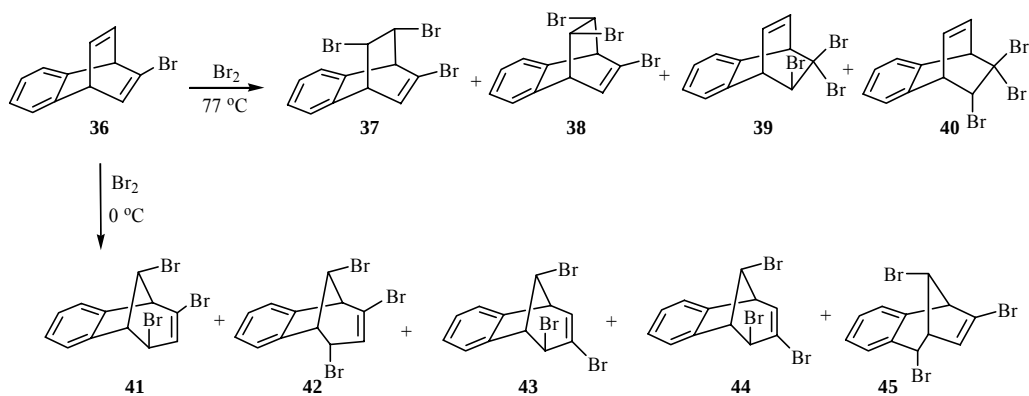
High temperature bromination method was also applied to benzobicyclic systems in order to investigate the mode of the reaction.

1.3.1 High Temperature Bromination of Benzobicyclic Systems

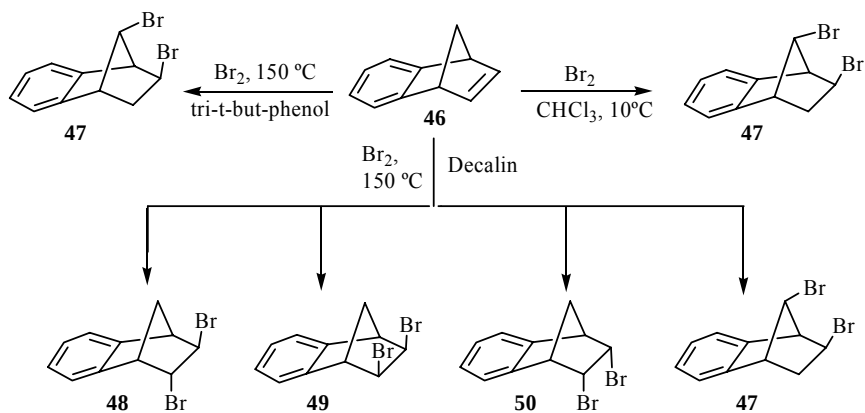
Earlier, in the course of bromination of 3-bromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene (**29**), Balci *et al.* noticed that the reaction temperature has a dramatically influence on the product distribution [14]. The bromination of **29** at -50 °C has been found to give only rearranged product, the tribromide **33** via Wagner-Meerwein rearrangement with accompanying aryl migration. The bromination of **29** at 0 °C produced *non*-rearranged tribromides **30-32** and **35** besides the rearranged products **33** and **34**.



In order to understand the different behaviour of the compound **29** at different temperatures, Balci *et al.* have investigated the bromination reaction of benzobarrelene derivative **36**. Electrophilic bromination of 2-bromobenzobarrelene **36** was carried out at 0 °C and only rearranged products **41-45** were obtained [15] contrary to the reaction of **29** at the same temperature. This showed that the reaction temperature (0°C) is not enough to prevent rearrangement. Therefore, the reaction temperature was raised to 77 °C and the expected *non*-rearranged products **37-40** were formed in high yields.



After bromination of [3.2.1] system **29** and [2.2.2] system **36** Balcı *et al.* have tested the bromination reaction of a [2.2.1] system **46**. The electrophilic addition of bromine to benzonorbornadiene **46** at 10 °C leads to the formation of rearranged product **47** in quantitative yield [16]. Nonrearranged product was not formed. Therefore, they tried the bromination reaction of **46** at 77 °C and they observed that *non*-rearranged product was formed in low yields. These results showed that the reaction temperature to prevent rearrangement depends on molecular structure. For the compound **29**, 0 °C is high enough to prevent skeletal rearrangement, on the other hand, for **36** a higher temperature, 77 °C, was desired. So, this fact encouraged authors to raise the bromination temperature higher in order to obtain *non*-rearranged bromination products derived from **46**. Indeed, the bromination reaction of benzonorbornadiene **46** at 150 °C produced the rearranged **47** and *non*-rearranged products **48-50** in a ratio of 1:4 [17].

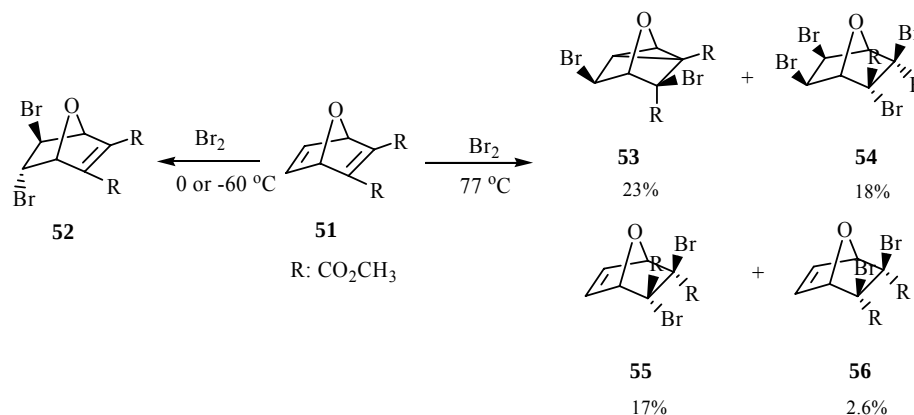


In general, electrophilic bromination of olefins yields *trans*-1,2-dibromides. *Cis*-Addition of bromine to double bond can not be explained via bromonium ion. Studies concerning the mechanism of *syn*-addition show that the *syn*-adduct can arise either from direct *syn*-collapse of an ion pair or from rotation followed by *anti*-collapse. Because of the rigid skeleton in **46**, a bond rotation is out of the question. In this case, they assumed that the high-temperature bromination is occurring by a free radical mechanism. Since radical intermediates are much less likely to rearrange, at higher temperatures they obtained mostly *non*-rearranged products. This could explain also their stereochemical results. Conducting the bromination reaction in the presence of free radical inhibitors like 2,4,6-tri-*tert*-butylphenol suppressed the formation of the *non*-rearranged products [17]. This strongly supports the assumption that there is a competition between radical and ionic reactions at high temperature.

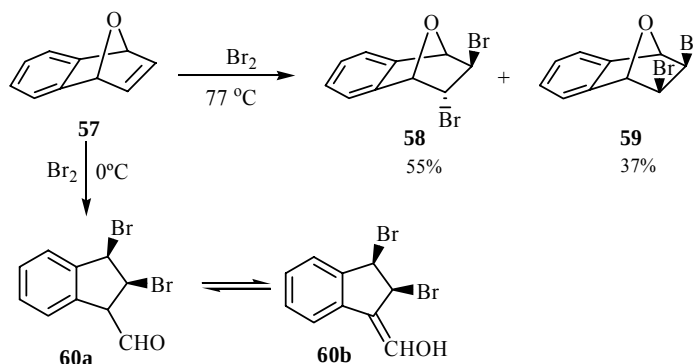
1.3.2 Heteroatom Effect on Bromination of Bicyclic Systems

In high temperature bromination reactions, electronic or steric factors determine the products. For example, benzonorbornadiene **46** needs higher temperature (150 °C) to obtain *non*-rearranged products [17]. Even at this temperature, rearranged product was also formed in yield 20%. In order to see the effect of the bridge atoms (oxa, aza), Balcı *et al.* have studied the bromination reactions of some heteronorbornadiene derivatives.

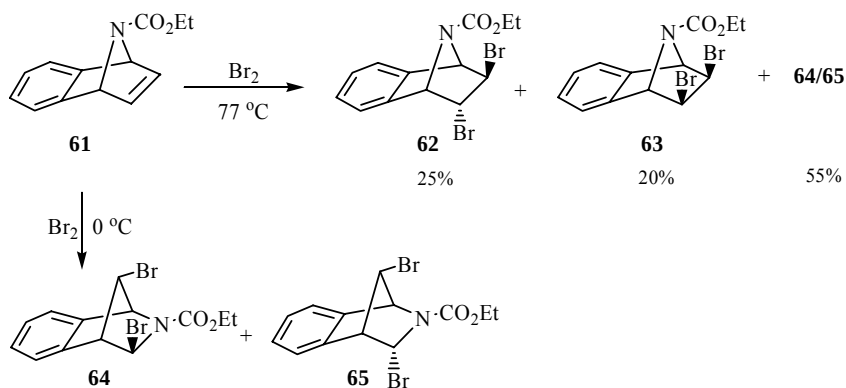
For example, high temperature bromination of oxanorbornadiene **51** at 77 °C gave four products **53-56**, which have mainly the *non*-rearranged skeletons [18].



However, oxabenzonorbornadiene **57** afforded *non*-rearranged products **58-59** at 77 °C in high yield [19].



On the other hand, bromination of aza compound **61** at 77 °C resulted in formation of rearranged **64-65** (55%) and *non*-rearranged products **62-63** (45%), respectively [20].



Bromo analogues of benzobicyclic alkenes behave differently in bromination reactions by comparison with parent molecules. For example, bromination of benzonorbornadiene **46** gives rearranged products even at 77 °C. However, bromination of 2-bromobenzonorbornadiene **66** at the same temperature results in formation of *non*-rearranged product in high yield [21]. Moreover, the reaction of 2,3,5-tribromobenzobarrelene **67** even at RT produced the *non*-rearranged product in quantitative yield [22]. This behavior of molecules shows that the introduction of heavy atoms to the double bonds prevents the skeletal rearrangement. It was assumed that the energies of the transition states are increased.

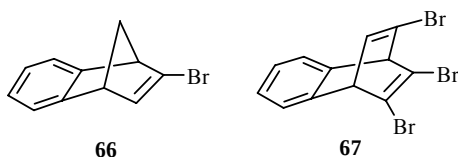
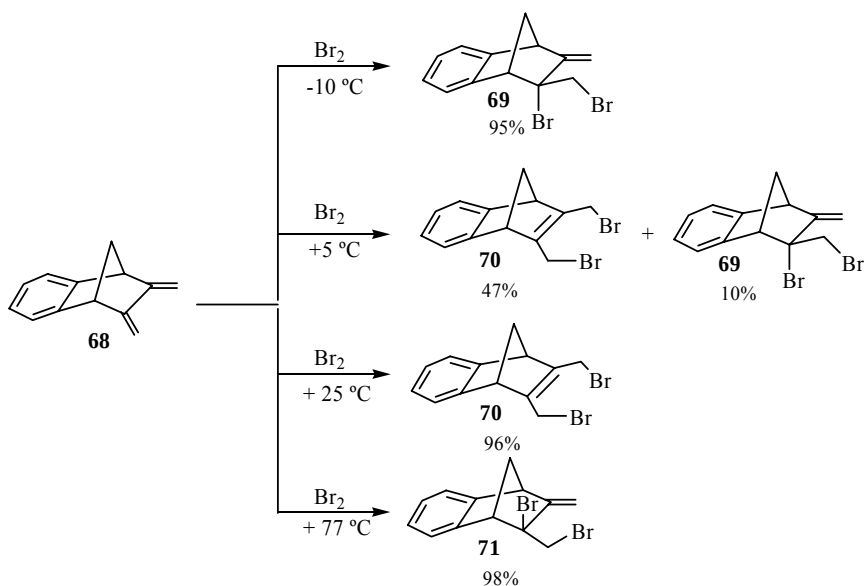


Figure 5 Substituted benzobicyclic systems.

1.3.3 High Temperature Bromination of *exo*-Cyclic Dienes

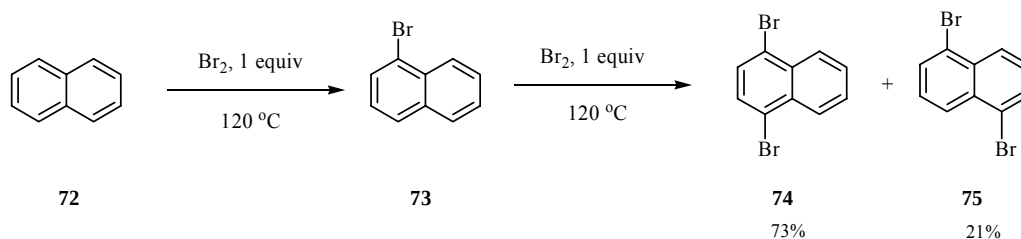
When electrophilic addition is carried out on a compound having *non*-conjugated dienes, the 1,2-*anti*-addition product is often obtained. In conjugated systems, the 1,4-*syn*-addition product is the most stable one (thermodynamically controlled product), and it predominates. In most cases, under the reaction conditions, the 1,2-addition product (kinetically controlled product) converts into a mixture of 1,2- and 1,4-addition products that is richer in the 1,4-addition product.

High temperature bromination *exo*-cyclic diene **68**, having benzobicyclic skeleton, gave interesting results [23]. For example, the reaction of **68** at -10 °C provided **69** as a sole product, which is formed by the 1,2-addition of bromine to the *exo*-cyclic double bond. Upon increasing the reaction temperature to 25 °C, 1,4-addition product **70** was obtained. The reaction of **68** at 77 °C resulted in formation of **71** in high yield. At first glance, this was surprising. But it was tested that the dibromide **71** is secondary product formed by thermal rearrangement of **69** and **70**.

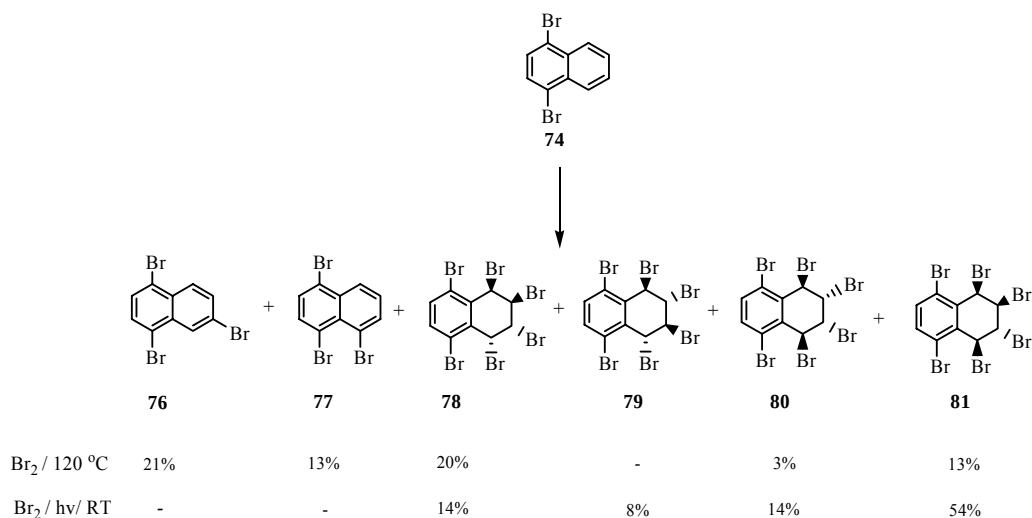


1.3.4 High Temperature Bromination of Aromatic Compounds

Bromination of naphthalene **72** at 120 °C with 1 equiv bromine gave 2-bromonaphthalene (**73**) in 90% yield as the sole product [24]. Further bromination of formed monobromide **73** at 120 °C with 1 equiv bromine afforded two dibromonaphthalene isomers **74** and **75** which were separated by crystallization and characterized as 1,4- and 1,5-dibromonaphthalene in a yield of 73 and 21%, respectively.



Further bromination of major component **74** at 120 °C without solvent resulted in the formation of five products **76**, **77**, **78**, **80** and **81**. Similar products were obtained by photochemical bromination at room temperature.



In summary, high temperature bromination of bicyclic olefins prevents Wagner-Meerwein rearrangement and provides ready access to various products which can not be synthesized under the normal bromination condition. High temperature

bromination of naphthalene provides the synthesis of highly substituted naphthalene derivatives.

1.3.5 Synthetic Aspect of High Temperature Bromination

Polymeric materials and synthetic fibers are extensively used in many areas. The demand for non-burning or flameretardant polymers is strong in various industries. Some of these flame retardant products contain brominated organic compounds such as polybrominated diphenyl ethers (PBDEs) **82**, hexabromocyclododecane (HBCD) **83**, tetrabromobisphenol A (TBBPA) **84** [25]. The compound **85** is also flame-retardant and it contains a brominated benzonorbornadiene moiety [26].

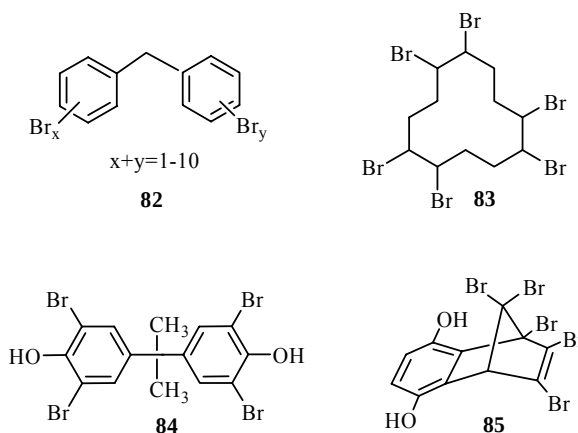


Figure 6 Polybrominated organic compounds.

Aside from the numerous industrial applications of these highly brominated compounds, such as pesticides, plastics, fire-retardants and pharmaceutical chemicals, they also play an important role as key compounds for the synthesis of other derivatives. For example, *di*-, *tri*- and *tetra*- bromobenzobarrelenes (**86**, **87**, **67** and **88**) firstly have been synthesized [15, 28], by the application of high temperature bromination reaction and were used for various purposes [27].

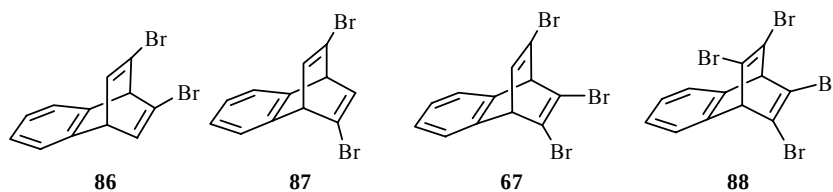


Figure 7 Di-, tri-, tetra-bromobenzobarralene derivatives.

High temperature bromination of benzonorbornadiene **46** allowed the synthesis of 2-bromobenzonorbornadiene **66** and 2,3-dibromobenzonorbornadiene **89** which are key compounds for synthesis of other derivatives [21].

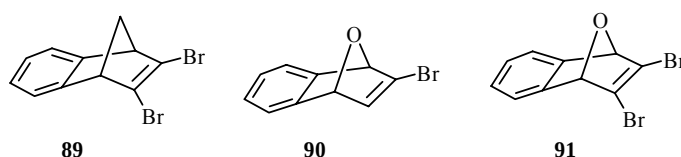
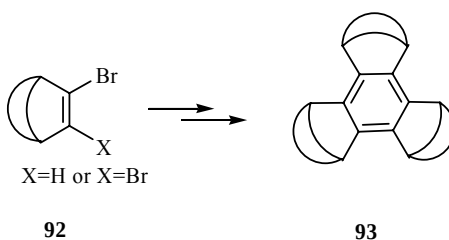


Figure 8 Bromobenzonorbornadiene derivatives.

The synthesis of mono- and dibromo-oxabenzonorbornadienes **90-91** was only accessible via this method [24]. Vinylic monobromides or dibromides **90-91** are indispensable key compounds for cyclotrimers **93** [28].



Schlosser and Castagnetti [38] used this method to obtain new naphthalene derivatives starting from dibromo oxabenzonorbornadiene derivatives. Kara *et al.* [30] obtained indanon derivatives starting from dibromo-oxabenzonorbornadienes.

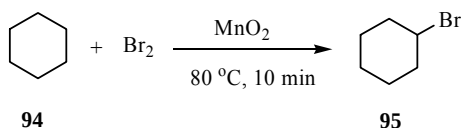
1.3.6 High Temperature Bromination of Saturated Hydrocarbons

Although saturated hydrocarbons are readily available and extremely cheap starting materials, they can not be used in synthetic chemistry without prior activation.

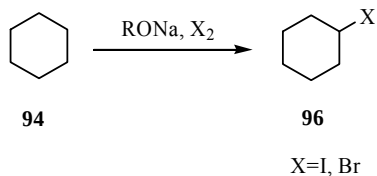
Efficient functionalization of alkanes leading to the production of useful organic chemicals in an industrial scale is of considerable interest for the chemical and pharmaceutical industries and remains a longterm challenge for chemists [31-34]. A number of methods employing transition metal reagents have been developed for the C–H bond activation of alkanes. However, these transformations, either stoichiometric or catalytic, often involve expensive metals such as Pd, Ru, Rh, Ir, or complex metal systems, and the recovery and direct reuse of catalysts are difficult [31-34].

The activation of alkanes can be done via halogenation with an appropriate method which leads to the direct synthesis of haloalkanes that are valuable and useful building blocks in synthesis. Among the haloalkanes, alkylbromides are the most important synthetic intermediates in chemical industry. For that reason, direct and selective bromination of alkanes would be of choice and it is certainly the ideal way to produce alkylbromides.

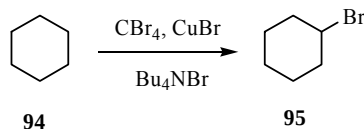
Considerable effort has been devoted to the selective halogenation [35-39] of saturated hydrocarbons and various reagents have been investigated. For example, Li *et al.* reported a novel chemoselective bromination of alkanes promoted by unactivated MnO₂ [37].



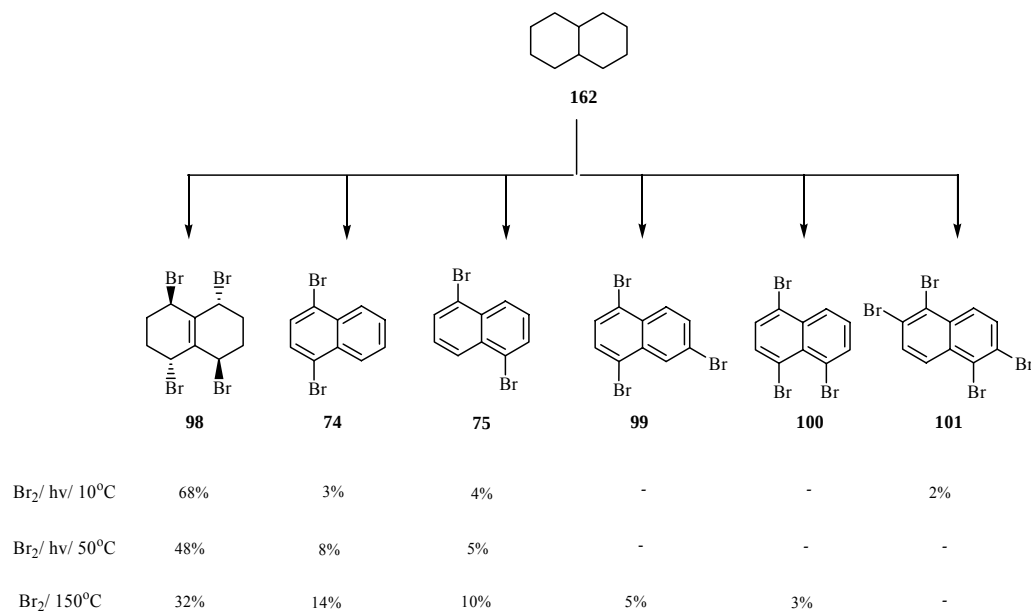
Wirth and Montoro reported that stoichiometric mixtures of elemental halogen and sodium alkoxides leads to the formation of alkyl hypohalides which can activate the C-H bonds of alkanes to furnish haloalkanes [38].



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 [39].

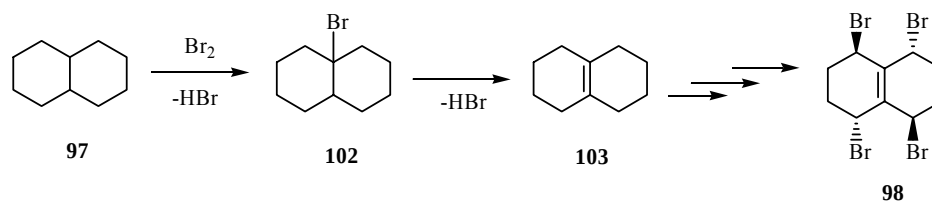


In this manner, Balci and Dastan have investigated the high temperature bromination of decalin **97**, a saturated bicyclic hydrocarbon [40]. They have reported that thermal bromination of decalin **97** gave *trans,cis,trans*-2,5,7,9-tetrabromooctalin, **98**, as the major product with remarkable regio- and stereospecificity along with smaller amounts of bromonaphthalene derivatives **74**, **75**, and **99-101** [40].



The formation of tetrabromide **98** was explained as follows: decalin **97** reacts with bromine radical to give a monobromide **102** from which HBr elimination affords octalin **103**. This alkene would undergo sequential allylic bromination reactions to furnish tetrabromide **98**. Although calculations demonstrate that the most stable tetrabromide is formed exclusively, it may well be that this is also the kinetically controlled product. Once the first bromine is placed on an allylic position, it may direct the second bromine *trans* to it either three or four carbons removed. If this

trans directing effect continues as subsequent bromines are placed on the ring, the diastereomer with all bromines *trans* would result. Such a kinetically controlled *trans* bromination causing the bromines to be as far as apart as possible could result from steric effects, bromine bridging in the radical, or a combination of these factors.



It is noteworthy that formation of tetrabromide **98** takes place with remarkable regio- and stereospecificity in contrast to the fact that radical reactions have a bad reputation for being not particularly selective.

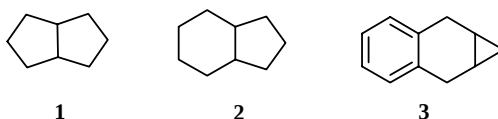
1.4 Aim of the Study

Although saturated hydrocarbons are readily available and extremely cheap starting materials, they can not be used in synthetic chemistry without prior activation.

Efficient functionalization of alkanes leading to the production of useful organic chemicals in an industrial scale is of considerable interest for the chemical and pharmaceutical industries and remains a long-term challenge for chemists. In this respect, halogenation of hydrocarbons which leads to a variety of useful synthetic intermediates is an open avenue which deserves special attention.

It is also noteworthy to mention that efficient methods for selective functionalizations of saturated bicyclic hydrocarbons still remains elusive, albeit a number of methods employing various reagents have been developed for the C–H bond activation of open chain and monocyclic alkanes.

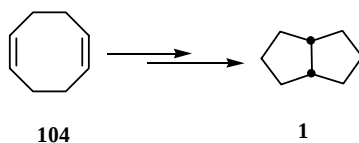
Encouraged by the pioneering work by Balci and Dastan [40] , we will investigate herein the high temperature bromination reactions as a method for functionalization of saturated bicyclic hydrocarbons such as octahydronaphthalene (**1**), octahydro-1H-indene (**2**) and 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (**3**). The scope and the limitations of the reaction will reveal the regio- and stereoselectivity. Furthermore, formation mechanism(s) of the product(s) will be discussed and the chemistry of these compounds will be extended for further functionalization.



CHAPTER 2

RESULTS AND DISCUSSION

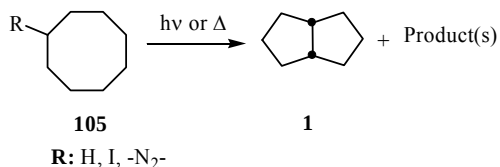
Our initial exploratory efforts directed towards the functionalization of saturated hydrocarbons involved the synthesis of octahydropentalene **1**. In the first part of the study, we concentrated on the synthesis of **1** and then submitted it to high temperature bromination reaction.



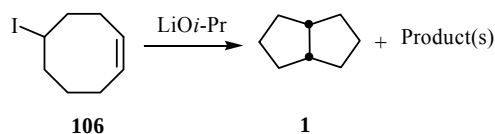
2.1 The Synthesis of Octahydropentalene (168)

2.1.1 Bicyclo[3.3.0] Skeleton

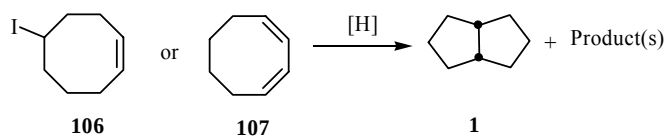
There exist some numerous synthetic routes which lead to the construction of the desired hydrocarbon skeleton **1** in the literature. Most of these methods were based on the reaction of an eight-membered ring analogue with a variety of reagents under appropriate conditions such as irradiation or thermolysis [41].



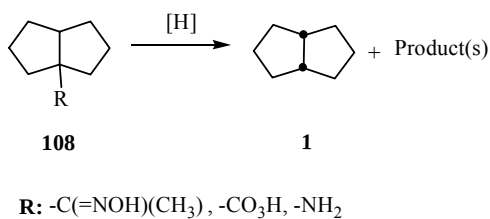
Base induced reaction of **106** affords the same skeleton along with some side products [42].



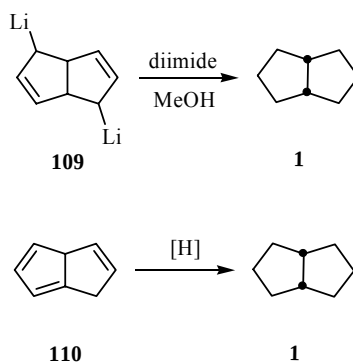
In addition, reduction of the unsaturated eight-membered rings such as **106** or **107** also provides hydrocarbon **1** [43].



It is also reported that some functionalized derivatives (R: -C(=NOH)(CH₃), -CO₃H, -NH₂) of bicyclo[3.3.0] skeleton **108** result in the formation of hydrocarbon **1** via reduction reactions [44].



Furthermore, reduction of unsaturated derivatives of the bicyclo[3.3.0] skeleton such as **109** and **110** gives the corresponding hydrocarbon **1** [45-46].



Despite the plethora of the aforementioned methods for the synthesis of **1**, all of them suffer from some drawbacks; i.e. low yields, formation of side products and/or

multistep synthesis. For that reason a simple, mild and efficient route which provides the desired hydrocarbon **1** in a reasonable yield would be welcome.

2.1.2 Transannular Cyclizations

Since ‘transannulation’ reactions were first described during independent electrophilic additions to medium ring cycloalkenes [47-48], they have been encountered in an enormous variety of carbo- and heterocyclic medium ring compounds having a wide array of differing functionalities. They occur frequently in medium, *i.e.* 8-, 9-, 10-, and 11-membered, rings where favored conformations allow opposite sides of the rings to come close to each other for bond formation. Indeed, the chemistry of these fascinating processes has now become part of the day-to-day armoury of modern synthetic chemists. An enormous variety of carbocyclic and heterocyclic medium ring compounds with a wide range of functional groups has been reported to undergo these fascinating processes for modern synthetic chemistry.

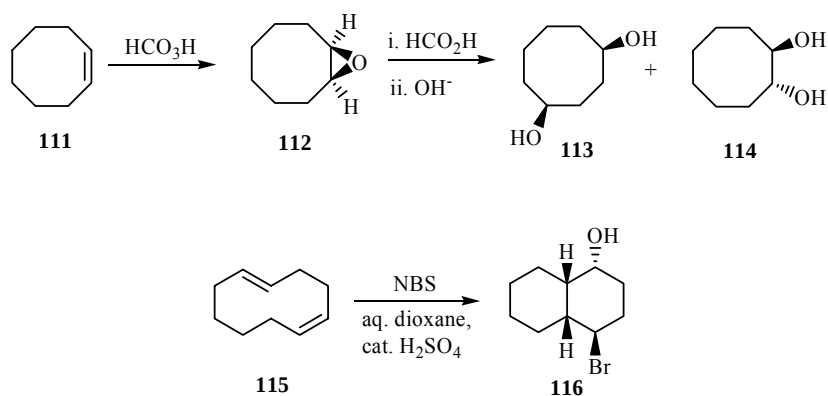
Transannular cyclizations which are defined as those reactions leading to the formation of a covalent bond between atoms on opposite sides of a ring compound are of much importance in the synthesis of polycyclic complex molecules. The transannular cyclization of medium-sized rings contributes to the enhancement of molecular rigidity and structural complexity, two properties often associated with biological activity in small molecules.

Furthermore, transannular cyclization is a sophisticated method for construction of polycyclic natural products and molecules of theoretical and structural interest. Such an intramolecular cyclization is largely dependent on the nature of the reaction (e.g., carbanions [49], carbocations [50] radicals [51], carbenes [52], pinacol coupling [53] and electrocyclic reaction [54]), reactivity of the two ends groups, and geometrical features of the reacting ring molecules. Transannular cyclizations require a suitable conformation of substrates and prudent selection of functional groups.

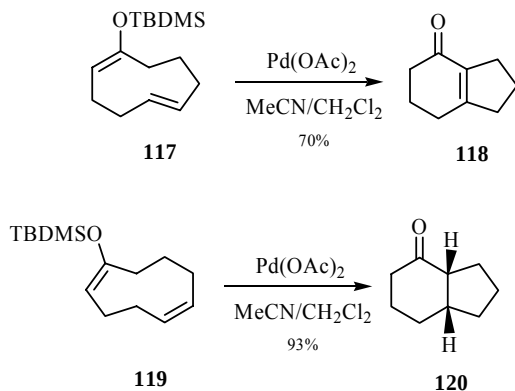
In this regard, comprehensive knowledge of factors governing reactivity will yield insight into widespread application of transannular reactions. Transannular cyclizations involving carbocations generated from cyclodeca- and cycloundecapolyenes have been the subject of extensive research, largely in connection with the

understanding of the biosynthesis of a wide range of polycyclic sesquiterpenes [55]. Indeed, these fundamental studies have now led to a number of new ‘biogenetically inspired’ syntheses of a large of complex ring-fused natural products of both synthetic significance and biological importance [56].

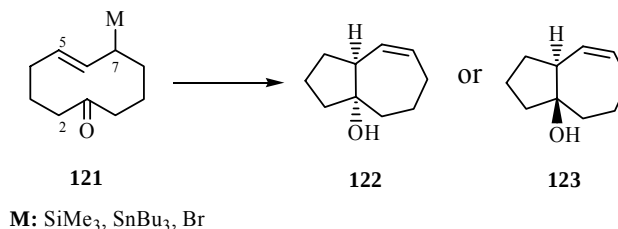
Probably, the most commonly encountered transannulation processes are those involving H-transfer reactions [57], from, for example, ring epoxides, i.e. **112** to **113** those involving ring closure reactions, i.e. **115** to **116** [58].



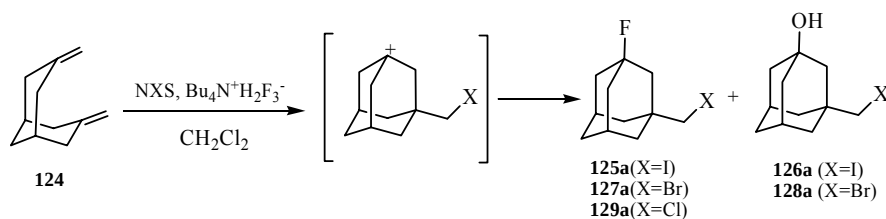
The transannular cyclizations of the two nine-membered enolsilanes **117** and **119** using stoichiometric $\text{Pd}(\text{OAc})_2$ led, respectively, to two different bicyclo[4.3.0]ketones **118** and **120** in good yields [68]. (*E*)-Cycloalkane enolsilane **117** produced the α - β -unsaturated ketone **118**, whereas the (*Z*)-cycloalkene enol silyl ether **119** led to the cis-bicycloalkenone **120**.



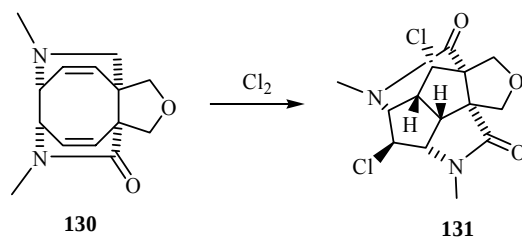
White *et al.* have reported that the regio- and stereochemistry of the transannular cyclizations of 5-cyclodecenones **121** can be controlled by substituents on the ring by the choice of reaction conditions [60].



Transannular cyclization of dialkylidene-substituted bicyclo[3.3.1]nonanes (dienes) by electropilic reagents (iodine, bromine, acids) is a selective method for the preparation of adamantane derivatives [61].

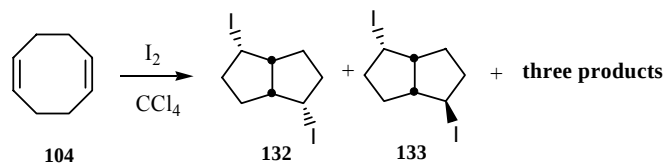


The topological connection between a cyclooctane and fused five-membered rings has long been recognized in terms of constructing the bicyclo[3.3.0] skeleton [62].

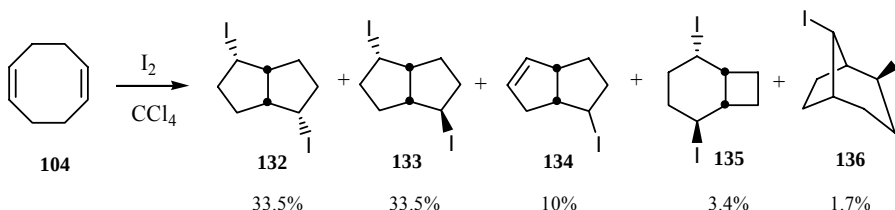


2.1.3 Iodination of *cis,cis*-1,5-cyclooctadiene (**104**): Transannular Cyclization

In order to obtain the desired hydrocarbon skeleton in a reasonable yield, we started with *cis,cis*-1,5-cyclooctadiene (COD) (**104**). Uemura *et al.* reported that the treatment of COD with iodine smoothly gave **132** and **133** [63] via a transannular cyclization along with the three unidentified minor products [64].



Repetition of the reaction according to the reported conditions afforded a complex mixture consisting of **132**, **133**, **134**, **135**, and **136** in a ratio of 20:20:6:2:1, respectively.

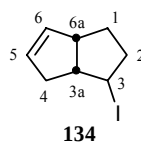


The major products, **132** and **133**, were isolated by the crystallization of the reaction mixture from hexane in a yield of 67%. This mixture was subjected to column chromatography to give **132** and **133** separately as white solids in approximately equal amounts. The spectral data for **132** and **133** were in full agreement with the those previously reported [63-64]. It is easy to distinguish compounds **132** and **133** on the basis of ^{13}C -NMR spectra which consist of four- and eight-lines, respectively.

After the removal of **132** and **133**, the residue was subjected to repeated column chromatography, and three compounds were also isolated: 3-iodo-1,2,3,3a,4,6a-hexahydropentalene (**134**), trans-2,5-diiodo-bicyclo[4.2.0]octane (**135**), and 2,8-diiodo-bicyclo[3.2.1]octane (**136**). The structures of all the compounds were determined by ^1H -, ^{13}C - and 2D-NMR experiments (DEPT, COSY, HMQC, HMBC)*.

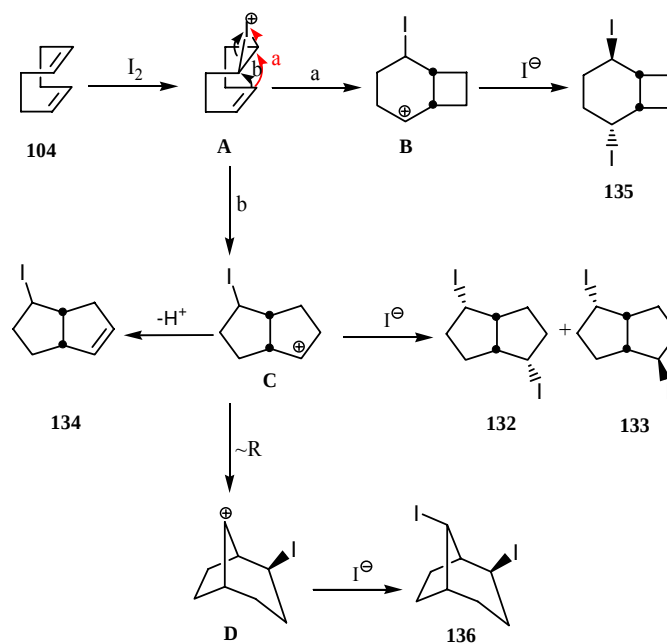
The ^1H -NMR spectral studies on **134** revealed the presence of olefinic protons (H_5 and H_6) at 5.65 ppm as broad singlet along with a quintet (H_3 , $J=5.2$ Hz) at 4.10 ppm and six sets of multiplets at 3.35 (H_{6a}), 3.25 (H_{3a}), 2.74 (H_4), 2.27-2.14 (H_1 and H_2), 2.14-2.00 ($\text{H}_{1'}$ and $\text{H}_{4'}$), 1.52 (H_2) ppm.

* See Appendix for spectral data.



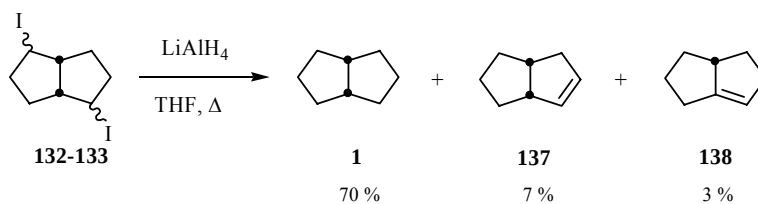
The ^{13}C -NMR spectrum of **201** also indicated two olefinic carbons at 134.5 (C_6) and 128.6 (C_5) along with six saturated carbon signals at 54.4 (C_{3a}), 49.6 (C_{6a}), 39.9 (C_4), 38.3 (C_2), 36.6 (C_3), 31.1 (C_1).

A plausible mechanism for the formation of the products is summarized below. The addition of iodine to one of the double bonds first gives the iodonium intermediate **A**, which then rearranges to two different carbocations, **B** and **C** via two possible transannular π participations. The attack of iodine on the formed carbocations, **B** and **C**, affords **135** and **132-133**, respectively. However, intermediate **C** may also eliminate hydrogen to give **134**, or may further rearrange by the alkyl shift to **D**, of which substitution gives **136**.



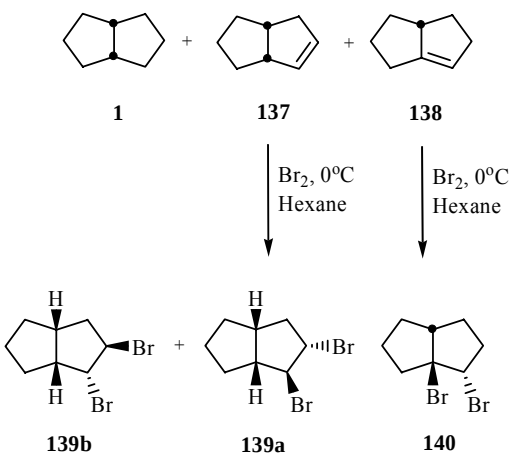
2.1.4 Reduction of **132** and **133** with LiAlH_4

Reduction of the mixture of **132** and **133** with LiAlH_4 in refluxing THF afforded octahydopentalene (**1**) as the major product in 70% yield with smaller amounts of **137** and **138** in a ratio of 20:2:1, respectively.



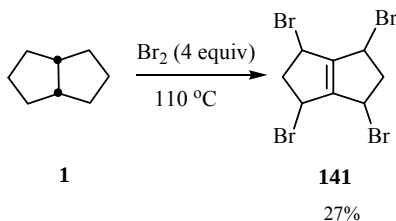
Compounds **137** and **138** probably arise from the competing elimination path under the given reaction conditions. Unfortunately, all of our initial attempts to separate the mixture by fractional distillation failed.

Then the mixture consisting of **1**, **137**, and **138** was treated with bromine at 0 °C in the dark in which the hydrocarbon **1** was successfully separated from the formed dibromides **139** and **140** by column chromatography or simple distillation in 70% yield.

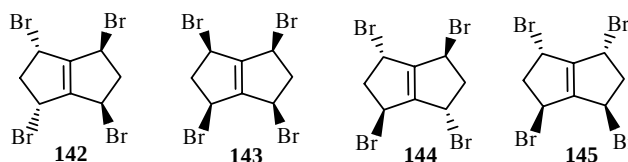


2.2 High Temperature Bromination of **1** with 4 equiv Br_2

The treatment of octahydropentalene (**1**) with 4 equiv of bromine at 110 °C over a period of 1.5 h afforded the tetrabromide **141** in a yield of 27%.



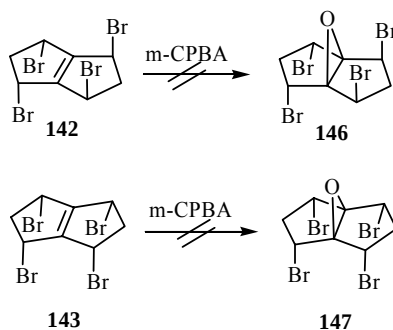
The ^1H - and ^{13}C -NMR studies of the tetrabromide showed the formation of a highly symmetrical compound. The ^{13}C -NMR spectrum consisted of three distinct carbon resonances indicating high symmetry in the molecule. This could be in agreement with four possible diastereomeric structures **142**, **143**, **144**, and **145**.



The ^1H -NMR spectrum of the isolated compound shows three sets of signals. The methine protons appear as a doublet of doublets at 5.04 ppm ($J=7.0, 1.5$ Hz) and the methylene protons appear as an AB-system as two doublets of triplets at 3.76 ppm (A-part of AB-system, $J=16.5, 7.1$ Hz) and 3.15 ppm (B-part of AB-system, $J=16.5, 1.5$ Hz). The magnitude of the coupling constants (J) between the methylenic protons of cyclopentene ring ($J=16.5$ Hz) was also in agreement with the literature [65-66].

In the case of **144** and **145** the methylenic protons are equal and would not give rise to the formation of an AB-system. Therefore, the structures **144** and **145** were excluded. However, on the basis of NMR data alone, we were not able to distinguish between the possible symmetrical tetrabromides **142** and **143**.

Then, we carried out some reactions with the bromination product such as epoxidation with the central double bond in order to distinguish between the isomers **142** and **143**. We envisaged that the epoxides **146** and **147** formed in this reaction would be different from each other.



The ^1H -NMR spectrum of compound **146** would show two different sets of AB-systems for the methylenic protons. On the other hand, for epoxide **147**, since the methylenic protons are equal, they would give rise to only one AB-system.

However, attempts to carry out epoxidation reaction with the central double bond, was unfortunately failed and the starting material remained essentially unaltered. Apparently steric effects associated with the adjacent bromine atoms preclude a reaction with the central double bond. Finally, the structure of tetrabromide was unambiguously identified by the X-ray crystallographic analysis to be *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene, compound **142**.

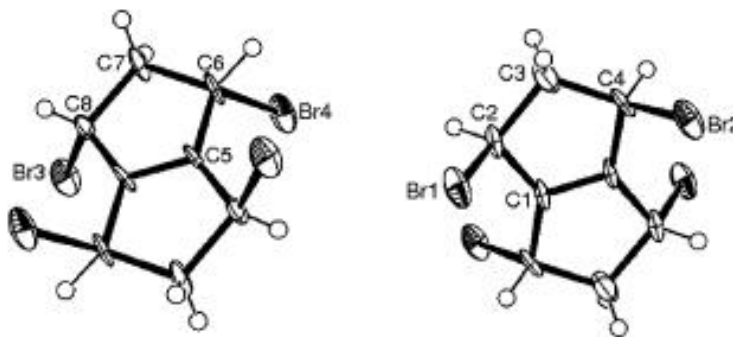
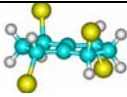
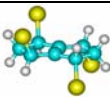
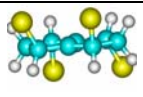
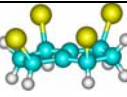


Figure 9 X-Ray Crystal Structure of **142**.

AM1 and MM+ molecular mechanics calculations show that the isomer **142** and **144** are close in energy and they are approximately 2–4 kcal/mol more stable than the other isomers. According to these values it was expected that the isomer **144** should also be formed. Careful examination of the reaction mixture did not reveal the formation of any trace of the isomer **144**, to where we assume that **142** is favored kinetically.

Table 1 The AM1 calculated heats of formation and MM+ relative strain energies in kcal/mol of diastereomeric tetrabromides **142-145**.

Tetrabromides	 144	 142	 145	 143
AM1	0.00	0.04	1.83	2.41
MM+	0.00	0.25	4.16	3.25

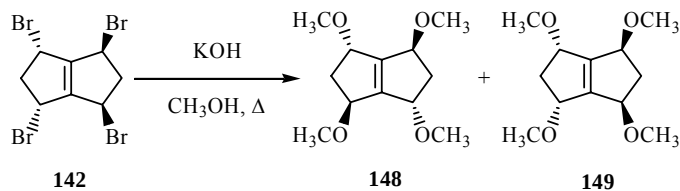
The appealing feature of high temperature bromination reaction is that it takes place with remarkable regio- and stereospecificity in the case of saturated bicyclic hydrocarbons. It may be recalled that decalin **97**, an unsaturated bicyclo[4.4.0] system, affords *trans,trans,trans*-2,5,7,9-tetrabromooctalin **98** with remarkable regio- and stereospecificity. On the other hand, octahydropentalene **1**, bicyclo[3.3.0] appendage provides *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene **142**. These results suggest, perhaps counterintuitively, that the configurations of bromines are not regardless of the size of the ring under investigation. Because in the case of a six-membered ring (decalin, **97**) bromines prefer all *trans*- arrangement perhaps relevant to steric factors whereas in the case of a five-membered ring (octahydropentalene, **1**) bromine atoms prefer *cis,trans,cis*- arrangement where the steric affects are relagate to a minor role.

In what follows, we will first try to expand the chemistry of compound **142** and then we will adress the relationship between the size of the carbocyclic ring and the spatial arrangement of bromine atoms throughout the high temperature bromination reactions. The sheer number of exemplified saturated hydrocarbons discussed so far, i.e. bicyclo[4.4.0] and bicyclo[3.3.0] systems, underscores the relative configuration of the bromine atoms in the products **98** and **142**.

2.3 Further Functionalization of Tetrabromide **142**

2.3.1 Substitution of Bromines

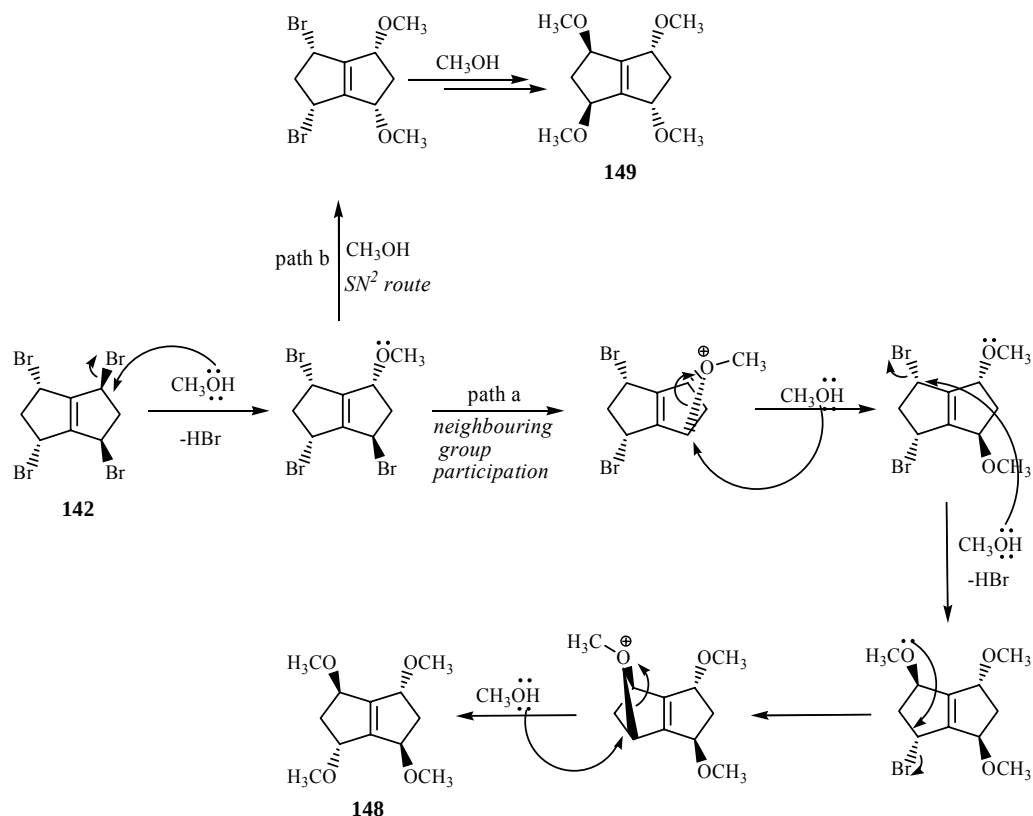
In order to further functionalize the isomer **142** it was treated with KOH in refluxing MeOH, in which the reaction afforded tetramethoxy compounds **148** and **149** in a ratio of 2:1, respectively.



The ¹H-NMR spectrum of **148** shows three sets of signals. The methoxyl protons give sharp singlet at 3.34 ppm whereas the protons adjacent to methoxyl group appear as a triplet at 4.53 ppm (*J*=5.0 Hz). The fact that the methylenic protons also appear as a triplet at 2.44 ppm (*J*=5.0 Hz) indicate the all-*trans*-configuration. A four-line ¹³C-NMR spectrum with signals at 155.0, 80.5, 56.9 and 42.9 ppm is also in agreement with the structure.

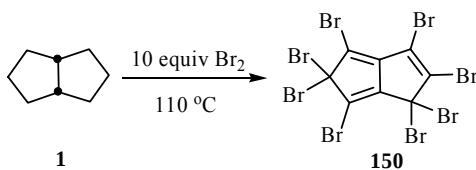
On the other hand, the ¹H-NMR spectrum of **149** consists of a doublet of doublets at 4.38 ppm (*J*=7.0, 3.6 Hz), a sharp singlet at 3.38 ppm and an AB-system at 2.92 (A-part of AB-system, *J*=14.1, 7.0 Hz) and 2.03 ppm (B-part of AB-system, *J*=14.1, 3.7 Hz), which strongly indicates the *cis*-orientation of the methoxyl groups as of the bromines in the case of tetrabromo compound **142**.

The stereochemical outcome of the reaction was also noteworthy that the bromine atoms are converted into methoxyl groups, perhaps via a mechanism where both monomolecular (S_N¹, path a) and unimolecular (S_N², path b) substitutions were involved as depicted below.

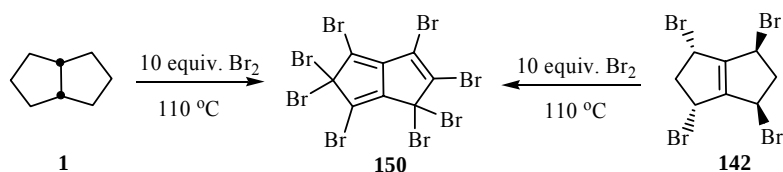


2.3.2 High Temperature Bromination of **1** with excess Br_2

Octahydronaphthalene **1** was treated with 10 equiv of bromine under the same reaction conditions as reported for the synthesis of **142**. Fractional crystallization and ^1H - and ^{13}C -NMR spectral studies indicated the formation of a product, which did not contain any protons. The ^{13}C -NMR spectrum showed eight distinct signals resonating at 145.7, 138.7, 134.8, 125.7, 118.4, 117.7, 64.4 and 45.7 ppm indicating the presence of an asymmetric structure.



Furthermore, high temperature bromination of **142** provided exactly the same compound **150** when submitted to the identical reaction conditions.



The structure of this compound **150** was unambiguously determined by X-ray crystallographic analysis, indicating the presence of eight bromine atoms.

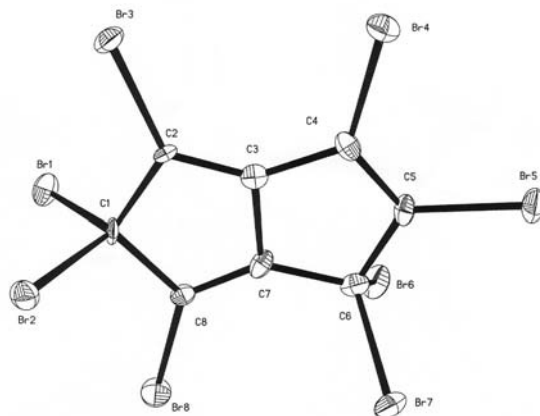
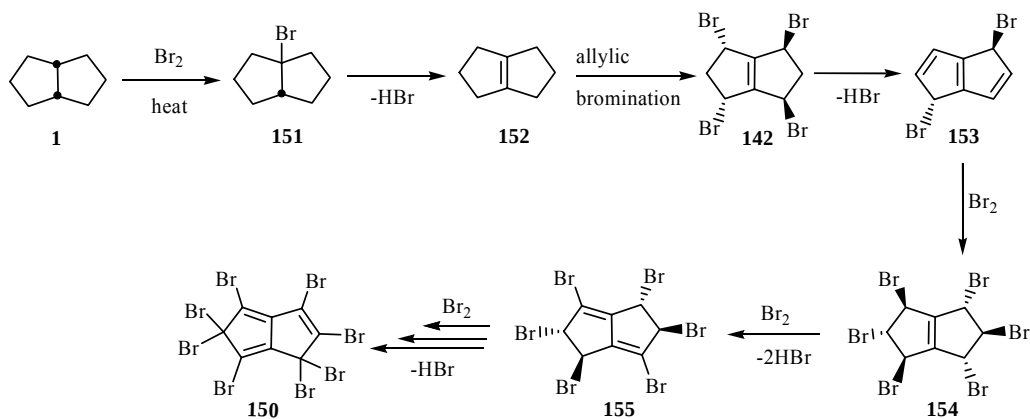


Figure 10 X-Ray Crystal Structure of **150**.

In view of the mechanism, we assume that octahydronaphthalene (**1**) reacts with bromine radical to give the monobromide **151**, from which HBr elimination affords the alkene **152**. This alkene would undergo sequential allylic bromination reactions to furnish tetrabromide **142** with remarkable regio- and stereospecificity. The formation of the octabromo **150** compound can be rationalized by tandem HBr elimination followed by bromine addition.



We assume that the octa-bromide **150** is probably the most stable product under the given reaction conditions. Greatifyingly, in an attempt to trap the intermediates such as penta- hexa- and heptabromides, we were able to isolate a few crystals of two intermediates as **154** and **155**. The structures of these intermediates were determined by X-ray crystallography which were shown below.

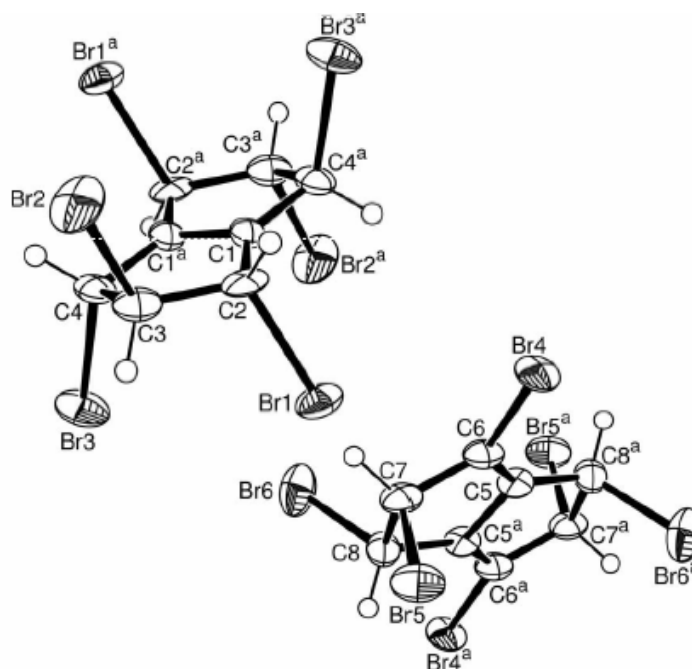


Figure 11 X-Ray Crystal Structures of Hexabromo Intermediates **154-155**.

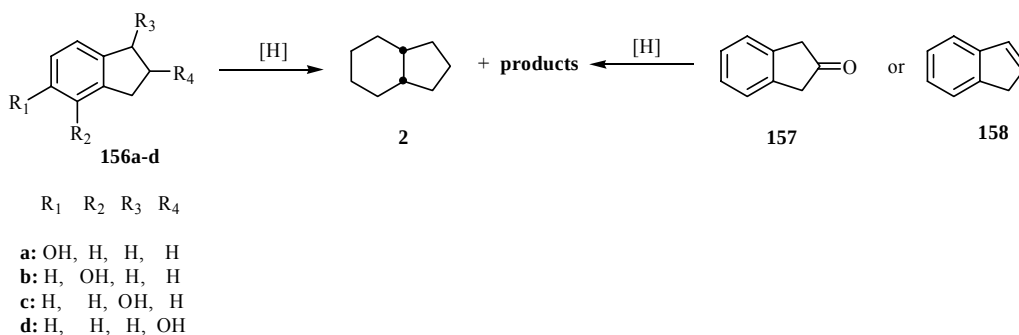
Thus far, as a method for functionalization of saturated hydrocarbons, the versatility of high temperature bromination reaction which takes place with remarkable regio- and stereospecificity was elucidated indirectly via tetrabromide **142**. It was noticed that tetrabromide **142** obtained by the high temperature bromination reaction of octahydopentalene **1** can easily be converted to some other derivatives such as the corresponding methyl ethers **148-149** and/or octabromide **150** which serve a great synthetic potential en route to pentalene derivatives.

In order to get further insights into the origin of the regio- and stereospecificity which determine the prominent feature of bromine atoms during high temperature bromination reactions, bicyclo[4.3.0] system, an unsymmetrical appendage was

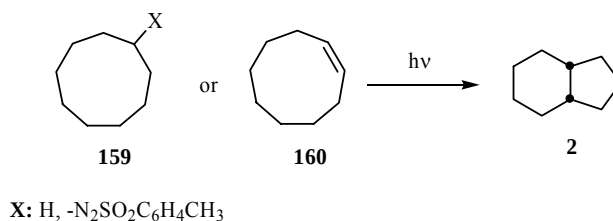
taken into account with the hope of shedding light to the exotic relationship between the size of the carbocyclic ring and the spatial arrangement of bromine atoms.

2.4 Bicyclo[4.3.0] Skeleton 169

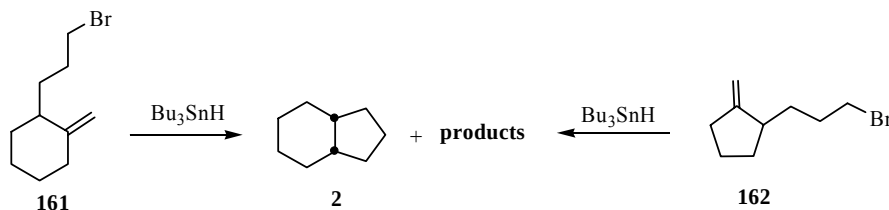
There are some numerous routes for the synthesis of bicyclo[4.3.0] skeleton **2**. Most of these methods were based on the reduction of the aromatic appendages (alcohol derivatives **156a-d** [67], keton **157** [68], indene **158** [69]) with an appropriate metal catalyst under a variety of reaction conditions, i.e. high temperature and pressure.



The irradiation of the nine-membered ring analogues such as **159** [70] and **160** [71] were also reported to give the same hydrocarbon **2**.

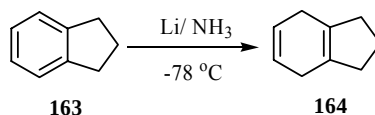


Radical cyclizations of bromo compounds such as **161** [72] or **162** [73] provide bicyclic hydrocarbon **2** albeit in low yields.

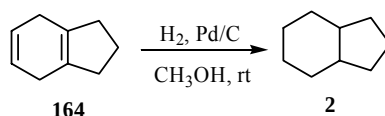


2.4.1 The Synthesis of Octahydro-1H-indene (2)

In order to obtain the bicyclo[4.3.0] skeleton **2** we started with indane **163**. Birch reduction of indane **163** at low temperatures provided the 2,3,4,7-tetrahydro-1H-indene (**164**) in 94% yield [74].

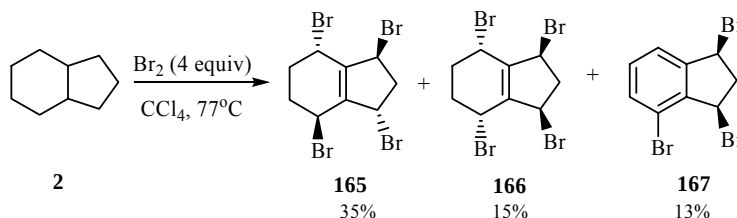


Catalytic hydrogenation of **164** with Pd/C in MeOH gave the desired octahydro-1H-indene (**2**) in 90% yield. The spectroscopic data for compound **2** was in agreement with literature [67-73].



2.4.2 High Temperature Bromination of 2 with 4 equiv Br₂

The treatment of octahydro-1H-indene (**2**) with 4 equiv of bromine at 77 °C in CCl₄ solution over a period of 20 min provided a mixture consisting of three products (1S,3S,4S,7S)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (**165**), (1R,3S,4S,7R)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (**166**) and (1S,3R)-1,3,4-tribromo-2,3-dihydro-1H-indene (**167**), 35, 15 and 13% yields, respectively.



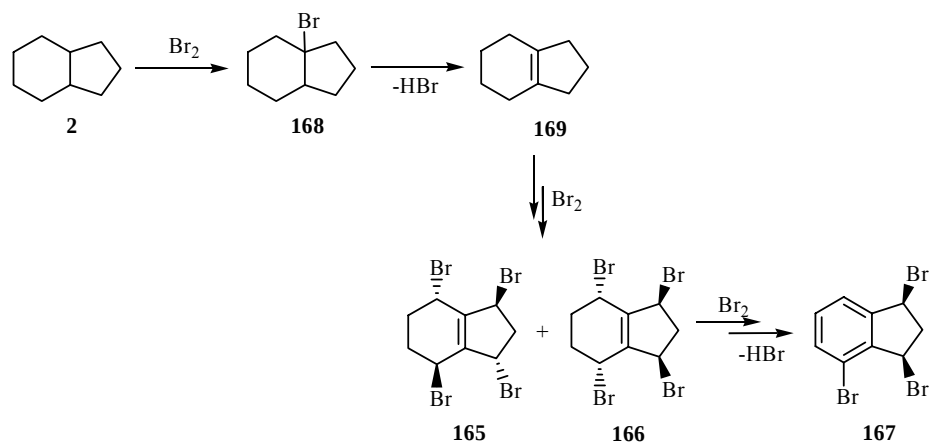
The ¹H-NMR spectrum of compound **165** indicate that the protons (H₁ and H₃) adjacent to bromine atoms in the five membered ring resonate at 5.12 ppm as triplet (J=5.5 Hz) whereas the protons adjacent to bromine atoms in the six-memebered ring (H₄ and H₇) resonate at 5.05 ppm as multiplets. On the other hand, the methylenic

protons of the five membered ring (H_2 and $H_{2'}$) give rise to a triplet ($J=5.5$ Hz) at 3.04 ppm which clearly indicate the *trans*- orientation of the bromines in this ring. 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.

Notably, the ^1H -NMR spectrum of **166** is quite different from that of **165**. The protons (H_1 and H_3) adjacent to bromine atoms of the five membered ring give rise to a doublet at 5.21 ppm whereas the protons (H_4 and H_7) adjacent to bromine atoms 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 (1H, dt, $J=16.7$, 7.0 Hz, H_2) and 2.82 (1H, d, $J=16.7$ Hz, $H_{2'}$) ppm which proves the *cis*- configuration of the bromine atoms along with a multiplet at 2.43-2.34 (4H, m, H_5 , $H_{5'}$, H_6 , $H_{6'}$) for methylenic protons of the six membered ring. A similar ^{13}C -NMR spectrum as in the case of compound **160** is obtained.

However, a nine line ^{13}C -NMR spectrum for compound **167** indicates the presence of an unsymmetrical structure. ^1H -NMR spectrum of compound **167** consists of seven distinct signals three of which are in the region of aromatic protons and resonate at 7.48 (1H, d, $J=7.8$ Hz, H_5), 7.40 (1H, d, $J=7.5$ Hz, H_7) and 7.19 (1H, t, $J=7.8$ Hz, H_6) ppm. H_3 and H_1 protons adjacent to bromine atoms give rise to a singlet at 5.65 ppm and a broad doublet at 4.84 ppm, respectively. The methylenic protons gives an AB-system at 3.77 (1H, dd, A-part of AB-system, $J=18.0$, 5.3 Hz, H_2) and 3.35 (1H, d, B-part of AB-system, $J=18.0$ Hz, $H_{2'}$) ppm that indicates the *cis*- configuration of bromine atoms in the unsaturated ring.

In view of formation mechanism of the products, more or less the same events as in the cases of decalin **97** and octahydropentalene **1** might be suggested. Initially, bromine reacts with octahydro-1H-indene **2** to give monobromide **168** from which HBr elimination affords 2,3,4,5,6,7-hexahydro-1H-indene (**169**). Sequential allylic bromination of intermediate **169** would result in the formation of compounds **165** and **166**. It is also tempt to think that compound **166** is not so stable as **165** under the reaction conditions which endeavors tandem bromination-elimination reactions providing compound **167**.



At this point, it is quite interesting but not surprising that high temperature bromination of an unsymmetrical saturated bicyclic hydrocarbon appendage, a [4.3.0]system, results in the formation of two isomeric tetrabromides **165** and **166** some part of which undergoes aromatization under the reaction conditions. Significantly, the regiospecificity of the high temperature bromination reaction is still preserved albeit the stereospecificity was diminished to lesser extent in the case of an unsymmetrical hydrocarbon appendage **2**, a bicyclic[4.3.0] system.

Our success exemplified with [4.4.0], [3.3.0] and [4.3.0] skeletons stimulated us to investigate the fate of a cyclopropane containing hydrocarbon, namely 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene **2**. The question to be addressed in this episode is that ‘what happens to the regio- and/or stereospecificity of high temperature bromination reaction in the presence of such a labile and strained small ring as cyclopropane?’. The answer would also shed light to some related mechanistical arguments.

2.5 Cyclopropane Case

2.5.1 Reaction of Cyclopropane Ring with Bromine

In many reactions, cyclopropane rings resemble double bonds in behavior and give analogous products [75]. It may be recalled that the σ -orbitals of cyclopropane rings are bent and in some respects resemble π orbitals. Molecular orbital calculations show that the carbon-carbon bonds in cyclopropane are not completely σ character. In normal C-C bonds, sp^3 orbitals overlap in such a way that the straight line

connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed away from the ring [76].



Figure 12 Orbital Overlap in Cyclopropane. The arrows point toward the center of electron density.

For cyclopropane, the angle (marked with Θ) is 21° . The bonds in cyclopropane are intermediates in character between σ and π , and are called bent or banana bonds.

Furthermore, angle strain in cyclopropane is 30 kcal/mol whereas six-membered rings are nearly strain free. Because of increased ground state energy resulting from angle strain, reactions which lead to the ring opening often proceed much more readily than do similar reactions in unsaturated hydrocarbons. For example, while normal saturated hydrocarbons are inert to bromine in dark, cyclopropane reacts rapidly, giving ring opening products [77].

Ionic brominations of cyclopropanes to produce 1,3-dibromides are possibly the most frequently cited aspect of cyclopropane chemistry; there is an unsatisfactorily insights to be gained from these statements, for 1,3-dibromides are often minor products.

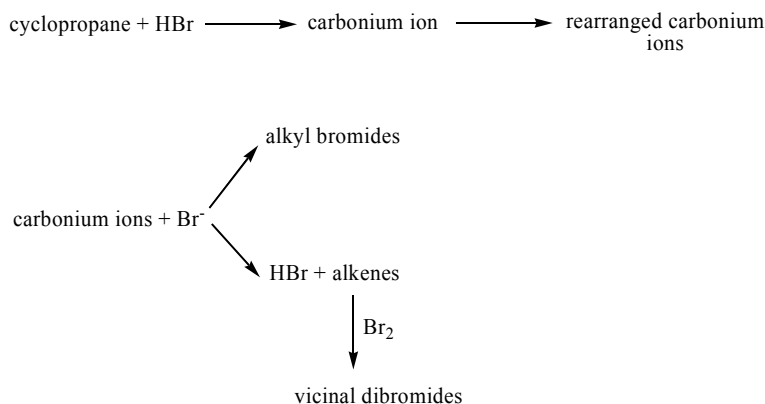
Ionic brominations of cyclopropanes are slow reactions if the ring is not heavily substituted with alkyl groups. For example, cyclopropane does not react with bromine without Lewis acid catalyst, such as AlCl_3 [78]. On the other hand, the radical chain reactions of cyclopropanes with bromine are rapid, clean reactions, even at -78°C , leading exclusively to 1,3-dibromides [79].

Further, the dibromides from ethylcyclopropane include significant amounts of 2,3-dibromopentanes (50%), which drives one to consider a variety of exotic explanations [80]. Similarly, 2,3-dibromobutanes were obtained on bromination of

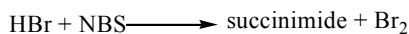
methylcyclopropane. These proved to be artifacts attributable to hydrogen bromide formation.

A simple set of observations provided a basis from which an understanding of the dark reactions could be developed [88]. An olefin reacts with Br_2 , exclusively when treated with a mixture of HBr and Br_2 in a nonpolar solvent (CH_2Cl_2 , CCl_4 , etc.). With the same reagent mixture, a cyclopropane reacts rapidly with hydrogen bromide.

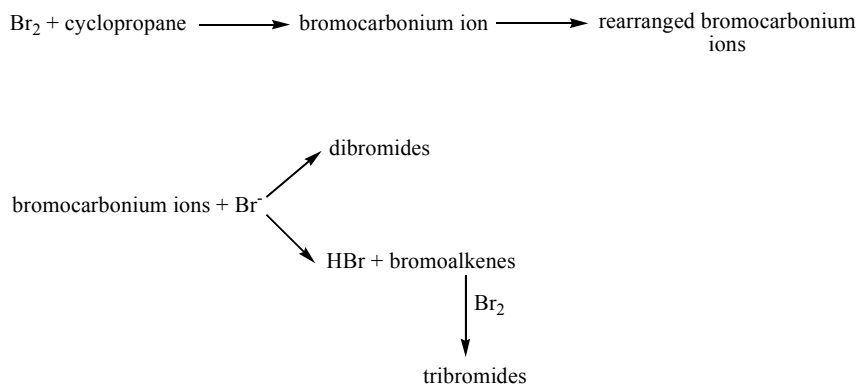
The reactions of a cyclopropane with hydrogen bromide can appear complex, apparently because carbonium ions are intermediates which either react to form bromides or lose a proton to make an olefin, the olefin reacting further either with hydrogen bromide, or by condensation, etc. The reaction of the cyclopropane-hydrogen bromide system is readily understood in detail if a mixture of HBr and Br_2 is used, since the Br_2 converts the olefins to stable dibromides. Examined in this way, the products are monobromides and dibromides; tribromides are absent. For the main, the monobromide is that predicted by a Markownikoff-type opening of the ring, accompanied by easily rationalized rearrangement products; the dibromides are all vicinal and can be explained as Br_2 adducts to the olefins expected from the carbonium ions needed to explain the monobromide products. Since cyclopropanes react more rapidly with hydrogen bromide than with bromine, it follows that the formation of hydrogen bromide in the reactions of cyclopropanes with bromine must result in the production of dibromides from several pathways, thus accounting for the confusion.



A clear picture of the dark reaction of bromine with cyclopropanes could be obtained only if the hydrogen bromide was efficiently scavenged. For the monoalkyl-, 1,2-dialkyl-, and 1,2,3-trialkylcyclopropanes this could be done by using N-bromosuccinimide in methylene chloride solvent as the scavenger system. Rapid scavenging occurs in this system because NBS is moderately soluble (0.25 M), and it reacts rapidly and irreversibly with hydrogen bromide [79].



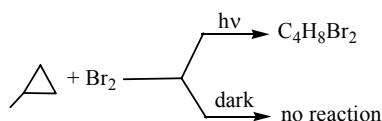
Study of the dark reactions of cyclopropanes with Br_2 -NBS reagent in methylene chloride leads to dibromides and tribromides; the monobromides and dibromides characteristic of HBr attack are conspicuously absent. The initial process is an opening of the ring to make a bromocarbonium ion of structure predicted by Markownikoff-type considerations.



With the Br_2 -NBS reagent, ratios of tribromides to dibromides are greater than 1.0 in some cases, indicating the large contribution that would have been made by HBr if it had not been scavenged. The usual reaction mixture of a cyclopropane + Br_2 can thus be recognized as a complex system because ring opening occurs by two distinct pathways: a slow reaction with Br_2 which leads to a set of di- and tribrominated alkanes and HBr, and a fast reaction of HBr leading to monobromides and another set of dibrominated alkanes.

There is only a sparse literature concerned with directive effects in ring-opening radical reactions of cyclopropanes. Under radical-chain conditions, cyclopropane is cleaved to 1,3-dihalopropanes [81].

Radical-chain brominations of cyclopropanes follow a simpler course, although complicated by questions about competing ionic reactions [81]. Fortunately, the latter do not present an insurmountable problem; it could be shown in each instance reported below that under the conditions employed for photobromination the dark reaction did not make a significant contribution. For example, a solution of methylcyclopropane and bromine in methylene chloride solvent does not react in the dark at -78° during the time required for complete discharge of bromine color in an identical experiment except for irradiation (1000-W Hg lamp, soft glass filter, cut off *ca.* 3500 Å).

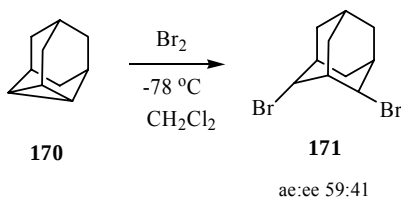


Conditions for photobromination without ionic contamination were found even with the more highly substituted alkylcyclopropanes; in no case did dark reactions contribute as much as 10% to the products. Photobrominations of alkylcyclopropanes are rapid clean reactions at -78° , yielding only 1,3-dibromoalkanes; no bromocyclopropanes were obtained [80].

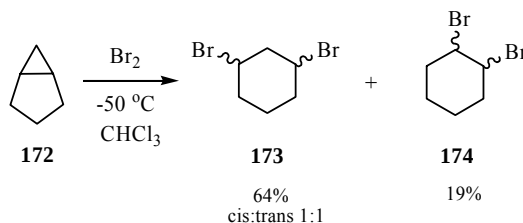
2.5.2 High Temperature Bromination of Cyclopropane Containing Hydrocarbons

It is generally the case that treatment of a cyclopropane ring with bromine gives the corresponding 1,3-dibromides where the three-membered ring does not survive under the reaction conditions.

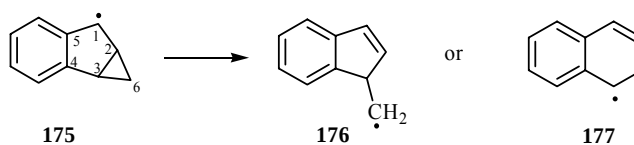
For example, Skell and *colleagues* have reported that the dark bromination of adamantane derived cyclopropane **170** resulted in the formation of 1,3-dibromide **171** exclusively where cyclopropane ring was cleaved, even at -78°C [79].



Similarly, Lambert *et al.* have reported that the reaction of bicyclo[3.1.0]hexane (**172**) with bromine afforded 1,3-dibromocyclohexanes (*cis*-, *trans*-) **173** as major products along with small amount of 1,2-dibromocyclohexanes (*cis*-, *trans*-) **174** where the ring scission was observed [82].

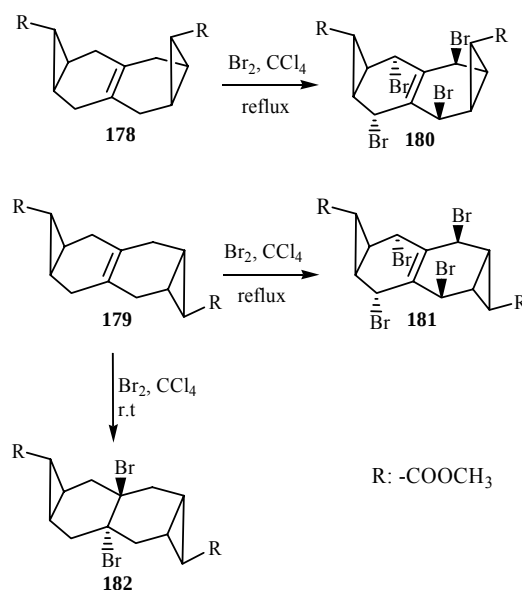


On the other hand, enormous effort has been devoted to the radical reactions (NBS brominations, organotin hydride reductions, etc.) of cyclopropane containing hydrocarbons, especially those by Friedrich and *colleagues* [83a] which are mainly related to cyclopropylcarbinyl-allylcarbinyl radical rearrangements. They have reported that free radical α bromination of cycloprop[2,3]indene with NBS at $77\text{ }^\circ\text{C}$ in CCl_4 proceeded via initial formation of the cyclopropylcarbinyl radical **175**. They found that the ratio of the products derived from the primary homoallyl radical **243** were five times greater than that obtained from the secondary benzylic homoallyl radical **177** which unexpectedly demonstrated that radical **175** preferred to undergo 2,6 bond cleavage to give a primary radical **176** rather than undergo 2,3 bond cleavage to give a benzylic radical **177**.



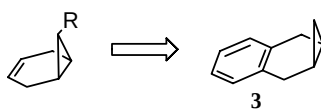
It seems quite paradoxical since benzylic radicals are considerably more stable than primary radicals due to electronic reasons. Nonetheless, several lines of evidence suggests that the direction of ring opening depends mainly upon overlap between the orbital containing the odd electron and the adjacent orbitals of the cyclopropane ring leading to the primary radical being most favorable in the course of the rearrangement inspite of the electronic affects.

However, Balci and *co-workers* have shown that it is possible to interrupt the opening of the cyclopropane ring via the application of high temperature bromination reactions [40]. For example, compound **178** which has a cyclopropane ring along with a double bond was treated with bromine in refluxing CCl₄ solution and the reaction provided the corresponding tetrabromide **180** where the opening of the cyclopropane ring is precluded. Similarly, compound **179** gave tetrabromide **181**. On the other hand, simple bromination of **179** resulted in the formation of dibromide **182**.



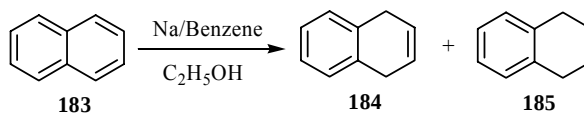
Here, bromination reaction was in favor of allylic positions despite the fact that two cyclopropane units, which were prone to undergo ring opening process, are present in the structure of the compounds **178** and **179**.

Inspired by these results we decided to investigate the fate of a similar cyclopropane which has active benzylic positions originating from the fused benzene ring in high temperature bromination reactions. The results would be quite important in view of the mechanism and chemoselectivity of the reaction. For this purpose, benzonorcarene **3** was chosen.

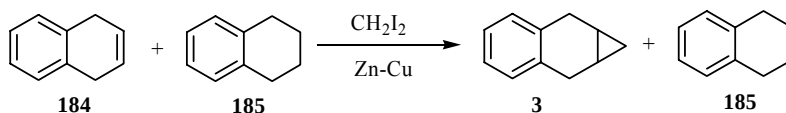


2.5.3 The Synthesis of 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (**3**) [82]*

In order to obtain benzonorcarane **3**, we started with naphthalene **183**. Birch reduction of naphthalene **183** afforded 1,4-dihydronaphthalene (**184**) in 94% yield along with small amount of 1,2,3,4-tetrahydronaphthalene **185** [84].



Then, the mixture consisting of **184** and **185** was directly subjected to Simmons-Smith cyclopropanation reaction to give benzonorcarane **3** [83a].

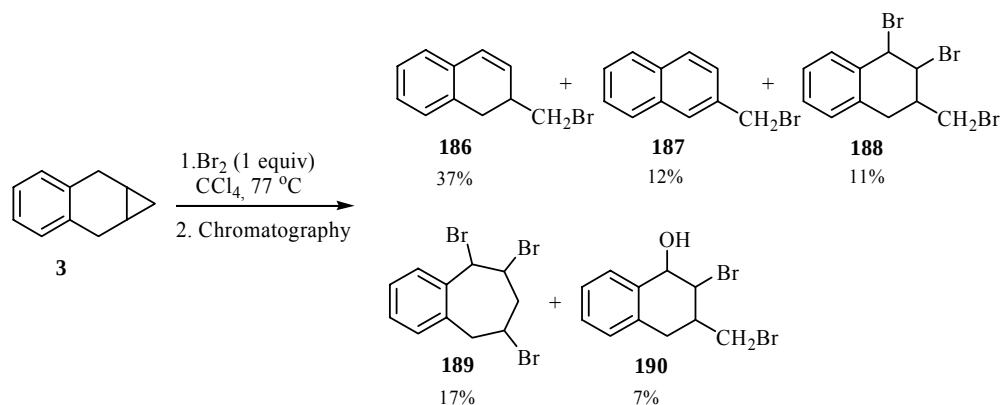


Benzonorcarane **3** was isolated from this mixture by fractional distillation under diminished pressure. The spectral data was consistent with the literature [84] and with those of authentic samples.

2.5.4 High Temperature Bromination of Benzonorcarane **3**

Benzonorcarane **3** was submitted to high temperature bromination reaction with 1 equiv of bromine in refluxing CCl₄ solution. The reaction provided a mixture consisting of five products after column chromatographic separation with hexane followed by hexane-ether as eluents; 2-(bromomethyl)-1,2-dihydronaphthalene (**186**), 2-(bromomethyl)naphthalene (**187**), 1,2-dibromo-3-(bromomethyl)-1,2,3,4-tetrahydronaphthalene (**188**), 5,6,8-tribromo-6,7,8,9-tetrahydro-5H-benzo[7]annulene (**189**) and 2-bromo-3-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**190**).

* A similar work was a dissertation presented in 1998 to the faculty of the Graduate School of Atatürk University by D. Demirici in partial fulfillment of the requirements for the degree of Master of Science.



All of the products **186-190** formed from the high temperature bromination reaction of **3** were characterized on the basis of NMR, IR, MS spectral data along with the combustion analysis.

The ¹H-NMR spectrum of compound **186** exhibited eight set of signals: two multiplets at 7.19-7.18 and 7.08 ppm for aromatic protons, an AB-system at 6.52 (1H, d, A-part of AB-system, J=9.5 Hz, H₄) and 5.95 (1H, dd, B-part of AB-system, J=9.5, 4.0 Hz, H₃) ppm for olefinic protons, another AB-system at 3.46 (1H, dd, A-part of AB-system, J=9.7, 5.5 Hz, H_{9a}) and 3.36 (1H, dd, B-part of AB-system, J=9.7, 8.0 Hz, H_{9b}) ppm for methylenic protons adjacent to bromine atom, along with two multiplets at 2.99-2.96 (2H, m, H₁), 2.86 (1H, m, H₂) for protons for H₁ and H₂ protons, respectively.

On the other hand, ¹H-NMR spectrum of compound **187** indicated three set of proton signals two of which belong to aromatics at 7.78-7.74 (4H) and 7.45-7.41 (3H) ppm alongside with a sharp singlet at 4.06 (2H) ppm belonging to the methylenic protons. An eleven-line ¹³C-NMR spectrum was also consistent with the structure.

Aromatic protons of compound **188** gave rise to three signals resonating at 7.17 (1H, d, J=7.7 Hz, H₈), 7.09-7.02 (2H, m, H₇, H₆) and 6.93 (1H, d, J=7.3 Hz, H₅) ppm. In addition, the protons (H₁ and H₂) adjacent to bromines resonate at 5.57 (1H, d, J=2,2 Hz, H₁) and 4.87 (1H, bs, H₂) ppm respectively. Methylenic protons (H₉) adjacent to bromine atom resonate at 3.35-3.25 (2H, m, H₉) whereas benzylic protons gave rise to an AB-system at 2.87 (1H, dd, A-part of AB-system, J=16.1, 5.1 Hz, H₄) and 2.62 (1H, dd, B-Part of AB-system, J=16,1, 11,2 Hz, H_{4'}) ppm. The proton (H₃) adjacent

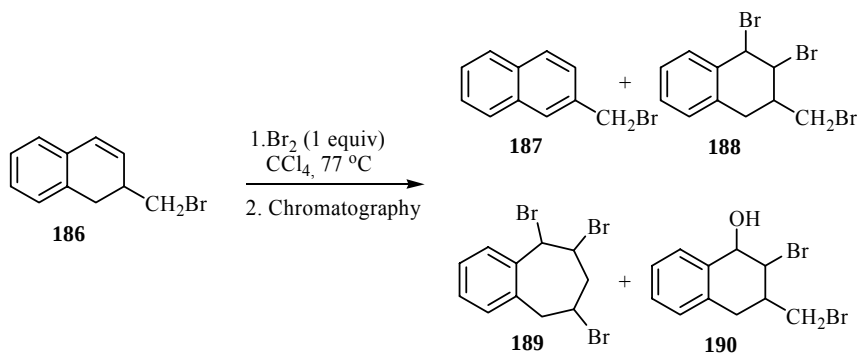
to both benzylic and methylenic protons gives a multiplet centered at 2.79 ppm. An eleven-line ^{13}C -NMR spectrum was also consistent with the structure. GC-MS spectrum indicated presence of a very weak M^+ signal at 383 along with a strong M^+ -Br signal at 304/302/300. The combustion analysis of **188** gave the correct elemental analysis.

In a similar vein, GC-MS spectrum of compound **189** shown a very weak M^+ signal at 386 along with a strong M^+ -Br signal at 304/302/300 indicating the isomeric relationship between compounds **188** and **189**, the latter having a completely different ^1H -NMR spectrum. ^1H -NMR spectrum of compound **189** consisted of eight signals; a multiplet at 7.25-7.11 (4H) ppm for aromatic protons, a doublet at 5.35 (1H, d, $J=5.4$ Hz, H_5) ppm, a multiplet at 4.62 (1H, m, H_6) ppm, two triplets at 4.42 (1H, t, $J=11.8$ Hz, H_9) and 3.88 (1H, t, $J=13.2$ Hz, H_9) ppm; a triplet of doublet at 3.46 (td, A-part of AB-system, $J=14.3, 2.3$ Hz, 1H, H_7) ppm and two doublets at 3.33 (d, $J=14.4$, 1H, H_7) and 2.82 (1H, d, $J=14.3$ Hz, H_8) ppm. The ^{13}C -NMR spectrum indicated eleven distinct carbon signals.

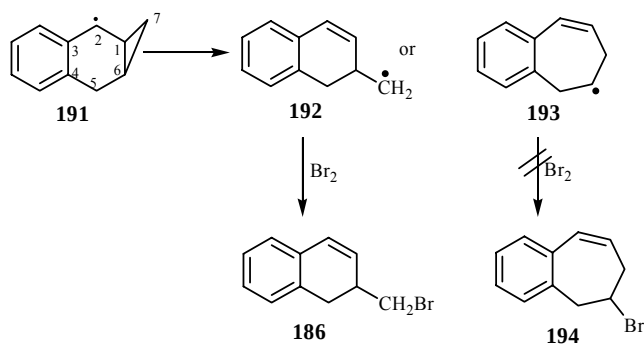
However, the fraction eluted with polar solvents (hexane-ether) was identified as alcohol **190** which was assumed to be formed during the column chromatographic separations via the hydrolysis of one of the bromines in compound **188**. GC-MS spectrum has shown an M^+ signal at 321/319/317 as triplet which suggested the presence of two bromines in the structure (M^+ -Br, 240/238 and M^+ -2Br, 159). ^1H -NMR spectrum of compound **190** indicated eleven distinct proton signals which were assigned also by 2D-NMR experiments to be as follows; the aromatic protons resonate at 7.54 (1H, d, $J=6.7$ Hz, H_8), 7.22-7.16 (2H, m, H_6 and H_7) and 7.05 (1H, d, $J=6.6$ Hz, H_5) ppm, the proton adjacent to hydroxyl group resonate at 4.95 (1H, dd, $J=9.1, 3.7$ Hz, H_1) ppm whereas the proton adjacent to bromine resonate at 4.17 (1H, t, $J=9.4$ Hz, H_2) ppm, benzylic protons appear as an AB-system at 3.79 (1H, dd, A-part of AB-system, $J=10.4, 5.3$ Hz, H_4) and 3.70 (1H, dd, B-part of AB-system, $J=10.4-2.6$ Hz, H_4) ppm, other protons resonate at 3.02 (1H, d, $J=7.4$ Hz, $-\text{CH}_2$); 2.96 (1H, d, $J=3.9$ Hz, $-\text{OH}$) and 2.44 (1H, m, H_3) ppm, respectively.

Suspiciously, after characterization, these compounds **186-190** might be secondary products which in turn arose from the high temperature bromination of a primary

compound (**186**) and/or hydrolysis (**188** to **190**) when exposed to column material (SiO_2) during the chromatographic separations. To abate the moot-point, compound **186** was submitted to high temperature bromination reaction under identical conditions. Fortunately, the reaction afforded a mixture consisting of **187-190**, undoubtedly indicating that these compounds **187-190** were secondary products.

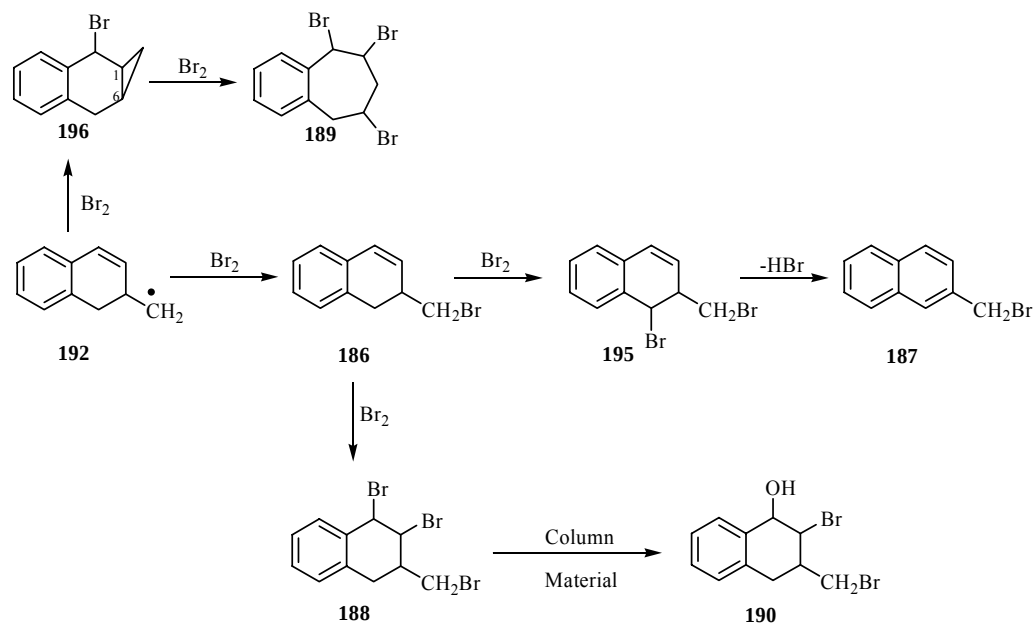


At this stage, the formation of such products as **186-190** from both **3** and **186** led us to propose a correlative mechanistic scenario as follows: there are two possibilities for the rearrangement of the radical system **191** (benzocyclo[4.1.0]hepten-2-yl). The radical prefers to undergo 1,7 bond cleavage to give a primary radical product **192** rather than undergo 1,6 bond cleavage to give benzylic radical product **193** as in the case of radical **175**. The absence of compound **194** derived from radical **193** in the reaction mixture further supports the assumption on cyclopropylcarbinyll-allylcarbinyll rearrangement.



After the formation of compound **186**, bromine can add to the double bond to give **188** and its hydrolysis in silica gel column affords **190**. On the other hand, the radical can further rearrange to give monobromide **196**. Radicalic addition of bromine to

internal 1,6 bond results in the formation of tribromide **189**. Additionally, benzylic bromination of compound **186** gives dibromide **195** from which HBr eliminations provides compound **187**.

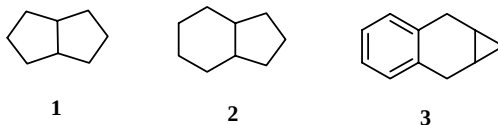


CHAPTER 3

CONCLUSION

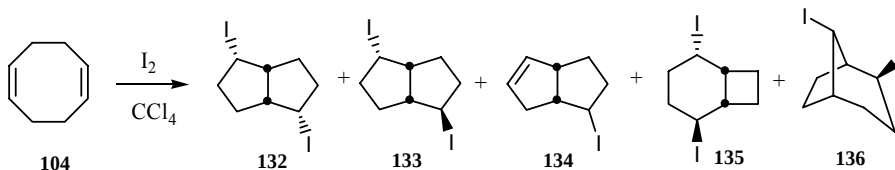
Although saturated hydrocarbons are readily available and extremely cheap starting materials, they can not be used in synthetic chemistry without prior activation. Efficient functionalization of alkanes leading to the production of useful organic chemicals in an industrial scale is of considerable interest for the chemical and pharmaceutical industries and remains a long-term challenge for chemists. In this respect, halogenation of hydrocarbons which leads to a variety of useful synthetic intermediates is an open avenue which deserves special attention. It is also noteworthy to mention that efficient methods for selective functionalizations of saturated bicyclic hydrocarbons still remains elusive, albeit a number of methods employing various reagents have been developed for the C–H bond activation of open chain and monocyclic alkanes.

Encouraged by the pioneering work by Balci and Dastan, we investigated herein the high temperature bromination reactions as a method for functionalization of saturated bicyclic hydrocarbons such as octahydropentalene (**1**), octahydro-1H-indene (**2**) and 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (**3**).

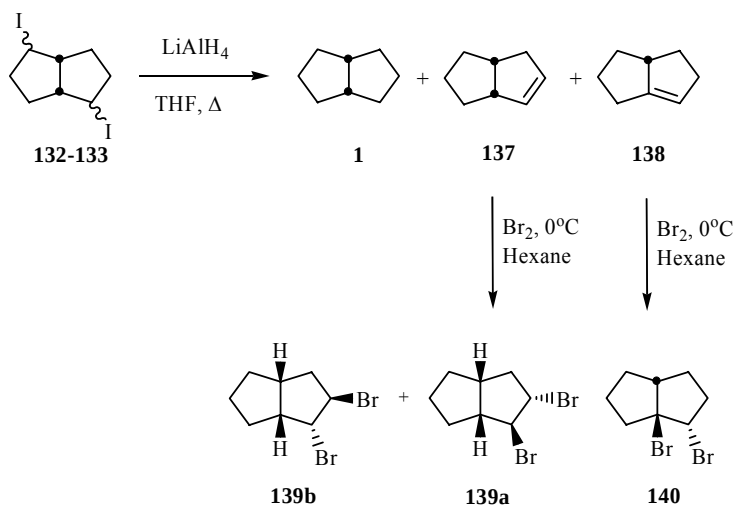


Initial exploratory efforts were directed toward the synthesis of the known octahydropentalene (**1**). Synthetic route, starting from iodination of *cis,cis*-1,5-cyclooctadiene (**104**), led to the formation of (1*S*,3*aR*,4*S*,6*aR*)-1,4-diiodo-octahydropentalene (**132**), (1*S*,3*aR*,4*R*,6*aR*)-1,4-diiodo-octahydropentalene (**133**), 3-iodo-1,2,3,3*a*,4,6*a*-hexahydropentalene (**134**), *trans*-2,5-diiodo-bicyclo[4.2.0]octane

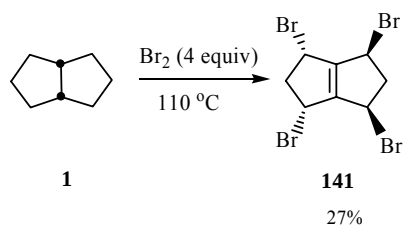
(**135**), and 2,8-diiodo-bicyclo[3.2.1]octane (**136**) via a transannular cyclization. The structure of these compounds were determined by ^1H -, ^{13}C - and 2D-NMR experiments (DEPT, COSY, HMQC, HMBC), GC-MS, IR and elemental analysis.



Hydride reduction of a mixture of (1*S*,3*aR*,4*S*,6*aR*)-1,4-diiodo-octahydropentalene (**132**) and (1*S*,3*aR*,4*R*,6*aR*)-1,4-diiodo-octahydropentalene (**133**) followed by dark bromination furnished octahydropentalene (**1**) in good yield.

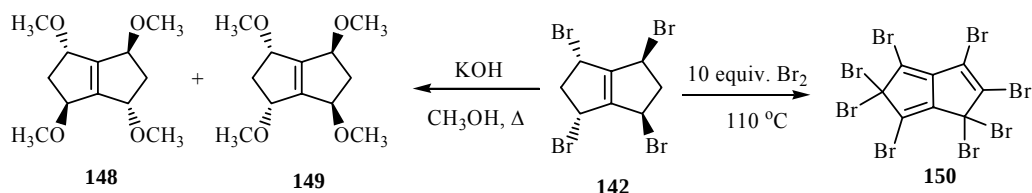


Greatifyingly, the treatment of octahydropentalene (**1**) with 4 equiv of bromine at 110°C afforded *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene (**142**) among the four possible diastereomeric tetrabromides with remarkable regio- and stereospecificity. The structure of this compound was unambiguously determined by spectroscopic methods including single crystal X-Ray analysis.



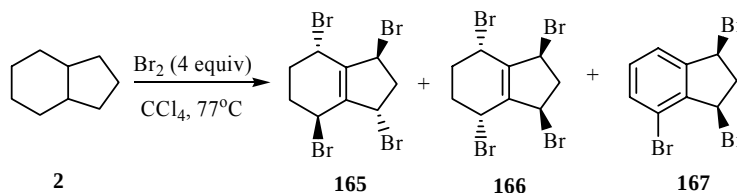
In contrast neither to the results obtained by decalin **97**, a [4.4.0] system, which gave *trans,trans,trans*-2,5,7,9-tetrabromooctalin (**98**), nor to the theoretical calculations; that result from octahydropentalene (**1**), a [3.3.0] system giving *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene (**142**) suggested that the spatial arrangement of bromine atoms in the product is probably related to the size of the ring under investigation rather than the steric affects which are relegated to a minor role.

In the second episode, the chemistry of *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene (**2**) was expanded. As a method for functionalization of saturated hydrocarbons, the versatility of high temperature bromination reaction which takes place with remarkable regio- and stereospecificity was elucidated indirectly via *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene (**142**). It was noticed that *cis,trans,cis*-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene (**142**) obtained by the high temperature bromination reaction of octahydropentalene (**1**) can easily be converted to some other derivatives such as the corresponding methyl ethers *trans,trans,trans*-1,3,4,6-tetramethoxy-1,2,3,4,5,6-hexahydropentalene (**148**), *cis,trans,cis*-1,3,4,6-tetramethoxy-1,2,3,4,5,6-hexahydropentalene (**149**) and/or perbromopentalene (**150**) which serve a great synthetic potential en route to pentalene derivatives.



In order to get further insights into the origin of the regio- and stereospecificity which determine the prominent feature of bromine atoms during high temperature

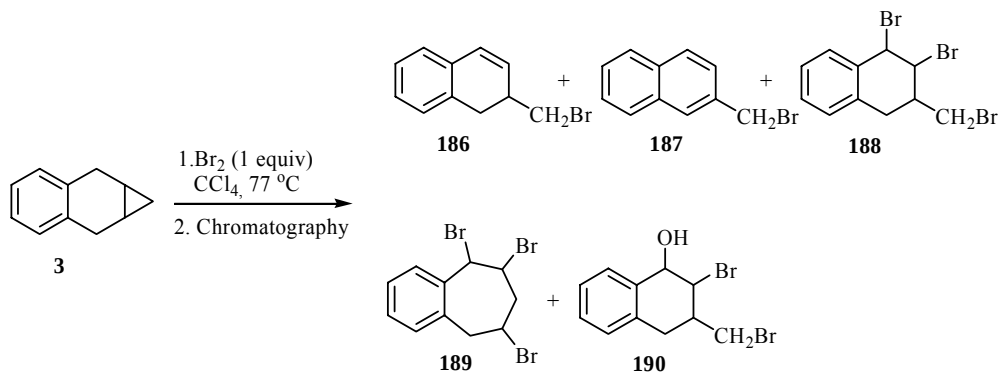
bromination reactions, octahydro-1H-indene (**2**), a [4.3.0] system, an unsymmetrical appendage was taken into account with the hope of shedding light to the exotic relationship between the size of the carbocyclic ring and the spatial arrangement of bromine atoms. After a two-step synthesis of octahydro-1H-indene (**2**), starting from Birch Reduction of 2,3-dihydro-1H-indene (**163**) followed by hydrogenolysis of 2,3,4,7-tetrahydro-1H-indene (**164**) with Pd/C, was submitted to high temperature bromination reaction with 4 equiv of bromine at 77 °C in CCl₄ solution to give (1S,3S,4S,7S)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (**165**), (1R,3S,4S,7R)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (**166**) and (1S,3R)-1,3,4-tribromo-2,3-dihydro-1H-indene (**167**) in a total yield of 63%.



At this stage, it is subtle but not surprising that high temperature bromination of an unsymmetrical saturated bicyclic hydrocarbon appendage, octahydro-1H-indene (**2**), a [4.3.0]system, results in the formation of two isomeric tetrabromides *trans,trans,trans*-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (**165**), *cis,trans,cis*-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (**166**) some part of which undergoes aromatization under the reaction conditions. Significantly, the regiospecificity of the high temperature bromination reaction is still preserved albeit the stereospecificity was diminished to lesser extent in the case of an unsymmetrical hydrocarbon appendage.

Finally, our success exemplified with [4.4.0], [3.3.0] and [4.3.0] skeletons stimulated us to investigate the fate of a cyclopropane containing hydrocarbon, namely 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (**3**) to reveal what happens to the regio- and/or stereoselectivity of high temperature bromination reaction if a labile and strained small ring as cyclopropane is incorporated to the hydrocarbon skeleton. In this respect, 1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (**3**) was first prepared from naphthalene (**183**) in two steps: Birch reduction followed by

Simmons-Smith cyclopropanation of 1,4-dihydronaphthalene (**184**); and then it was submitted to high temperature bromination reaction with 1 equiv of bromine in refluxing CCl₄ solution to provide a mixture consisting of 2-(bromomethyl)-1,2-dihydronaphthalene (**186**), 2-(bromomethyl)naphthalene (**187**), 1,2-dibromo-3-(bromomethyl)-1,2,3,4-tetrahydronaphthalene (**188**), 5,6,8-tribromo-6,7,8,9-tetrahydro-5H-benzo[7]annulene (**189**), and 2-bromo-3-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**190**).



However, it was noticed that both the regio- and/or stereoselectivity of high temperature bromination reaction was completely lost in the presence of such a labile and strained small ring as cyclopropane in the hydrocarbon skeleton due to the great tendency of the intermediate radical **191** to undergo cyclopropylcarbinyll-allylcarbinyll rearrangement.

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] systems, underscores the appealing feature of high temperature bromination reactions that take place with remarkable regio- and stereospecificity. 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 (^1H , ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX-400, Ultra Shield 400 MHz, High Performance digital FT-NMR spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane (SiMe_4) reference and deuteriochloroform (CDCl_3) as the solvent. Coupling constants (J) are reported in hertz (Hz). Spin multiplicities are mentioned as: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet).

Infrared Spectra were recorded on a Mattson model 1000 FT-IR spectrometer and a Perkin Elmer 1600 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm^{-1}). GC/Mass spectra obtained by Thermo Quest Trace Finnigan Automass Multi instrument were reported in electron impact mode (70eV).

Melting points were determined on a capillary melting apparatus and are uncorrected. Elemental Analyses were performed by the way of METU Central Laboratory.

Commercially available reagents were of reagent-grade quality and used as received from Merck and Fluka company. Column chromatography was conducted on Fluka Silicagel (60-200 mesh) and TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical plates.

Anhydrous solvents were prepared according to the standard methodologies [85]. All extracts were dried over anhydrous magnesium sulfate (MgSO_4) and solvents were concentrated under reduced pressure by using rotary evaporator.

4.2 Iodination of cis,cis-1,5-cyclooctadiene (104)

A solution of iodine (17.8 g, 70 mmol) and cis,cis-cycloocta-1,5-diene **4** (5.04 g, 46.7 mmol) in CCl₄ (100 mL) was stirred at 25 °C for 24 h. The mixture was then washed with aqueous Na₂S₂O₃ to remove excess iodine, washed with brine, and dried over MgSO₄. Evaporation of the solvent in vacuo and crystallization from hexane left a pale yellow solid mixture of **132** and **133**. The crystals were subjected to column chromatography on silica gel with hexane as eluent to give each of pure 1,4-diiodooctahydropentalene **132** (5.7 g, 31.5 mmol, 34%), and **133** (5.6 g, 31.5 mmol, 34%) as white solids, the former being eluted first. Then the repeated column chromatographic separations of the remaining mixture on silica gel with hexane as an eluent also gave **134** (1.71 g, 9.5 mmol, 11%), **135** (0.57 g, 3.15 mmol, 4%), and **136** (0.29 g, 1.6 mmol, 2%).

(1S(R),3aR(S),4S(R),6aR(S))-1,4-diiodooctahydropentalene (132)⁶³: White needle crystals from hexane, mp 67-68 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.92 (2H, m, H₁ and H₄); 3.08 (2H, m, H_{3a}, H_{6a}); 2.16 (2H, m, H₃, H₆); 2.03 (4H, m, H₂, H₅); 1.26 (2H, m, H_{3'}, H_{6'}); ¹³C NMR (100 MHz, CDCl₃) δ 56.2 (C_{3a}, C_{6a}), 39.2 (C₂, C₅), 32.2 (C₁, C₄), 31.9 (C₃, C₆); IR (CHCl₃, cm⁻¹): 3007, 2965, 2930, 2839, 1448, 1280, 1252, 1182, 1085, 1015, 910, 819, 791, 749; MS (*m/z*, %): 362 (M⁺, 0.5), 236 (12), 235 (-HI, 84), 234 (20), 108 (27), 107 (-2HI, 65), 106 (19), 79 (100).

(1R(S),3aR(S),4S(R),6aR(S))-1,4-diiodooctahydropentalene (133)⁶³: White needle crystals from hexane, mp 79-80 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.92 (1H, m, H₄); 3.82 (1H, m, H₁); 2.87 (1H, m, H_{3a}); 2.69 (1H, m, H_{6a}); 2.13–2.14 (2H, m, H₂, H₅); 1.97–1.87 (3H, m, H_{2'}, H_{5'}, H₆); 1.66 (1H, m, H₃); 1.44 (2H, m, H_{3'}, H_{6'}); ¹³C NMR (100 MHz, CDCl₃) δ 55.1 (C_{3a}), 48.4 (C_{6a}), 40.3 (C₂), 37.4 (C₅), 34.9 (C₆), 32.1 (C₄), 31.2 (C₁), 31.1 (C₃); IR (CHCl₃, cm⁻¹): 2951, 2930, 2846, 1455, 1343, 1259, 1210, 1175, 1064, 910, 791, 756; MS (*m/z*, %): (M⁺, 0.3), 236 (26), 235 (-HI, 100), 234 (62), 108 (55), 107 (-2HI, 85), 106 (48), 79 (95).

(3R(S),3aS(R),6aR(S))-3-iodo-1,2,3,3a,4,6a-hexahydropental (134): Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 5.65 (2H, br s, H₅ and H₆); 4.10 (1H, q, J=5.2 Hz, H₃); 3.35 (1H, m, H_{6a}); 3.25 (1H, m, H_{3a}); 2.74 (1H, ddd, A-part of AB-system,

$J=17.2, 9.4, 1.5$ Hz, H_4); 2.27–2.14 (2H, m, H_1, H_2); 2.14–2.00 (2H, m, H_1, H_4); 1.52 (1H, m, H_2); ^{13}C NMR (100 MHz, CDCl_3) δ 134.5 (C_6), 128.6 (C_5), 54.4 (C_{3a}), 49.6 (C_{6a}), 39.9 (C_4), 38.3 (C_2), 36.6 (C_3), 31.1 (C_1); IR (CHCl_3 , cm^{-1}): 3107, 3093, 3065, 3051, 3037, 3024, 3010, 2996, 2982, 2940, 2927, 2885, 2844, 1557, 1529, 1494, 1391, 1335, 1218, 1211, 1204, 1038, 934, 865, 830, 789, 775, 768, 754, 657, 629; MS (m/z , %): 234(M^+ , 6), 108 (26) 107 (-HI, 94) 106 (51) 79 (100). Anal. Calcd for $\text{C}_8\text{H}_{11}\text{I}$: C, 41.05; H, 4.74. Found: C, 41.01; H, 4.81.

Trans-2,5-diiodo-bicyclo[4.2.0]octane (135): Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 4.00 (1H, qui, $J=6.2$ Hz, H_5); 3.72 (1H, h, $J=6.0$ Hz, H_2); 2.72 (1H, dqui, $J=6.3, 1.5$ Hz, H_1); 2.54–2.45 (1H, m, H_4); 2.43–2.38 (2H, m, H_4 and H_6); 2.15–2.09 (1H, m, H_7); 2.05–1.97 (1H, m, H_7); 1.78–1.69 (1H, m, H_3); 1.62–1.52 (2H, m, H_3 and H_8); 1.50–1.40 (1H, m, H_8); ^{13}C NMR (100 MHz, CDCl_3) δ 49.3 (C_4), 49.2 (C_3), 48.9 (C_1), 41.5 (C_6), 36.1 (C_7), 32.7 (C_8), 28.1 (C_5), 19.2 (C_2); IR (CHCl_3 , cm^{-1}): 3032, 2877, 2729, 1650, 1458, 1378, 1218, 1146, 1038, 984, 954, 908, 878, 789, 763, 748, 648, 532, 516; MS (m/z , %): 362(M^+ , 0.4), 236 (8), 235 (-HI, 47), 234 (21), 108 (12), 107 (-2HI, 37), 106 (12), 79 (100). Anal. Calcd for $\text{C}_8\text{H}_{12}\text{I}_2$: C, 26.54; H, 3.34. Found: C, 26.48; H, 3.44.

2-Exo,9-exo-2,9-diiodo-bicyclo[3.2.1]octane (136): Colorless liquid; ^1H NMR (400 MHz, CDCl_3) δ 4.33 (1H, dd, $J=11.4, 5.8$ Hz, H_2); 4.11 (1H, s, H_9); 2.82 (1H, br d, $J=3.3$ Hz, H_1); 2.54 (1H, br s, H_5); 2.23–2.14 (3H, m, H_3, H_6 and H_7); 2.02 (1H, dt, $J=12.6, 6.0$ Hz, H_3); 1.94 (1H, t, JZ 10.4–Hz, H_7); 1.64 (1H, dt, $J=13.4, 5.0$ Hz, H_4); 1.51 (1H, br t, $J=9.3$ Hz, H_6); 1.39 (1H, ddt, $J=13.4, 5.0, 1.2$ Hz, H_4); ^{13}C NMR (100 MHz, CDCl_3) δ 55.9 (C_1), 44.9 (C_5), 36.1 (C_8), 36.0 (C_4), 31.6 (C_2), 31.5 (C_3), 26.8 (C_6), 25.3 (C_7); IR (CHCl_3 , cm^{-1}): 3107, 3037, 2996, 2982, 2954, 2871, 1619, 1543, 1446, 1391, 1328, 1252, 1169, 809, 802, 796, 789, 775, 761, 747, 733, 719, 706, 692, 678, 657, 643, 609; MS (m/z , %): 362(M^+ , 5), 236 (45), 235 (KHI, 100), 234 (85), 233 (40), 108 (84), 107 (K_2HI , 100), 106 (60), 79 (100). Anal. Calcd for $\text{C}_8\text{H}_{12}\text{I}_2$: C, 26.54; H, 3.34. Found: C, 26.51; H, 3.40; m/z (EI) 362 (5).

4.3 Reduction of 132 and 133 with LiAlH₄

To a suspension of LiAlH₄ (3.5 g, 92 mmol) in 100 mL THF was dropwise added a mixture of 5 and 6 (16 g, 44 mmol) in 50 mL THF and the mixture was heated under reflux during 20 h. After cooling to room temperature, excess LiAlH₄ was destroyed with saturated NH₄Cl solution (300 mL), then the mixture was extracted with ether (3x150 mL), washed with brine (500 mL), dried over MgSO₄ and the solvent was simply distilled to give a 4 g mixture of **1**, **137** and **138**, in a ratio of 20:2:1, respectively (80%). This mixture was directly treated with bromine in the following step.

4.4 Bromination of the mixture of 1, 137, and 138 at 0 °C

Bromine (1.6 g, 10 mmol) in 10 mL hexane was added dropwise to a solution of 3, 10, 11 (4 g, 36 mmol) in 20 mL hexane at 0 °C in the dark during 30 min. The mixture was directly subjected to column chromatography on silica gel with pentane as an eluent to give each pure **1** (3.5 g, 31.6 mmol, 70%), **139a** and **139b** (0.84 g, 3.1 mmol, 7%), and **140** (0.4 g, 1.6 mmol, 4%).

Octahdropentalene (1): Volatile colorless liquid bp 125–130 8C; ¹H NMR (400 MHz, CDCl₃) δ 2.20–2.25 (2H, m, H_{3a} and H_{6a}); 1.60 1.68 (4H, m, H₁, H₃, H₄, H₆); 1.49–1.54 (2H, m, H₂ and H₅); 1.36–1.40 (2H, m, H_{2'} and H_{5'}); 1.15–1.21 (4H, m, H_{1'}, H_{3'}, H_{4'}, H_{6'}); ¹³C NMR (100 MHz, CDCl₃) δ 43.5 (C_{3a}, C_{6a}), 34.7 (C₁, C₃, C₄, C₆), 26.7 (C₂, C₅); IR (CHCl₃, cm⁻¹): 3154, 3034, 3000, 2901, 1622, 1559, 1470, 1380, 1237, 1161, 1095, 915. Anal. Calcd for C₈H₁₄: C, 87.19; H, 12.81. Found: C, 87.01; H, 12.91.

(1R(S),2R(S),3aS(R),6aS(R))-1,2-dibromooctahdropentalene (139a): Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 4.51 (1H, t, J=5.8 Hz, H₁); 4.46 (1H, q, J=5.0 Hz, H₂); 2.99–2.92 (1H, m, H_{6a}); 2.88–2.78 (1H, m, H_{3a}); 2.24–2.17 (1H, m, H₃); 2.14–2.07 (1H, m, H_{3'}); 1.86–1.78 (1H, m, H₄); 1.75–1.73 (3H, m, H₅, H₆ and H₆₀); 1.57– 1.53 (1H, m, H_{5'}); 1.41–1.34 (1H, m, H_{4'}); ¹³C NMR (100 MHz, CDCl₃) δ 63.3 (C₁), 57.4 (C₂), 46.5 (C_{6a}), 42.4 (C_{3a}), 41.1 (C₃), 33.8 (C₄), 30.1 (C₆), 27.9 (C₅); IR (CHCl₃, cm⁻¹): 3097, 3019, 2864, 2758, 2622, 2253, 1519, 1374, 1215, 1014, 908,

848, 792, 764, 747, 728, 670, 624; MS (*m/z*, %): 269/267/265 (M^+ , 10, 20, 10), 187/185 (M^+ -Br, 43, 41), 106 (53), 105 (100), 104 (53), 79 (85). Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51. Found: C, 35.81; H, 4.50.

(1S(R),2S(R),3aS(R),6aS(R))-1,2-dibromooctahydropentalene (139b): Colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06–3.98 (1H, m, H_2); 3.64 (1H, t, $J=8.8$ Hz, H_1); 2.75–2.68 (1H, m, H_{6a}); 2.61–2.50 (2H, m, H_3 and H_{3a}); 1.72–1.63 (5H, m, H_4 , H_5 , H_5' , H_6 , and H_6'); 1.59–1.50 (2H, m, $H_{3'}$ and $H_{4'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.0 (C_1), 54.3 (C_2), 53.0 (C_{6a}), 42.6 (C_3), 41.1 (C_{3a}), 33.9 (C_4), 31.8 (C_6), 25.1 (C_5); IR ($CHCl_3$, cm^{-1}): 3107, 3024, 2968, 2954, 2940, 2927, 2913, 2885, 2857, 1598, 1543, 1453, 1398, 1301, 1218, 1162, 906, 892, 885, 872, 858, 844, 830, 816, 782, 754, 740, 726, 719, 706, 678, 602; MS (*m/z*, %): 269/267/265 (M^+ , 8, 20, 12), 187/185 (M^+ -Br, 48, 48), 106 (65), 105 (100), 104 (58), 79 (87). Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51. Found: C, 35.81; H, 4.50.

1,6a-Dibromooctahydropentalene (140): Colorless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (1H, dd, $J=10.9$, 6.5 Hz, H_1); 2.93 (1H, ddd, $J=9.5$, 9.1, 2.7 Hz, H_{3a}); 2.26–2.09 (4H, m); 1.95–1.92 (2H, m); 1.84–1.74 (2H, m); 1.41–1.39 (1H, m); 1.34–1.26 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.0 (C_{6a}), 62.4 (C_1), 54.4 (C_{3a}), 44.4 (C_2), 36.0 (C_6), 35.0 (C_4), 30.5 (C_3), 26.3 (C_5); IR ($CHCl_3$, cm^{-1}): 3079, 3012, 2959, 2869, 1452, 1297, 1261, 1216, 1180, 1070, 946, 921, 888, 828, 770, 753, 733, 704, 669, 580; MS (*m/z*, %): 187 (M^+ -Br, 53), 186 (M^+ -HBr, 30), 108 (35), 107 (97), 79 (100). Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51. Found: C, 35.81; H, 4.50.

4.5 Bromination of octahydropentalene (1) at 110 °C

To 1.0 g (9 mmol) of octahydropentalene (**1**) was added dropwise 2 mL of (40 mmol) bromine at 110 °C over 1.5 h while stirring. The resulting solution was stirred at the same temperature for an additional 15 min. After cooling to room temperature, the mixture was treated with 30 mL of CH_2Cl_2 and the solvent was removed by rotary evaporation. The distillation of the reaction mixture allowed us to recover the starting material in 39% yield. Then 20 mL of hexane was added and the mixture was allowed to stand one night at room temperature to give solid 14.

Recrystallization from hexane gave pure tetrabromide **142** (1.03 g, 27% (isolated yield), 46% based on the consumed material).

(1R(S),3S(R),4S(R),6R(S))-1,3,4,6-tetrabromo-1,2,3,4,5,6-hexahydropentalene

(142): White crystals from CH₂Cl₂, mp 182 °C (decomposition); ¹H NMR (400 MHz, CDCl₃) δ 5.04 (1H, dd, J=7.1, 1.5 Hz, H₁); 3.76 (1H, dt, A-part of AB-system, J=16.5, 7.1 Hz, H₂); 3.15 (1H, dt, B-part of AB-system, J=16.5, 1.5 Hz, H_{2'}); ¹³C NMR (100 MHz, CDCl₃) δ 154.2 (C₃), 51.3 (C₁), 43.3 (C₂); IR (CHCl₃, cm⁻¹): 3075, 3020, 2939, 1501, 1215, 1210, 1071, 782, 764, 747, 670, 508. Anal. Calcd for C₈H₈Br₄: C, 22.67; H, 1.90. Found: C, 22.61; H, 1.95.

4.6 Treatment of 142 with KOH

A solution of 0.3 g (0.7 mmol) of **142** in 40 mL methanol was dropwise added to a solution of 0.1 g (1.5 mmol) KOH in 50 mL methanol and the flask was heated up to reflux during 15 h. After cooling to room temperature, the mixture was diluted with water and extracted with CH₂Cl₂ (3x150 mL), dried over MgSO₄ and the solvent was evaporated to give 110 mg crude product (77%). The residue was subjected repeated column chromatography using hexane–ethyl acetate as an eluent (10/1) to give **148** (50 mg, 0.22 mmol, 38%), **149** (25 mg, 0.11 mmol, 19%).

(1R(S),3R(S),4R(S),6R(S))-1,3,4,6-tetramethoxy-1, 2,3,4,5,6-hexahydropentalene

(148): Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 4.53 (4H, t, J=5.0 Hz); 3.34 (12H, s); 2.44 (4H, t, J=5.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 155.0 (=C), 80.5 (OCH₃), 56.9 (CH), 42.9 (CH₂); IR (CHCl₃, cm⁻¹): 3057, 3019, 2976, 2834, 2763, 2377, 2224, 1451, 1391, 1369, 1331, 1271, 1255, 1216, 1184, 1086, 1015, 901, 743; MS (*m/z*, %): 228 (M⁺, 1), 196 (M⁺-OCH₃, 5), 180 (5), 169 (100), 150 (15), 138 (55), 126 (30), 108 (25), 94 (30), 74 (95), 62 (10), 44 (30). Anal. Calcd for C₁₂H₂₀O₄: C, 63.14; H, 8.83. Found: C, 63.04; H, 8.91.

(1R(S),3S(R),4S(R),6R(S))-1,3,4,6-tetramethoxy-1,2,3,4,5,6-hexahydropentalene

(149): Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 4.38 (2H, dd, J=7.0, 3.6 Hz, H₁); 3.38 (12H, s, OCH₃); 2.92 (2H, dt, A-part of AB system, J=14.1–7.0 Hz, H₂); 2.03 (2H, dt, B-part of AB system, J=14.1–3.7 Hz, H_{2'}); ¹³C NMR (100 MHz,

CDCl₃) δ 155.0 (=C), 80.9 (OCH₃), 57.0 (CH), 41.8 (CH₂); IR (CHCl₃, cm⁻¹): 3144, 3046, 3030, 2986, 2436, 2393, 2246, 1516, 1418, 1271, 1249, 1189, 911, 797, 754; MS (*m/z*, %): 196 (M⁺OCH₃, 10), 180 (10), 169 (100), 150 (20), 138 (60), 126 (25), 108 (30), 94 (25), 74 (95), 62 (15), 44 (35). Anal. Calcd for C₁₂H₂₀O₄: C, 63.14; H, 8.83. Found: C, 63.04; H, 8.91.

4.7 Bromination of octahdropentalene (**1**) at 110 °C with 10 equiv bromine

To 1.0 g (9 mmol) of octahdropentalene (**1**) was added dropwise 5 mL of (80 mmol) bromine at 110 °C over 3 h while stirring. The resulting solution was stirred at the same temperature for an additional 15 min. After cooling to room temperature, the mixture including unreacted hydrocarbon was treated with 30 mL of CH₂Cl₂ and the solvent was removed by rotary evaporation. Then 20 mL of hexane was added and the mixture was allowed to stand one night at room temperature to give octabromide **150**, which was recrystallized from n-hexane-CH₂Cl₂ (1.6 g, 2.2 mmol, 48%).

1,1,2,3,4,5,5,6-Octabromo-1,5-dihdropentalene (150): Yellow crystals from n-hexane-CH₂Cl₂; mp 212 °C (decomposition); ¹³C NMR (100 MHz, CDCl₃) δ 145.7, 138.7, 134.8, 125.7, 118.4, 117.7, 64.4, 45.7; IR (CHCl₃, cm⁻¹): 2972, 2930, 2860, 1275, 1266, 1224, 1189, 1106, 1057, 775, 756, 728, 609. Anal. Calcd for C₈Br₈: C, 13.07. Found: C, 13.05.

4.8 Birch Reduction of 2,3-dihydro-1H-indene⁷⁴

Ammonia (500 ml) was condensed in a three-necked flask equipped with a mechanical stirrer and a condenser. A dry ice-acetone bath was used to maintain the temperature at -78 °C. Lithium (10.5 g, 1.5 mol) was introduced into the flask in small pieces, resulting in a deep blue solution. This solution was then stirred vigorously for additional 2 h to ensure that lithium was dissolved completely in the liquid ammonia. A solution of 59 g (0.50 mol) of indane in 120 ml absolute ethanol was then added dropwise over 1 h, and the mixture was stirred for an additional 7 h at -78 °C. The flask was opened to air and warmed to room temperature with stirring to evaporate most of the ammonia. Methanol (100 ml) was added to the flask

carefully to react with excess lithium. The resulting brown solution was quenched with 300 ml water and extracted with three 200 ml portions of pentane. Pentane layers were combined and dried over Na₂SO₄. Evaporation of the pentane gave **164** (56.9 g, 94%) as a colorless liquid.

Bicyclo[4.3.0]-nona-1(6),3-diene (164): Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 5.76 (2H, bs, olefinic); 2.67 (4H, s, H₄ and H₇); 2.30 (4H, t, J=7.6 Hz, H₁ and H₃); 1.89 (2H, qui, J=7.4 Hz, H₂); ¹³C NMR (100 MHz, CDCl₃) δ 131.7 (C_{3a}, C_{6a}), 124.6 (C₅, C₆), 35.5 (C₄, C₇), 27.6 (C₁, C₃), 21.4 (C₂).

4.9 Hydrogenation of 164: Into a 50 ml, two-necked, round-bottomed flask were placed Pd/C (10%) (100 mg) catalyst and of Bicyclo[4.3.0]-nona-1(6),3-diene (**230**) 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 4 h the solution was decanted from the catalyst. Evaporation of the solvent provided **169** (0.824 g 6.6 mmol, 80%).

Octahydro-1H-indene (2): Colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 2.34-2.27 (4H, m); 1.99-1.94 (4H, m); 1.87 (2H, qui, J=7.4 Hz); 1.68-1.65 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ 37.5, 32.0, 27.2, 24.8, 23.1.

4.10 High Temperature Bromination of 2 with 4 equiv Br₂

1.0 g (8.05 mmol) of octahydro-1H-indene (**2**) was dissolved in 50 ml of carbon tetrachloride in a 100 ml flask, which was equipped with reflux condenser. While stirring magnetically, the solution was heated until carbon tetrachloride began to reflux. To the refluxing solution was then added a hot solution of bromine (5.15 g, 32.2 mmol) in 20 ml of CCl₄, dropwise over a period of 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 submitted to column chromatography on silica gel (80g). Elution with hexane gave three products: **165** (0.703 g, 2.06 mmol, 35 %), **166**(0.341 g, 1 mmol, 15%), **167** (0.273 g, 0.771 mmol, 13%).

(1S,3S,4S,7S)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (165): ^1H NMR (400 MHz, CDCl_3) δ 5.12 (2H, t, $J=5.5$ Hz, H_1 , H_3); 5.05 (2H, m, H_4 , H_7); 3.04 (2H, t, $J=5.5$ Hz, H_2 , H_6); 2.52-2.25 (4H, AA'BB'-system, H_5 , H_5' , H_6 and H_6'); ^{13}C NMR (100 MHz, CDCl_3) δ 142.1 (C_{3a} , C_{7a}), 50.7 (C_1 , C_3), 46.0 (C_2), 42.1 (C_4 , C_7), 27.9 (C_5 , C_6); IR (CHCl_3 , cm^{-1}): 2958, 2917, 2848, 2360, 2341, 1458, 1430, 1386, 1299, 1260, 1170, 1082, 961, 881, 764, 729, 607. Anal. Calcd for $\text{C}_9\text{H}_8\text{Br}_4$: C, 24.69, H, 2.30. Found: C, 24.63, H, 2.36.

(1R,3S,4S,7R)-1,3,4,7-tetrabromo-2,3,4,5,6,7-hexahydro-1H-indene (166): ^1H NMR (400 MHz, CDCl_3) δ 5.21 (2H, d, $J=7.0$ Hz, H_1 , H_3); 4.95-4.93 (2H, m, H_4 , H_7); 3.22 (1H, dt, $J=16.7$, 7.0 Hz, H_2); 2.82 (1H, d, $J=16.7$ Hz, H_6); 2.43-2.34 (4H, m, H_5 , H_6); ^{13}C NMR (100 MHz, CDCl_3) δ 143.2 (C_{3a} , C_{7a}), 51.4 (C_1 , C_3), 43.1 (C_2), 42.1 (C_4 , C_7), 31.7 (C_5 , C_6); IR (CHCl_3 , cm^{-1}): 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 $\text{C}_9\text{H}_8\text{Br}_4$: C, 24.69, H, 2.30. Found: C, 24.63, H, 2.36.

1,3,4-tribromo-2,3-dihydro-1H-indene (167): ^1H NMR (400 MHz, CDCl_3) δ 7.48 (1H, d, $J=7.8$ Hz, H_5); 7.40 (1H, d, $J=7.5$ Hz, H_7); 7.19 (1H, t, $J=7.8$ Hz, H_6); 5.65 (1H, bs, H_3); 4.84 (1H, bd, $J=5.3$ Hz, H_1); 3.77 (1H, dd, A-part of AB-system, $J=18.0$, 5.3 Hz, H_2); 3.35 (1H, d, B-part of AB-system, $J=18.0$ Hz, H_2); ^{13}C NMR (100 MHz, CDCl_3) δ 142.5, 141.1, 132.6, 129.5, 124.4, 120.0, 57.2, 52.3, 42.8; IR (CHCl_3 , cm^{-1}): 3005, 2918, 2849, 2352, 2318, 1732, 1644, 1571, 1556, 1456, 1376, 1275, 1212, 1111, 947, 885, 764, 750, 620. Anal. Calcd for $\text{C}_9\text{H}_7\text{Br}_3$: C, 30.46, H, 1.99. Found: C, 30.38, H, 2.02.

4.11 Preparation of 1,4-Dihydronaphthalene (3)⁸³

In a one-liter three neck flask equipped with a dropping funnel, a efficient condenser and a mechanical stirrer were placed 32 g.(0.25 mole) of naphthalene and 23 g. (1 mole) of sodium cut into small pieces. The mixture was heated in a heating mantle at 140-145° and, as the naphthalene and sodium melted, the mixture was stirred vigorously until a thorough emulsion of sodium and naphthalene was obtained. Continuing the stirring, the mixture was allowed to cool to a bath temperature of 60°

when 75 cc. of dry benzene was run in. The bath was raised to 90-100° to effect moderate refluxing of the benzene and 300 cc. of absolute alcohol was added at such a rate as to maintain well-controlled reflux. After about three-fourths of the alcohol was added, it was well to add more benzene to permit efficient stirring. After the alcohol was added, the mixture was allowed to cool. The precipitated sodium ethylate was decomposed by pouring the reaction products into a solution of 112 g. of concentrated hydrochloric acid in 750 g of chopped ice. The upper benzene layer was removed and the aqueous layer was extracted with two 100 ml portions of benzene. The combined benzene extracts were washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The benzene was removed rotary-evaporator. The fraction boiling at 210-212 °C was saved as **184** and the yield was 30 g, 94% yield. This material contains **185** (ca. 26%) as over-reduction product.

1,4-dihydronaphthalene (184): ¹H-NMR (400 MHz, CDCl₃) δ 7.29-7.17 (4H, m, aromatic); 6.06 (2H, bs, olefinic); 3.53 (4H, s, methylenic); ¹³C-NMR (100 MHz, CDCl₃) δ 133.6 (C), 127.9 (CH), 125.4 (CH), 124.3 (CH), 29.3 (CH₂).

1,2,3,4-tetrahydronaphthalene (185): ¹H-NMR (400 MHz, CDCl₃) δ 7.29-7.17 (4H, m, aromatic); 2.96-2.90 (4H, m, benzylic); 1.97-1.94 (4H, m, methylenic); ¹³C-NMR (100 MHz, CDCl₃) δ 136.5 (C), 128.6 (CH), 125.0 (CH), 29.0 (CH₂), 22.9 (CH₂).

4.12 Preparation of Benzobicyclo[4.1.0]heptene

A 500-ml, three-necked round bottom flask is fitted with a condenser, pressure-equalising dropping funnel, and equipped with mechanical stirrer. Into the flask, 52 g (0.80 mole), 8 g (0.08 mole) copper (I) chloride, 75 ml anhydrous ether and 70 g (0.40 mole) dibromomethane were added. To the addition funnel 26 g (0.20 mole) 1,4-Dihydronaphthalene in 50 ml anhydrous ether was added. The apparatus was positioned in a water bath which is preheated to 45-50 °C. Then, the alkene was added to the reaction mixture over 5-10 min. The stirring were continued for an additional 3 hours. After the reaction was complete, the water bath was removed, and the reaction mixture cooled in an ice bath, diluted with pentane (200 ml), and while being stirred, treated by dropwise addition of saturated ammonium chloride solution

(150 ml). The organic layer was separated and the aqueous layer washed with pentane (2x50 ml). The combined organic layer was washed with 10% sodium hydroxide solution (1x100 ml) and dried over magnesium sulphate. The solvent was evaporated and the remaining oil was fractionally distilled under diminished pressure (11 mmHg). The fraction boiling at 93 °C was saved as benzobicyclo[4.1.0]heptene (**3**) which was crystallized from pentane as colorless crystals, m.p. 31-32 °C. The yield of **3** was 26 g (90%).

Benzobicyclo[4.1.0]heptene (3): $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.98-6.54 (2H, m, aromatic); 6.87-6.85 (2H, m, aromatic); 2.96 (2H, d, A-part of AB-system, $J=15.6$, 2.9 Hz, benzylic); 2.80 (2H, d, B-part of AB-system, $J=15.7$, 2.8 Hz, benzylic); 1.10 (2H, m, H_2 and H_2'), 0.18 (1H, dt, A-part of AB-system, $J=11.5$, 4.9 Hz, H_1); -0.01 (1H, dd, B-part of AB-system, $J=9.5$, 4.8 Hz, H_1'); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 134.8 (C), 128.9 (CH), 126.0 (CH), 29.3 (CH_2), 10.0 (CH_2), 2.99 (CH).

4.13 High Temperature Bromination of **3**

2.0 g (13.86 mmol) of benzonorcarene **7** was dissolved in 30 mL of carbon tetrachloride in a 100 mL flask, which was equipped with reflux condenser. The solution was heated until carbon tetrachloride started to reflux while stirring magnetically. To the refluxing solution was added dropwise a hot solution of bromine (2.4 g, 15.0 mmol) in 3 mL of carbon tetrachloride during 5 min. The resulting reaction mixture was heated for 2 min at reflux temperature. After being cooled to room temperature the solvent was evaporated. The residue was chromatographed on silica gel (100 g). Elution with hexane afforded **186** (580 mg, 2.59 mmol, 37%), **187** (180 mg, 0.81 mmol, 12%), **1885** (300 mg, 0.81 mmol, 11%), **189** (440 mg, 1.15 mmol, 17%),. Further elution with hexane-ether furnished the alcohol **190** (154 mg, 0.50 mmol, 7%).

2-(bromomethyl)-1,2-dihydronaphthalene (186): Colorless liquid, $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.19-7.18 (3H, m, aromatic), 7.08 (1H, m, aromatic); 6.52 (1H, d, A-part of AB-system, $J=9.5$ Hz, H_4); 5.95 (1H, dd, B-part of AB-system, $J=9.5$, 4.0 Hz, H_3); 3.46 (1H, dd, A-part of AB-system, $J=9.7$, 5.5 Hz, H_{9a}); 3.36 (1H, dd, B-part of AB-system, $J=9.7$, 8.0 Hz, H_{9b}); 2.99-2.96 (2H, m, H_1), 2.86 (1H, m, H_2); $^{13}\text{C-NMR}$

(100 MHz, CDCl₃) δ 133.4, 133.1, 129.1, 128.2, 127.5, 126.8, 126.1, 36.4, 36.2, 32.0; IR (KBr, cm⁻¹): 3056, 3014, 2937, 2909, 2867, 2811, 2350, 1902, 1483, 1420, 1273, 1210, 910, 749, 686, 630, 533; MS (*m/z*, %): 223/222 (M⁺, 29, 28), 145 (M⁺-Br, 100). Anal. Calcd for C₁₁H₁₁Br: C, 59.22; H, 4.97. Found: C, 60.96; H, 3.18.

2-(bromomethyl)-naphthalene (187): White solid (ethanol); mp. 52-53 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.78-7.74 (4H, m, aromatic); 7.45-7.41 (3H, m, aromatic); 4.06 (2H, s, -CH₂); ¹³C-NMR (100 MHz, CDCl₃) δ 135.1, 133.1, 133.0, 128.8, 127.9, 127.9, 127.7, 126.8, 126.6, 126.5, 34.1; IR (KBr, cm⁻¹): 3042, 3014, 2972, 2961, 2853, 1644, 1413, 1350, 1252, 1210, 1120, 910, 875, 812, 749, 665, 567, 476. Anal. Calcd for C₁₁H₉Br: C, 59.76; H, 4.10. Found: C, 56.95; H, 4.10.

1,2-dibromo-3-(bromomethyl)-1,2,3,4-tetrahydronaphthalene (188): White solid, mp. 72-74 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.17 (1H, d, J=7.7 Hz, H₈); 7.09-7.02 (2H, m, H₇, H₆); 6.93 (1H, d, J=7.3 Hz, H₅); 5.57 (1H, d, J=2.2 Hz, H₁); 4.87 (1H, bs, H₂); 3.35-3.25 (2H, m, H₉); 2.87 (1H, dd, A-part of AB-system, J=16.1, 5.1 Hz, H₄); 2.62 (1H, dd, B-Part of AB-system, J=16.1, 11.2 Hz, H₄); 2.79 (1H, m, H₃); ¹³C-NMR (100 MHz, CDCl₃) δ 133.5, 132.6, 131.0, 129.0, 129.0, 55.2, 51.3, 36.0, 35.2, 30.5; IR (KBr, cm⁻¹): 3049, 3021, 2965, 2845, 2965, 2909, 2832, 2329, 1525, 1425, 1259, 1234, 1217, 1143, 1097, 1031, 910, 742, 651, 595; MS (*m/z*, %): 383 (M⁺, 0.1), 304/302/300 (M⁺-Br, 21, 39, 27), 222/220 (M⁺-2Br, 34, 41), 140 (M⁺-3Br, 100). Anal. Calcd for C₁₁H₁₁Br₃: C, 34.50; H, 2.90. Found: C, 34.66; H, 3.25.

5,6,8-tribromo-6,7,8,9-tetrahydro-5H-benzo[7]annulene (189): White solid (ether-hexane); mp. 105-106 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.25-7.11 (4H, m, aromatic); 5.35 (1H, d, J=5.4 Hz, H₅); 4.62 (1H, m, H₆); 4.42 (1H, t, J=11.8 Hz, H₉); 3.88 (1H, t, J=13.2 Hz, H₉); 3.46 (td, J=14.3, 2.3 Hz, 1H, H₇); 3.33 (d, J=14.4, 1H, H₇); 2.82 (1H, d, J=14.3 Hz, H₈); ¹³C-NMR (100 MHz, CDCl₃) δ 139.8, 138.2, 133.4, 131.8, 129.3, 58.1, 54.1, 48.4, 47.6, 47.2; IR (KBr, cm⁻¹): 3028, 3018, 3000, 2951, 2916, 2343, 2337, 1630, 1492, 1433, 1367, 1253, 1205, 1170, 1113, 1083, 931, 742, 665, 581, 455; MS (*m/z*, %): 386 (M⁺, 0.1), 304/302/300 (M⁺-Br, 11, 23, 12), 222/220 (M⁺-2Br, 40, 44), 141 (M⁺-3Br, 100). Anal. Calcd for C₁₁H₁₁Br₃: C, 34.50; H, 2.90. Found: C, 34.85; H, 3.74.

2-bromo-3-(bromomethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (190): White solid (ether-hexane), mp. 103-104 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.54 (1H, d, J=6.7 Hz, H₈); 7.22-7.16 (2H, m, H₆ and H₇); 7.05 (1H, d, J=6.6 Hz, H₅); 4.95 (1H, dd, J=9.1, 3.7Hz, H₁); 4.17 (1H, t, J=9,4 Hz, H₂); 3.79 (1H, dd, A-part of AB-system, J=10.4, 5.3 Hz, H₄); 3.70 (1H, dd, B-part of AB-system, J=10.4-2.6 Hz, H₄); 3.02 (1H, d, J=7.4 Hz, -CH₂); 2.96 (1H, d, J=3.9 Hz, -OH); 2.44 (1H, m, H₃); ¹³C-NMR (100 MHz,CDCl₃) δ 137.4, 135.3, 130.1, 130.0, 128.9, 128.9, 77.1, 65.3, 42.8, 40.9, 35.8; IR (KBr, cm⁻¹): 3447, 3280, 2958, 2909, 2835, 2357, 1623, 1476, 1433, 1420, 1326, 1259, 1230, 1174, 1153, 1036, 1022, 904, 749, 70, 649, 581; MS (*m/z*, %): 321/319/317 (M⁺, 9, 18, 11), 240/238 (M⁺-Br, 100, 94), 159 (M⁺-2Br, 21). Anal. Calcd for C₁₁H₁₂Br₂O: C, 41.28; H, 3.78. Found: C,41.31; H, 4.16.

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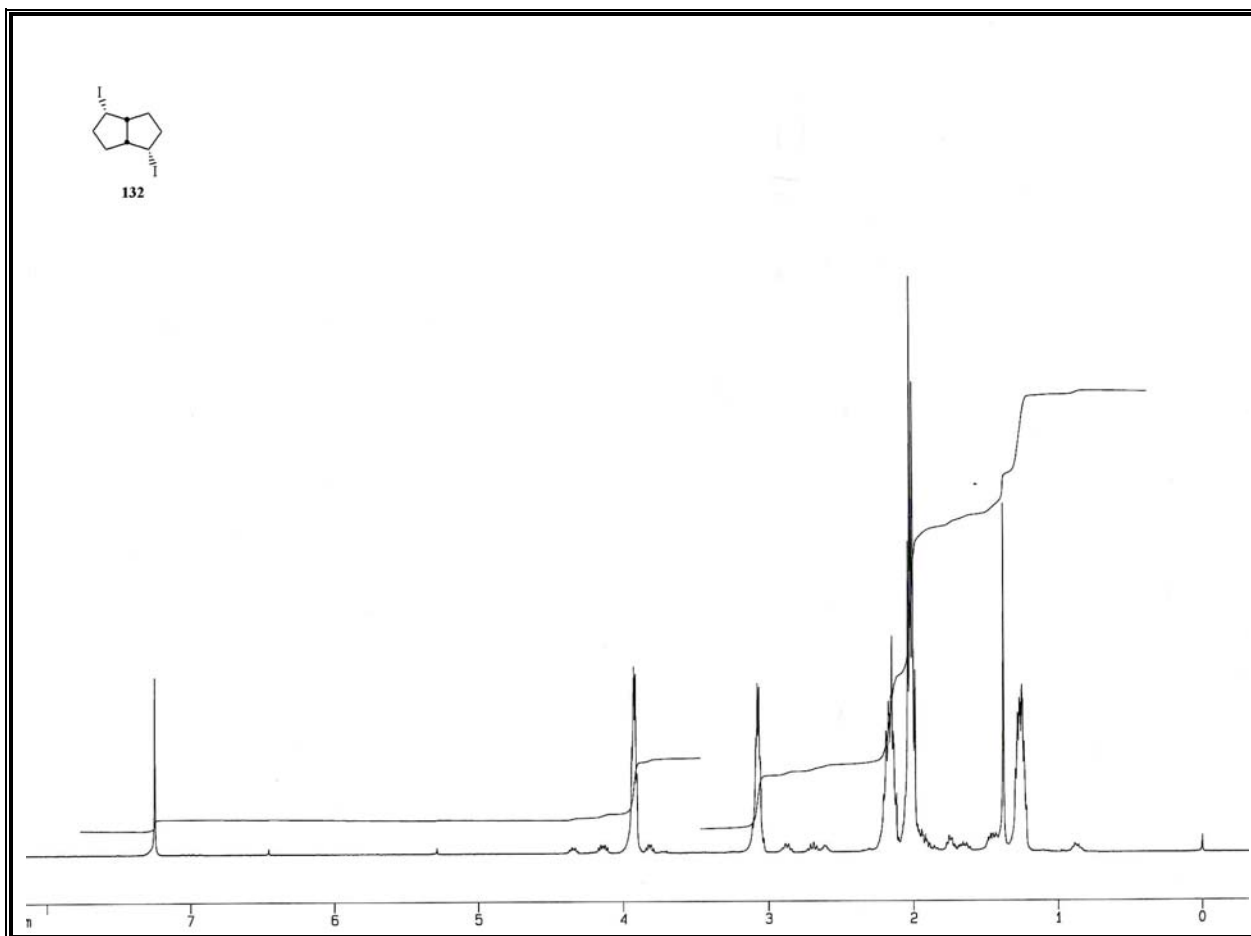


Figure A1 ^1H -NMR Spectrum of Compound 132.

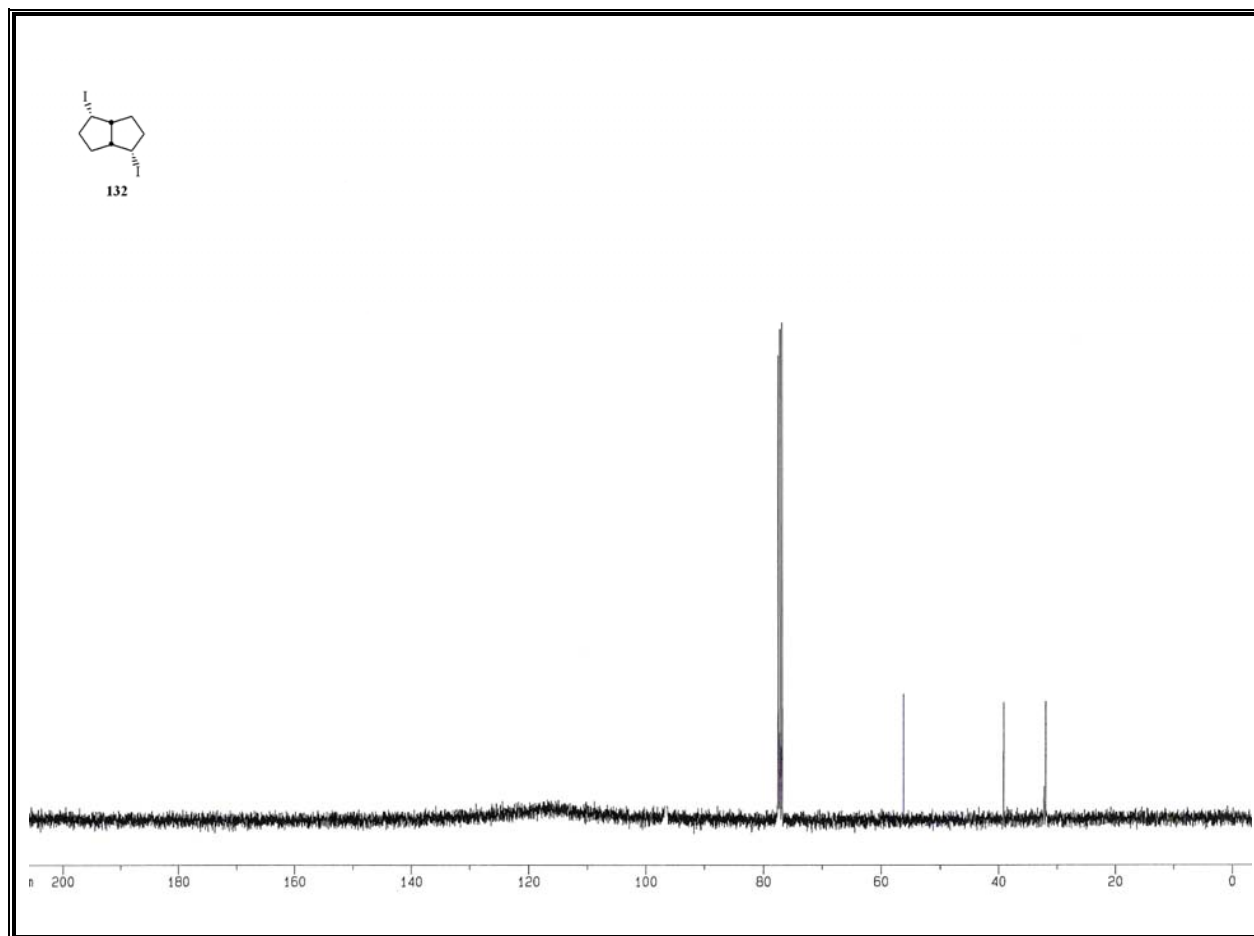


Figure A2 ^{13}C -NMR Spectrum of Compound **132**.

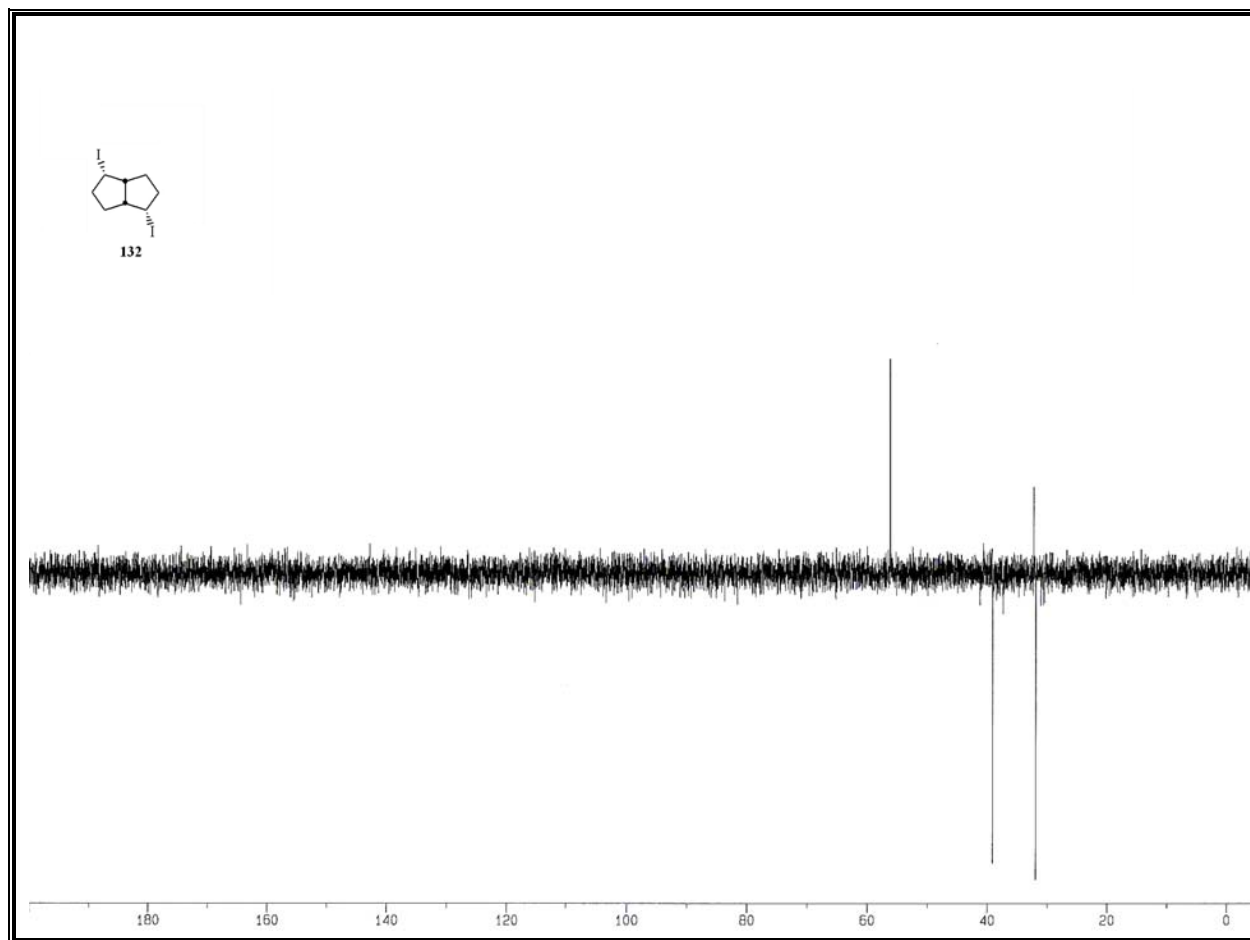


Figure A3 DEPT-135 Spectrum of Compound **132**.

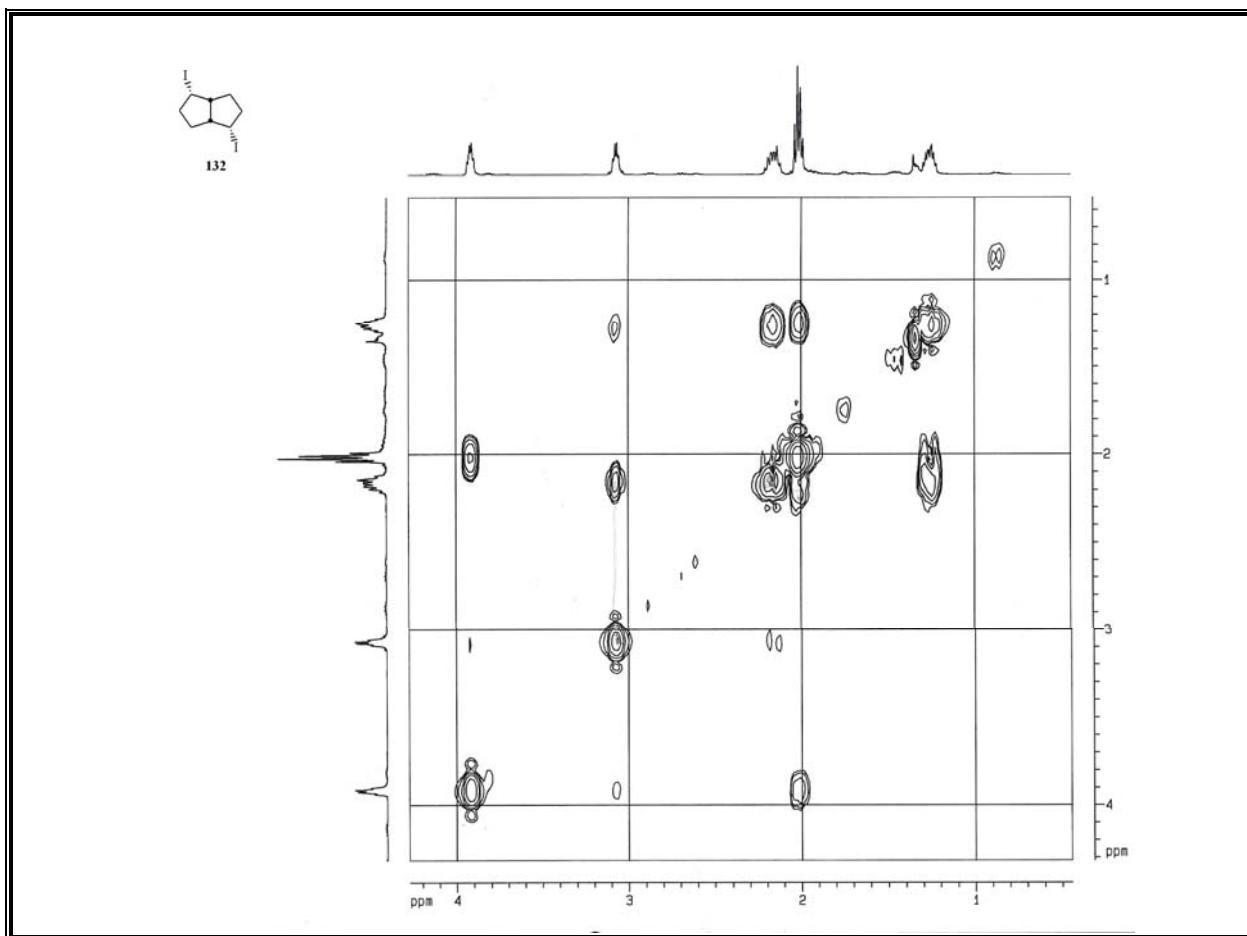


Figure A4 COSY Spectrum of Compound **132**.

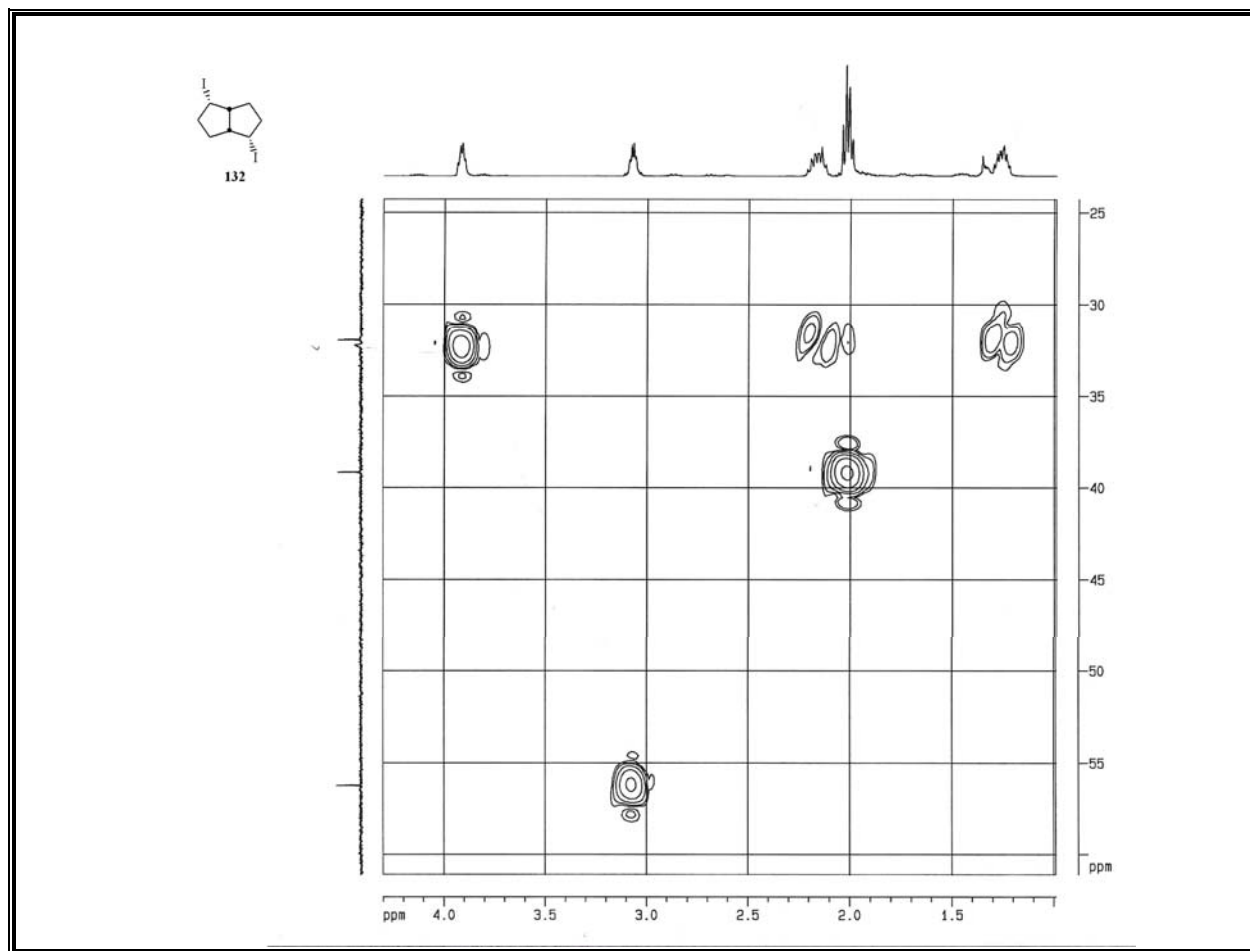


Figure A5 HMQC Spectrum of Compound 132.

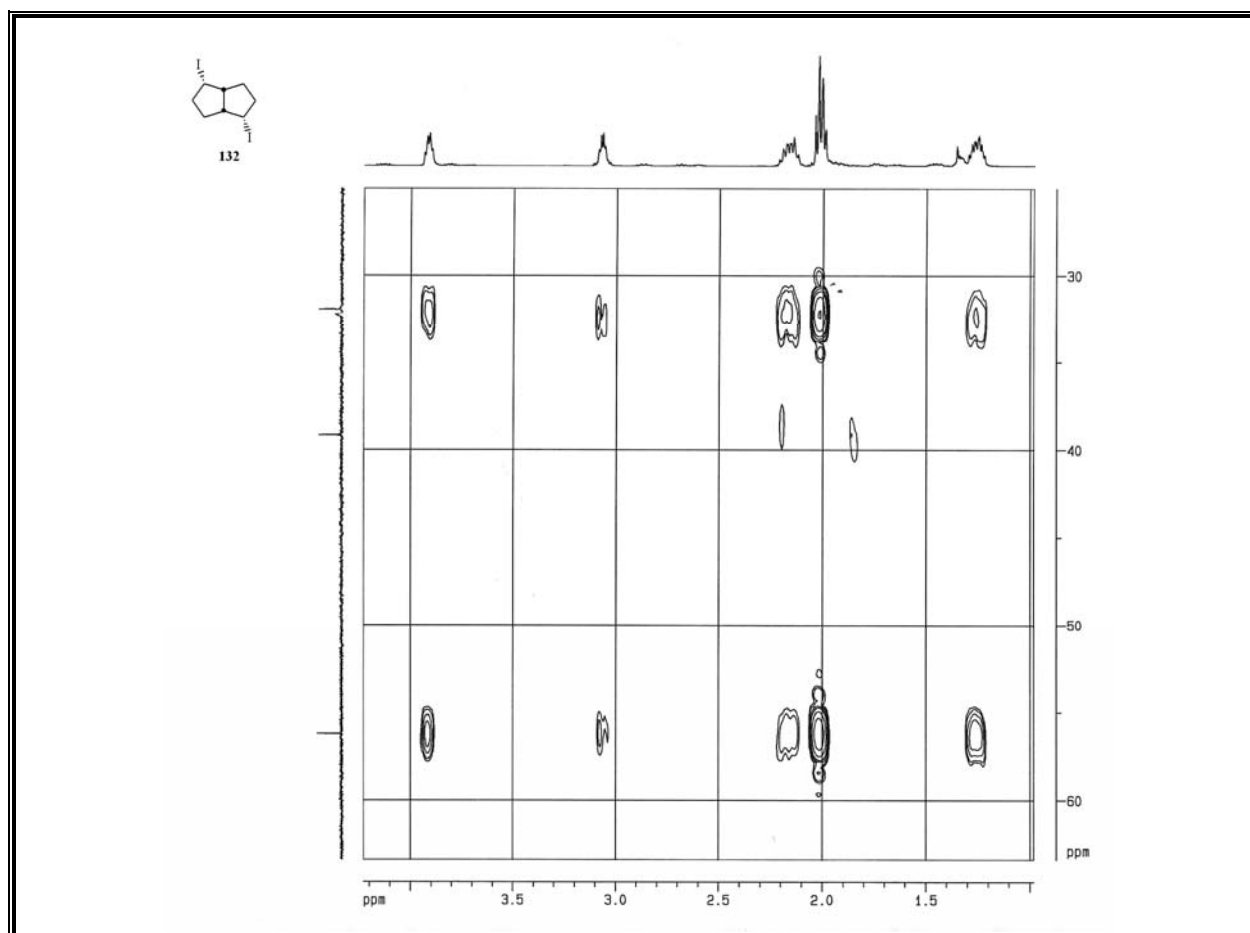


Figure A6 HMBC Spectrum of Compound 132.

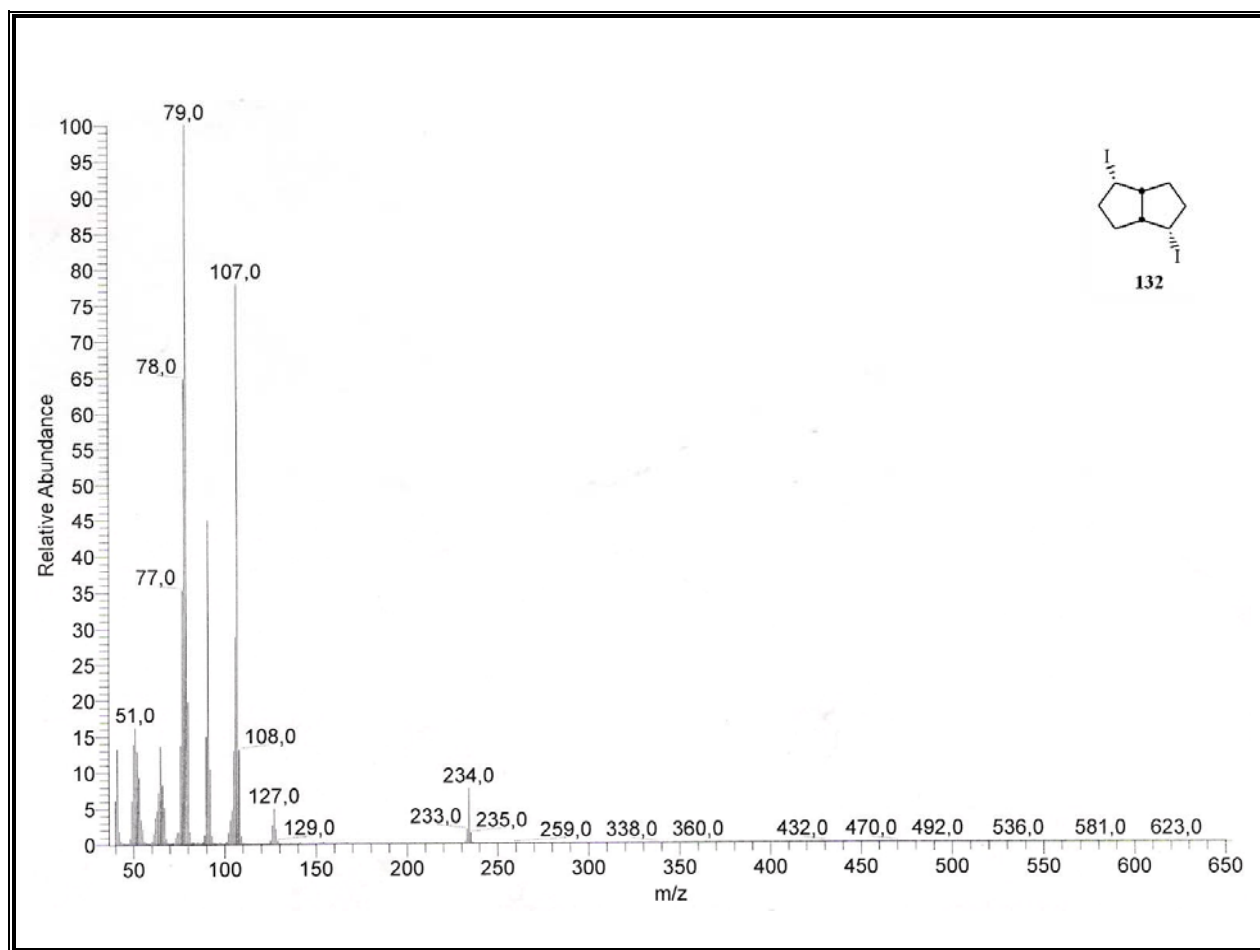


Figure A7 GC-MS Spectrum of Compound **132**.

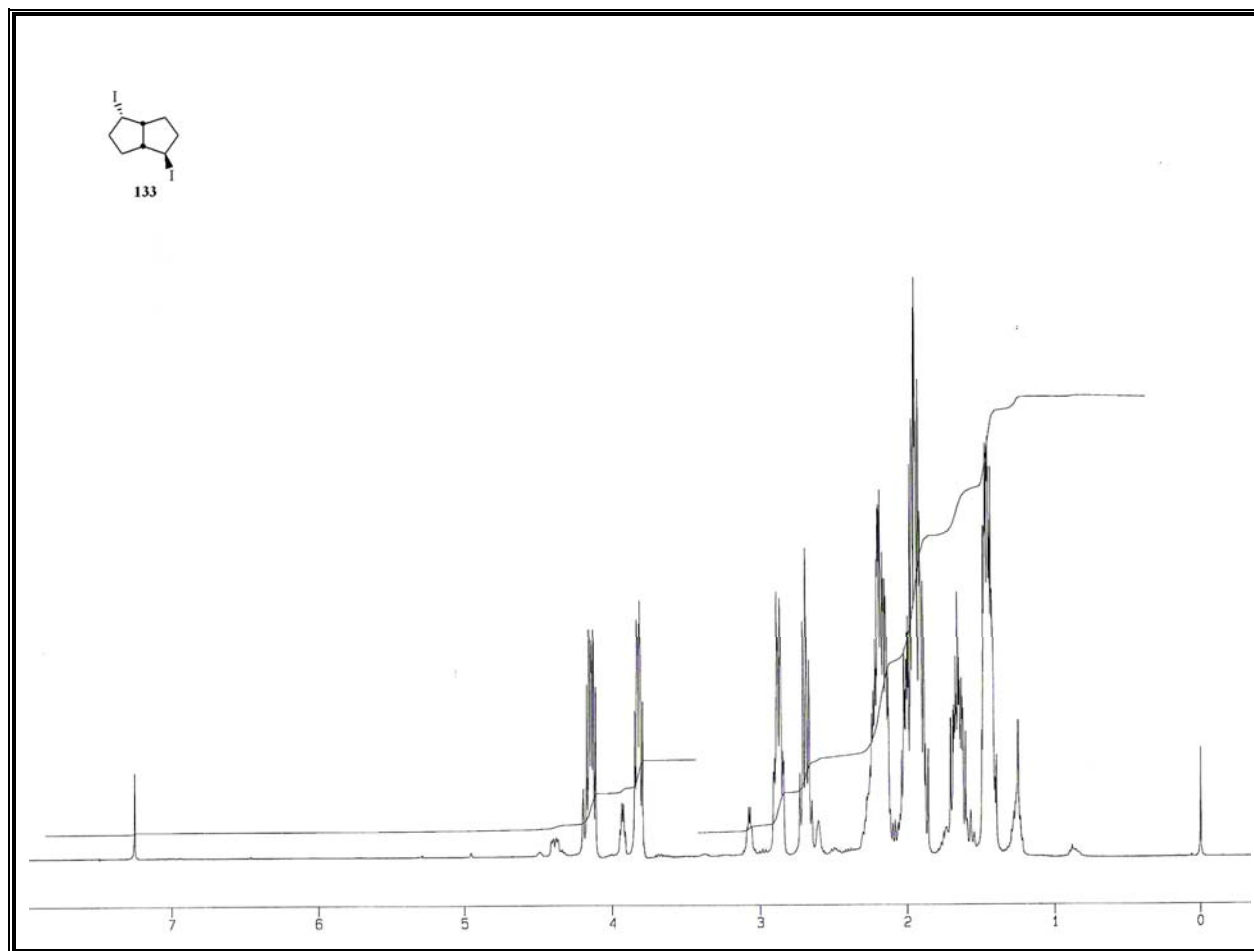


Figure A8 ^1H -NMR Spectrum of Compound **133**.

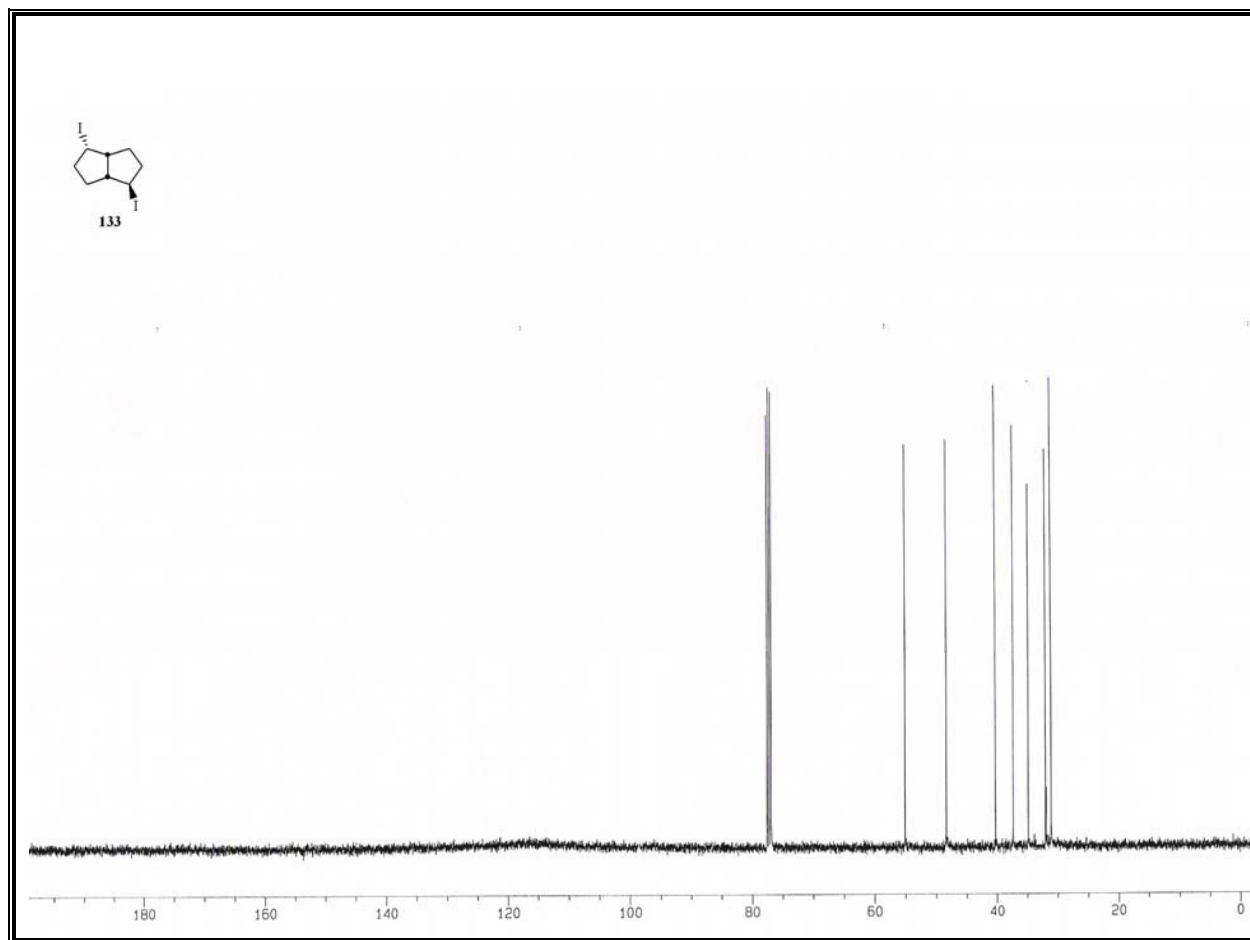


Figure A9 ^{13}C -NMR Spectrum of Compound **133**.

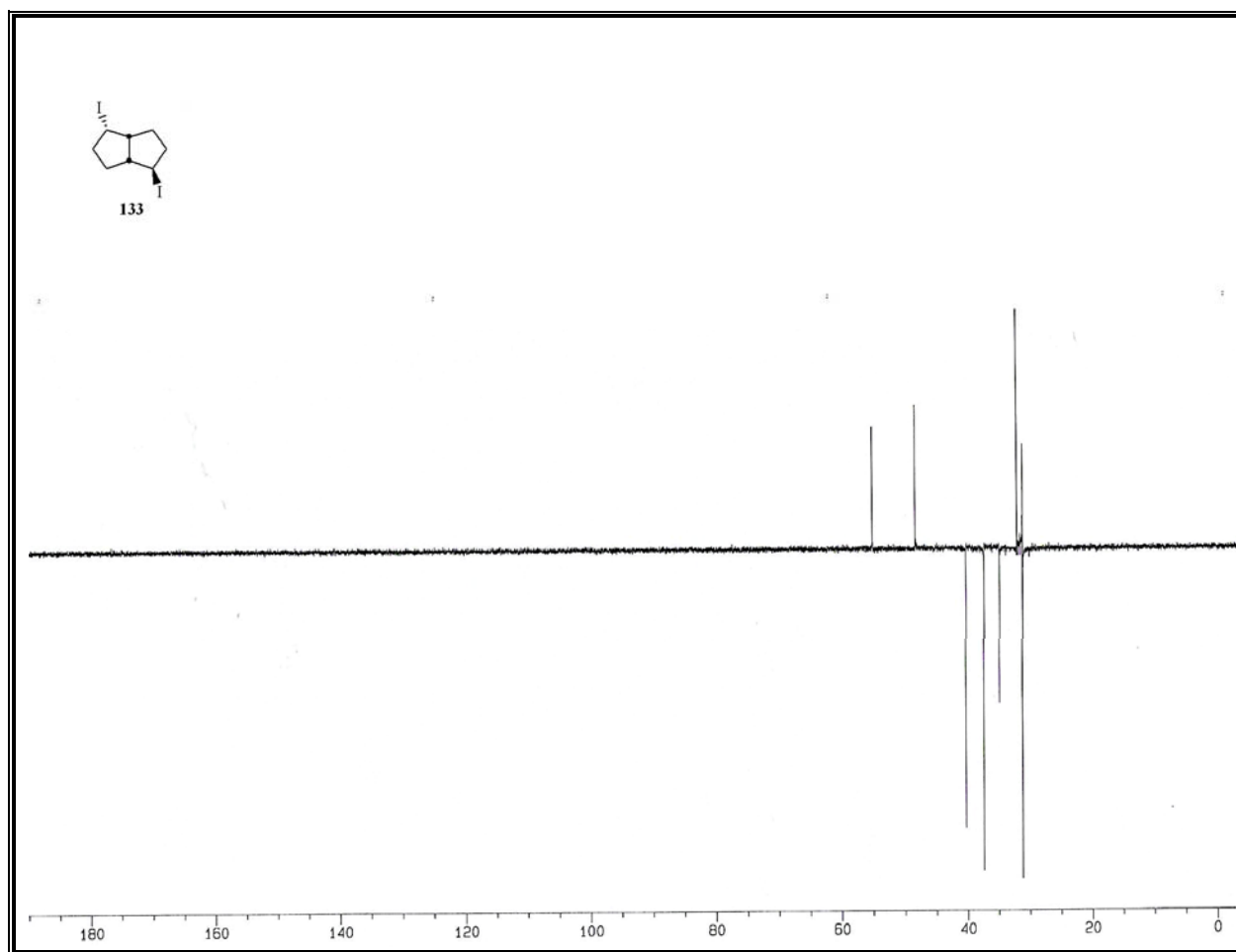


Figure A10 DEPT 135 Spectrum of Compound **133**.

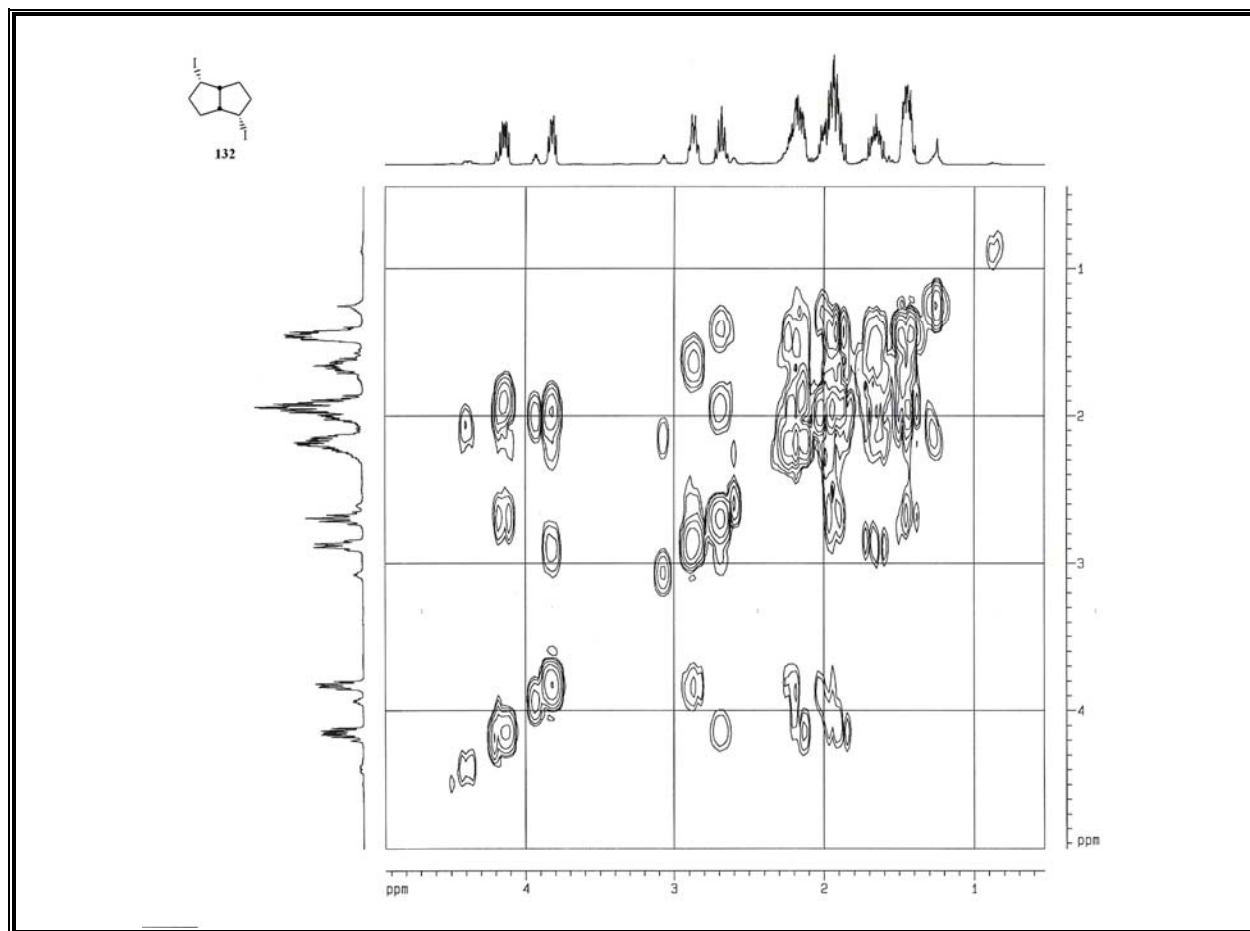


Figure A11 COSY Spectrum of Compound 133.

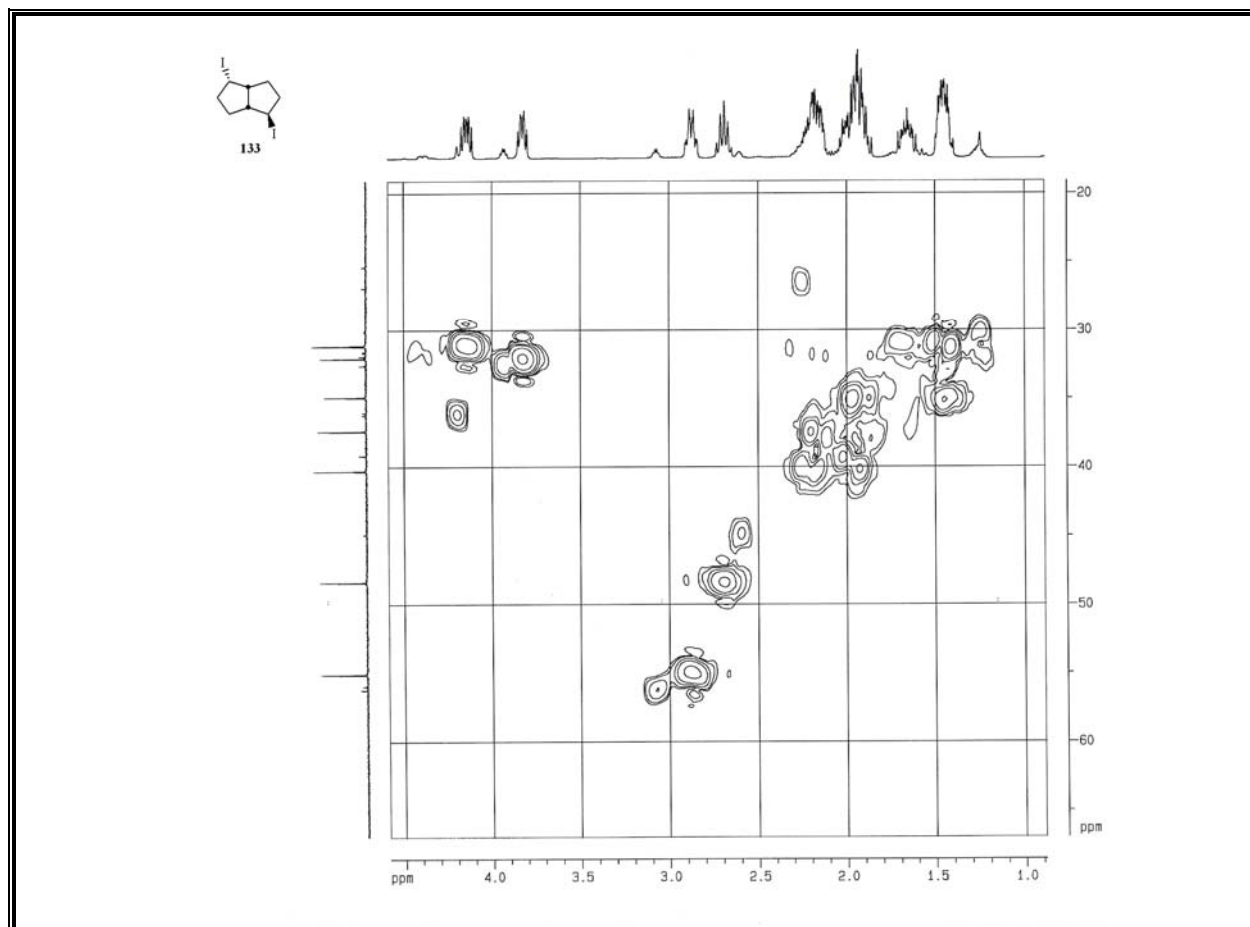


Figure A12 HMBC Spectrum of Compound **133**.

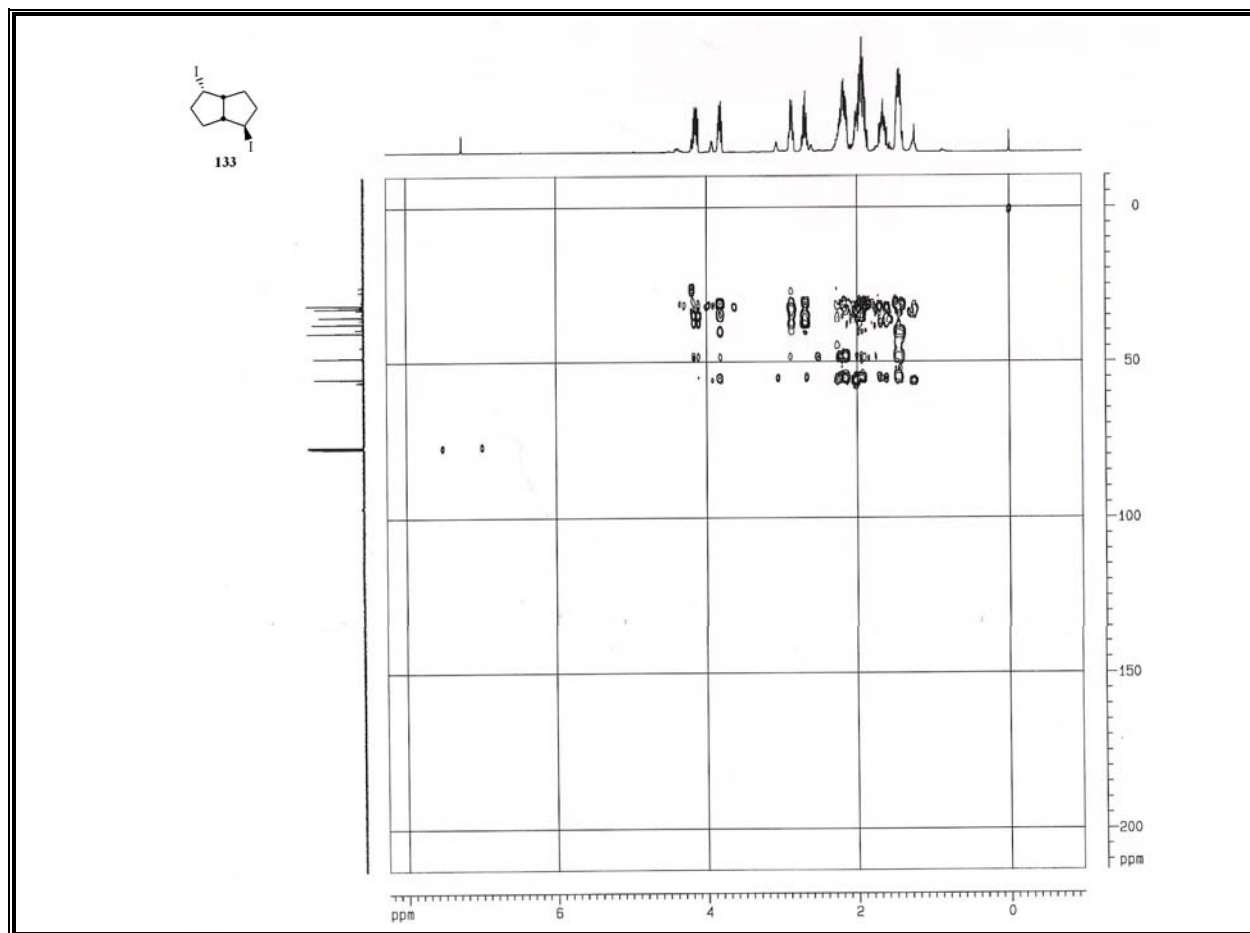


Figure A13 HMBC Spectrum of Compound 133.

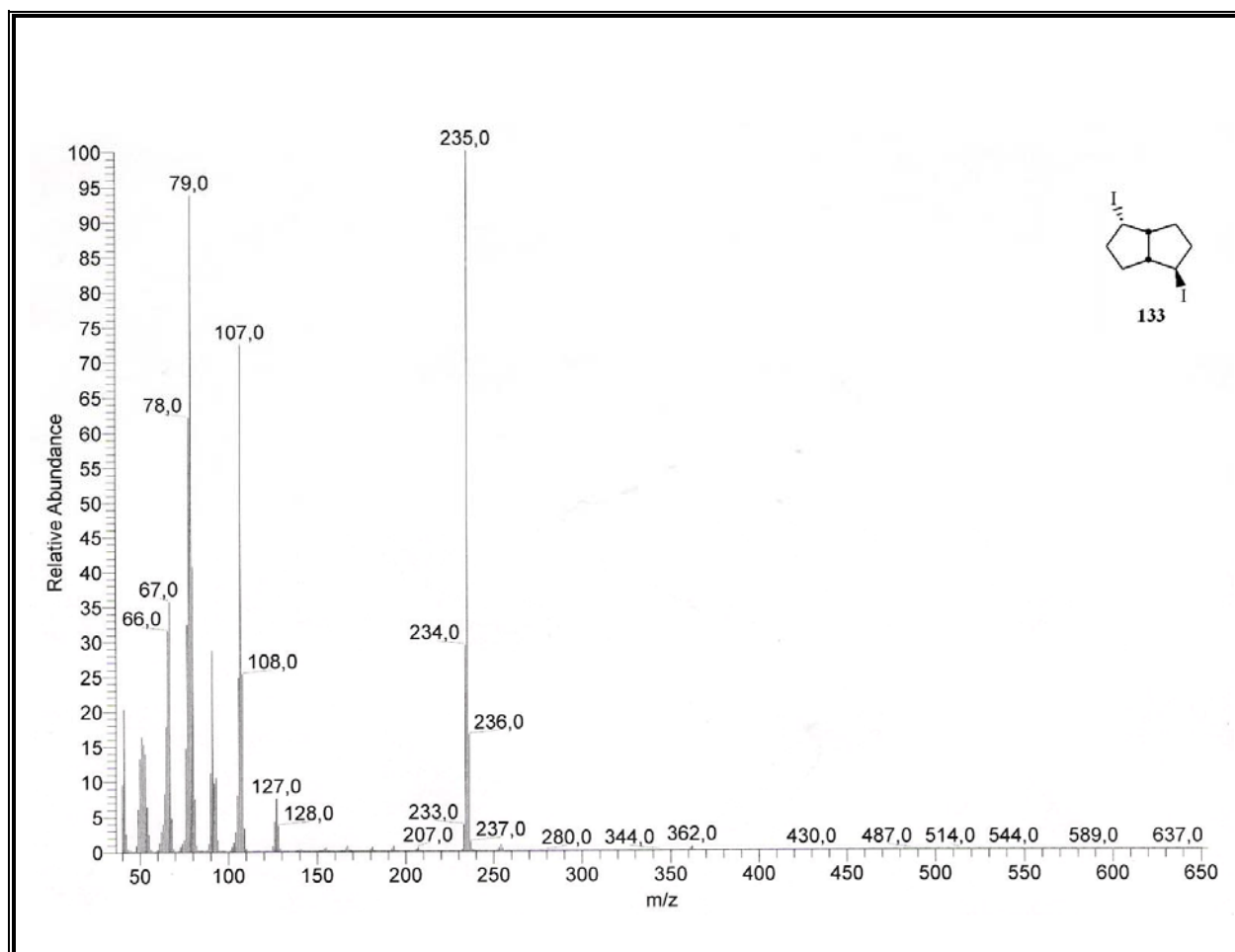


Figure A14 GC-MS Spectrum of Compound 133.

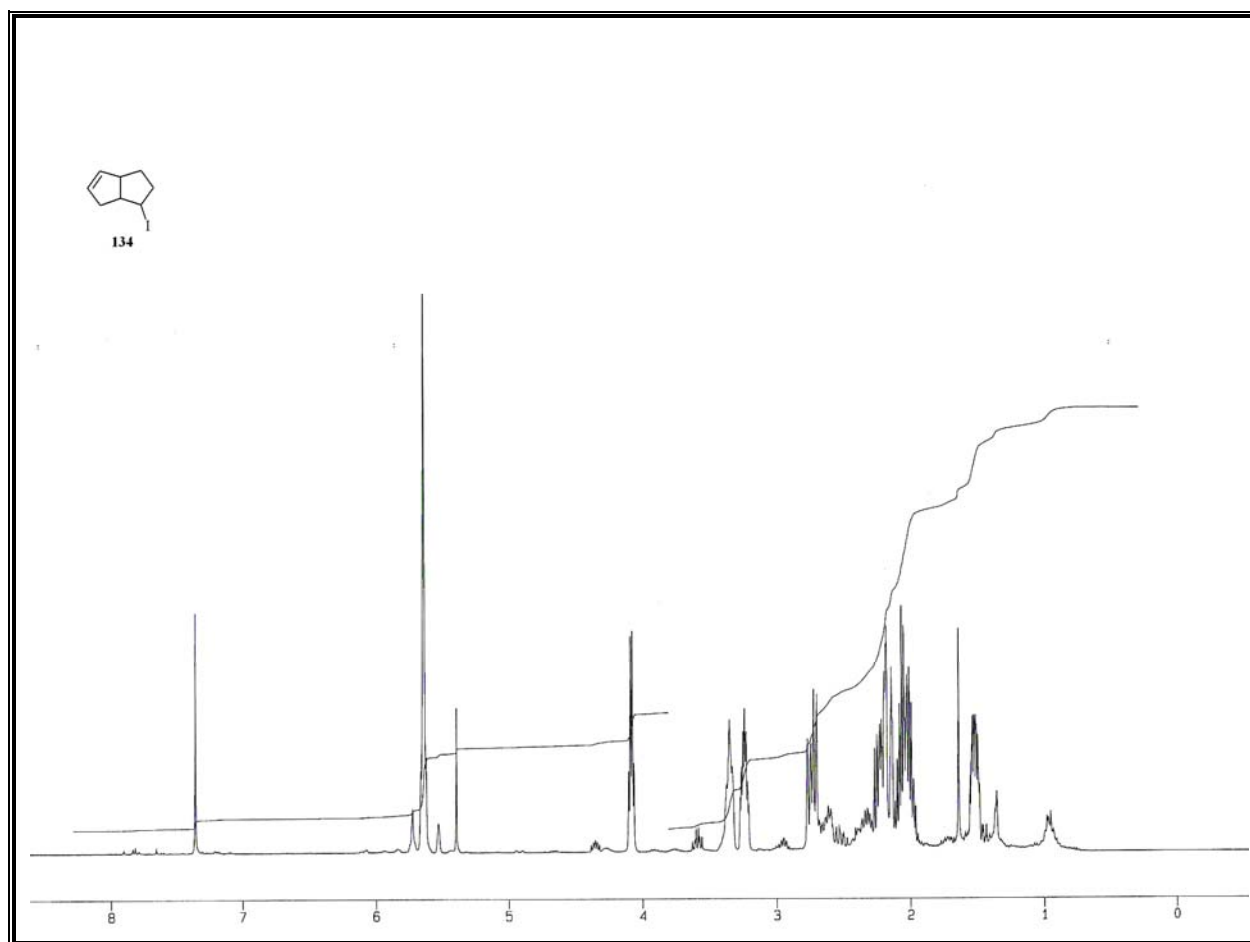


Figure A15 ^1H -NMR Spectrum of Compound **134**.

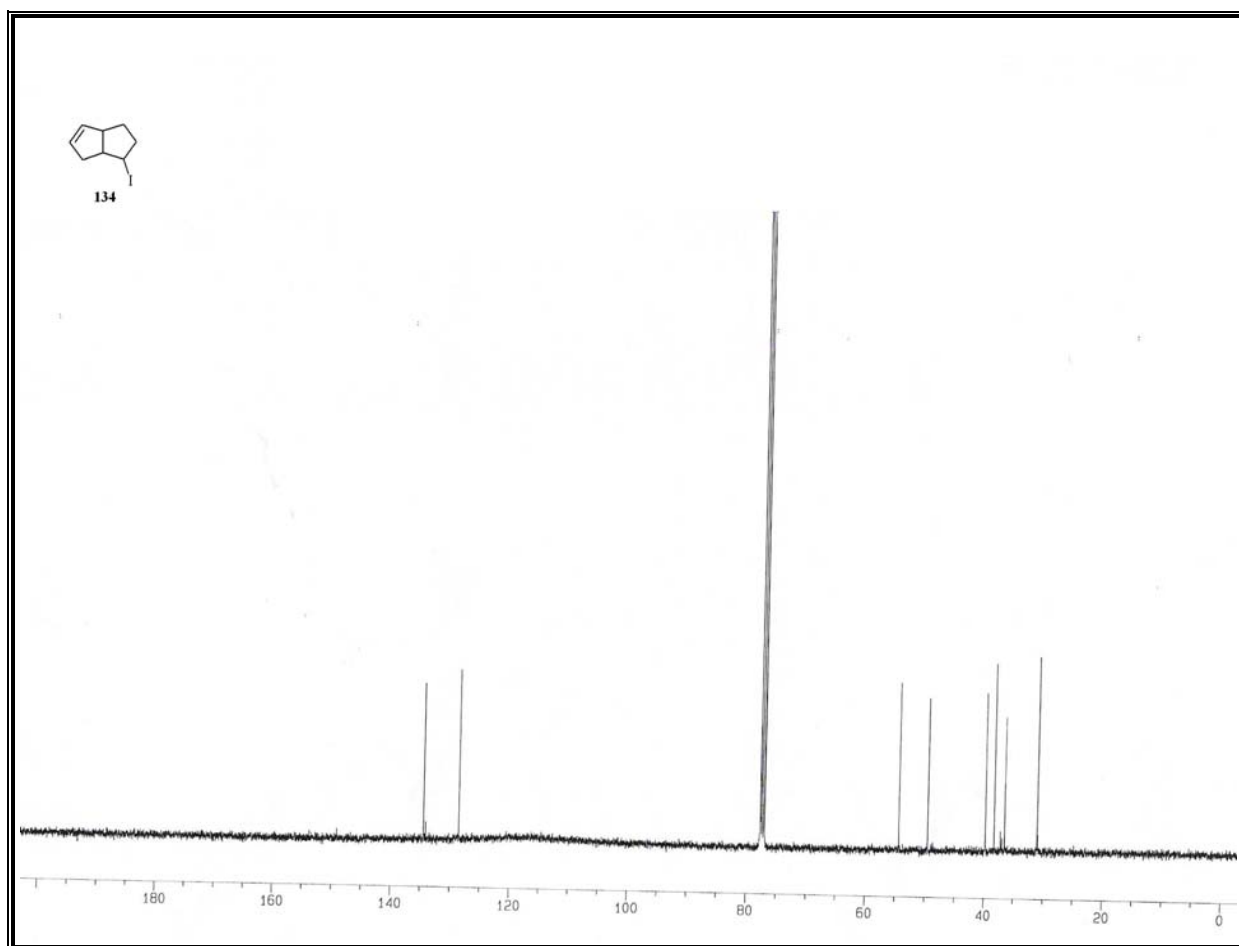


Figure A16 ^{13}C -NMR Spectrum of Compound **134**.

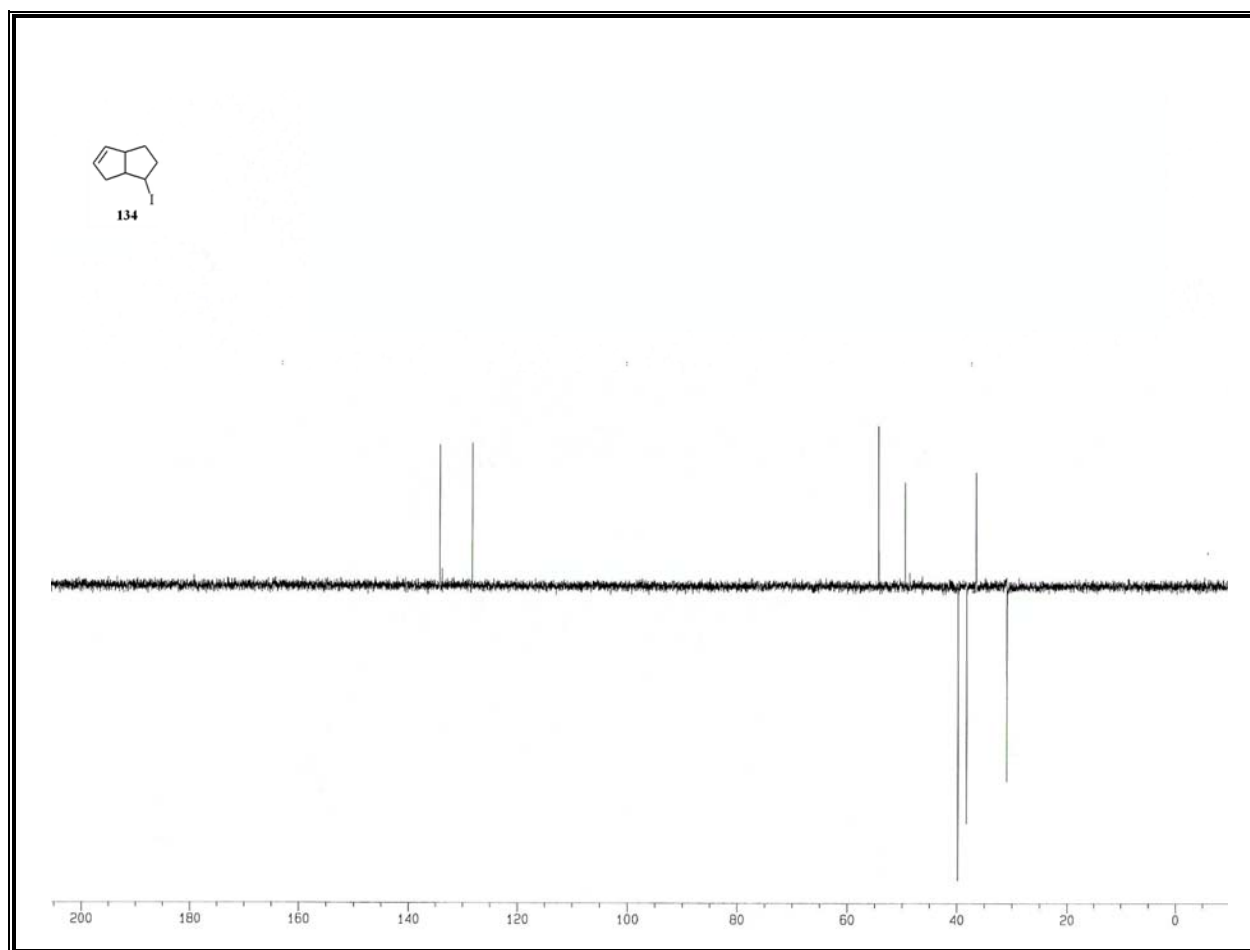


Figure A17DEPT-135 Spectrum of Compound **134**.

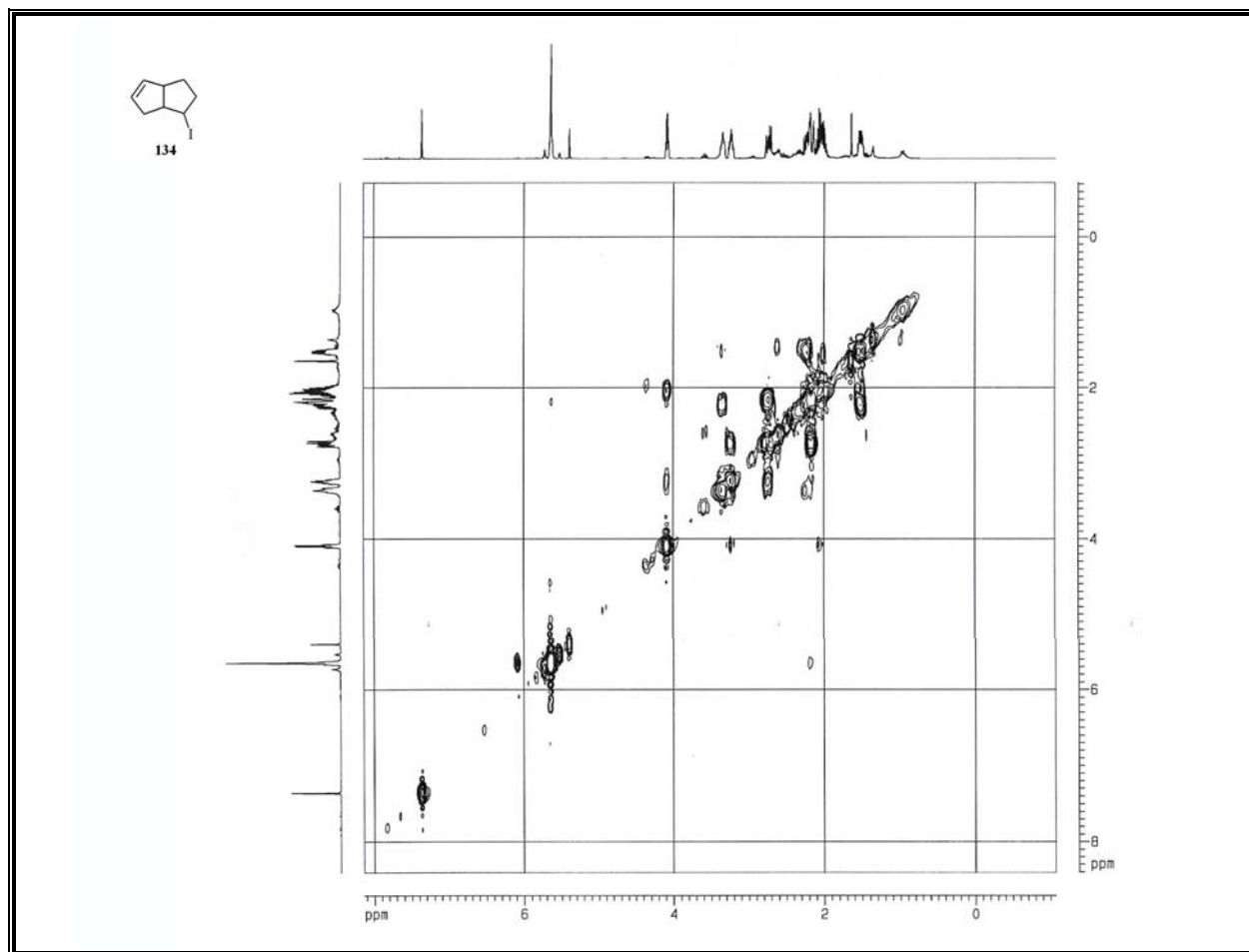


Figure A18 COSY Spectrum of Compound **134**.

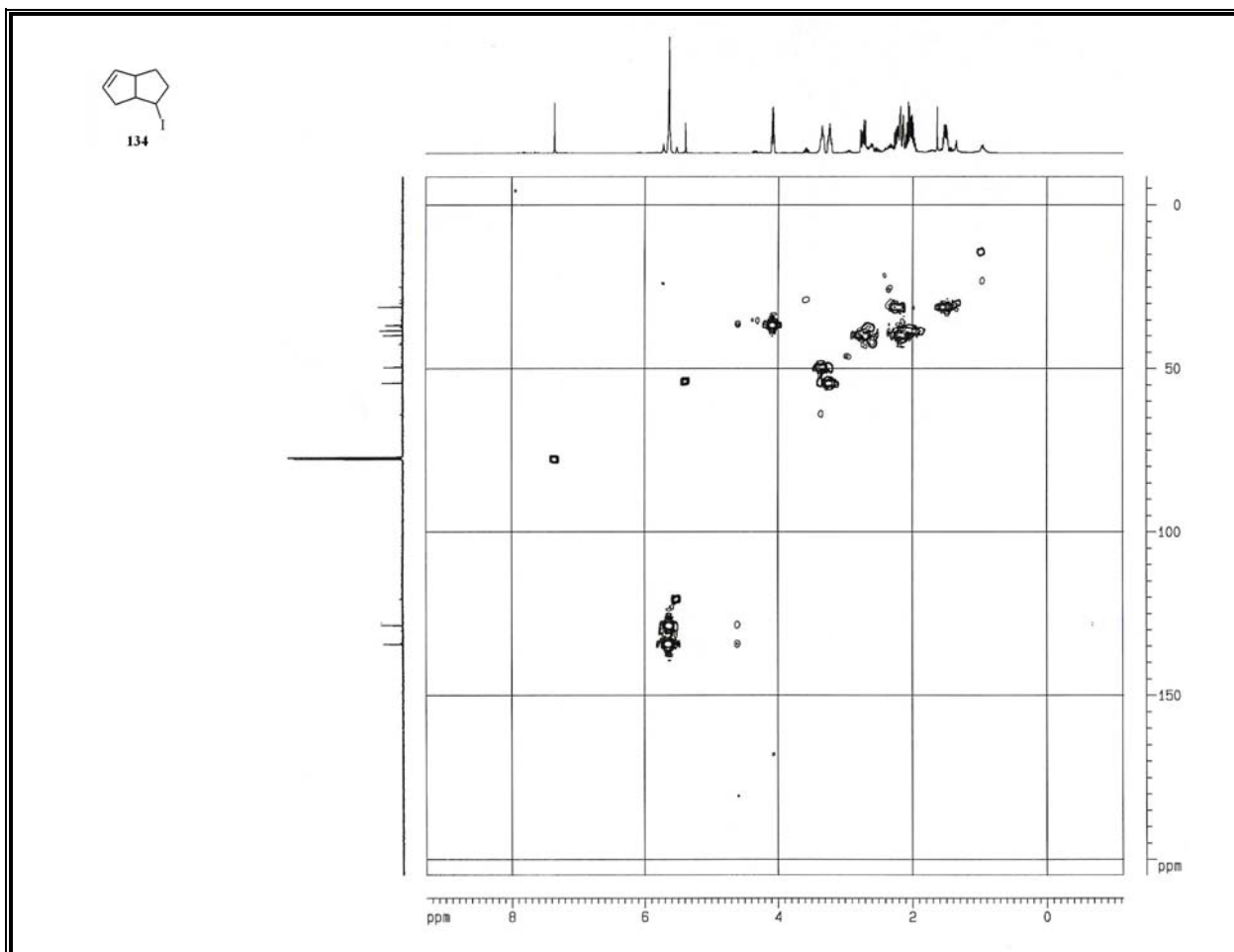


Figure A19 HMQC Spectrum of Compound 134.

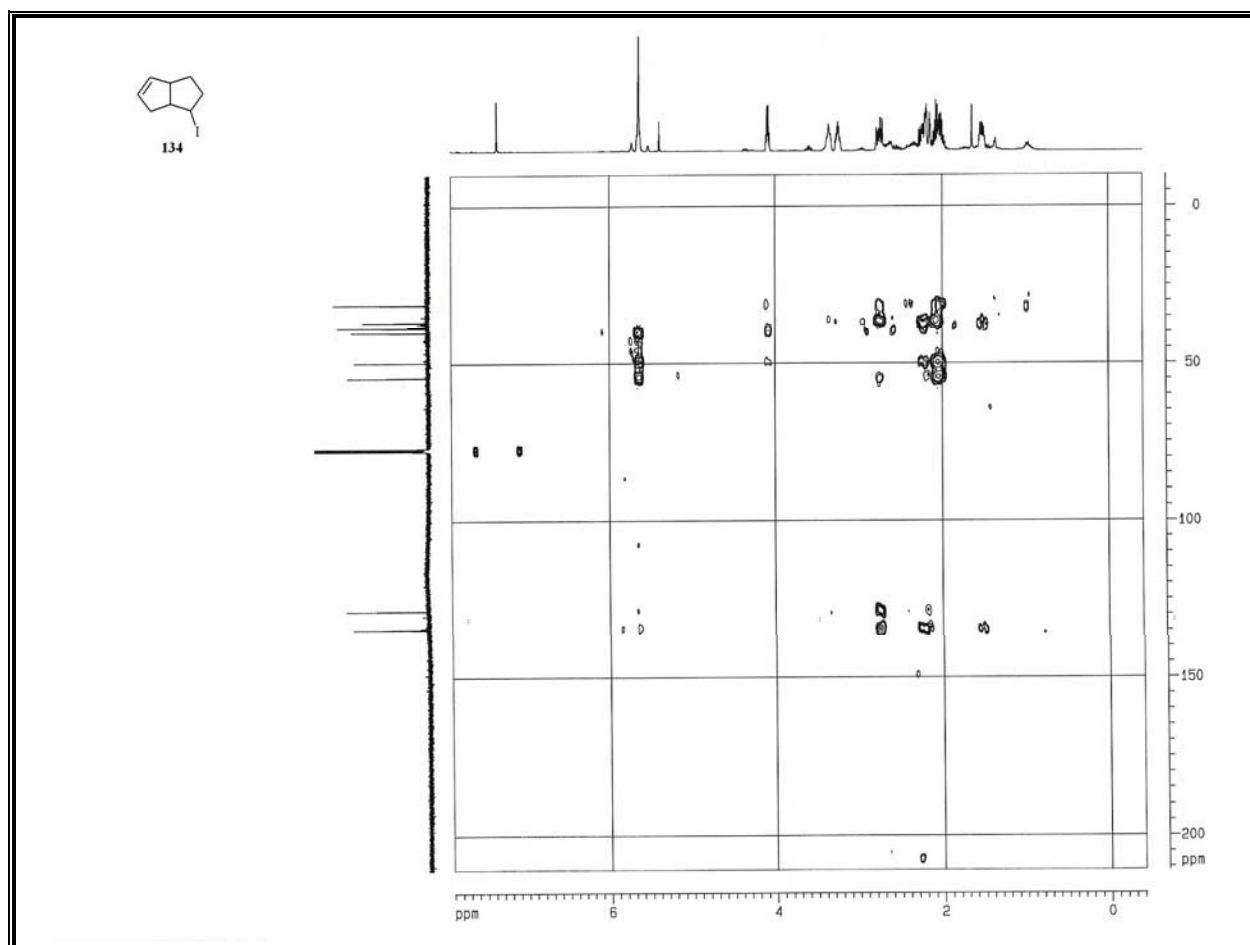


Figure A20 HMBC Spectrum of Compound **134**.

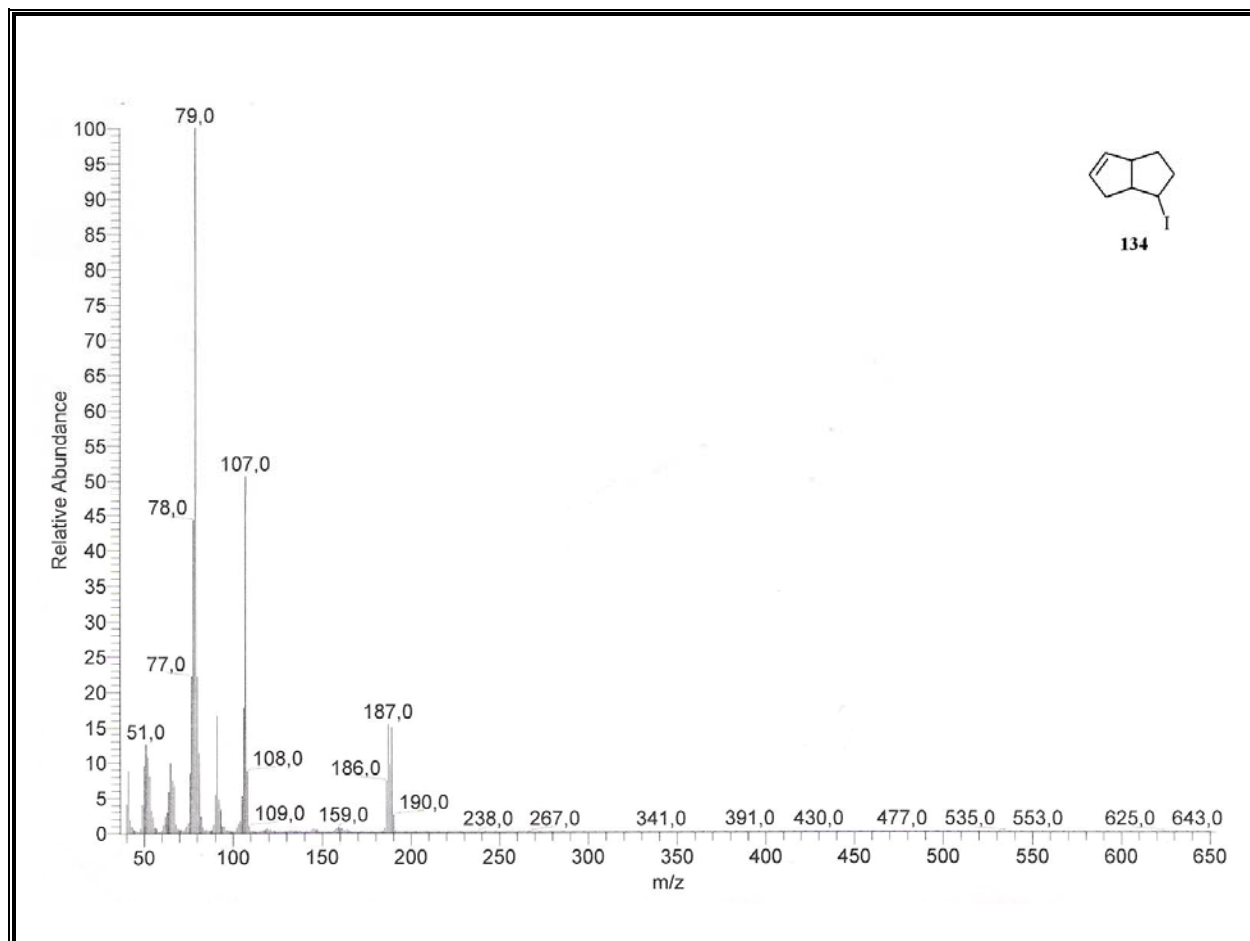


Figure A21 GC-MS Spectrum of Compound **134**.

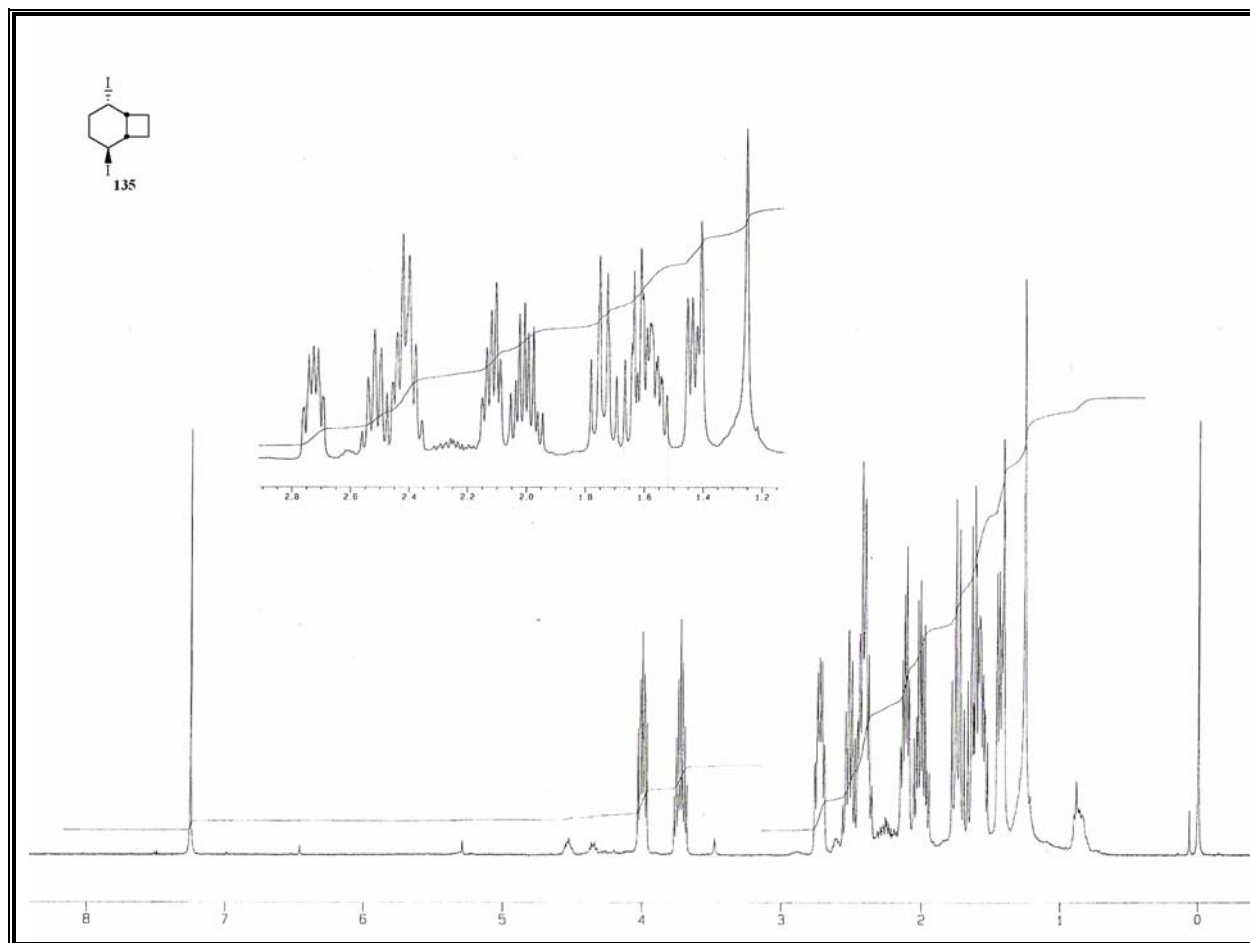


Figure A22 ^1H -NMR Spectrum of Compound 135.

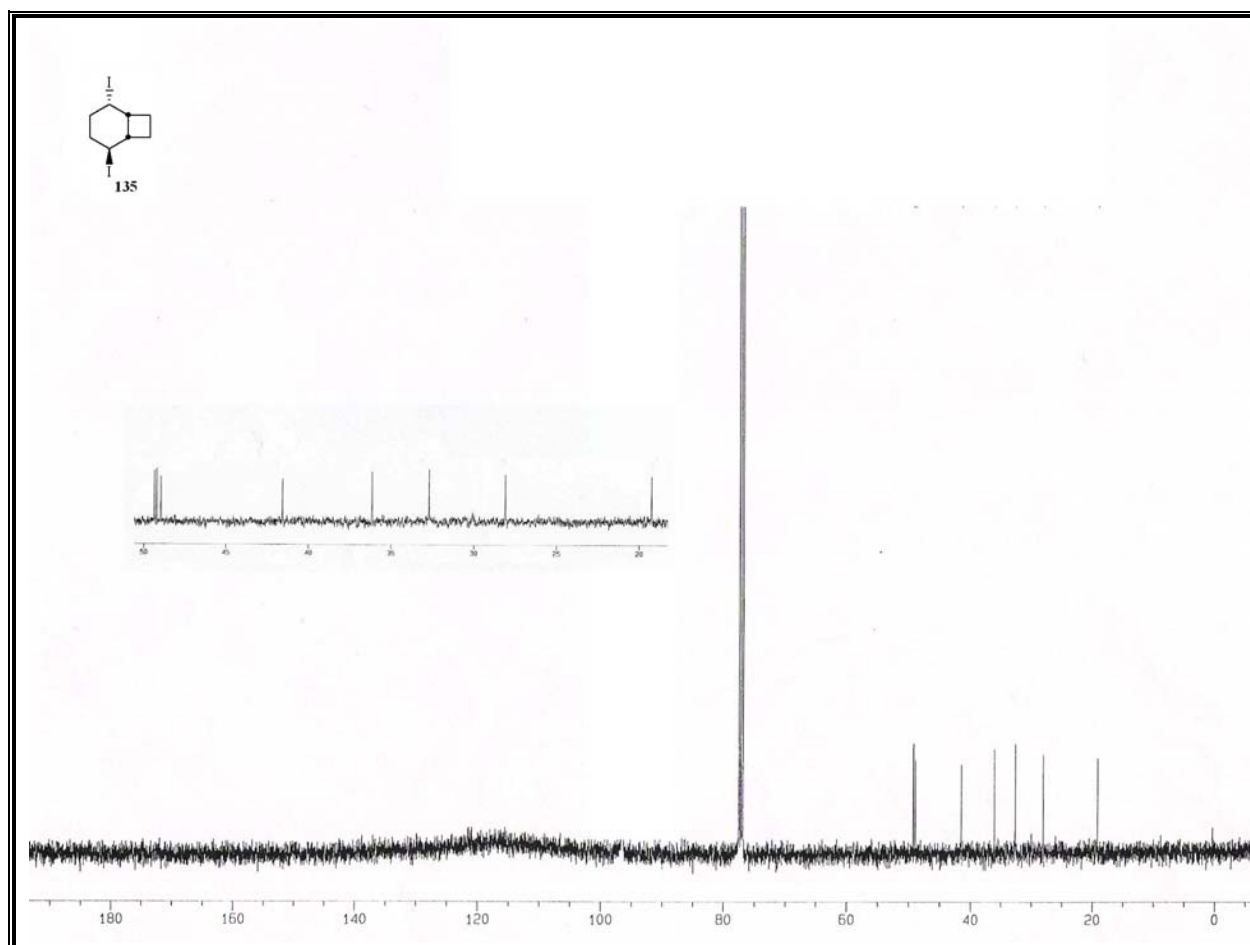


Figure A23 ^{13}C -NMR Spectrum of Compound 135.

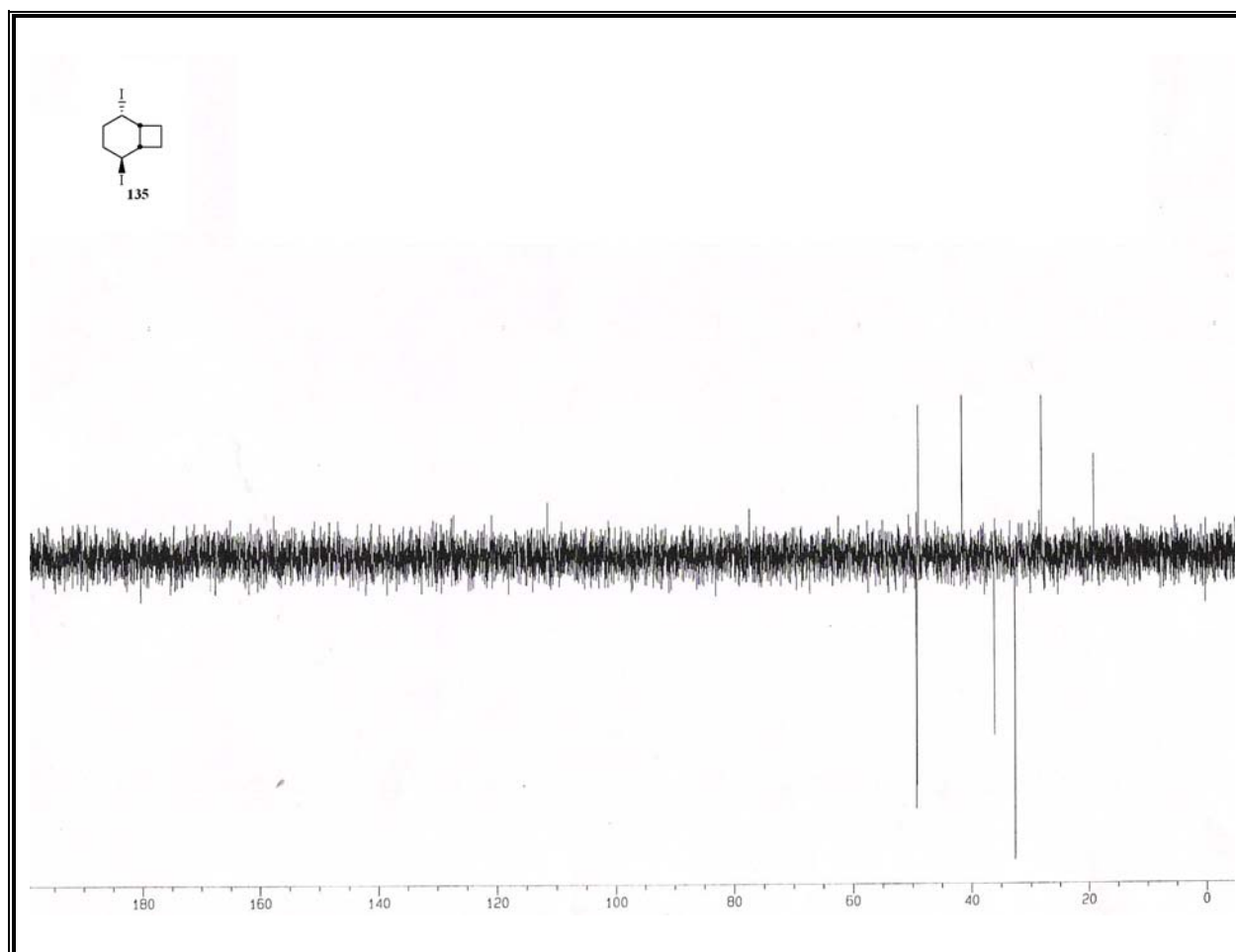


Figure A24 DEPT-135 Spectrum of Compound **135**.

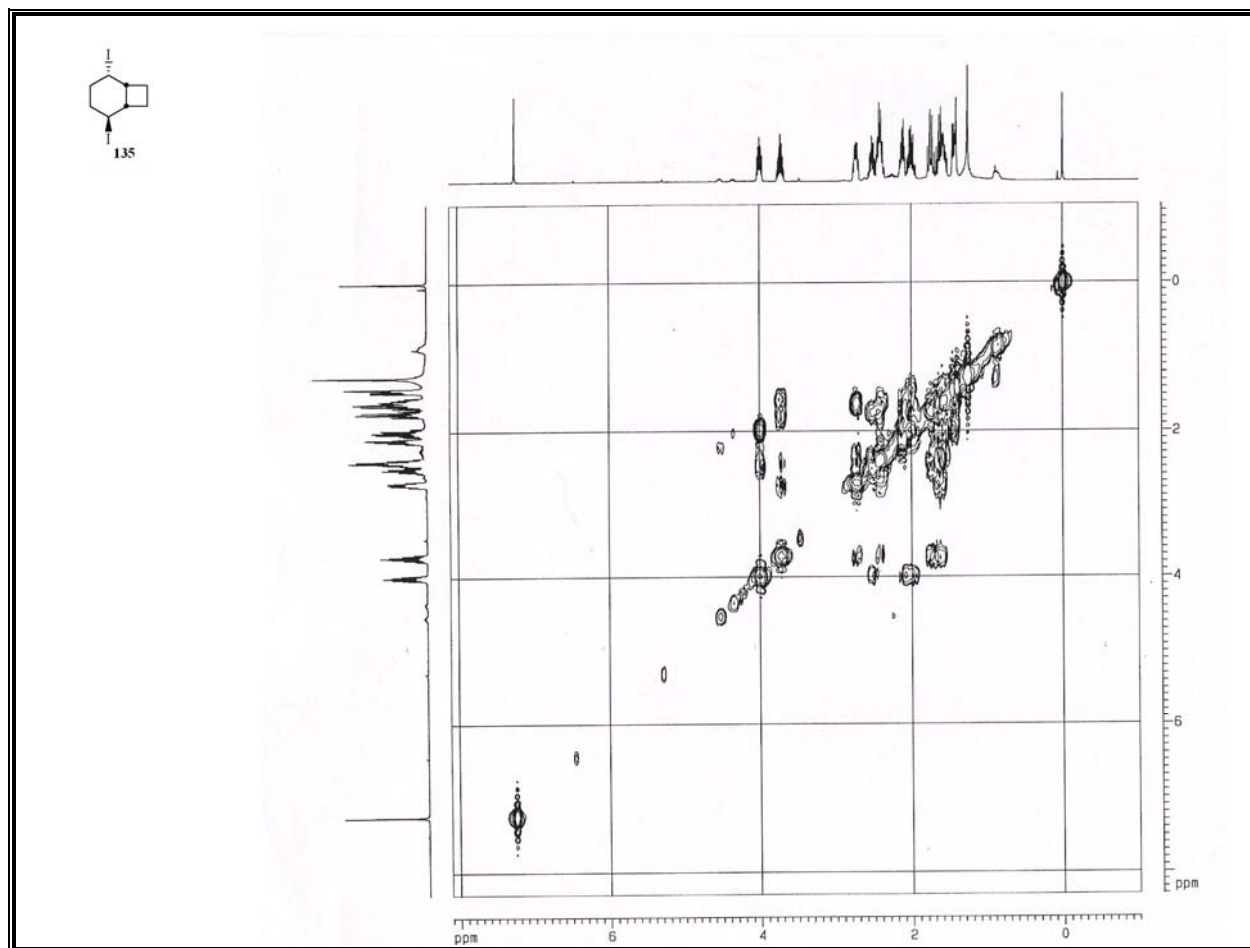


Figure A25 COSY Spectrum of Compound 135.

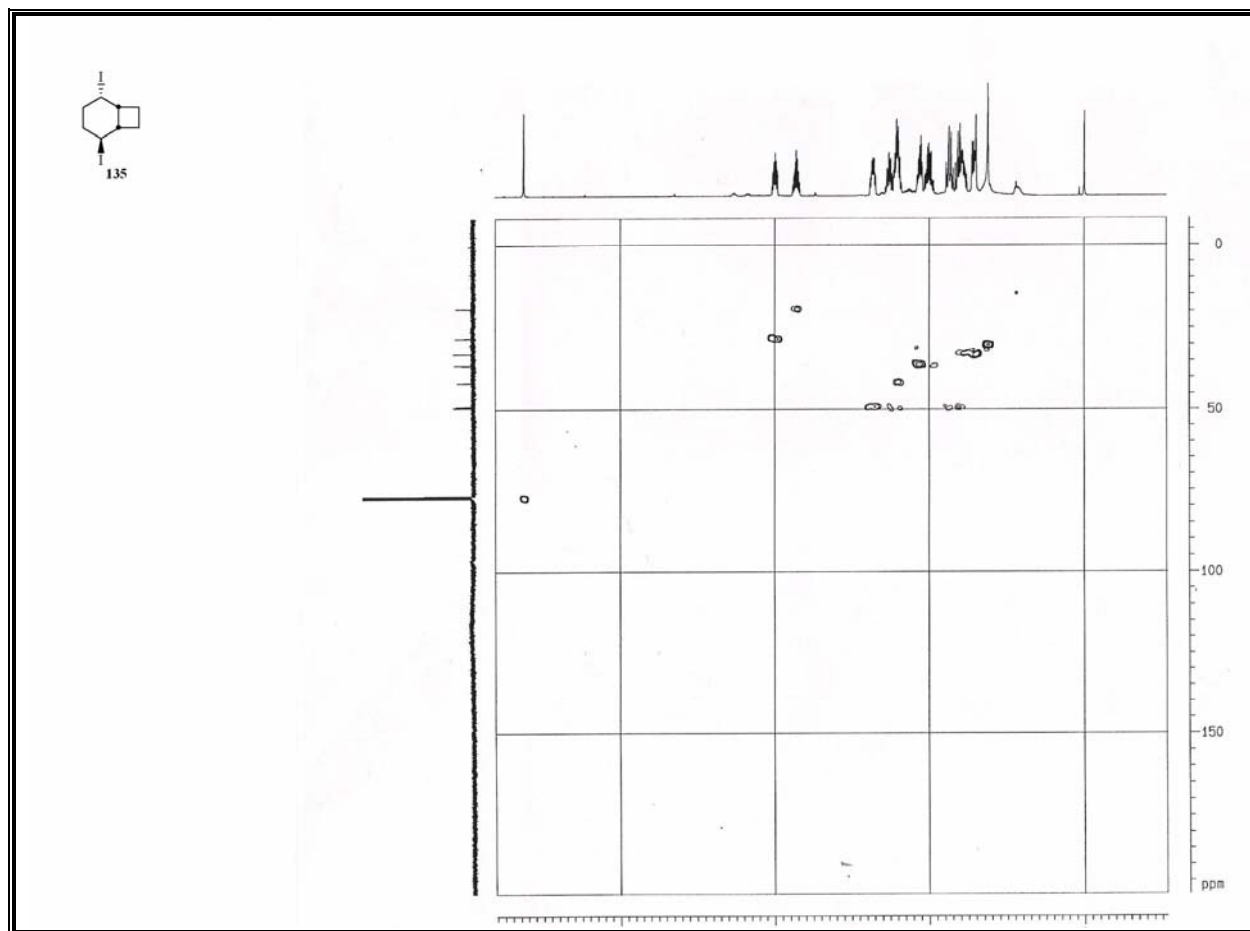


Figure A26 HMQC Spectrum of Compound 135.

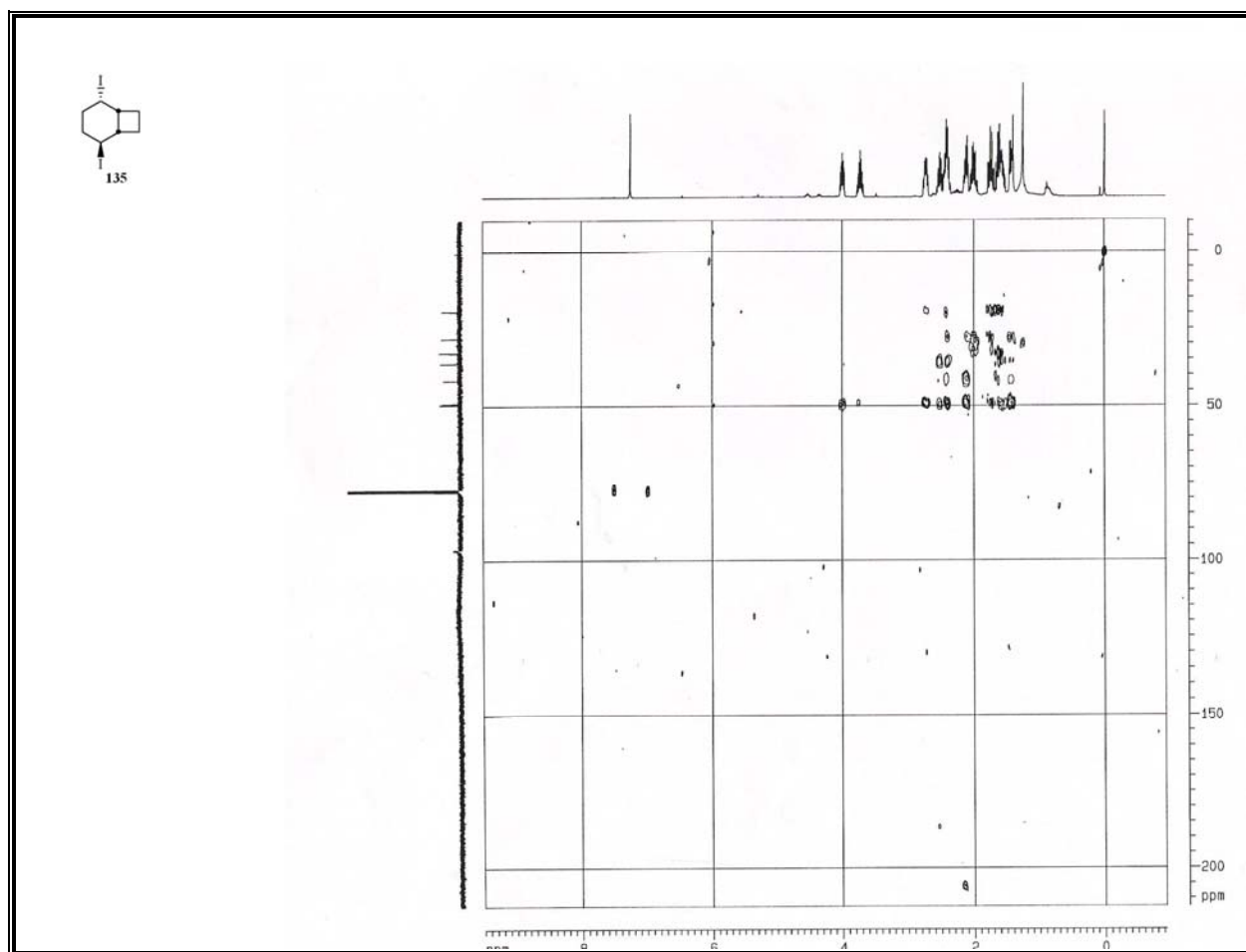


Figure A27 HMBC Spectrum of Compound **135**.

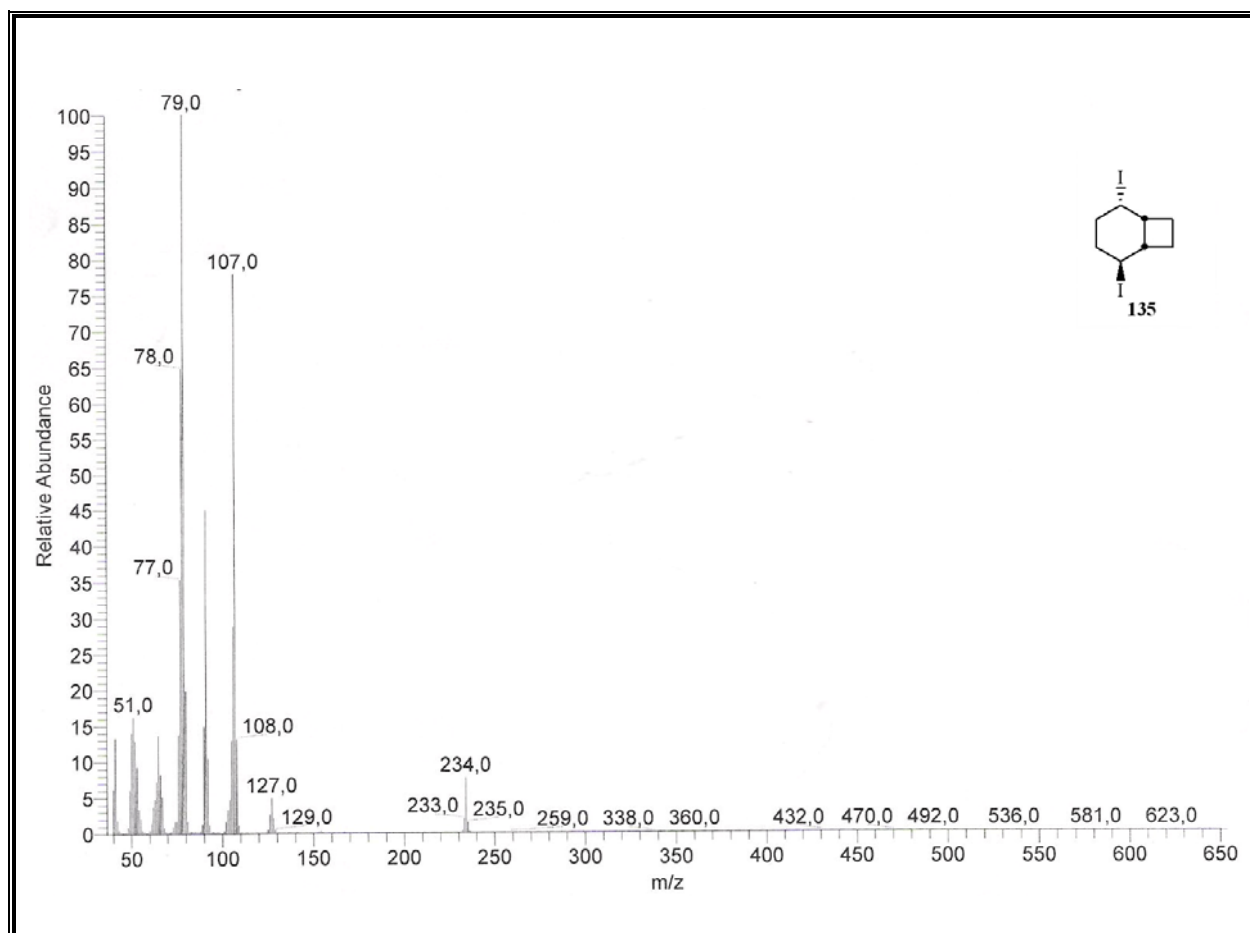


Figure A28 GC-MS Spectrum of Compound 135.

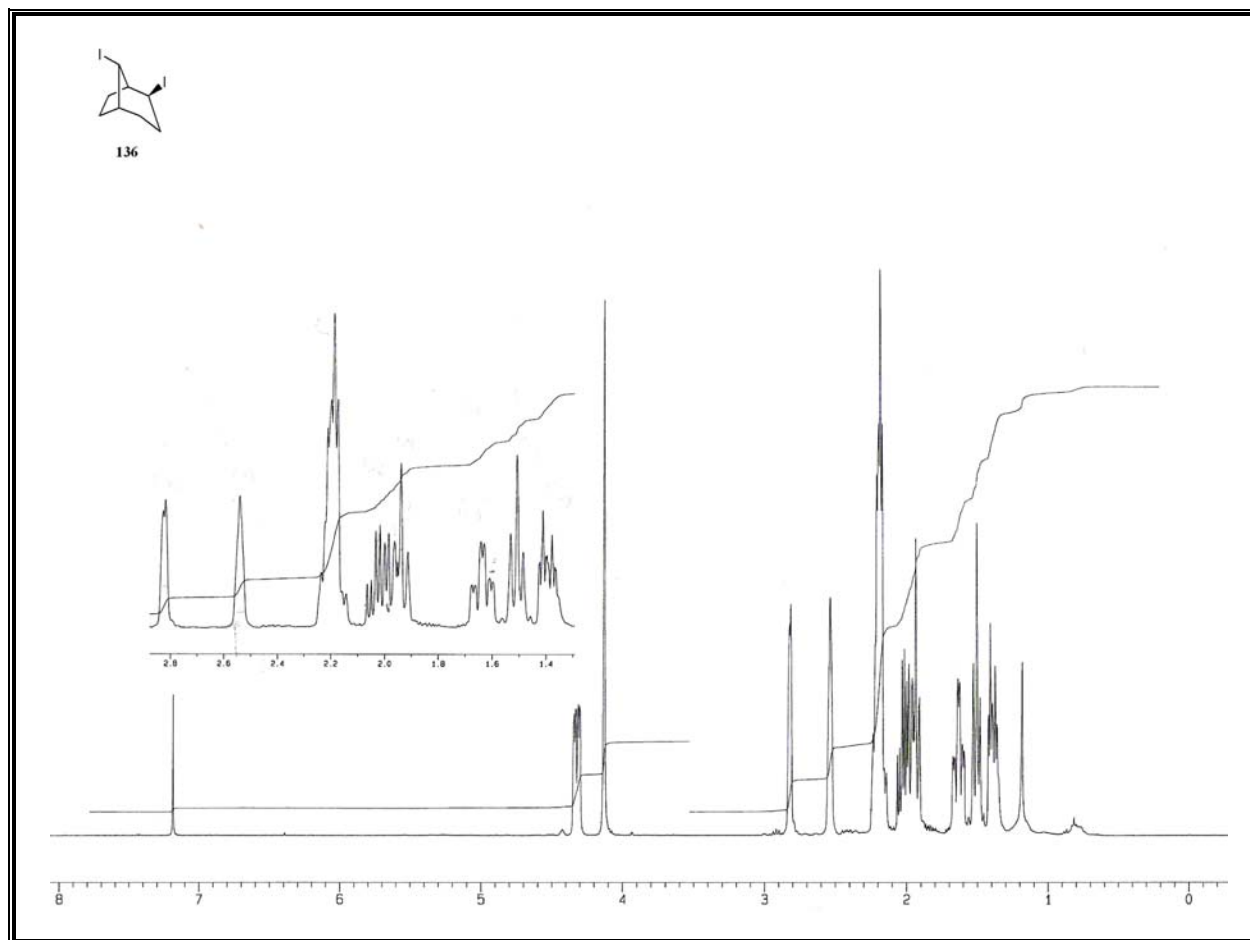


Figure A29 ^1H -NMR Spectrum of Compound 136.

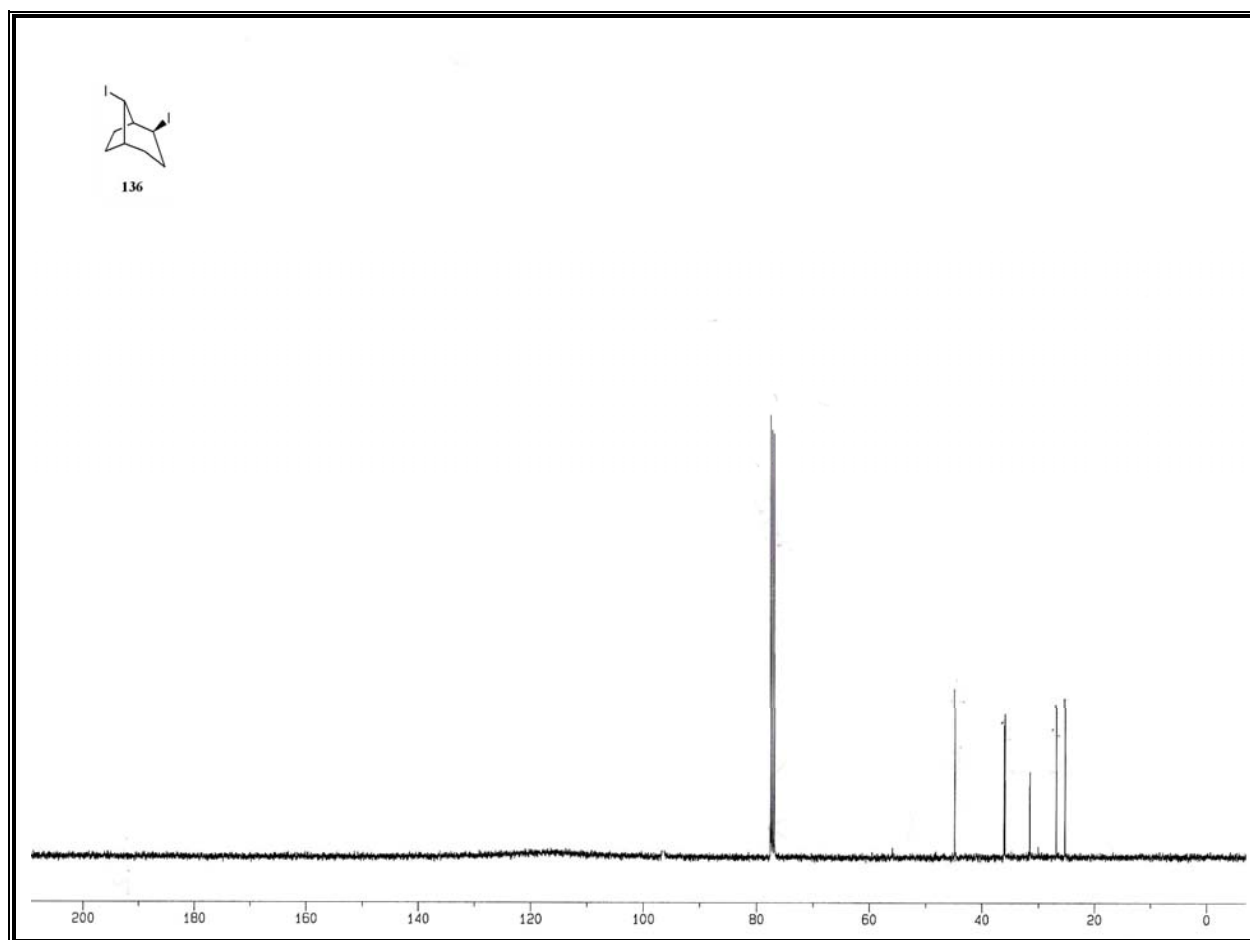


Figure A30 ^{13}C -NMR Spectrum of Compound **136**.

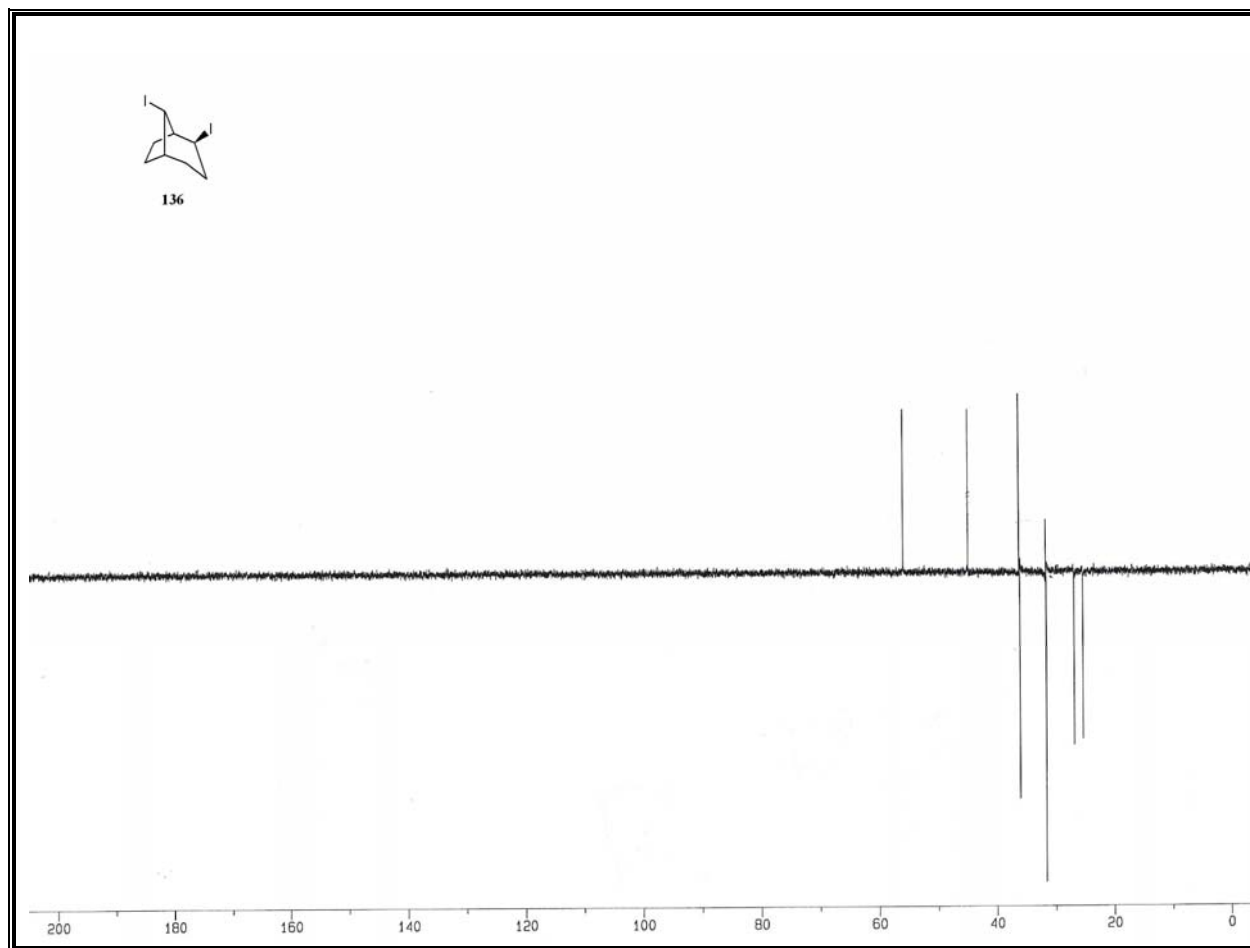


Figure A31 DEPT-135 Spectrum of Compound **136**.

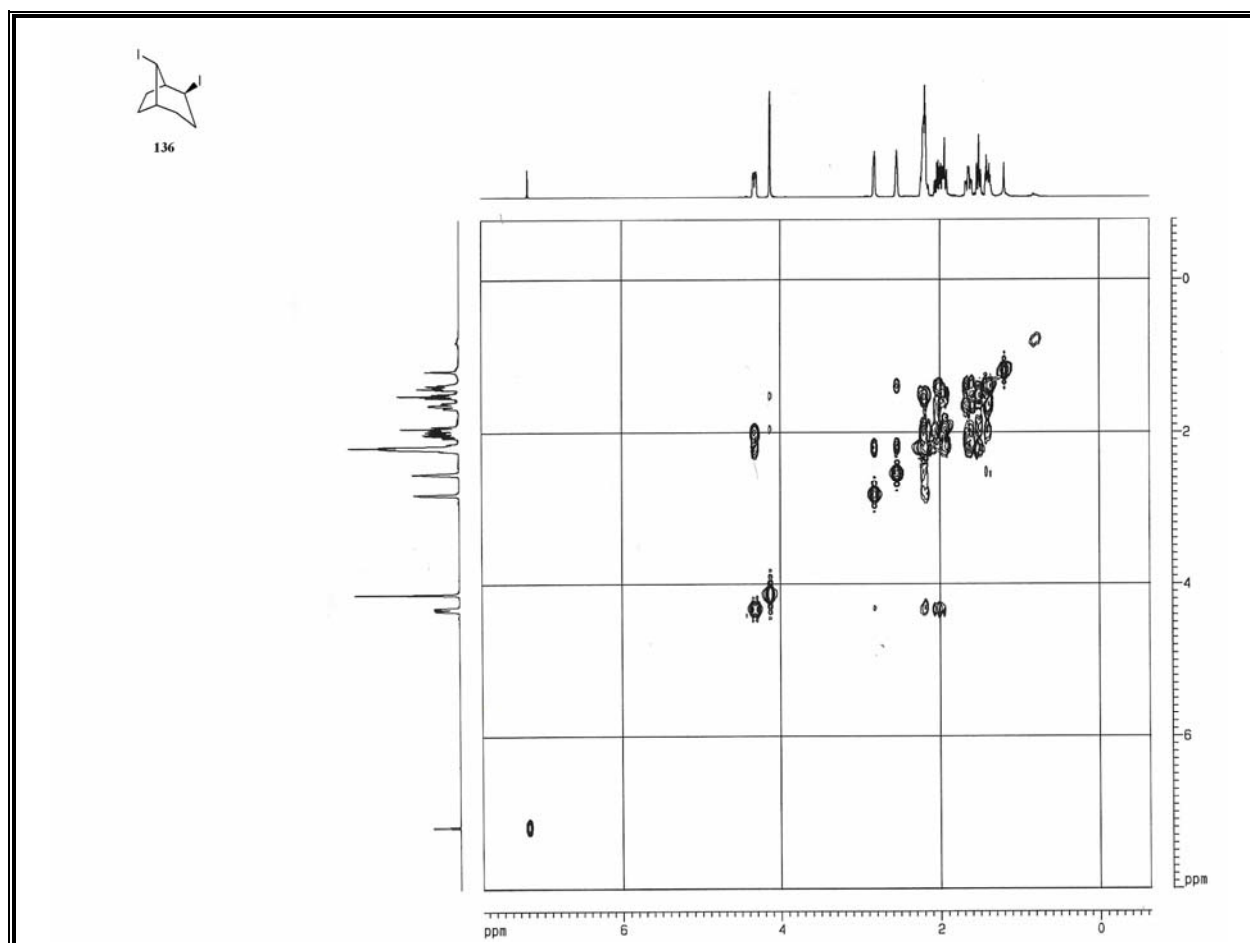


Figure A32 COSY Spectrum of Compound **136**.

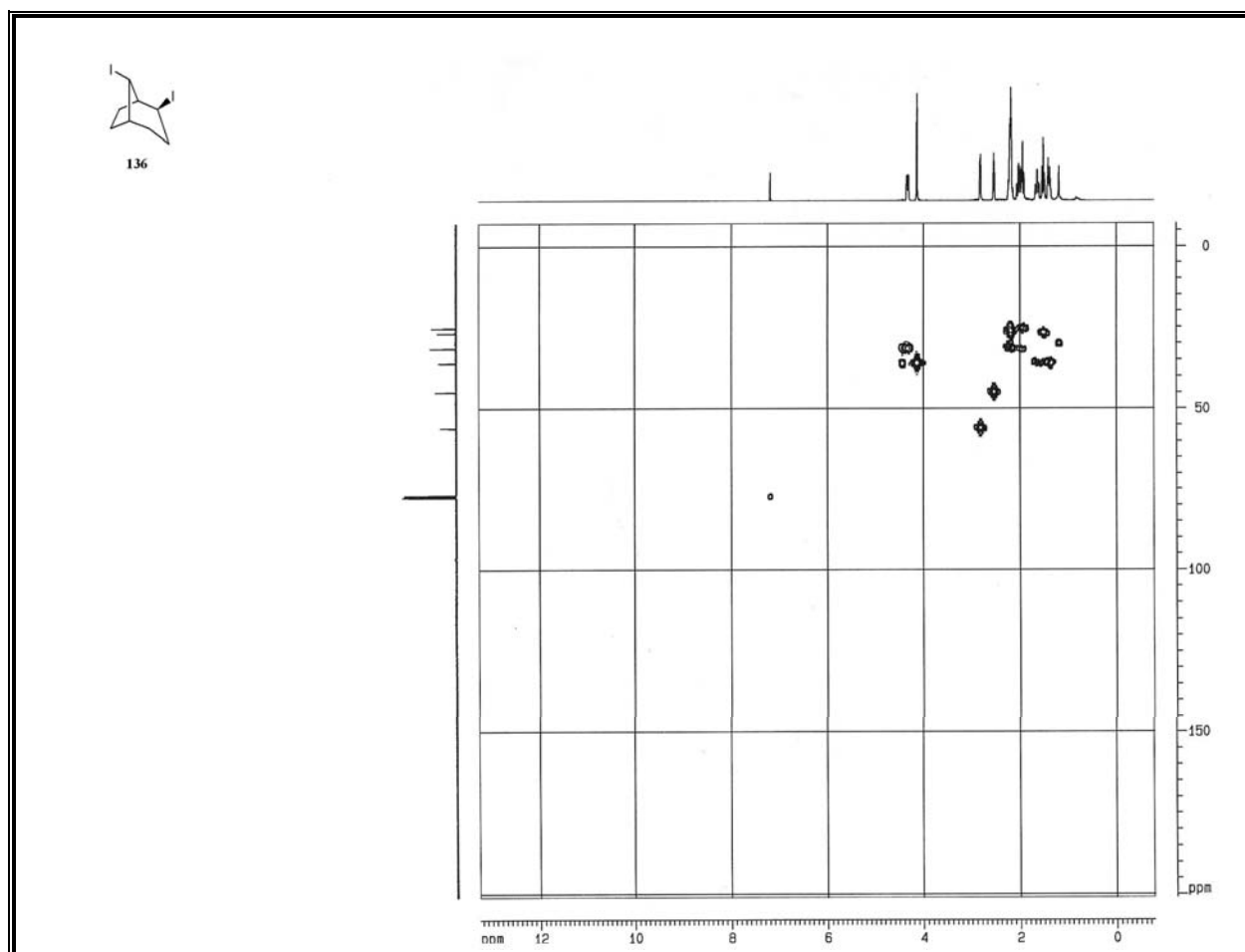


Figure A33 HMOC Spectrum of Compound **136**.

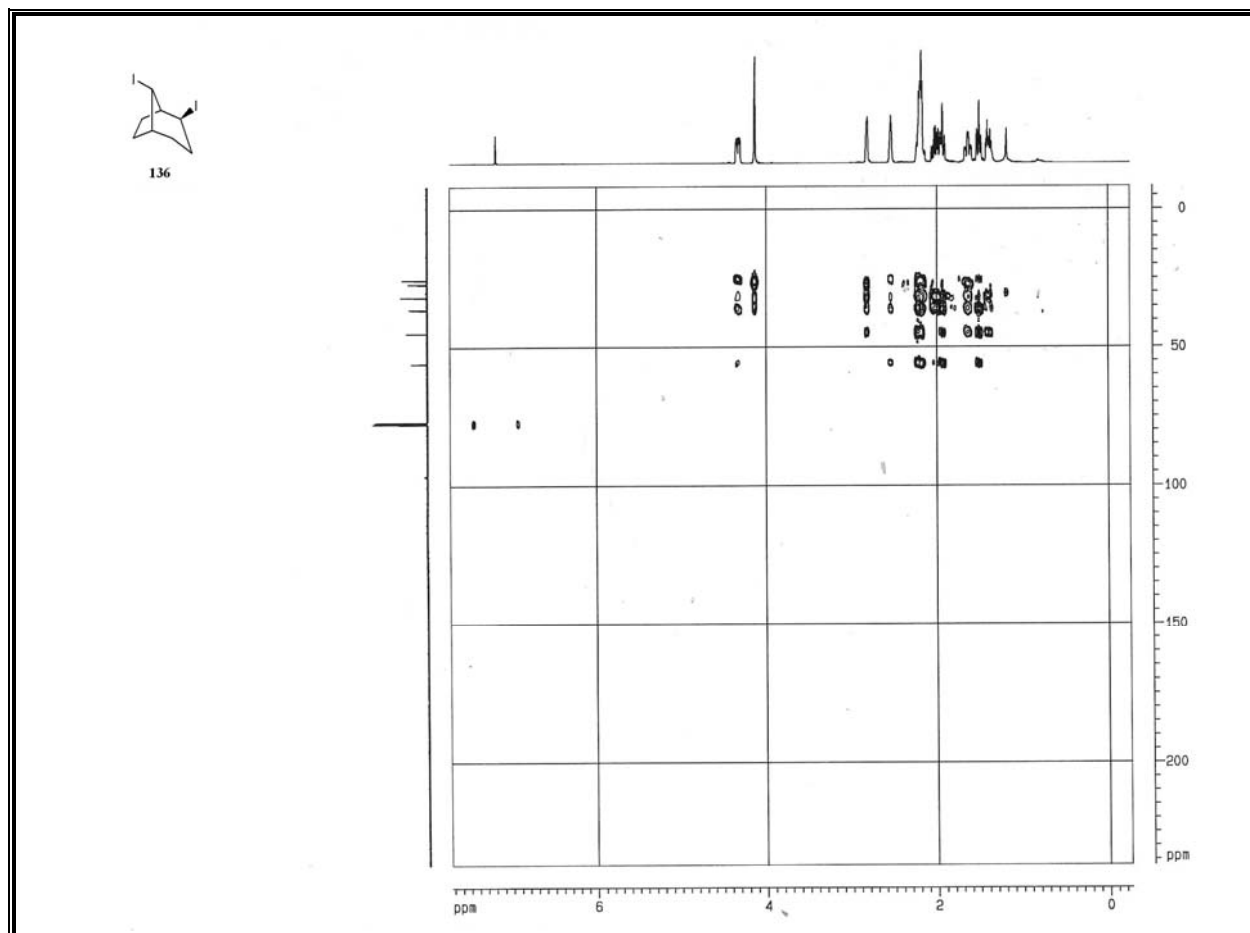


Figure A34 HMBC spectrum of Compound **136**.

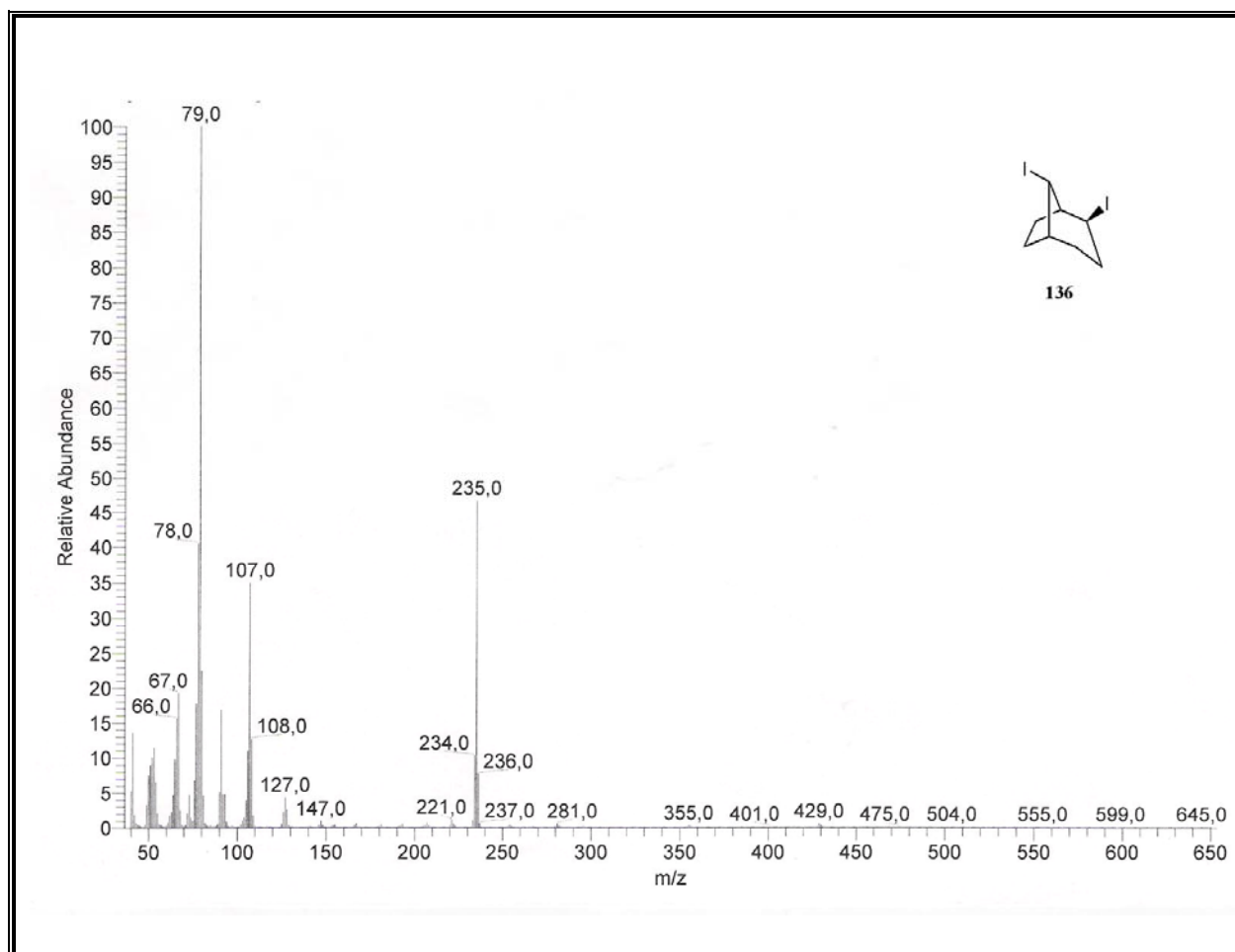


Figure A35 GC-MS Spectrum of Compound **136**.

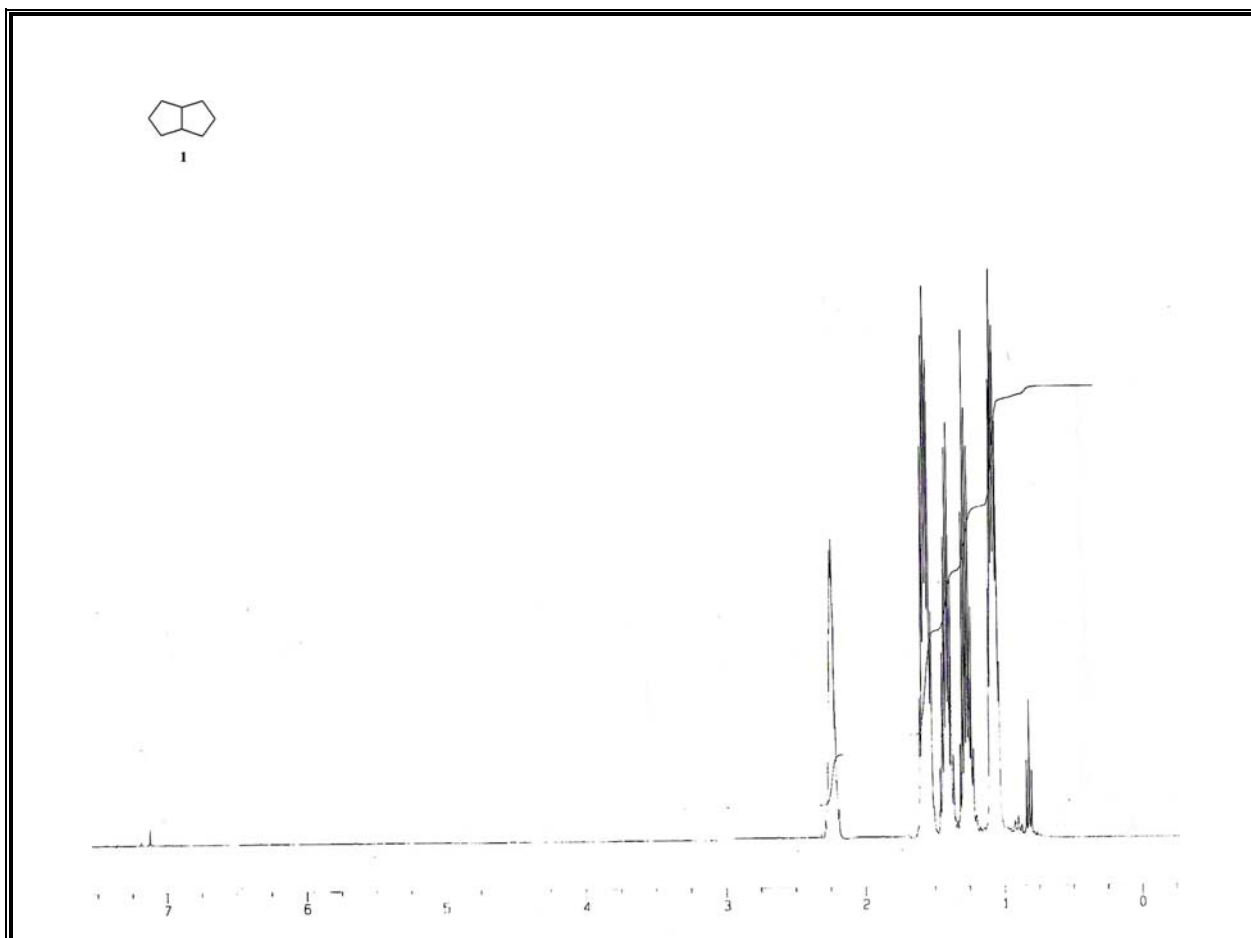


Figure A36 ^1H -NMR Spectrum of Compound **1**.

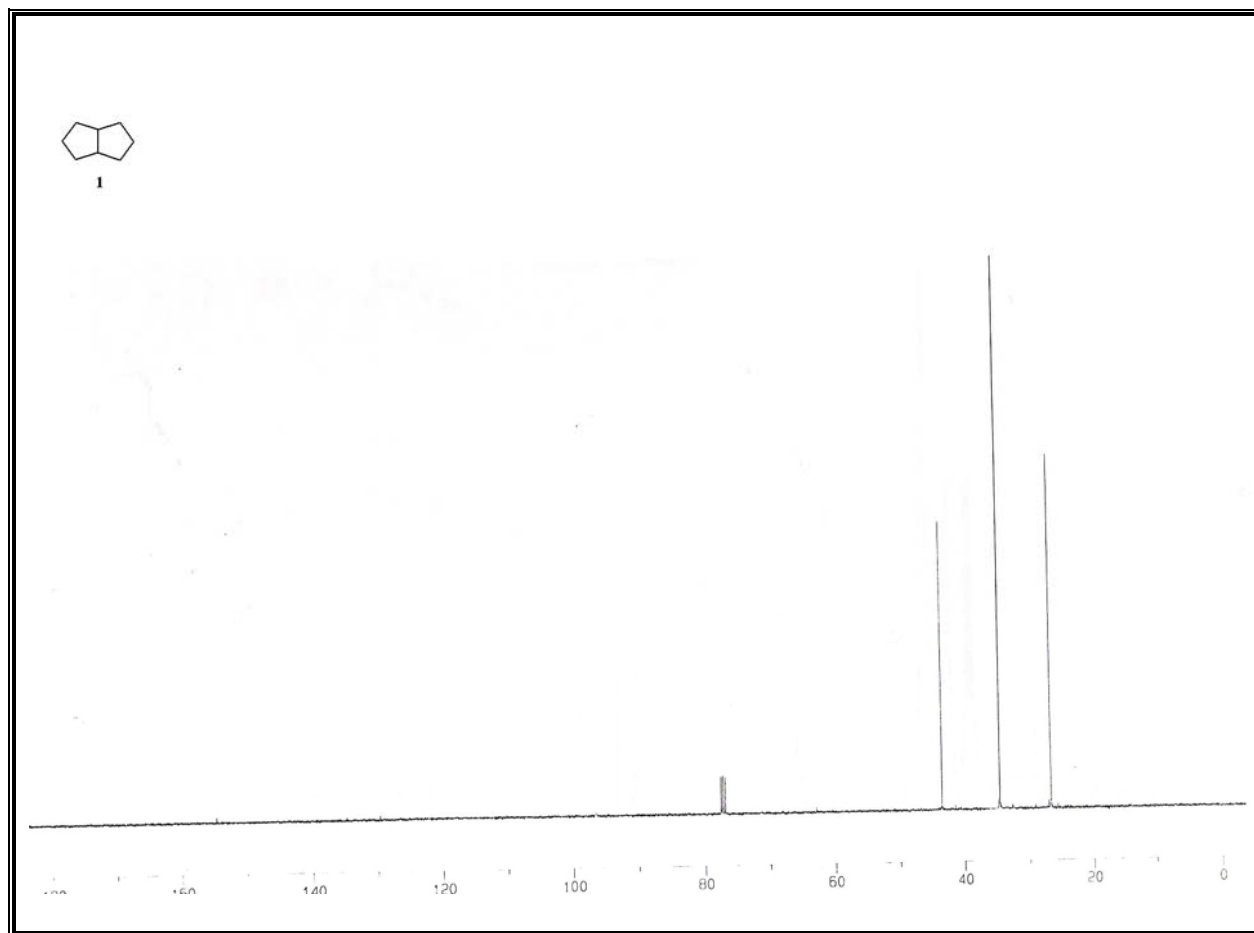


Figure A37 ^{13}C -NMR Spectrum of Compound 1.

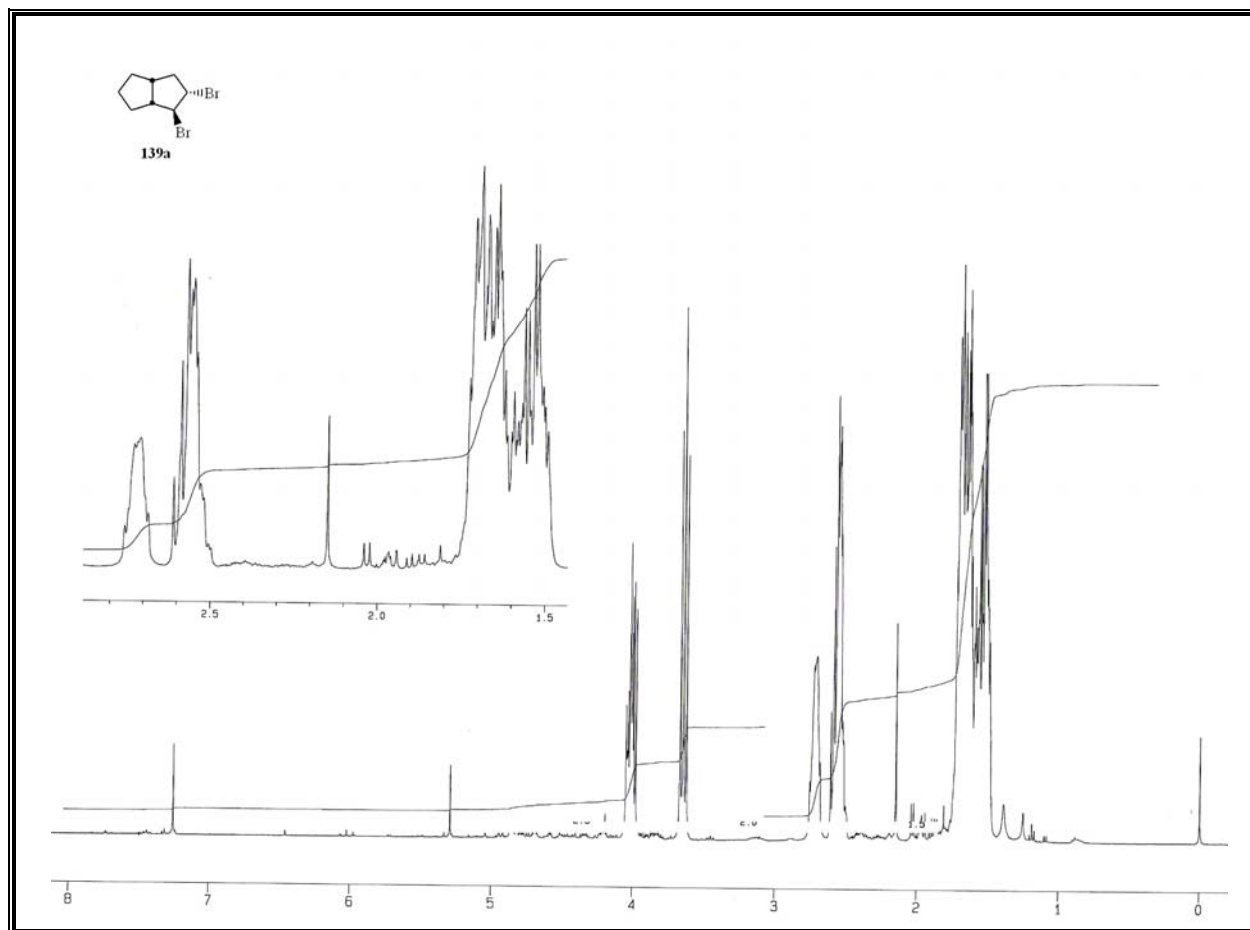


Figure A38 ^1H -NMR Spectrum of Compound **139a**.

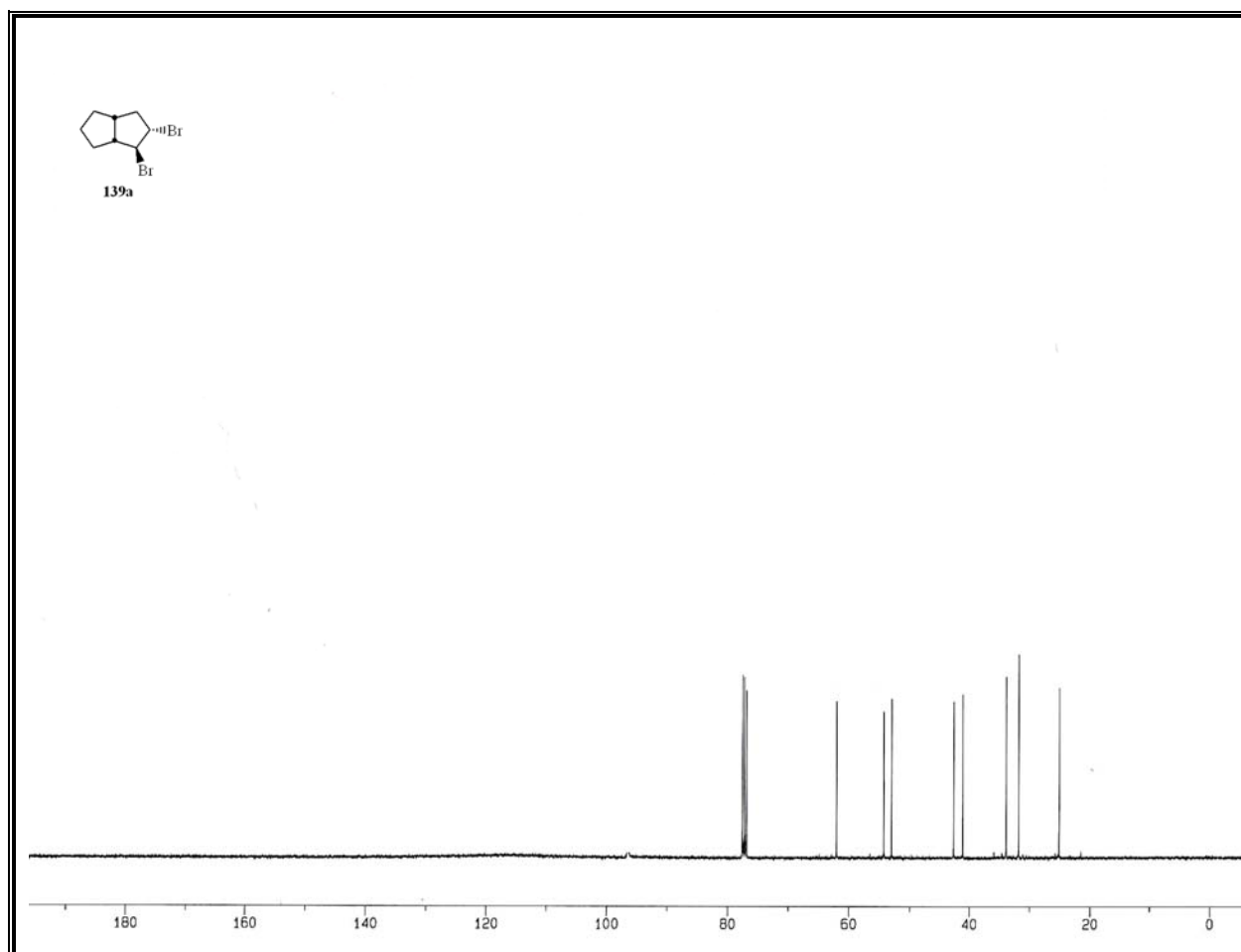


Figure A39 ^{13}C -NMR Spectrum of Compound **139a**.

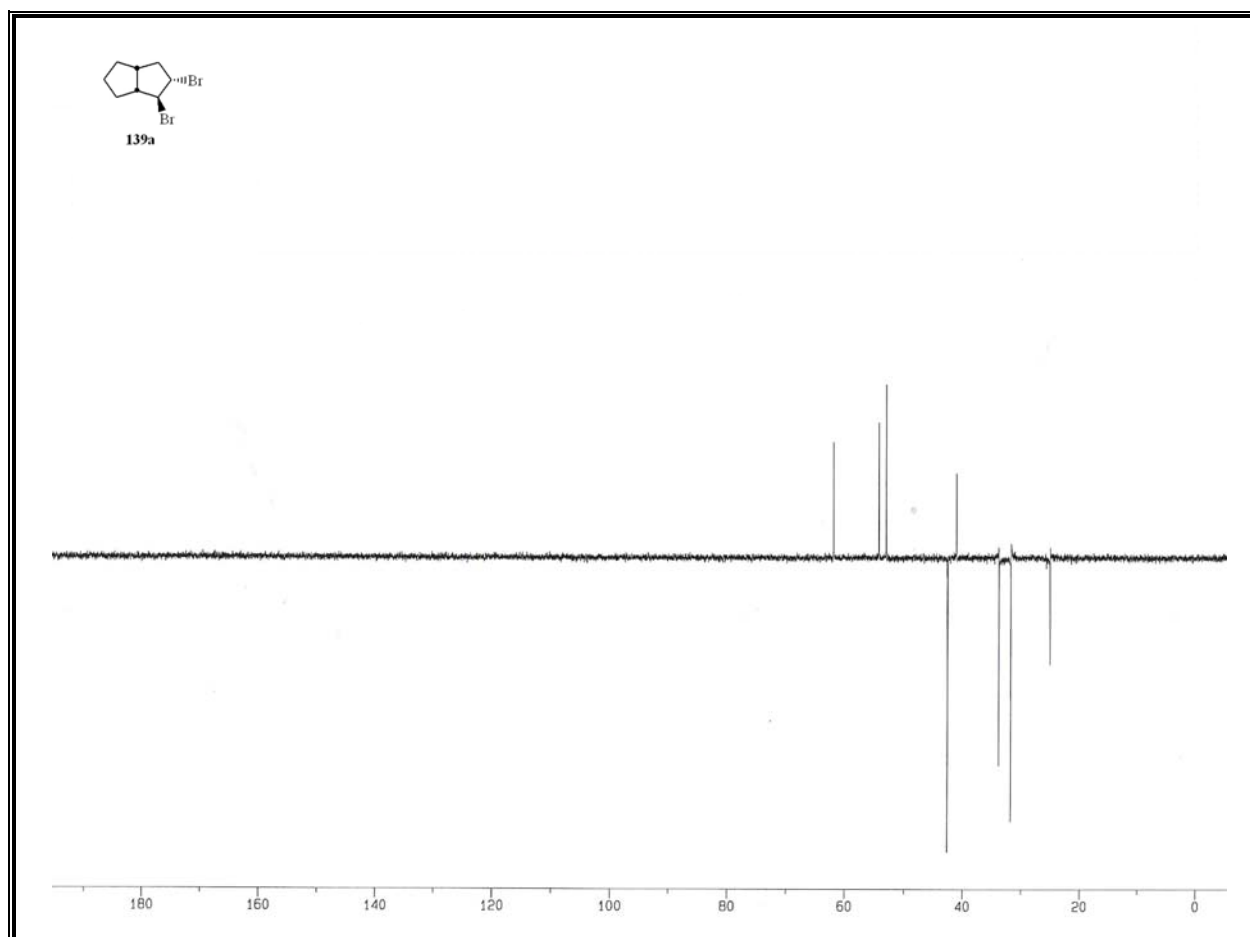


Figure A40 DEPT-135 Spectrum of Compound **139a**.

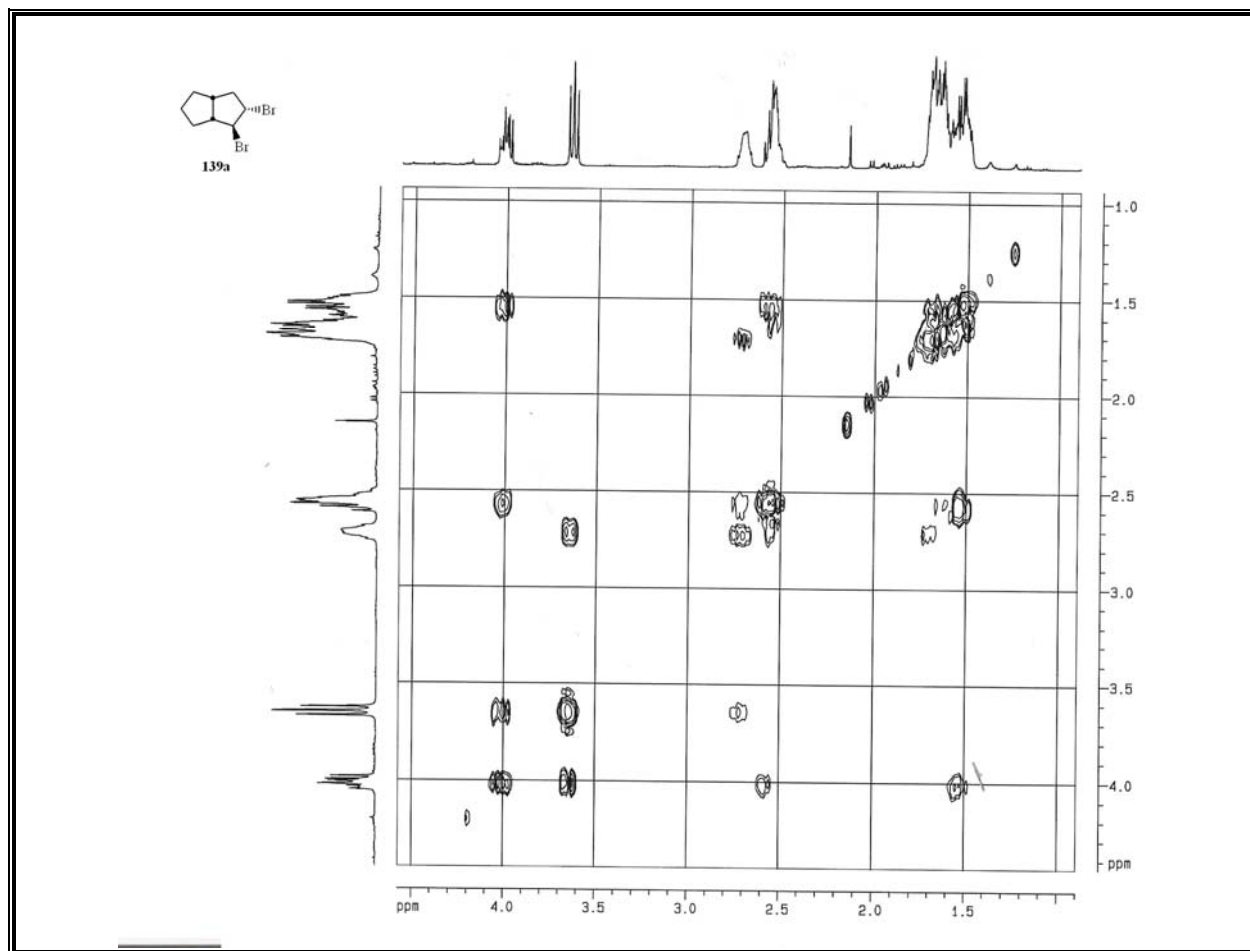


Figure A41 COSY Spectrum of Compound **139a**.

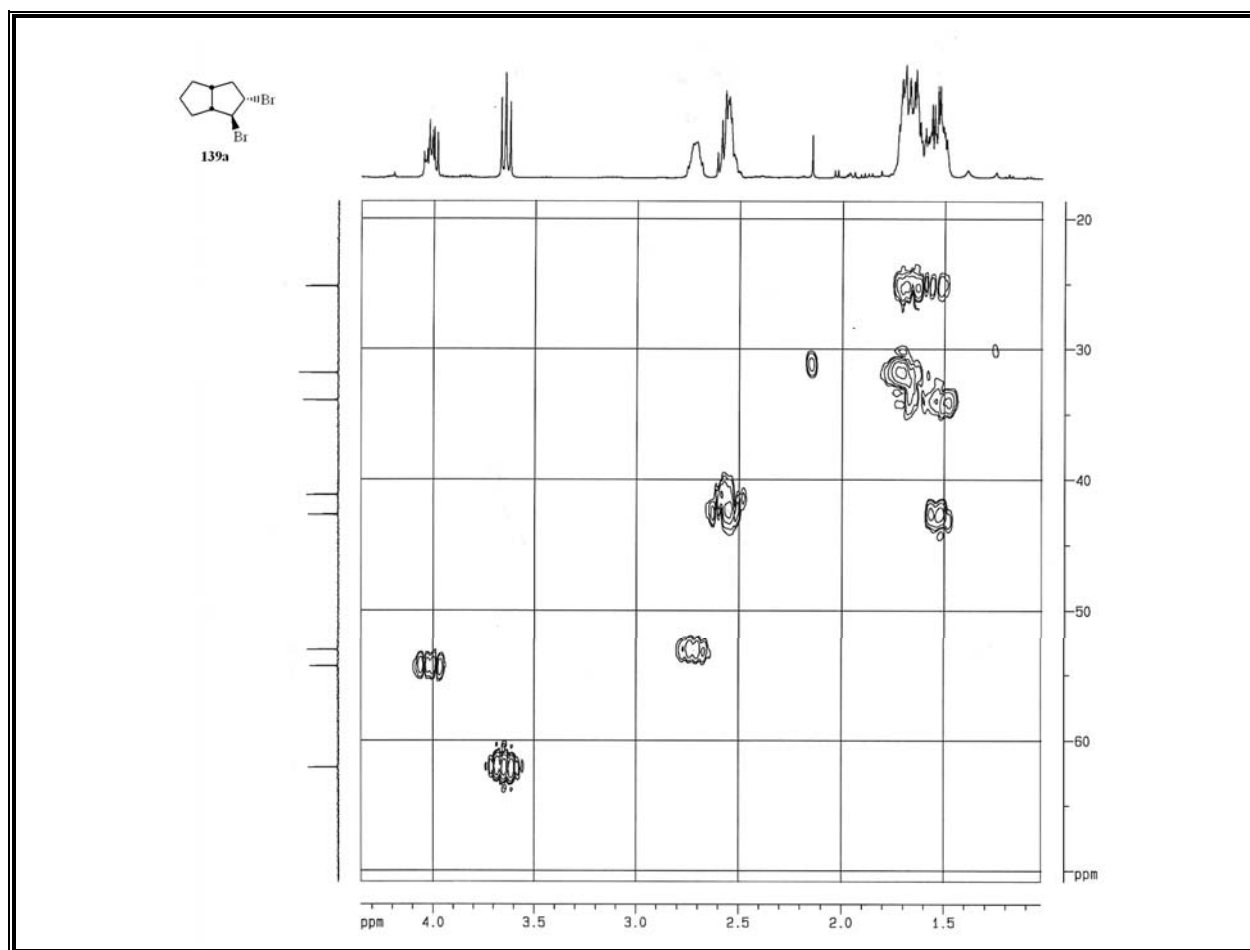


Figure A42 HMQC Spectrum of Compound **139a**.

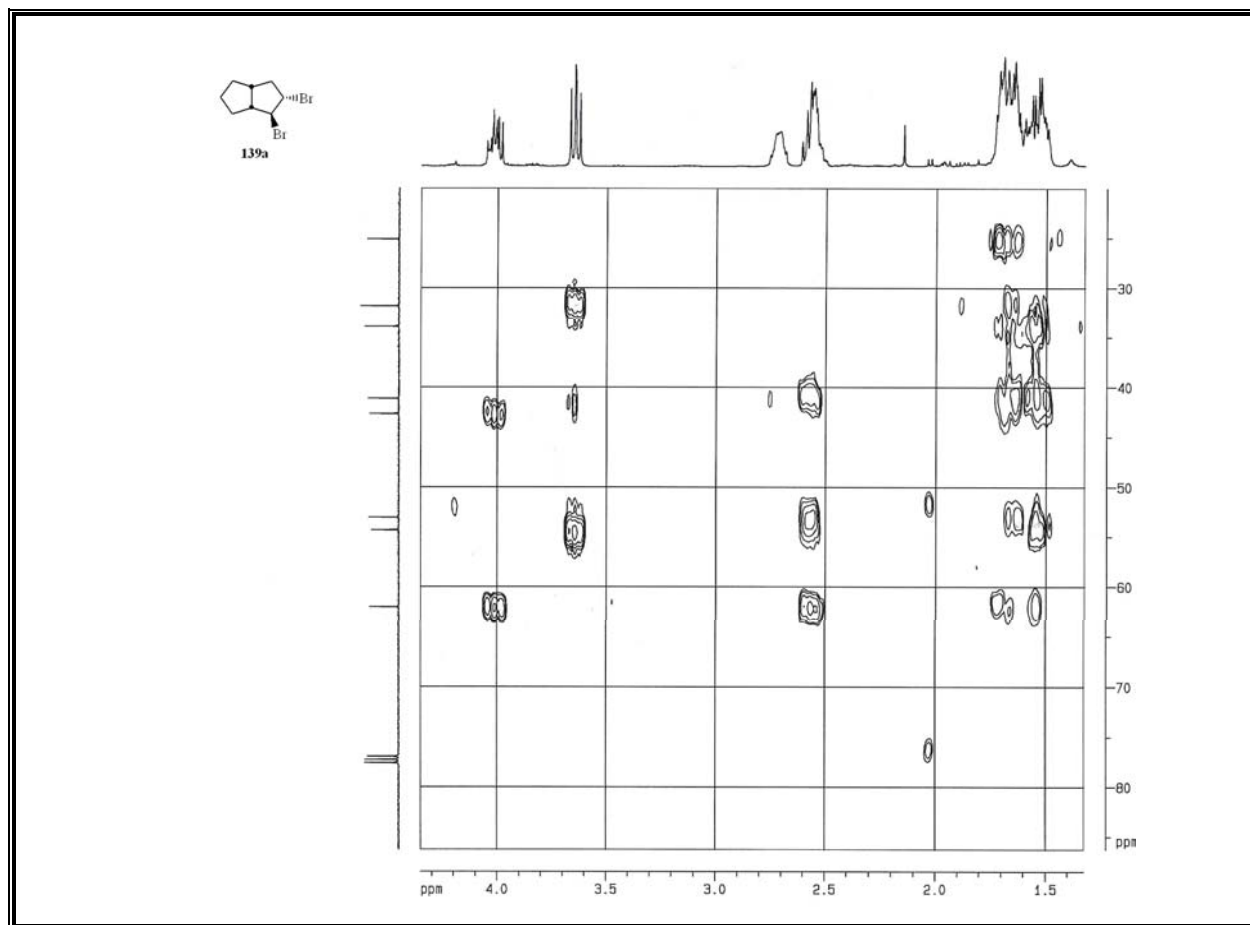


Figure A43 HMBC Spectrum of Compound **139a**.

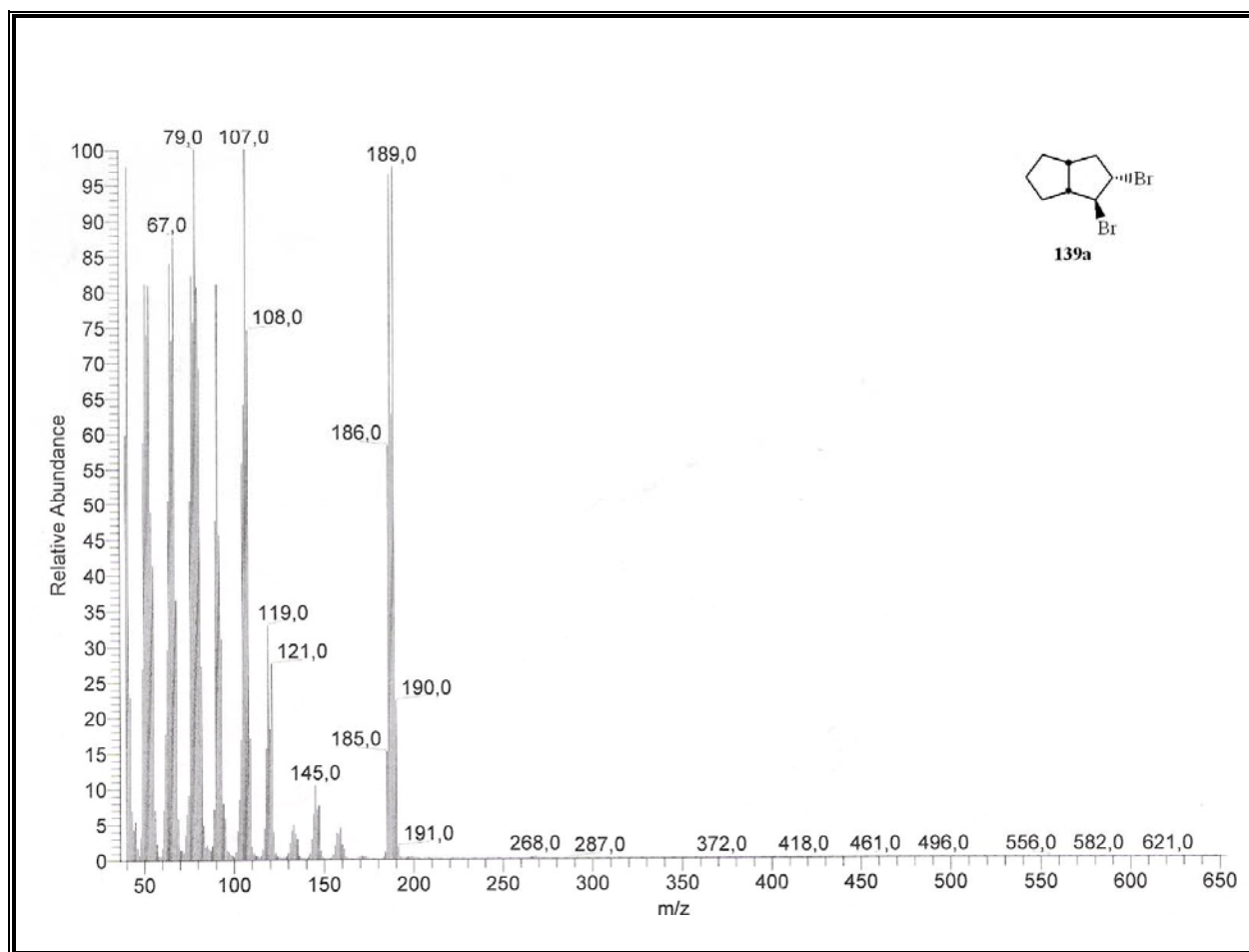


Figure A44 GC-MS spectrum of Compound **139a**.

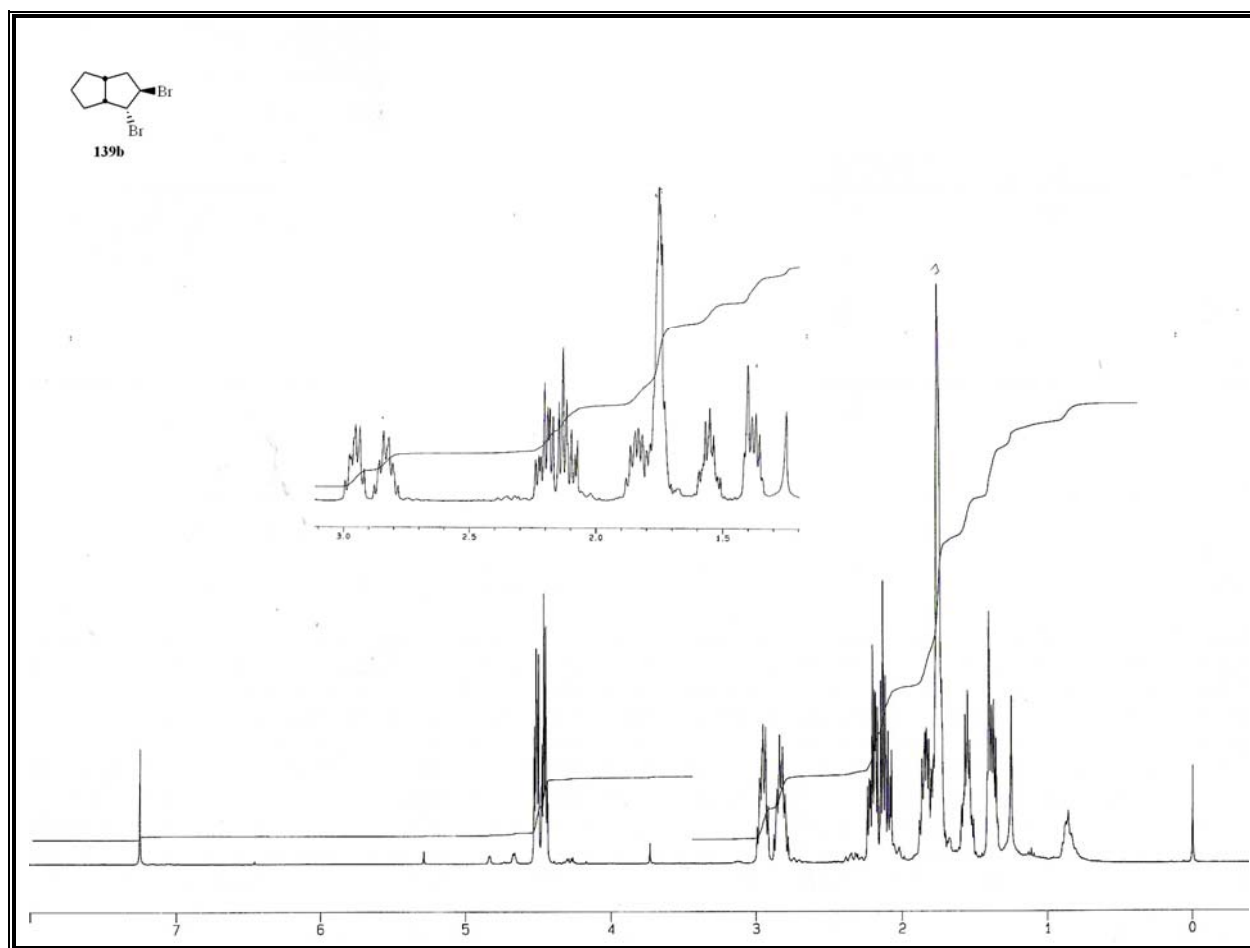


Figure A45 ^1H -NMR Spectrum of Compound **139b**.

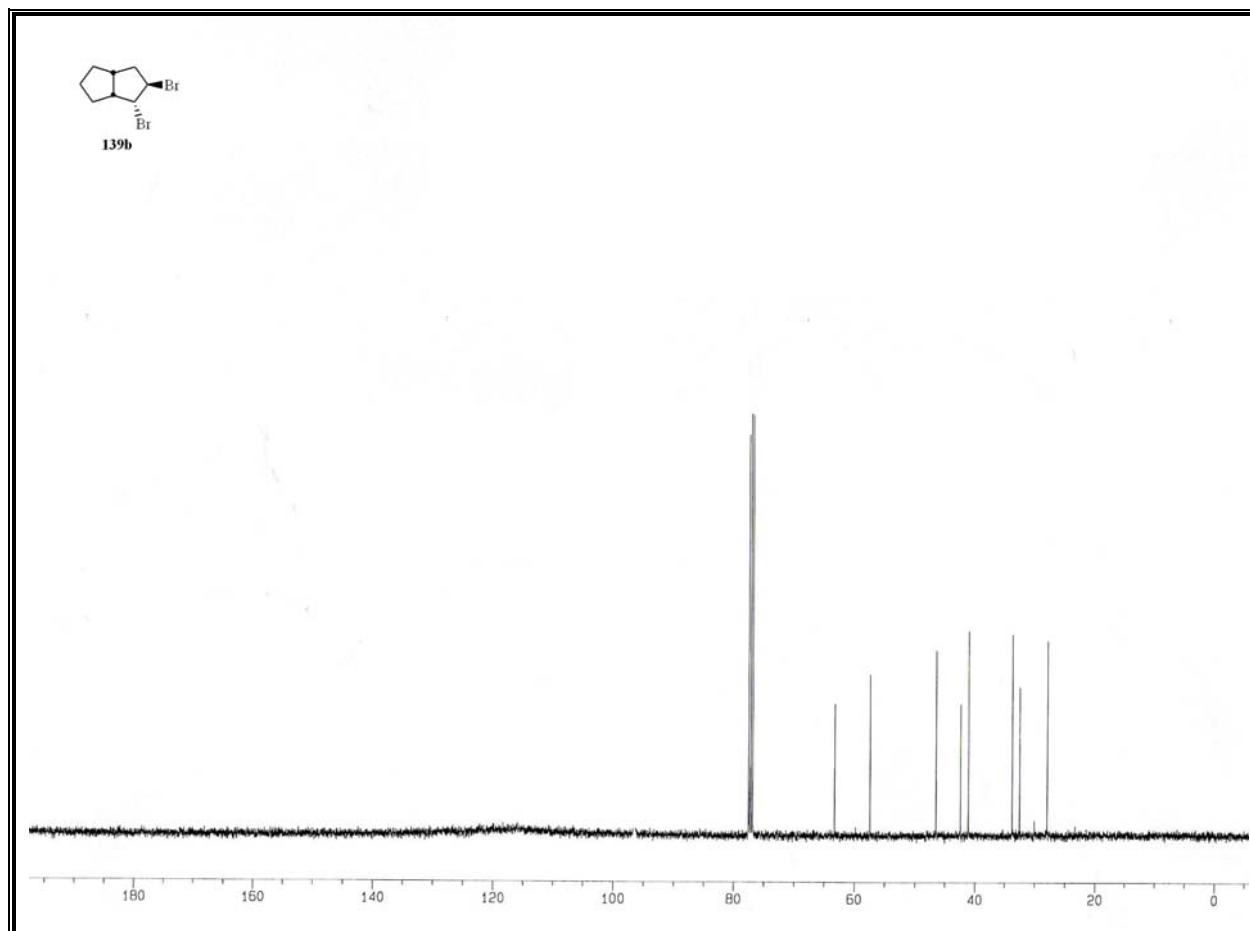


Figure A46 ^{13}C -NMR Spectrum of Compound **139b**.

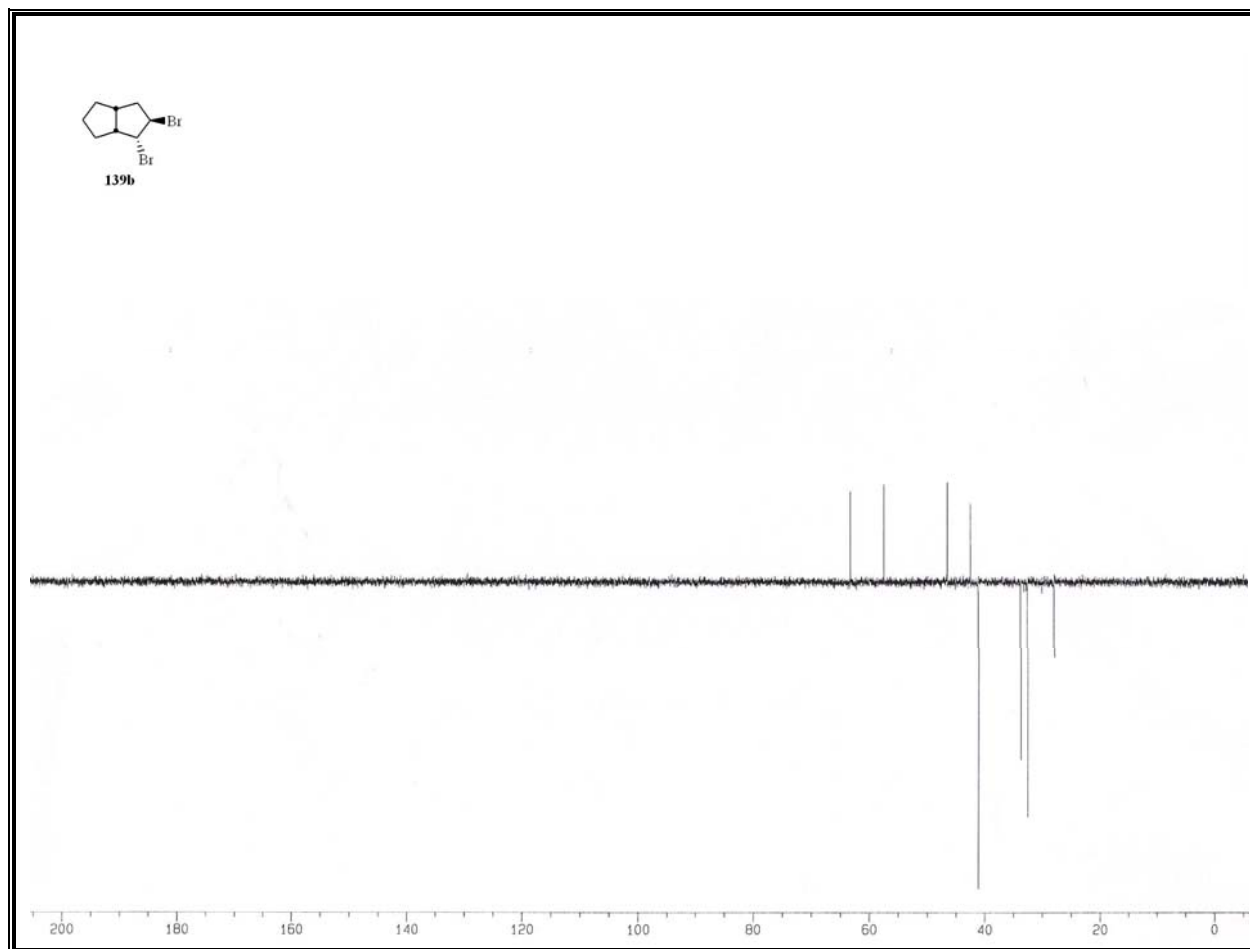


Figure A47 DEPT-135 Spectrum of Compound **139b**.

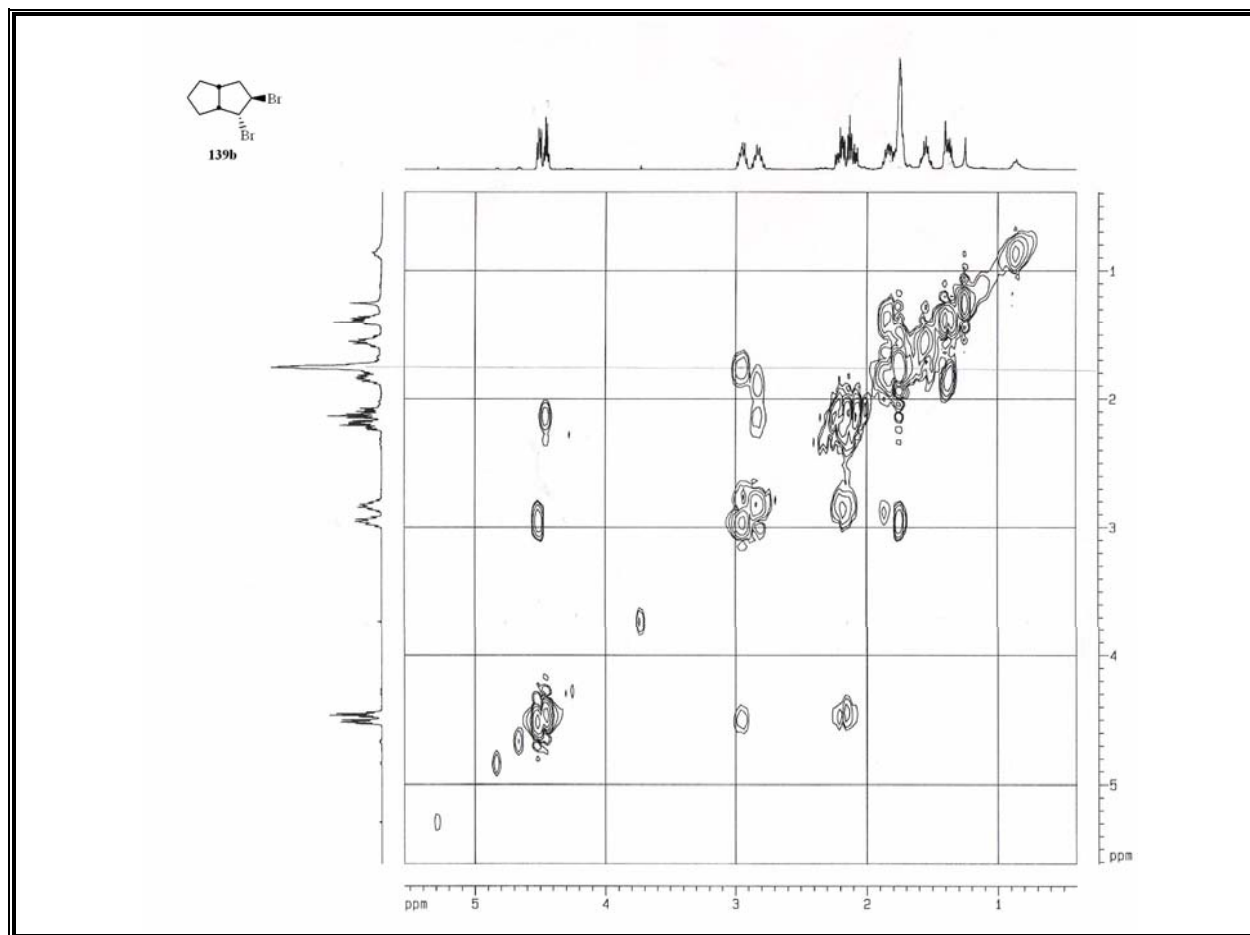


Figure A48 COSY Spectrum of Compound **139b**.

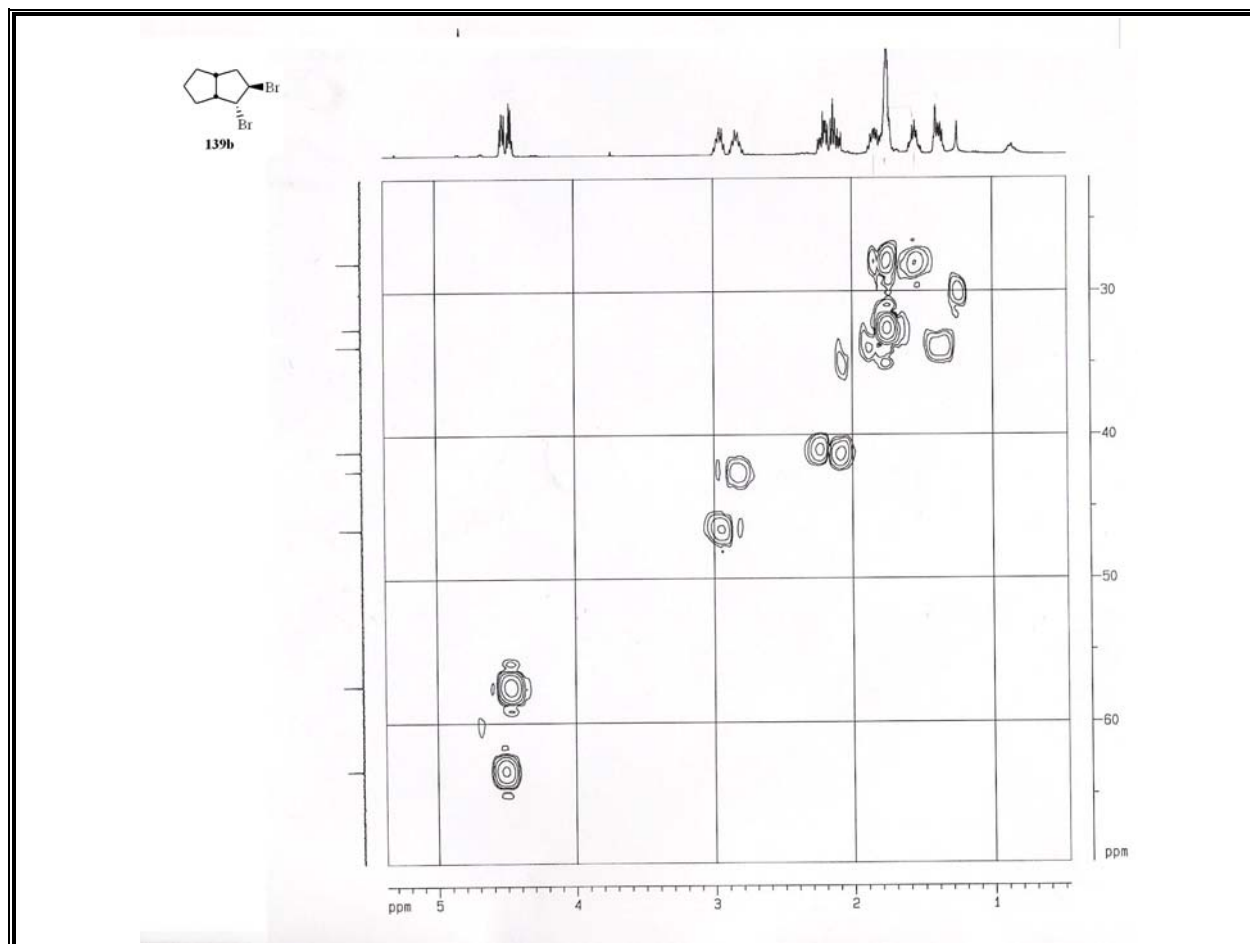


Figure A49 HMQC Spectrum of Compound **139b**.

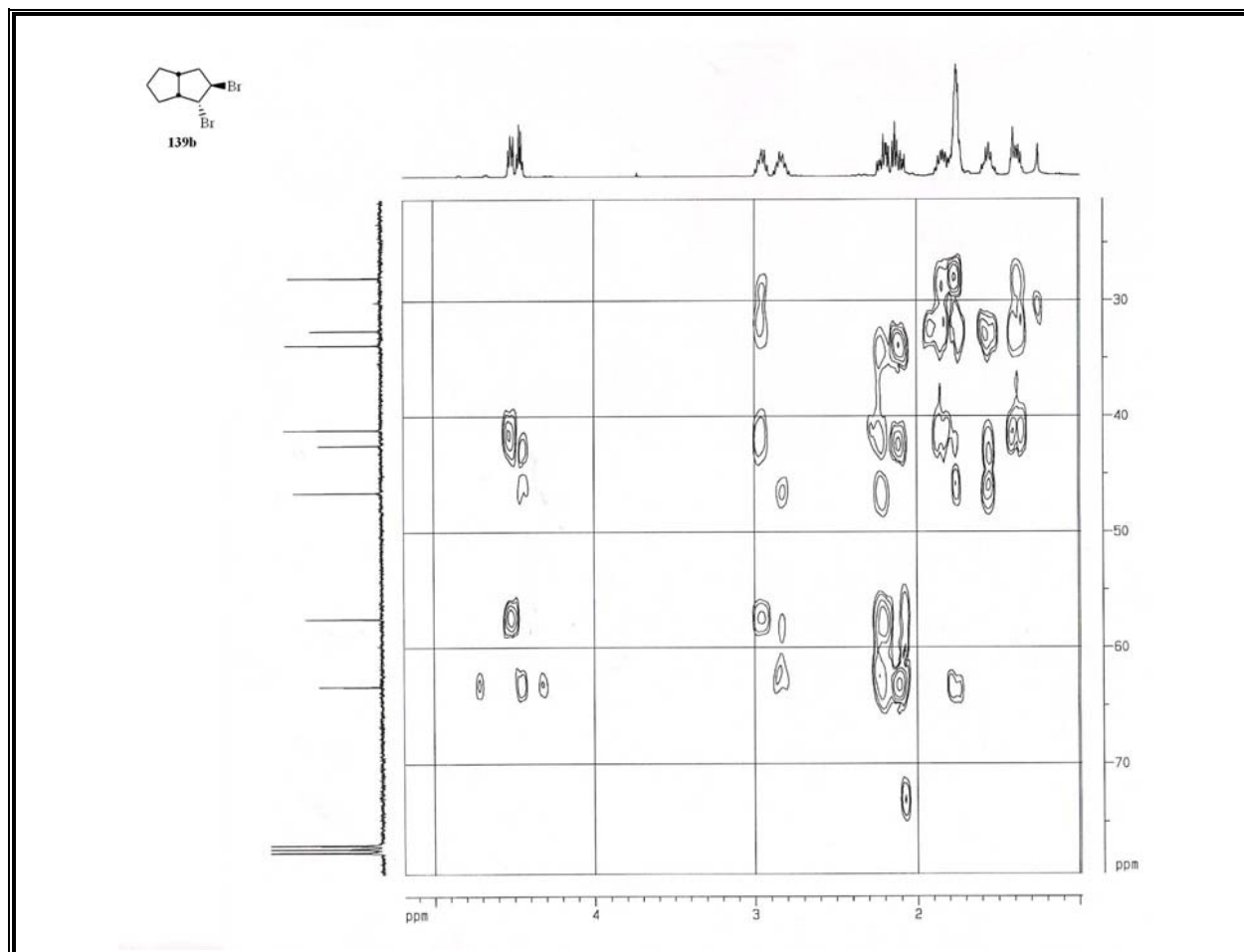


Figure A50 HMBC Spectrum of Compound **139b**.

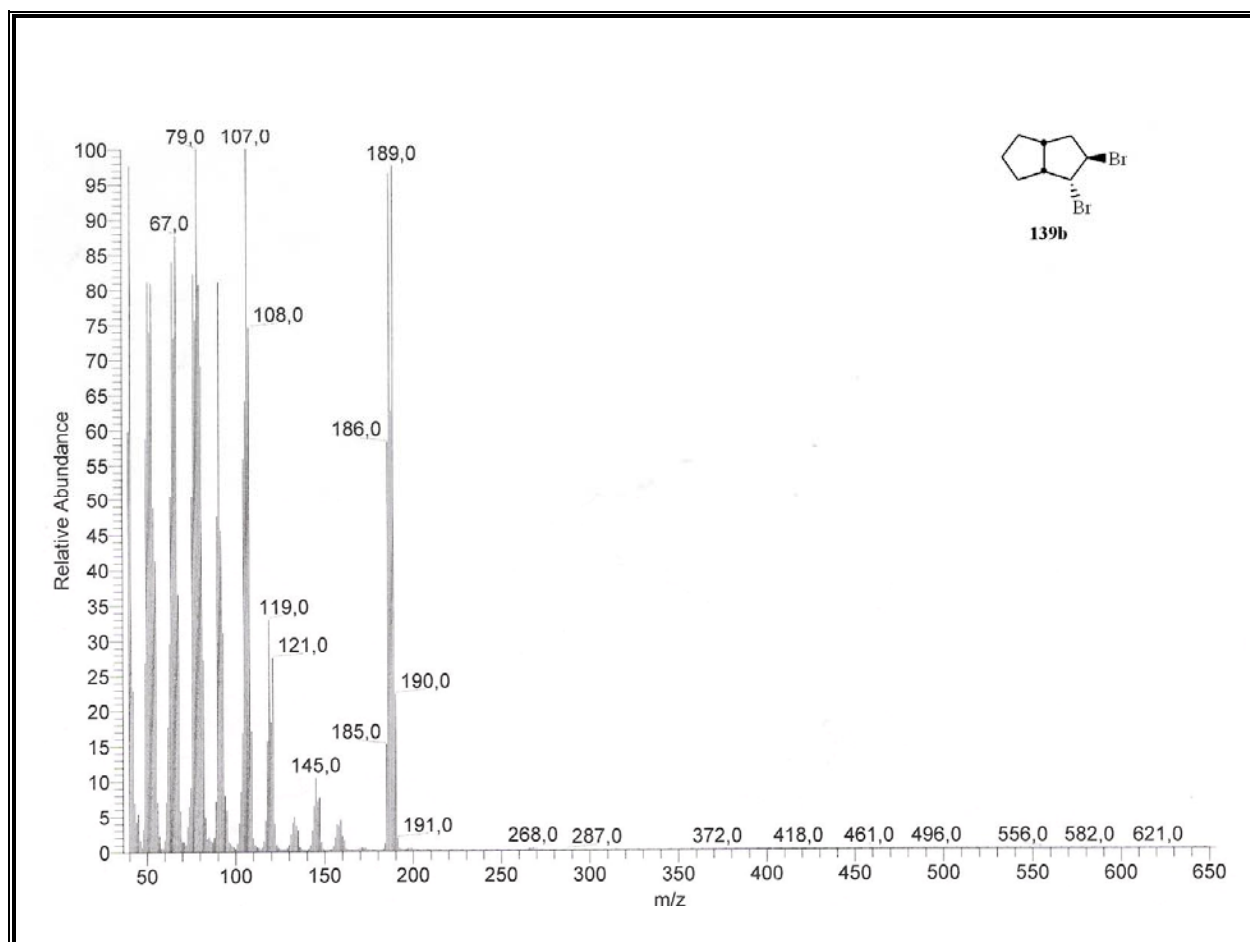


Figure A51 GC-MS spectrum of Compound **139b**.

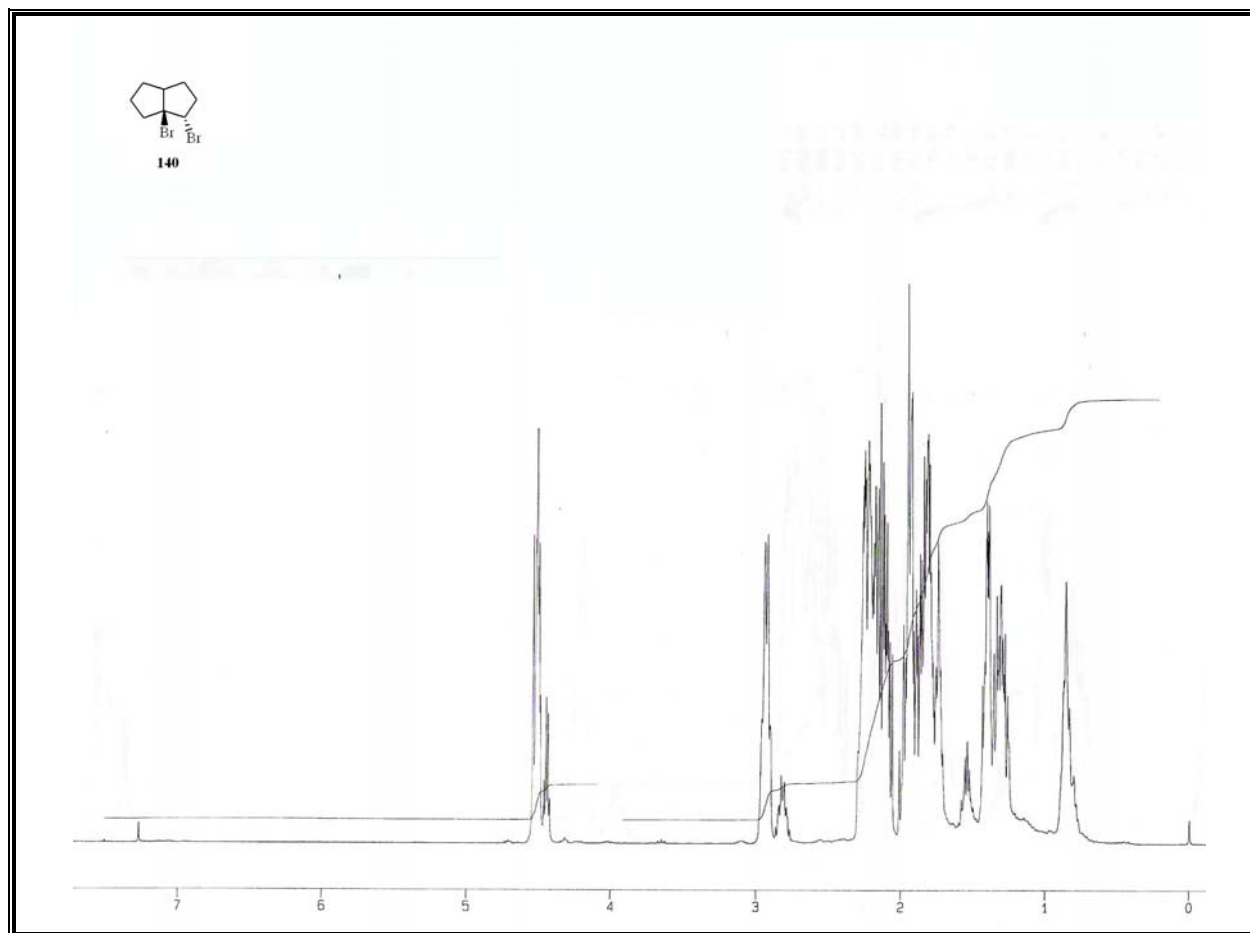


Figure A52 ^1H -NMR Spectrum of Compound **140**.

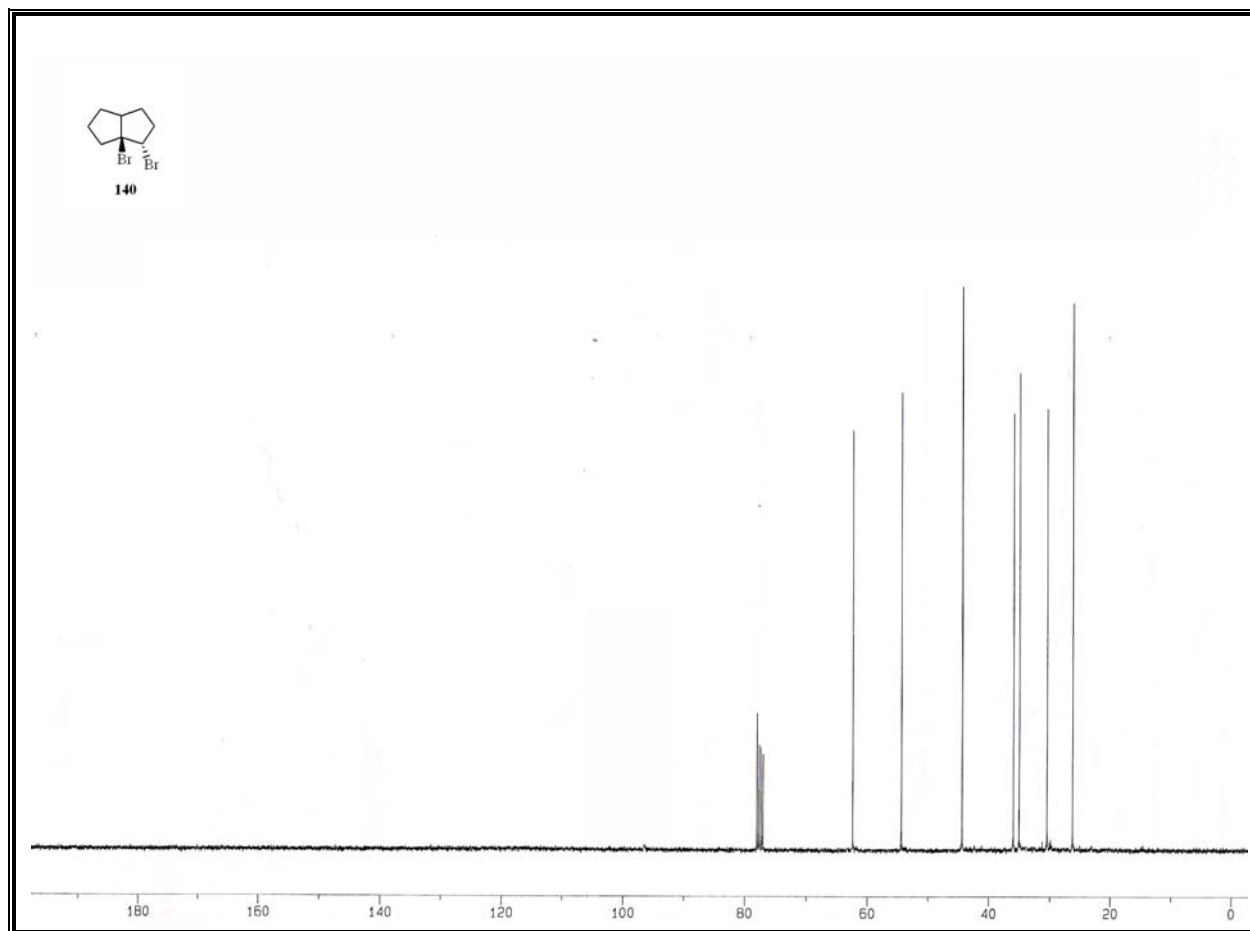


Figure A53 ^{13}C -NMR Spectrum of Compound **140**.

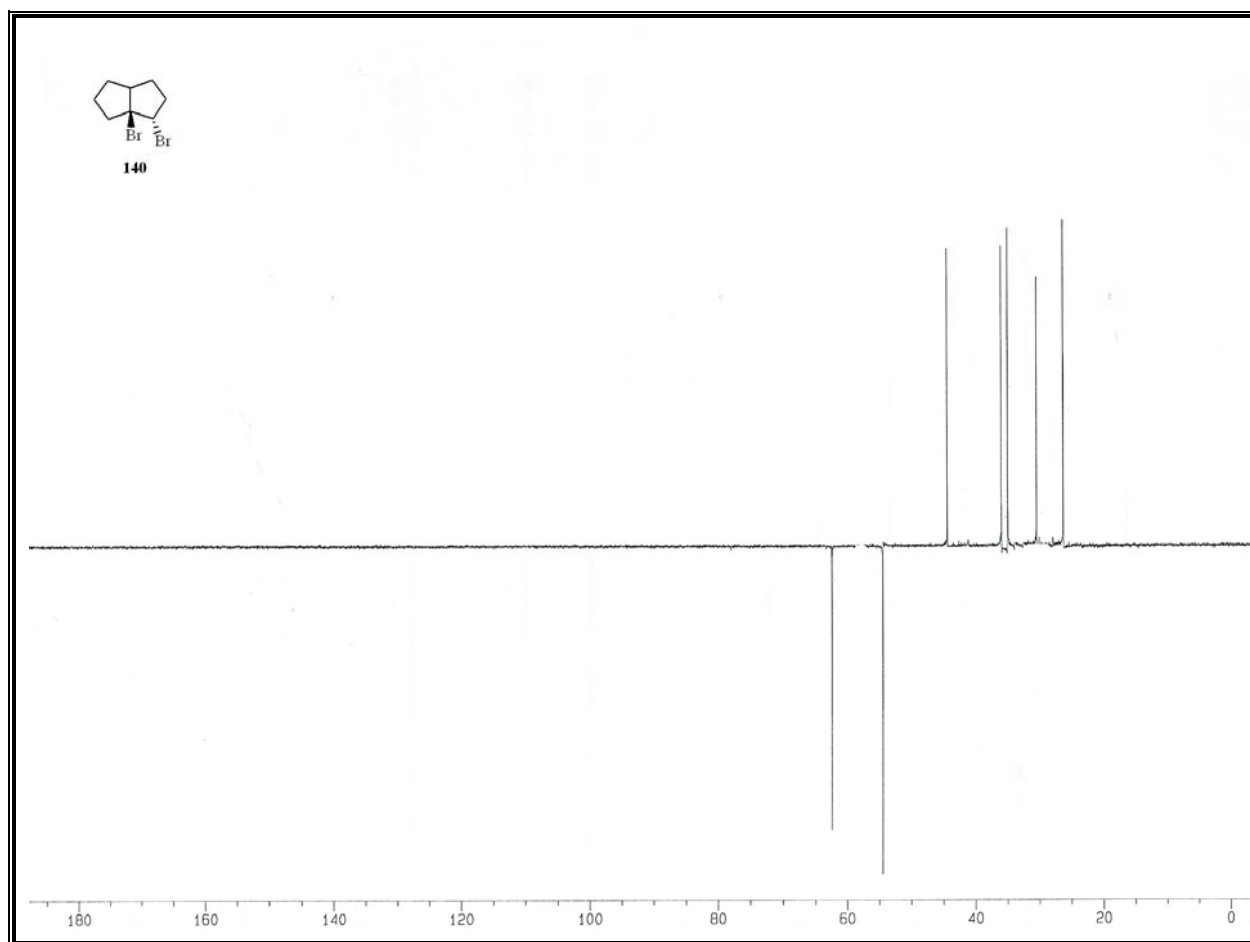


Figure A54 DEPT-135 Srectrum of Compound **140**.

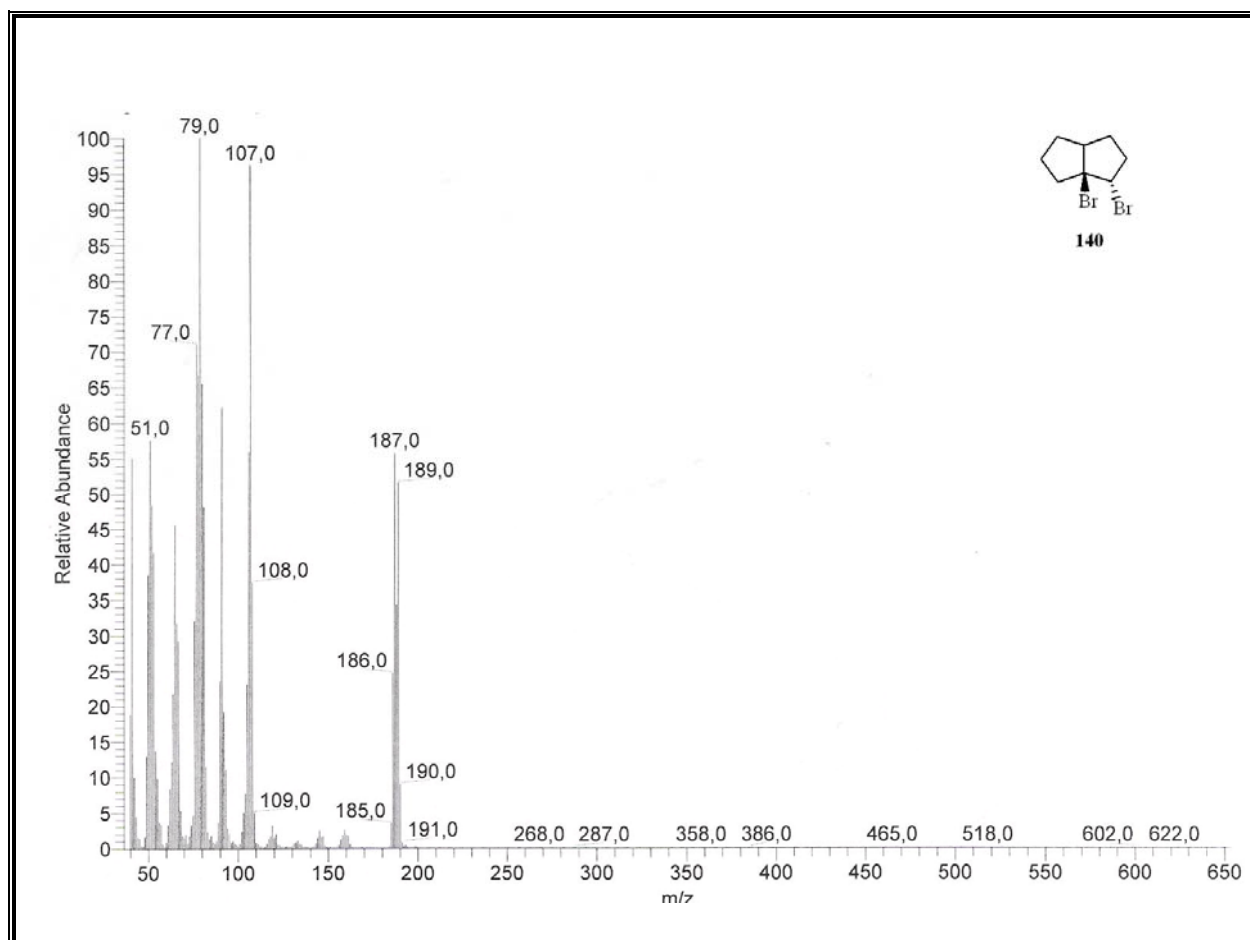


Figure A55 GC-MS Spectrum of Compound **140**.

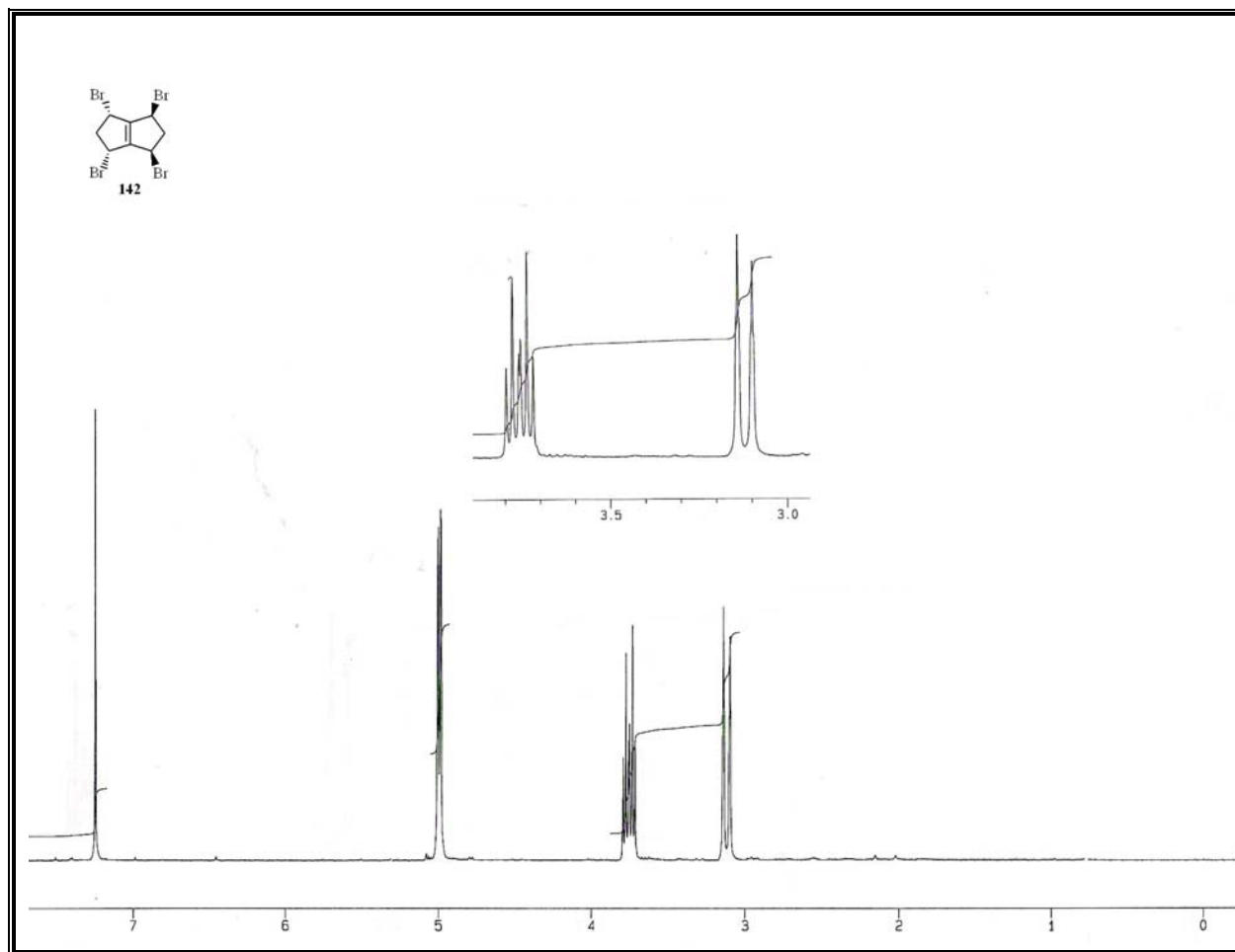


Figure A56 ^1H -NMR Spectrum of Compound 142.

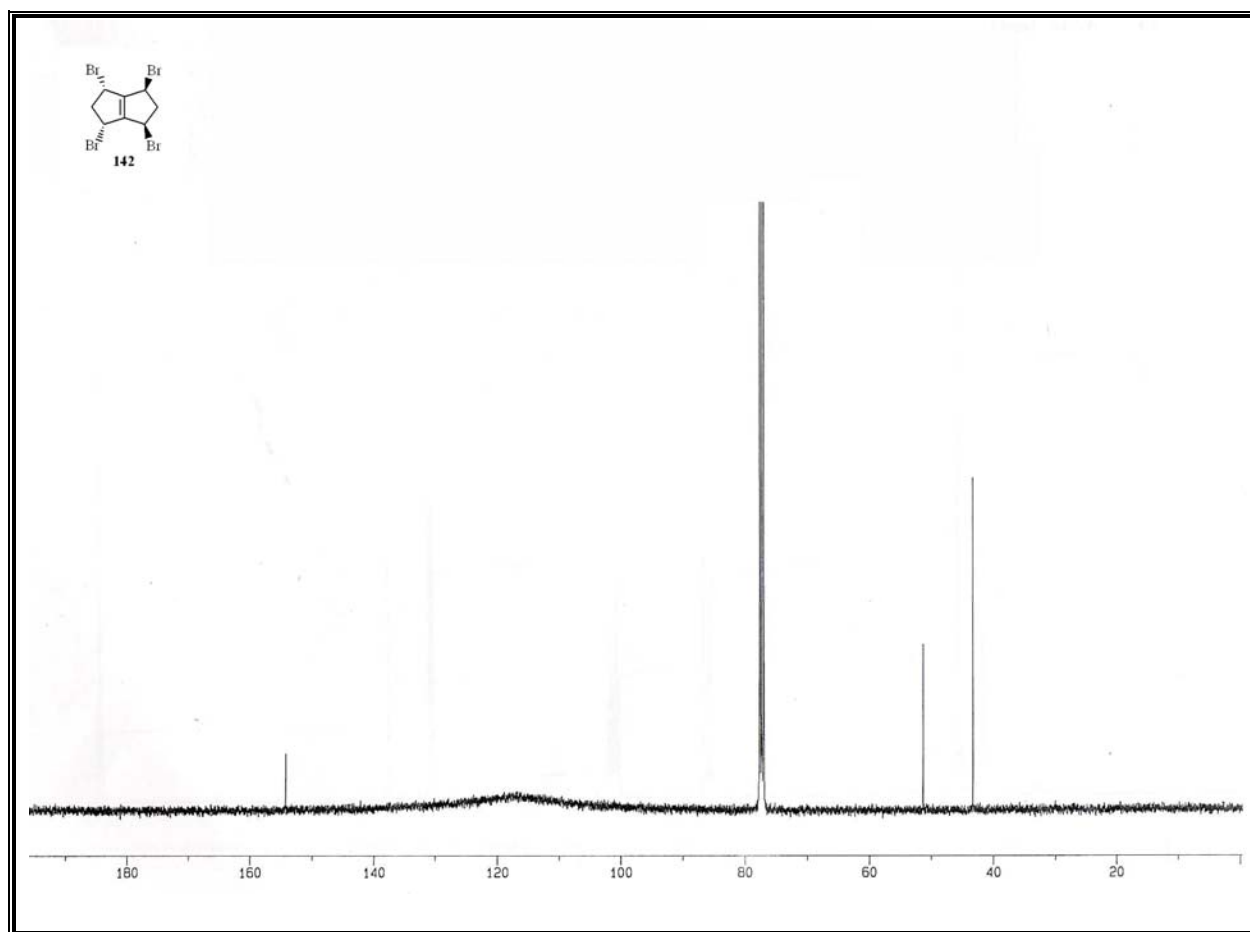


Figure A57 ^{13}C -NMR Spectrum of Compound **142**.

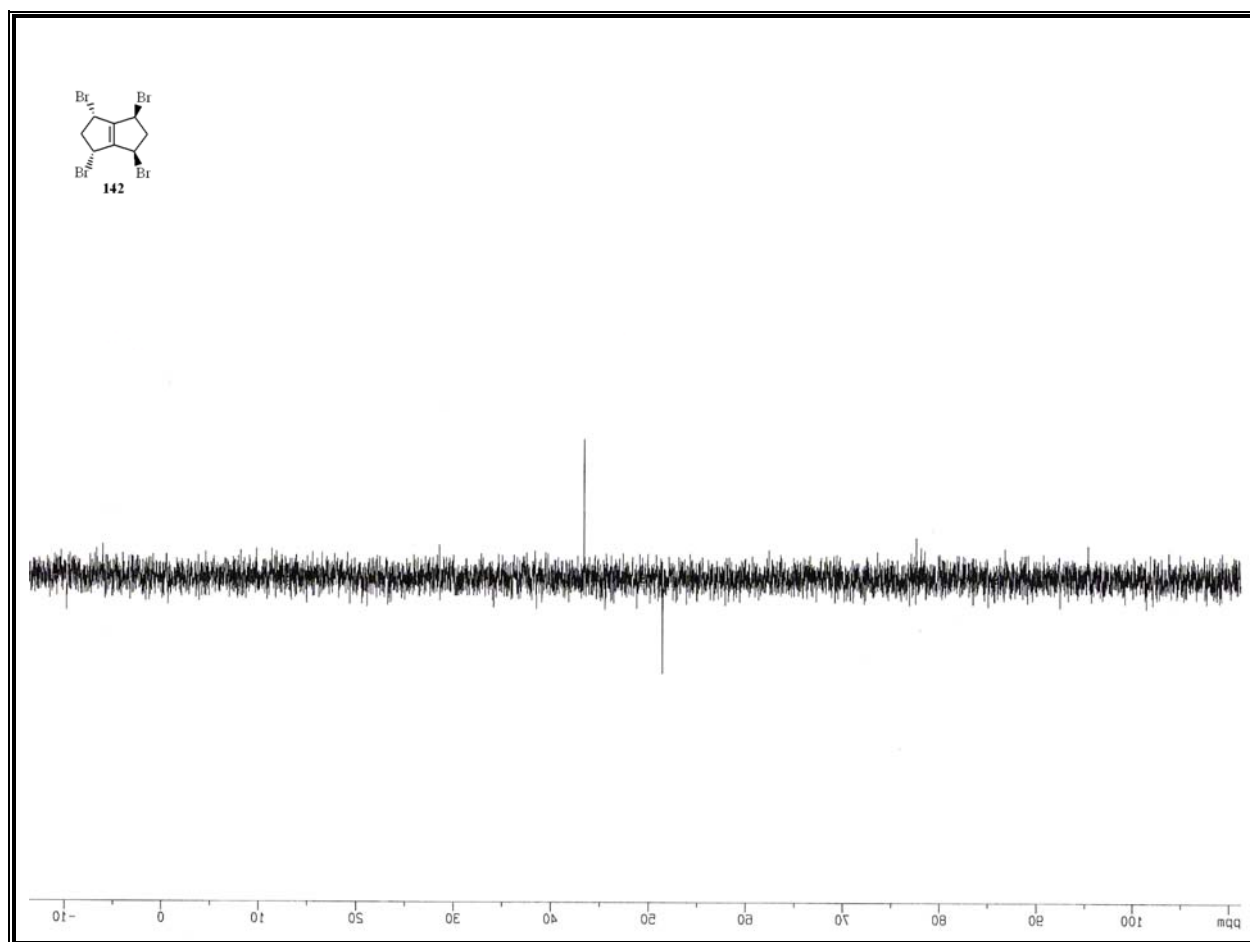


Figure A58 DEPT-135 Spectrum of Compound **142**.

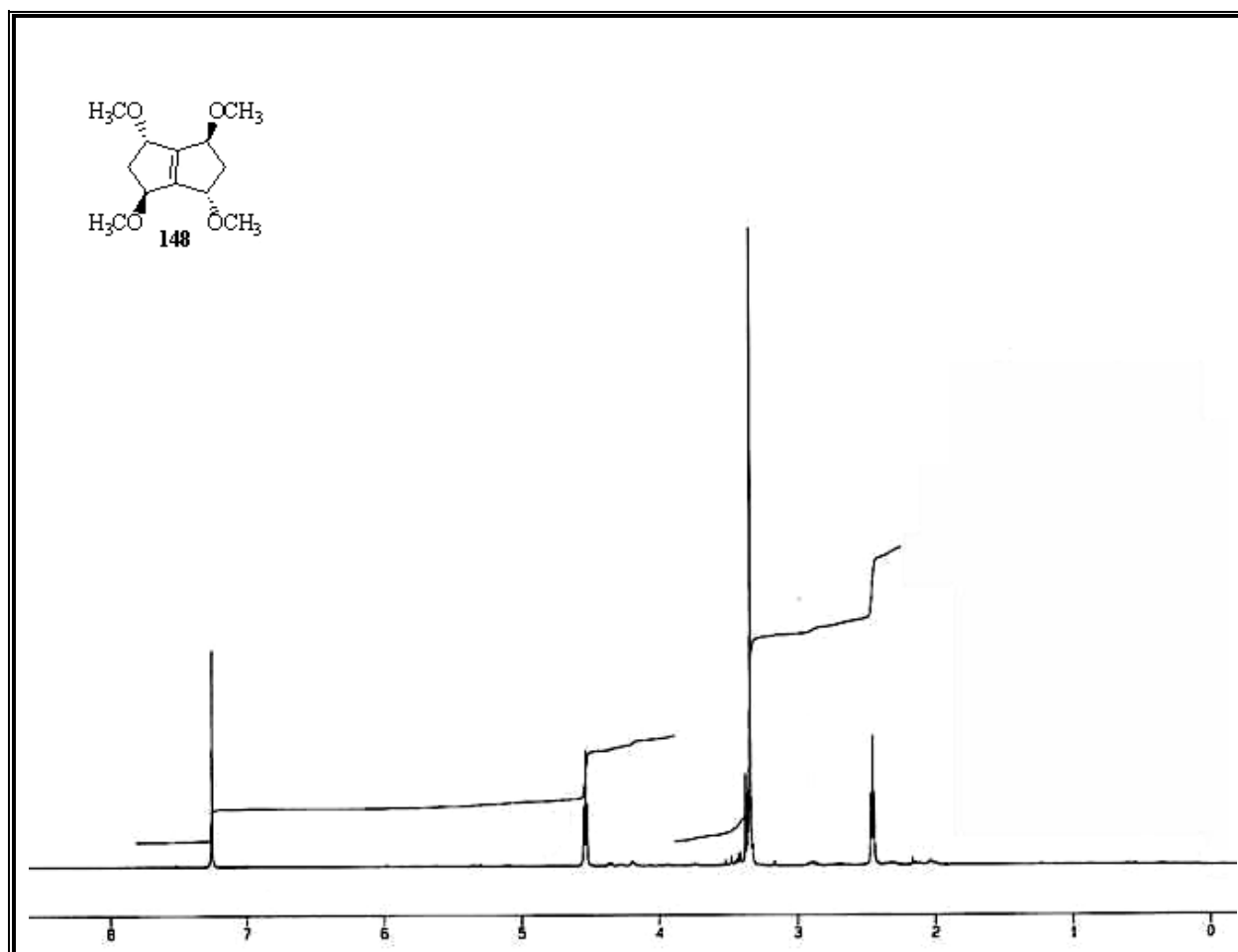


Figure A59 ^1H -NMR Spectrum of Compound **148**.

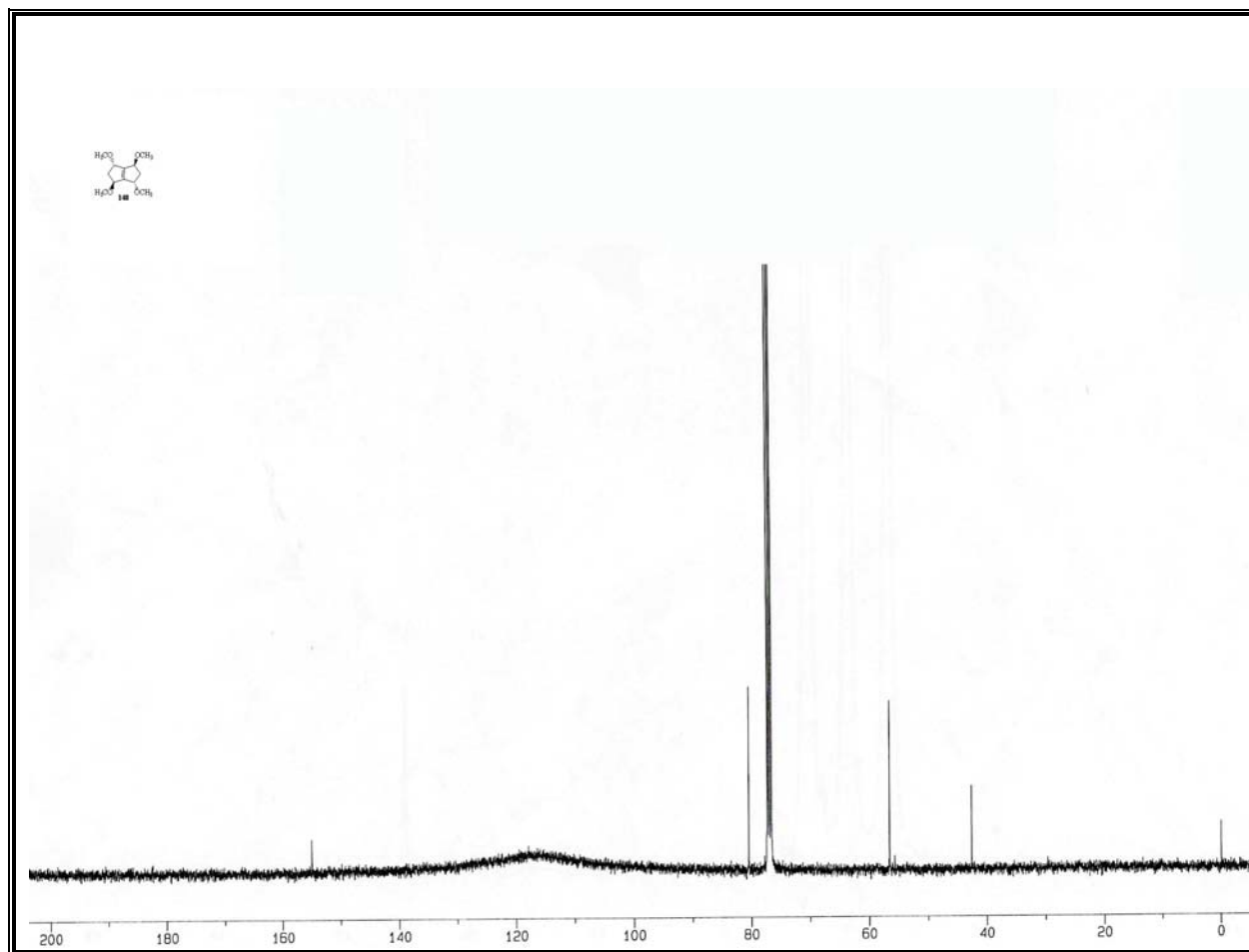


Figure A60 ^{13}C -NMR Spectrum of Compound **148**.

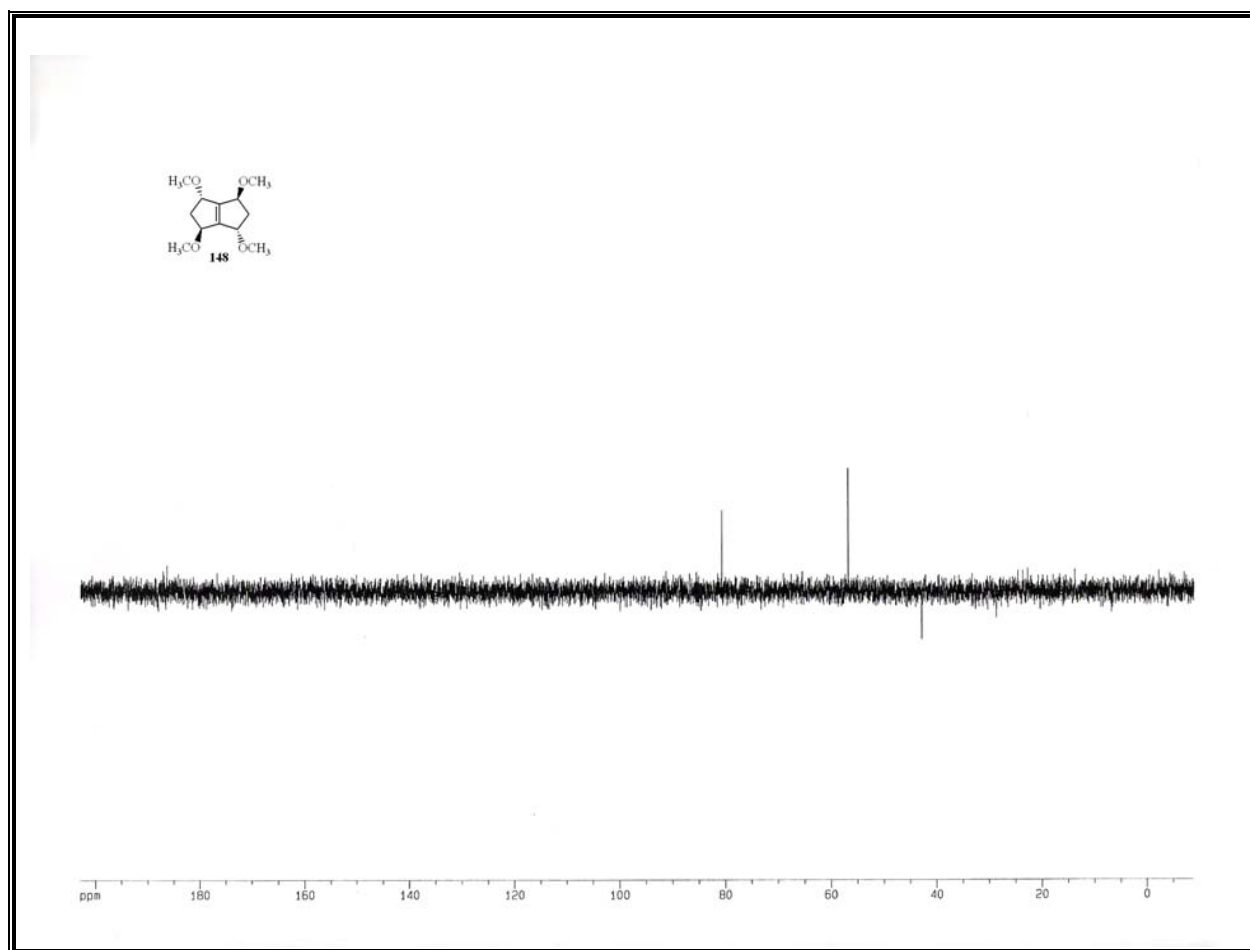


Figure A61 DEPT-135 Spectrum of Compound **148**.

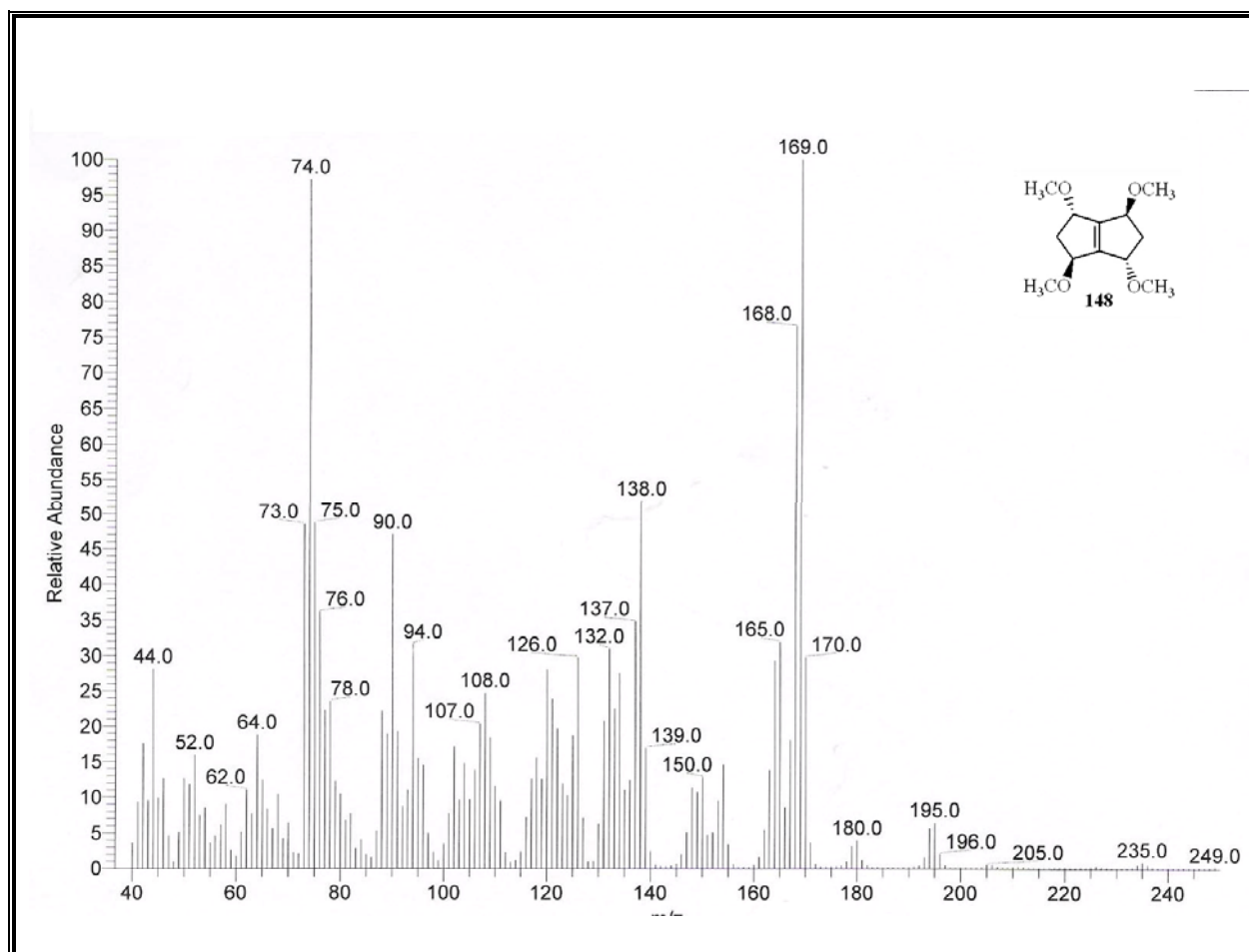


Figure A62 GC-MS Spectrum of Compound **148**.

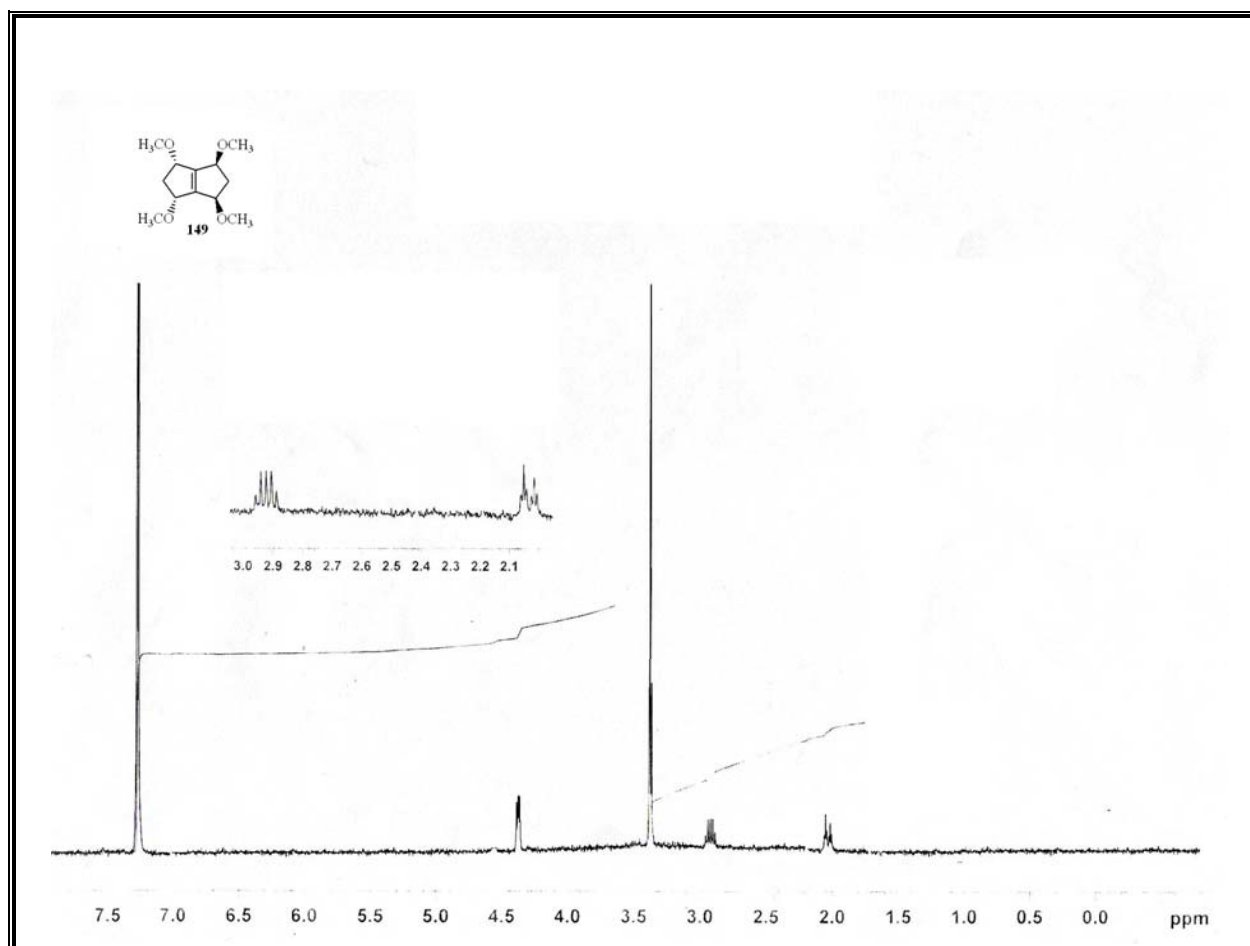


Figure A63 ^1H -NMR Spectrum of Compound 149.

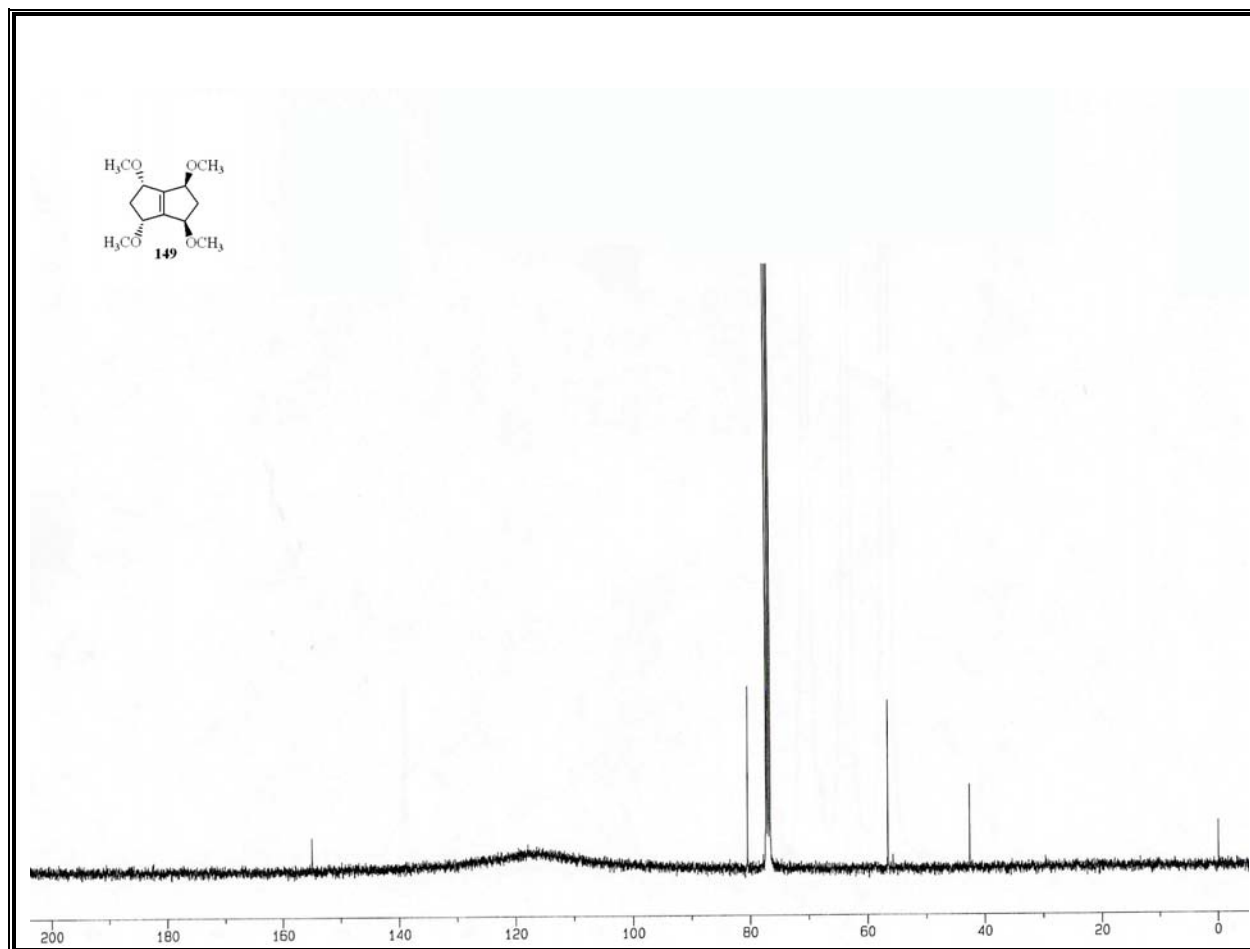


Figure A64 ^{13}C -NMR Spectrum of Compound 149.

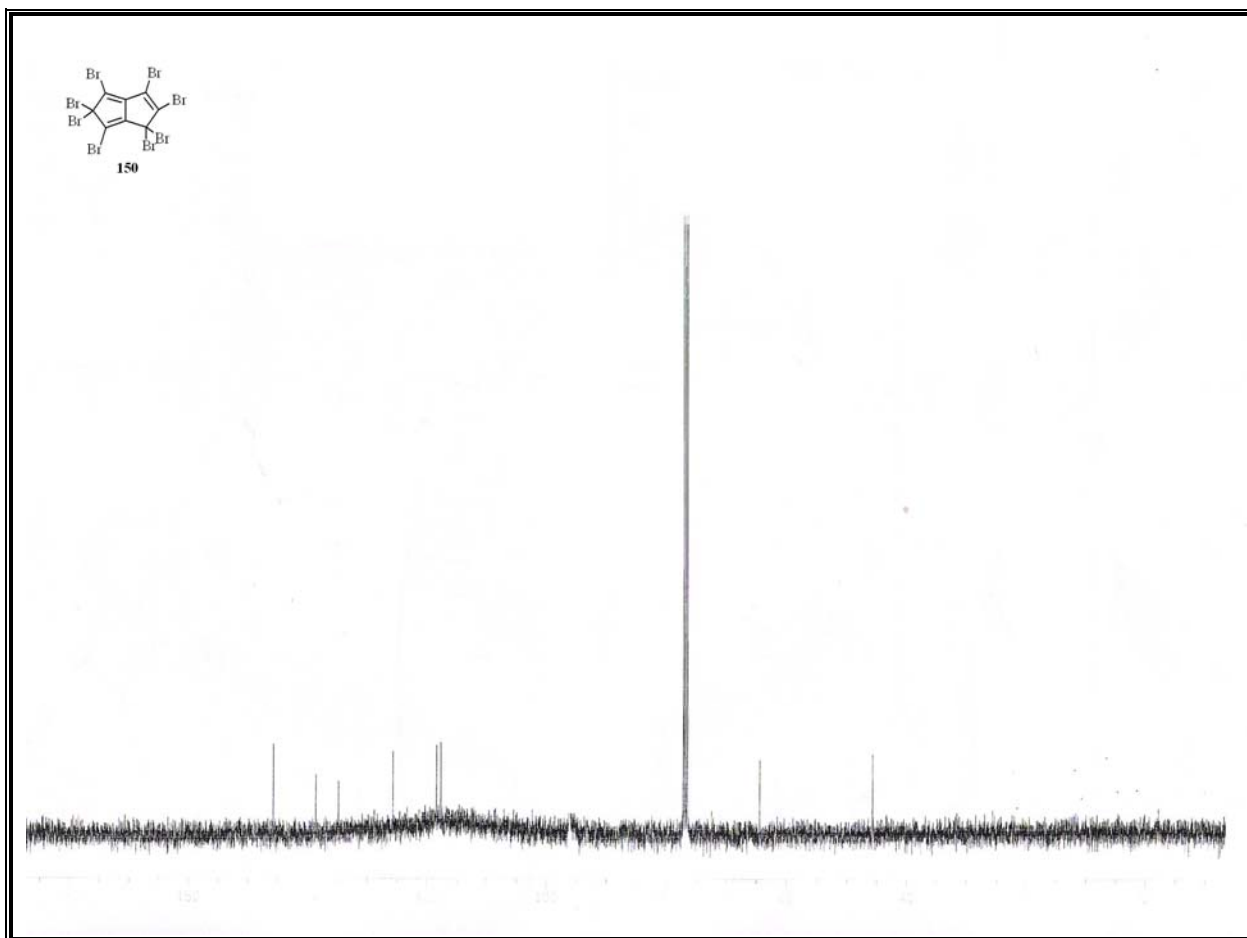


Figure A65 ^{13}C -NMR Spectrum of Compound **150**.

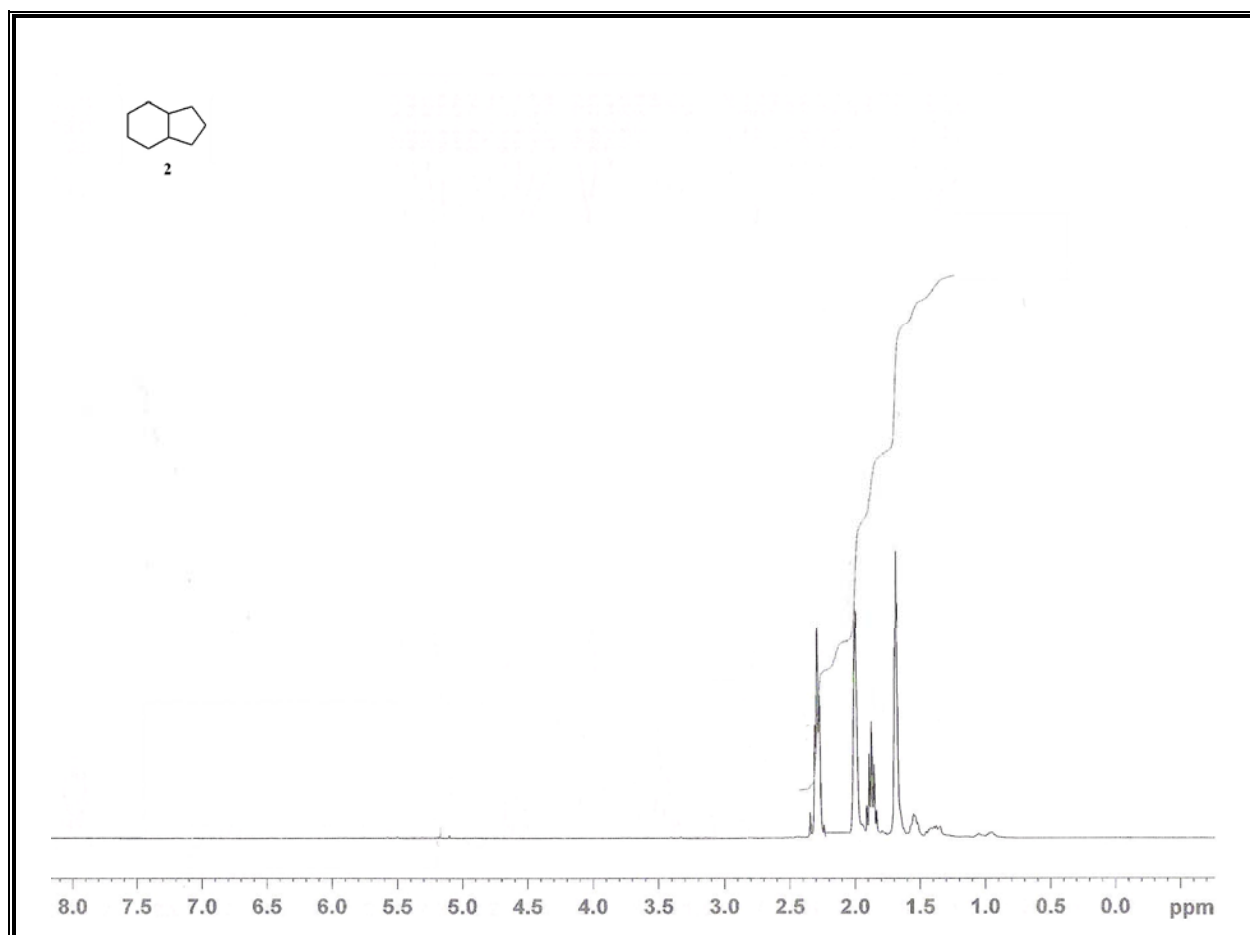


Figure A66 ^1H -NMR Spectrum of Compound 2.

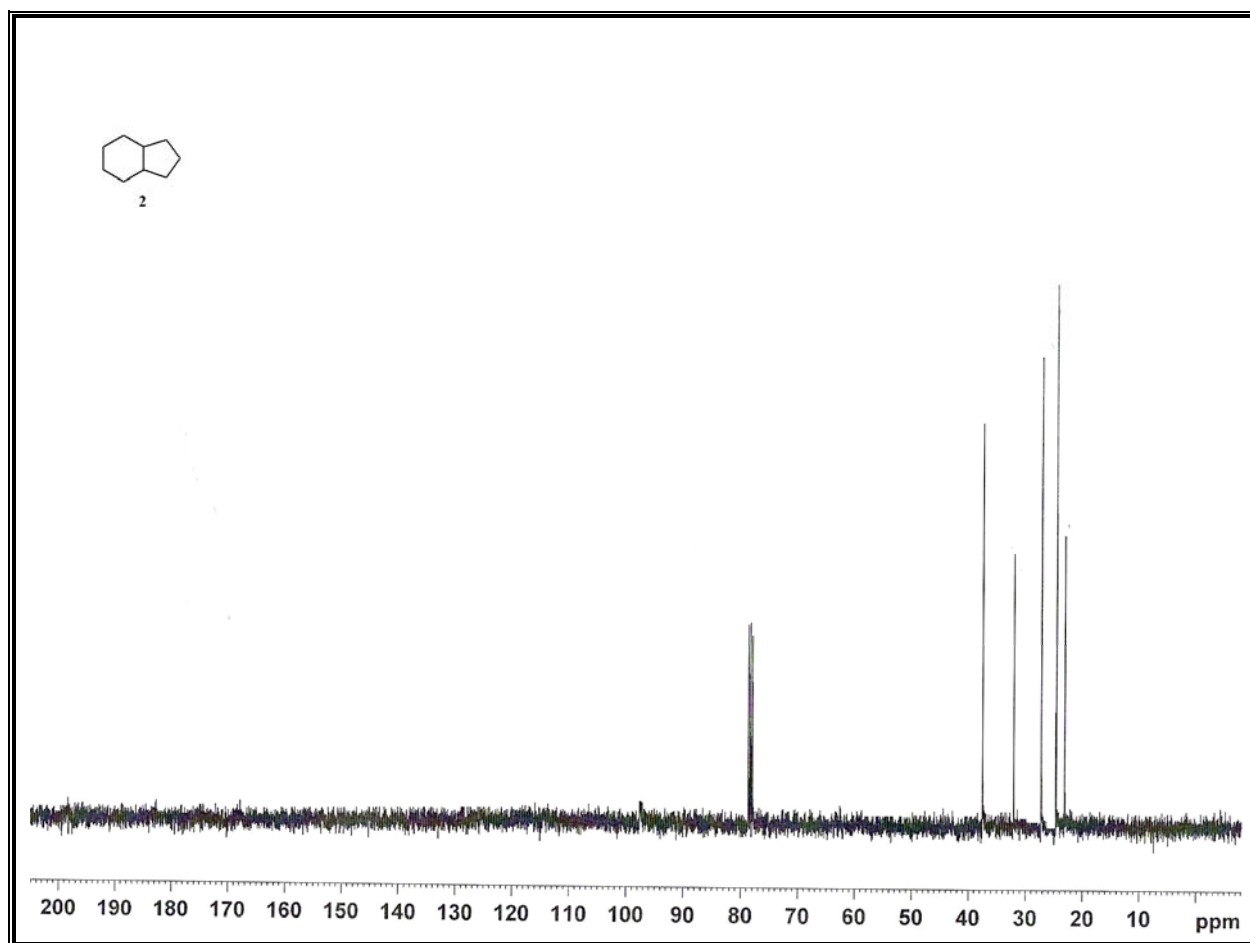


Figure A67 ^{13}C -NMR Spectrum of Compound 2.

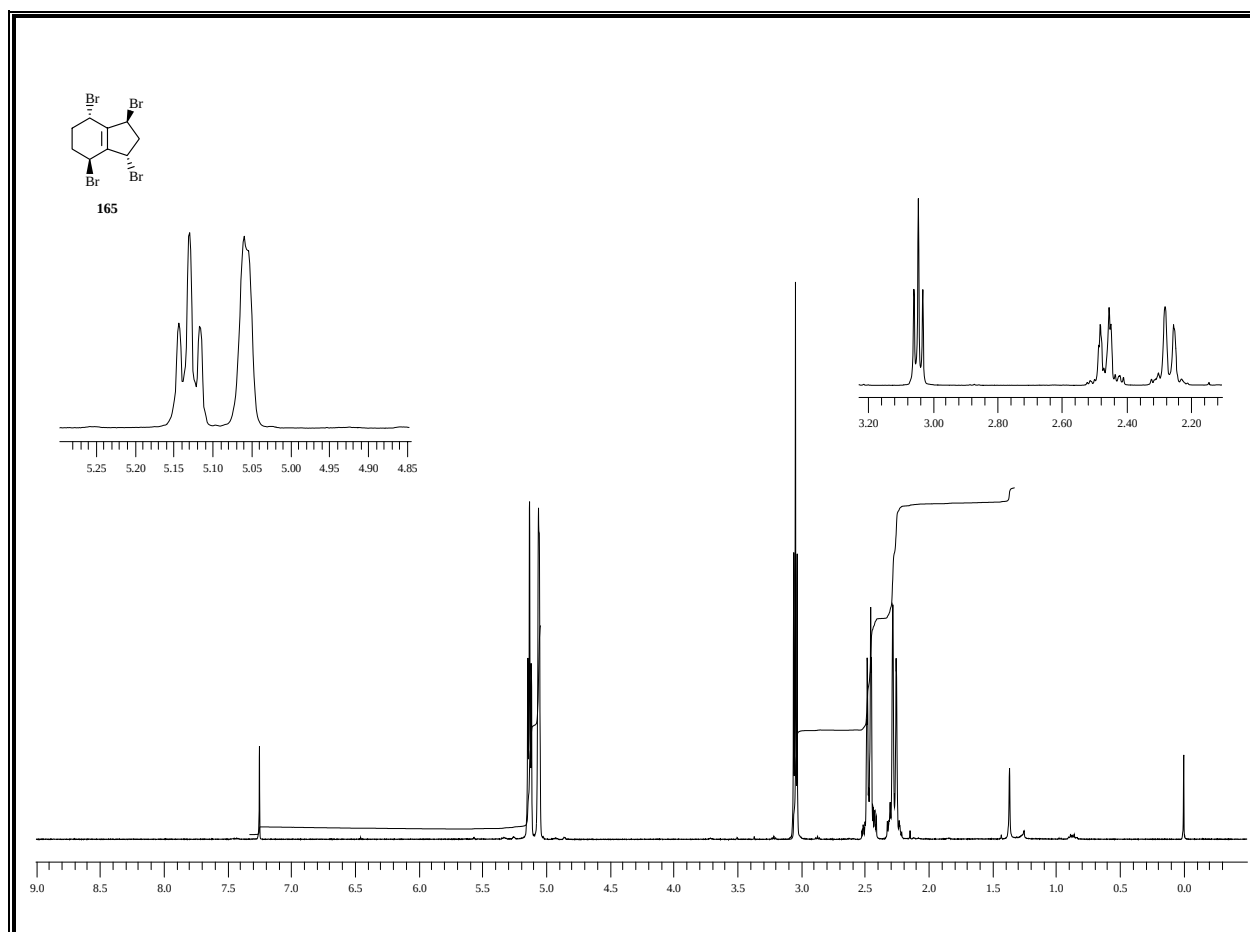


Figure A68 ^1H -NMR Spectrum of Compound 165.

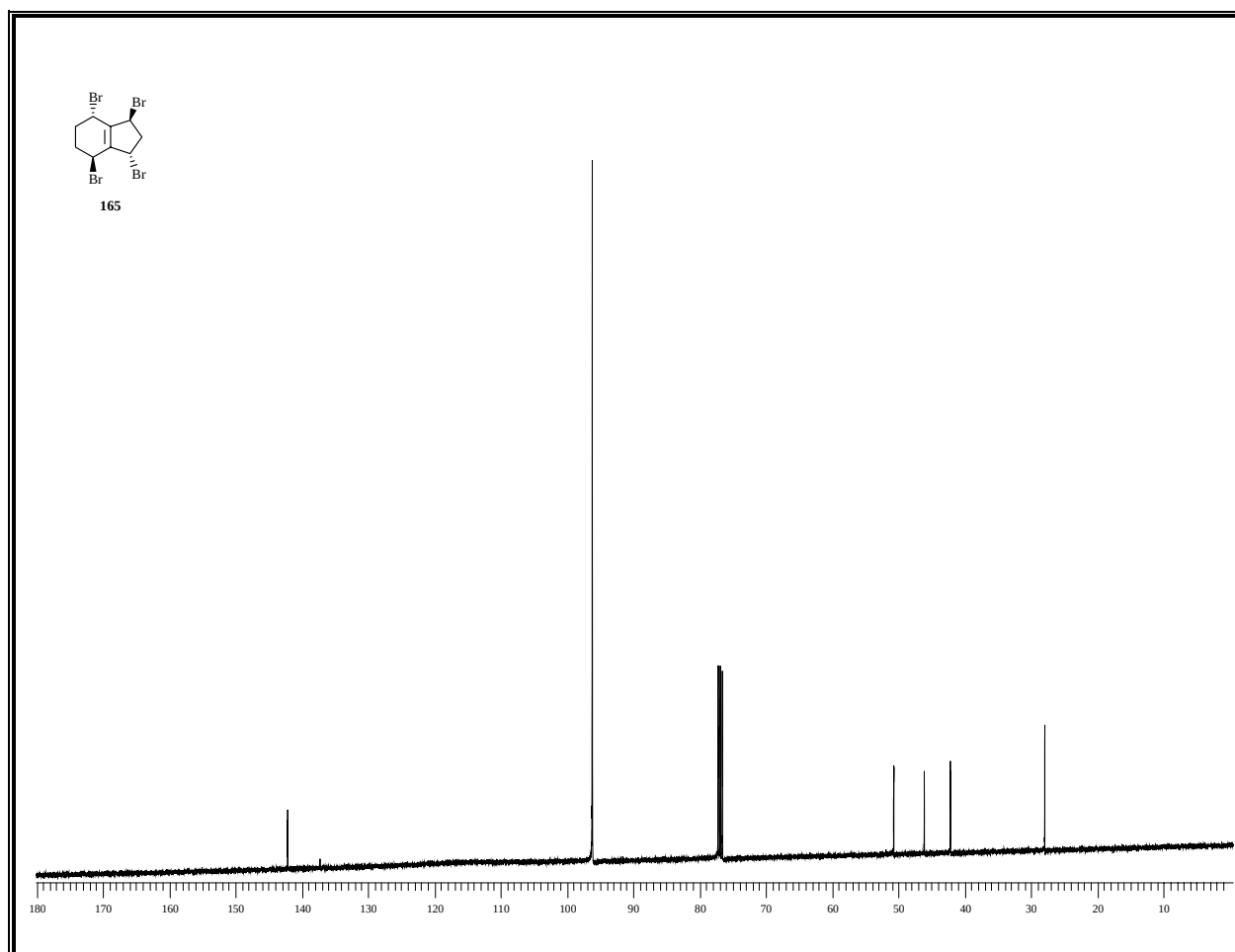


Figure A69 ^{13}C -NMR Spectrum of Compound **165**.

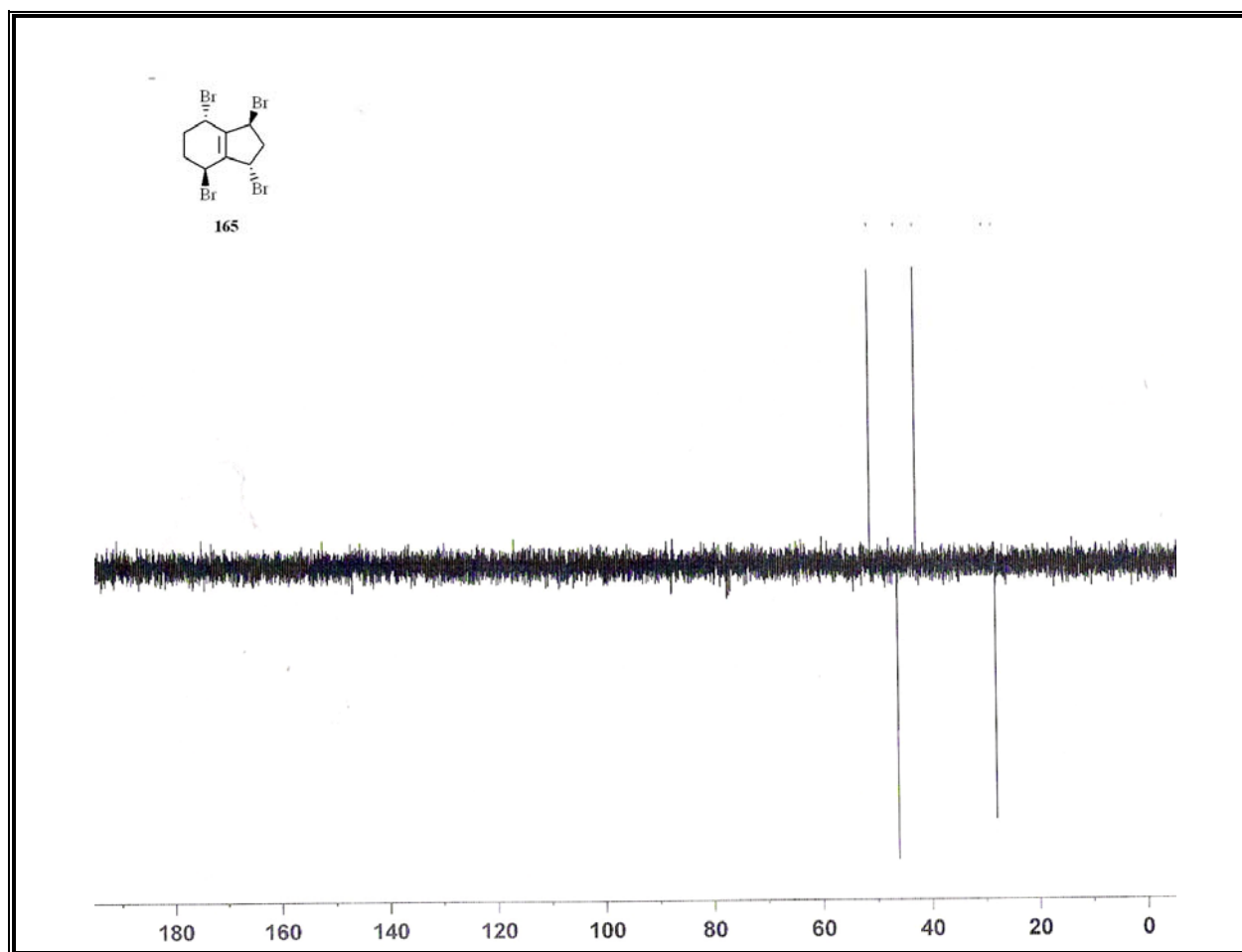


Figure A70 DEPT-135 Spectrum of Compound **165**.

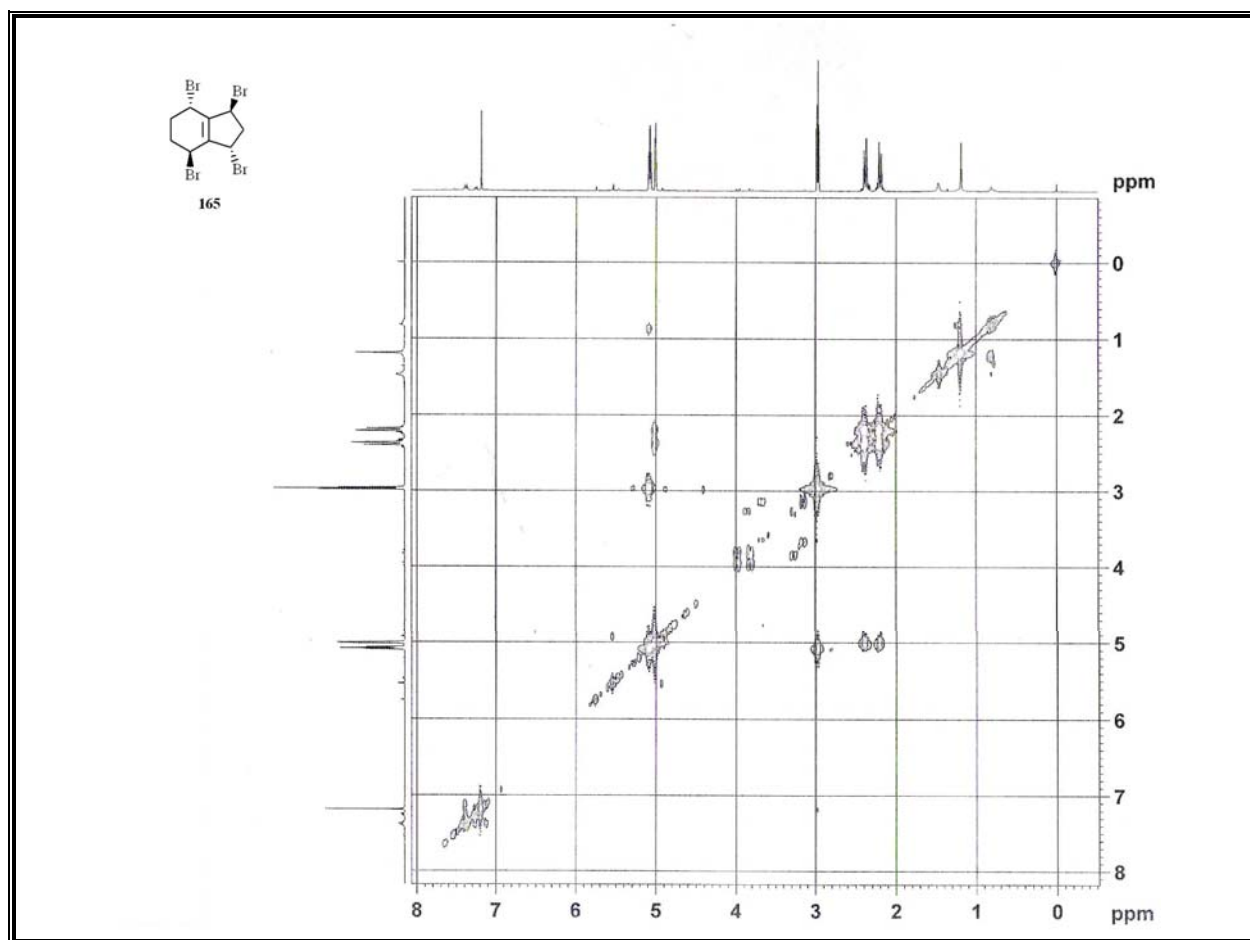


Figure A71 COSY Spectrum of Compound **165**.

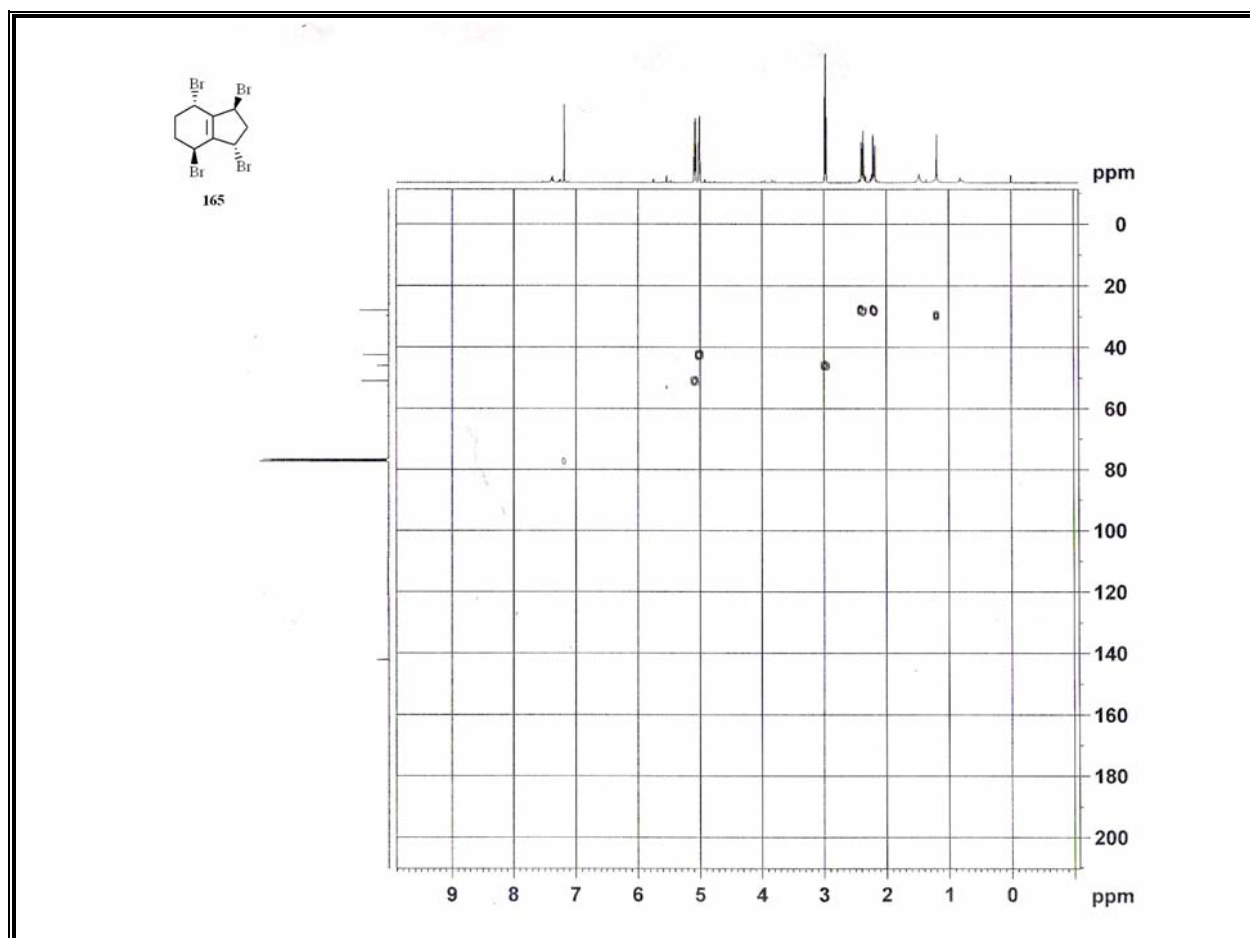


Figure A72 HMQC Spectrum of Compound **165**.

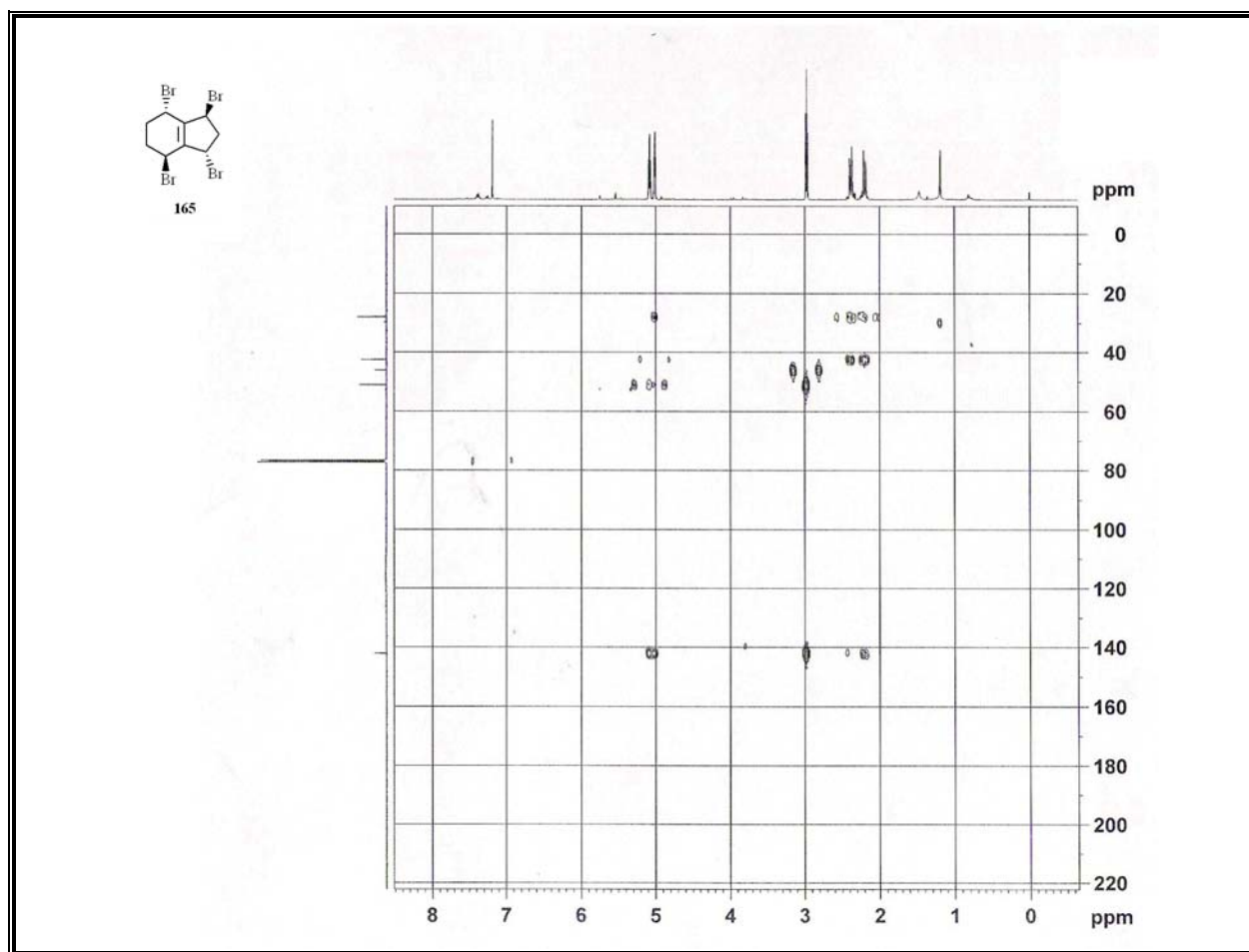


Figure A73 HMBC Spectrum of Compound **165**.

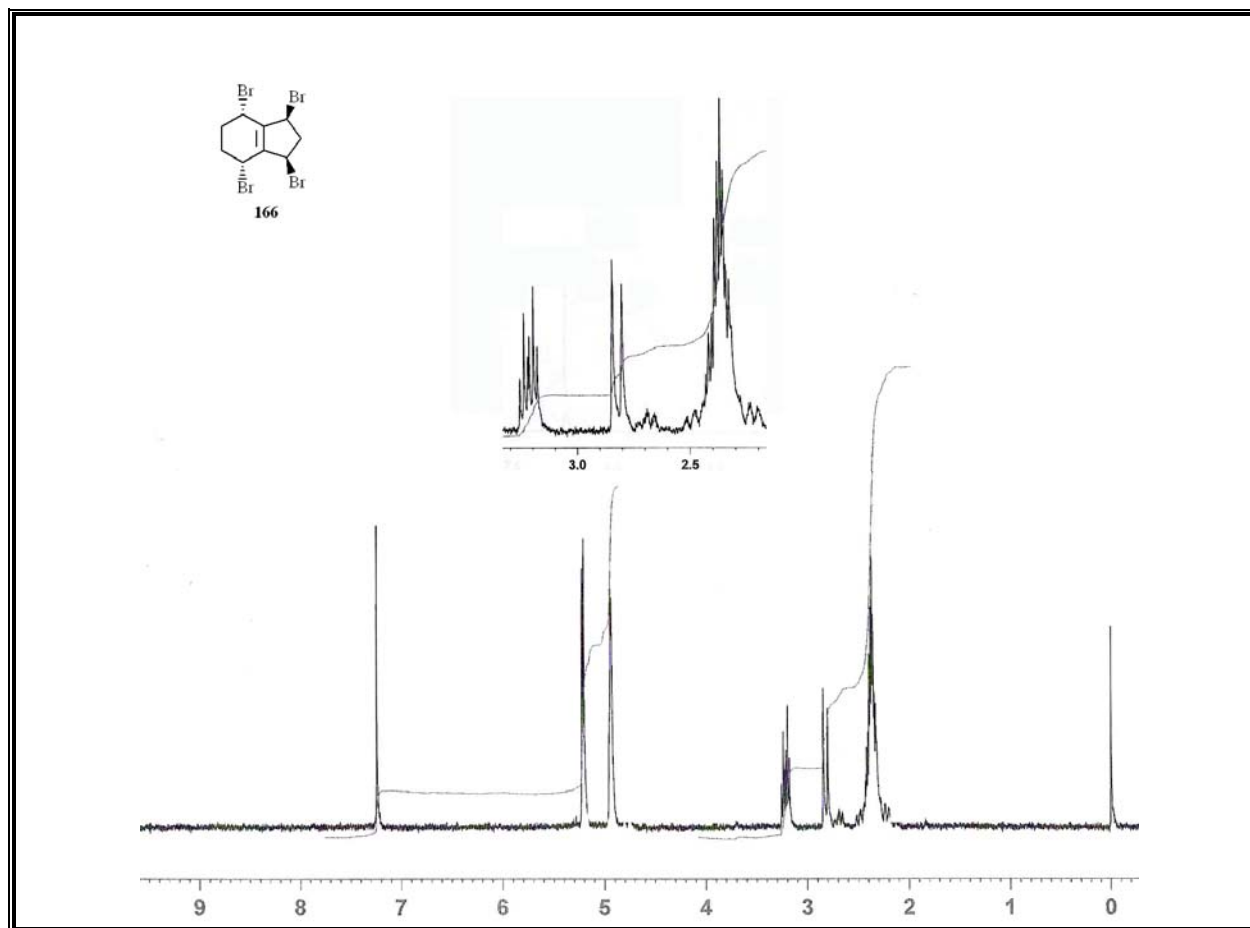


Figure A74 ^1H -NMR Spectrum of Compound **166**.

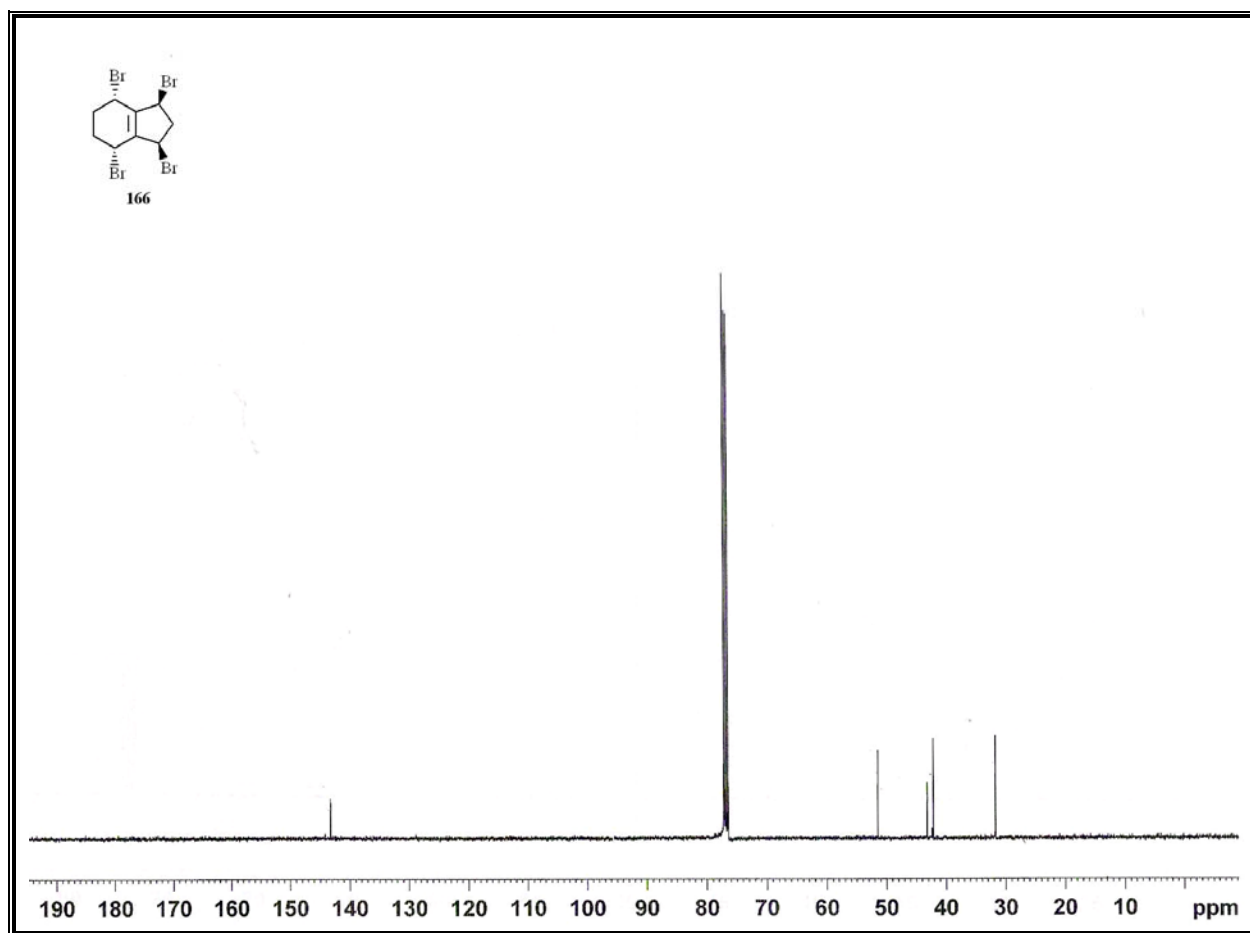


Figure A75 ^{13}C -NMR Spectrum of Compound **166**.

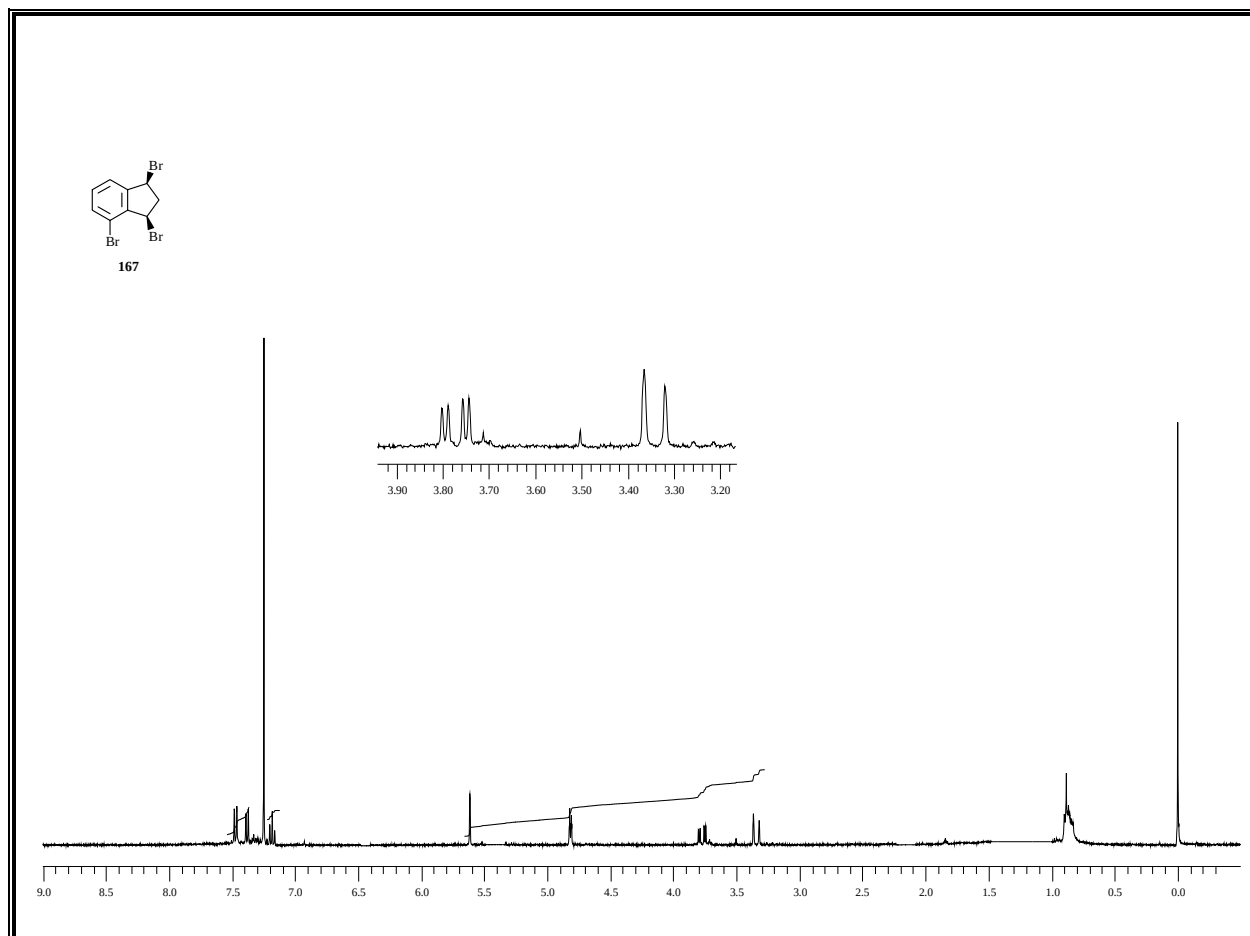


Figure A76 ^1H -NMR Spectrum of Compound **167**.

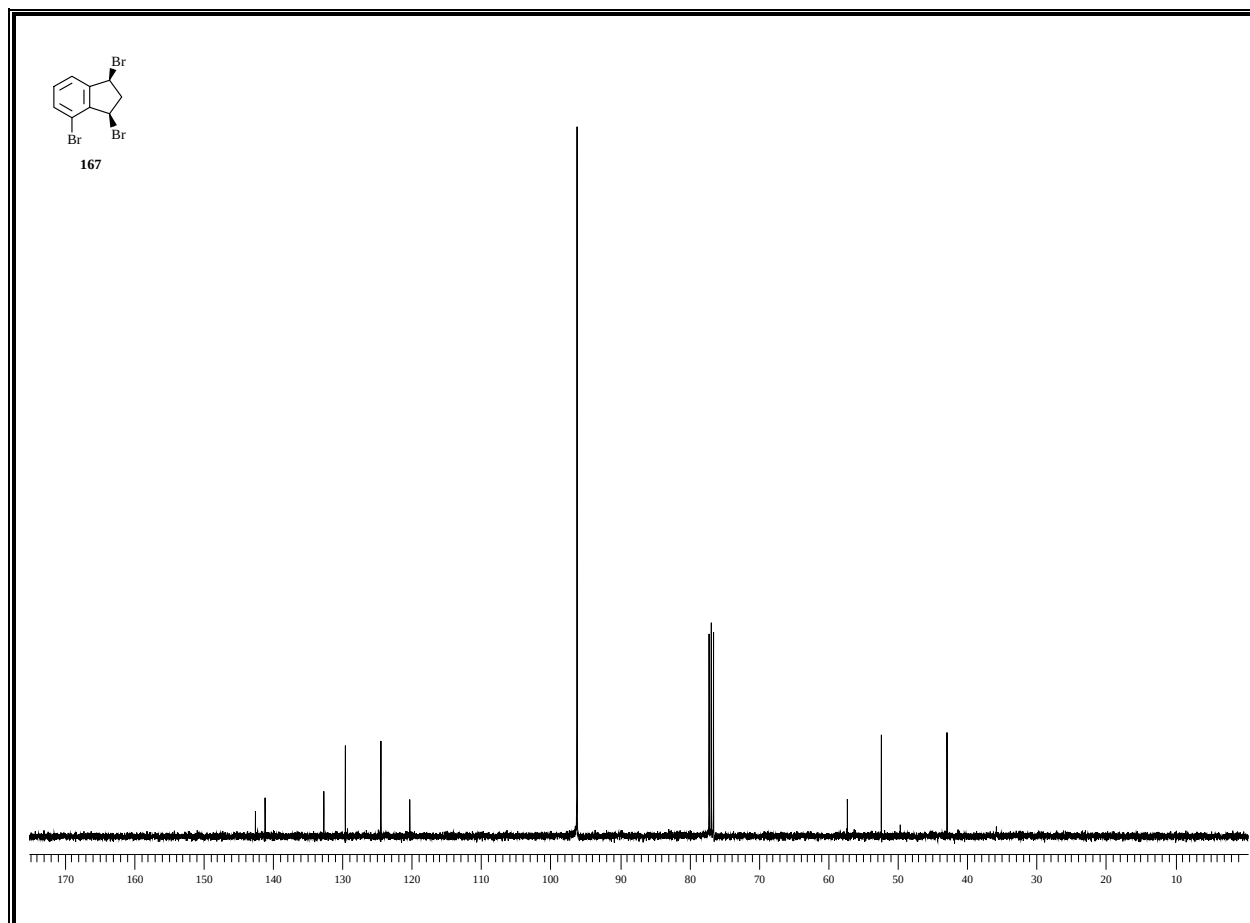


Figure A77 ^{13}C -NMR Spectrum of Compound **167**.

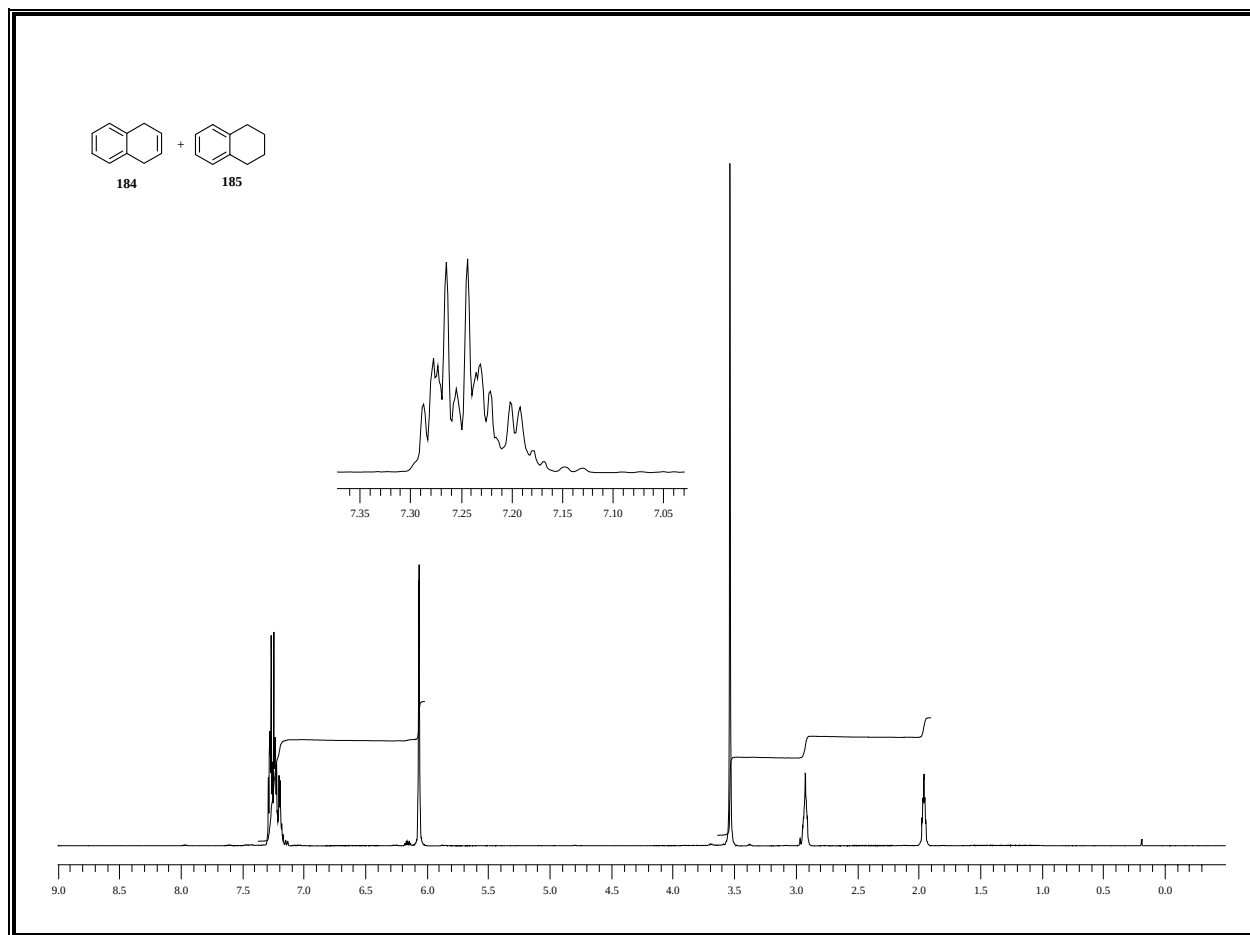


Figure A78 ^1H -NMR Spectrum of Compound **184** and **185**.

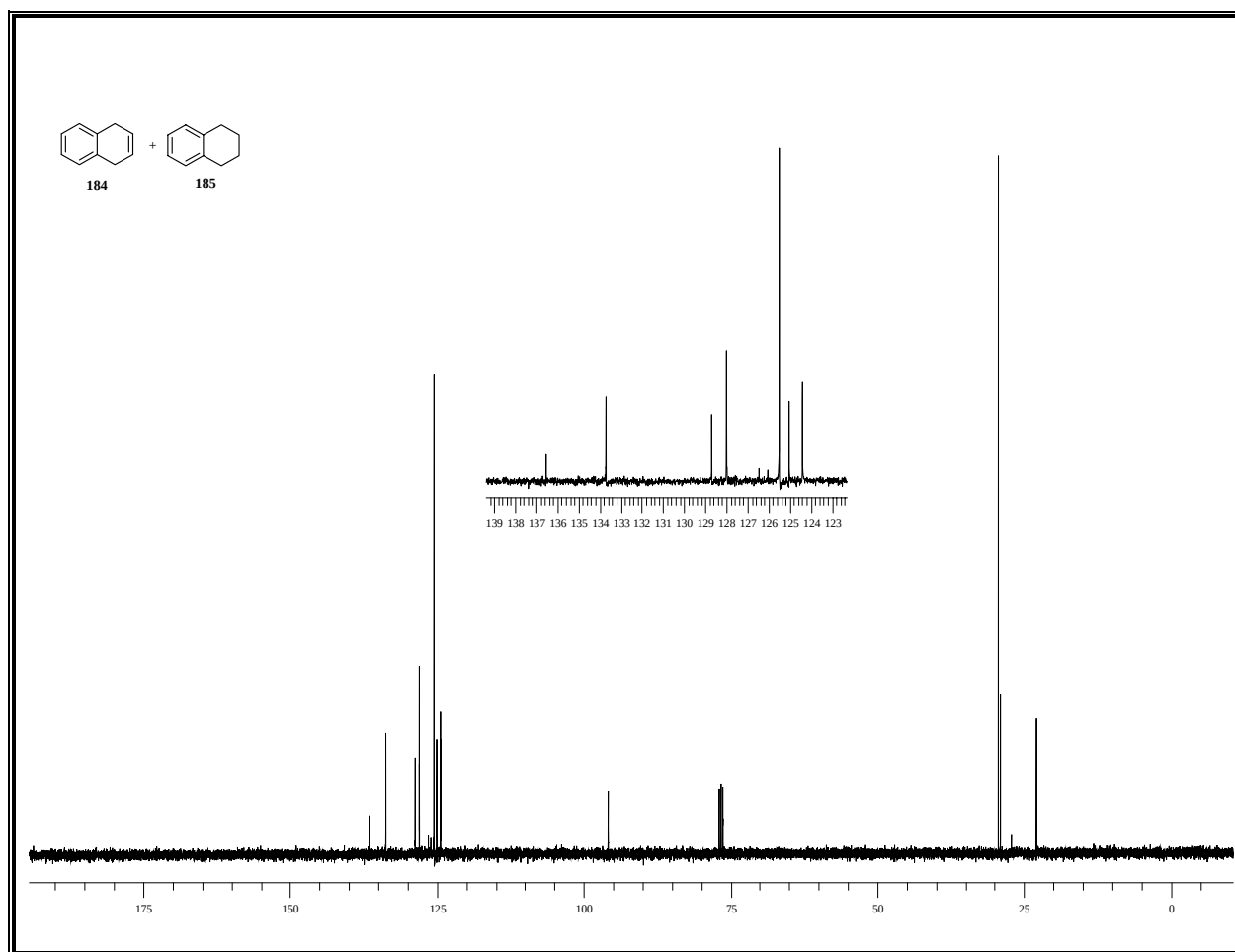


Figure A79 ^{13}C -NMR Spectrum of **184** and **185**.

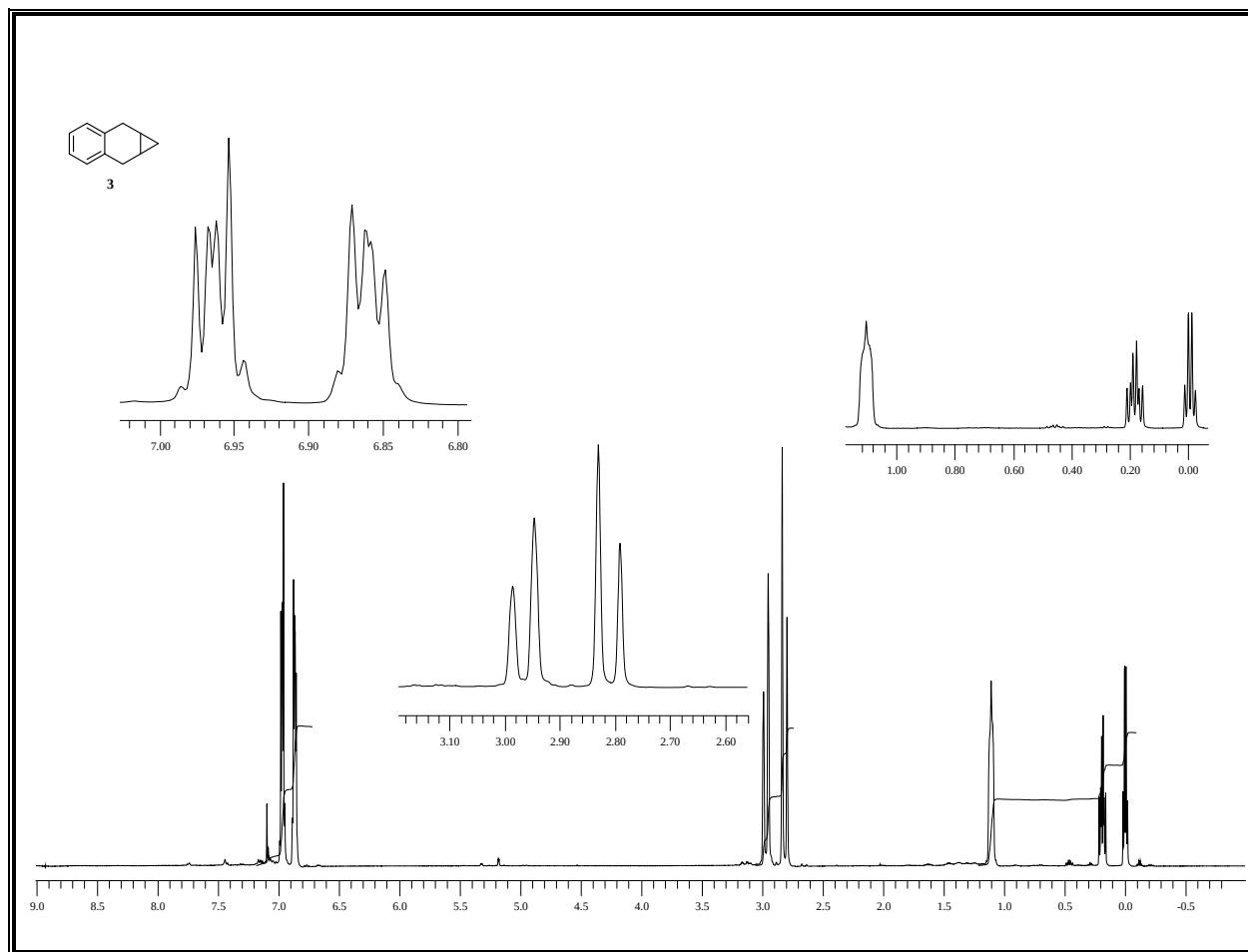


Figure A80 ^1H -NMR Spectrum of **3**.

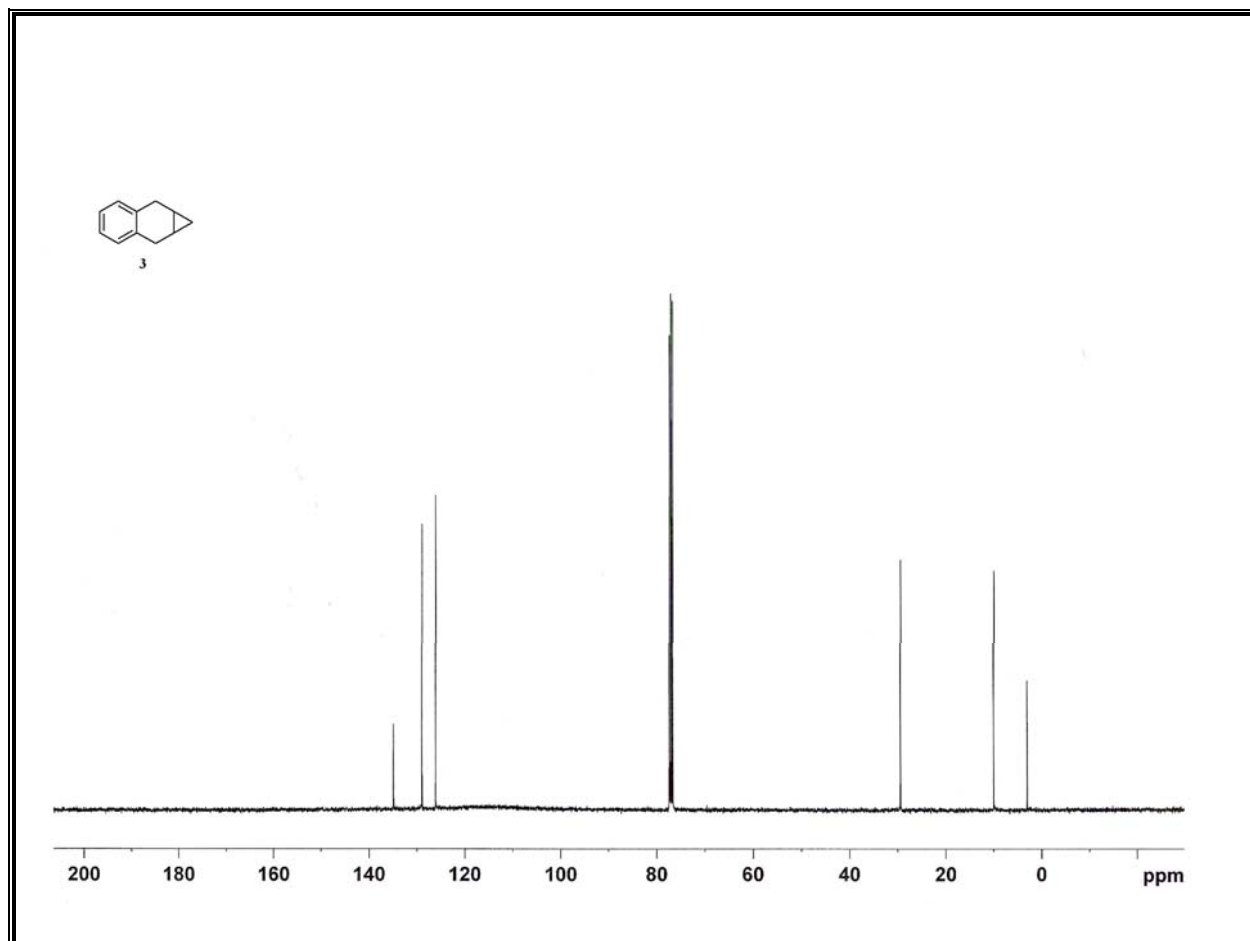


Figure A81 ^{13}C -NMR Spectrum of **3**.

Figure A82 ^1H -NMR Spectrum of **186**.

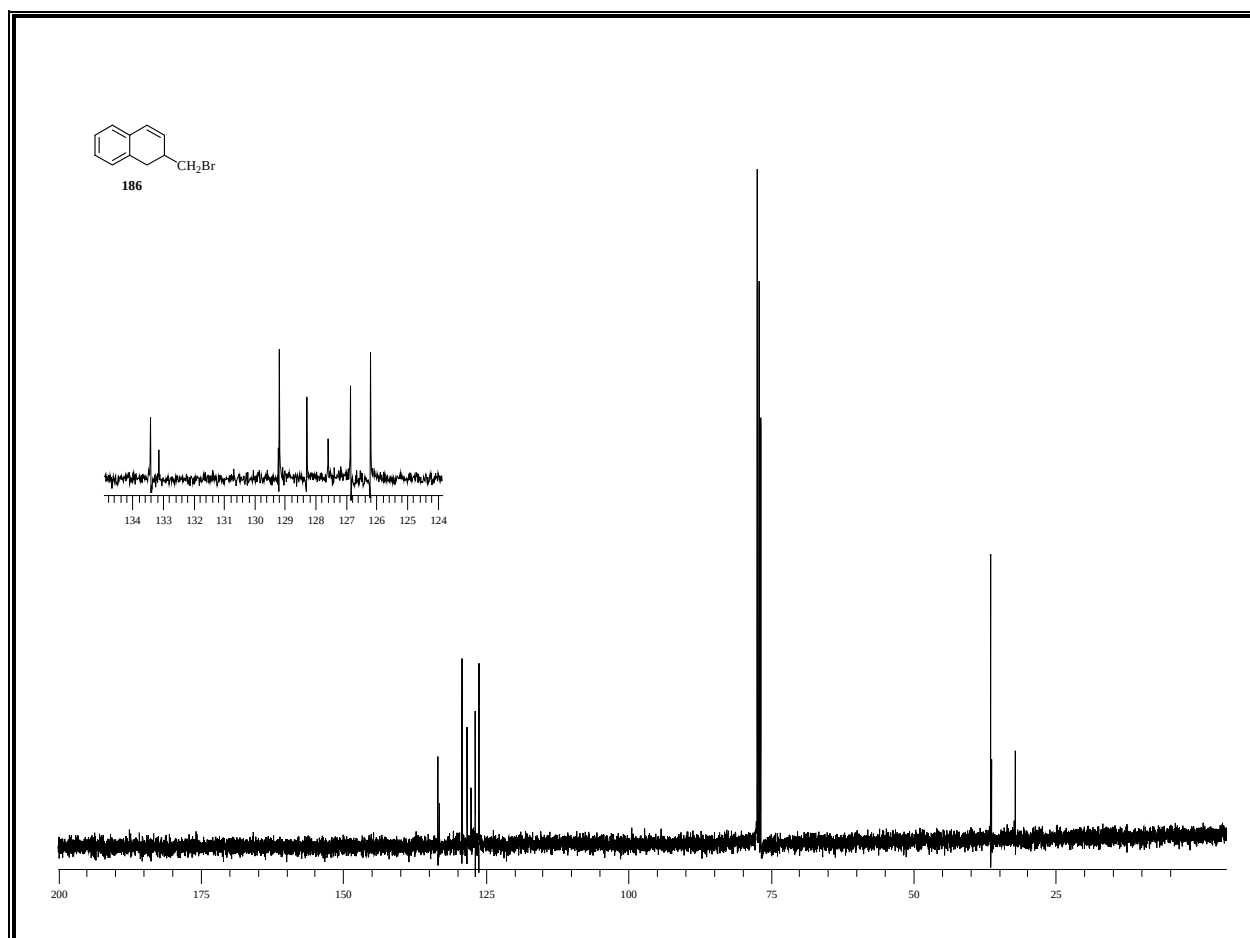


Figure A83 ^{13}C -NMR Spectrum of **186**.

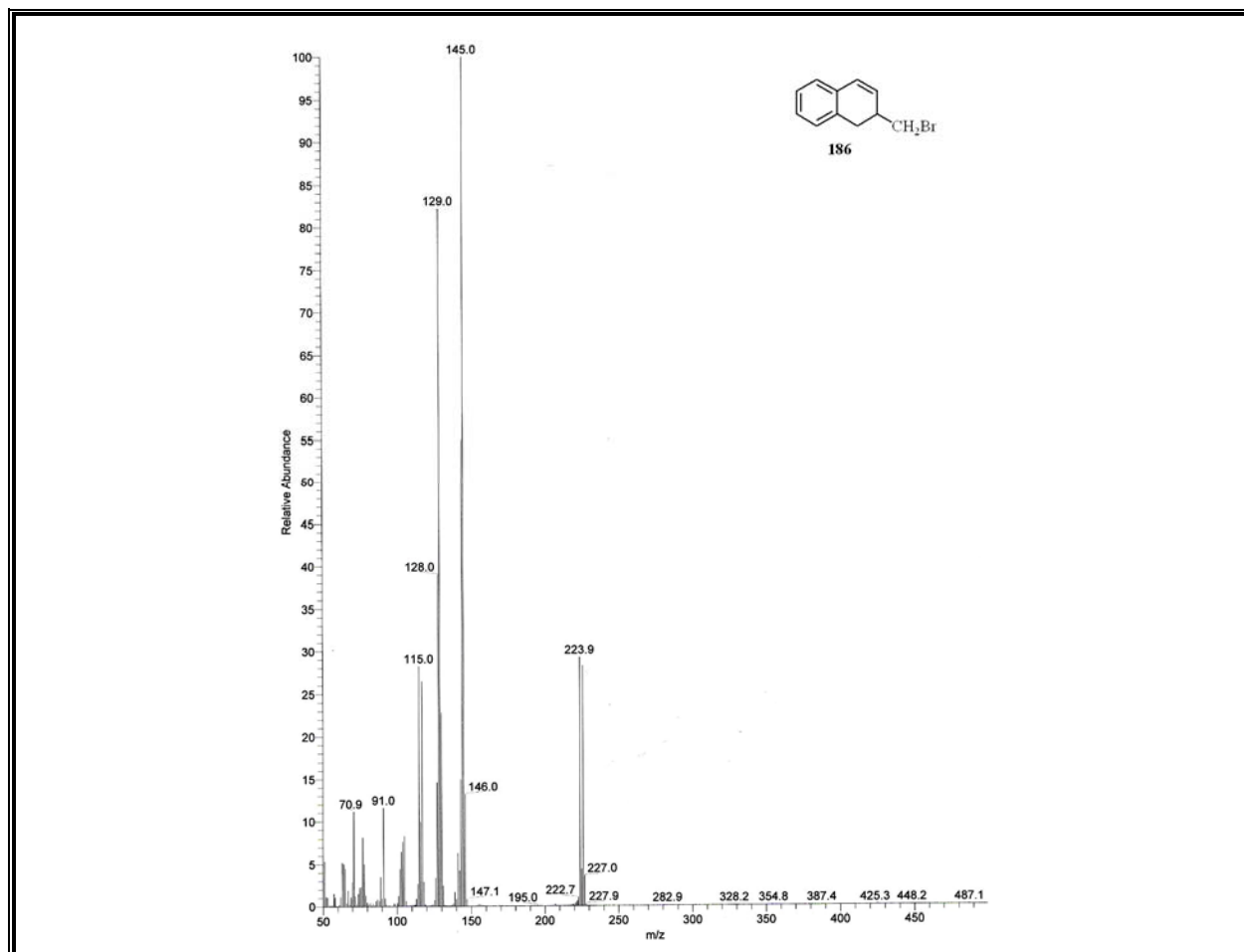


Figure A84 GC-MS Spectrum of Compound **186**.

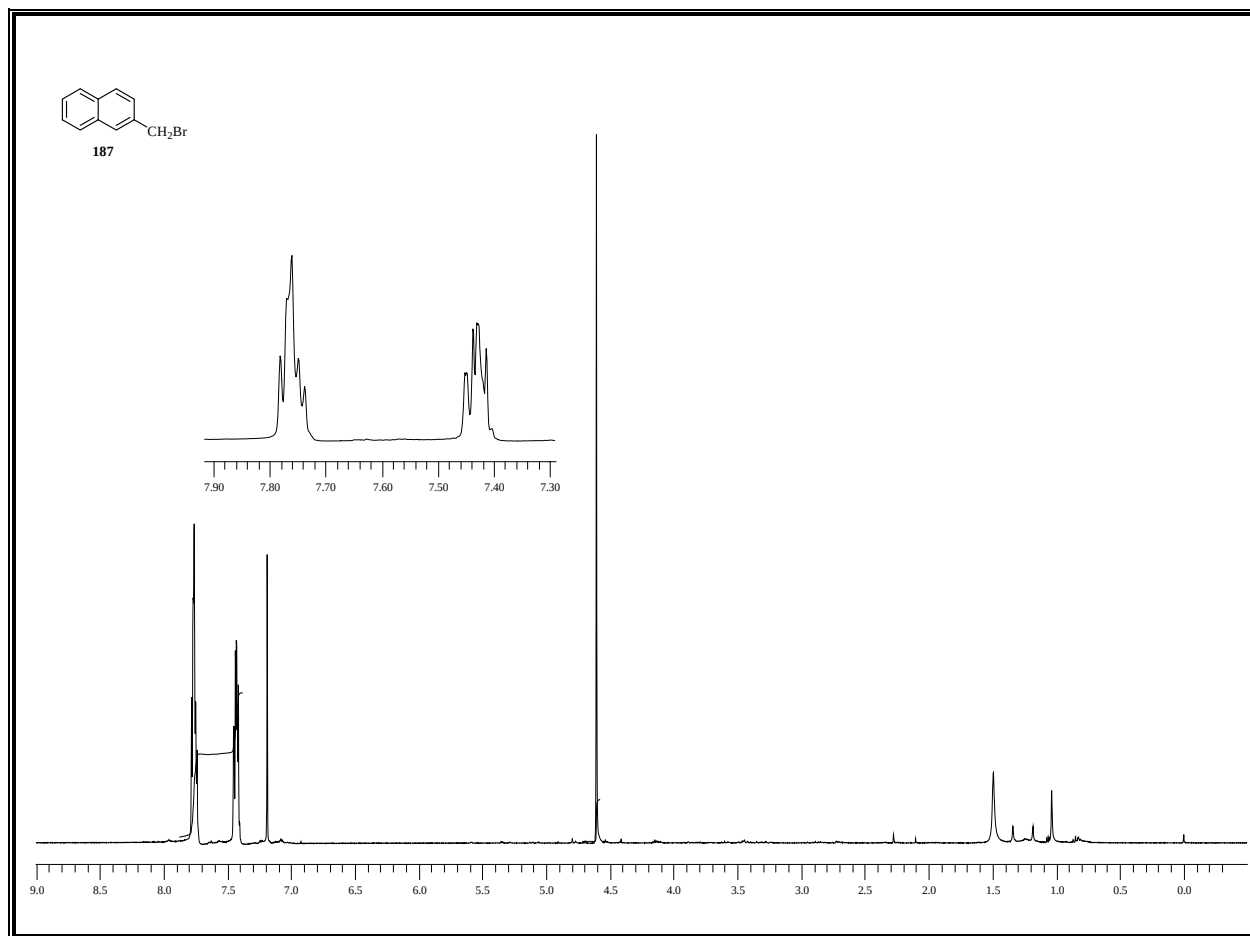


Figure A85 ^1H -NMR Spectrum of **187**.

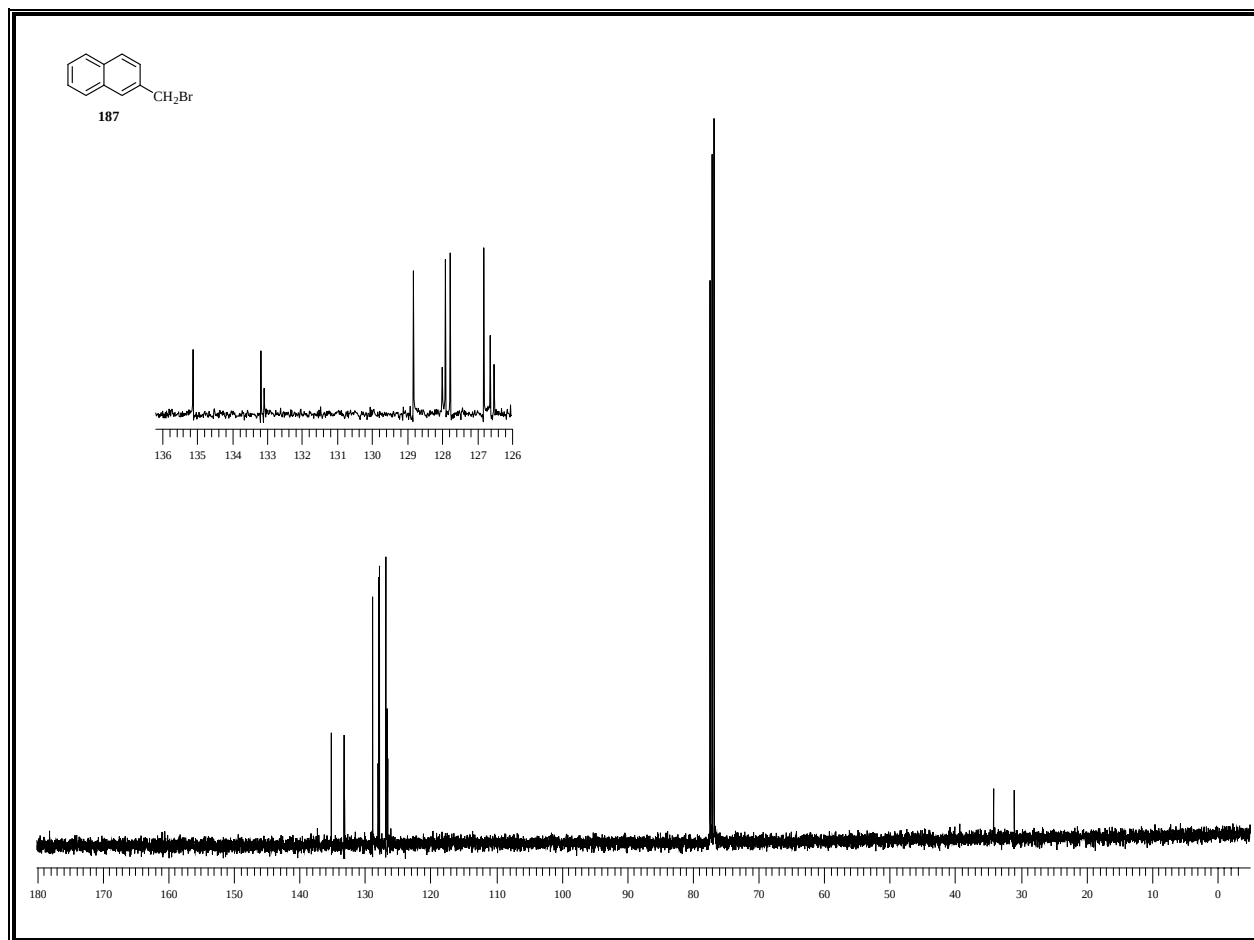


Figure A86 ^{13}C -NMR Spectrum of **187**.

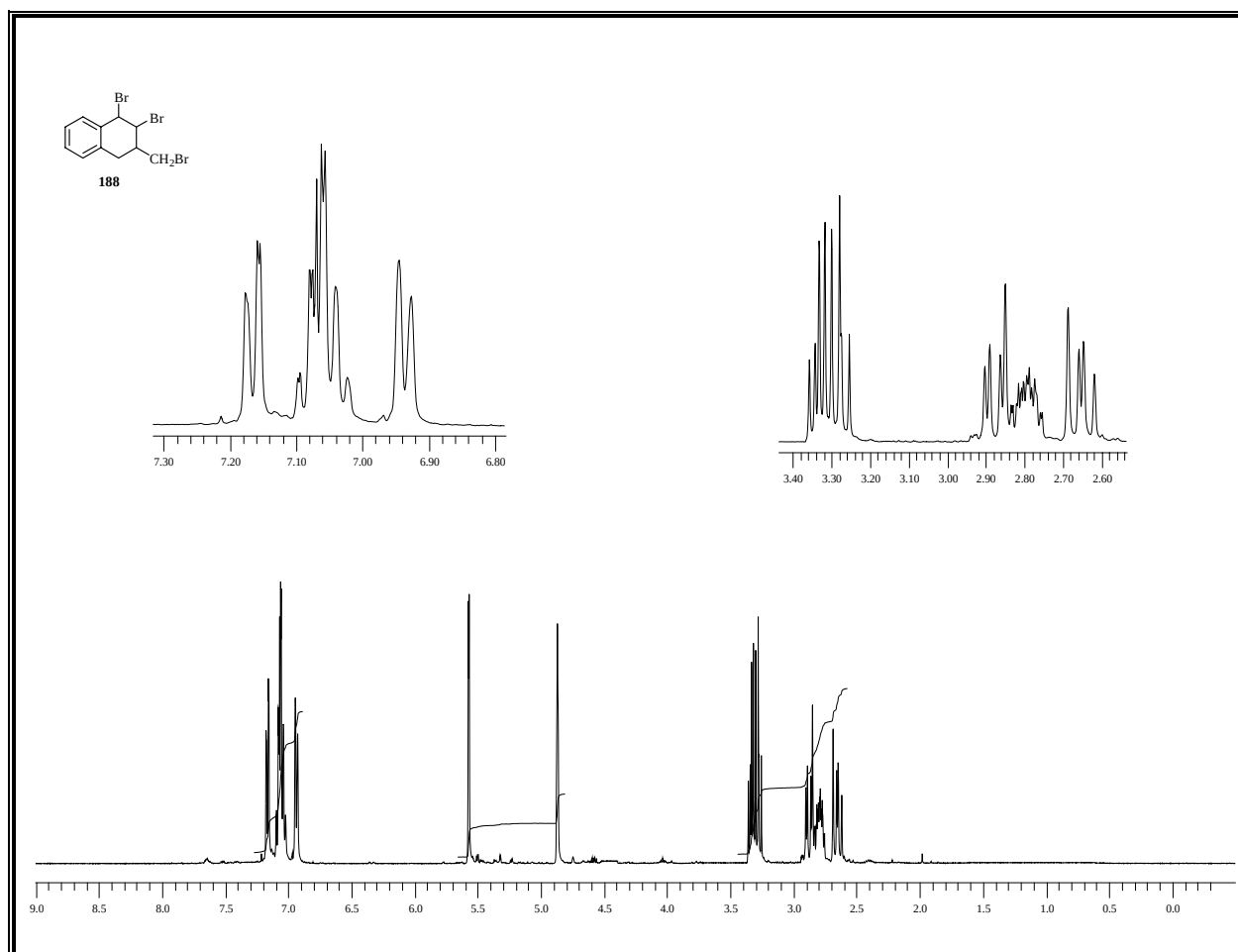


Figure A87 ^1H -NMR Spectrum of Compound **188**.

Figure A88 ^{13}C -NMR Spectrum of Compound **188**.

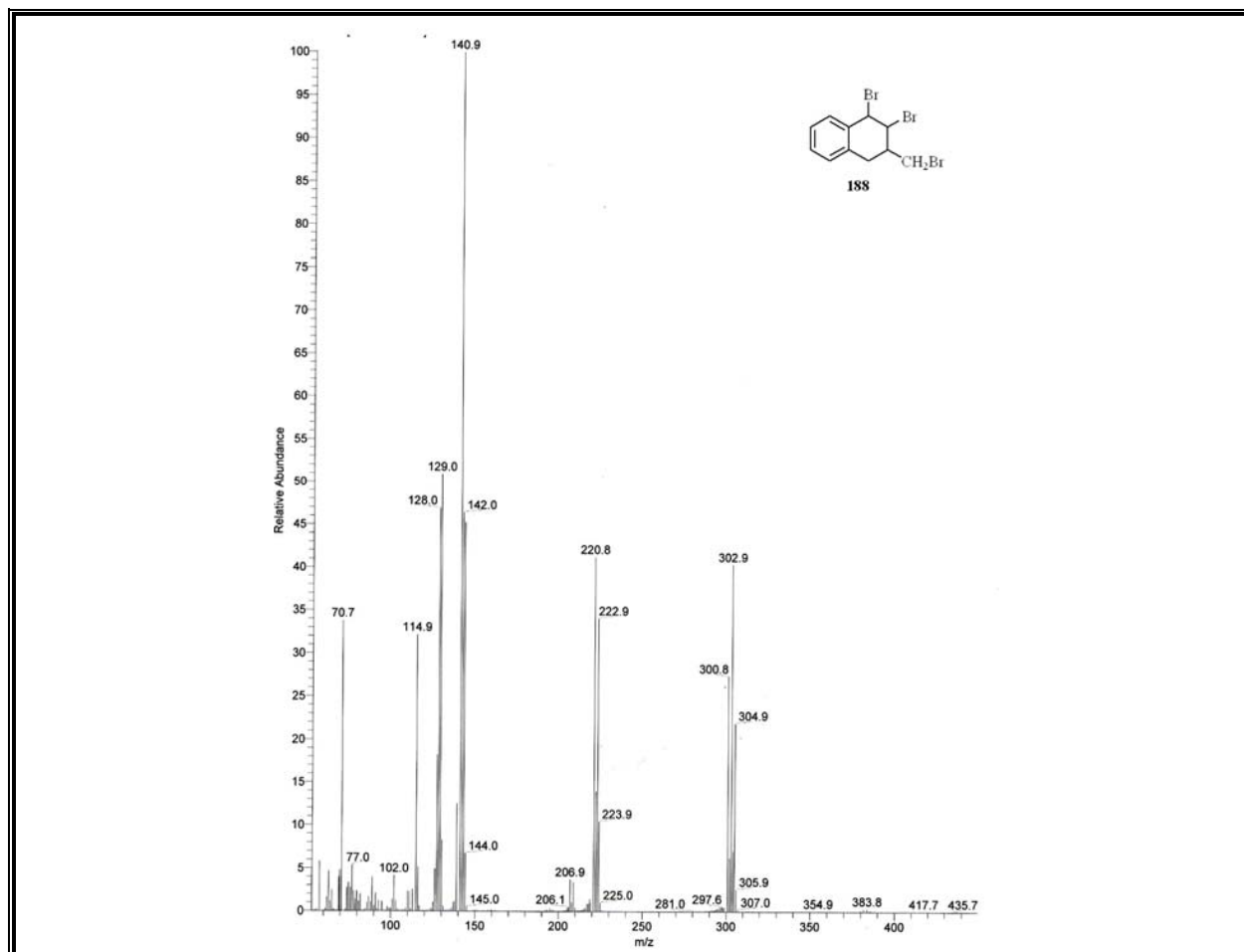


Figure A89 GC-MS Spectrum of Compound **188**.

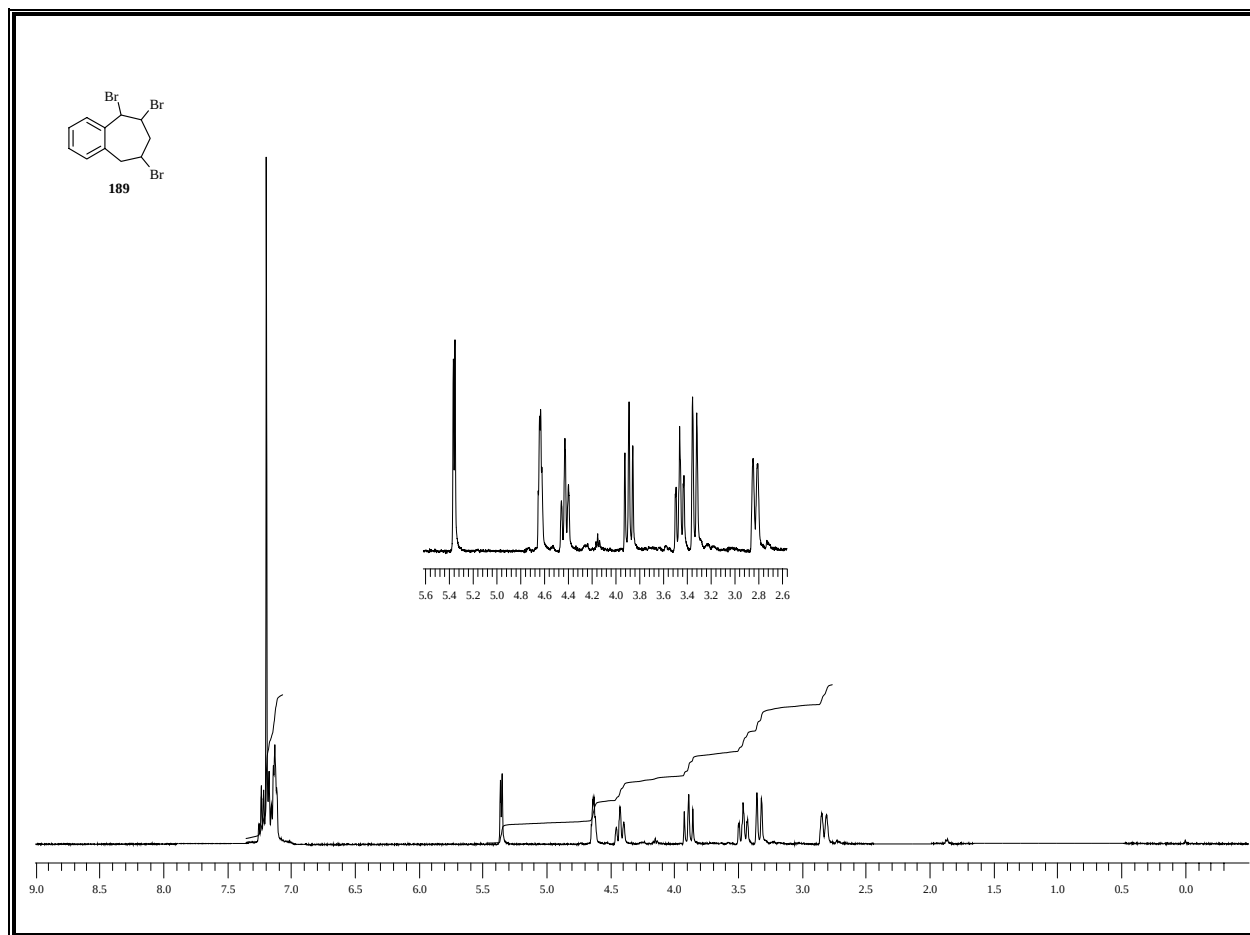


Figure A90 ^1H -NMR Spectrum of Compound **189**.

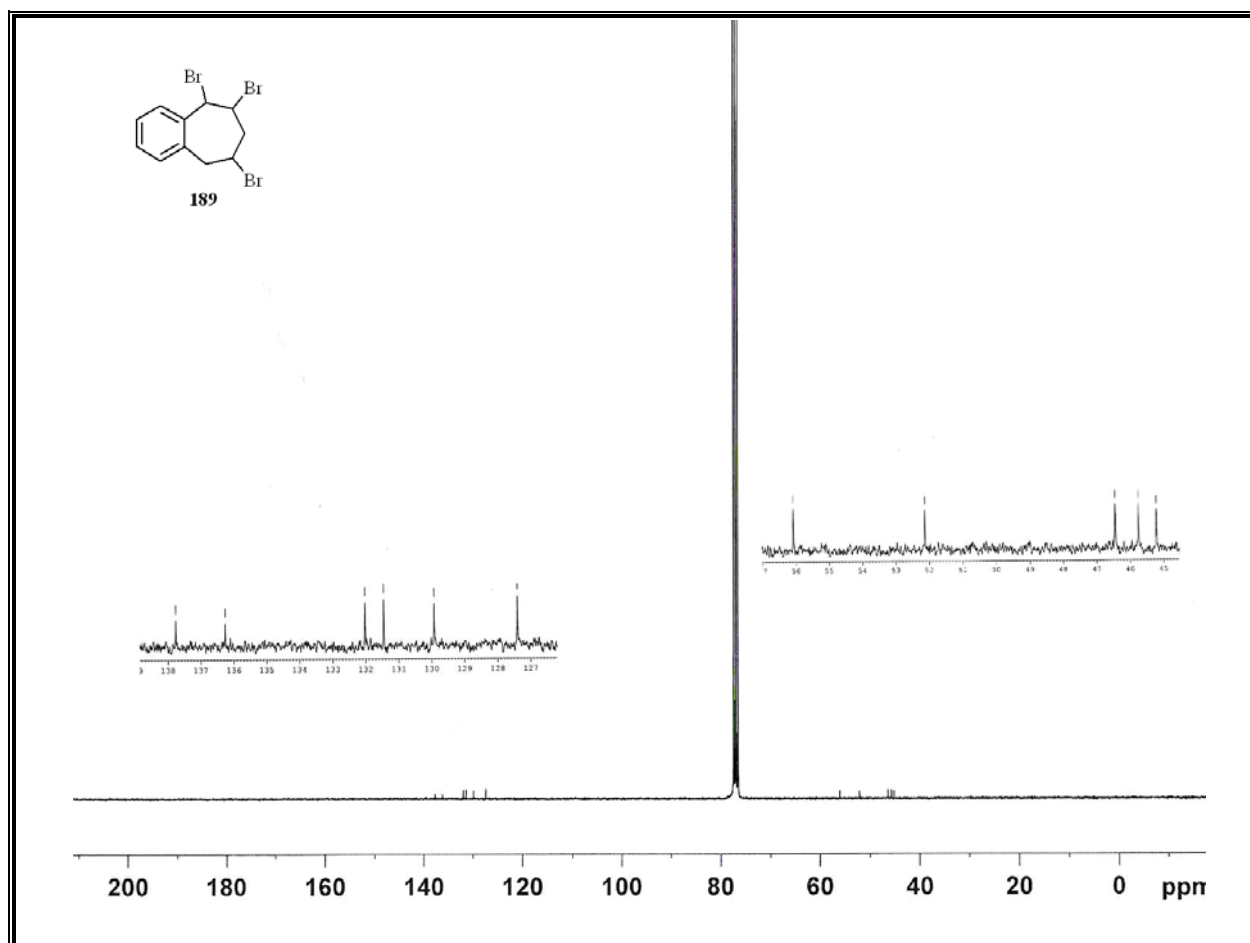


Figure A91 ¹H-NMR Spectrum of Compound **189**.

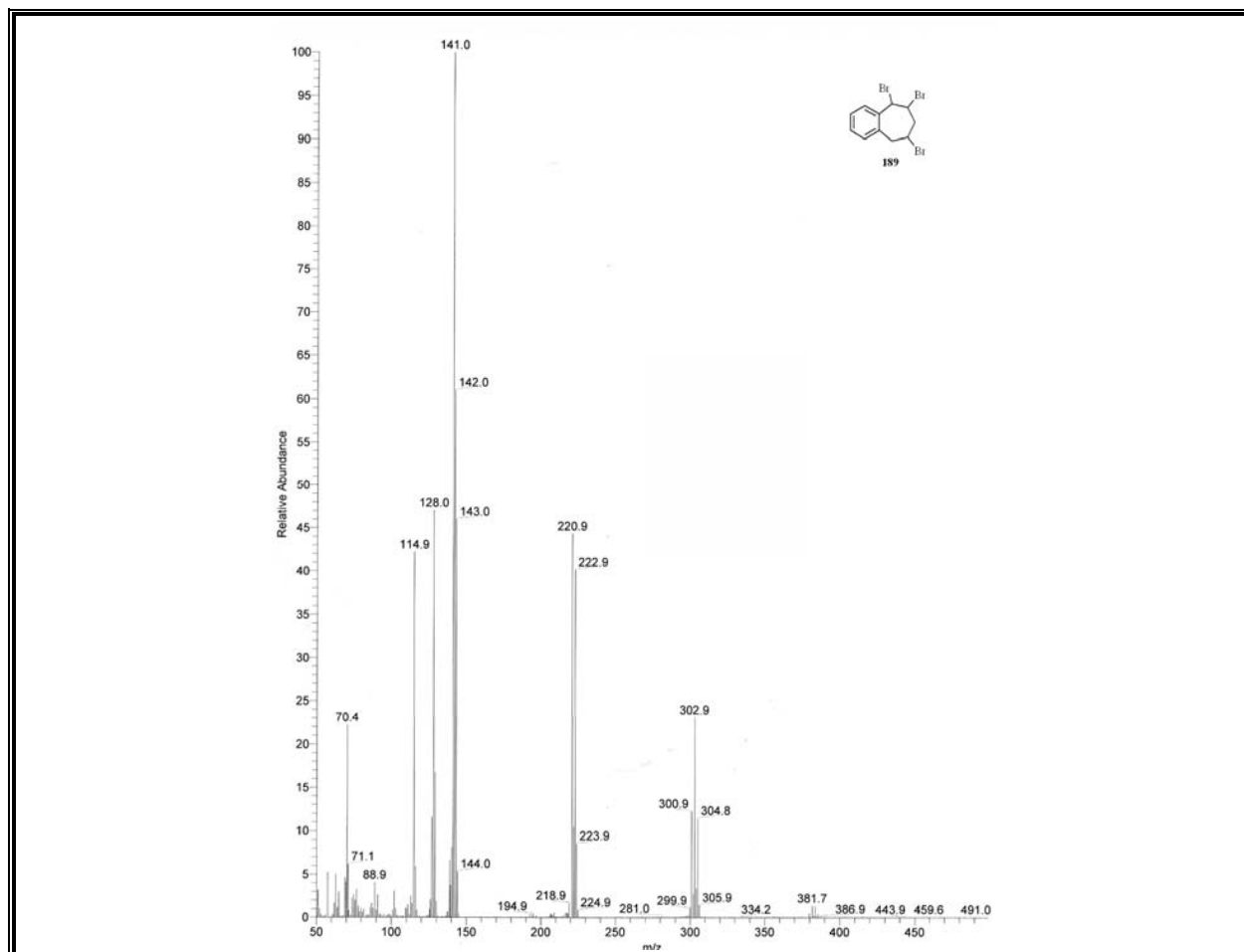


Figure A92 GC-MS Spectrum of Compound **189**.

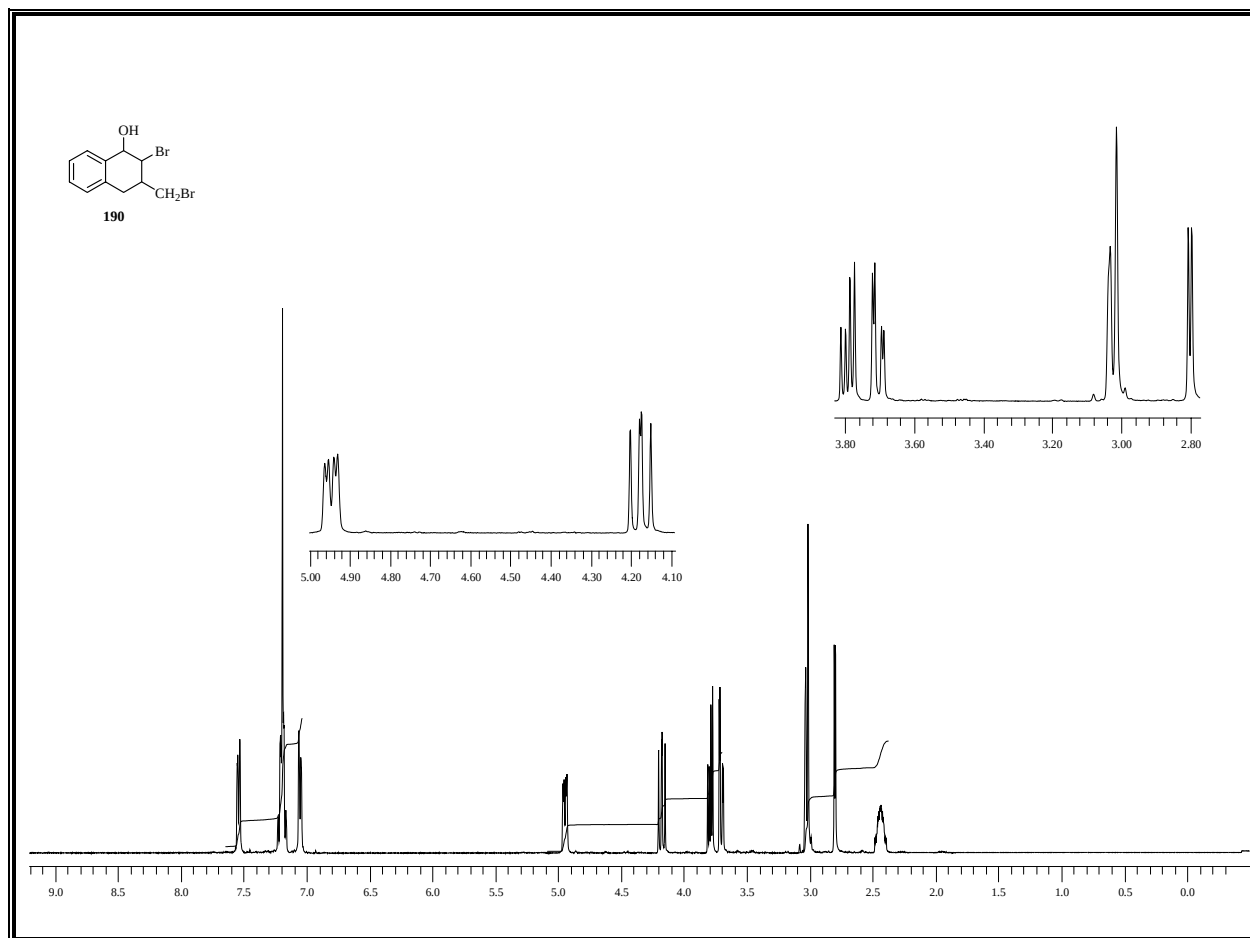


Figure A93 ^1H -NMR Spectrum of Compound **190**.

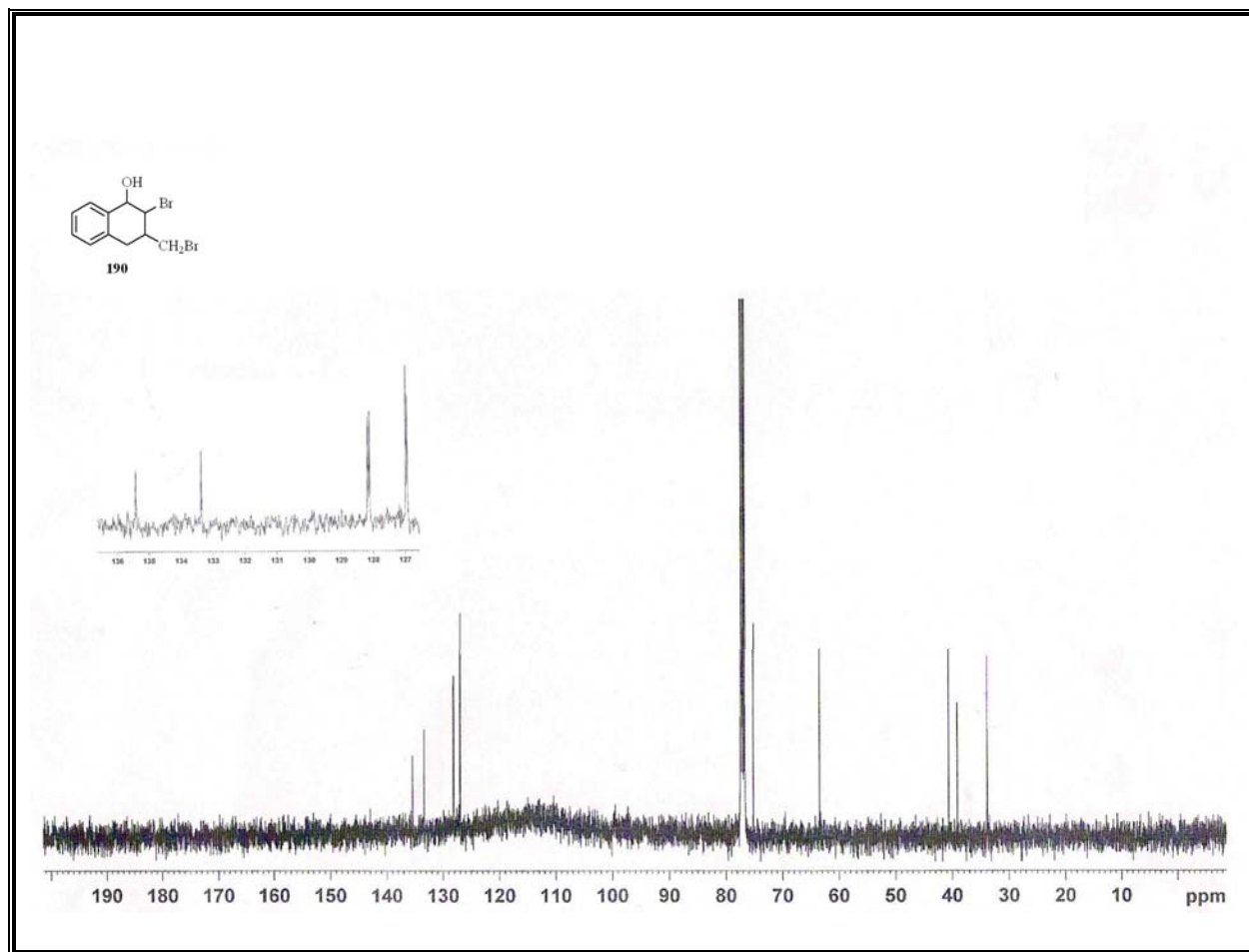


Figure A94 ^{13}C -NMR Spectrum of Compound **190**.

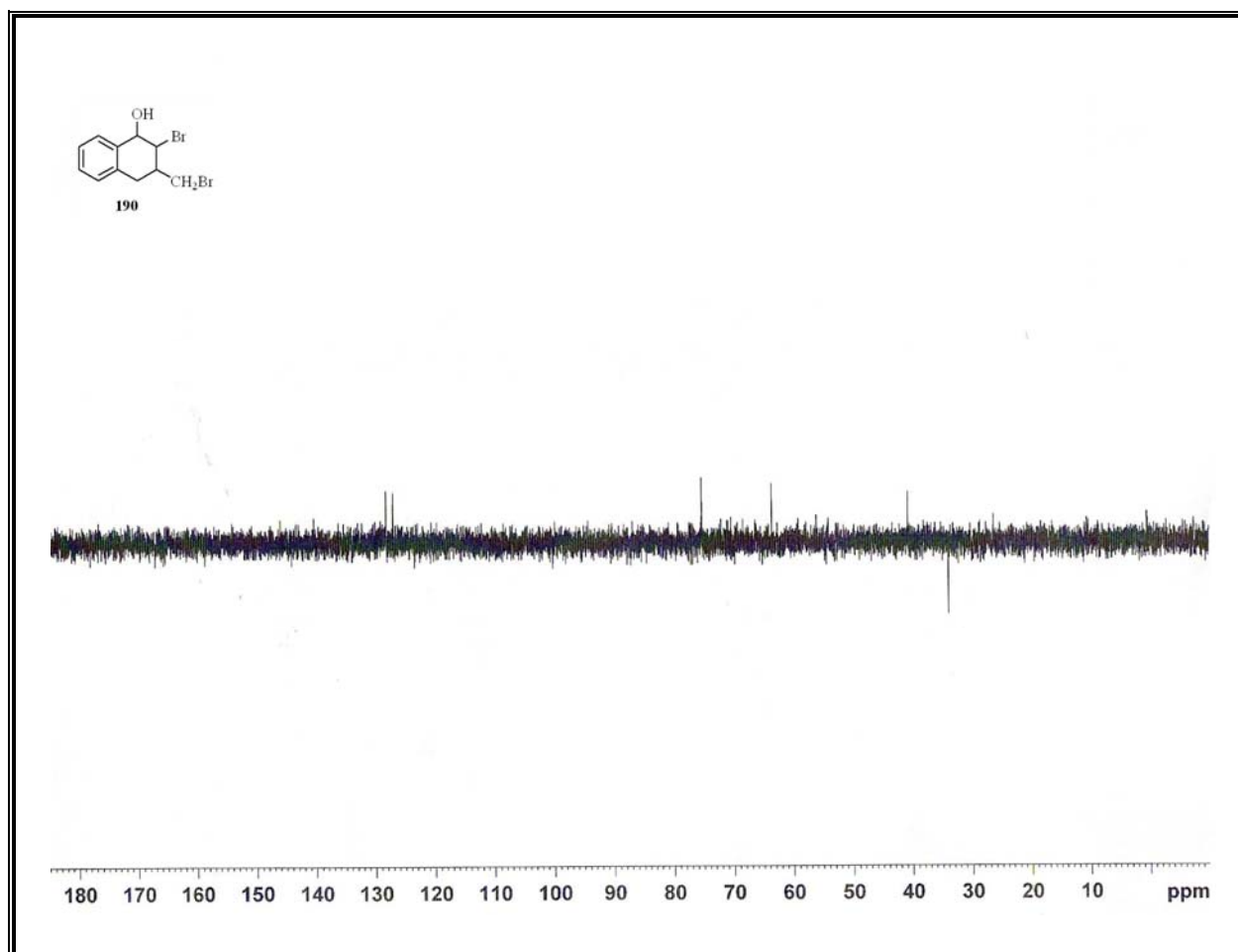


Figure A95 DEPT 135 Spectrum of Compound **190**.

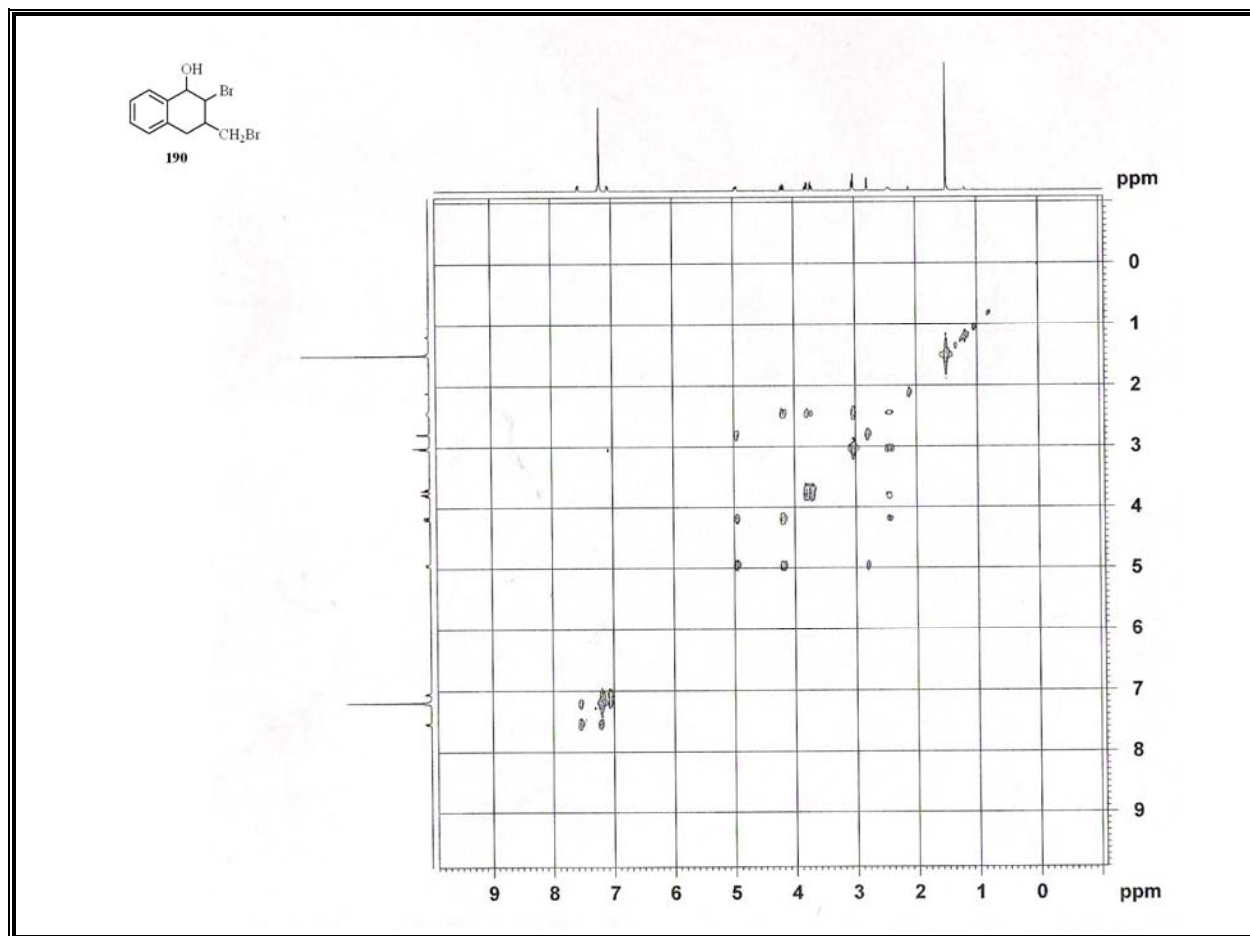


Figure A96 COSY Spectrum of Compound **190**.

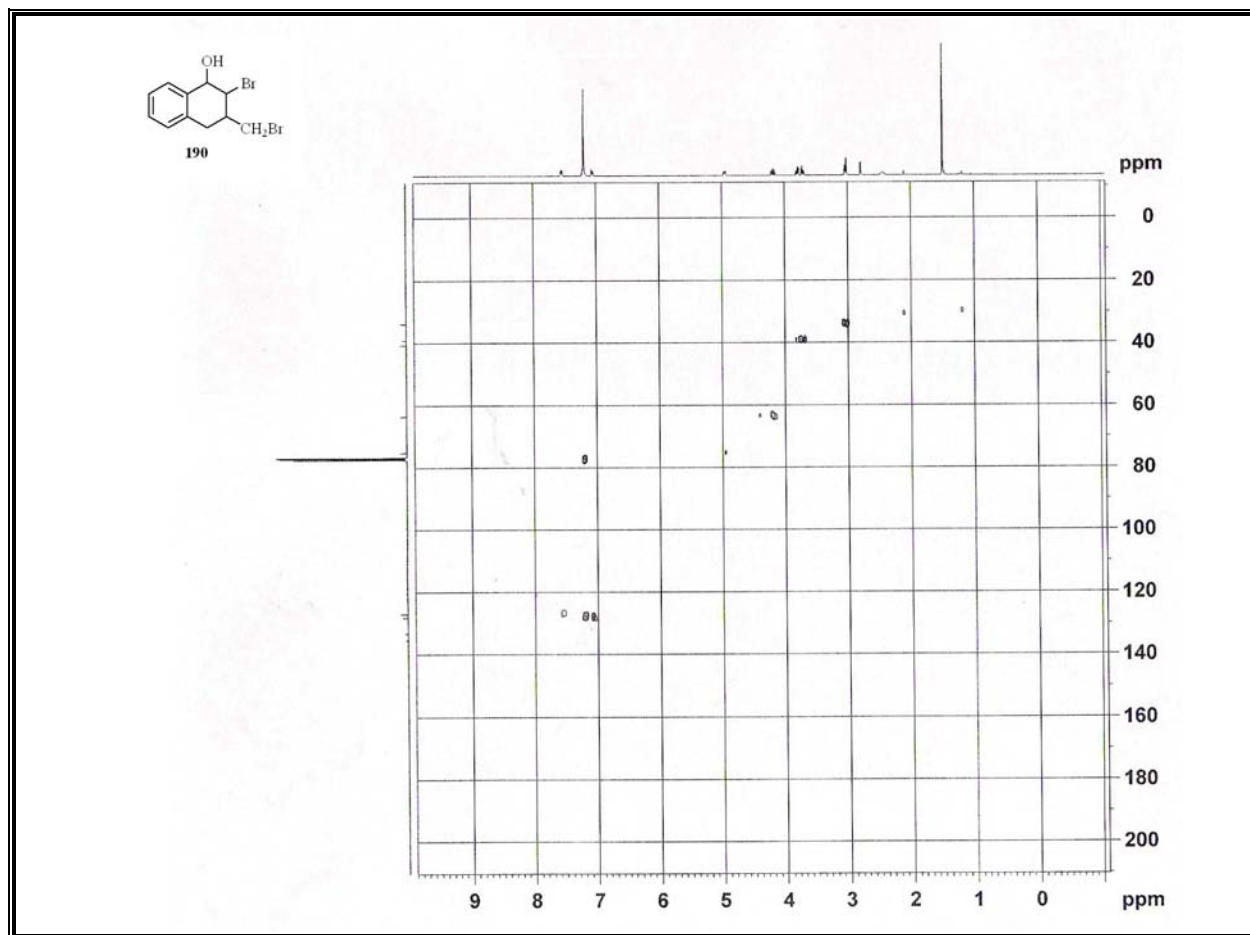


Figure A97 HMQC Spectrum of Compound **190**.

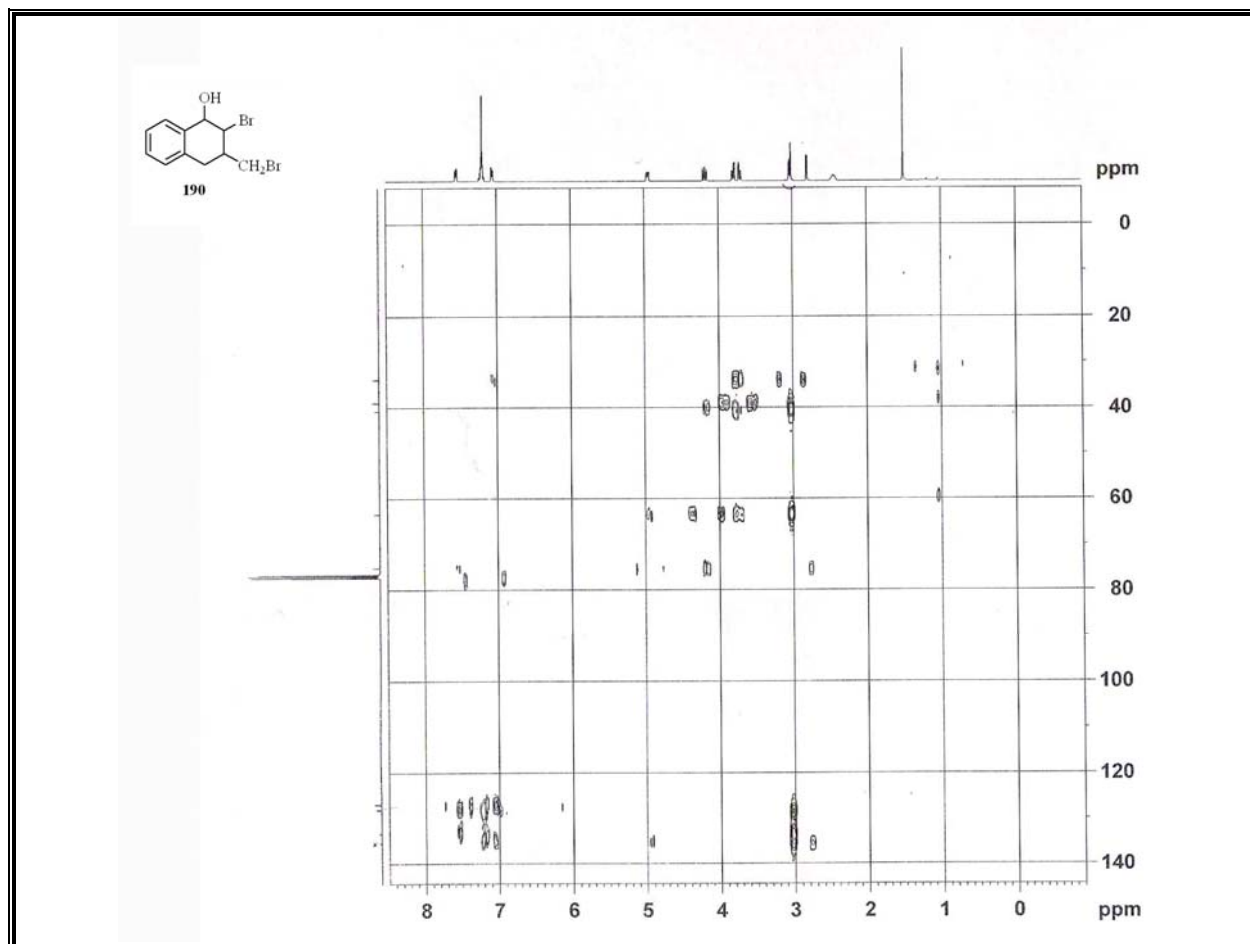


Figure A98 HMBC Spectrum of Compound **190**.

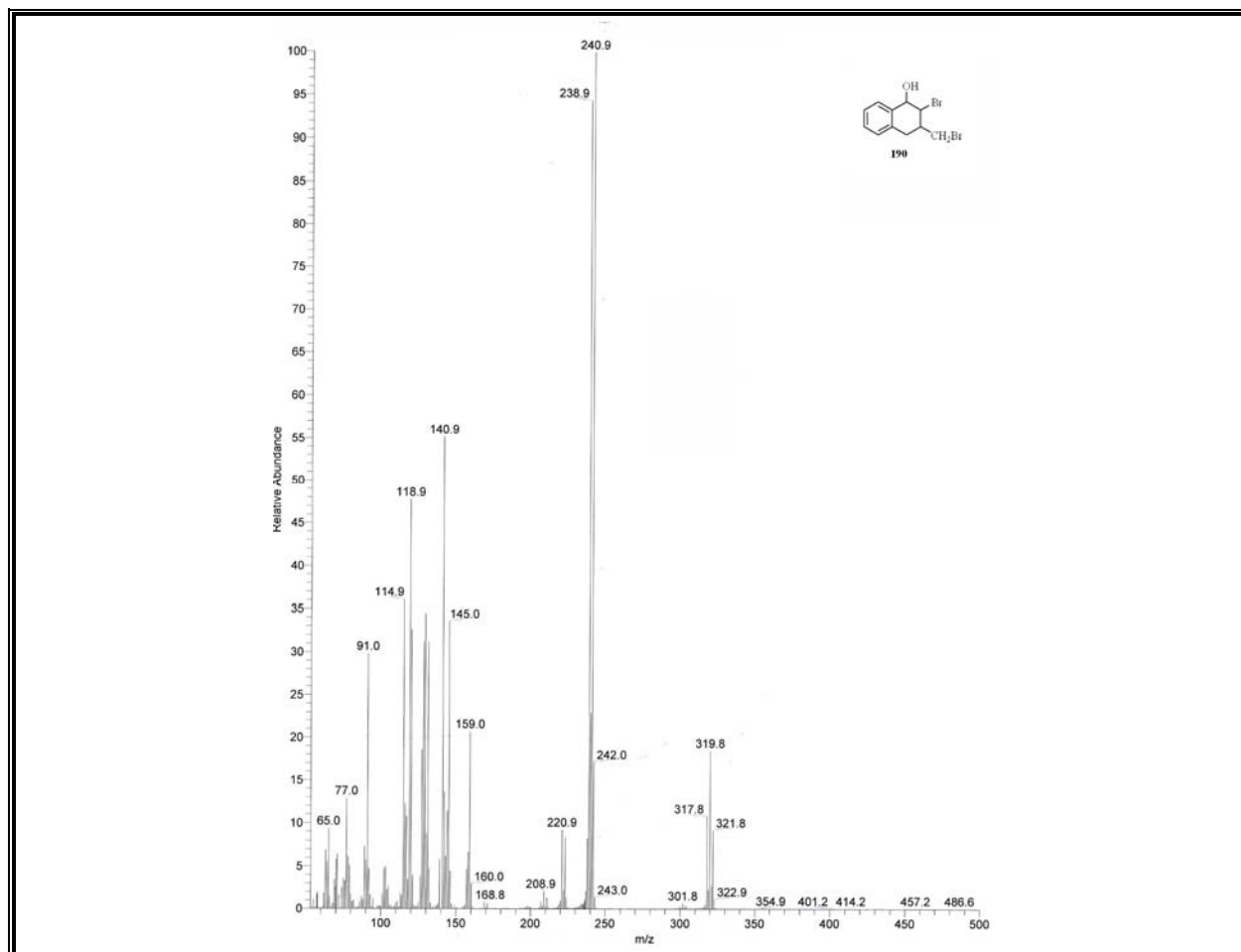


Figure A99 GC-MS Spectrum of Compound **190**.