BICYCLIC STRAINED ALLENES:

INCORPORATION OF AN ALLENE UNIT INTO ALPHA-PINENE AND BENZONORBORNADIENE

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ABSTRACT

BICYCLIC STRAINED ALLENES:

INCORPORATION OF AN ALLENE UNIT INTO ALPHA-PINENE AND BENZONORBORNADIENE

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Supervisor: Prof. Dr. Metin Balcı

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The synthesis of cyclic allenes with eight or less skeletal C-atoms, known as highly strained organic compounds, has for the past decades attracted increasing interest. From among the numerous synthetic approaches to the cyclic allenes, Doering-Moore-Skattebol method and β-elimination method are most widely studied in the literature.

The first part of study describes an investigation aimed at the incorporation of an allene unit into a natural compound, being α-pinene, by using β-elimination method. The two double-bond isomers **310** and **299b** were synthesized as key compounds and they were exposed to β-elimination reaction respectively. Treatment of **310** with *t*-BuOK resulted in the formation of ketone **308** and diene **313**. For the formation of **308**, the cyclic allene **300** was proposed as an intermediate. Treatment of the second isomer, **299b**, with *t*-BuOK gave rise to the diene **313** and the dimerization product **322**. The underlying mechanism of this transformation was

discussed. On the basis of density-functional-theory (DFT) calculations on the allene **300** and the alkyne **320**, the formation of the latter as the intermediate was excluded.

In the second part of study, the stability of *endo*-carbene **304** was investigated. According to the theoretical and experimental results in literature about during the formation of intermediate **264**, no *exo*-carbene **330** structure could be optimized in its free carbene form. It directly isomerizes to the bicyclic allene **264** during the optimization. At this point, we were curious about the stability of *endo*-cyclopropylidene **304** that was not discussed before in literature. The *exo*-face of benzonorbornadiene (**301**) was protected with bromine and ethyl groups. First, the addition of bromofluorocarbene to *anti*-7-ethylbenzonorbornadiene (**352**) was aimed to isolate the *endo*-adduct **302b**. However, no carbene addition reaction was observed. Theoretical calculations indicated ethyl group located at C-7 carbon atom of **301**, caused pyramidalization on double bond respect to the methoxy derivative, **363b.** As a result, more strained energy and deformation of planarity on double bond retarted carbene addition. Therefore, the bromine was introduced to C-7 carbon atom. Treatment of bromofluorocyclopropane **302a** with MeLi in the presence of furan, gave furan adduct **306a** confirmed the formation of allene **305a** as a reactive intermediate. Theoretical calculations showed *endo*-carbene **304a** was optimized in the free carbene form whereas *exo*-carbene **330** was not. However, it readily isomerizes to allene **305a** afforded furan adduct **306a**. Hence, the required energy for isomerization of carbene **304a** to allene **305a** is approximately 0.03 kcal/mol retarted to the formation of insertion or any other addition products.

Keywords: Allene, Bicyclic Allene, Carbenoid, Carbene, Alpha-pinene, Doering-Moore-Skattebol Method, β-Elimination Method, Benzonorbornadiene, Pyramidalization, DFT Method, Theoretical Calculations.

ÖZ

GERİLİMLİ BİSİKLİK ALLENLER:

ALLEN BİRİMİNİN ALFA-PİNEN VE BENZONORBORNADİEN MOLEKÜLLERİNE DAHİL EDİLMESİ

Kılbaş, Benan

Doktora, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Ocak 2009, 166 sayfa

Yüksek gerilimli organik bileşikler olarak bilinen sekiz ya da daha az karbon iskeletine sahip siklik allenlerin sentezi organik kimyada özellikle son on yıldır ilgi konusu olmuştur. Siklik allen sentez yöntemleri arasında en çok kullanılan yöntemler, Doering-Moore-Skattebol metodu ve β-eliminasyon metodudur.

Çalışmanın ilk kısmında, β-eliminasyon metodu kullanılarak doğal bir bileşik olan α-pinen içerisine allen biriminin oluşturulması amaçlanmıştır. Birbirinin çift bağ izomeri olan **310** ve **299b** bileşikleri sırasıyla β-eliminasyon reaksiyonuna tabi tutulmuştur. **310** bileşiğinin *t*-BuOK ile reaksiyonu sonucu keton **308** ve dien **313** elde edilmiştir. **308** in oluşumundan, reaksiyon ara ürünü olarak allen biriminin oluştuğu varsayılmıştır. Diğer izomer **299b** nin, *t*-BuOK ile reaksiyonu sonucu dien **313** ve dimer ürünü **322** elde edilmiştir. Bu reaksiyonlar sırasındaki oluşan mekanizmalar tartışılmıştır. Yapılan teorik hesaplamalar, reaktif ara ürünün allen **300** olduğu ve alkin **320** olamayacağını göstermiştir.

Çalışmanın ikinci kısmında, *endo*-karben **304** ara ürününün kararlılığı araştırılmıştır. Literatürdeki teorik ve deneysel sonuçlara göre, **264** nolu araürünün oluşumu sırasında, *ekzo*-karben **330** araürününün oluşamayacağı ve direk olarak bisiklik allene **264** izomerize olduğu gözlenmiştir. Bu noktada, daha önce literatürde tartışılmayan *endo*-siklopropilidenin **304** kararlılığı merak konusu olmuştur. Benzonorbornadienin (**301**) *ekzo* yüzü sırasıyla etil ve brom gruplarıyla korunmuştur. Öncelikle, *endo*-ürünün **302b** izole edimesi için bromflorkarbenin *anti*-7-etilbenzonorbornadiene katılması amaçlanmıştır. Fakat herhangi bir karben katılması gözlenememiştir. Teorik hesaplar, **301** nolu bileşiğin C-7 karbon atomu üzerine yerleştirilen etil grubu, metoksi türevinin aksine, çift bağlarda piramitleşmeye sebebiyet verdiğini göstermiştir. Sonuç olarak, artan gerilim enerjisi ve çift bağdaki deformasyon karben ekleme reaksiyonuna engel teşkil etmiştir. O zaman C-7 karbon atomu üzerine brom takılmıştır. Bromflorsiklopropanın **302a** furan eşliğinde MeLi ile muamelesi, allen **305a** araürününün oluşumunu doğrulayan **306a** nolu furan maddesini vermiştir. Teorik hesaplar, *ekzo*-karbenin **330** aksine, *endo*-karbenin **304a** serbest karben şeklinde optimize olabildiğini göstermiştir. Fakat oluşan *endo*-karbenin **304a** hızlı bir şekilde allene **305a** izomerize olduğu ve akabinde, furan **306a** maddesinin oluştuğu belirtilmiştir. Zaten, karbenin **304a** allene **305a** izomerize olması için gereken enerjinin 0.03 kcal/mol olduğu ve bunun da inzersiyon (araya girme) ya da başka katılma reaksiyonlarının oluşumunu engellediğini göstermiştir.

Anahtar Kelimeler: Allen, Bisiklik Allen, Karbenoid, Karben, Alfa-pinen, Doering-Moore-Skattebol Metod, β-Eliminasyon Metod, Benzonorbornadien, Piramitleşme, DFT Metod, Teorik Hesaplamalar.

To my wife Arife and my son Ömer Yiğit

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LIST OF ABBREVIATIONS

AM1	: Austin model 1
B3LYP	: Becke 3 parameter functional and Lee, Yang, Parr correlation functional
COSY	: Correlation spectroscopy
DEPT	: Distortionless enhancement by polarization transfer
DFT	: Density functional theory
DMSO	: Dimethylsulfoxide
DPIBF	: Diphenylisobenzofuran
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
KOBu*t*	: Potassium *tert*-butoxide
MCSCF	: Multi-configuration self-consistent field
MeLi	: Methyllithium
MNDO	: Modified neglect of diatomic overlap
MPn	: Moller Plesset
n-BuLi	: *n*-Butyllithium
NMR	: Nuclear magnetic resonance
ppm	: Parts per million
PTC	: Phase Transfer Catalyst
TS	: Transition structure
UV	: Ultra-violet

CHAPTER 1

INTRODUCTION

Many hydrocarbons are known whose molecules contain more than one double or triple bond. A hydrocarbon containing two double bonds is called dienes. The multiple bonds of polyunsaturated compounds are classified as being cumulated, conjugated, or isolated (*Figure 1*).

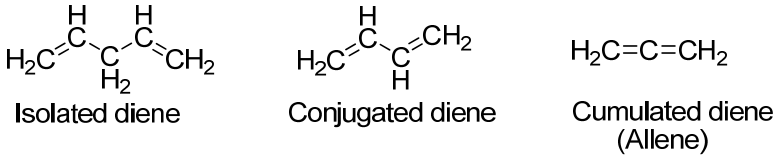


Figure 1: Diene classes

Isolated dienes have at least one sp^2-hybridized carbon atom, however they are independent each other. That is, between the two double bonds, there is at least one sp^3-hybridized carbon atom. The reactivity and stability of these compounds is similar to ordinary olefins. Conjugated dienes are the most stable dienes due to conjugation. They undergo not only classical 1,2-addition reaction, but also 1,4-addition reaction.

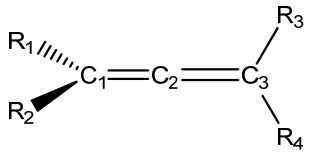


Figure 2: Allene structure

As shown in Figure 2, central carbon has sp hybridization and terminal carbons have sp^2 hybridization. R_1, R_2, C_1 and R_3, R_4, C_3 form two planes, which are orthogonal to each other. C_1-carbon atom forms a double bond with C_2-carbon atom, whereas C_2-carbon atom with C_3-carbon atom. These two π-bonds are perpendicular to each other. Therefore, allenes are not conjugated dienes; so they are called as cumulated dienes (*Figure 3)*.

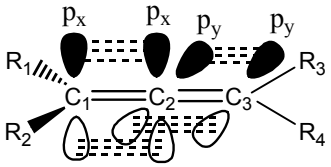


Figure 3: The geometry of allenic π bonds

Due to the high *s* character and linear geometry of the central atom, allenes have shorter π-bonds than olefins [3]. For instance, π-bond length is 1,33 Å for ethylene, whereas that of allene is between 1,309-1,312 Å [4]. These properties provide us to differantiate allenes from the other types of alkenes by spectroscopic analysis. For instance, in ^{13}C-NMR spectra, double bond carbons of olefins resonate between 120-140 ppm. On the other hand, central carbon of allenes resonates between 201-220 ppm [5]. Also for IR analysis, it is possible to see the differences such that, the vibration of π-bonds in olefins around 1650 cm^{-1}, however it is between 1900-2000 cm^{-1} in allenes [6,7].

When comparing the hydrogenation energies of isolated, conjugated and cumulated, it is observed that allenes have the highest energy [8].

1) isolated diene	(1,4-Pentadiene)	-60,79 kcal/mol
2) conjugated diene	(1,3-Butadiene)	-57,06 kcal/mol
3) allene	(1,2-Propadiene)	-71,28 kcal/mol

The hydrogenation energy of 1,4-pentadiene is twice more than a double bond (-30 kcal / mol) as expected. 3 kcal/mol increase in 1,3-butadiene arises from

the resonance of π bonds. In contrast, 1,2-propadiene has an excess of 11 kcal/mol approximately.

Although the parent allene does not have any chiral carbon atom, when different substituents are introduced to terminal carbon atoms, it becomes optically active (*Figure 4)*. Having two planes, which are orthogonal, causes them to be optically active [9-10]. In Figure 4, it is obvious that, the molecule gains enantiomerism due to the mirror image and they are superimposable.

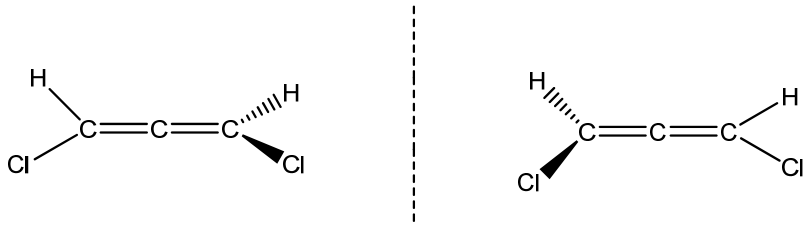


Figure 4: Two enantiomeric forms of 1,3-dichloropropadiene.

Linear allenes are inherently not "strained". So they are present in nature. The first authentic naturally occuring allene, the antibiotic *mycomycin (Figure 5)*, was characterized in 1952 by Celmer and Solomons, which is a kind of a fungal metabolite [11].

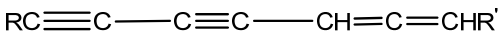


Figure 5: General structure of mycomcin

Other types of allenes undoubtedly occur in higher organisms, examples reported recently include *fucoxanthin*, a carotenoid pigment of Brown algae (*Figure 6)* [12].

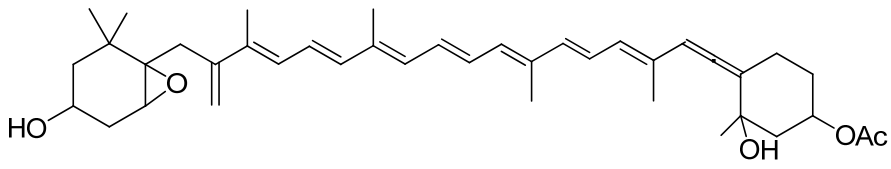


Figure 6: Structure of fucoxanthin

The optically active cumulenes are also present in nature such as two bromoallenic aliphatic fatty acids; the anaspidean mollusk *Aplysia dactylomela* and from the red algae *Laurencia obtuse* (*Figure 7*) [13].

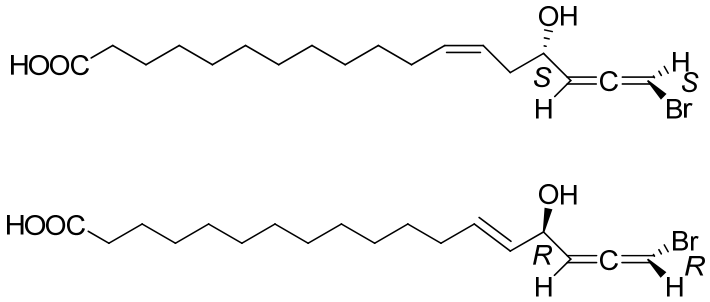


Figure 7: Chiral two bromoallenic aliphatic fatty acids

1.1 STRAINED CYCLIC ALLENES

Chemists have always been fascinated by the cumulated diene system of allenes with its extraordinary properties, such as the axial chirality of the elongated tetrahedron and a higher reactivity than non-cumulated C-C double bonds [14]. Although the development of synthetic methodologies directed towards the synthesis of allenes has been confined to the last three decades with the few pioneering efforts being scattered across the first of these decades, the past sliver of this century provides enough evidence that allenes contunious to entertain scientists in laboratories around the world in good numbers. Johnson [15], Balcı and Taşkesenligil [16] comprehensively reviewed this field in two separate reports. Christl and colleagues have updated this survey in a companion to another account [14].

Linear allenes are not inherently “strained”. Strain implies some deviation from an ideal bonding geometry; this is not true for compounds, which contain ordinary sp^2-hybridized carbons. Nevertheless, the electronic structure of cumulenes, their ability to form stabilized intermediates does render them highly reactive; many allenes dimerize easily. The strain in cyclic allenes arises from the deformation of linear geometry, that is, the deformation of C=C=C angle. The equilibrium geometry

for allene is linear with orthogonal pairs of substituents. Ring constraints bend the allene and exert torsion toward a planar arrangement of ligands.

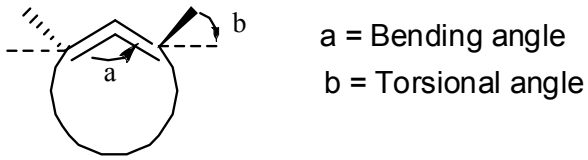


Figure 8: Bending and torsional angles in cycloallenes

The bending and torsion angles in cyclic allenes make them unisolable and highly reactive intermediates *(Figure 8)*. The synthesis of cyclic allenes having eight or less carbon atoms in their skeletons, known as highly strained organic compounds, has for the past decades attracted increasing interest [14-16]. Besides for synthesis, theoretical chemists have been keen on investigating them in order to obtain insight into their structural properties and unusual physical properties [17]. They are nonplanar, chiral allenes rather than planar zwitterionic or carbene-like species, even in the case of the highly strained cyclohexa-1,2-diene (**4**) and cyclohepta-1,2-diene (**3**) [18].

Model semi empirical and ab initio [15,16a] molecular orbital calculations show that the bending potential is remarkably soft for the first 20º, resulting in only ca. 4 kcal/mol estimated strain, but rises steeply beyond this. Moreover, calculations show that bending and torsion are coupled motions; optimized structures for artificially bent allene show the hydrogens twisted toward planarity. In bent allenes, the majority of strain derives from the weakened π bonds. Bending also destroys the degeneracy of π and π^* orbitals; correlation with orbitals of planar allene.

Molecular models readily demonstrate that rings of ten or more carbons will accommodate an allene without geometric deformation and its concomitant strain. In rings of nine or fewer, there should be increasing strain, as the allene bends. Eventually the allene may be forced to planarity, although it is not yet known for what ring size this occurs.

Predicted bending angles and out of plane torsional angles from MNDO calculations are summarized below *(Figure 9).*

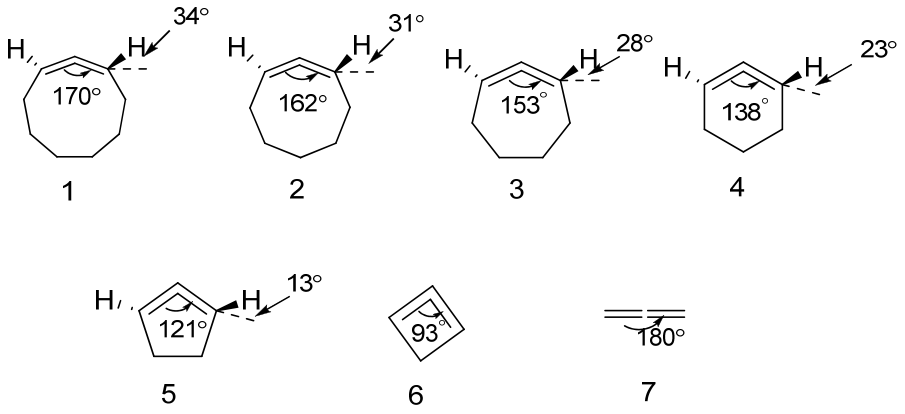


Figure 9: Predicted angles by using MNDO method

In smaller cyclic allenes, ring constraints must increase bending, torsion, and strain. Crude strain estimates of 30, 20, 15, and 10 kcal/mol for five to eight membered ring allenes, respectively [15,16a]. Because bent, planar allene should be unstrained by ring constraints, the maximum strain that might be accommodated by an allene unit must be 46 kcal/mol, which corresponds to the ground state rotational barrier.

Most recently, Johnson *et al.* [16b] has estimated the strain for small-ring cyclic allenes. They have used isodemic and homodesmic equation to estimate strain for the homologous series of cyclic allenes. For the cyclic allene series, estimates for allene functional group strain include: 1,2-cyclobutadiene (**6**), 65(kcal/mol); 1,2-cyclopentadiene (**5**), 51 (kcal/mol); 1,2-cyclohexadiene (**4**), 32 (kcal/mol); 1,2-cycloheptadiene (**3**), 14 (kcal/mol); 1,2-cyclooctadiene (**2**), 5 (kcal/mol); 1,2-cyclononadiene (**1**), 2 (kcal/mol).

After given the brief information about theoretical calculations in bending, torsion and strain energy of cyclic allenes, what about the experimental studies in cyclic allenes up to now?

Due to the linear arrangement of the carbon atoms and the orthogonal disposition of the bonding planes of the termini relative to each other in the equilibrium geometry, the three carbon atoms of an allene moiety can be accommodated without strain only in rings of at least 10 carbon atoms *(Figure 10)* [15]. Thus, 1,2-cyclodecadiene (**8**) should behave as a non-cyclic 1,3-dialkylallene. The strain is still not significant in 1,2-cyclononadiene (**1**), because it is stable at room temperature and dimerizes only heating at temperatures above 100 ºC [19]. In contrast, 1,2-cyclooctadiene (**2**) can not be isolated owing to its rapid dimerization at room temperature [20,21]. However, NMR spectra of **2** [22] and 1,2,5-cyclooctatriene (**9**) [23] were obtained at low temperatures. However, this was not possible with cyclic allenes containing less than eight carbon atoms, except for 1,2,4,6-cycloheptatetraene (**10**) in carcerated in a molecular container [24].

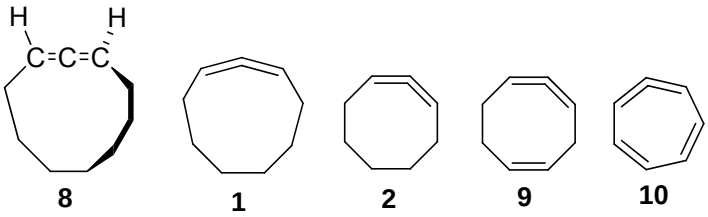


Figure 10: A selection of cyclic cumulenes I

However, if the ring size is decreased, the linear perpendicular allene will be twisted and bent until, at same point, the energy by π-bonding in the two double bonds will be insufficient to offset the increased strain. Morover, ring constraints will exert torsion toward a planar arrangement of ligands. Therefore, one of the fundamental questions is the influence of ring size on the barrier to π-bond rotation.

Cyclohepta-1,2-diene (**3**) and its derivatives have been generated and chemically trapped [20]. Balci and Jones [18] provided evidence for the allenic structure by isolation of optically active cycloadducts. Considerable controversy has arisen over the structure of cyclohexa-1,2-diene (**4**) *(Figure 11).*

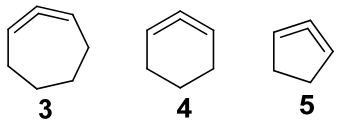
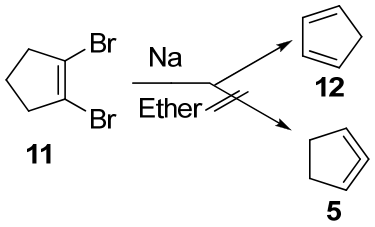


Figure 11: A selection of cyclic cumulenes II

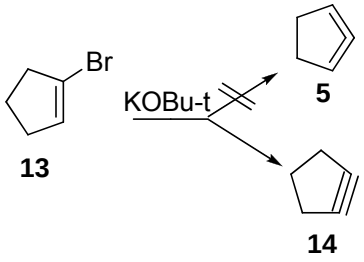
1.1.1 Five-Membered-Ring Allenes

A number of attempts to generate cyclopenta-1,2-diene (**5**), or one of its derivatives have been summarized by Balcı *et al.* [16]. The first study for the synthesis of **5** was done by Favorskii in 1935 [25]. He isolated 1,3-cyclopentadiene (**12**) instead of allene **5** by treating 1,2-dibromocyclopentene (**11**) with sodium (*Scheme 1*).



Scheme 1

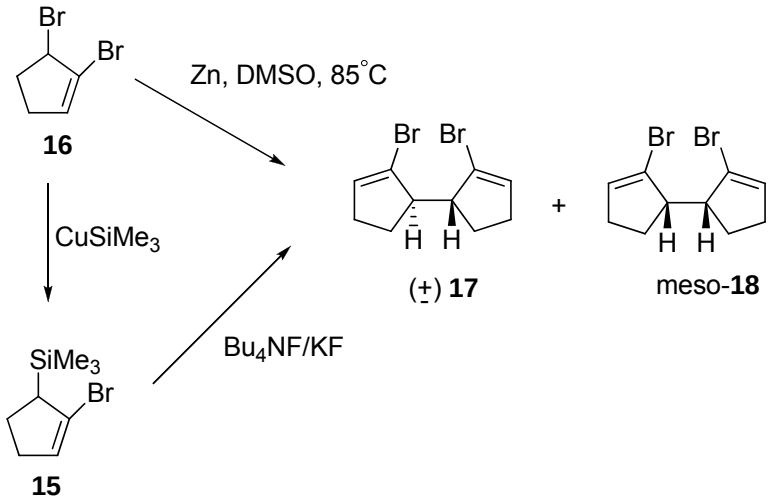
Dehydrohalogenation of 1-bromocyclopentene (**13**) gave no more result except the formation of cyclopentyne (**14**) (*Scheme 2*).



Scheme 2

Recently, Ceylan *et al.* [26,27] have applied fluoride ion-promoted elimination of a β-halogenosilane to **15** and zinc-catalyzed elimination to **16** to generate the higly strained cyclopenta-1,2-diene (**5**) (*Scheme 3*). Reaction of **15** with

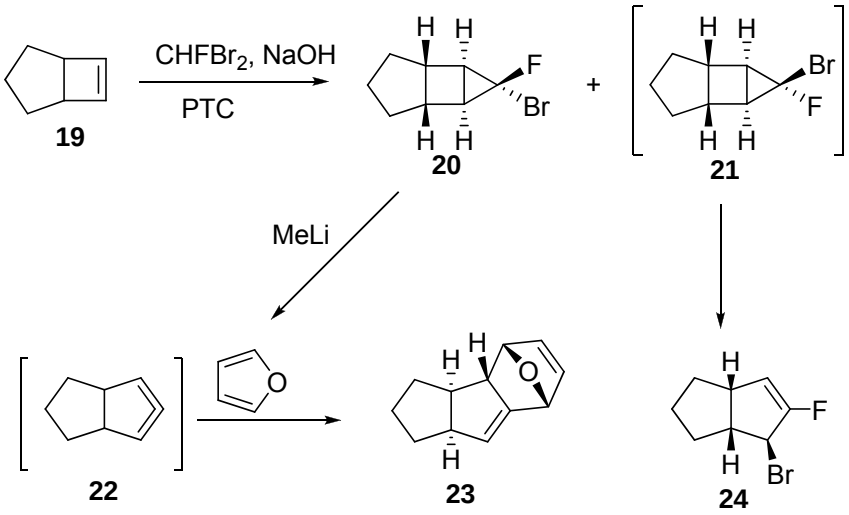
Bu_4NF and KF under different conditions resulted in the formation of two isomeric Wurtz-like condensation products **17** and **18**. On the other hand, treatment of **16** with activated zinc again gave the same isomeric mixture of **17** and **18** instead of cyclopenta-1,2-diene (**5**). So far cyclopenta-1,2-diene (**5**) still remains as an elusive compound.



Scheme 3

Only the application of the Doering-Moore-Skattebøl (DMS) reaction, probably the most general procedure for synthesizing allenes [28], led to the first liberation of a derivative **5**, that is bicycle[3.3.0]octa-2,3-diene (**22**) *(Scheme 4)* [29]. Since dichloro- and dibromocarbene adducts of cyclobutene and its derivatives are unstable and rearrange to 2,3-dihalocyclopentenes even under the conditions of their preparation [30-33], bicyclohept-6-ene (**19**) as treated with bromofluorocarbene [28]. The addition proceeded from the *exo*-face of **19** with formation of the diastereomeric products **20** and **21**.

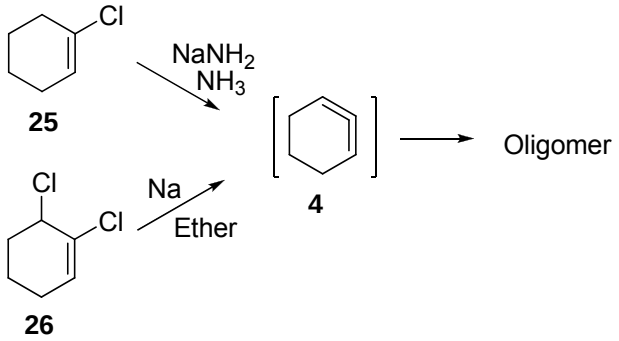
The treatment of **20** with alkyllithium in the presence of furan gave rise to the tetracyclic product **23**, which is obviously a [4+2]-cycloadduct of furan to the 1,2-cyclopentadiene derivative **22** [28].



Scheme 4

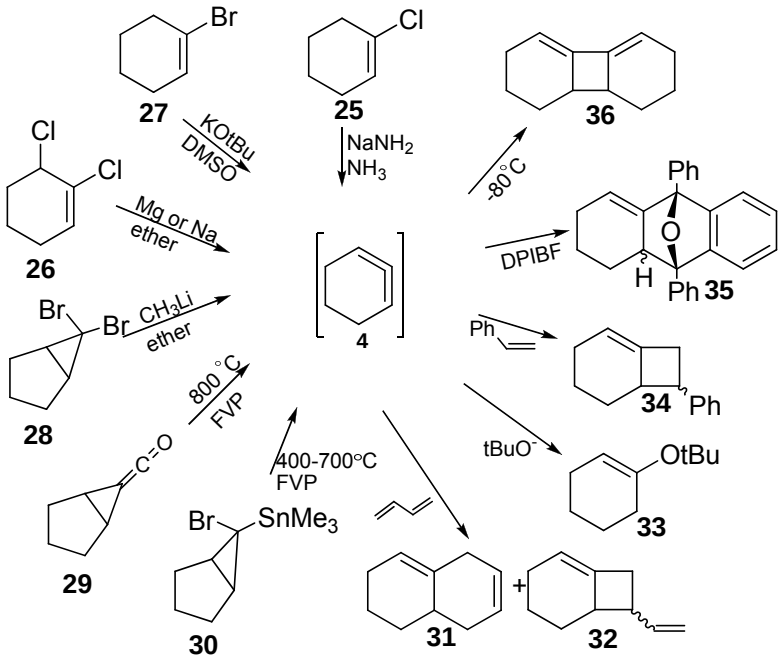
1.1.2 Six-Membered-Ring Allenes

An enormous amount of work has been dedicated to six-membered cyclic allenes. Firstly, Favorskii *et al.* tried to synthesize unsubstituted cyclohexa-1,2-diene (**4**) in 1935 [25]. They claimed that dehalogenation of 1-chlorocyclohexene (**25**) and dichloro derivative **26** forms a non-volatile oligomer [34] and the intermediate in these two reactions is cyclohexa-1,2-diene **4** *(Scheme 5).*



Scheme 5

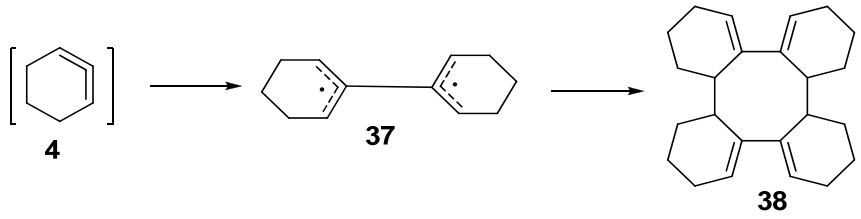
Johnson reviewed that there are much more synthetic methods leading to **4**, and some of them are summarized below [15] *(Scheme 6)*.



Scheme 6

The formation of cyclohexa-1,2-diene (**4**) was shown by Wittig and Fritge [35] in 1966 for the first time. Dehydrobromination of 1-bromocyclohexene (**27**) with a base gave [2+2] dimerization product **36** in 17% yield, and the intermediate in the reaction was also trapped with diphenylbenzoisofurane (DPIBF) which clearly indicates the formation of cyclohexa-1,2-diene (**4**) [36,37].

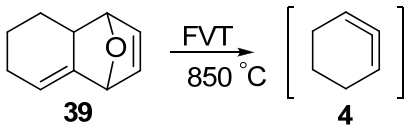
In the known routes to **4**, the most efficient method is the reaction of 6,6-dibromobicyclo[3.1.0] hexane (**28**) with methyl lithium, a reaction first reported by Moore and Moser [38]. Trapping by [2+2] cycloaddition with styrene was investigated. The same authors also reported that, allene **4** yields mostly two stereoisomeric tetramers **38** at -80 ºC (61%), probably formed by dimerization of bisallyl intermediate **37** *(Scheme 7).* At 35 ºC, the major product was crystalline dimer **36** 55% yield.



Scheme 7

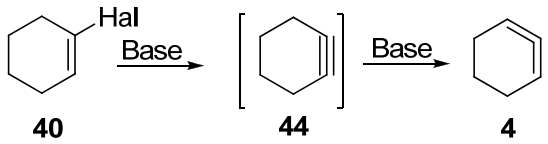
Johnson and Shakespeare [39] described a new synthetic approach to cyclic allenes **4**. Dehydrobromination of 1-bromocyclohexene (**27**) with KO*t*Bu leading to the allene intermediate **4** was also trapped with DPBIF to give two stereoisomeric cycloadducts (**35**). Additionally, Bottini *et al.* [39] provided evidence against cyclohexyne (**44**) intermediate in these reactions with the labelling studies. They also trapped the allene **4** with other reactive dienes like 2,4-hexadiene, 1,3-cyclohexadiene, 2,3-dimethylbutadiene, *cis*-pentadiene, furan and 2-methylfuran. They compared their relative reactivities to cyclohexa-1,2-diene (**4**) at 60 ºC and found 0.17, 1.85, 1.00, 47, 0.17, 0.12, respectively [40].

Werstiuk *et al*. [41] observed **4** by means of ultraviolet photoelectron spectroscopy as product of the flash vacuum thermolysis (FVT) at of **39** 850 ºC, the [4+2]-cycloadduct of furan to **4** [40]. The first two vertical ionization energies were measured to be 8.4 and 10.4 eV and agree well with the calculated values [41]. Possibly this is the only study providing direct experimental data for **4**, although two further papers claimed to do so *(Scheme 8).*



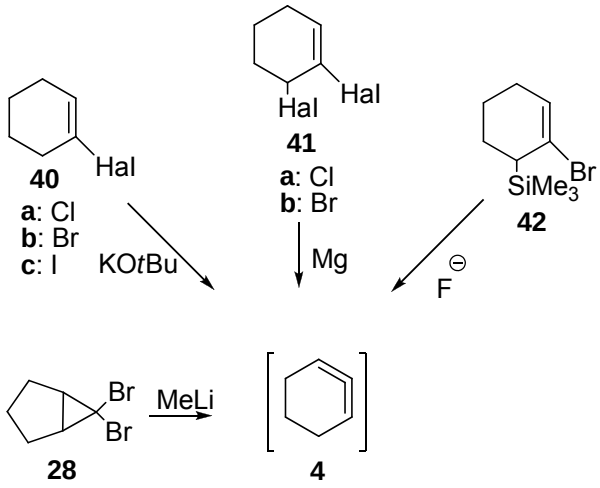
Scheme 8

Considering the reaction of 1-halocyclohexenes (**40**) with a strong base, the question arises, which intermediate (cyclohexa-1,2-diene (**4**) or cyclohexyne (**44**)) is preferentially formed. The trapped allene **4** may also be formed by the initial formation of alkyne (**44**) followed by base-catalysed rearrangement *(Scheme 9)*.



Scheme 9

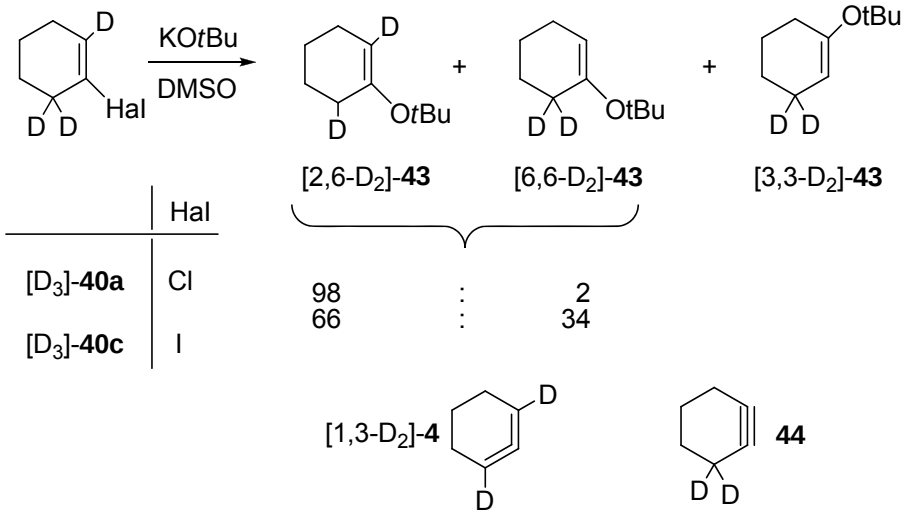
In the case of the cyclo adducts **35** of DBIBF, it was proved, however, that they do not result via the adduct of cyclohexyne [34,35]. The general problem was systematically investigated by trapping the intermediates by nucleophiles. Also methyl derivatives of **40** were utilized, in recently published articles [34-35]. It turned out that relative rates of elimination leading to **4**, and the cyclohexyne (**44**) depend on the kind of halogen in **40**, the base and also solvent. The attack of the nucleophile at the central allene carbon atom of **4** is highly characteristic, giving rise to an allyl anion derivative, from which the isolated products are formed *(Scheme 10).*



Scheme 10

Caubère *et al.* [41,42] treated **40a** with sodium amide-sodium *tert*-butoxide ($NaNH_2$-NaO*t*Bu) in tetrahydrofuran (THF) in the presence of secondary amines and obtained enamines. Analogously, the corresponding thioenol ethers were formed from **40a** and sodium amide-sodium thiolate in the presence or absence of NaO*t*Bu.

It was shown, however, that cyclohexyne (**44**) rather than **4** is the decisive intermediate route to the enamines as well as the thioenol ethers [41,42]. As already mentioned above, the enol ether **43** arises inter alia from **40b** and KO*t*Bu in DMSO. The highest yield (47%) was obtained in refluxing THF *(Scheme 11)* [39].

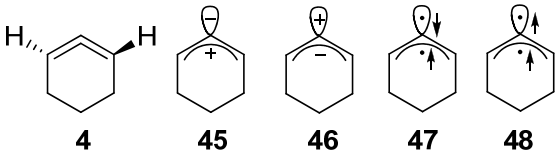


Scheme 11

The mechanism of this substitution was scrutinized by treatment of 2,6,6-trideutero-1-chloro ([D_3]-**40a**) and 1-iodocyclohexene ([D_3]-**40c**) with KO*t*Bu in DMSO. In the case of [D_3]-**40a**, the products [2,6-D_2]-**43** and [6,6-D_2]-**43**, which bear the functional group at the same carbon atom as the substrate, on one side and [3,3-D_2]-**43** on the other resulted in a ratio of 98:2, whereas when using of [D_3]-**40c** this ratio was 66:34. These findings allow the conclusion that the intermediates [1,3-D_2]-**4** and [3,3-D_2]-cyclohexyne (**44**), determining the products, emerge from [D_3]-**40a** and [D_3]-**40c** in ratios of 96:4 and 32:68, respectively. In **40**, a chlorine atom clearly favors the generation of **4** whereas a bromine and an iodine atom in this order increasingly cause the formation of cyclohexyne (**44**). Among the solvents, DMSO promotes the route to **4** better THF and diglyme [39].

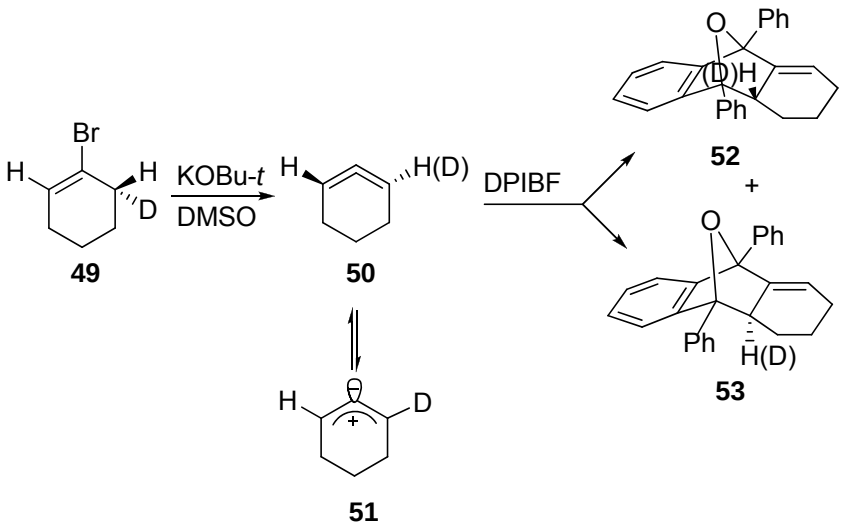
Actually, there has been much more debates for the structure of cyclohexa-1,2-diene (**4**), in part because of some misunderstandable suggestions about the structure of planar allene. Bottini *et al.* [39] claimed initial formation of a bent, twisted allene which rapidly isomerizes to the diradical **47** that is the active agent in

both [2+2] and [2+4] cycloaddition reactions [40]. Moore and Moser [38] and Greenberg and Liebman [43] proposed zwitterion **45** for cyclohexa-1,2-diene (**4**) and this finding was supported with INDO semiemprical calculations by Dilon and Underwood *(Scheme 12)* [44].



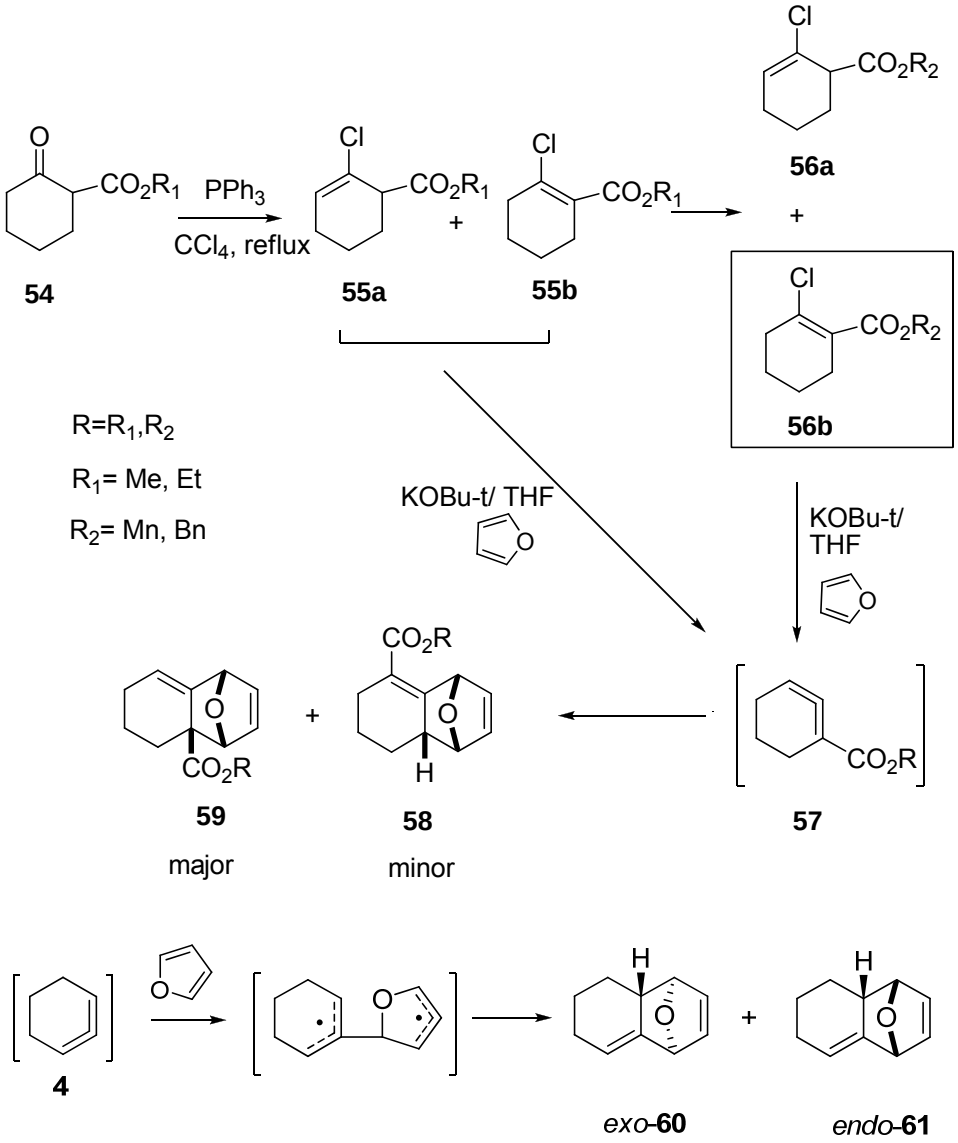
Scheme 12

On the other hand, Balci and Jones have reported the dehydrohalogenation of optically active 1-bromo-6-deuteriocyclohexene (**49**) and trapped allene **50** with DPIBF. The resulting products, **52** and **53**, were optically active and having nonplanar structures [18b,18c]. Evidently, this pioneering case showed a principle which was thereby established that allene **50** is chiral meaning that it has a single structure. It was further suggested that at around 80 ^{o}C, conversion of the nonplanar form of cyclohexa-1,2-diene to a symmetrical isomer (presumably **51**) competes with its reaction with the allene trap. The chirality of cyclohexa-1,2-diene (**4**) was also supported with MCSCF calculations *(Scheme 13)* [15,16].



Scheme 13

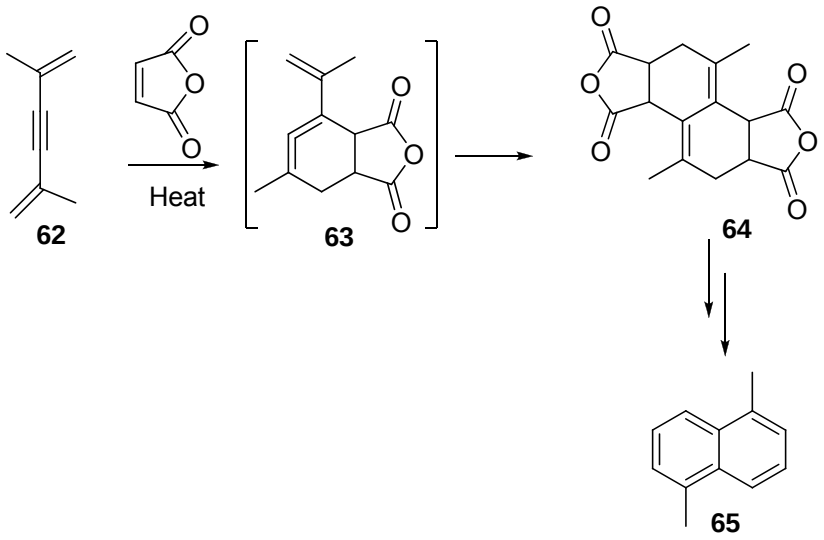
Tolbert *et al*. proposed mechanism convincing theoretical evidence that even [4+2] cycloadducts of cyclohexa-1,2-diene (**4**) with conjugated dienes such as furan proceed in two steps via a diradical intermediate *(Scheme 14)* [45].



Scheme 14

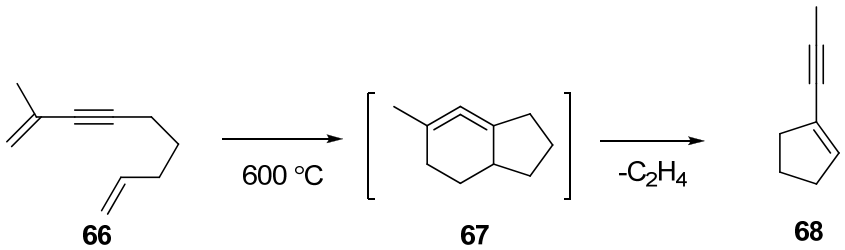
The formal [4+2] cycloaddition of conjugated enynes to alkenes, sometimes called a 'dehydro' Diels-Alder reaction, leads to 1,2-cyclohexadiene (**4**) and derivatives thereof. Such processes take place if the product is able to undergo a reaction that provides a stable compound. Miller *et al.* [46,47] quoted a number of such cycloadditons recently and revisited two examples from the 1930s and 1940s.

They showed that the acetylene subunit is changed initially in the acid-catalyzed process and hence derivatives of 1,2-cyclohexadiene can not be an intermediates. Neverthless, the reaction of a divinylacetylene with 2 equivalents of a typical dienophile is best described in terms of two consecutive concerted [4+2] cycloaddition. This type of reaction was discovered by Butz *et al*. [48a] in 1940s and supported by further examples in later years [48b-f]. They studied the double cycloaddition of maleic anhydride to dienyne **62**, and appear to be the first to have suggested an intermediate 1,2-cyclohexadiene derivative **63** *(Scheme 15).*



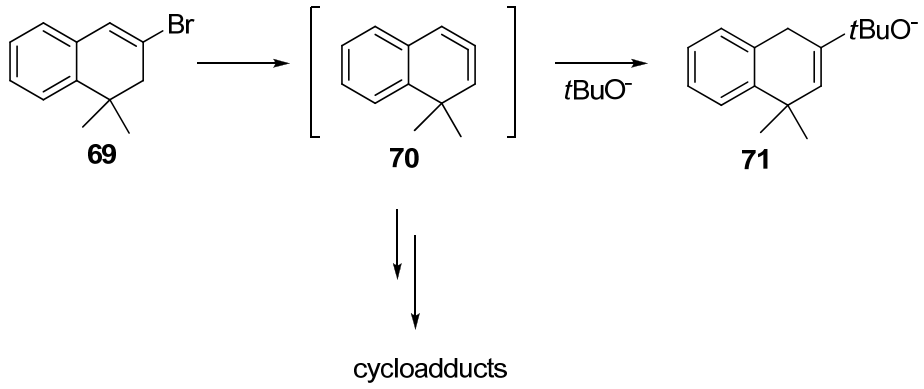
Scheme 15

Johnson *et al.* [49], have shown by the gas-phase pyrolysis of 2-methylnona-1,8-dien-3-yne (**66**) *(Scheme 16)* that the intramolecular [4+2] cycloaddition can be enforced. The resulting 1,2-cyclohexadiene **67** was subject to a retrograde 'dehydro' Diels-Alder reaction giving rise to the propynlcyclopentene **68** and ethylene.



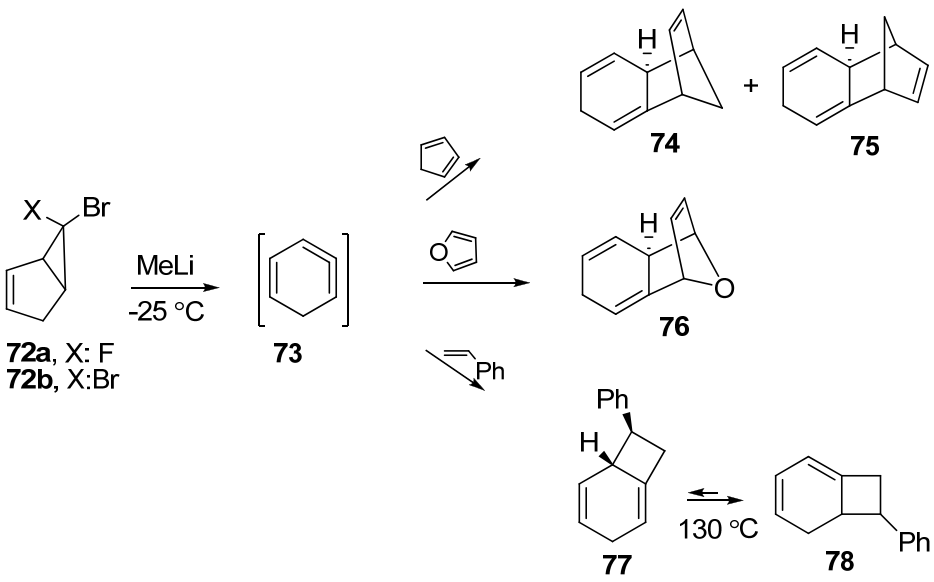
Scheme 16

The first known example of a 1,2,4-cyclohexatriene was recently published by Miller *et al.*, who pointed out this as an "isoaromatic" molecule [50]. Dehydrobromination of **69** in the presence of diphenylisobenzofuran afforded two cycloadducts, which appear to result from an allene **70** *(Scheme 17).*



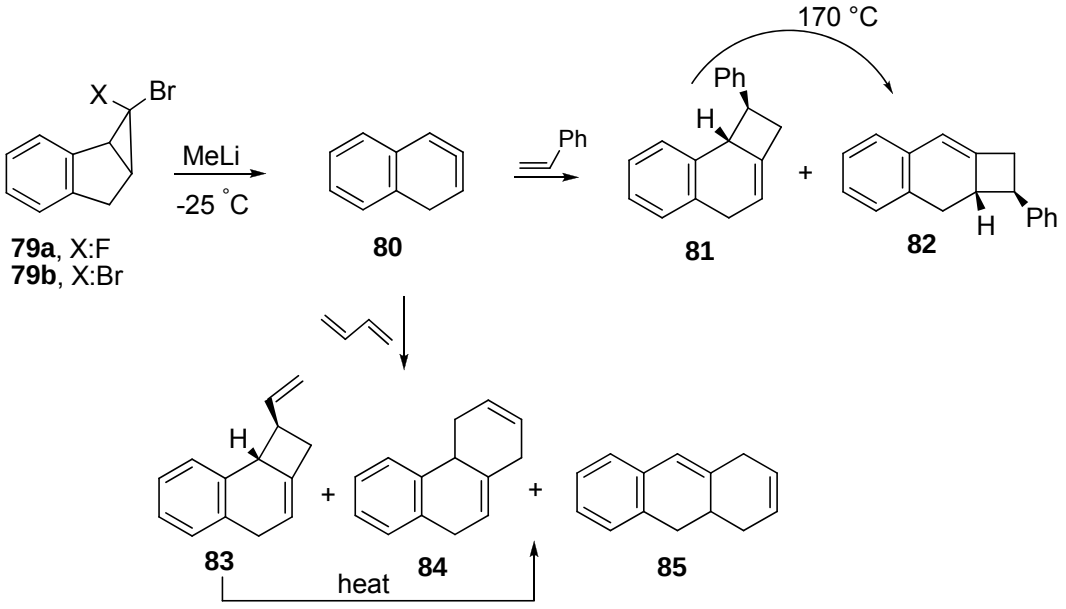
Scheme 17

Recently, Christl *et al.* [51a] have described cyclohexa-1,2,4-triene (**73**) and its benzo derivative (**139**) for the first time using the Doering-Moore-Skattebøl method starting from **72** and **79**, respectively. They proved its existence chemically by means of trapping reactions *(Scheme 18).*



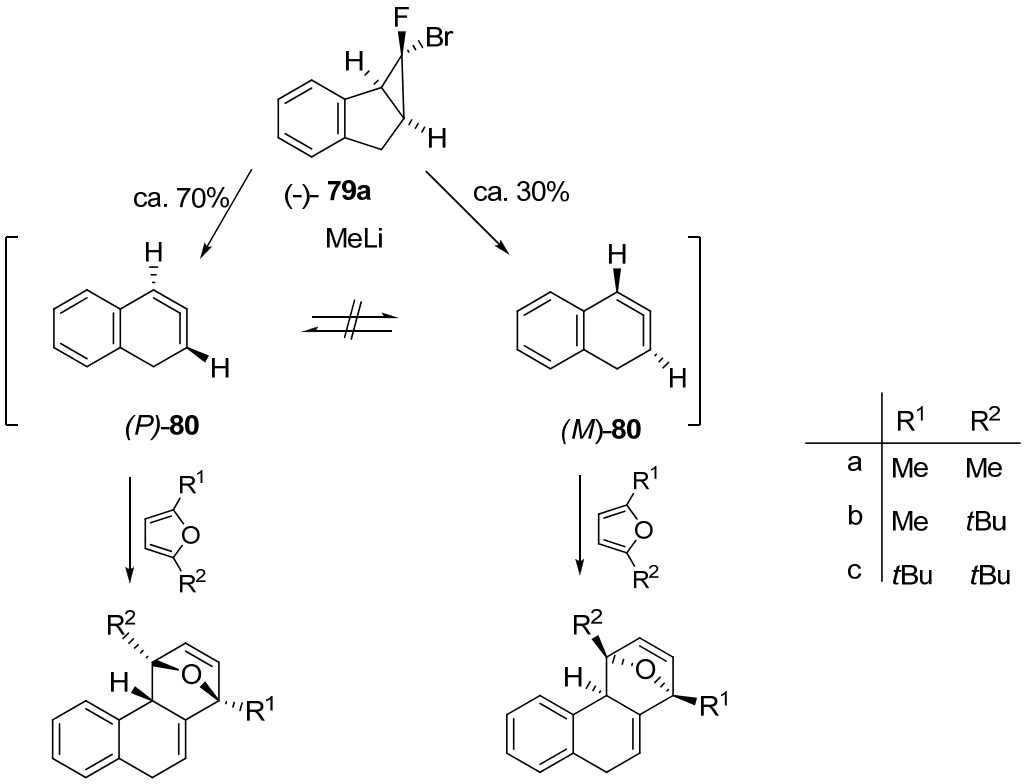
Scheme 18

Besides the trapping products, some isomerization products were also observed. For example, the kinetically controlled products **77** and **81** formed with high selectivity isomerized at high temperatures to the thermodynamically more stable compound **78** and **82** respectively [51a] *(Scheme 19).*



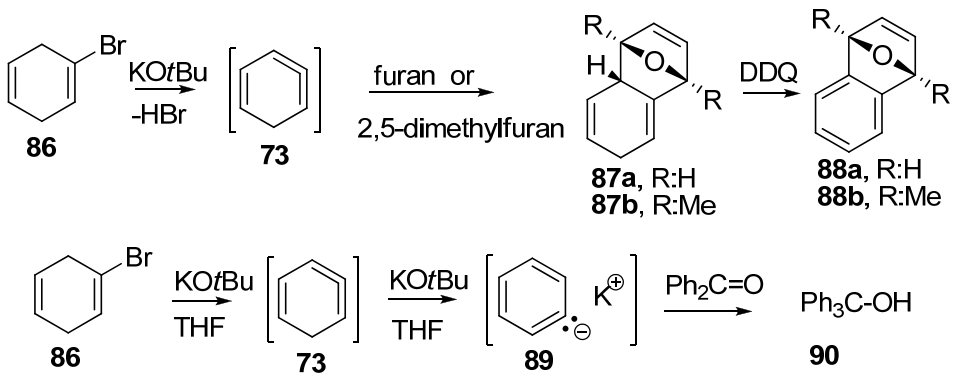
Scheme 19

Most recently Christl *et al*. [51b] have synthesized enantiomerically pure precursor of a six-membered cyclic allene 'isonaphthalene' for the first time. The treatment of (-)-**79a**, dissolved in 2,5-dimethyl-2-tert-butyl-5-methyl-, or 2,5-bis(tert butyl) furan, with methyllithium gave rise to the [4+2] cycloadducts of **80**. They showed that six-membered cyclic allene **80** is a chiral molecule *(Scheme 20).*



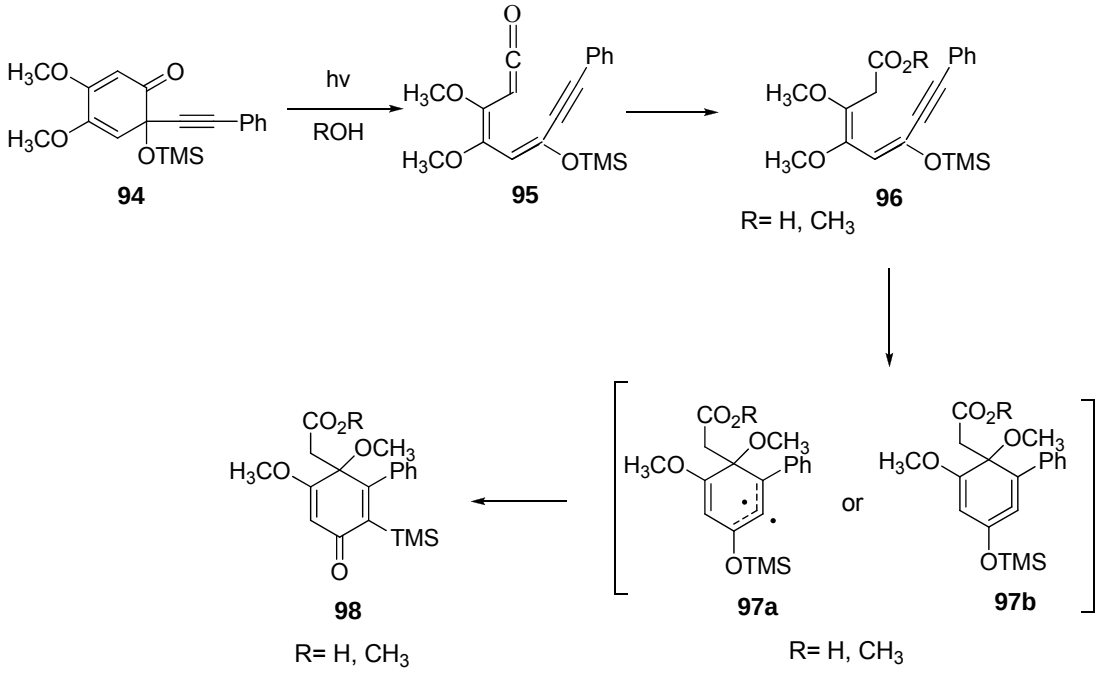
Scheme 20

Christl *et al.* [52] have also trapped the intermediate cyclohexa-1,2,4-triene (**73**), generated by dehydrohalogenation of **86**, with a base, with furan to form [4+2] cycloaddition products **87** and **88** respectively. They have used benzophenone whether allene was an intermediate or not. They have proved that, phenyl anion **89** formed by deprotonation of **73** added to the carbonyl group of benzophenone to form triphenylmethanol *(Scheme 21).*



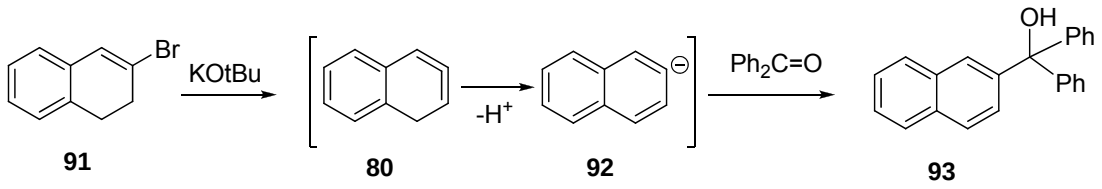
Scheme 21

Zertuche *et al.* [54] have reported the photolysis of **94** that involves the electrocyclic ring opening. This process generates ketene **95**, which is immediately captured by nucleophilic species present in the reaction media to give dienyne **96**. They have demonstrated using HF and MP2 ab initio calculations that the electrocyclization of **96** can generate intermediates that can be best described as the cyclic allene **97** *(Scheme 22)*.



Scheme 22

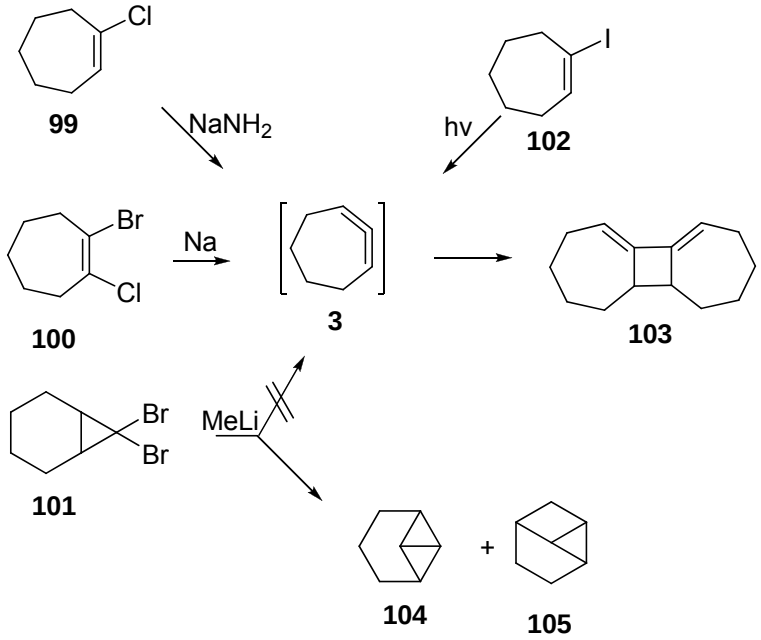
More recently, Christl *et al.* [53] have applied β-elimination reaction to generate the isonaphthalene intermediate (**80**) by treating 3-bromo-1,2-dihydronaphthalene (**91**) with KO*t*Bu. The outcome of this reaction is rationalized by the elimination of HBr from **91** by assuming with formation of the desired intermediate (**80**). Interestingly, the intermediacy of the naphtha-2-yl anion (**92**), which was trapped by benzophenone to form the tertiary alcohol (**93**), emerged from the deprotonation of **91**. This route is shown briefly in Scheme 23.



Scheme 23

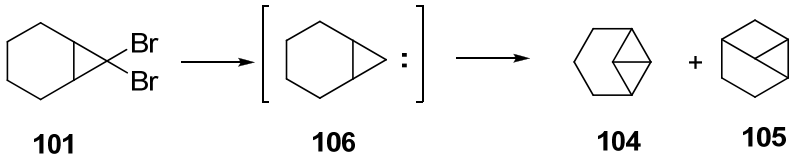
1.1.3 Seven-Membered-Ring Allenes

In 1936, Favorskii [25,55] tried to synthesize a distillable hydrocarbon by treating 1-bromo-2-chlorocycloheptene (**100**)with Na in ether, and claimed that it was cyclohepta-1,2-diene (**3**) *(Scheme 24)*, this result remained unchallenged until 1961 . When Ball and Landor [20] isolated dimer **103** from dehydrohalogenation of 1-chlorocycloheptene (**99**), it was realized that the hydrocarbon suggested by Faworskii was the same dimer. Consequently, it was proved that cyclohepta-1,2-diene (**3**) is so reactive to be isolated, or even to be observed spectroscopically [18c,35]. One other approach to synthesize **3** has been photolysis of vinyl iodide **102**, a reaction reported recently by Kropp [56]. There exist some numerous routes for preparing allene **3** as intermediate some of which are summarized in *(Scheme 24).*



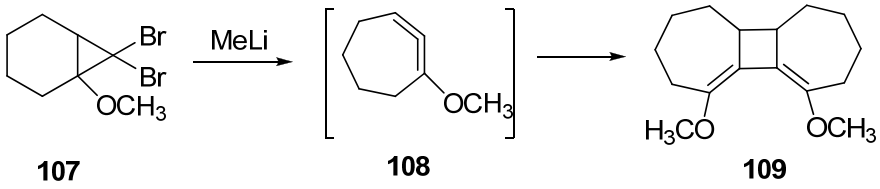
Scheme 24

Cyclohepta-1,2-diene (**3**) can easily be isolated by β-elimination method, however paradoxically, Doering-Moore-Skattebøl method did not work by the reaction of dibromonorcarane (**101**) with MeLi to form **3**. However, the insertion products **104** and **105** were formed instead of **3**. Köbrich and Goyert [57] claimed that, a carbenoid structure of free carbene was assumed to be involved as the intermediate in the formation of those insertion products. Morover, DFT calculations by Schleyer *et al*. have shown that the ring opening of **106** to **3** has unusually high activation energy barrier of 14.6 kcal/mol due to the unfavourable conformational changes in the cyclohexane moiety of **106** during the reaction [58]. However, activation barriers for intramolecular CH-insertions were found to be 6.4 and 9.1 kcal/mol, respectively *(Scheme 25)*.



Scheme 25

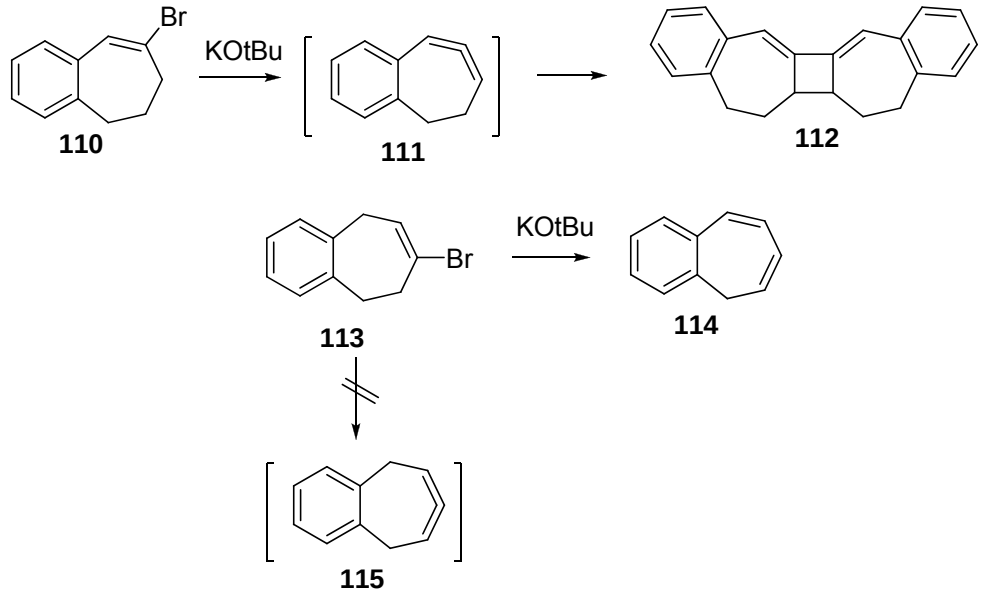
Interestingly, when the same method was applied for methoxy derivative **107**, dimer **109** was isolated in 85% yield *(Scheme 26)*. Later on, substituent effects on carbene-carbenoid-allene rearrangement will be discussed in details.



Scheme 26

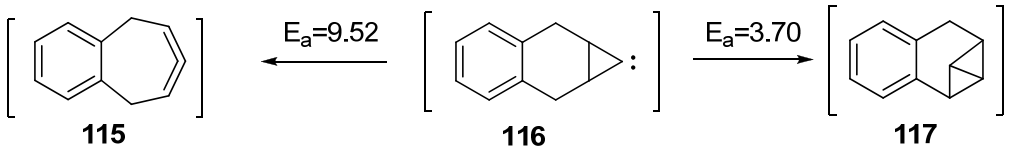
Due to the inexplicity of Doering-Moore-Skattebøl approach for the synthesis of a seven-membered-ring allene, Balci *et al*. [59] applied the base-catalyzed elimination method using the appropriate vinylcycloalkenes, **110** and **113**, to generate the benzo-annulated seven-membered-ring allenes, **111** and **115**. Although they succeeded in isolating the dimer **112**, confirming the formation of cycloallene

111, the reaction of **113** with base gave the hydrocarbon **114**, instead of the expected allene **115**. Some of the derivatives of **111** were also reported in the literature [60]. However, the synthesis of **115** has not been achieved before *(Scheme 27).*



Scheme 27

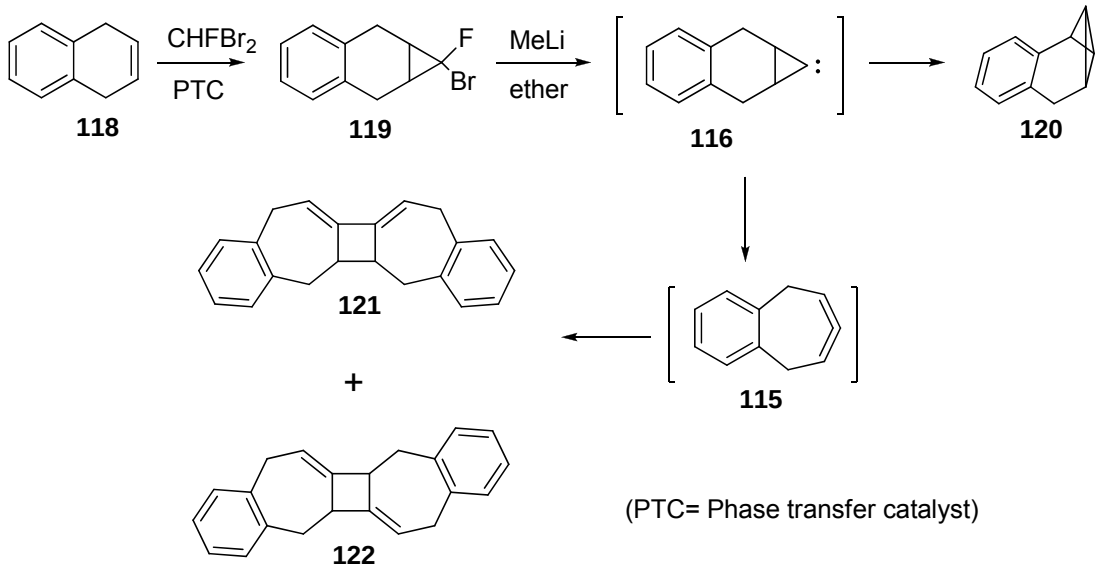
Most recently, Azizoğlu *et al*. [61] have performed density functional theory (DFT) calculations to answer the question 'why the Doering-Moore-Skattebøl approach fail to provide the symmetrical allene **115** *(Scheme 28).*



Scheme 28

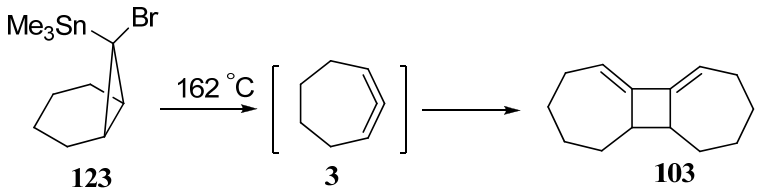
Theoretical calculations showed that, insertion product **117** as well as allene **115** can be generated when Doering-Moore-Skattebøl route is applied to generate **115**. After the explicability of this approach shown by computational methods, they planned to generate seven-membered-ring allene **115** by experimentally. Addition of fluorobromocarbene to 1,4-dihydronaphthalene **118** afforded the expected addition product **119**. The reaction **119** with methyllithium gave not only the insertion product

120, but also two dimeric products arising from the initially formed allene intermediate **115** *(Scheme 29).*



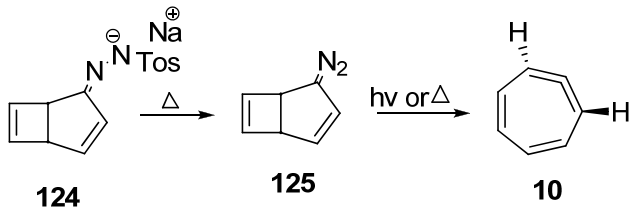
Scheme 29

High temperature thermolysis of *exo(endo)*-7-bromo-7-(trimethylstannyl)-bicyclo [4.1.0]heptane **123** [16a] in benzene (162 ºC) afforded the cyclohepta-1,2-diene dimer **103**. The mechanism of this reaction was established by running the reaction in different solvents and the involvement of a free carbene was postulated as the precursor for allene formation *(Scheme 30).*



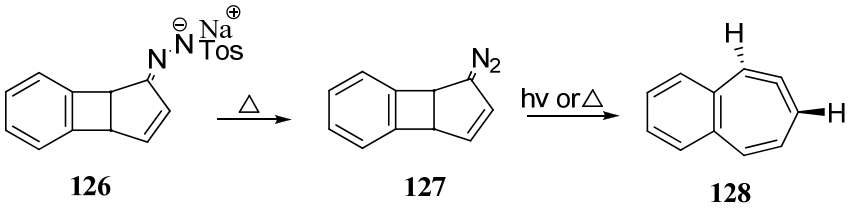
Scheme 30

Chapman and Abelt [62] have used diazo precursor **124** to generate the parent cyclohepta-1,2,4,6-tetraene **10** *(Scheme 31).*



Scheme 31

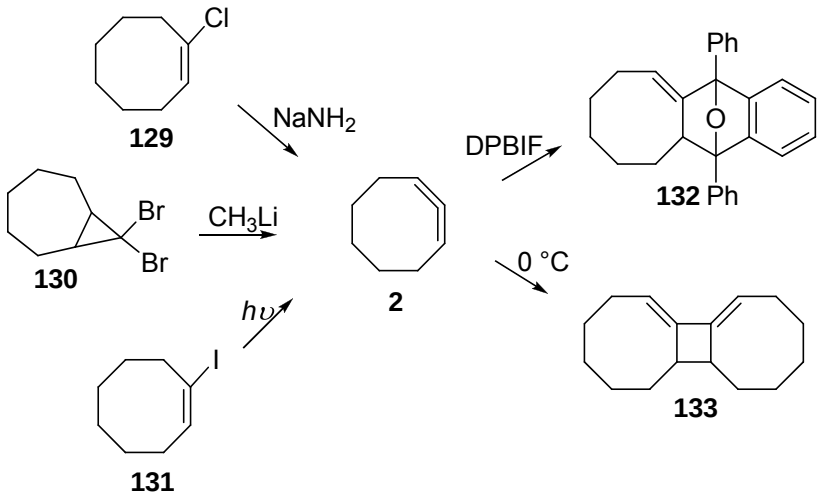
In a recent matrix isolation study McMahon *et al.* [63] have reported the generation, spectroscopic characterization, photochemical and thermal reactivity of 4,5-benzocyclohepta-1,2,4,6-tetraene **128** *(Scheme 32).*



Scheme 32

1.1.4 Eight-Membered-Ring Allenes

Ball and Landor [20a] first synthesized cycloocta-1,2-diene (**2**) in 1961. Allen dimer **133** is isolated from the dehydrohalogenation of 1-chlorocyclooctene (**129**). Wittig [35] has trapped allene **2** with DPIBF by the same methodology. Marquis and Gardner [64] have applied carbenoid method for the synthesis of **2**; dibromocarbene addition product **130** was treated with MeLi and converted to allene **2**. Kropp [56] has suggested that the photolysis of 1-iodocyclooctene **131** in methanol would yield **2** *(Scheme 33).*



Scheme 33

The eight-membered-ring allenes **134-136** represent the range of compounds known and the last two are stable compounds *(Figure 12)*. Allene **135** [16] is the only eight membered cycloallene stable at 20 ºC. In contrast to parent compound **2** and methyl-derivative **134,** allene **135** did not dimerize, even on prolonged standing at ambient temperature.

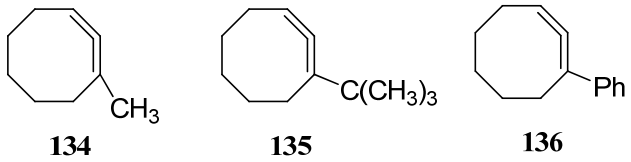
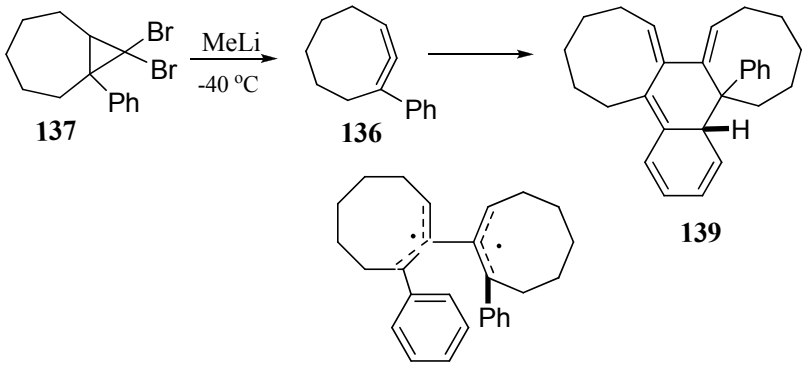


Figure 12: Examples of cycloocta-1,2-diene (**2**)

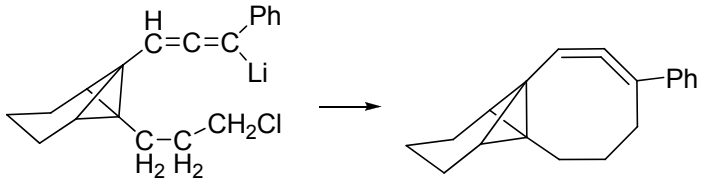
However, 1-phenylcycloocta-1,2-diene **136** [16] generated by application of the Doering-Moore-Skattebøl route to dibromocarbene adduct **137,** dimerizes in an unusual manner to give product **139** *(Scheme 34)*. The structure of **139** was confirmed by X-ray structure analysis. It is now well established that cyclic allenes dimerize by way of a diradical. The formation of **139** can be rationalized by formation of the diradical **138** as the intermediate. The fast collapse of **138** to **139** is probably caused by the conformation of the eight-membered rings placing the reaction centers in suitable positions.



137 **136** **139** **138**

Scheme 34

An interesting cycloocta-1,2-diene derivative is **141** that contains a propellane subunit. It was recently synthesized by Kreuzholz and Szeimies starting from the allenic tautomer **140** in 59% yield, but an attempted distillation causes complete polymerization [65] *(Scheme 35).*

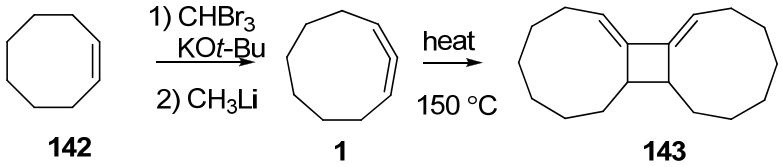


140 **141**

Scheme 35

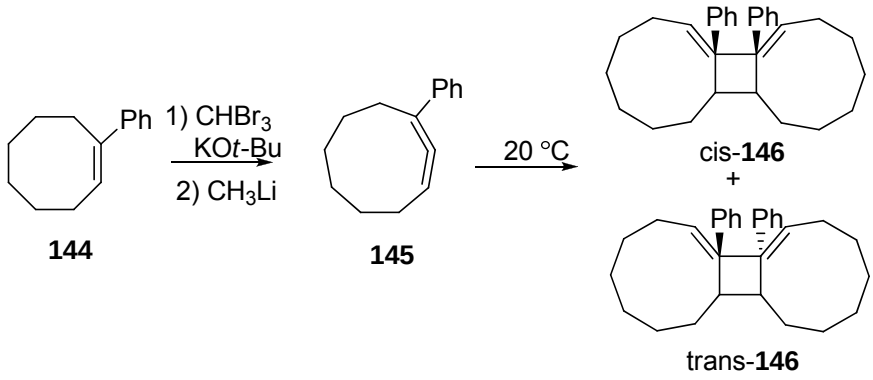
1.1.5 Nine-Membered-Ring Allenes

At room temperature, cyclonona-1,2-diene (**1**) is a distillable liquid, and can be stored virtually unlimited. It, the best studied cyclic allene, was first synthesized in 1951 by Blomquist and co-workers [66]. As later shown by Skattebøl, this compound is easily prepared in high yield by ring expansion of cyclooctene (**142**) [67,68]. Allene **1** dimerizes upon heating *(Scheme 36).*



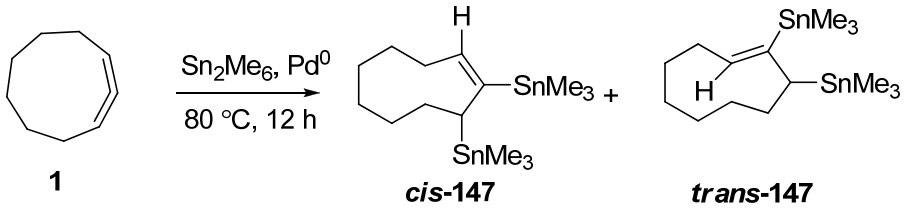
Scheme 36

However, Christl *et al.* [69] reported that 1-phenylcyclonona-1,2-diene (**145**) which has been generated by application of this method to 1-phenylcyclooctene (**144**) dimerizes slowly at room temperature to give *cis*- and *trans*-**146** in a 1:1 ratio. In other word, the phenyl group decreases the stability of formed allene (**145**) *(Scheme 37).*



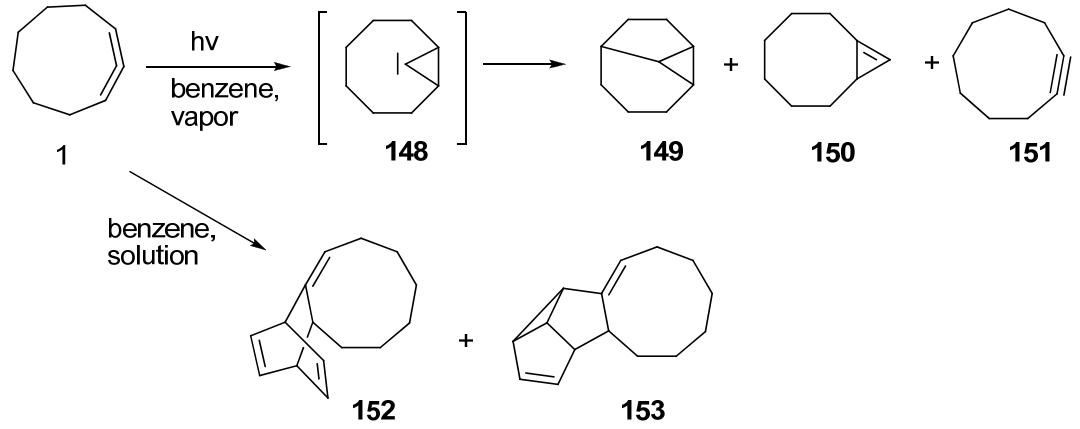
Scheme 37

Stable cyclo-1,2-dienes can be converted into synthetically promising compounds. For example, it has been demonstrated recently [70] that reaction of parent cyclonona-1,2-diene (**1)** with Sn_2Me_6 and $[Pd(Ph_3)_4]$ in the absence of solvent at 80 ºC provides in excellent yield *cis* and *trans*-**147**. These compounds furnish useful doubly functionalized medium-ring cycloalkenes *(Scheme 38).*



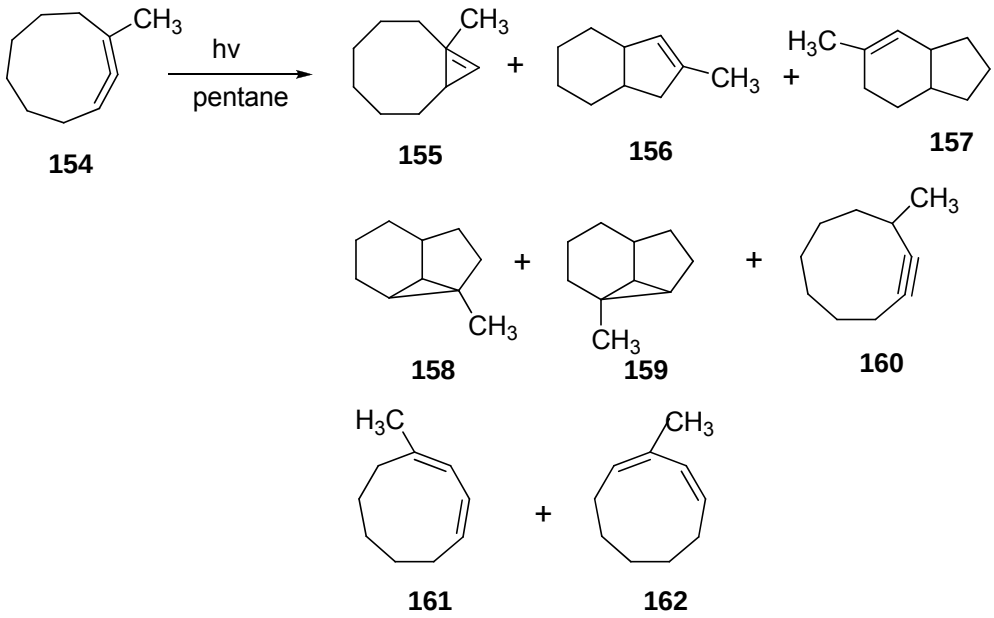
Scheme 38

The photochemistry of cyclonona-1,2-diene (**1)** was reported by Ward and Karafiath [71] as early as 1969. Benzene-sensitized irradiation in the vapor phase resulted in the formation of **149** while direct irradiation furnished four C_9 isomers from which only **149** was characterized. Gilbert *et al*. [72] reported the formation of **152** and **153** in benzene solution. However, Stierman and Johnson [73] reinvestigated the photochemical reaction of **1** and characterized other products as bicyclo[6.1.0]non-9-ene (**150**) and cyclononyne (**151)** *(Scheme 39).*



Scheme 39

Recently, Johnson *et al*. [74] studied the photoreaction of 1-methylcyclonona-1,2-diene (**154**), which was synthesized by the Doering-Moore-Skattebøl method, in order to determine the substituent effect on the mechanism. Direct irradiation of **154** afforded as primary products the eight isomers **155-162**. In contrast to the apparently concerted reaction of **1**, methyl derivative **154** seems to favor vinylcarbene intermediates *(Scheme 40).*

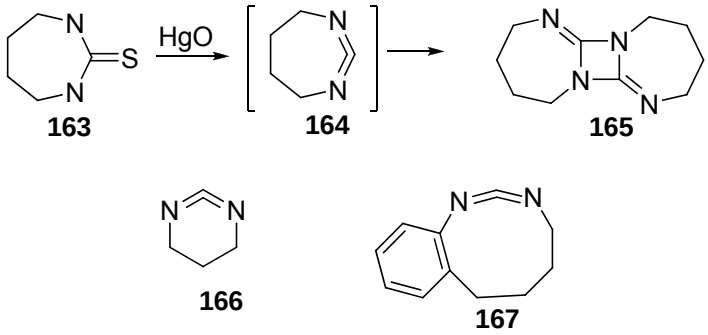


Scheme 40

1.1.6 Strained Heteroallenes

Heteroallenes are those substances in which one or more carbon atoms of the allene are substituted by a heteroatom. An enormous variety of heteroallenes are known, however only a few have been incorporated in rings. There are no exact theoretical estimates of strain or predicted structures, but generally they are inherently bent. In general, their weaker π bonds present a much softer bending potential than for carbon analogues [15].

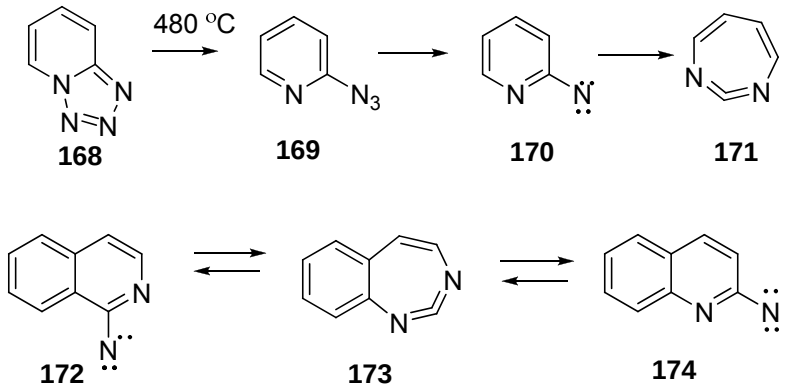
Carbodiimides are the typical heteroallenes which the terminal carbon atoms of allene are exchanged with nitrogen atoms. Firstly, Richter *et al.* have described one more cyclic carbodiimides according to the ring size [75] *(Scheme 41)*



Scheme 41

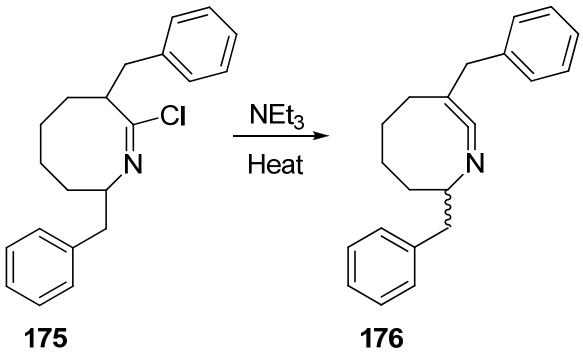
Eight-membered-ring carbodimides proved to be the smallest isolable structure, this compound easily oligomerized and was undistillable. Seven-membered-ring one (**164**) synthesized by another method afforded only [2+2] dimer **165** and a possible trimer. However, synthesis of **166** was unsuccessful.

Wentrup *et al.* have synthesized carbodimides by rearrangements of singlet nitrenes [76] *(Scheme 42).*



Scheme 42

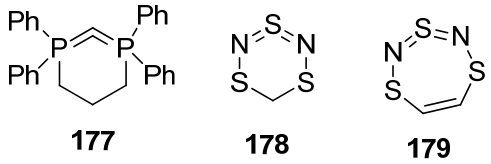
In 1981, Firl *et al*. reported the synthesis of strained ketenimine (**176**) as a mixture of diastereoisomers [77] *(Scheme 43).*



175 **176**

Scheme 43

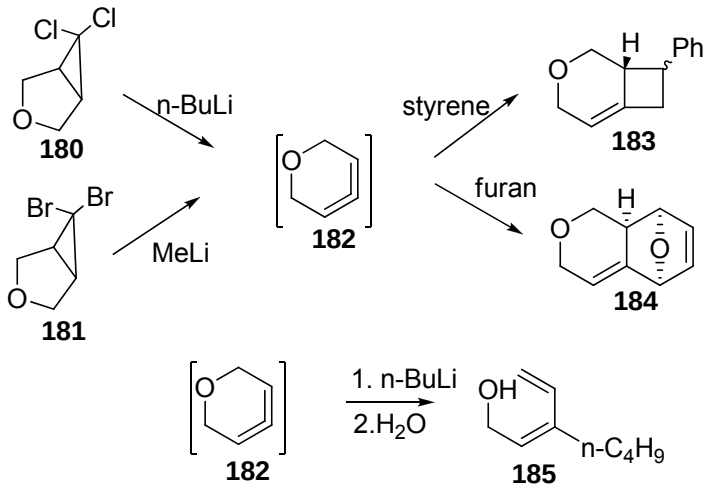
Carbodiphospharane (**177**) was isolated as a crystalline substance. Trithiadiazine (**178-179**) was also described as a red crystalline substance [78] *(Scheme 44).*



177 **178** **179**

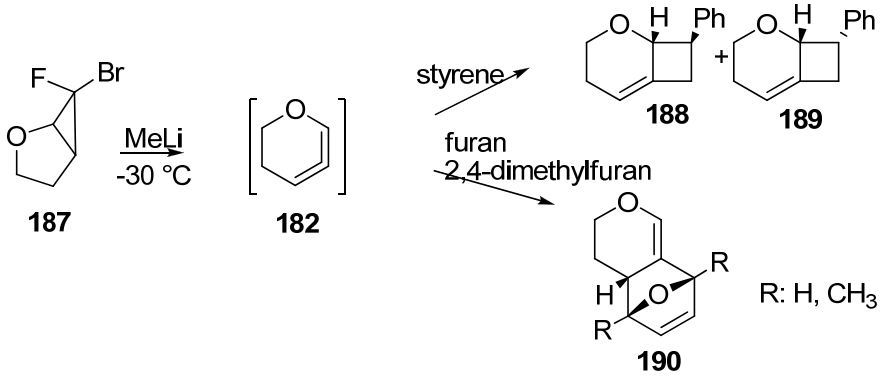
Scheme 44

In literature, heteroatom derivatives of cyclohexa-1,2-diene (**4**) is rather known and synthesized respect to other heterocumulenes. Among these, oxa-derivatives are the best known. As described before, cyclic allene **4** is best generated by treatment of 6,6-bicyclo[3.1.0]hexane with methyllithium [16a]. Hence, 6,6-chloro-**180** and 6,6-dibromo-2-oxabicyclo[3.1.0]hexane (**181)** were used as a potential precursors for **182** by Schreck and Christl [79]. They trapped it with styrene and furan to give **183** and **184**, respectively. Besides, they proposed that due to the smaller covalent radius of the oxygen atom, the oxa-derivative **182** should have a more bent allene moiety in comparison to cyclohexa-1,2-diene (**4**) and, as a consequence, should exhibit a higher strain energy. Despite this, cycloaddition products with activated alkenes are formed in similar yields as in the case of **4**. They also reported that a specific feature of **182** is the addition of the nucleophile, *n*-butyllithium to give **185** *(Scheme 45).*



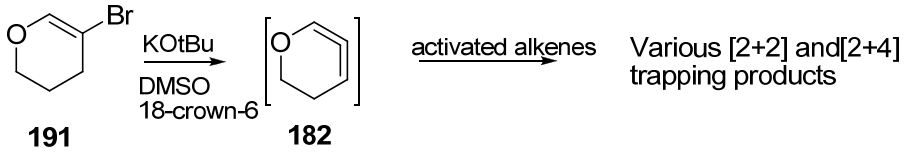
Scheme 45

Later, Christl and Braun [80] have obtained the best results by the treatment of *exo*-6-bromo-*endo*-6-fluoro-2-oxabicyclo[3.1.0]hexane (**187**) with methyllithium. An interesting feature of these trapping experiments was the observation of different chemoselectivity. [2+4] cycloaddition reactions with the allene **182** take place exclusively at the double bond most remote from the oxygen atom, whereas [2+2] cycloaddition reactions prefer the enol ether double bond. In the case of the [2+4] cycloaddition reaction the electron-pure double bond, which is that more remote form the oxygen atom, will react preferentially with electron-rich dienes. For the formation of the [2+2] cycloaddition products a two-step mechanism involving diradical intermediates was offered [81,82] *(Scheme 46).*



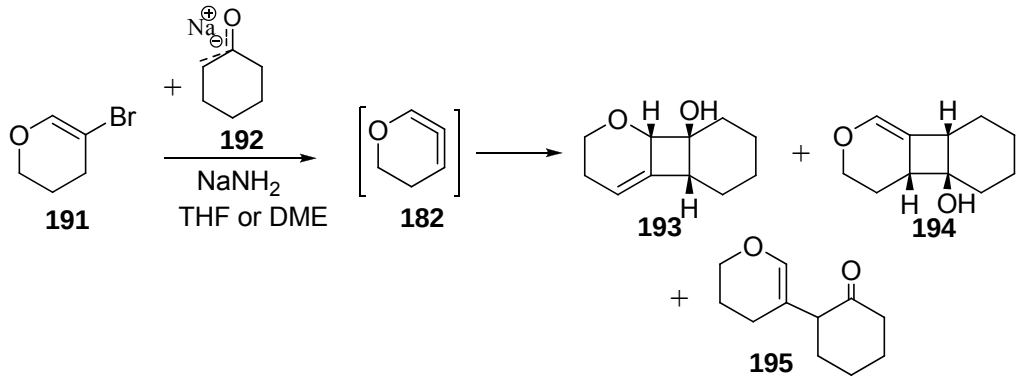
Scheme 46

1-Oxa-2,3-cyclohexadiene (**182**) was also generated by Ruzziconi *et al*. [83] independently by treatment of 5-bromo-3,4-dihydro-2H-pyran (**191**) with KOtBu base in the presence of 18-crown-6 in DMSO as a solvent. It was trapped with various dienes and dienophiles and also observed the same stereoselectivity *(Scheme 47).*



Scheme 47

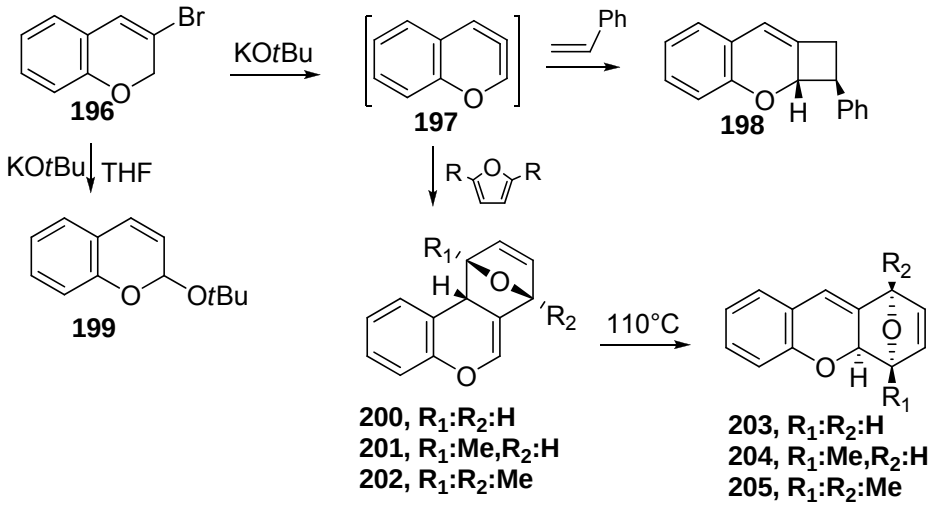
Furthermore, Caubere *et al.* [84, 85] have generated **182** by reacting **191** with cyclohexanone enolate as activating agent for sodium amide, and intercepted it with cyclohexanone enolate in [2+2] cycloaddition to yield **193**, **194** and **195**. They explained the formation of **195** by attack of enolate **193** to the central allene carbon atom. This methodology shows the synthetic potential of strained cyclic allenes in the synthesis of polycyclic oxygenated heterocycles *(Scheme 48).*



Scheme 48

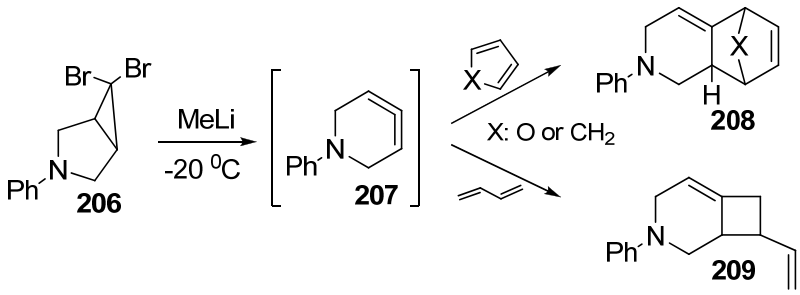
Christl *et al.* [86] reported that the treatment of 3-bromo-2*H*-chromene (**196**), dissolved in furan, 2-methylfuran or 2,5-dimethylfuran, with KO*t*Bu, results in the formation of the epoxybenzo[*c*]chromene derivatives **200-202** in yields of 28-59%. Likewise, *exo*-2-Phenylcyclobuta[*b*]chromene (**198**) was produced in styrene. With tetrahydrofuran as the solvent, 2-*tert*-butoxy-2H-chromene (**199**) was observed as the

only product (79% yield) in the absence of activated alkenes. The epoxybenzochromenes **200-202** rearrange on heating to give the epoxyxanthene derivatives **203-205** *(Scheme 49)*.



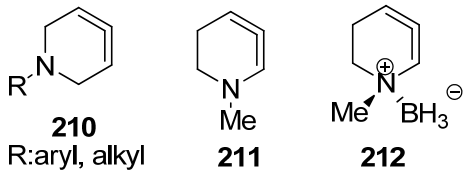
Scheme 49

Isodihydropyridines **210-212** are another heteroatom derivatives of cyclohexa-1,2-diene (**4**)**,** can be synthesized by Doering-Moore-Skattebøl method. By this way, the first isodihydropyridine **207** has been recently generated from 6,6-dibromo-3-phenyl-3-azabicyclo[3.1.0]hexane (**206**) with methyllithium [87]. In the presence of buta-1,3-diene, furan, or cyclopenta-1,3-diene, **207** was trapped successfully to yield [2+4] and [2+2] cycloaddition products; **208** and **209** *(Scheme 50)*.



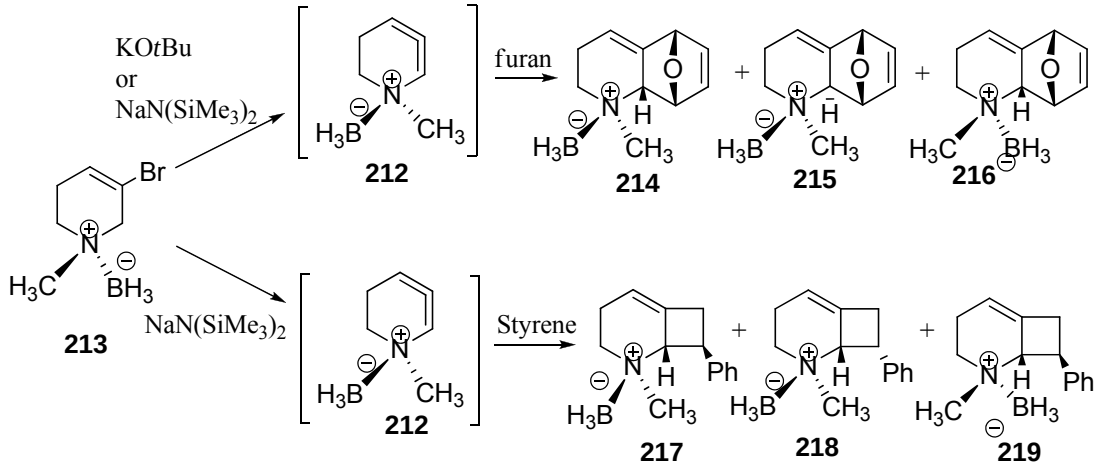
Scheme 50

In contrast to 1-azacyclohexa-3,4-dienes **210**, attempts to generate 1-methyl-1-azacyclohexa-2,3-diene (**211**) failed. However, the intermediacy of its borane complex **212** has been secured by the isolation of cycloadducts of **212** with furan and styrene [88] *(Scheme 51).*



Scheme 51

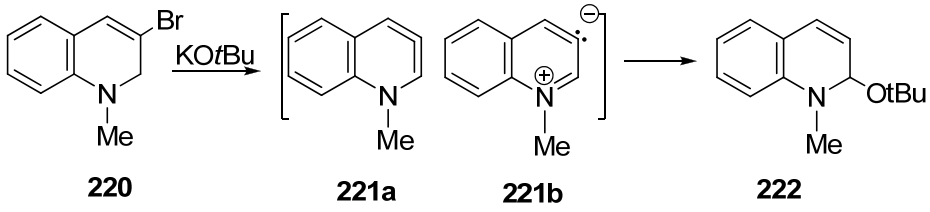
Christl *et al.* [88] reported that the compound **213** reacts rather readily with KO*t*Bu in the presence of furan, providing the hexahydroepoxyquinolines **214-216**, although the yield turned out to be only 13%. On replacement of KO*t*Bu by sodium bis(trimethylsilyl)amide, the yield increased to 20%, with the ratio of **214**/**215**/**216** being about 3:2:1. When styrene was used instead of furan, with $NaN(SiMe_3)_2$ as base, the hexahydrocyclobutapyridines **217-219** were obtained in 30% yield in a ratio of ca. 6:2:1 *(Scheme 52).*



Scheme 52

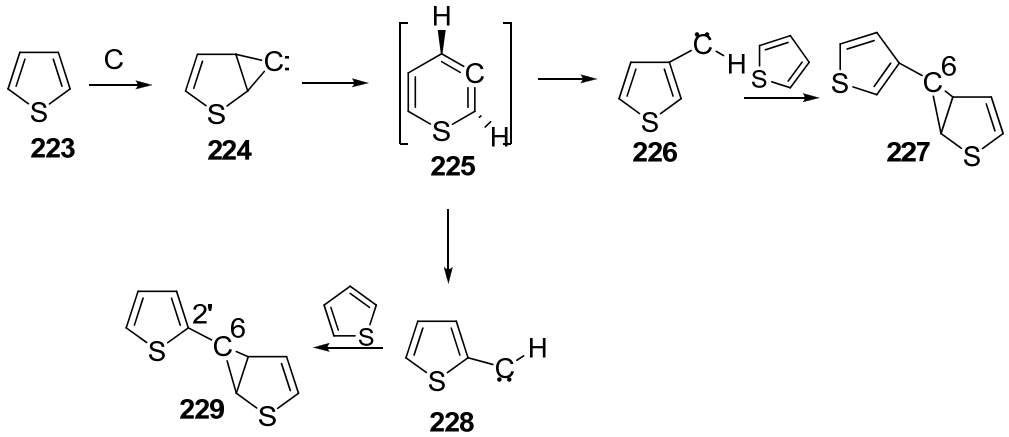
More recently, Christl *et al.* [89] have provided the generation and interception of **221**. They treated 220 with KO*t*Bu in $[D_8]$-THF and the mixture was analysed by NMR spectroscopy. The formed product was characterized as **222**. The

formation of **222** can be rationalized by formation of the title cycloallene **221** followed by trapping with by KO*t*Bu. Probably, the rate of trapping is so fast that, cycloaddition of **221** with furan and styrene can not compete *(Scheme 53).*



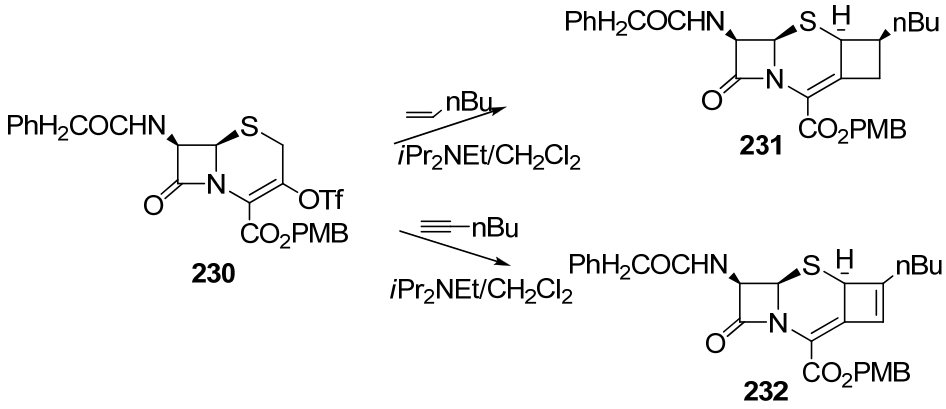
Scheme 53

Shevlin *et al.* [90, 91] have reported that the reaction of arc-generated atomic carbon with thiophene (**223**) at 77 K yielded two new products, **227** and **229**, in a ratio of 2,5:1 [92]. These formed products possibly result from the reaction of thiophene with the carbenes **226** and **228**, which can arise from a simple C-H insertion by a carbon atom on **223**. However, the reaction of ^{13}C atoms with **223** using the same conditions revealed that **229** was labelled in the 2′- and 6-positions in a 5:1 ratio while **227** is labelled exclusively in the 6-position. These results clearly demonstrate that carbenes **226** and **228** have been produced by the 'cumulene-to-carbene' rearrangement of the initially formed allene **225** *(Scheme 54).*



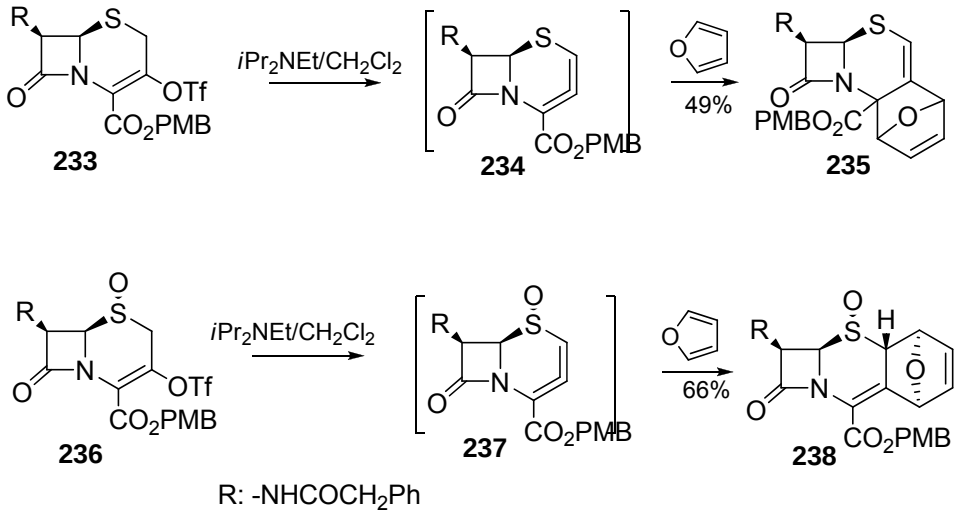
Scheme 54

The synthetic potential of strained cyclic heteroallenes has been nicely reported by Elliot *et al.* [93, 94]. The liberation of the cephalosporins **230** proceeds under astoundingly mild conditions and their interception, even with nonactivated olefins and acetylenes, takes place with high efficiency *(Scheme 55).*



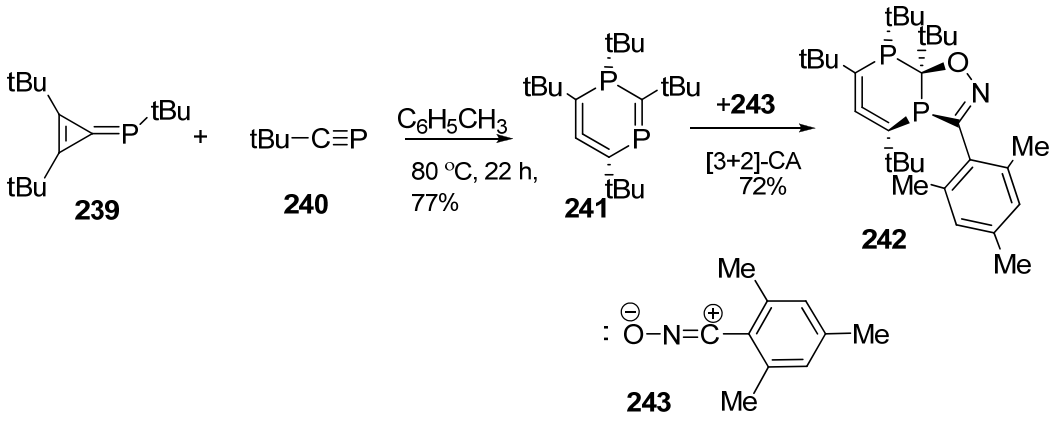
Scheme 55

Morover, reactions of **234** and **237** with furan resulted in the formation of the [2+4] cycloaddition products, **235** and **238**, respectively. These reactions have rationalized by invoking the intermediacy of the six-membered cyclic hetereoallene **234** or **237**. As can be seen from reaction of **233**, the [2+4] cycloadditions take place at the less electron-rich 3,4-double bond to give **235**. However, when cephalosporin α-sulfoxide triflate **236** was treated with *i*-Pr_2Net in the presence of furan, **238** was isolated in 66% yield as the sole product contrary to the reaction of **233**. The oxidation state of sulphur determines the regiochemistry of the addition. In the case of the sulfoxide **236**, the 2,3-double bond is more electron-deficient [93,94] *(Scheme 56)*.



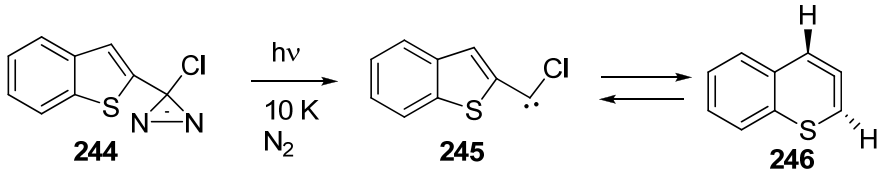
Scheme 56

More recently, Regitz *et al.* [95] have prepared an isolable diphosphaisobenzene **241**, the first stable derivative of cyclohexa-1,2-diene (**4**) with only two heteroatoms in the six-membered ring, starting from phosphatriafulvene (**239**) which is reacted with the kinetically stabilized phosphaalkyne **240** at 80 ºC. The forming product, isobenzene **242**, is characterized by an unexpected thermal stability and was obtained as a red oil in 77 % yield by bulb-to-bulb distillation. For unequivocal confirmation of its isobenzene structure, **241** was converted to the crystalline adduct **242** by treatment with 2,4,6-trimethylbenzonitrile oxide (**243**); this reaction proceeds chemo-, regio- and stereoselectively. A single-crystal X-ray structure analysis confirmed not only the constitution but also the relative configuration of the 5,7,8,8a-tetra-*tert*-butyl-3-(2,4,6-trimethylphenyl)-8a*H*-6δ^2-[1,3]diphosphinino[1,2-*d*][1,2,4] oxazaphosphole (**242**) and thus also those of **241** *(Scheme 57).*



Scheme 57

Most recently, the highly strained cyclic allene 2,3-didehydro-2*H*-thiopyran (**246**) was generated by irradiation of matrix-isolated 2-benzothienylchlorocarbene (**245**) [96] *(Scheme 58).*



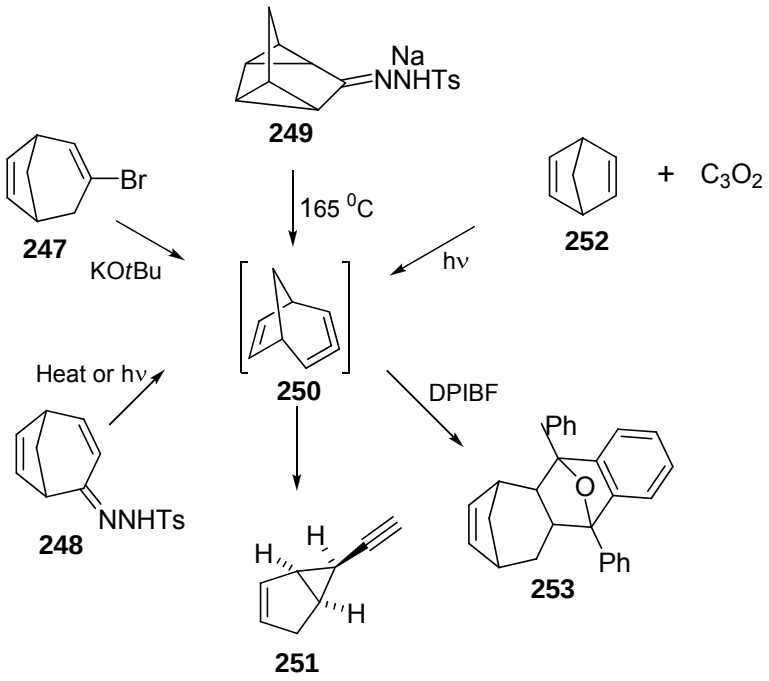
Scheme 58

1.2 Strained Bicyclic Allenes

In literatures, there have been much more studies about the cyclic allenes, however, reports on bicyclic allenes are remarkably limited.

Bergman and Rajadhyaksha [97] were the first to generate bicyclo[3.2.1]octa-2,3,6-diene (**250**), however they considered it as a homoconjugated carbene rather than a cyclic allene. They used two alternative methods directed to generation of **250**. β- elimination from 3-bromobicyclo[3.2.1]octa-2,6-diene (**247**) with base in DMSO at room temperature and thermolysis of the tetracyclo[3.2.1.$0^{2,7}$.$0^{4,6}$]octan-3-one tosylhydrazone sodium salt (**249**) afforded **250** as intermediate. Of course, **250** could not be observed, but rearranged to *endo*-6-ethynlbicyclo[3.1.0]hex-2-2ene **(251)**, which was isolated in moderate yields. Obviously, the conversion into **251** can

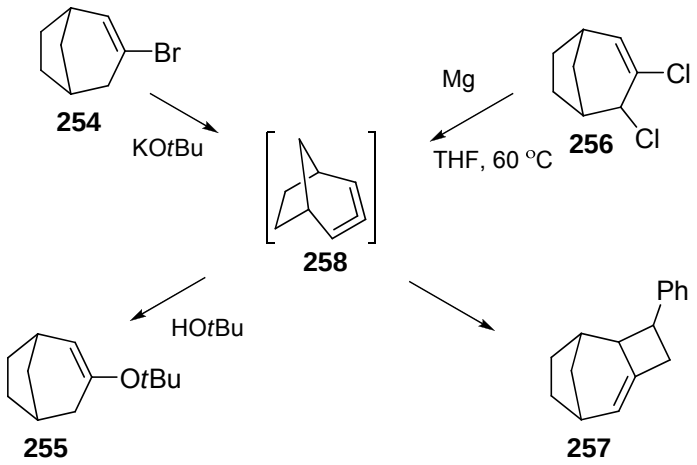
compete with oligomerzation of **250**, a dimer of which has not been described. A small amount of **251** was also obtained on photolysis of a mixture of norbornadiene and carbon suboxide [98] *(Scheme 59).*



Scheme 59

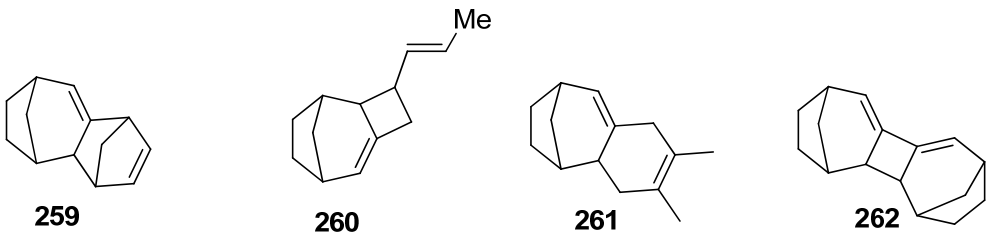
That the precursor to **251** should be the cyclic allene **250** was proved by Balci and Jones [18b] who treated **247** at 53 ºC with KO*t*Bu in THF in the presence of DPIBF and isolated to four diastereomeric [4+2]-cycloadducts **253**. Apparently, the rearrangement of **250** to **251** is considerably slower than the trapping by DPIBF. The replacement of KO*t*Bu by enantiopure potassium menthoxide gave rise to optically active products **253**. On conducting this experiment at 100 ºC, **253** was shown racemic. These findings indicate that **250** is chiral and undergoes enantiomerization with about the same ease as 1,2-cyclohexadiene (**4**) [18a,b]. When the reaction of **247** with potassium menthoxide at 53 ºC was carried out in absence of DPIBF, the resulting **251** was optically active. This suggests that the progenitor of **251** has the allene structure **250** rather than other conceivable constitutions [98,99]. Even early quantum-chemical calculations on **250** showed a strongly bent, chiral structure, although the enantiomerization barrier was not correctly estimated [36].

Bicyclo[3.2.1]octa-diene (**258**), was reported for the first time by Devaprabhakara *et al.* [100], who isolated the enol ether 255 in 62% yield after the treatment of 3-bromobicyclo[3.2.1]oct-2-ene (**254**) with base in DMSO *(Scheme 60)*. When this reaction was performed in the presence of styrene, two [2+2]-cycloadducts of **258** were obtained in 50% yield. Rather, a mixture of diastereoisomers of **257** of the same kind should have been formed as it was collected in 82% yield by Bottini and Hilton [40] after the reaction of dichloride **256** with magnesium in the presence of styrene.



Scheme 60

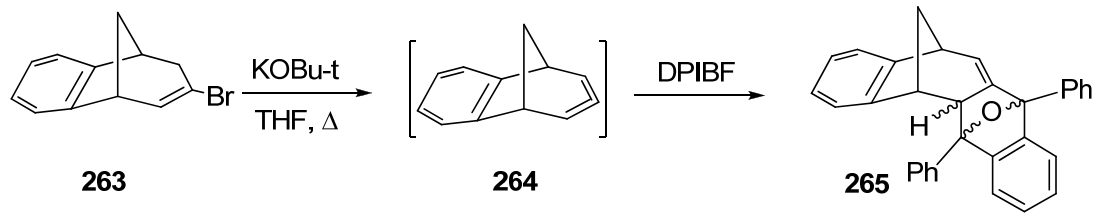
In addition to styrene, Bottini and Hilton [40] used trapping agents such as 1-3-cyclopentadiene, 1,3-pentadiene and 2,3-dimethyl-1,3-butadiene to intercept **258**, and those trapping agents gave products shown in Scheme 61.



Scheme 61

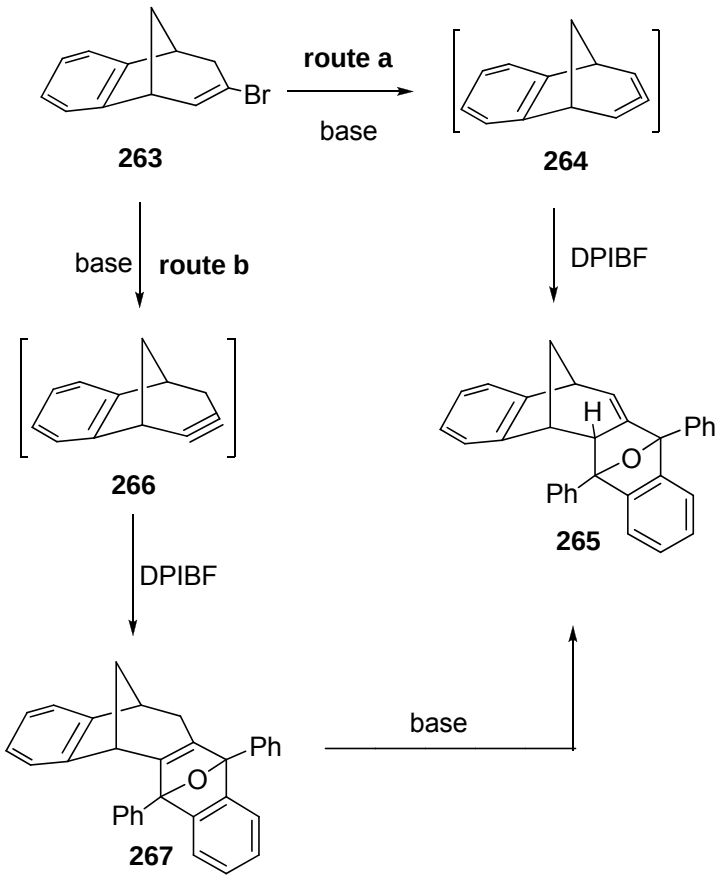
In a clutch of papers Balcı *et al.* investigated the fate of bicyclic allene **264** [101-107]. Compound **263** was treated with KOBu-*t* in the presence of DPIBF and

compound **265** was isolated of which formation is most reasonably explained by the intermediacy of allene **264** *(Scheme 62).*



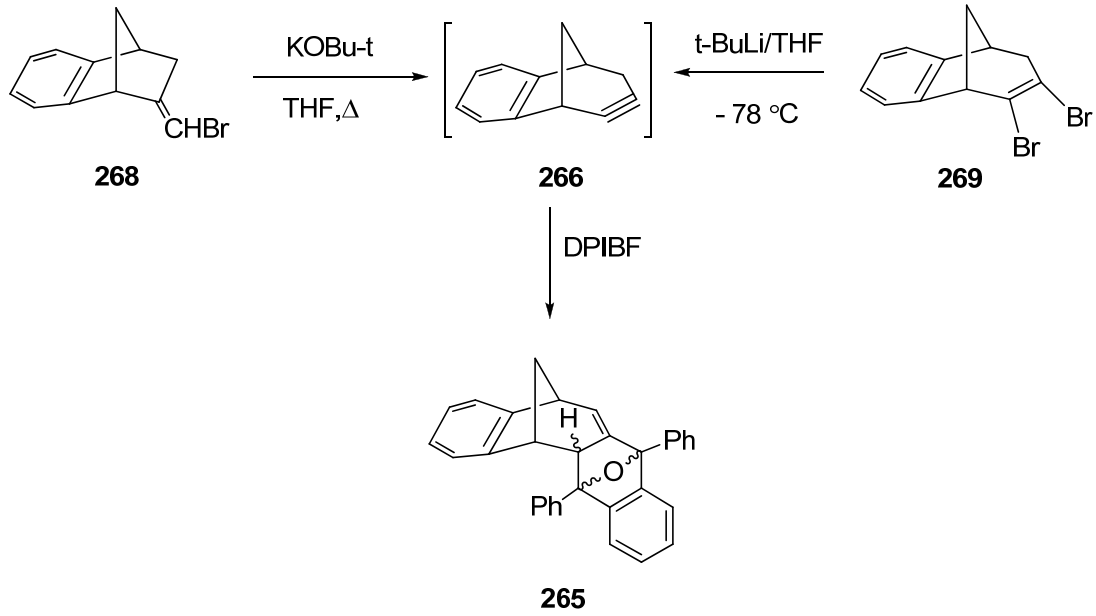
Scheme 62

However, as they have realized, an alternate mechanism for the formation of **265** may operate via the bicyclic alkyne **266** in which the base-promoted isomerization of the double bond would give the observed products *(Scheme 63).*



Scheme 63

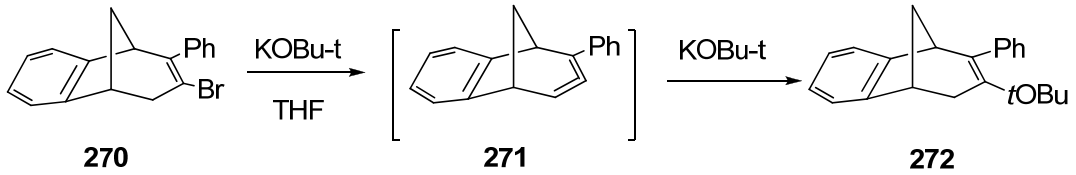
In order to distinguish between these two possible mechanisms, Balci *et al.* have investigated the generation of the alkyne **266** on two independent routes and isolated the same cycloadducts **265**, which clearly indicates that the intermediate is the alkyne **266** *(Scheme 64).*



268 **266** **269** **265**

Scheme 64

Since even with these results allene formation cannot be excluded in the base promoted reaction of **263**, they have repeated the reaction by using phenyl derivative to prevent the proton abstraction from the methyl group, **270**. The isolation of enol ether **272** proved the formation of allene **271**, which was trapped by *tert*-butoxide ion *(Scheme 65)*.

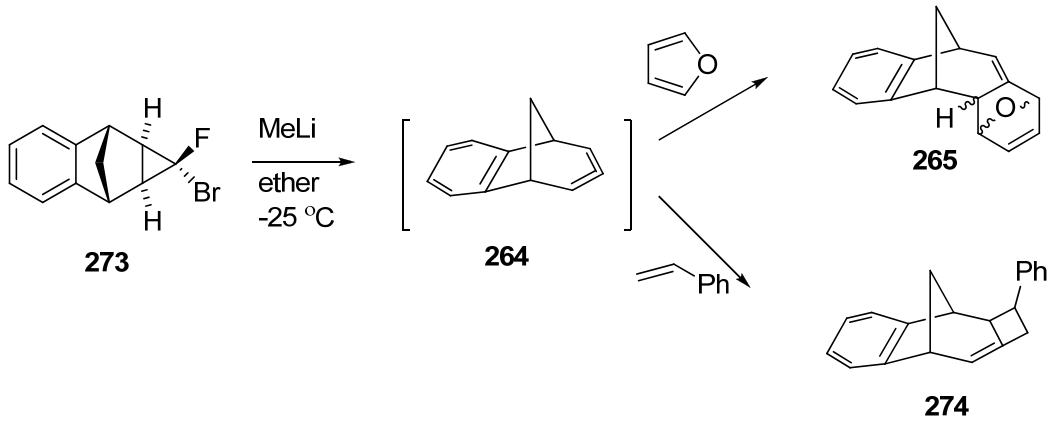


270 **271** **272**

Scheme 65

More recently, Balcı *et al*. [108] has continued their studies in strained bicyclic allenes by improving a series of synthetic routes. The bromofluorocarbene

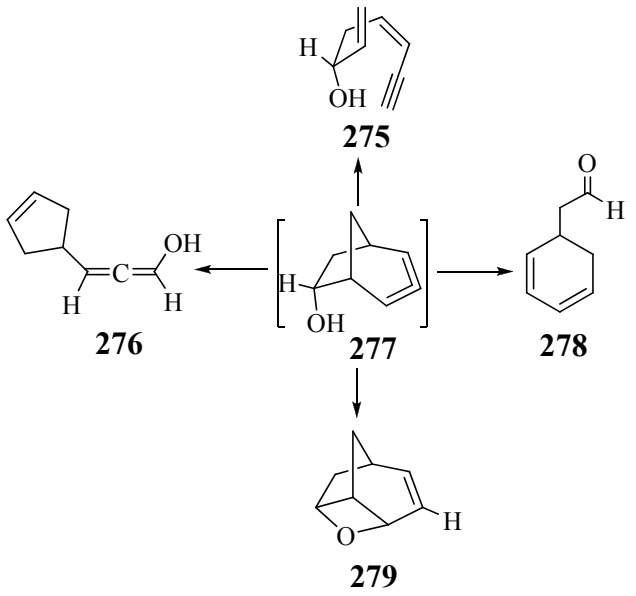
adduct **273** of benzonorbornadiene proved to be a reliable precursor of $3\delta^2$-1,5-dihydro-1,5-methanobenzocycloheptene (**264**), the benzo derivative of **250**. Exposure of **273** to methyllithium in the presence of furan gave rise to cycloadducts of **264**, namely two [4+2]cycloadduct **265** and several [2+2]cycloadducts **266** in 45% and 30% yields, respectively *(Scheme 66).*



273 **264** **265** **274**

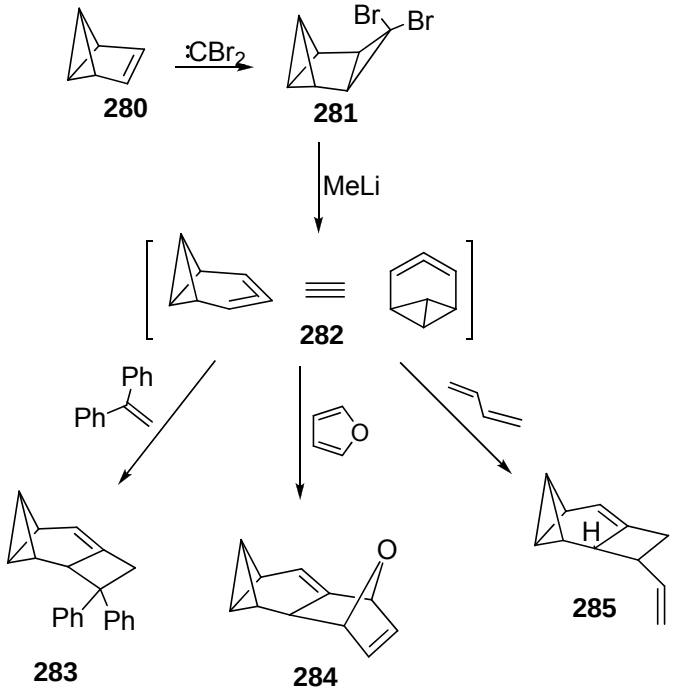
Scheme 66

Sevin and Doğan have focused on the possibilities of intramolecular trapping and fragmentation products of *endo*-bicyclo[3.2.1]octa-2,3-dien-6-ol (**277**) with the concerted reaction mechanism by using quantum chemical calculations [109]. The computational calculations show that the formations of cyclohexa-2,4-dien-1-ylacetaldehyde (**278**) and (5*Z*)-octa-1,5-dien-7-yn-3-ol (**275**) are competitive and appear more favour than the intramolecular trapping product 2-oxatricyclo[4.2.1.$0^{3,8}$]non-4-ene (**279**) *(Scheme 67).*



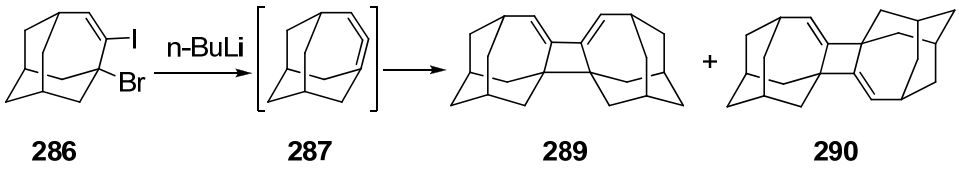
Scheme 67

Christl *et al.* [110] synthesized highly strained tricyclic allene **282** and trapped it varies different dienes *(Scheme 68).*



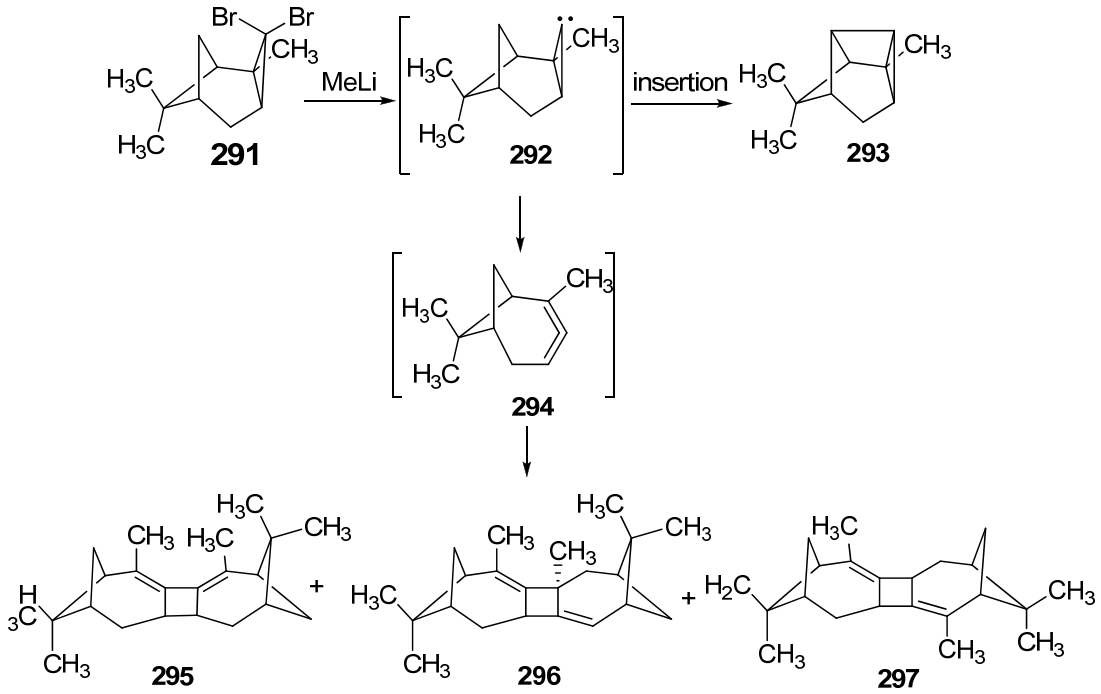
Scheme 68

Okazaki *et al.* [111] reported a novel tricyclic allene **287**, which readily dimerizes or being trapped with DPIBF *(Scheme 69).*



Scheme 69

Lastly, we conclude this section with the report of Balcı *et al*. in 2004 [112]. This study described an investigation aimed at the incorporation of an allene unit into a natural product, being α-pinene by DMS method. The application of carbenoid method to α-pinene resulted in the formation of products **293**-**297** [38]. The formation of **293** clearly indicates the presence of free carbene **292** that undergoes CH-insertion whereas three dimeric products **295**-**297** confirms the existence of the allene **294** at the same time in the reaction mixture *(Scheme 70).*

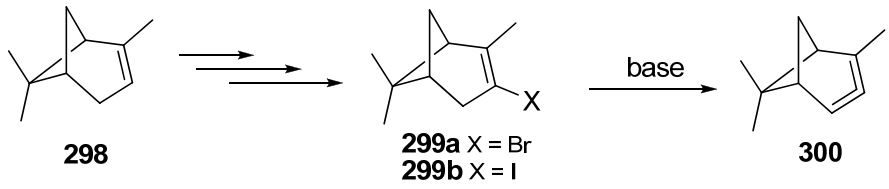


Scheme 70

1.3 THE AIM OF THE STUDY

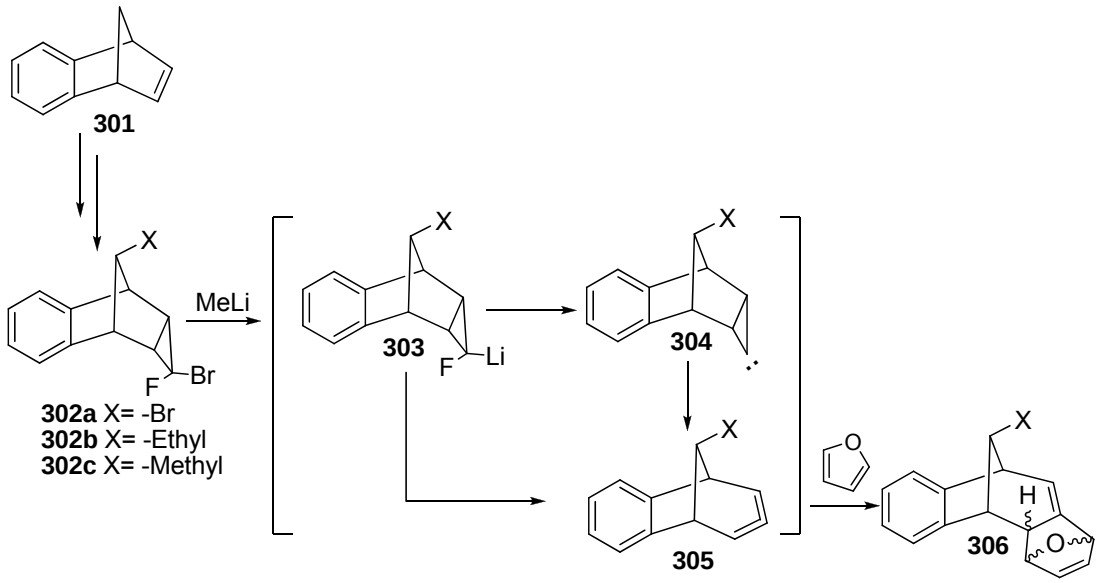
The synthesis of bicyclic allenes are of considerable interest in organic chemistry because of their high strain and reactivity. However, the studies on bicyclic allenes are remarkably limited when compared with the cyclic allenes.

As mentioned before, Balci *et al*. [112] described an investigation aimed at the incorporation of an allene unit into a natural product, being α-pinene via Doering-Moore-Skattebøl *(Scheme 70)*. Although the Doering–Moore–Skattebøl method was successful in obtaining the desired allene, it gave the ring-enlarged product **294** where the allene bonds are located in a seven-membered ring. Hence, incorporation of an allene unit into the α-pinene (**298**) skeleton without ring enlargement would generate the six-membered cyclic allene **300**, which would cause considerable deviation from linear geometry. In the first part of the study, we will present a method of accessing the highly reactive intermediate **300** by application of a β-elimination route, as outlined in (*Scheme 71)*.



Scheme 71

In the second part of the study is aimed to develop synthetic strategy leading to the dihalocyclopropane **302** and to investigate its reaction with MeLi to test the behaviour of the *endo*-carbenoid-carbene-allene isomerization **303-305**. The primarily formed carbene may resist isomerization to form allenic intermediate In addition, the substituent effect on double bond pyramidalization will be investigated *(Scheme 72)*.


301
X
MeLi
F
Br
302a X= -Br
302b X= -Ethyl
302c X= -Methyl
303
F
Li
304
305
O
306
H
O

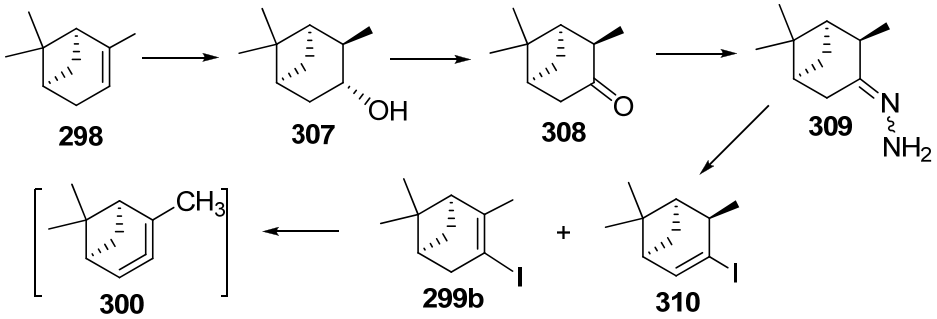
Scheme 72

CHAPTER 2

RESULTS AND DISCUSSION

From among the numerous synthetic approaches [14-16] to the cyclic allenes, Doering-Moore-Skattebol method and β-elimination method are most widely studied in the literature. The first one, discovered by Moore [68b,113] and co-workers and Skattebol [67a], is the conversion of 1,1-dihalocyclopropanes [114,115] to the corresponding cyclic allenes upon treatment with alkyl lithium reagents. The latter, first attempted by Favorskii [25] to prepare cyclopenta-1,2-diene by the treatment of vinyl bromide with KO*t*Bu, is the reaction of the corresponding vinyl halides with bases [52,88,89,116].

Our initial exploratory efforts directed towards the generation of six-membered-ring allenes involved the synthesis of key compounds as precursors. In the first episode, we focused on the generation of 2,6,6-trimethylbicyclo[3.1.1]hepta-2,3-diene (**300**) via β-elimination method. Synthetic pathway was depicted below *(Scheme 73)*.



Scheme 73

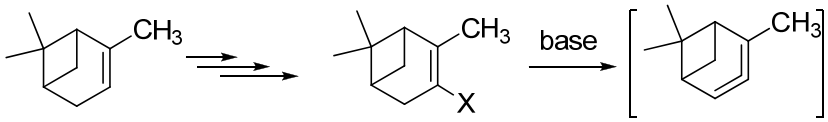
2.1 THE REACTION PATH FOR THE SYNTHESIS OF 2,6,6-TRIMETHYL-BICYCLO[3.1.1]HEPTA-2,3-DIENE (300)

2.1.1 The Synthesis of (*1R,2R,3R,5S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ol (307)

Before starting the synthesis of **307**, we want to explain the reason that why *1S*-(-)-α-pinene (**298**) was preferred as a starting material?

α-Pinene (**298**), $C_{10}H_{14}$, (IUPAC Name: 2,6,6-trimethylbicyclo[3.1.1]hept-2-ene) is widely distributed in nature, being found in most essential oils of the *Coniferae*. Due to this abundance, there are much more studies starting from 19th century on α-pinene in the literature. However, they were complicated because α-pinene readily undergoes molecular rearrangements [117]. Many rearrangements of α-pinene are of the *Wagner-Meerwein* type [118], which takes place via the formation of a carbonium ion. Furthermore, the presence of a four-membered ring in α-pinene makes the molecule more strained. Therefore, the incorporation of an allene unit into a six-membered ring may cause some difficulties.

In order to obtain the allene **300**, vinyl halides **299** are required as the key compounds shown in Scheme 74.

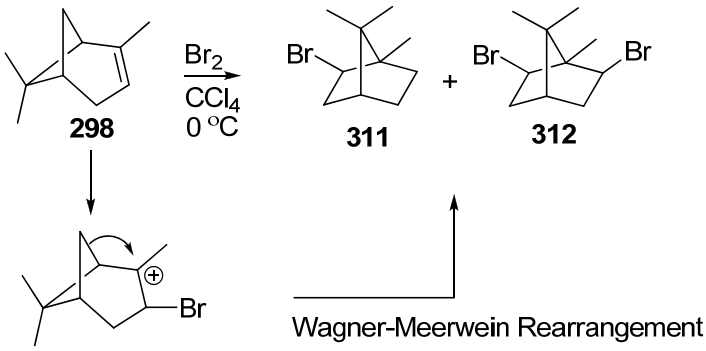


298 **299a X = Br** **299b X = I** **300**

Scheme 74

A few years ago, Balcı *et al.* attempted to synthesize the vinyl bromide **299a** by bromination of **298** followed by HBr elimination. None of their efforts produced the desired bromine addition products. Since the α-pinene skeleton has a large tendency for the *Wagner-Meerwein* rearrangement, they isolated in all cases the

rearranged dibromides instead of the desired normal addition products. [119-122] *(Scheme 75)*.

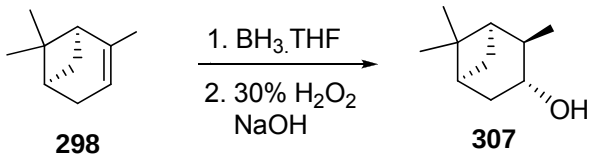


Scheme 75

Therefore, in the light of the literature and report data, we turned our attention to the synthesis of the corresponding vinyl iodide **299b**, as the key intermediate, an efficient leaving group.

The addition of a compound containing a hydrogen-boron bond to alkene is the starting point for a number of highly useful synthetic procedures. This addition, called "*hydroboration*", was discovered by Herbert C. Brown [123]. In this addition, contrast to *Markovnikov addition* product, the boron atom becomes attached to the less substituted carbon atom of the double bond, and a hydrogen atom is transferred from the boron atom to the other carbon atom of the double bond. Thus, hydroboration is regioselective. For this reason, in order to obtain a secondary alcohol, *1S*-(-)-α-pinene (**298**) was exposed to hydroboration reaction. To a solution of *1S*-(-)-α-pinene (**298**) and sufficient amount of $NaBH_4$ in THF was added dropwise $BF_3.OEt_2$ solution which was then pre-cooled and maintained at 0 ºC under nitrogen atmosphere. After a while, the addition of NaOH (3M) and 30% H_2O_2 solution into the medium, the reaction was completed. After hydrolytic work-up and evaporation of the solvent, the crystalline material **307** was obtained 92% yield.

The data for *(1R,2R,3R,5S)*-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ol (**307**) was in good agreement with those previously reported [124] *(Scheme 76)*.

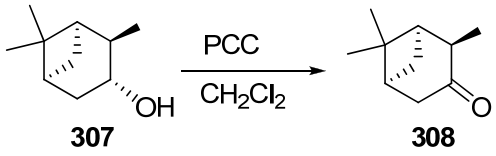


Scheme 76

2.1.2 The Synthesis of *(1R,2R,5S)*-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-one (308)

The secondary alcohol can easily be oxidized to corresponding ketone via pyridinium chlorochromate (PCC). So that, a solution of pyridinium chlorochromate (PCC) in CH_2Cl_2 was added to solution of **307** in CH_2Cl_2 at 0 ºC. After the addition was completed, the mixture was stirred at room temperature for 3h. The solvent was evaporated and than the residue was exposed to hydrolytic work-up with water and CH_2Cl_2. After the removal of the solvent followed by distillation the desired ketone **308** was obtained in 90 % yield.

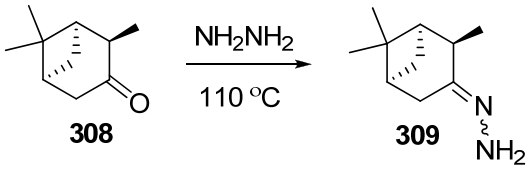
Characterization of **308** was based on ^{1}H- and ^{13}C-NMR spectral data, which was also consistent with the literature data [125] *(Scheme 77)*.



Scheme 77

2.1.3 The Synthesis of *(1R,2R,*3E*,5S)*- and *(1R,2R,*3Z*,5S)*-2,6,6-trimethylbicyclo[3.1.1]heptanes-3-one Hydrazone (309)

For the synthesis of key compounds vinyl iodide, ketone **308** was reacted with sufficient amount of neat hydrazine hydrate at 110 ºC for 18 hours in the absence of solvent. The residue was extracted with water and chloroform. After drying and removal of solvent *Z* and *E* isomer mixture of hydrazone derivative **309** (93%) was produced quantitatively *(Z)/(E)* 1:3 *(Scheme 78)* [126].

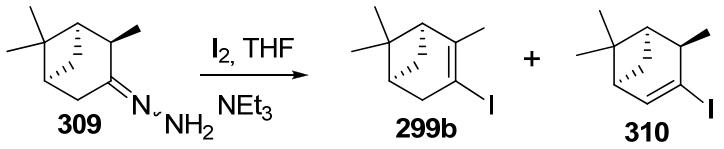


Scheme 78

Characterization of **309**, was based on ^{1}H and ^{13}C NMR and also GC MS spectral data. According to the GC-MS spectrum, molecular ion peak was 167 for $[M+H]^{+}$.^{1}H NMR spectrum of **309** revealed nine sets of proton signals; the broad singlet appears at 4.92 ppm indicated the presence of NH_2 protons. There are eighteen lines in ^{13}C-NMR for *(E)* and *(Z)*- isomers. So, no doubts remain as to proposed structure due to extremely characteristic spectroscopic data.

2.1.4 The synthesis of *(1S,5S)*-3-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (299b) and *(1S,4R,5R)*-3-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (310)

A solution of iodine in 160 mL of THF was added to a mechanically stirred solution of hydrazone derivative (**309**) and sufficient amount of triethyl amine in 300 mL THF. The reaction was taken place at room temperature under the nitrogen atmosphere for 1 h. After reaction was completed, the solvent was evaporated. The vinyl iodides **299b** and **310** were isolated by vacuum distillation (2:3 ratio, 24.7%). These isomers were separated by column chromotograpy (100 g silica gel: 0.4 g $AgNO_3$) eluting with hexane *(Scheme 79)* [56].

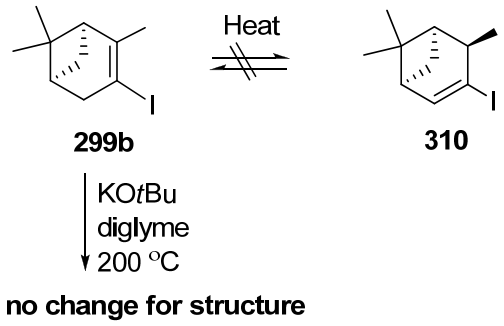


Scheme 79

The structure of both isomers have been elucidated on the basis of ^{1}H and ^{13}C NMR and also GC MS spectral data. According to the GC MS spectrum, molecular ion peak was 263 for $[M]^{+}$. Differantiation of both isomers was done by the NMR spectra. ^{1}H NMR spectrum indicated nine sets of proton signals for both of them.

The olefinic proton resonates as doublet at 6.72 ppm with *J*= 6.8 for **310**, however there is no olefinic proton resonance for **299b**. Although both isomers have also the same number of lines in ^{13}C NMR spectrum, **310** reveals one quaternary olefinic carbon atom appears at 102.8 ppm, whereas **299b** has two quaternary olefinic carbon atoms appear at 148.4 and 90.4 ppm.

After characterization of vinyl iodides **310** and **299b**, it was proposed to submit them to elimination reactions. Before attempting that reaction, we checked the thermal stabilities of **310** and **299b** separately. Since, the structures of those isomers can have a tendency to interconversion each other. If it was, then it may be difficult to suggest a mechanism for the incorporation of an allene unit at the end of the β-elimination reactions separately. After checking the thermal stabilities of them, we found that no interconversion takes place at temperatures of up to 250 ºC. Furthermore, the vinyl iodide **299b** was stable in the presence of base even at 200 ºC *(Scheme 80)*.

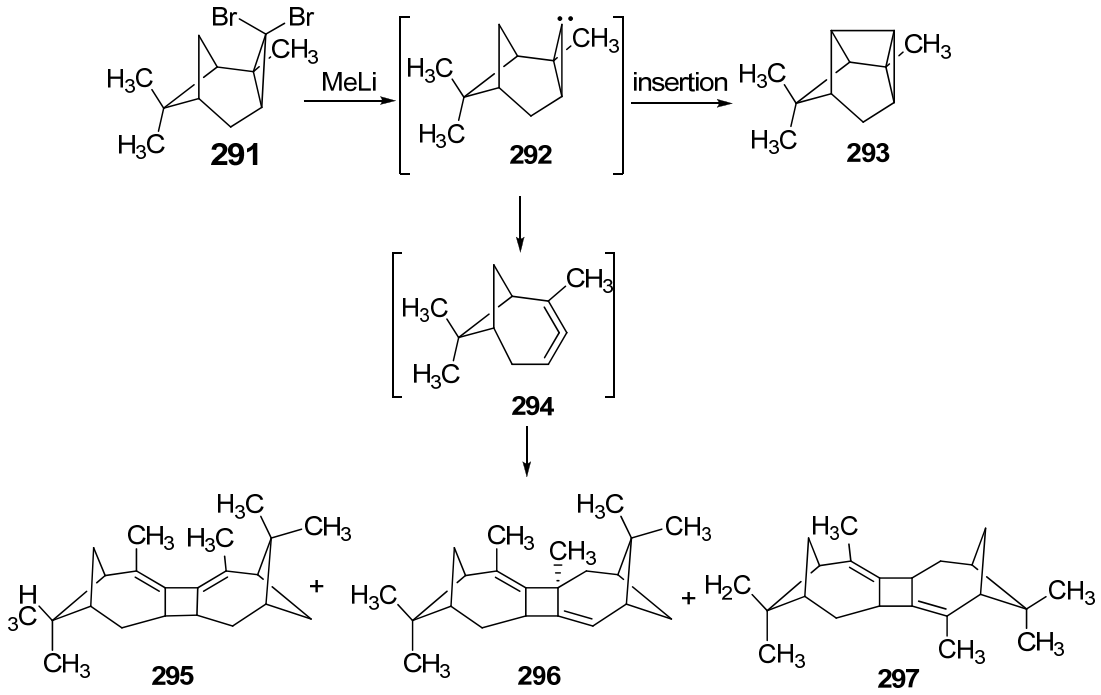


Scheme 80

During the thermal stability test, cyclobutane ring could be opened and some rearrangements might be occurred. However, it did not happen since the methyl groups of cyclobutane ring prevented to ring opening reactions. After the determination of the thermal stability, vinyl halides were submitted to elimination.

2.1.5 Reaction of *(1S,4R,5R)*-3-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (310) with *t*-BuOK

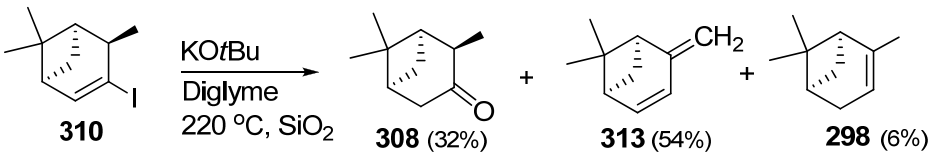
In this step, we aimed to generate an allene unit into a natural product α-pinene, by using β-elimination method. Baird *et al*. and Waegell *et al*. [127] tried to incorporate an allene unit into α-pinene skeleton independently, however they reported that insertion products were formed rather than the allenic products. Later on Balci *et al*. [112] described that, the reaction of dibromide (**291**) formed by the addition of dibromocarbene to α-pinene (**298**) with methyllithium exclusively forms also dimerization products (**295-297**) arising from the initially formed allene moiety *(Scheme 81)*.



Scheme 81

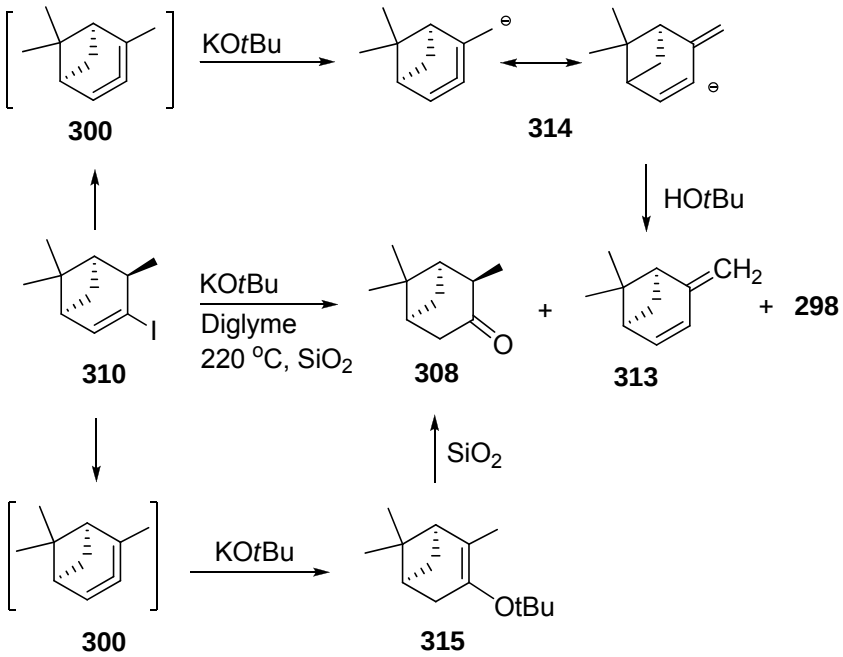
Although Balci *et al*. [112] has proved an allene intermediate by applying DMS method, they obtained seven-membered-ring, that is ring-enlarged product. Hence, incorporation of an allene unit into α–pinene (**298**) skeleton without any ring enlargement would generate a six-membered ring allene **300** which would cause considerable deformation from the linear geometry. Therefore, we were interested in the synthesis of **300**.

Compound **310** was submitted to the base-induced HI-elimination in diglyme at 220 ºC in a sealed tube using KO*t*Bu as a base, in which dehydroiodonation occurred and three products **313**, **308** and **298** were formed in 54, 32 and 6% yields, respectively *(Scheme 82).* When less than 2 equiv. of KO*t*Bu were employed, **310** was not consumed completely. Approximately 5 equiv. of KO*t*Bu changed the ratio of products.



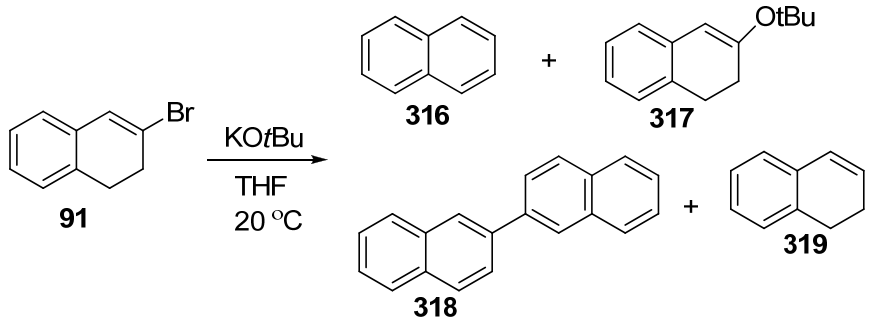
Scheme 82

The formation of the ketone **308** may be rationalized according to Scheme 83. Nucleophilic addition of *t*-BuOK to the central allene C–atom of the formed allenic intermediate **300** gives rise to the enol ether **315**. The hydrolysis of the latter (on silica gel) produces the ketone **308**. Furthermore, deprotonation of **300** by the strong base might also generate the allylic anion **314,** which can take up H^+ to form the conjugated diene **313**.



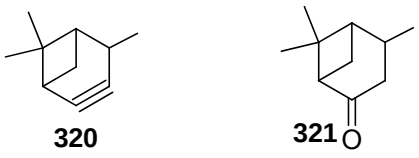
Scheme 83

Recently, Christl *et al.* [53] reacted the allene precursor 3-bromo-1,2-dihydronaphthalene (and derivatives thereof) (**91**) with *t*-BuOK and obtained a mixture of naphthalene (**316**) and enol ether (**317**) as the major products, **318** and **319** as the minors. The formation of the major product was also rationalized by the formation of the desired allene intermediate *(Scheme 84)*.



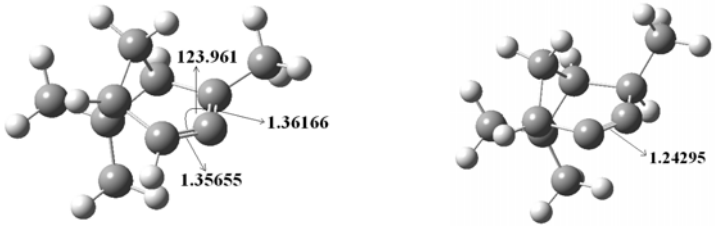
Scheme 84

Actually, we did not have any evidence for the alternative β-elimination, which would lead to the formation of a cyclic alkyne **320**. Bottini *et al.* [39] reported that the change of halide from bromide or iodide to chloride, the use of DMSO in state of Et_2O as solvent, and elevated temperatures all favor allene formation at the cost of alkyne formation. Therefore, we also run the elimination reaction of **310** in DMSO to see whether the product distribution would be affected or not. However, careful analysis of the reaction mixture did not reveal any remarkable change in the product distribution. Actually, the formation of **308** can also be explained by formation of alkyne **320,** followed by addition of *t*-BuOH. However, an asymmetric alkyne can be attacked at two different C-atoms. The observation that the ketone **321** was not detected at all also excludes the formation of **320** *(Scheme 85)*.



Scheme 85

For further support the allene formation we carried out DFT calculations on the cyclic allene and the alkyne and found that the cyclic allene **300** is *ca.* 10.6 kcal/mol more stable than the cyclic alkyne **320** *(Figure 13)*.



300	**320**
E = 0.0	*E*= 10.6

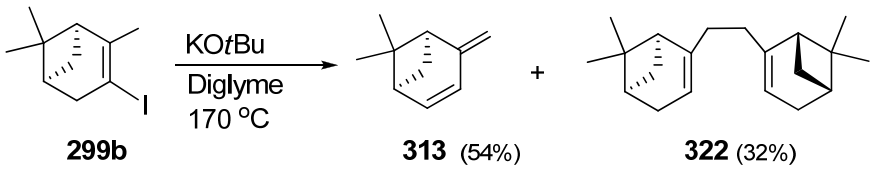
Figure 13: The optimized structures of allene **300** and alkyne **320** and the calculated relative energies at B3LYP/LanL2DZ level some selected bond distances (Å).

The structure of ketone **308** and diene **313** (called in literature as 'verbenene') have been elucidated on the basis of ^{1}H and ^{13}C NMR. The spectroscopic data for ketone derivative (**308**) and diene (**313**) was in good agreement with those previously reported [125,128].

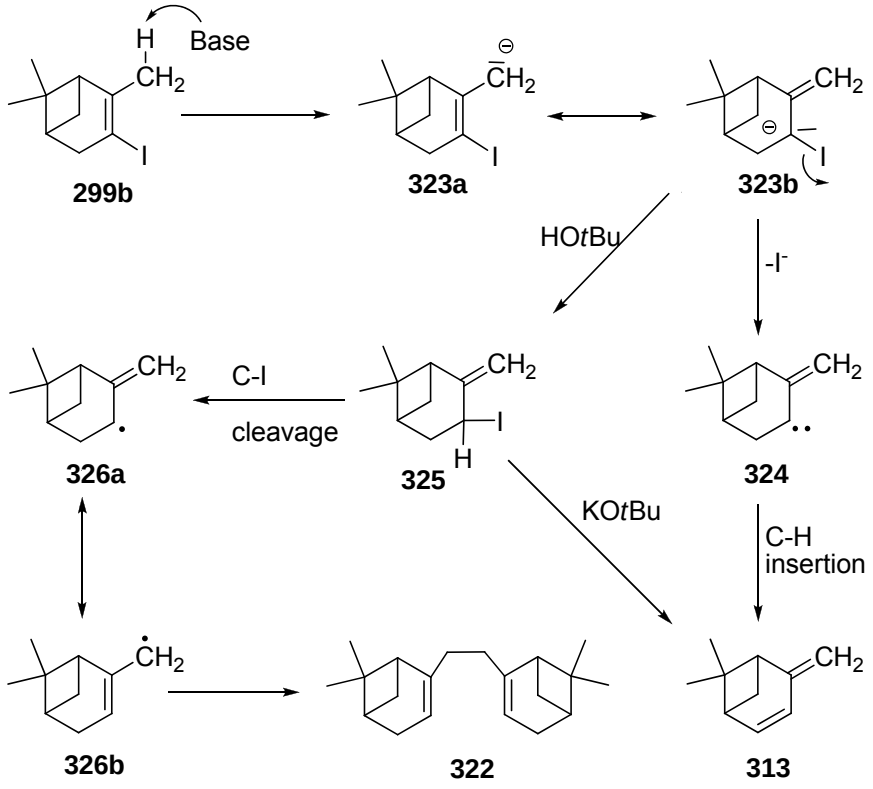
2.1.6 Reaction of *(1S,5S)*-3-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (299b) with *t*-BuOK

Finally, the isomer **299b** was submitted to base-induced HI elimination *(Scheme 86)*. Dehydroiodination occurred at lower temperature (sealed tube, diglyme, 170 ºC), and two compounds, the diene **313** and the dimerization product **322** [129], were formed in 54% and 32% yield, respectively. Meticulous examination of the reaction mixture did not reveal the formation of any other products. Ketone **308**, which had been formed by elimination of **310**, was not detected. Based on this observation, we assume that the allenic intermediate **300** was not formed during the

elimination reaction of **299b**. The underlying reaction mechanism is not entirely clear at this stage. However, we tentatively propose the following a pathway according to *Scheme 87*.



Scheme 86



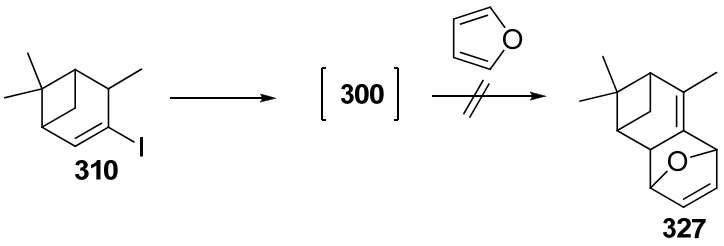
Scheme 87

In the first step, the base deprotonates the methyl group (instead of the adjacent CH_2 group) under formation of the carbanion **323**. The latter then may displace the I-atom to form the corresponding carbene **324**, which, in turn, undergoes C–H insertion resulting in the formation of the conjugated diene **313** as the major

product. Furthermore, the allylic anion **323** can take up H^+ to produce the kinetically controlled product **325**.

DFT calculations (at the RB3LYP/LanL2DZ level of theory) showed that the energy difference between **299b** and **325** is *ca*. 3.4 kcal/mol, the isomer **299b** being thermodynamically more stable. At a reaction temperature of 170 ºC, the C–I bond can easily undergo homolytic cleavage yielding the allylic radical **326**, whose dimerization gives rise to the **322**.

To trap the cyclic allene **300** directly with a diene, base-supported elimination of **310** was conducted in the presence of furan in a sealed tube at elevated temperature (*Scheme 88*). However, careful GC/MS studies of the resulting reaction mixture did not reveal any evidence for the formation of a trapping product **327**. The reaction mixture mainly consisted of the dimerization product **322**, beside a complex product mixture.



Scheme 88

The structure of **313** and **322** have been elucidated on the basis of ^1H and ^{13}C NMR and also GC MS spectral data. According to the GC MS spectrum, molecular ion peak of **322** was 270 for $[M]^+$. To be sure that one of our products was dimer, we compared the NMR spectrum of **322** with starting material α-pinene (**298**), it has been seen that only one proton deficiency in the ^1H NMR spectrum of dimer **322** indicated one of the methyl group converted to methylene group. That is, the integration value was changed from 3 to 2. All these spectroscopic data of proposed structures were in good agreement with those previously reported [128,129].

Finally, we have described a route to the highly strained cyclic allene **300**, which can be generated from 3-iodo-4,6,6-trimethylbicyclo[3.1.1]hept-2-ene (**310**) by β-elimination of HI with *t*-BuOK as base. Alkyne formation was excluded on the basis of the formed products and according to theoretical calculations. Interestingly, base-supported elimination of the isomer **299b** followed a different route and gave the insertion and dimerization products **313** and **322**, respectively.

2.2 THE INVESTIGATION OF *ENDO* CYCLOPROPYLIDENOIDS-CYCLOPROPYLIDENE-ALLENE ISOMERIZATION IN THE BICYCLIC SYSTEMS.

Carbenes are molecules containing divalent carbon atoms. Each divalent carbon has two unshared electrons, which are often shown when writing the structures of carbenes (*Figure 14*). On the other hand, carbenes are neutral molecules.

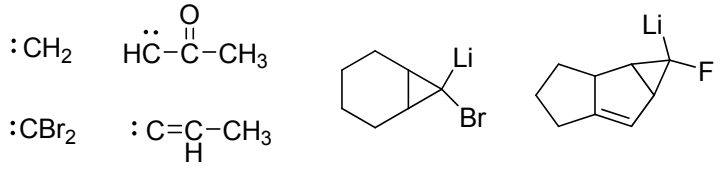


Figure 14: Some typical carbenes and carbenoids

Carbenes are also versatile intermediates that undergo insertion, rearrangement and facile addition reactions in which their importance to synthetic chemists can hardly be overestimated [114,130]. The most common and thoroughly investigated reaction of carbenes is their addition to carbon-carbon double bonds, which provide ready access to cyclopropane derivatives and/or the corresponding rearranged products.

The rather vague term *carbenoids* is used to refer to molecules in which all the carbons are tetravalent, but which have properties resembling those of carbenes [131]. Those properties often include the ability to transfer divalent carbons and their substituents to other molecules. Typically, carbenoids have carbon atoms that are

simultaneously bonded both to metal atoms and to halogen atoms. It is often difficult to be certain whether a 'carbene' reaction in solution is actually the reaction of a free carbene or the reaction of a carbenoid [132].

Although carbenes can be formed by a wide variety of reactions [133], halocarbenes are commonly prepared by reactions of strong bases with organic polyhalides that lack hydrogens on β-carbons, and therefore cannot undergo the usual β-elimination reactions [134]. Instead, the bases abstract protons from the polyhalogenated carbons. The resulting carbanions then lose halide ions to form carbenes, as shown in Figure 15.

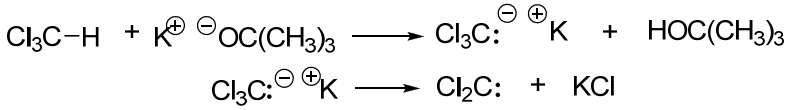


Figure 15: Generation of dihalocarbene

Polyhalides with bromine or iodine atoms can react with organolithium reagents to form α-halolithium reagents, which are frequently stable at dry ice temperatures (*Figure 16*). At higher temperatures, they react to yield products similar to those obtained from carbenes formed by other methods. However, the ratios of products can vary depending on the types of halogen, suggesting that the α-halolithium compounds act as carbenoids rather than dissociating to form free carbenes [135].

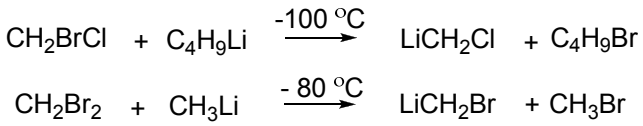
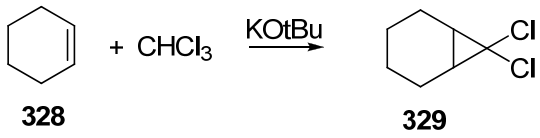


Figure 16: The formation of α-halolithium reagents

The current interest in carbene chemistry stems in large part from the demonstration by Doering and Hoffmann, in 1954, that dihalocarbenes can add to alkenes to form cyclopropane derivatives in high yields *(Scheme 89)* [136].



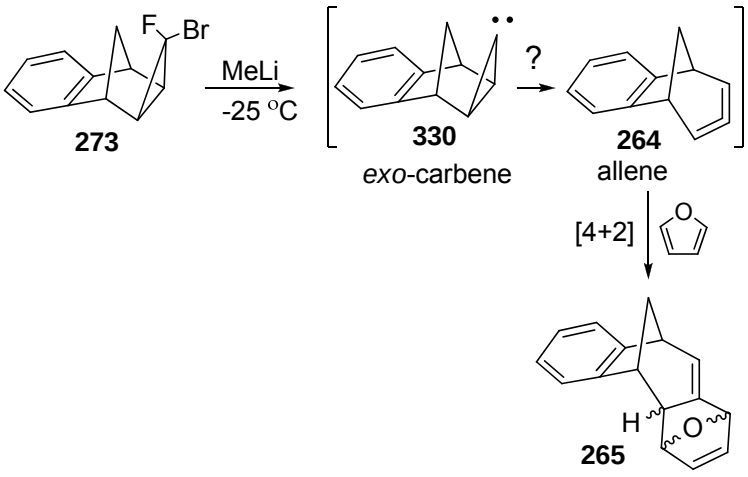
328 **329**

Scheme 89

After that, *gem*-dihalocyclopropanes play an important role in synthetic organic chemistry. They are valuable subtrates for the preparation of monohalocyclopropanes, cyclopropanes, cyclopropenes, benzocyclopropenes, bicyclobutanes, allenes, cumulenes and many other hydrocarbon systems, both unsubstituted and possessing useful functional groups [114b].

It is known that, bicyclic olefines mainly undergo reactions from the *exo*-face of the double bond. However, the *endo*-addition of dihalocarbenes on bicyclic systems is remarkably limited in the literatures.

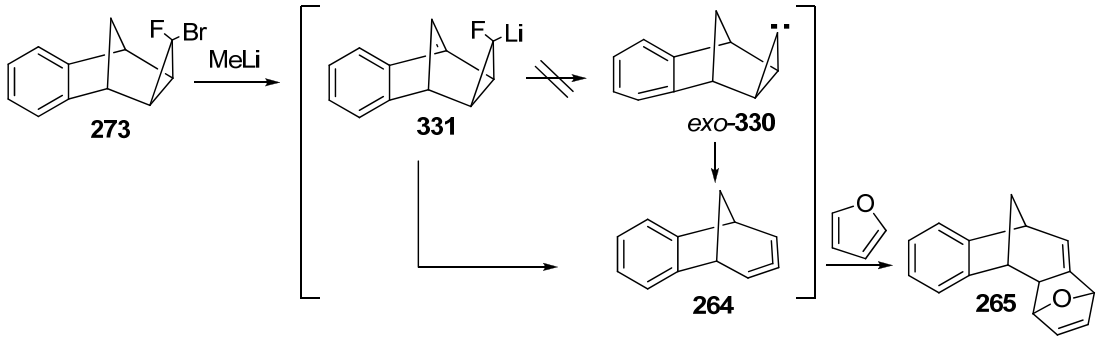
As mentioned before, Balci and Özen reported that the bromofluorocarbene adduct **273** of benzonorbornadiene proved to be a reliable precursor of $3\delta^2$-1,5-dihydro-1,5-methanobenzocycloheptadiene (**264**), the benzo derivative of **250** [108]. However, there was no further information about the possible formation of free-carbene intermediate *exo*-**330** in their report *(Scheme 90).*



273 **330** *exo*-carbene **264** allene **265**

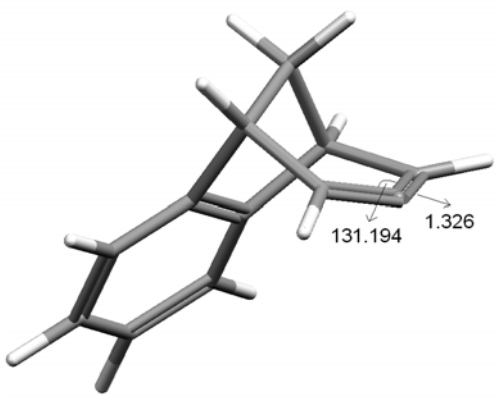
Scheme 90

Most recently, Azizoglu [119] applied some theoretical calculations about during the formation of intermediate **264**. Theoretical calculations (B3LYP/6-31(d) level showed that no *exo*-carbene structure could be optimized in its free carbene form. It also isomerizes to the bicyclic allene during the optimization. Hence, *exo*-carbene is not initial intermediate during the allene formation (*Scheme 91*).

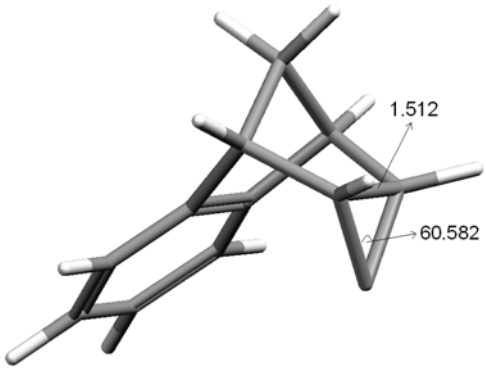


Scheme 91

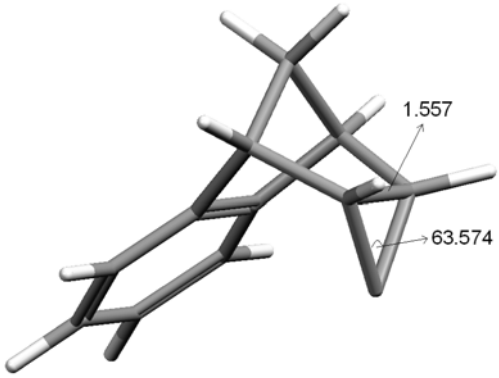
Azizoglu [119] also reported some theoretical calculations about the stability of *endo*-cyclopropylidene. According to his claim, *endo*-cyclopropylidene was optimized as a free carbene *(Figure 17)*.



264



***endo*-330**



TS6 (*endo*-330→264)

Figure 17: Optimized structures of **264**, *endo*-**330** and transition structures T-S6 (*endo*-**330** → **264**)

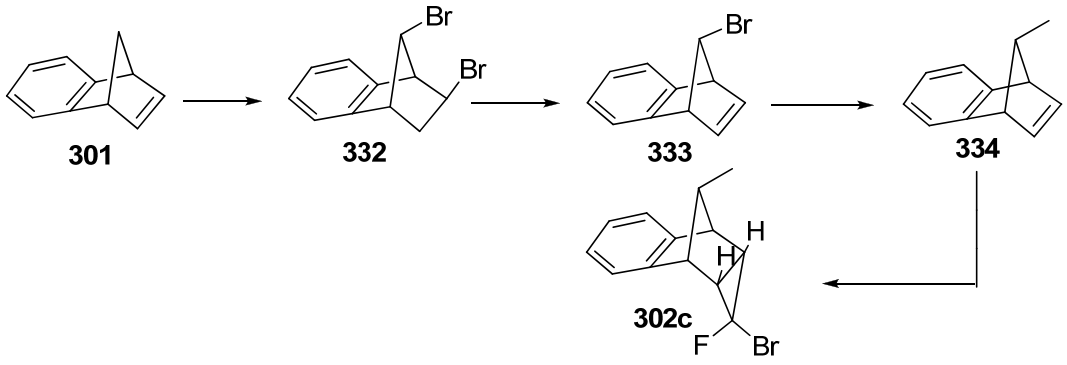
For this reason, in our episode 2, it has been aimed to develop synthetic strategy leading to the dihalocyclopropane and to investigate its reaction with MeLi to test the behaviour of the *endo*-cyclopropylidene **330** which affords whether allene or carbene additon products. In addition, the substituent effect on double bond pyramidalization has been investigated.

Normally, the addition of dihalocarbene proceeds predominantly from the *exo* face of benzonorbornadiene. To hinder this reaction, the *exo*-face of

benzonorbornadiene was protected with suitable substituents to provide the addition of dihalocarbene from the *endo*-face.

2.3 REACTION PATH FOR THE SYNTHESIS OF *anti*-12-METHYL-10-*exo*-BROMO-10-*endo*-FLUOROTRICYCLO[6.3.1.$0^{2,7}$.$0^{9,11}$]DODECA-2,4,6-TRIENE (302c)

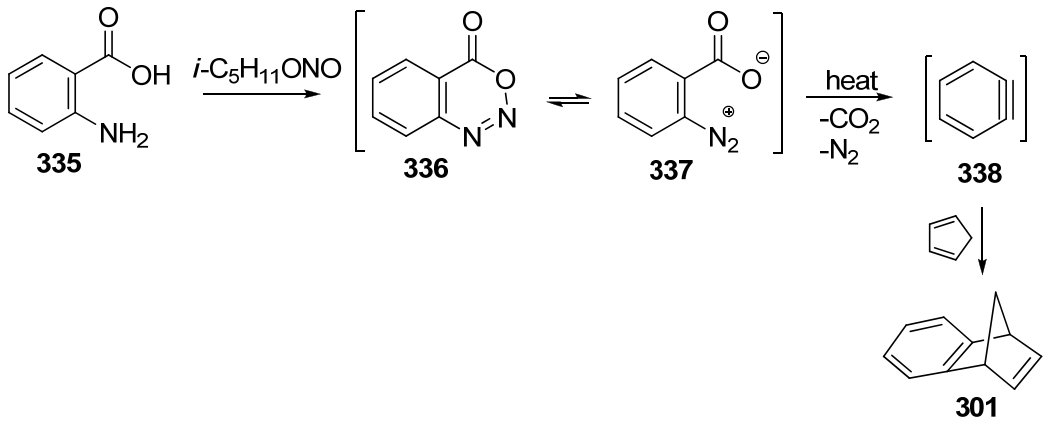
The synthetic path for **302c** was depicted below. According to this path, the dibromo compound **332** will be synthesized from the bromination of benzonorbornadiene (**301**). Then, it will be treated with the suitable base to afford **333**. If bromine group at 7-position of benzonorbornadiene is exchanged with methyl group to yield **334**, the corresponding bromofluorocarbene adduct **302c** can be synthesized by using the carbene addition procedure *(Scheme 92)*.



Scheme 92

2.3.1 The Synthesis of Benzonorbornadiene (301)

A solution of acetone, anthranilic acid and cyclopentadiene was added to a refluxing solution of *iso*-amylnitrite in methylene chloride. After the addition was completed, the entire mixture was refluxed until gas evolution ceased. This usually took 2-5 hours. Then, the solvent was removed under reduced pressure. Suitable work-up and vacuum distillation procedure afforded benzonorbornadiene (**301**) with 40% yield [137] *(Scheme 93)*.



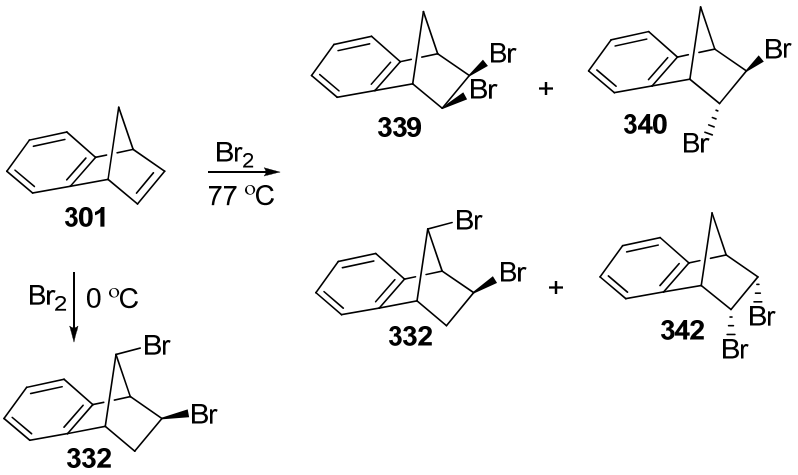
Scheme 93

Characterization of benzonorbornadiene (**301**) was based on the ^{1}H and ^{13}C NMR spectral data, which was also consistent with the literature data [138].

2.3.2 The Synthesis of 2-*exo*-7-anti-Dibromobenzonorborn-5-ene (332)

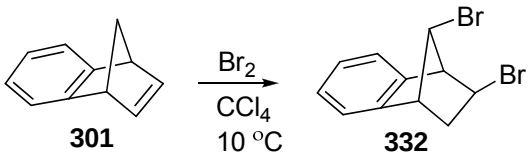
Benzonorbornadiene (**301**) readily undergoes molecular rearrangements. Rearrangements of **301** are of the *Wagner-Meerwein* type [118], which takes place via the formation of a carbonium ion.

Benzonorbornadiene (**301**) affords the possibilities of several mechanistically interesting investigations in the low and high temperature bromination reactions. Balci *et al.* [122] reported that high temperature bromination of benzonorbornadiene (**301**) resulted in the formation of small amount of **332** and non-rearranged products, **339**, **340**, **341** and **342**. High temperature bromination prevents skeletal rearrangement *(Scheme 94)*.



Scheme 94

However, the electrophilic addition of bromine to benzonorbornadiene (**301**) gives rearranged dibromide **332** in quantitative yield at 10 ºC, which was first reported by Wittig and Knauss [139]. According to this literature, to a magnetically stirred solution of **301** in carbon tetrachloride cooled to 0 ºC was added dropwise a solution of bromine in carbontetrachloride. After completion of the addition, the solution allowed to warm to room temperature. The solvent removed under reduced pressure. The residue was crystallized from ethanol to give *Wagner-Meerwein* rearranged dibromide **332**. The crude yield of reaction was 95% *(Scheme 95).*

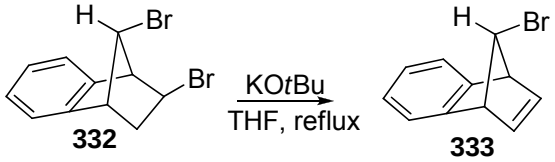


Scheme 95

Characterization of 2-*exo*-7-anti-dibromobenzonorborn-5-ene (**332**) was based on the ^{1}H and ^{13}C NMR spectral data, which was also consistent with the literature data [122, 138,139].

2.3.3 The Synthesis of *anti*-7-Bromobenzonorbornadiene (333)

Wilt *et al.* reported that dehydrobromination of **332** in DMSO gives *anti*-7-bromobenzonorbornadiene (**333**) with 67 % yield [139]. However, when dibromide compound **332** in freshly distilled THF was added dropwise to a mechanically stirred solution of potassium *t*-butoxide in the same solvent at reflux temperature under nitrogen atmosphere, the desired compound **333** was obtained in 91% yield. The oily residue was crystallized from hexane to give colorless crystals of **333** *(Scheme 96)*.

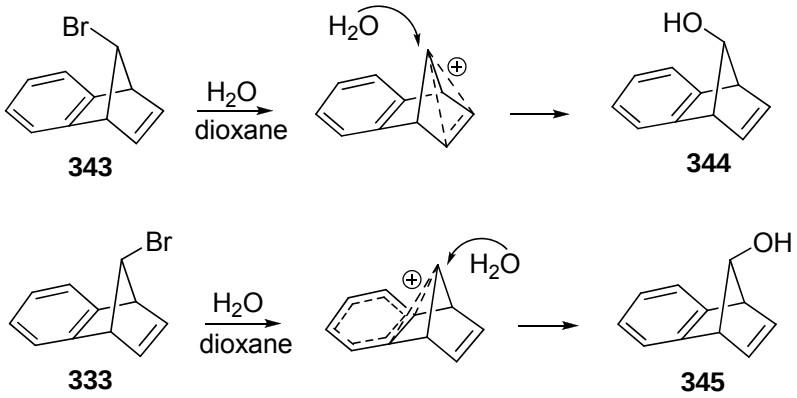


Scheme 96

Characterization of *anti*-7-bromobenzonorbornadiene (**333**) was based on the ^{1}H and ^{13}C NMR spectral data, which was also consistent with the literature data [139].

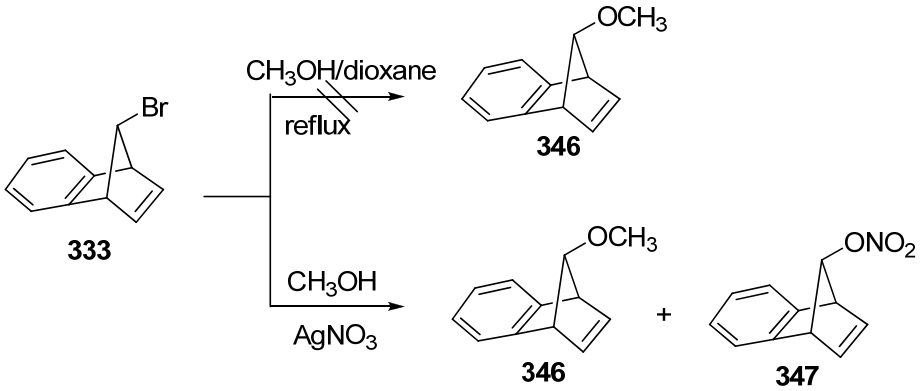
2.3.4 The Synthesis of *anti*-7-Methylbenzonorbornadiene (334)

Wilt and Chenier studied the solvolysis reaction of halogenated benzonorbornadienes extensively [140]. The authors reported that both *syn*- and *anti*-7-bromobenzonorbornadienes (**343** and **333**) solvolyze in aqueous dioxane with the retention of configuration to yield **344** and **345**, respectively. They explained these experimental results in terms of the contrast in π-participation between aromatic and olefinic abilities to stabilize homoallylic cationic centers formed by ionization of **343** and its anti epimer **333** as shown in Scheme 97. Cristol and Nachtigall [141] also reported similar results in the acetolysis of chloro derivatives of **343** and **333**.



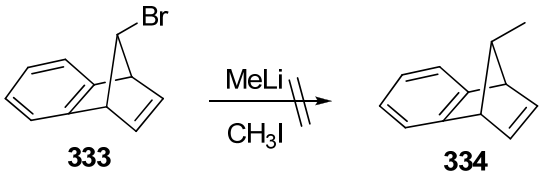
Scheme 97

More recently, Azizoglu [119] tried to solvolyze **333** in methanol and dioxane solution. However, they did not obtain the corresponding product **346**. The ether **346** was synthesized with silver nitrate in methanol *(Scheme 98).*



Scheme 98

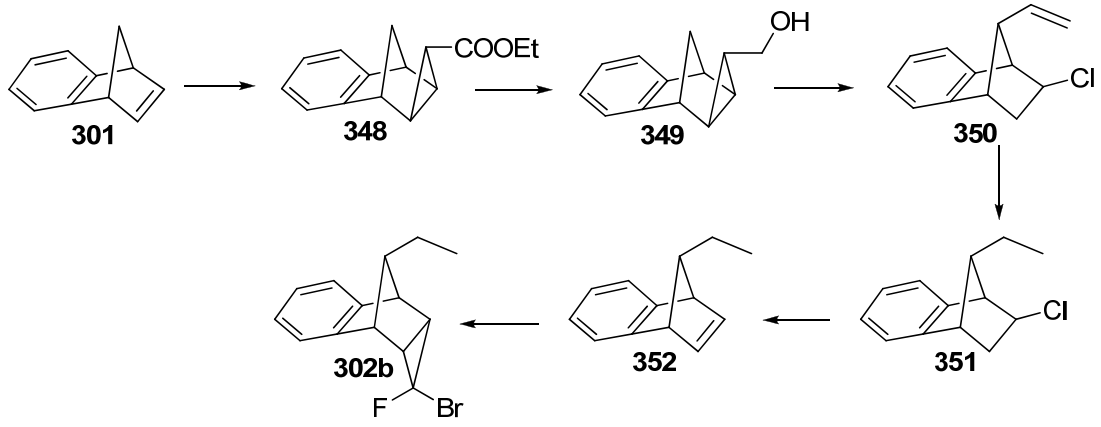
In the light of the literature data, we aimed to synthesize *anti*-7-methylbenzonorbornadiene (**334**). **333** was treated with methyllithium, than methyl iodide was added into a solution in order to proceed a substitution. However, the expected reaction did not work. We also tried *Grignard* method, unfortunately no reaction took place. It was realized that the formation of a carboanion at 7-position can not be possible. Since π-participation of aromatic and olefinic abilities prevented to make a carbanion at bridge position *(Scheme 99)*.



Scheme 99

2.4 REACTION PATH FOR THE SYNTHESIS OF *anti*-12-ETHYL-10-*exo*-BROMO-10-*endo*-FLUOROTRICYCLO[6.3.1.02,7.09,11]DODECA-2,4,6-TRIENE (302b)

The synthetic path for **302b** was depicted below. According to this path, benzonorbornadiene (**301**) will be exposed to carbene addition reaction. Afterwards, ester **348** will be reduced to corresponding alcohol **349**. An alcohol **349** will be treated with thionyl chloride, to synthesize rearranged product **350**. After hydrogenation of **350**, the resulted compound **351** will be eliminated to **352**. Finally, we will try to synthesize fluorobromoadduct **302** *(Scheme 100)*.

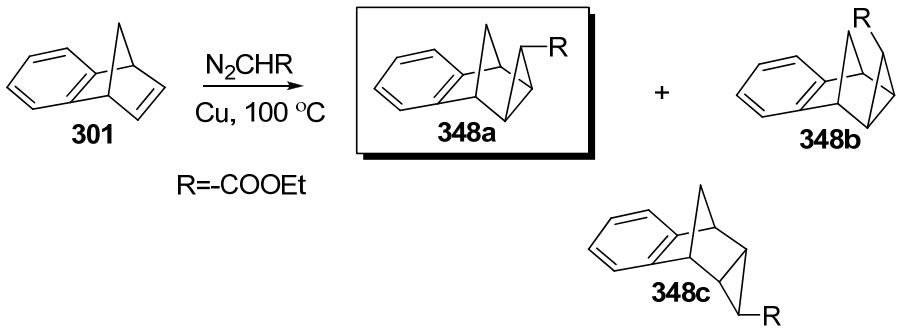


Scheme 100

2.4.1 Synthesis of *Exo,anti*-10-carboethoxytetracyclo[6.3.1.0^{2,7}.0^{8,9}]dodeca-2,4,6-triene (348).

Ghenciulescu *et al*. [142] reported that ester **348** can be synthesized by the reaction of benzonorbornadiene (**301**) with ethyldiazoacetate. According to this

literature, benzonorbornadiene (**301**) and copper (used as catalyst) were placed in 100 ºC oil bath without any solvent. Then, ethyldiazoacetate was added dropwise to the reaction medium. After completion of the reaction, residue was submitted to rapid silica filtration. After eluting with corresponding solvent mixture, three isomers **348a-348c** were isolated. After crystallization, **348a** was obtained in a yield of 19% *(Scheme 101)*.

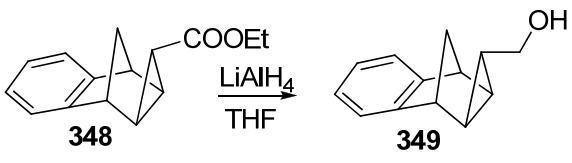


Scheme 101

The structure of **348a** and compound **348b** have been elucidated on the basis of ^{1}H and ^{13}C NMR. The spectroscopic data for both of them was in good agreement with those previously reported [142]. However, **348c** was not purified. It was isolated as mixture **348a**.

2.4.2 *exo,anti*-10-Hydroxymethyltetracyclo[6.3.1.02,7.08,9]dodeca-2,4,6-triene (349).

The ester **348a** was easily reduced to alcohol **349** by reacting with lithium aluminum hydride in THF at 0 ºC. After hydrolytic work-up and evaporation of solvent, the desired alcohol **349** was obtained in 90% yield [142] *(Scheme 102)*.



Scheme 102

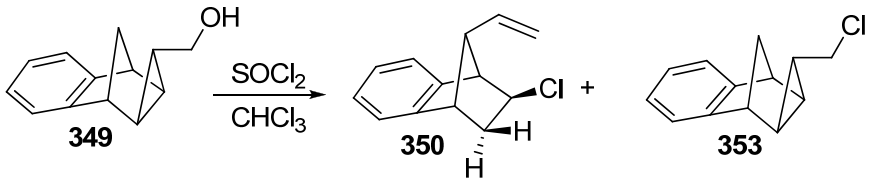
Characterization of **349** was based on the ^{1}H and ^{13}C NMR spectral data, which was also consistent with the literature data [142].

2.4.3 The Synthesis of *anti*-9-chloro-11-vinyltricyclo[6.3.1.02,7.08,9]unadeca-2,4,6-triene (350).

An important method for the synthesis of alkyl chlorides is the reaction of alcohols with reagents such as HCl or $SOCl_2$. The formation of alkyl chlorides as rearranged products depends on both the reaction conditions and reagents used. As mentioned before, strained systems such as α-pinene (**298**), benzonorbornadiene (**301**) and cyclopropane are most likely to undergo rearrangements upon halogenations.

Most recently, Menzek *et al.* [142c] have reported that the transformation of cyclopropylmethanols into homoallylic halides is a useful reaction and received considerable attention.

According to this literature, alcohol **349** was reacted with thionyl chloride in chloroform at low temperature for about 30 minutes. After hydrolytic work-up and and removal of solvent, the two constitutionally isomeric chlorides **350** and **353** were obtained and they were separated by column chromatograpy eluting with hexane. The desired vinylic halide **350** were isolated in 74% yield *(Scheme 103)*.



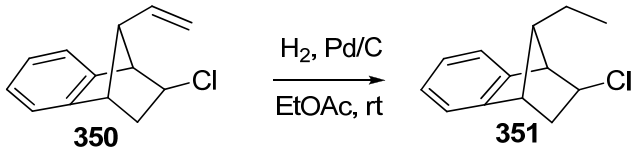
Scheme 103

Characterization of **350** was based on the ^{1}H- and ^{13}C-NMR spectral data, which was also consistent with the literature data [142c]. The compound **350** could easily be distinguished from nonrearranged **353**. Nonrearranged product **353** has a symmetrical structure and exhibits an *AA'BB'* for the aromatic protons in the ^{1}H NMR spectrum. However, the structure of rearranged compound **350** is

nonsymmetric and results from the opening of the cyclopropane ring and skeleton rearrangement. Furthermore, signals of a vinyl group are visible in spectrum which is also the evidence of rearrangement. Due to nonsymmetrical structure of **350**, methylenic protons resonate as an *AB* system. The H-atom in *endo*-position (*trans* to Cl) resonates as doublet of doublets at 2.14 ppm split by the geminal and vicinal protons, which is located at the C-atom carrying the -Cl substituent. The H-atom in *exo*-position (*cis* to Cl) appears as doublet of triplets at 2.43 ppm with *J*= 13.40, 3.87 Hz. There are thirteen signals in ^{13}C NMR for **350**, hence no doubt remain as to proposed structure due to extremely characteristic spectroscopic data.

2.4.4 The Synthesis of *anti*-9-chloro-11-ethylltricyclo[6.3.1.02,7.08,9]unadeca-2,4,6-triene (351).

Catalytic hydrogenation of **350** with Pd/C in EtOAc gave the desired product (**351**) in 90% yield *(Scheme 104)*.



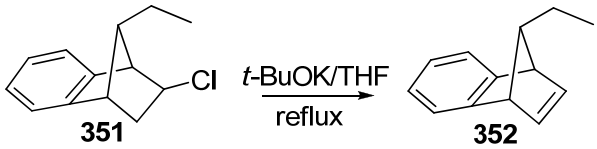
350 **351**

Scheme 104

Characterization of **351** was based on ^{1}H and ^{13}C NMR spectral data. ^{1}H NMR spectrum of **351** revealed eleven sets of proton signals. Absence of olefinic protons indicated hydrogenation was succeeded. Methylenic protons adjacent to bridge C-atom, gave *AB* system. *A*-part of the *AB* system appears as doublet of quartets at 1.90-1.73 ppm with *J*= 14.6, 7.4 Hz, *B*-part of *AB* system appears as doublet of quintets at 1.70-1.60 ppm with *J*= 14.6, 7.4 Hz as well. Compound **351** gained a methyl group resonated as triplet at 0.98 ppm with *J*= 7.5 Hz. There are thirteen lines in ^{13}C NMR for **351**. So, no doubts remain as to proposed structure due to extremely characteristic spectroscopic data.

2.4.5 The Synthesis of *anti*-7-Ethylbenzonorbornadiene (352).

To synthesize *anti*-7-ethylbenzonorbornadiene (**352**), the reaction of chloride **351** with *t*-BuOK was investigated. From this reaction, compound **352** was obtained in a yield of 68% *(Scheme 105)*.



Scheme 105

Characterization of **352** was based on ^{1}H and ^{13}C NMR spectral data. ^{1}H NMR spectrum of **352** revealed seven sets of proton signals. Compound **352** could easily be identified; it has a symmetrical structure and exhibits *AA'BB'* system for the aromatic H-atoms, and the structure is consistent with a nine-line ^{13}C NMR spectrum.

2.4.6 Reaction of fluorobromocarbene with *anti*-7-Ethylbenzonorbornadiene (352).

The most common and thoroughly investigated reaction of carbenes is the addition to carbon-carbon double bonds. Since dihalocarbenes are electrophilic reagents they can easily undergo addition reactions with electron rich double bonds even at low temperatures to give cyclopropane derivatives.

Since the alkenes are normally planar. However there are some cases in which the double bonds are distorted from the planarity. The distortion is defined as π pyramidalization in the literature [143] *(Figure 18).*

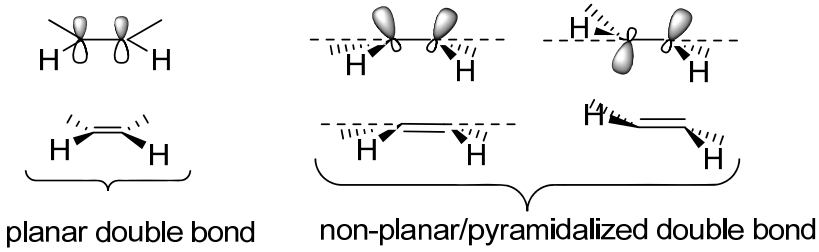
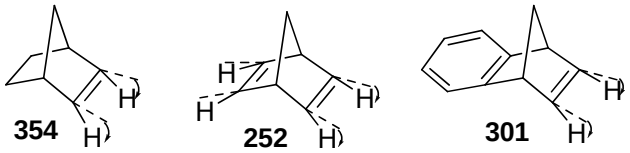


Figure 18: Planar and pyramidalized double bonds

Strained and/or pyramidalized alkenes contain carbon-carbon double bond in which one or both the sp^2 carbon atoms do not lie in the plane of the attached atoms [144]. As a consequence of the double bond pyramidalization, the two faces of double bond are no longer equivalent. This extraordinary geometrical feature causes the very noticable π-facial stereoselectivity in addition reactions to carbon double bonds [145]. The degree of pyramidalization is influenced by the electron density of the alkenyl π-bond [146].

For instance, theoretical calculations showed that, the double bonds in norbornene (**354**) is pyramidalized in the *endo*-direction about 7º. Norbornadiene (**252**) and benzonorbornadiene (**301**) are bent to a smaller extent in the *endo* direction, the pyramidalization angle being approximately 2-4º [143b,147] *(Scheme 106)*.

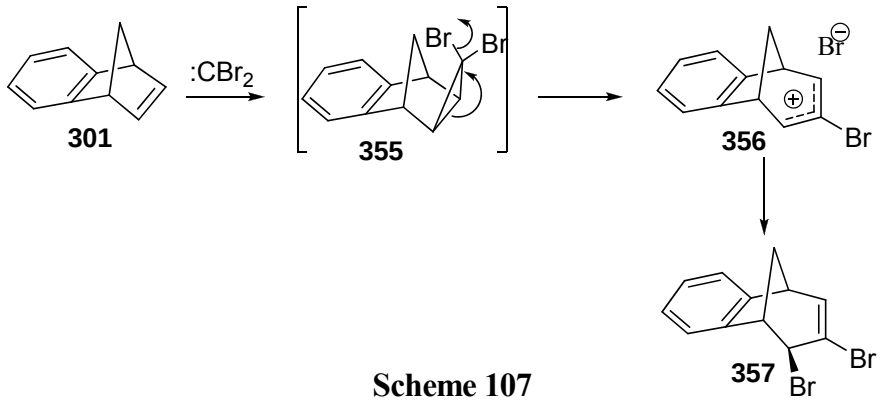


Scheme 106

Therefore, their two π-faces of the double bond are chemically non-equivalent and they are attacked by a variety of reagents preferentially from the *exo*-face of the double bond [148].

The addition of dihalocarbenes to norbornene (**354**), norbornadiene (**252**), and benzonorbornadiene (**301**) provides the most direct route to compounds containing the bicyclo[3.2.1]octyl ring system [149]. The reaction involves addition of the carbene to the *exo*-face of the bicyclic alkene to give initially a *gem*-dichlorocyclopropane, which under the reaction conditions usually undergoes ring opening to afford a rearranged, ring expanded dihalide. Kitahonoki *et al.* [150] reported that the reaction involves addition of the carbene to the *exo*-face of benzonorbornadiene (**301**) to give initially a *gem*-dibromocyclopropane **355**, which

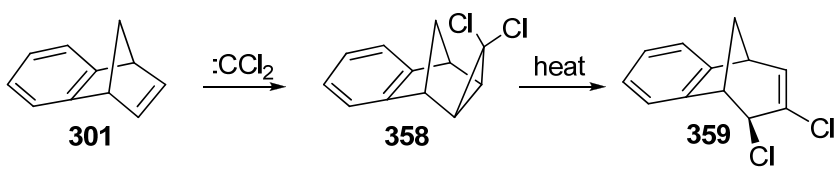
under the reaction conditions usually undergoes ring opening to afford a rearranged, ring-expanded dihalide **357** *(Scheme 107).*



Scheme 107

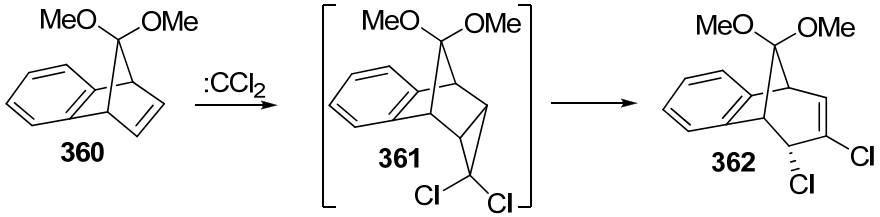
Woodward and Hoffman [151] claimed that the stereochemical outcome of *gem*-dihalocyclopropane ring opening has been rationalized in terms of orbital symmetry constraints. The reaction involves cyclopropyl to allyl cation interconversion with participation of the cyclopropyl bonding electrons from the face of the cyclopropyl ring opposite to that of the departing halide ion **356**, then affords the allylic halide **357**, of defined stereochemistry. In a converse argument, for those cases in which the *gem*-dihalocyclopropane can not be isolated or detected, the stereochemistry of the allylic halide defines the stereochemistry of carbene addition; *exo* halogen orientation implies *exo*-addition of dihalocarbene.

Recently, Wege [152] reported that the addition of dichlorocarbene to benzonorbornadiene (**301**) at 0 ºC permitted the isolation of the *exo*-adduct **358**, which underwent isomerization to the *exo* allylic chloride **359** only upon prolonged storage, or upon distillation. All previous reports of the addition of dichlorocarbene to **301** have only recorded the direct isolation of the rearranged material **359** *(Scheme 108).*



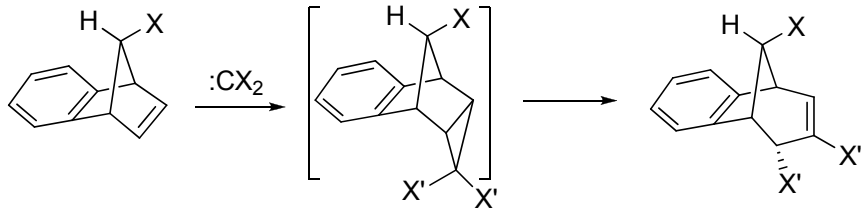
Scheme 108

Moreover, Wege [152] explained the addition of dichlorocarbene to 7,7-dimethoxy benzonorbornadiene (**360**) in which a substituent shields the *exo* face of the double bond. The dichloride **362** was isolated as the only product, which results from the ring opening of an adduct **361** under the reaction conditions *(Scheme 109).*



Scheme 109

Most recently, Azizoglu [119] has tried to isolate *endo* adduct **364**. Some different substituents were located at the C-7 carbon atom and also different dihalocarbene were used to test the stability of the endo adduct **364**. Unfortunately, it has been realized that addition of dihalocarbene to **363**, undergoes directly ring opening reaction to afford ring-expanded halide **365** *(Scheme 110).*



363a X=-Br
363b X=-OMe

364a X'=-Br
364b X'=-Cl

365a X'=-Br
365b X'=-Cl

Scheme 110

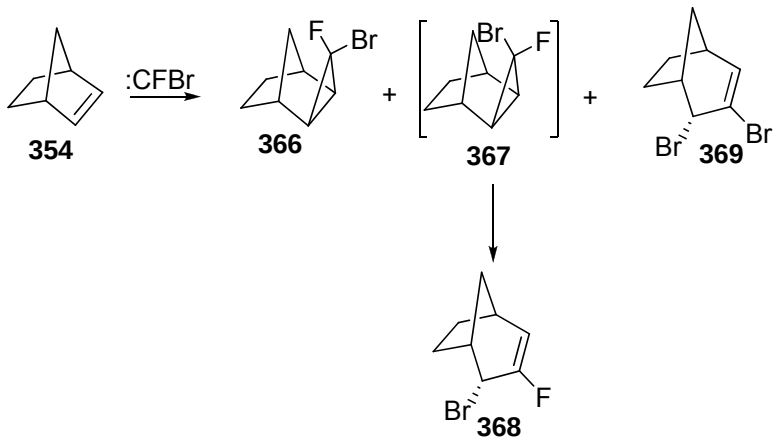
As a result, it is evident that in the addition of dibromocarbene and dichlorocarbene to *anti*-7-bromobenzonorbornadiene (**363a**) and *anti*-7-methoxybenzonorbornadiene (**363b**), attack of the carbene occurs exclusively at the *endo* face of the π-bond, leading to the adduct **364a** and **364b**. However, they suffer stereoelectronically-controlled ring opening under the reaction conditions to give the ring-expanded dihalide **365a** and **365b**. This predominant *endo*-addition is a

consequence of shielding of the *exo*-face by the bromine and methoxy substituents at C-7 position in compound **363**.

In the light of these literature data, we decided to achieve the reaction of bromofluorocarbene with *anti*-7-ethyl-benzonorbornadiene (**352**) to isolate gem-fluorobromocyclopropane without ring opening reaction.

However, *gem*-bromofluorocyclopropanes are often unstable, so there is a limited amount of information available concerning their generation and applications despite their potential usefulness in organic chemistry [114b].

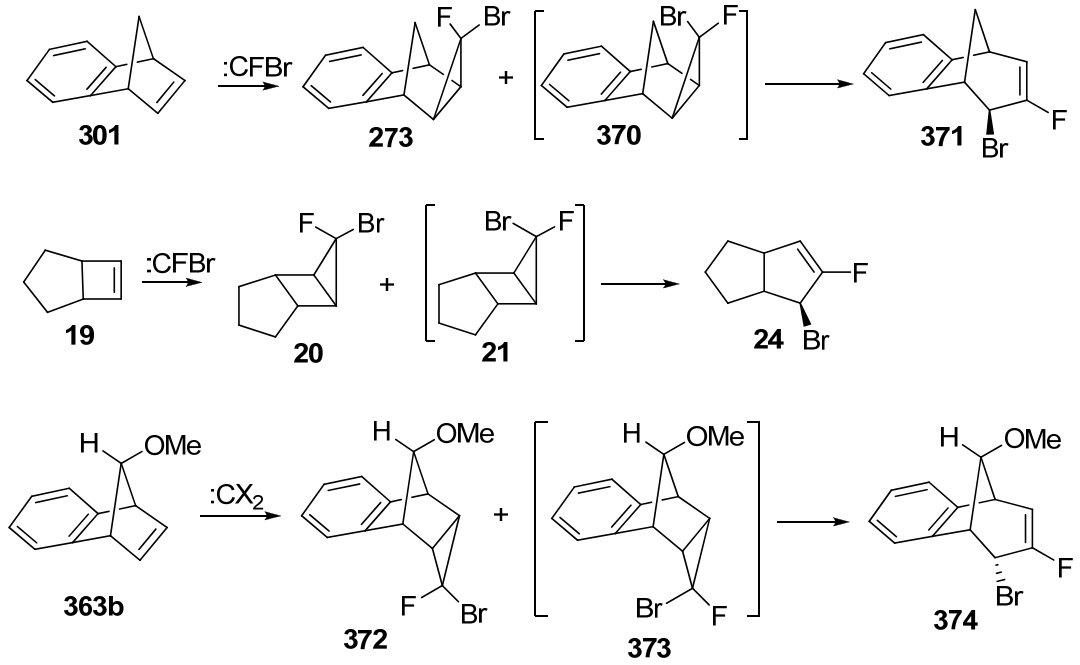
Jefford and Hill reported the addition of bromofluorocarbene to the bicyclic olefin, norbornene (**354**) for the first time [153]. They isolated three products, **366**, **368**, and **369**, by fractional distillation and thin layer chromatography. Compound **366** is suprisingly stable; heating to 110 ºC for 4 hours is without effect, so the rearranged product **368** undoubtedly arise spontaneously from the epimeric adduct **367**. The unexpected formation of the dibromo product **369** results from the presence of some undetected bromoform in difluorobromomethane *(Scheme 111)*.



Scheme 111

More recently, Balci *et al.* [29,108,119] have reported that the addition of bromofluorocarbene to benzonorbornadiene (**301**), bicyclo[3.2.0]hept-6-ene (**19**) and *anti*-7-methoxybenzonorbornadiene (**363b**) affords unrearranged

bromofluorocyclopropane, **273**, **20** and **372**, in addition to the *exo*-bromofluoro ring-opened product, **371**, **24** and **374** respectively *(Scheme 112)*.



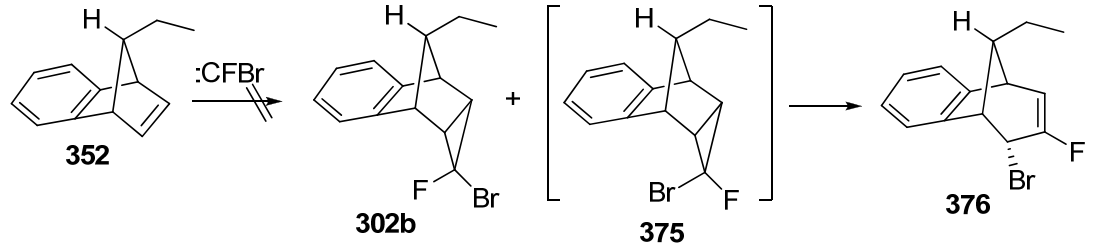
Scheme 112

Due to the above experiences in the literatures, the addition of bromofluorocarbene to *anti*-7-ethylbenzonorbornadiene (**352**) was aimed to isolate the *endo*-adduct **302b**.

First of all, dibromofluoromethane, precursor of bromofluorocarbene, should have been prepared, since this reagent was not commercially available. According to the literature [154a], it was obtained from the reaction of antimony trifluoride with bromoform under the nitrogen atmosphere with 35 % yield. The careful distillation was needed to remove any impurities, such as bromoform, which would give dibromocarbene with bases if it were present in the dibromofluoromethane.

Later, bromofluorocarbene was generated from $CHBr_2F$ and concentrated sodium hydroxide solution under the phase transfer conditions reacted with *anti*-7-ethylbenzonorbornadiene (**352**) at 50 ºC without using any solvent [154b,155]. The corresponding work-up procedure was applied to the reaction mixture.

Unfortunately, the analysis of the reaction mixture by NMR spectra did not reveal the formation of the addition product (**302b**) *(Scheme 113).*

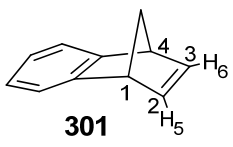
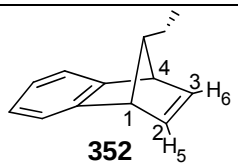
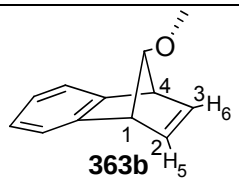


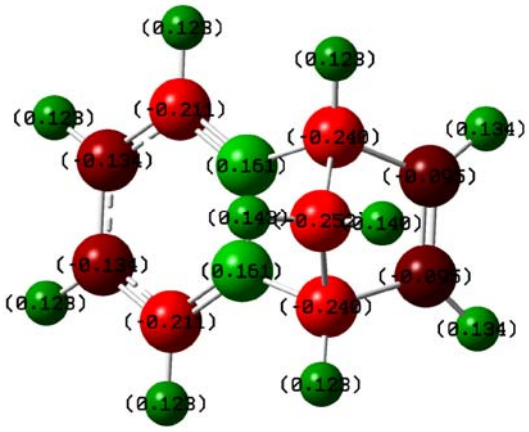
Scheme 113

Attempts different conditions to isolate *gem*-bromofluorocyclopropane (**302b**), did not change the fate. However, Azizoglu [113] reported that fluorobromocarbene addition to *anti*-7-methoxybenzonorbornadiene (**363b**) afforded *gem*-fluorobromocyclopropane **372** and ring-opening adduct **374**. Therefore, substituent located at C-7 position affects directly carbene addition to olefin.

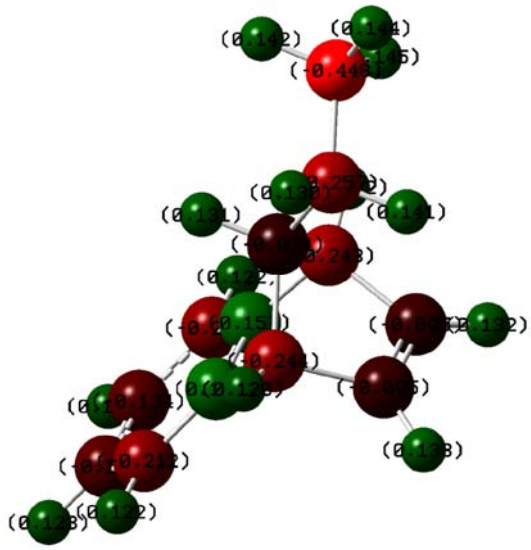
According to the theoretical calculations (B3LYP/6-31G(d)), when $–CH_2CH_3$ is accommodated to C-7 carbon atom, surprisingly the pyramidalization of double bond increases respect to the methoxy derivative **363b** *(Table 1-Figure 19).* As a result, more strained energy and deformation of planarity on double bond prevented carbene addition to compound **352** *(Scheme 113).*

Table 1: Pyramidalization angles & charge distributions on double bonds.Two charge values are given due to unsymmetrical double bonds.

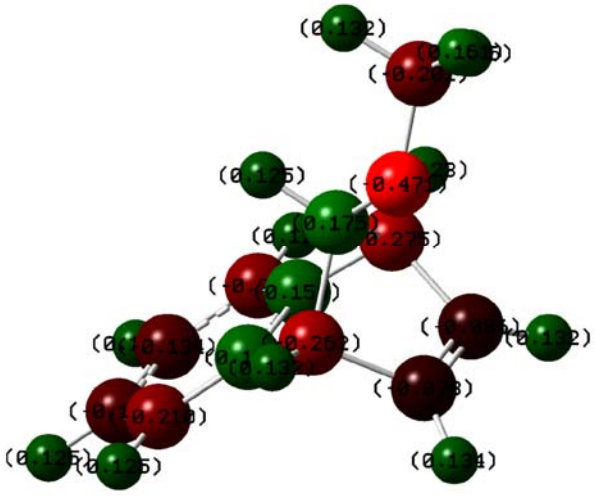
	 **301**	 **352**	 **363b**
$C_1C_2C_3H_6$	-174.79975	-175.12106	-176.17040
$C_4C_3C_2H_5$	174.79923	175.00120	176.06344
Charge on C_2 / C_3	-0.095 / -0.095	-0.095 / -0.095	-0.078 / -0.086



benzonorbornadiene (**301**)



anti-7-Ethylbenzonorbornadiene (**352**)

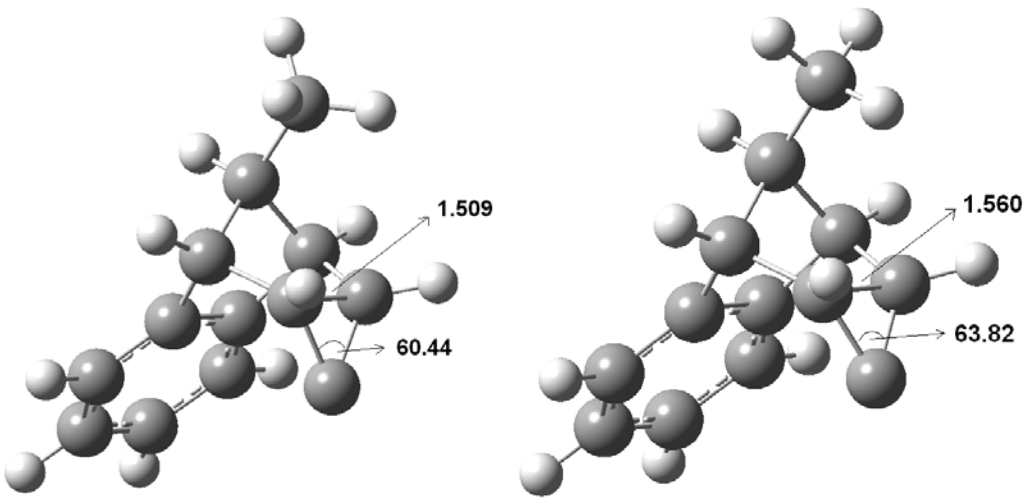


anti-7-Methoxy-benzonorbornadiene (**363b**)

Figure 19: Charge distributions

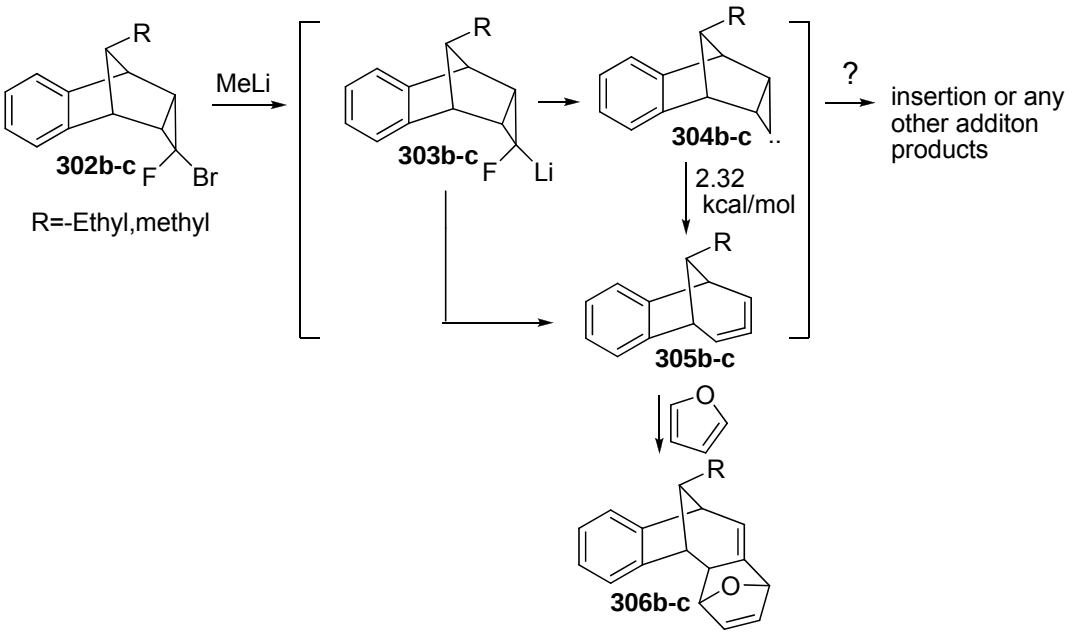
Finally, attempt of carbene addition to *anti*-7-ethylbenzonorbornadiene (**352**) was retarded by pyramidalization effect.

If *gem*-bromofluorocyclopropane adduct **302b** would be formed, what would happen by the treatment of desired product **302b-c** with methyllithium? Theoretical calculations at B3LYP/6-31G(d) level shows that *endo*-carbene **304b-c** be formed in a free carbene (*Figure 20*). Furthermore, theoretical calculations show that the formed free carbene **304b-c** can easily isomerize to the corresponding allene **305b-c** with a small barrier of 2.32 kcal/mol. The formed allene may be trapped with dienes such as furan etc *(Scheme 114).*



304b **TS8 (304b => 305b)**

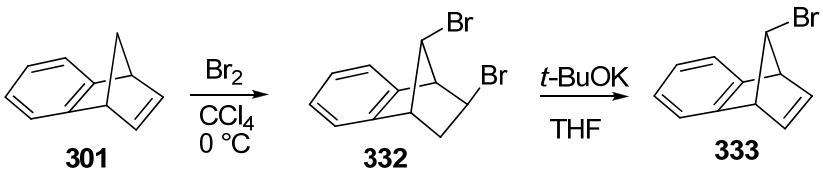
Figure 20: Optimized structure of **304b-c** and transition structure **TS8** (**304b** => **305b**) at B3LYP/6-31G(d)



Scheme 114

2.5 REACTION PATH FOR THE SYNTHESIS OF *anti*-12-BROMO-10-*exo*-BROMO-10-*endo*-FLUOROTRICYCLO[6.3.1.02,7.09,11]DODECA-2,4,6-TRIENE (302a)

After unsuccesfull attempt to add a carbene addition to *anti*-7-ethylbenzonorbornadiene (**352**), we decided to change the substituent located at C-7 carbon atom. For this reason, benzonorbornadiene (**301**) was reacted with bromine to give the rearranged product **332** as described in the literature [122,139]. Elimination of HBr resulted in the formation of **333**, where bromine atom is located in *exo*-position. After that, the corresponding bromofluorocarbene adduct **302a** can be synthesized by using the carbene addition procedure *(Scheme 115).*

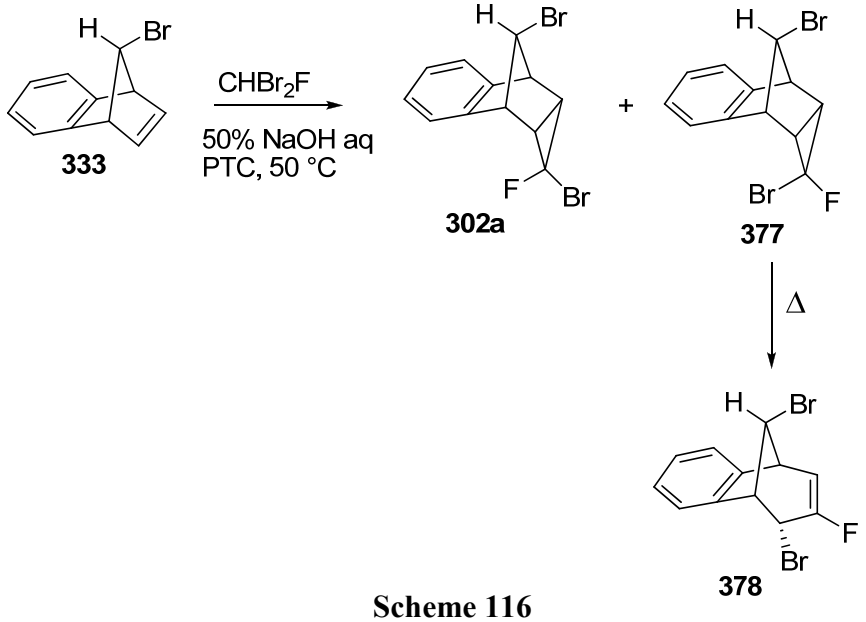


Scheme 115

As mentioned before, the synthetic routes of **301**, **332** and **333** were reported to reach the corresponding product **302c**, so no need to further explanation.

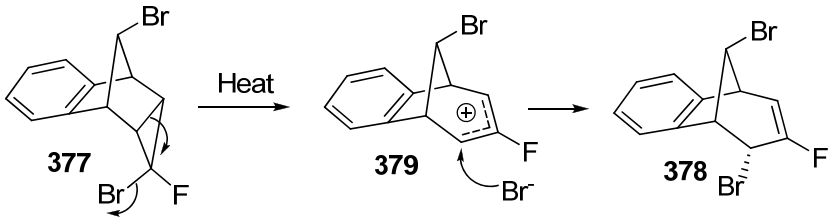
2.5.1 The Reaction of Fluorobromo Carbene with *anti*-7-Bromobenzonorbornadiene (333)

The addition of fluorobromocarbene, generated from $CHBr_2F$ and sodium hydroxide under phase-transfer conditions, to *anti*-7-bromobenzonorbornadiene (**330**) at 50 ºC without using any solvent afforded two products, *gem*-dihalocyclopropane **302a** and the *endo*-bromofluoro ring-opened product **378** in a ratio of 3:2 with total yield of 16 % (based on recovered starting material with three sequential reactions). Vacuum distillation method was used for separation of starting material. During the vacuum distillation, it was realized that compound **377** was directly isomerized to ring-expanded dihalide **378**. As a result, **377** was not isolated *(Scheme 116)*. During the reaction, the temperature should be kept at 50 ºC, since the yield of products decreases drastically above or below this temperature. Other important point is the selection of suitable phase-transfer catalytst. At the start of synthesis **302a**, benzyltriethylammonium chloride was used as a phase transfer catalyst (PTC) and the yield of this reaction was 11%. On the contrary, the reaction yield increased to 16% when benzyltributylammonium chloride was used instead of it.



Scheme 116

According to the Woodward-Hoffman rules relating with the stereochemical outcome of *gem*-bromofluorocyclopropane, ring opening rationalized in terms of orbital symmetry constraints [151], this reaction involves the cyclopropyl to allyl cation interconversion with participation of cyclopropyl bonding electrons from the face of cyclopropyl ring opposite to that of the departing bromine anion. Collapse of the resulting ion pair **379**, then affords the allylic halide **378** *(Scheme 117).*



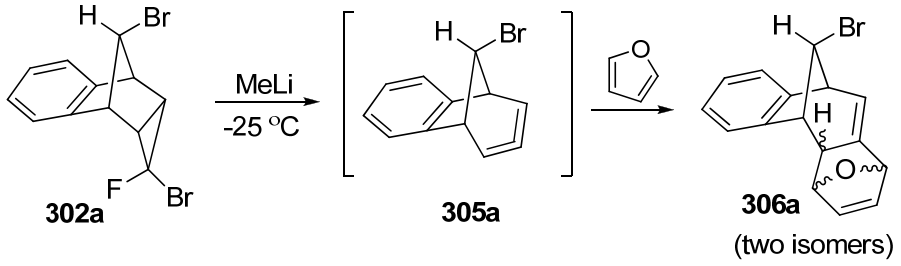
Scheme 117

Characterization of *gem*-fluorobromocyclopropane **302a** and ring-expanded dihalide **378** were based on ^{1}H and ^{13}C NMR spectral data. ^{1}H NMR spectrum of **302a** revealed four sets of proton signals. Compound **302a** could easily be distinguished from ring-opened product **378**; **302a** has a symmetrical structure and exhibits *AA'BB'* system for the aromatic protons, and it is consistent with a seven-line ^{13}C NMR spectrum. However, ^{1}H NMR spectrum of **378** revealed seven sets of proton signals and the structure of rearranged compound **378** is nonsymmetric and results from the opening of the cyclopropane ring. There are twelve lines in ^{13}C NMR for **378**, hence no doubt remain as to proposed structures due to extremely characteristic spectroscopic data.

2.5.2 The Reaction of the Bromofluorocyclopropane 302a with Methyllithium

To investigate the reaction of the *endo*-carbenoid, bromofluorocyclopropane **302a** was submitted to the last step of Doering-Moore-Skatebøl reaction. Therefore, to a magnetically stirring solution of bromofluorocyclopropane **302a** in dry ether was added dropwise MeLi in ether at –25 ºC in the presence of the freshly distilled furan, as the trapping reagent. After the usual work-up procedure, the two isomers of **306a** were obtained in a total yield 25%. The formation of this trapping product **306a**

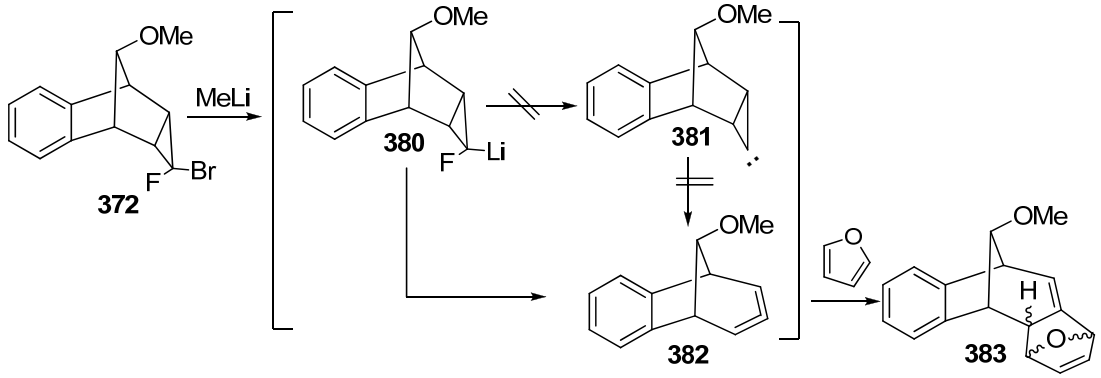
confirmed the formation of the bicyclic allene **305a** as a reactive intermediate *(Scheme 118).*



Scheme 118

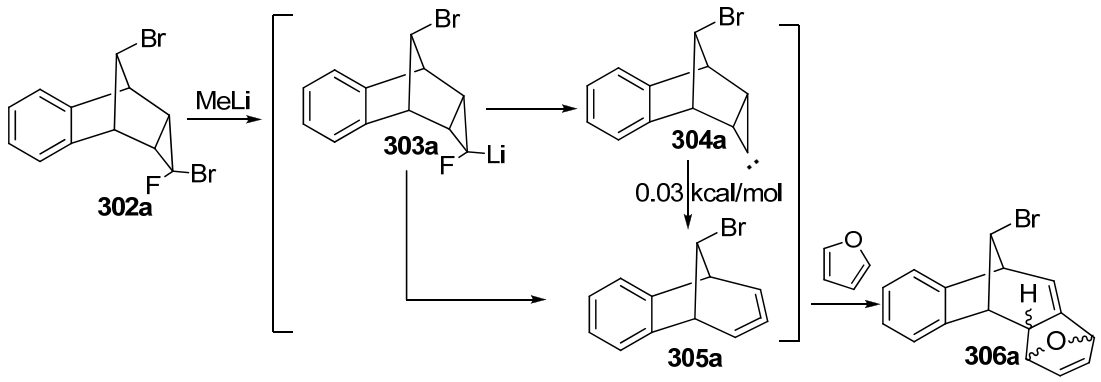
Even furan adducts **306a** including two isomers confirmed the formation of an allene unit **305a** as a reactive intermediate, we were not sure about the structure of initially formed intermediate whether it was a carbenoid or carbene.

Most recently, Azizoğlu [119] has reported that, treatment of *gem*-bromofluorocyclopropane **372** with methyllithium afforded **383** that was the evidence of bicyclic allene **382** as an intermediate. According to his theoretical calculations, the structure of *endo*-carbene **381** could not be optimized in the free carbene form, since its optimization gave directly the bicyclic allene structure **382** as a minima. As a result, *endo*-carbene is not initial intermediate during the allene formation *(Scheme 119).*



Scheme 119

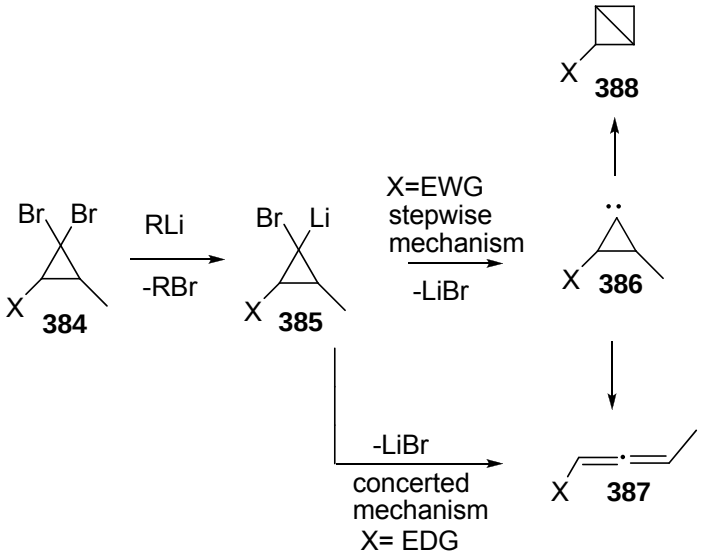
However, theoretical results (B3LYP/6-31G(d)) about carbene-carbenoid-allene isomerization of **302a** is quite different from **372**. The theoretical calculations indicated that *endo*-carbene **304a** were optimized in the free carbene form. However, it readily isomerizes to allene **305a** afforded furan adduct **306a**. Since, theoretical calculation also showed that required energy for isomerization of carbene **304a** to allene **305a** is approximately 0.03 kcal/mol retarted the formation of insertion or any other additon products *(Scheme 120).*



Scheme 120

In conclusion, bicyclic allene unit **305a** can be formed from both carbenoid **303a** and *endo*-carbene **304a** intermediates.

Most recently, Azizoğlu *et al.* [156] has reported theoretical calculations about substituent effects on the ring-opening mechanism of lithium bromocyclopropylidenoids to allenes. They claimed that two pathways can be considered for the ring opening reactions of carbenoid to allene; the reaction may either proceed in a concerted fashion or stepwise with the intermediacy of a free cyclopropylidene. In both cases, the efficiency of the process depends on the easiness of the splitting off the bromide anion. This means, electron-withdrawing substituents impede the reaction whereas electron-donating groups +M lower the barrier to allene formation *(Scheme 121)*. The experimentally obtained from **372** and **302a** confirmed that –OMe and –Br substituents located at C-7 carbon atom (electron-donating groups) enhance the concerted isomerization of a carbenoid to an allene without the intermediacy of a free carbene.



Scheme 121

The trapping of allene **305a** with furan may result in the formation of four possible isomers which can be represented as; syn-*exo* isomer **306a1**, anti-*exo* isomer **306a2**, syn-*endo* isomer **306a3**, anti-*endo* isomer **306a4** as shown in Figure 21.

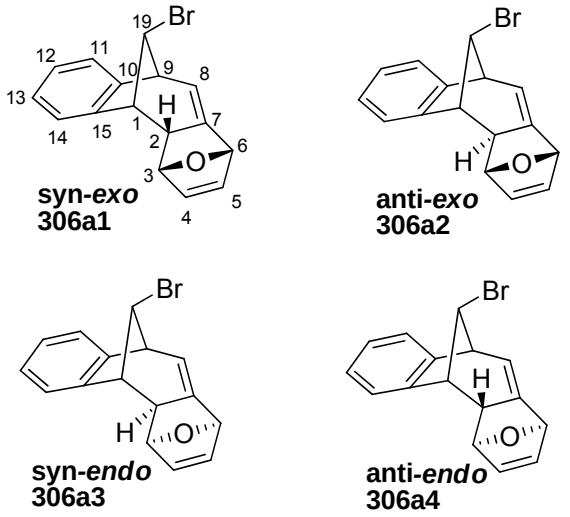
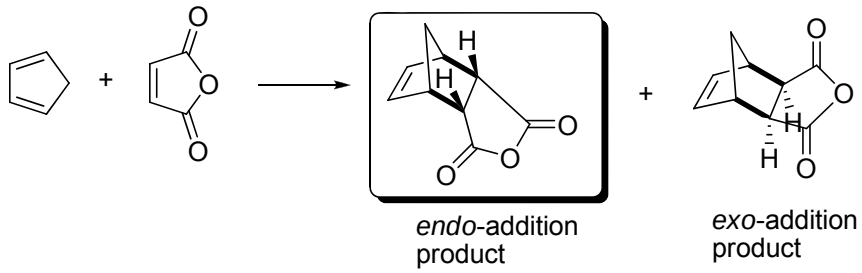


Figure 21: Possible isomers of the allene adduct **306a**

It is known, that cycloaddition reactions on bicyclic systems have generally tendency to *endo*-selectivity. For example, the cycloaddition reaction of cyclopentadiene with maleic anhydride theoretically gives both *endo* and *exo*-Diels-Alder products *(Scheme 122).* Although, *exo*-addition product is thermodynamically

more stable, experimental results indicate that, formation of *endo*-addition products are preffered. Both cycloaddition products are thermally allowed according to the Woodward-Hoffman rules. However, *endo*-transition structure between HOMO of diene, and LUMO of dienophile shows that *endo*-addition is more stable due to secondary orbital interaction between the unreacted carbonyl carbons' orbitals and C-3 and C-4 carbons' orbitals of cyclopentadiene.



Scheme 122

In the light of the above expression, the obtained furan adducts may be syn-*exo* **306a1** and anti-*endo* **306a4**. However, this information can not determine the exact structures of obtained furan adducts. In order to be sure about which isomer energetically the most stable one, the theoretical calculations were carried out by using Gaussian 98W program [157]. The geometry optimizations of all the structures, **306a1-4**, were achieved at the B3LYP/6-31+G(d,p) level. Energies were refined by using B3LYP/6-31+G(d,p) single point evaluations. Stationary points were characterized as minima or transition structures by way of an analytic evaluation of harmonic vibrational frequencies at the level of geometry optimization. The results of calculations summarized in Table 2 showed that **306a1** and **306a4** are the lowest one in energy, including zero point correction.

Table 2: Absolute energies (E, in hartree/particle), zero-point vibrational energies (ZPVE, in kcal/mol), and energies relative to the isomer that has a lowest energy, including zero-point corrections (in kcal/mol) for the isomers, **306a1**, **306a2**, **306a3**, and **306a4**.

	Energy	**ZPVE**	**Relative Energy**
306a1	-3264.44365	155.25	0.00
306a2	-3264.43579	155.17	4.85
306a3	-3264.43727	155.25	4.01
306a4	-3264.44227	155.26	0.88

Optimized structures of **306a1-4** at B3LYP/6-31+G(d,p) level are shown in Figure 22. These structures are visualized by using Molden [158] and Mercury [159] programs.

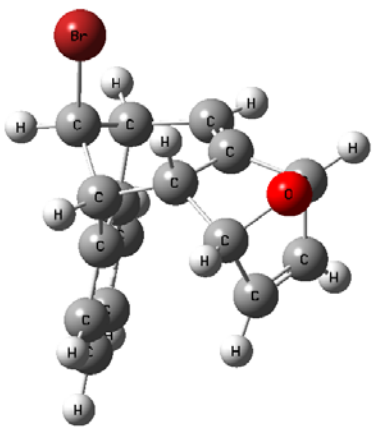
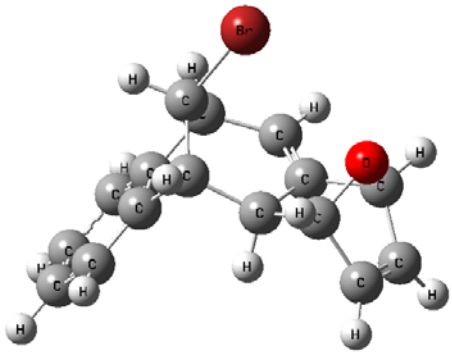
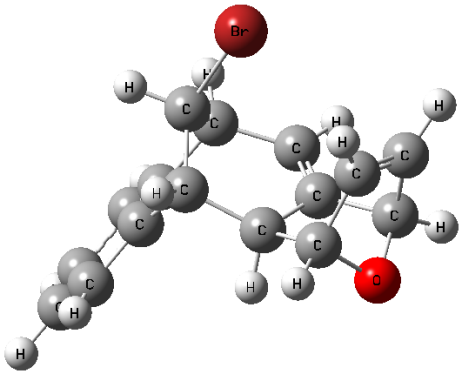
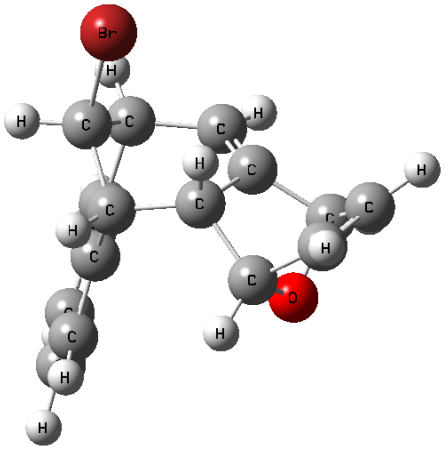
	
306a1	**306a2**
-3264.196242	-3264.188511
	
306a3	**306a4**
-3264.189861	-3264.194842

Figure 22: Optimized structures of **306a1**, **306a2, 306a3** and **306a4** at B3LYP/6-31+G(d,p) level.

On the basis of the geometry optimized structures of **306a1-4** shown in Figure 22, the dihedral angles between adjacent protons (H_n-H_{n+1}) contributed to characterization of isomers were found to be as given in Table 3.

Table 3: The dihedral angles between H_1-H_2, H_2-H_3, H_3-H_4, H_8-H_9 protons for **306a1-4** molecules from the geometry optimization at B3LYP/6-31+G(d,p) level.

	H_1-H_2	H_2-H_3	H_3-H_4	H_8-H_9
306a1	-56.66 º	51.96 º	32.83 º	-31.27 º
306a2	90.30 º	-98.52 º	31.91 º	-4.22 º
306a3	92.10 º	-54.42 º	-33.94 º	-8.29 º
306a4	-55.90 º	95.93 º	-32.24 º	-35.65 º

After, discussing the energetically comparison of possible isomers **306a1-4**, another theoretical calculation was investigated about the dihedral angles (ϕ) between vicinal protons *(Table 3)*. It was known that, vicinal proton-proton coupling depends primarily on the dihedral angle (ϕ). The relationship between the dihedral angle and vicinal coupling was first predicted by Karplus and Conroy [160]. They reported that, vicinal coupling between protons is nearly zero when dihedral angle is approximately 90º. On the other hand, the vicinal coupling constants increase when the dihedral angle gets closer to 0º and 180º.

The compound syn-*exo* **306a1** and syn-*endo* **306a3** furan adducts could easily be distinguished from anti-*exo* **306a2** and anti-*endo* **306a4** furan adducts. According to the Table 3, dihedral angle between H_2 and H_3 protons for **306a1** and **306a3** are approximately 52º and 54.4º, whereas for **306a2** and **306a4** are 98.5º and 95.9º respectively. According to the ^{1}H NMR spectrum of furan adducts, **306a1** and **306a3**, H_2 proton resonates at 3.33 ppm as a quartet (J = 3.6 Hz) for **306a1** and resonates at 2.60 ppm as a triplet (J = 3.6 Hz) for **306a3** as well. COSY spectra of both isomers indicate that H_2 proton has a definite correlation with H_3 protons. Therefore, it is likely that the trapped isomers are neither **306a2** nor **306a4** in this case. As a result, the proposed structures are **306a1** and **306a3**. The compound syn-*exo* furan adduct **306a1** could also be distinguished from syn-*endo* **306a3** as well. Dihedral angle between H_1 and H_2 protons for **306a1** is approximately -57º, whereas

for **306a3** is approximately 92.1º. According to the ^{1}H NMR spectrum of **306a1**, H_1 proton appears at 3.50 ppm as a triplet with J = 4.0 Hz, and its COSY spectrum confirmed the correlation with H_{16} and H_2. However, from ^{1}H NMR spectrum **306a3**, H_1 proton appears at 3.33 ppm as a doublet with J = 3.6 Hz, and its COSY spectrum only revealed the correlation with H_{16}. Furthermore, dihedral angle between H_8 and H_9 of **306a3** is nearly -8.3º, whereas for **306a1** is nearly -31.3º. These values indicated that, the coupling constant (J_{89}) between H_8 and H_9 of **306a3** should be much more that of the **306a1**. According to the ^{1}H NMR spectrum, coupling constant (J_{89}) between H_9 and H_8 proton **306a1** was found around 4.8 Hz, whereas for **306a3** was found around 6.8 Hz. In addition, the yields of the isomers (**306a1**, 20%; **306a3**, 5%) supported the calculated relative energies of isomers and also confirmed the *endo*-selectivity during the reaction. Hence no doubt remain as to proposed structures due to extremely characteristic spectroscopic and theoretical data.

CHAPTER 3

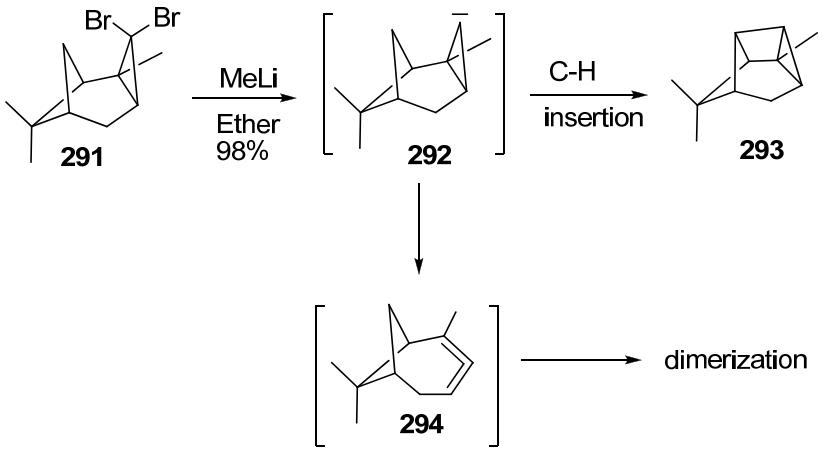
CONCLUSION

Chemists have always been fascinated by the cumulated diene system of allenes with its extraordinary properties, such as the axial chirality of the elongated tetrahedron and a higher reactivity than non-cumulated C-C double bonds. Although the development of synthetic methodologies directed towards the synthesis of allenes has been confined to the last three decades with the few pioneering efforts being scattered across the first of these decades, the past sliver of this century provides enough evidence that allenes continious to entertain scientists in laboratories around the world in good numbers.

The synthesis of bicyclic allenes are of considerable interest in organic chemistry because of their high strain and reactivity. However, the studies on bicyclic allenes are remarkably limited when compared with the cyclic allenes.

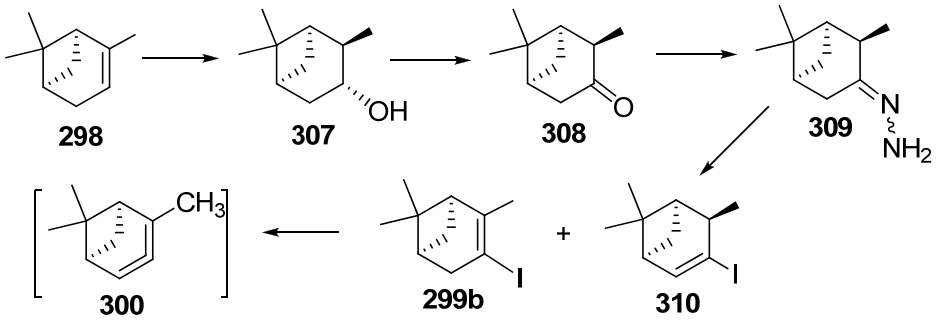
From among the numerous synthetic approaches to the cyclic allenes, Doering-Moore-Skattebol method and β-elimination method are most widely studied in the literature.

More recently, Balcı *et al.* [112] has reported both the experimental and theoretical studies related with Doering-Moore-Skattebol reaction to generate the cyclic allene incorporated into natural compound, α-pinene (**298**). Four products were isolated successfully *(Scheme 123).* Major product was the carbene insertion product **293**; the others were derived from the allene dimerization reaction.



Scheme 123

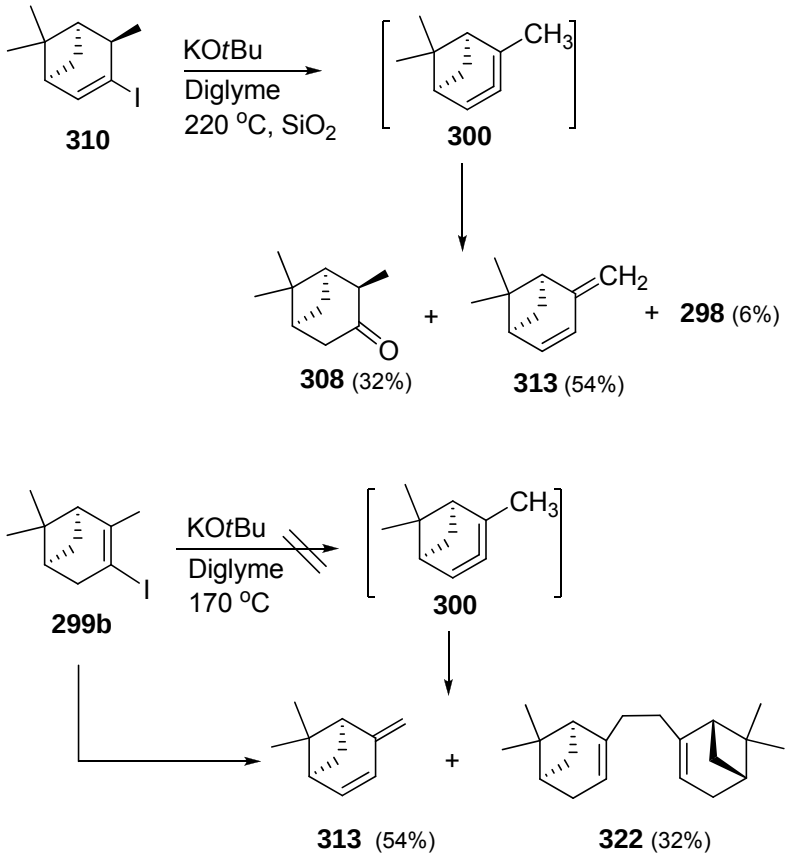
Although the Doering–Moore–Skattebøl method was successful in obtaining the desired allene, it gave the ring-enlarged product **294** where the allene bonds are located in a seven-membered ring. Hence, incorporation of an allene unit into the α-pinene (**298**) skeleton without ring enlargement would generate the six-membered cyclic allene **300**, which would cause considerable deviation from linear geometry. In the first part of the study, we aimed a method of accessing the highly reactive intermediate **300** by application of a β-elimination route, as shown in Scheme 124.



Scheme 124

First, hydroboration of **298** followed oxidation with pyridinium chlorochromate (PCC) gave ketone **308**, which was converted to the hydrazone derivative **310** as a mixture of (*E*)/(*Z*)-isomers by treatment with hydrazine hydrate at 110 ºC. The two double-bond isomers 3-iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (**299b**) and 3-iodo-4,6,6-tri- methylbicyclo[3.1.1]hept-2-ene (**310**) were

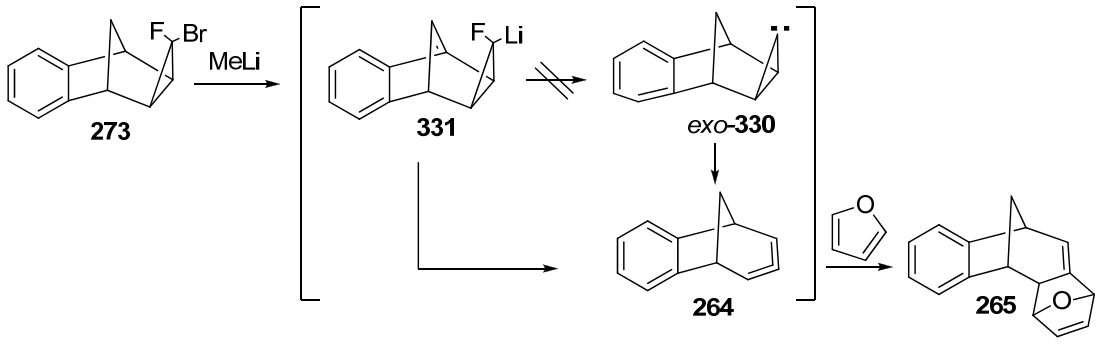
synthesized by reacting 2,6,6-trimethylbicyclo[3.1.1]heptan-3-one (**308**) with hydrazine, followed by treatment with I_2 in the presence of Et_3N. Treatment of **310** with *t*-BuOK as base in diglyme at 220 °C resulted in the formation of **308** and 6,6-dimethyl-4-methylidenebicyclo[3.1.1]hept-2-ene (**313**). For the formation of **308**, the cyclic allene **300** was proposed as an intermediate. Treatment of the second isomer, **299b**, with t-BuOK at 170 °C gave rise to the diene **313** and the dimerization product **322** *(Scheme 125).*



Scheme 125

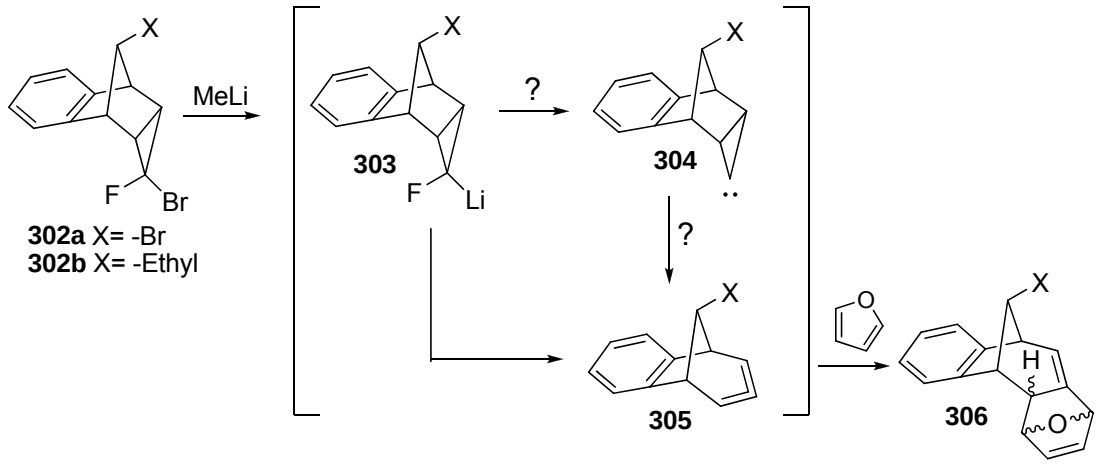
Finally, we have described a route to the highly strained cyclic allene **300**, which can be generated from 3-iodo-4,6,6-trimethylbicyclo[3.1.1]hept-2-ene (**310**) by β-elimination of HI with *t*-BuOK as base. Alkyne formation was excluded on the basis of the formed products and according to theoretical calculations. Interestingly, base-supported elimination of the isomer **299b** followed a different route and gave the insertion and dimerization products **313** and **322**, respectively.

In the second part of study, the stability of *endo*-carbene **304** was investigated. As mentioned before, Balcı and Özen reported that the bromofluorocarbene adduct **273** of benzonorbornadiene (**301**) proved to be a reliable precursor of $3\delta^2$-1,5-dihydro-1,5-methanobenzocycloheptene **(264)**, the benzo derivative of **250** [108]. According to the theoretical calculations [119] about during the formation of intermediate **264**, no *exo*-carbene **330** structure could be optimized in its free carbene form. It also isomerizes to the bicyclic allene **264** during the optimization. Hence, *exo*-carbene **330** is not initial intermediate during the allene formation (*Scheme 126)*.



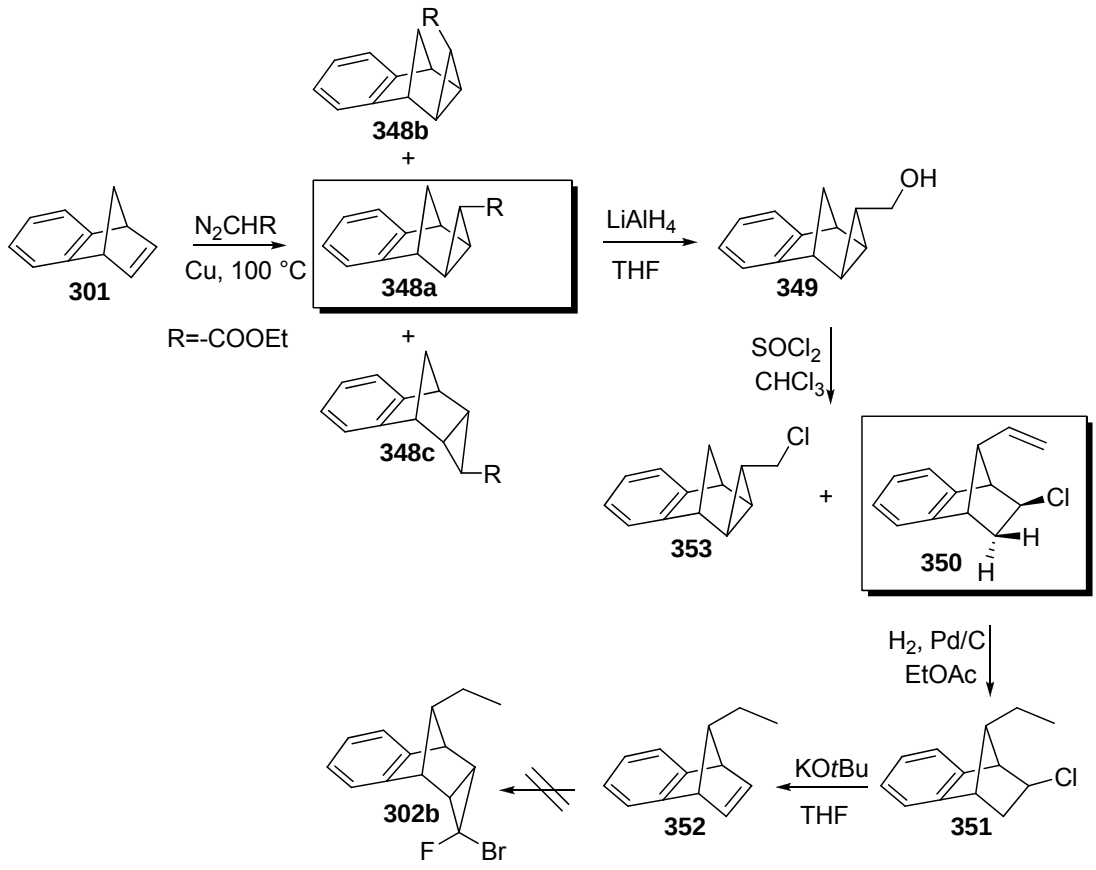
Scheme 126

At this point, we were curious about the stability of *endo*-cyclopropylidene **304** that was not discussed before in literature (*Scheme 127*).



Scheme 127

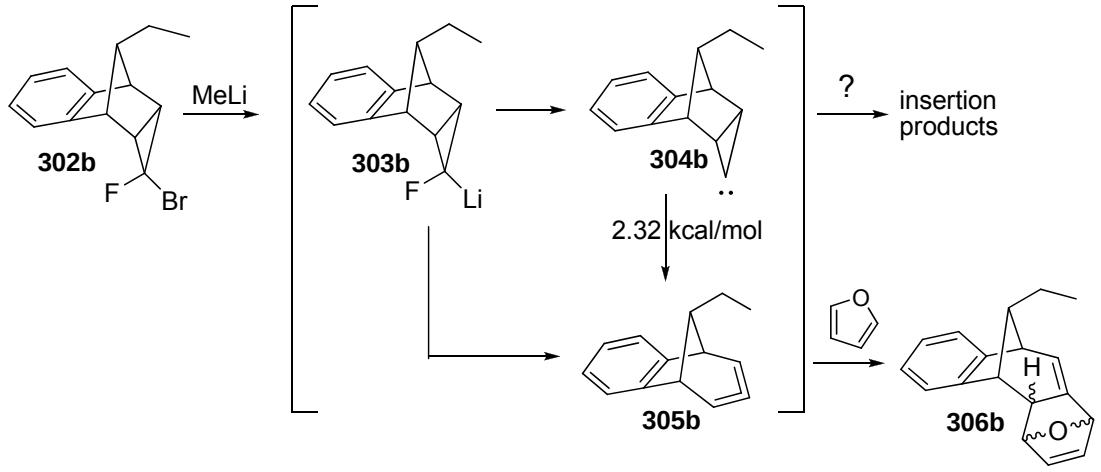
Normally, the addition of dihalocarbene proceeds predominantly from the *exo* face of the benzonorbornadiene (**301**). To hinder this reaction, the *exo* face of benzonorbornadiene (**301**) was protected with bromine and ethyl groups. For this reason, the *endo*-addition of dihalocarbene to *anti*-7-ethylbenzonorbornadiene (**352**) and *anti*-7-bromobenzonorbornadiene (**333**) were aimed to isolate the *gem*-dihalocyclopropanes **302a-b**, which under the reaction conditions does not undergo the ring opening to afford a rearranged, ring-expanded dihalides. For the synthesis of **302b**, benzonorbornadiene (**301**) was exposed to carbene addition reaction. Afterwards, ester **348** was reduced to corresponding alcohol **349**. An alcohol **349** was treated with thionyl chloride, the rearranged product **350** was synthesized. After hydrogenation of **350**, the resulted compound **351** was eliminated to **352**. Finally, addition of bromofluorocarbene to *anti*-7-ethylbenzonorbornadiene (**352**) was aimed to isolate the *endo*-adduct (**302b**). However, no carbene addition reaction was observed *(Scheme 128).*



Scheme 128

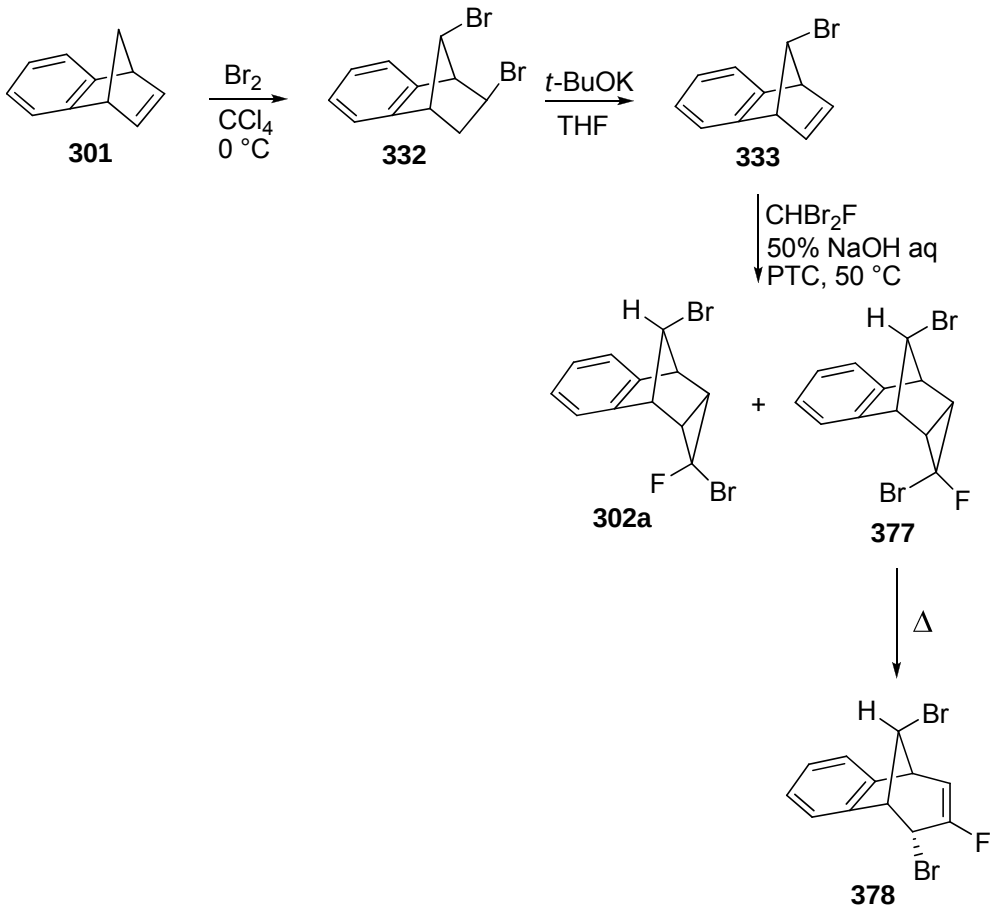
According to the theoretical calculations (B3LYP/6-31G(d)), when $-CH_2CH_3$ is accommodated to C-7 carbon atom, surprisingly the pyramidalization of double bond increased respect to the methoxy derivative **363b** *(Table 1-Figure 19).* As a result, more strained energy and deformation of planarity on double bond prevented carbene addition to compound **352** *(Scheme 113).*

According to the theoretical calculations at B3LYP/6-31G(d) level, if *gem*-cyclopropane adduct (**302b**) would be formed, endo-carbene **304b** can be an initial intermediate as a free carbene form. Furthermore, calculations show also that the formed free carbene **304b**, can easily isomerize to the corresponding allene **305b** with a small barrier of 2.32 kcal/mol *(Scheme 129).*



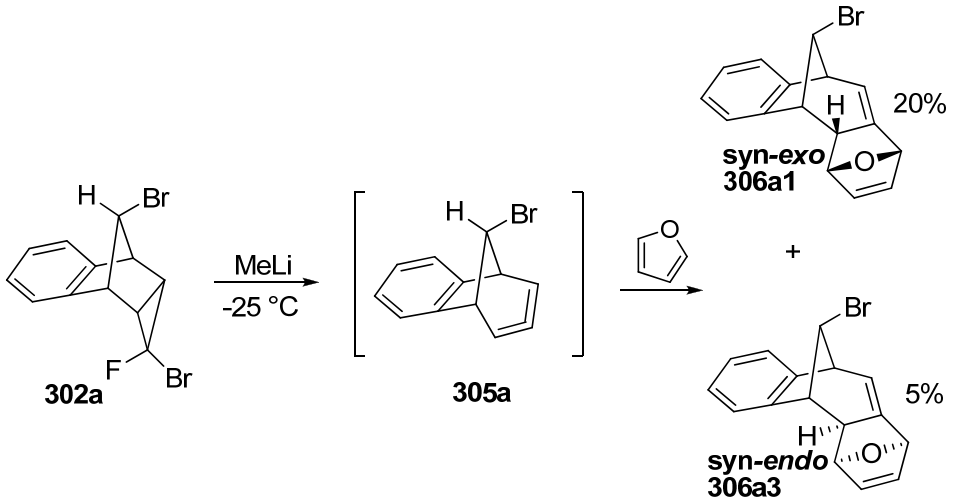
Scheme 129

After unsuccesfull attempt to add a carbene to *anti*-7-ethylbenzonorbornadiene (**352)**, we decided to change the substituent located at C-7 carbon atom. For this reason, benzonorbornadiene (**301**) was reacted with bromine to give the rearranged product **332** as described in the literature [122,139]. Elimination of HBr resulted in the formation of **333**, where bromine atom is located in *exo*-position. After that, the corresponding bromofluorocarbene adduct **302a** and the *endo*-bromofluoro ring-opened product **378** was synthesized by using the carbene addition procedure *(Scheme 130).*



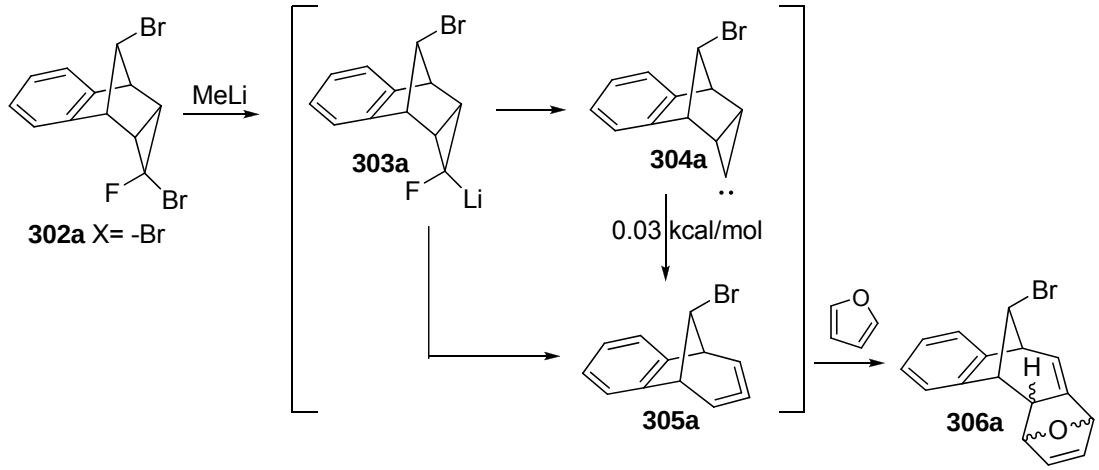
Scheme 130

To investigate the reaction of the *endo*-carbenoid **303a**, bromofluorocyclopropane **302a** was submitted to the last step of Doering-Moore-Skatebøl reaction. Treatment of bromofluorocyclopropane **302a** with MeLi in the presence of furan, the two isomers **306a1** and **306a3** were obtained in a total yield 25%. The formation of this trapping products **306a1** and **306a3** confirmed the formation of the bicyclic allene **305a** as a reactive intermediate *(Scheme 131).*



Scheme 131

According to the theoretical results (B3LYP/6-31G(d)) about carbene-carbenoid-allene isomerization of **302a**, *endo*-carbene **304a** was optimized in the free carbene form whereas *exo*-carbene **330** was not . However, it readily isomerizes to allene **305a** afforded furan adduct **306a**. Since, theoretical calculation also showed that required energy for isomerization of carbene **304a** to allene **305a** is approximately 0.03 kcal/mol retarted to the formation of insertion or any other addition products *(Scheme 132).*



Scheme 132

CHAPTER 4

EXPERIMENTAL

4.1 General Experiment Techniques

Nuclear Magnetic Resonance (^{1}H, ^{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 deuterochloroform ($CDCl_3$) 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 (70 eV).

Melting points were determined on a capillary melting apparatus and are uncorrected. Elemental Analysis were performed by the way of TUBITAK Test and Analyses center, Besevler, Ankara and Ataturk University Chemistry Department, Erzurum.

Commercially available reagents were of reagent-grade quality and used as received from Merck, Fluka and Aldrich 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 [154a]. All extracts were dried over anhydrous sodium sulfate (Na_2SO_4) and solvents were concentrated under reduced pressure by using rotary evaporator.

4.2 (1S,2S,3S,5R)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ol (307)

To a solution of *S*-(-)-α-pinene (**298**) (68.0 g, 0.50 mol) and $NaBH_4$ (19 g, 0.50 mol) in THF (160 ml) was added dropwise precooled $BF_3{\cdot}OEt_2$ (71.0 g, 0.50 mol) at 0 ºC under N_2 atmosphere. The mixture was kept 3 h at this temperature. Then, 3M aq. NaOH (167 ml) and 30% H_2O_2 solution (250 ml) were added at –10 °C. After stirring for 2 h, the reaction was complete, and the solvent was evaporated. After addition of H_2O, the mixture was extracted with CH_2Cl_2, the organic phase was washed with saturated aq. $NaHCO_3$ solution and H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave crystalline **307** (71 g, 92%). M.p. 53–55 °C.

307: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (dt, *J* = 9.2, 4.9, 1H, -OH), 2.70 – 2.63 (m, 1H), 2.55 – 2.51 (m, 1H), 2.12 – 2.07 (m, 2H), 1.96 (dt, *J* = 6.3, 1.7, 1H), 1.87 (ddd, *J* = 13.9, 4.5, 2.6, 1H), 1.62 (br.s, 1H), 1.39 (s, 3H), 1.30 (d, *J* = 7.4, 3H), 1.21 (d, *J* = 9.8, 1H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.9, 48.2, 48.1, 42.2, 39.5, 38.6, 34.8, 28.1, 24.1, 21.2.

4.3 (*1S,2S,5R*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-one (308).

A solution of pyridinium chlorochromate (PCC; 119.8 g, 1.40 mol) in CH_2Cl_2 (800 ml) was added to a solution of **307** (71.0 g, 0.46 mol) in CH_2Cl_2 (250 ml) at 0 °C. When the addition was completed, the mixture was stirred at r.t. for 3 h. The solvent was evaporated, and the residue was worked up by extraction with H_2O and CH_2Cl_2. The organic phase was washed with saturated aq. $NaHCO_3$ solution and H_2O, and dried (Na_2SO_4). After the removal of the solvent, the residue was passed over silica gel (70 g), eluting with CH_2Cl_2, and then further purified by distillation at 55 °C /5 Torr to give colorless liquid **308** (63.0 g, 90%).

308: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 – 2.64 (m, 2 H), 2.55 – 2.45 (m, 3 H), 2.19 – 2.14 (m, 1 H), 2.1 (dt, *J* = 6.4, 1.5, 1 H), 1.36 (s, 3 H), 1.24 (d, *J* = 7.5, 3 H), 0.93 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.0 (-CO carbon), 51.6, 45.4, 45.0, 39.5, 39.3, 34.8, 27.5, 22.3, 17.1.

4.4 (*1S,2S,3E,5R*)- and (*1S,2S,3Z,5R*)-2,6,6-Trimethylbicyclo-[3.1.1]heptan-3-one Hydrazone (309).

Compound **308** (63.0 g, 0.412 mol) was reacted with neat hydrazine hydrate (21.6 g, 0.45 mol) at 110 °C for 18 h. The residue was extracted with H_2O and $CHCl_3$. The organic phase was washed with saturated aq. $NaHCO_3$ soln. and H_2O, and dried (K_2CO_3). After removal of the solvent, colorless oily **309** (64.0 g, 93%) was obtained as a (Z)/(E) 1:3 mixture.

309: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (br.s, -NH_2), 2.81 – 2.26 (m), 2.48 – 2.26 (m), 2.03 (m), 1.82 – 1.79 (dt, *J* = 5.7, 2.0), 1.26 (s), 1.19 (d, *J* = 6.3), 1.12 (d, *J* = 7.0), 0.88 (s), 0.83 (s). ^{13}C NMR (100 MHz, $CDCl_3$; δ (*E*)-isomer): 153.9, 46.2, 38.8, 38.3, 30.9, 28.6, 27.1, 20.1, 18.6. ^{13}C-NMR (100 MHz, $CDCl_3$; (*Z*)-isomer): 154.4, 46.4, 43.4, 38.7, 38.3, 33.7, 27.1, 22.2, 20.0. IR (KBr): 3465 (w), 3400 (m), 3209 (w), 2974 (s), 2939 (s), 2865 (s), 1635 (m), 1469 (m), 1365 (m). EI MS (70 eV): 167 (100, $[M+H]^+$), 151 (62), 134 (14), 83 (19). Anal. calc. for $C_{10}H_{18}N_2$: C 72.24, H 10.91; found: C 72.06, H 10.82.

4.5 (*1R,5R*)-3-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (299b) and (*1S,4S,5S*)-3-Iodo-4,6,6-trimethylbicyclo[3.1.1]hept-2-ene (310).

A solution of I_2 (97.0 g, 0.38 mol) in anhydrous THF (160 ml) was added to a mechanically stirred soln. of **309** (64.0 g, 0.383 mol) and Et_3N (40.5 g, 0.4 mol) in THF (300 ml) over a period of 15 min. After the addition, the mixture was stirred for 1 h at r.t. When the reaction was complete, the solvent was evaporated, H_2O (300 ml) was added, and the mixture was extracted with hexane. The organic phase was washed with saturated aq. NaCl solution and H_2O, dried (Na_2SO_4), and concentrated. The products were distilled under vacuum to afford **299b** and **310** in a ratio of 2:3 (total yield: 25 g, 24.7%). The two isomers **299b** and **310** (500 mg) were separated by column chromatograpy (100 g SiO_2 with 0.4 g $AgNO_3$; hexane). Compound **310** was isolated first.

310: (first fraction; anal. pure). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, *J* = 6.8, 1H, H_2), 2.57 (tq, *J* = 7.0, 2.3, 1H, H_4), 2.27 (dt, A-part of AB system, *J* = 9.1, 5.5, 1H, H_{7a}), 2.1 (q-like, *J* = 6.8, 1H, H_1), 1.98 (dt, *J* = 6.3, 2.3, 1H, H_5), 1.35 (d, B-part of AB-system, *J* = 9.1, 1H, H_{7b}), 1.29 (s, 3H, H_9), 1.11 (d, *J* = 7.0, 3H, H_8), 0.95 (s, 3H, H_{10}). ^{13}C NMR (100 MHz, CDCl3): δ 146.8, 117.3, 49.4, 46.7, 46, 42.4, 26.3, 25.7, 22, 20.1. IR (KBr): 3037 (w), 2963 (s), 1711 (m), 1382 (m), 1365 (m), 957 (m). EI MS (70 eV): 263 (100, $[M+H]^+$), 220 (97), 135 (28), 93 (38), 92 (67). Anal. calc. for $C_{10}H_{15}I$: C 45.82, H 5.77; found: C 45.68, H. 5.62.

299b: (second fraction; 90% pure). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (dt, A-part of AB-system, *J* = 17.0, 2.1, 1H, H_{4a}), 2.65 (dt, B-part of AB system *J* =17.0, 2.3, 1H, H_{4b}), 2.4 (dt, A-part of AB system, *J* = 8.9, 5.5, 1H, H_{7a}), 2.25 (dd, *J* = 5.5, 3.8, 1H, H_1), 1.93 (m, 1H, H_5), 1.82 (t, *J* = 2.1, 3H, H_8), 1.35 (d, B-part of AB system, *J* = 8.9, 1H, H_{7b}), 1.27 (s, 3H, H_9), 0.86 (s, 3H, H_{10}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 90.4, 49.6, 46.4, 45.6, 43.9, 31.6, 27.6, 25.8, 21.4. IR (KBr): 2861 (s), 1641 (w), 1465 (m), 1381 (m), 1367 (m), 898 (m). EI MS (70 eV): 263 (55, $[M+H]^+$); 220 (100), 135 (54), 93 (58), 91 (67). Anal. calc. for $C_{10}H_{15}I$: C 45.82, H 5.77; found: C 45.98, H 5.92.

4.6 Reaction of 310 with *t*-BuOK

A solution of *t*-BuOK (2.24 g, 0.02 mol) and **310** (2.0 g, 0.007 mol) in diglyme (25 ml) was placed in a glass tube. The tube was sealed and heated to 220 °C for 8 h. Then, H_2O was added, and the mixture was extracted with Et_2O (3 × 100 ml). The organic phase was washed with saturated aq. $NaHCO_3$ solution and H_2O, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromotograpy (40 g SiO_2; hexane) to afford the diene **313** (0.55 g, 54%) followed by α-pinene (**298**; 0.063 g, 6%). Further elution with CH_2Cl_2 provided the ketone **308** (0.37 g, 32%).

6,6-Dimethyl-4-methylidenebicyclo[3.1.1]hept-2-ene (**313**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (t, *J* = 7.5, 1H, H_2), 6.01 (d, J = 8.5, 1H, H_3), 4.66 (s, 1H, H_{8a}), 4.63 (s, 1H, H_{8b}), 2.63 (br.t, *J* = 5.6, 1H, H_5), 2.55 (ddd, A-part of

AB system, J = 8.5, 5.4, 3.0, 1H, H_{7a}), 2.28 (br.q, J = 6.0, 1H, H_1), 1.5 (d, B-part of AB system J = 8.5, 1H, H_{7b}), 1.35 (s, 3H, H_9), 0.85 (s, 3H, H_{10}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 138.3, 126.6, 107.3, 51.9, 43.7, 43, 36.1, 26.3, 22.4.

4.7 Reaction of 299b with *t*-BuOK

A solution of *t*-BuOK (3.36 g, 0.03 mol) and **299b** (2.5 g, 0.0085 mol) in diglyme (15 ml) was heated in a sealed glass tube at 170 °C for 8 h. Then, H_2O was added, and the residue was extracted with Et_2O (3 × 50 ml). The organic phase was washed with saturated aq. $NaHCO_3$ solution and H_2O, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromotography (25 g SiO_2; pentane). The first fraction gave **313** (0.41 g, 32%), and the second fraction afforded the dimer **322** (1.45 g, 56%).

2,2'-Ethane-1,2-diylbis(6,6-dimethylbicyclo[3.1.1]hept-2-ene)- (**322**):Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (br. s, 1H, H_3), 2.35 (dt, A-part of AB system, J = 8.5, 5.6, 1H, H_{7a}), 2.25 – 2.15 (br. AB system, J = 17.3, 2H, H_4), 2.05 (m, 1H, H_5), 1.9 (t, J = 5.3, 1H, H_1), 1.87 (s, 2H, H_8), 1.26 (s, 3H, H_9), 1.16 (d, B-part of AB-system, J = 8.5, 1H, H_{7b}), 0.84 (s, 3H, H_{10}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 116.1, 46.3, 41.3, 38.4, 35.2, 32, 31.7, 26.8, 21.7. EI MS (70 eV): 271 (9, $[M+H]^+$), 228 (20), 202 (6), 171 (10), 135 (50), 93 (100).

4.8 The Synthesis of Benzonorbornadiene (301)

In a 2 L three-necked flask equipped with stirrer, condenser, and addition funnel was placed a solution of *i*-amylnitrite (64.35 g, 0.55 mole) and methylene chloride (800 ml). A solution of anthranilic acid, (68.5 g, 0.50 mole), freshly cracked cyclopentadiene (33.0 g, 0.50 mole) and acetone (300 ml) was added to the stirred solution over a 1 hour period. The reaction was heated until the methylene chloride started to reflux and gas evolution was observed. If the solution was not heated initially, a white solid would begin to separate on one occasion. As soon as the reaction progressed, sufficient heat was evolved to maintain gentle reflux. After the addition was complete, the reaction was refluxed for four hours and cooled by

permitting it to stand overnight at room temperature. The solvents were removed under reduced pressure and the black oil diluted with 900 ml of n-hexane and 700 ml of saturated $NaHCO_3$ solution in 2 liters beaker. After considerable CO_2 evolution, the layers were seperated and the aqueous layer extracted with n-hexane two times. The combined hexane layers were washed three times with 150 ml portions of saturated $NaHCO_3$ solution, twice with saturated NaCl solution, and dried over anhydrous $MgSO_4$. Removal of the hexane at reduced pressure and distillation through a 10-in. Vigreux column afforded *i*-amyl alcohol, b.p. 45 ºC/10 mm, and 28.50 g benzonorbornadiene (**301)**, b.p. 72-81 ºC/10 mm, 40% yield.

301: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.25 (AA′BB′ system, 4H, aryl), 7.15 (t, *J* =1.8, 2H, olefinic), 4.25 (t, *J* = 1.7, 2H, bridge-head protons), 2.71 (dd, A part of AB system, *J* = 1.5, 7.0, 1H, H_{7syn}), 2.63 (d, B part of AB system, *J* = 7.0, 1H, H_{7anti}), ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (C_2 and C_3) 143.5, 124.7, 122.0 (aryl carbons), 70.6 (C_7), 50.9 (C_1 and C_4).

4.9 The Reaction of Benzonorbornadiene with Ethyldiazoacetate

Benzonorbornadiene (**301**) (4.0 g, 28.02 mmol) and copper (200 mg, 3.076 mmol) were placed in a 100 ºC oil bath without any solvent. Than, ethyldiazoacetate (6.42g, 56.316 mmol) was added to the stirred solution for 3 h. The mixture was kept 1 h at this temperature. After completion of the reaction, residue was submitted to rapid filtration. After that, H_2O was added, and the residue was extracted with hexane (3×50 ml). The organic phase was washed with saturated aq. $NaHCO_3$ solution and H_2O, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromotography (120 g SiO_2; EtOAc/hexane 3:97). Unreacted benzonorbornadiene (**301**), a mixture of **348a** and **348c** (3.250 g) and **348b** (800 mg, % 6.2) were obtained respectively. A mixture of **348a** and **348c** were one more crystallized in hexane/EtOAc solution and finally **348a** (2.35 g, % 18.3) and a mixture of **348a** and **348c** (900 mg) were obtained.

***exo,anti*-10-Carboethoxytetracyclo[6.3.1.0^{2,7}.0^{8,9}]dodeca-2,4,6-triene**

(**348a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-6.98 (AA′BB′ system, 4H, aryl), 4.06

(q, *J* = 7.2 Hz, 2H, methylenic), 3.37 (br.s, 2H, bridge-head protons), 2.5 (t, *J* = 2.4 Hz, 1H, cyclopropane), 1.66 (d, *J* = 2.4 Hz, 2H, cyclopropane), 1.48 (d, A-part of the AB system, *J* = 10.0 Hz, 1H, bridge proton), 1.32 (d, B-part of the AB system, *J* = 10.0 Hz, 1H, bridge proton), 1.23 (t, *J* = 7.2 Hz, 3H, methyl proton). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (CO), 150.3, 125.6, 121.5, 60.6, 43.4, 39.8, 30.5, 29.3, 14.7.

***exo,syn*-10-Carboethoxytetracyclo[6.3.1.0^{2,7}.0^{8,9}]dodeca-2,4,6-triene** (**348b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-6.98 (AA′BB′ system, 4H, aryl); 4.19 (q, *J* = 7.2 Hz, 2H, methylenic), 3.5 (br.s, 2H, bridge-head protons), 2.16 (t, *J* = 7.6 Hz, 1H, cyclopropane), 1.41 (d, *J* = 7.2 Hz, 2H, cyclopropane), 1.37 (d, A-part of the AB system, *J* = 11.2 Hz, 1H, bridge proton), 1.32 (t, *J* = 7.2 Hz, 3H, methyl proton), 1.28 (d, B-part of the AB system, *J* = 11.2 Hz, 1H, bridge proton). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (CO), 151.4, 125.4, 121.3, 61.1, 43.8, 40.3, 35.6, 27.6, 14.5.

4.10 Reduction of 348a with $LiAlH_4$

To a solution of $LiAlH_4$ (1.0 g, 31.25 mmol) in THF (50 ml) was added dropwise **348a** (2.28 g, 1.0 mmol) in THF (5 ml) at 0 ºC under N_2 atmosphere. After addition was complete, the mixture was allowed to warm to r.t. After stirring for 1 day, the mixture was cooled again, and carefully water was added. Gas evolution was observed. The reaction solvent was evaporated and residue was extracted with ether/water (50 ml/ 50 ml). Organic phase wad dried over Na_2SO_4. After evaporation of solvent, alcohol **349** was obtained (1.674 g, 9.00 mmol, 90%) as a colorless oily residue.

***exo,anti*-10-Hydroxymethyltetracyclo[6.3.1.02,7.08,9]dodeca-2,4,6-triene** (**349**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04-6.86 (AA′BB′ system, 4H, aryl), 3.24 (d, *J* = 7.2 Hz, 2H, methylenic), 3.17 (br.s, 2H, bridge-head protons), 3.0 (br., 1H, -OH), 1.98 (tt, J = 7.2, 1.6 Hz, 1H, cyclopropane), 1.41 (d, A-part of the AB system, *J* = 9.6 Hz, 1H, bridge proton), 1.14 (d, B-part of the AB system, *J* = 9.6 Hz, 1H, bridge proton), 0.85 (d, *J* = 1.60 Hz, 2H, cyclopropane). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 124.9, 120.8, 64.2, 42.9, 38.9, 30.5, 26.3.

4.11 The Reaction of 349 with Thionyl Chloride

A stirred solution of **349** (1.2 g, 6.452 mmol) in 20 ml of chloroform was cooled to -5 ºC and treated dropwise with a solution of $SOCl_2$ (8 ml) in 20 ml of chloroform for 30 min. Gas evolution was observed. After the addition was complete, the mixture was allowed to r.t. After stirring 1 day, the solvent and excess $SOCl_2$ were removed by evaporation. The residue was submitted to column chromatograpy (silica gel, 110 g) eluting with hexane and non-rearranged product **353** (% 5 according to the crude NMR spectrum) and the rearranged product **350** (974 mg, % 74) was obtained as a colorless crystal (m.p. 28 -30 ºC).

***anti*-9-Chloro-11-vinyltricyclo[6.3.1.02,7.08,9]unadeca-2,4,6-triene** (**350**):^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.03 (m, 4H, aromatic), 6.37 (ddd, *J* = 17.2, 10.3, 8.3 Hz, 1H, H_{12}), 5.14 (dd, A part of the AB system, *J* = 17.2, 1.6 Hz, 1H, H_{13a}), 5.05 (d, B-part of the AB system, *J* = 10.3 Hz, 1H, H_{13b}), 3.85 (ddd, *J* = 7.8, 3.7, 0.7 Hz, 1H, H_9), 3.46 (br.s, 1H, H_8), (br.d, *J* = 3.3 Hz, 1H, H_1), 2.86 (d, 8.3 Hz, 1H, H_{11}), 2.4 (dt, A part of the AB system, *J* = 13.4, 3.7 Hz, 1H, H_{10a}), 2.08 (dd, B-part of the AB system, *J* = 13.4, 7.8, 1H, H_{10b}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 145.4, 137.2, 126.9, 129.1, 121.4, 120.1, 117.7, 64.2, 58.5, 57.1, 48.5, 37.6.

4.12 Hydrogenation of 350

Into a 50 ml, two-necked, round-bottomed flask were placed Pd/C (10%) (100 mg) catalyst and of **350** 1.0 g (4.88 mmol) in EtOAc (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 **351** as a colorless liquid (0.9 g 4.35 mmol, 90%).

***anti*-9-Chloro-11-ethyltricyclo[6.3.1.02,7.08,9]unadeca-2,4,6-triene** (**351**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.00 (m, 4H, aromatic), 3.79 (dd, *J* = 7.1, 3.8 Hz, 1H, H_9), 3.40 (br.s, 1H, H_8), 3.22 (br.d, *J* = 3.40 Hz, 1H, H_1), 2.30 (dt, A-part of

the AB system, J = 13.40, 3.8 Hz, 1H, H_{10a}), 2.11-2.02 (m, 2H, H_{10b}, H_{11}), 1.87 – 1.74 (dqui., A-part of the AB system, J = 14.6, 7.3, 1H, H_{12a}), 1.74 – 1.60 (dqui., B-part of the AB system, J = 14.6, 7.3, 1H, H_{12b}), 0.98 (t, J = 7.3 Hz, 1H, H_{13}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.4, 126.5, 126.5, 121.4, 121.1, 63.8, 58.7, 54.5, 47.2, 37.3, 22.7, 12.8. IR (KBr): 2968 (s), 2872 (m), 1463 (m), 1378 (w), 1296 (w), 1265 (w), 1013 (w), 964 (w), 888 (w), 747 (s). Anal. calc. for $C_{13}H_{15}Cl$: C 75.53, H 7.31; found: C 75.86, H. 7.64.

4.13 The Synthesis of *anti*-7-Ethylbenzonorbornadiene (352)

To a stirred solution of **351** (0.9 g, 4.35 mmol) in dry THF (35 ml) was added *t*-BuOK (2.44 g, 21.75 mmol) at reflux temperature. The mixture was stirred for 3 days. After evaporation of the solvent, H_2O (40 ml) was added. The mixture was extracted with $CHCl_3$ (3 × 30 ml). The combined organic layer was washed with saturated aq. $NaHCO_3$ solution and dried ($CaCl_2$). After evaporation of the solvent, residue was submitted to column chromotograpy eluting with hexane. **352** was obtained as a colorless liquid (0.5 g, 2.91 mmol, 67%).

352: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-6.84 (AA′BB′ system, 4H, aryl); 6.56 (s, 2H, olefinic), 3.66 (d, J = 1.3 Hz, 2H, bridge-head protons), 2.56 (t, J = 7.4 Hz, 1H, bridge), 1.46 (qui., J = 7.4 Hz, 2H, methylenic), 0.84 (t, J = 7.4 Hz, 3H, methyl). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.5, 139.4, 124.0, 121.2, 84.1, 53.7, 21.5, 12.6. IR (KBr): 3068 (w), 2960 (m), 1453 (m), 1377 (w), 1318 (w), 1299 (w), 789 (s), 742 (s), 697 (w). Anal. calc. for $C_{13}H_{14}$: C 91.71, H 8.29; found: C 91.96, H 8.43.

4.14 The Synthesis of 2-*exo*-7-*anti*-Dibromobenzonorborn-5-ene (332)

To a magnetically stirred solution of benzonorbornadiene (**301**) (10 g, 70.41 mmol) in 150 ml carbontetrachloride cooled to 10 °C was added dropwise a solution of bromine (11.53 g, 72.15 mmol) in 40 ml carbontetrachloride during 15 minutes. After completion of the addition, the solution was allowed to warm to room temperature. The solvents were removed under reduced pressure. The residue was

crystallized from ethanol to give the dibromo compound **332** as colorless crystals, (21.06 g, 99%); m.p. 76.4-77.2 ºC.

332: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.04 (m, 4H, aryl), 4.04 (s, 1H, H_7), 3.69 (dd, J = 4.7, 7.9, 1H, H_2), 3.66 (s, 1H, H_1), 3.43 (s, 1H, H_4), 2.79 (dt, A-part of AB system, J = 4.2, 13.3, 1H, H_{3exo}), 2.13 (dd, B-part of AB system, J =8.0, 13.2, 1H, H_{3endo}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.6, 128.2, 127.7, 122.2, 121.7, 56.9, 55.7, 51.6, 45.0, 37.1.

4.15 The Synthesis of *anti*-7-Bromobenzonorbornadiene (333)

To a magnetically stirred solution of 5.13 g (16.98 mmol) of **332** in dry and freshly distilled THF (80 ml) was added a solution of 1.92 g (17.12 mmol) of potassium *tert*-butoxide in 40 ml of dry and freshly distilled THF. The resulting mixture was refluxed for one hour and then cooled to room temperature. The mixture was diluted with water, and the aqueous phase was extracted with ether, washed with water, and dried over $MgSO_4$. The solvents were removed under reduced pressure. The residue was crystallized from hexane to yield *anti*-7-bromo-benzonorbornadiene (**333**) as colorless crystals, (3.45 g, 92%), m.p. 53.2-53.6 ºC, b.p. 99.5 ºC / 5 mm.

333: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.00 (AA′BB′ system, 4H, aryl), 6.73 (s, 2H, olefinic), 4.39 (s, 1H, bridge), 4.08 (s, 2H, bridge-head protons). ^{13}C NMR (100 MHz, $CDCl_3$: δ 147.1, 139.5, 125.6, 122.0, 74.1, 57.4.

4.16 Preparation of Dibromofluoromethane

A 250 ml two-necked flask, equipped with a condenser and nitrogen stream system, was charged with 57 g (225 mmol) of $CHBr_3$ and 15 g of (84 mmol) SbF_3, which was dried in vacuo at the reflux temperature of xylene for six hours before starting the experiment. The reaction flask was immersed in an oil bath at 120 ºC, the mixture was stirred for five minutes and then 3 ml of bromine was added. After a short while, the dark red became homogeneous and a mixture of the dibromofluoromethane and bromine began to distil into the receiving flask cooled with an ice bath. The initial exotherm resulted in a head temperature of 100 ºC, but

most of the distillate came over at 60-80 ºC. The distillate was washed with 10 % Na_2SO_3 solution until the color of bromine disappeared. Lower organic phase was washed with water, dried over $CaCl_2$, and distilled carefully to give $CHBr_2F$ as colorless liquid. The yield was 12 g (35 %), b.p. 66-67 ºC.

4.17 Addition of Bromofluorocarbene to anti-7-Bromobenzonorbornadiene (333)

To magnetically stirred solution of *anti*-7-bromobenzonorbornadiene **(333)** (10.0 g, 45.23 mmol), benzyltributylammonium chloride (1.0 g) and dibromofluoromethane (20 g) heated to 50 °C was added dropwise a solution of 60% NaOH (30 ml) during four hours. After the completion of addition, the reaction mixture was stirred for two hours. Then, the solution was allowed to cool to room temperature. The mixture was diluted with water and thorougly extracted with methylene chloride, and the combined extracts were washed with water, dried over $CaCl_2$, and evaporated. Unreacted alkene was recovered by distillation (110-115 °C / 5 mm), and the distillation residue was saved. The recovered alkene **333** was resubmitted to the reaction conditions as twice, using the same quantities of $CHBr_2F$, NaOH, and phase-transfer catalyst. Workup as before and distillation afforded unchanged *anti*-7-bromobenzonorbornadiene (**333**) (6.1 g). The combined distillation residues were submitted to rapid silica filtration using silica gel (120 g) eluting with hexane. Three products were isolated; starting material **333** (700 mg), **302a** (512 mg, 10.7%), **378** (250 mg, 5.3%) in that order from the column chromatography.

302a: colorless crystal (m.p. 135-137 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.02 (AA′BB′ system, 4H, aryl), 4.22 (s, 1H, H_{12}), 3.71 (br.s, 2H, H_1 and H_8), 2.71 (br.s, 2H, H_9 and H_{11}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (d, J = 4.1 Hz), 127.5, 122.0, 94.7 (d, J = 339.7 Hz), 72.4 (d, J = 7.5 Hz), 51.9, 37.8 (d, 13.3 Hz); IR (KBr) 3042 (w), 2996 (w), 1461(m), 1365 (m), 1230 (s), 1193 (w), 1006 (s), 956 (m), 907 (m), 783 (s), 737 (s); Elemental Anal. Calc. for $C_{12}H_{19}Br_2F$: C, 43.41; H, 2.73. Found: C, 43.43; H, 2.78.

378: colorless crystal (m.p. 76-78 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.16 (m, 4H, aryl), 5.73 (dd, *J* = 12.0, 7.2 Hz, 1H, H_9), 5.20 (d, *J* = 5.2 Hz, 1H, H_{11}), 4.56 (t, *J* = 4.0 Hz, 1H, H_{12}), 3.66 (q-like, *J* = 5.2 Hz, 1H, H_1), 3.59 (dt, *J* = 7.2, 3.2 Hz, H_8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (d, *J* = 260.5 Hz), 147.8, 138.5, 128.8, 127.9, 127.2, 121.6, 109.3 (d, *J* = 15.0 Hz), 54.3, 52.5 (d, *J* = 7.1 Hz), 45.2, 44.9. IR (KBr) 2947 (w), 1670 (s), 1465 (m), 1357 (s), 1283 (s), 1236 (s), 1132 (s), 1100 (w), 951 (w), 862 (m), 797 (s), 759 (s); Elemental Anal. Calc. for $C_{12}H_{19}Br_2F$: C, 43.41; H, 2.73. Found: C, 43.22; H, 2.69.

4.18 The Reaction of the Bromofluorocyclopropane 302a with Methyllithium

To a magnetically stirring solution of **302a** (500 mg, 1.51 mmol) in ether was added dropwise a solution of 1.6 M MeLi (5.28 mmol, 3.30 ml) in ether over ten minutes at –25 ºC under nitrogen atmosphere. Then, furan (250 mg, 3.70 mmol) was added dropwise over five minutes at the same temperature. The reaction mixture was stirred continually and allowed to warm to room temperature over four hours. The reaction mixture was quenched carefully with water. The mixture was extracted with ether, and the organic layer was washed with saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The oily residue was submitted to column chromatograpy (120 g SiO_2) eluting with CH_2Cl_2/hexane (8:92) to give **306a1** (85 mg, 20%) and **306a4** (29 mg, 5%) respectively.

***anti*-16-bromo-*syn*-*exo*-17-oxapentacyclo-[7.6.1.1^{3,6}.0^{2,7}.0^{10,15}]-heptadeca-4,7,10,12,14-pentaene (306a1)**: colorless crystal (m.p. 140-142 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.2 Hz, 1H, aryl, H_{14}), 7.09 (dt, *J* = 7.2, 1.2 Hz, 1H, aryl, H_{13}), 7.0 (dt, *J* = 7.2, 1.2 Hz, 1H, aryl, H_{12}), 6.85 (d, *J* = 7.2 Hz, 1H, aryl, H_{11}), 5.50 (dd, A-part of AB system *J* = 5.6, 1.6, 1H, H_4), 5.60 (dd, *J* = 1.2, 2.4 Hz, 1H, H_8), 5.36 (dd, B-part of AB system, *J* = 5.6, 1.2 Hz, 1H, H_5), 5.03 (d, *J* = 0.8 Hz, 1H, H_6), 4.92 (d, *J* = 3.6 Hz, 1H, H_3), 4.45 (t, *J* = 4.4 Hz, 1H, H_{16}), 3.54 (t, *J* = 4.4 Hz, 1H, H_9), 3.49 (t, *J* = 4.0 Hz, 1H, H_1), 3.27 (q-like, *J* = 3.6 Hz, 1H, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 138.1, 134.1, 130.3, 130.0, 127.6, 125.6, 125.1, 119.4, 116.9, 80.4, 79.9, 53.0, 48.1, 45.4, 41.2. IR (KBr) 3004 (m), 2931 (w), 2895 (w), 1462 (m),

1308 (m), 1283 (s), 1287 (m), 891 (s), 848 (s), 820 (m), 777 (s); Elemental Anal. Calc. for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 64.04; H 4.43.

***anti*-16-bromo-*syn*-*endo*-17-oxapentacyclo-[7.6.1.1^{3,6}.0^{2,7}.0^{10,15}]heptadeca-4,7,10,12,14-pentaene (306a3)**: colorless crystal. (m.p. 146-148 ºC), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.13 (m, 4H, aryl), 6.32 (dd, A-part of AB system, *J* = 5.6, 1.6 Hz, 1H, H_5), 6.30 (dd, B- part of AB system, *J* = 5.6, 1.2 Hz, 1H, H_5), 5.89 (dd, *J* = 6.8, 2.8, 1H, H_8), 5.12 (s, 1H, H_6), 5.09 (d, *J* = 4.0 Hz, 1H, H_3), 4.46 (t, *J* = 3.6, 1H, H_{16}), 3.65 (dd, *J* = 6.8, 3.6, 1H, H_9), 3.33 (d, *J* = 3.6 Hz, 1H, H_1), 2.60 (t, *J* = 3.6 Hz, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 143.3, 139.5, 134.1, 130.9, 126.5, 126.3, 121.5, 119.8, 115.9, 80.5, 79.4, 48.55, 44.6, 44.1, 43.3; IR (KBr) 2923 (w), 1463 (m), 1378 (w), 1262 (w), 1141 (w), 724 (w); Elemental Anal. Calc. for $C_{16}H_{13}BrO$: C, 63.81; H, 4.35. Found: C, 64.18; H 4.53.

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APPENDIX

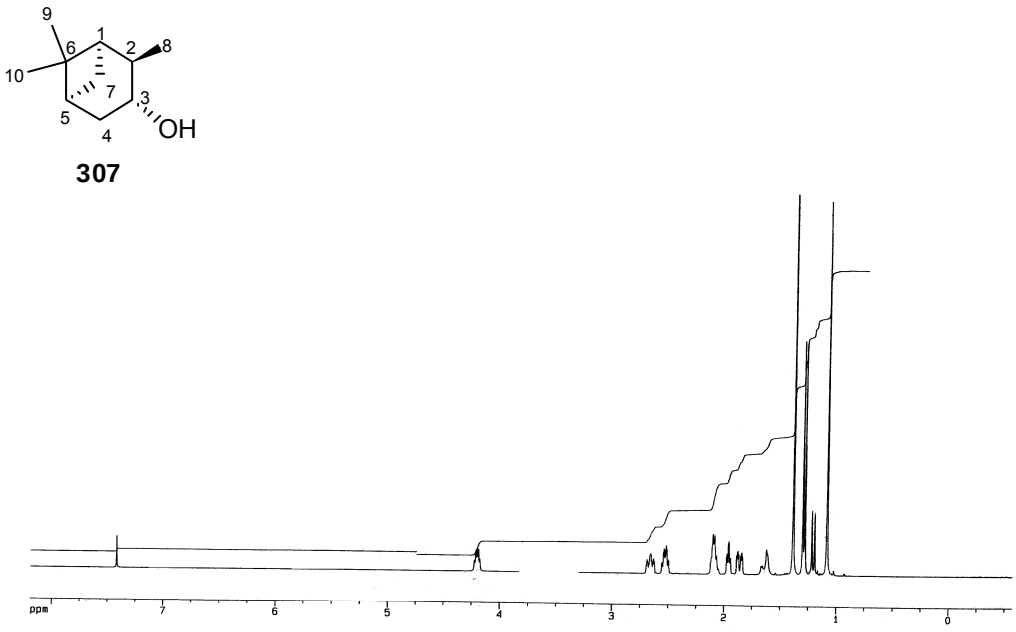


Figure 23: ^{1}H NMR spectrum of **307**

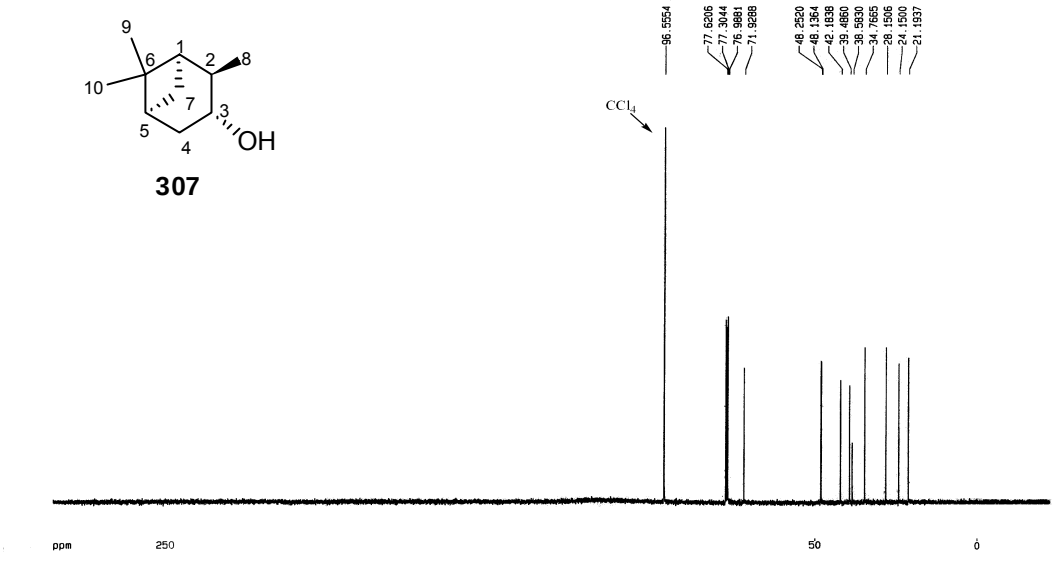


Figure 24: ^{13}C NMR spectrum of **307**

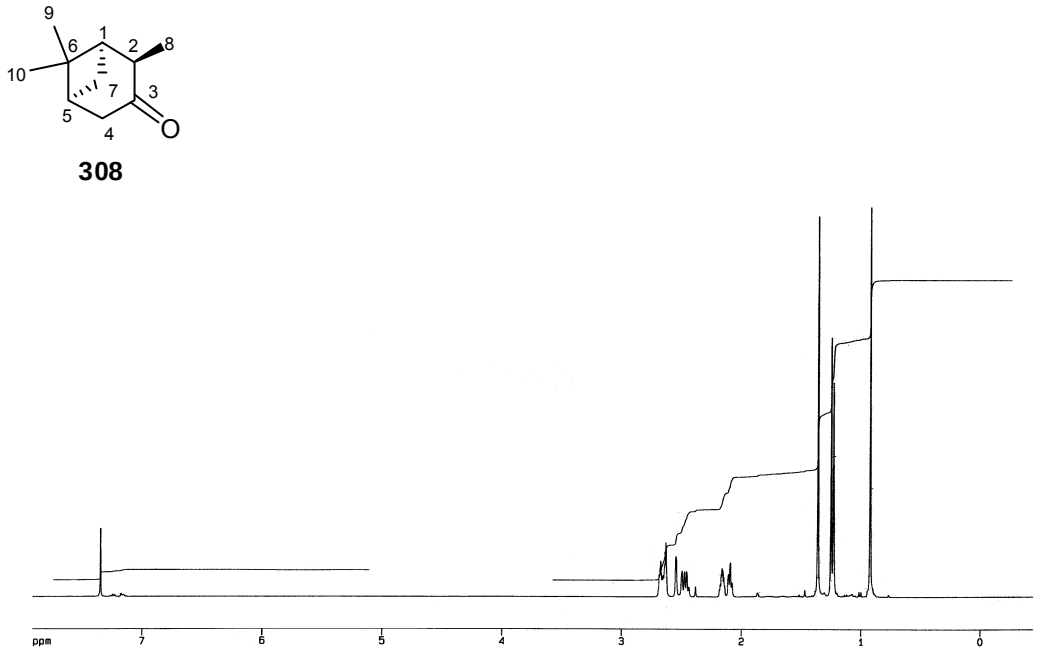


Figure 25: ^{1}H NMR spectrum of **308**

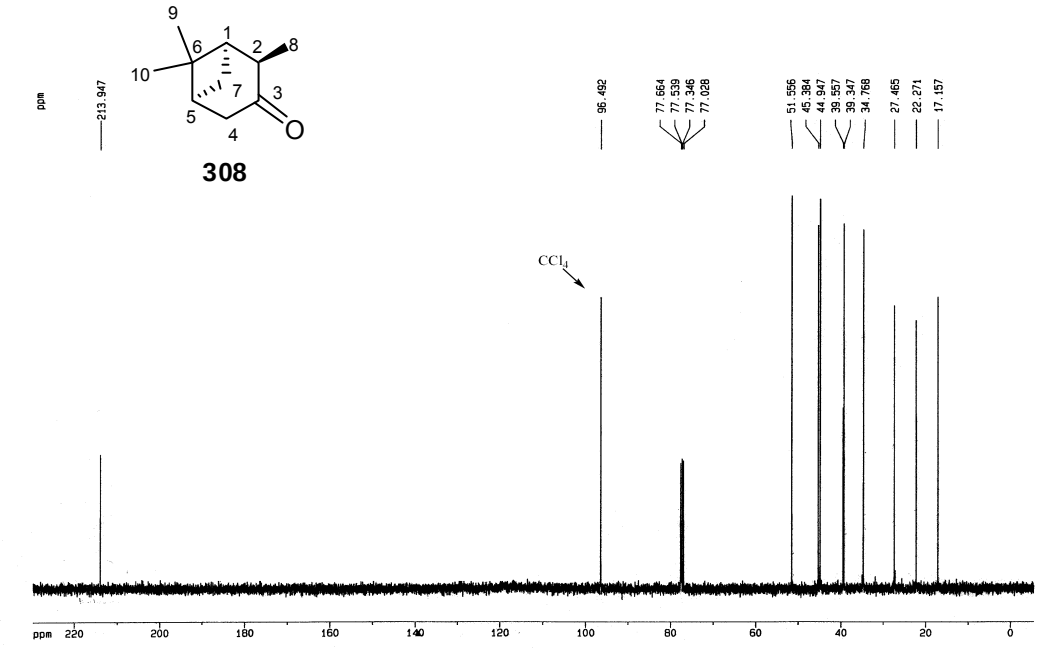


Figure 26: ^{13}C NMR spectrum of **308**

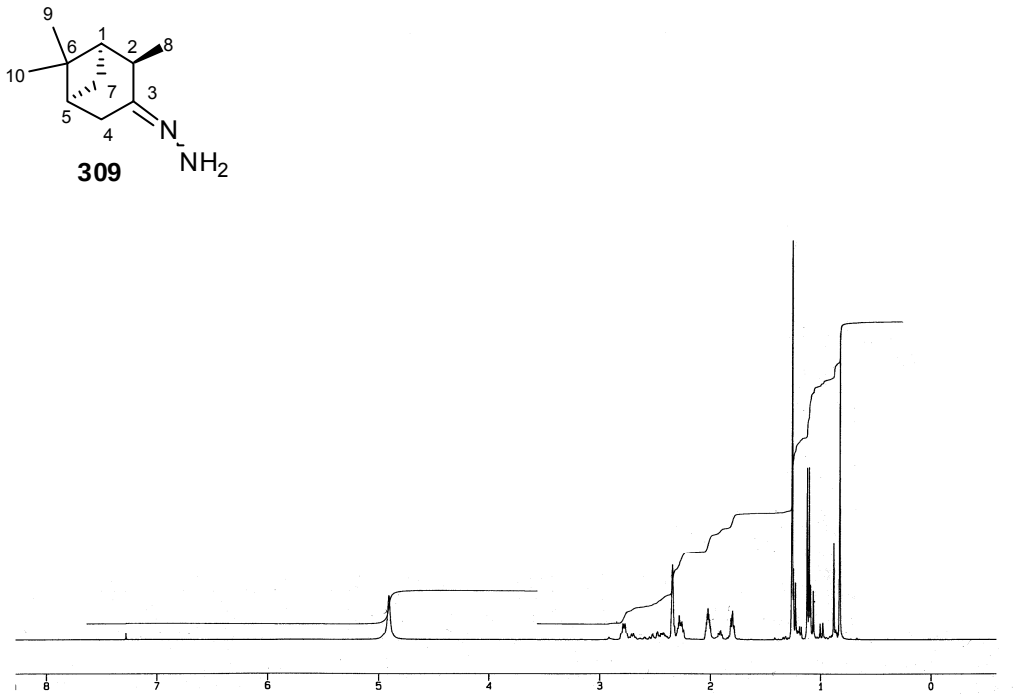


Figure 27: ^{1}H NMR spectrum of **309**

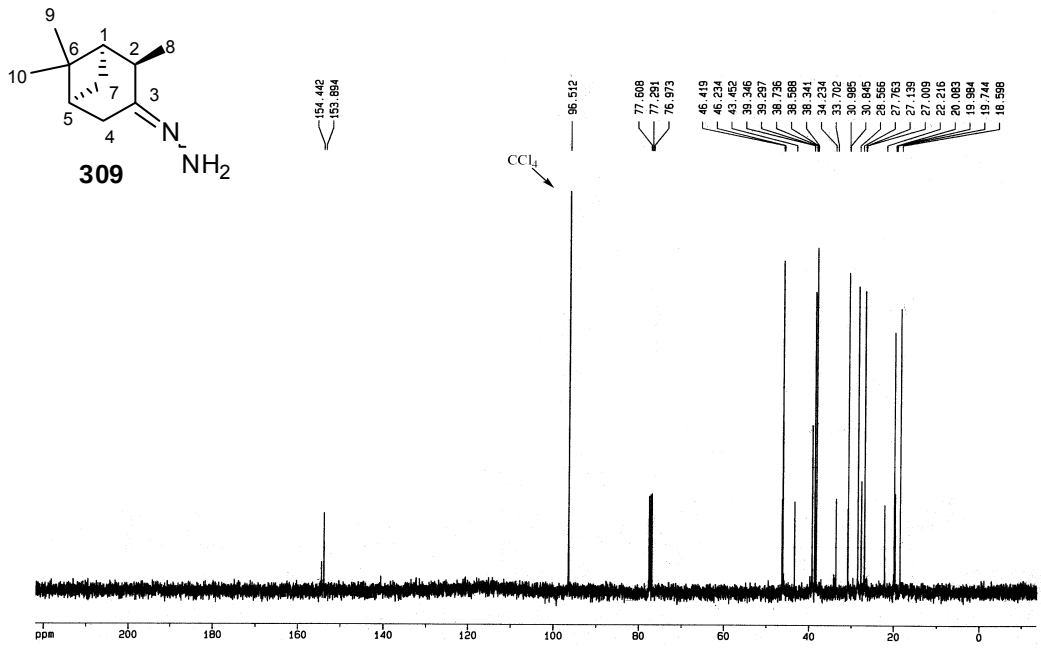
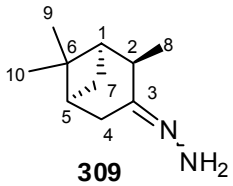


Figure 28: ^{13}C NMR spectrum of **309**



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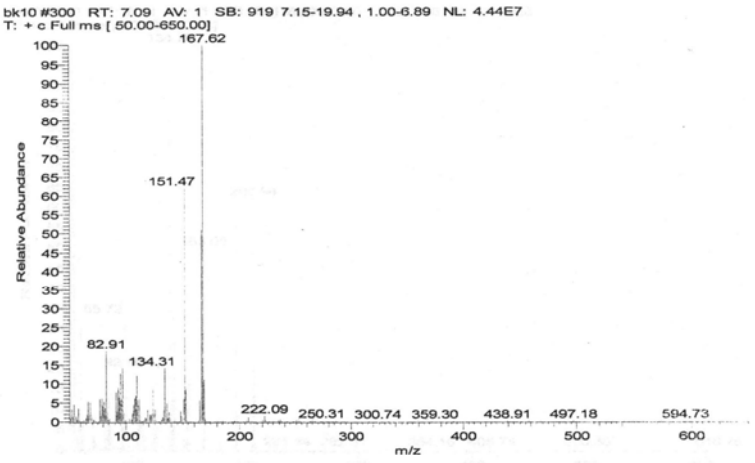


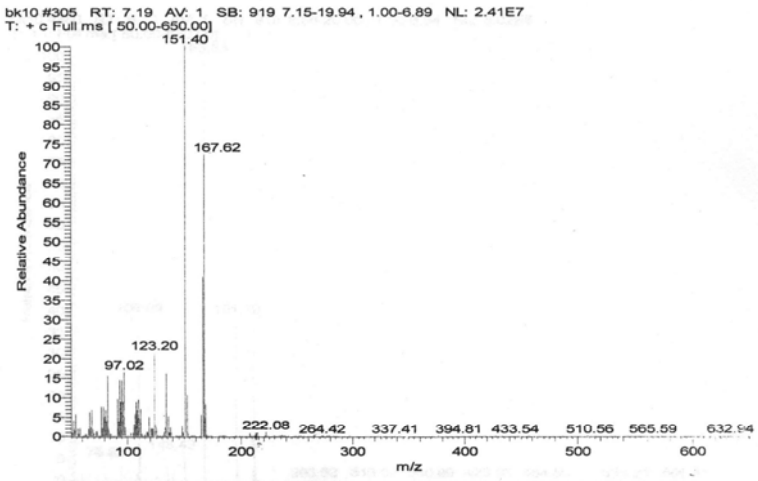


Figure 29: MS spectrum of *anti* & *syn* **309**

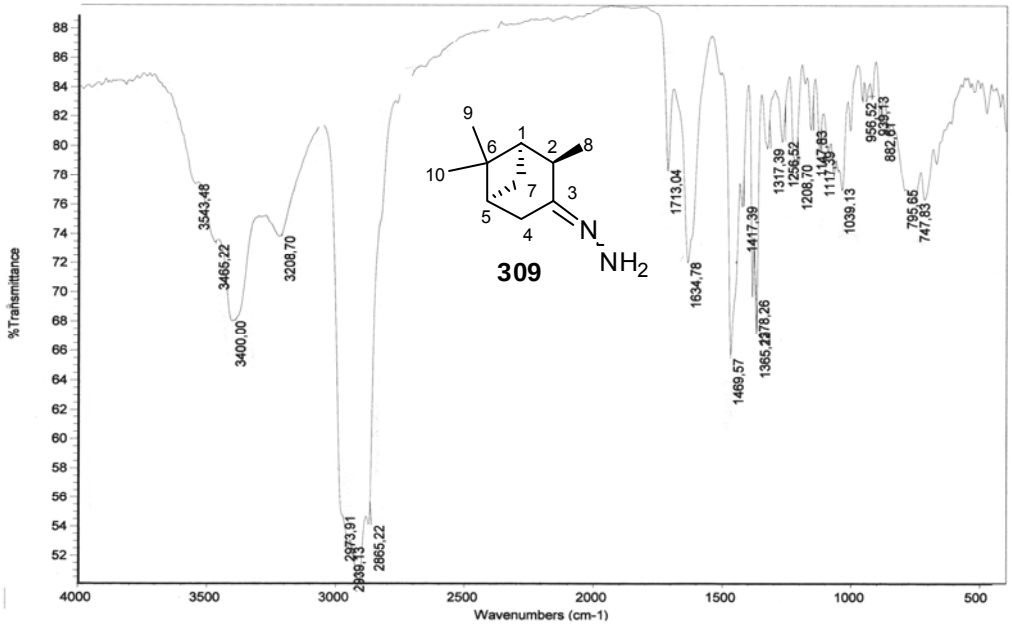


Figure 30: IR spectrum of **309**

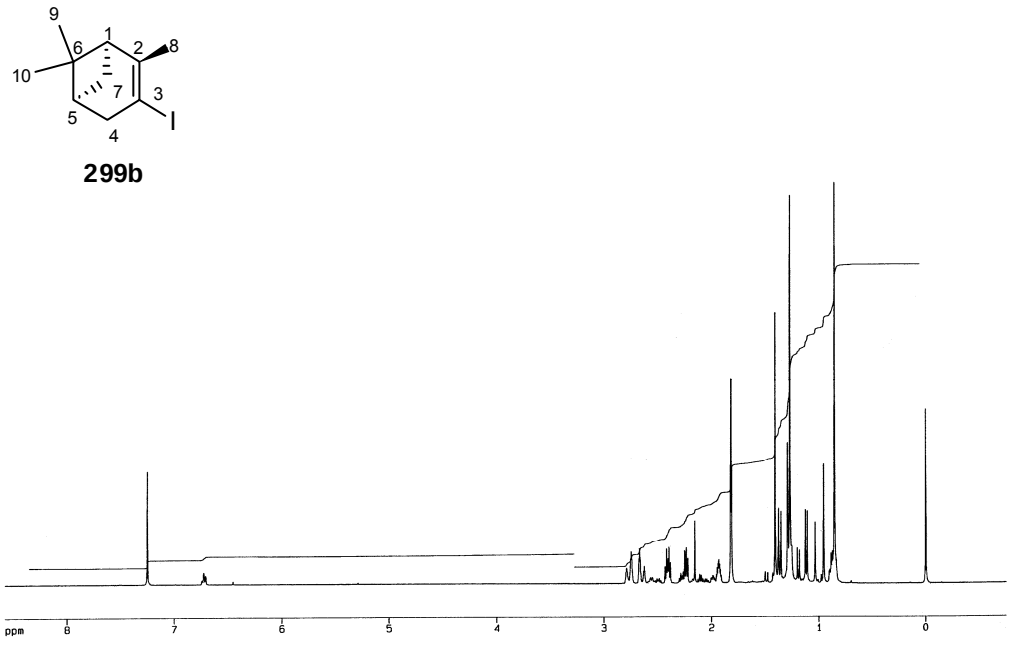


Figure 31: ^{1}H NMR spectrum of **299b**

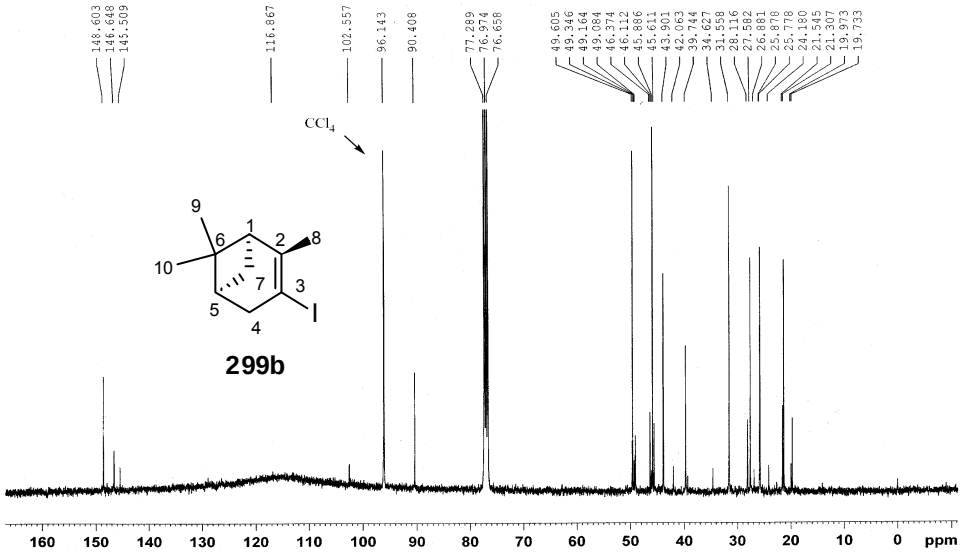


Figure 32: ^{13}C NMR spectrum of **299b**

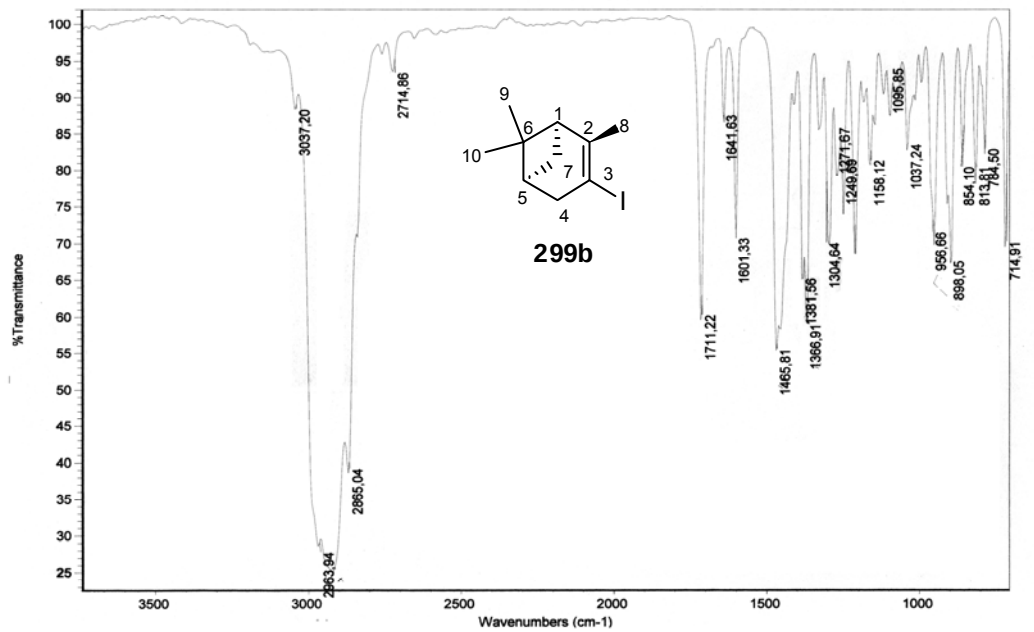


Figure 33: IR spectrum of **299b**

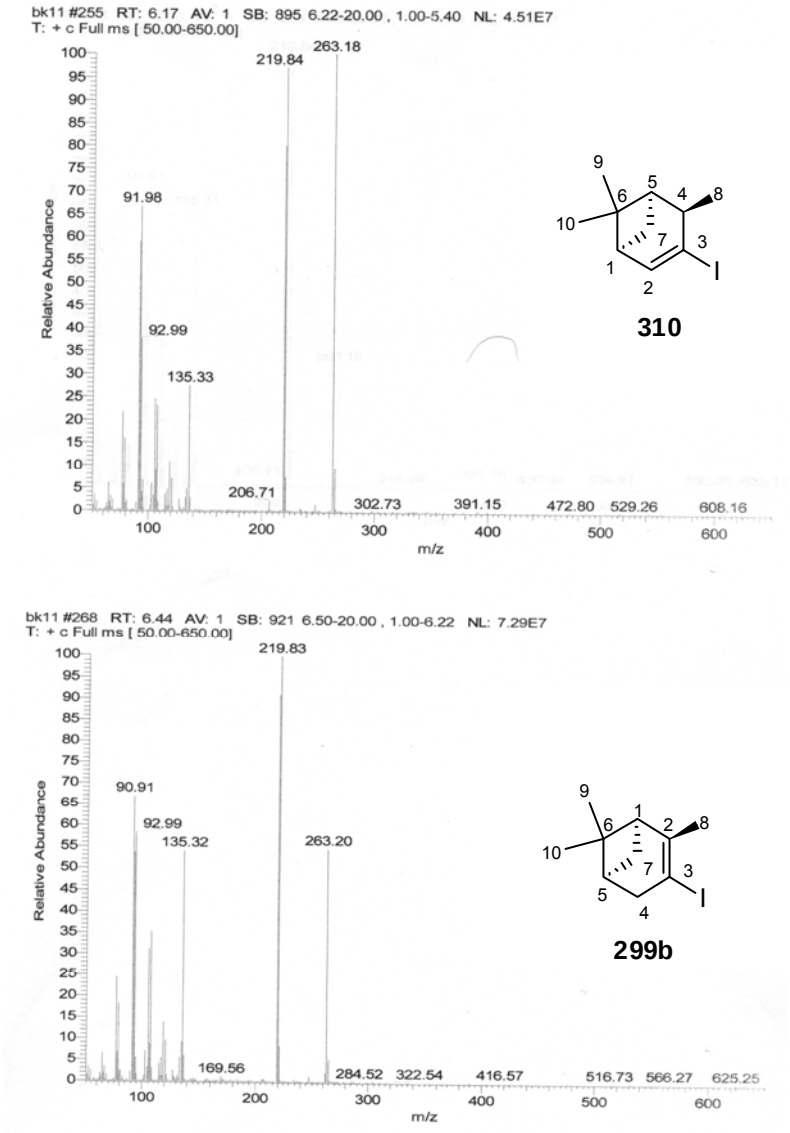
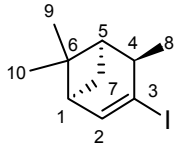


Figure 34: MS spectrum of **299b** and **310**



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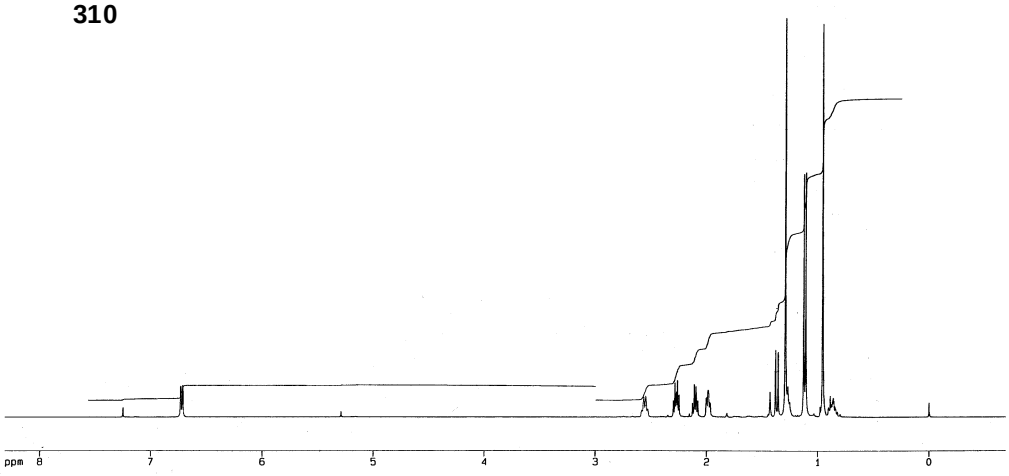
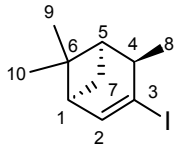


Figure 35: ^{1}H NMR spectrum of **310**



310

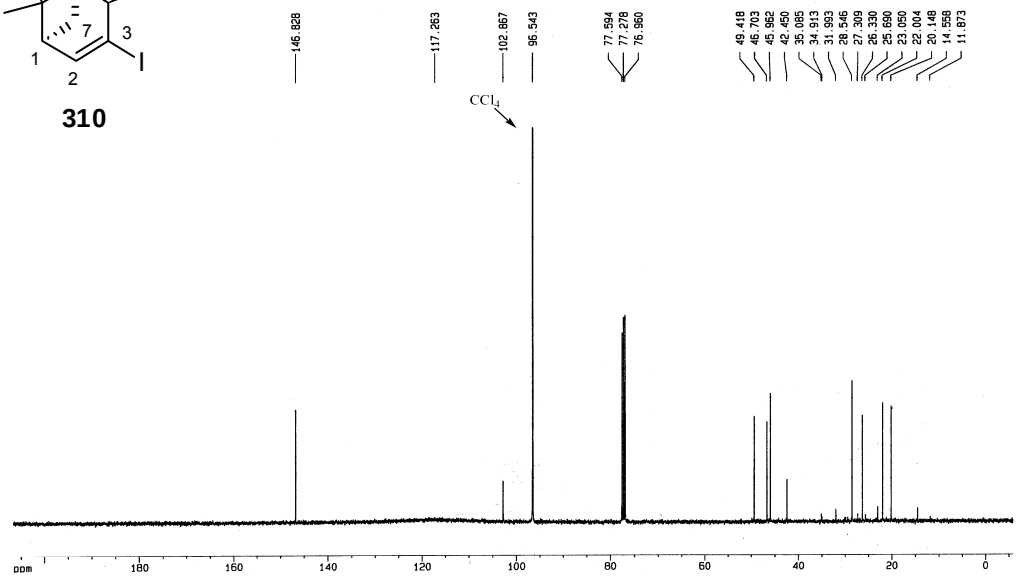


Figure 36: ^{13}C NMR spectrum of **310**

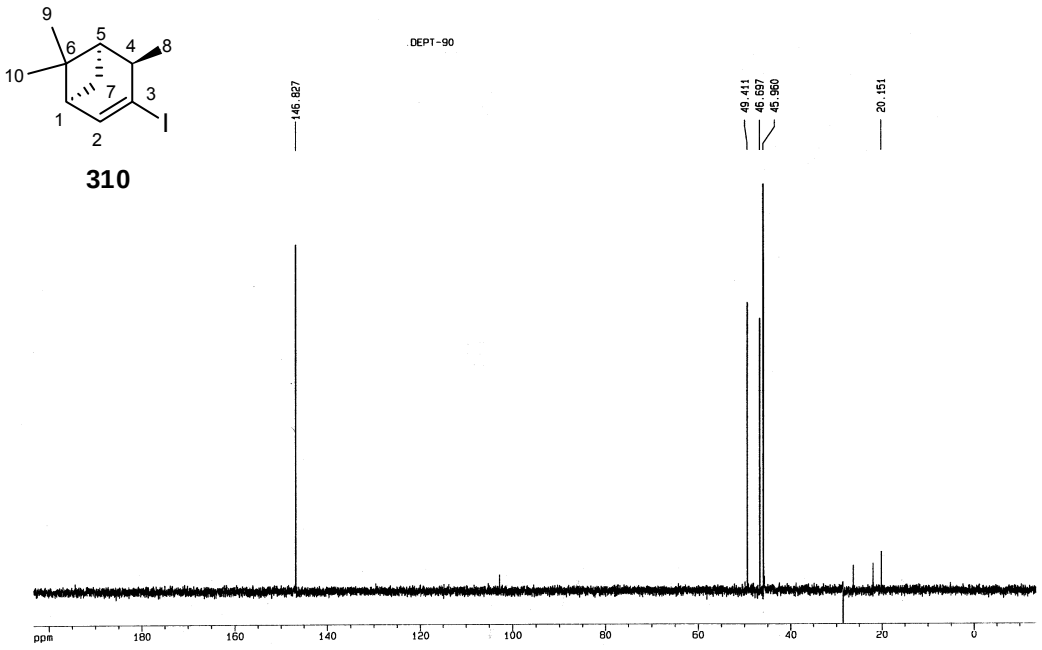


Figure 37: DEPT 90 spectrum of **310**

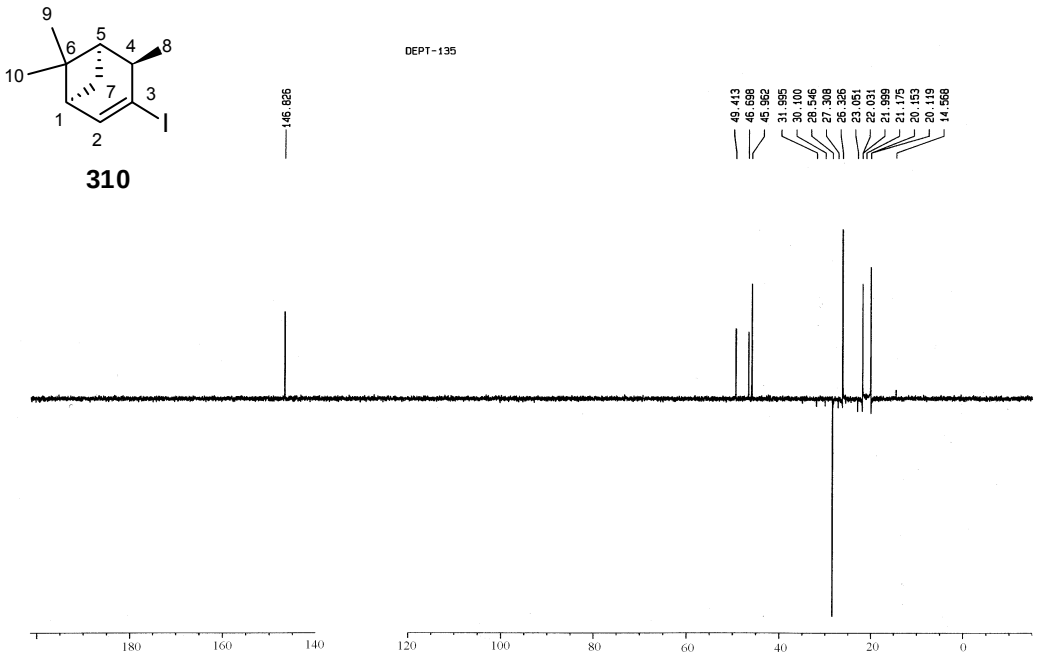


Figure 38: DEPT 135 spectrum of **310**

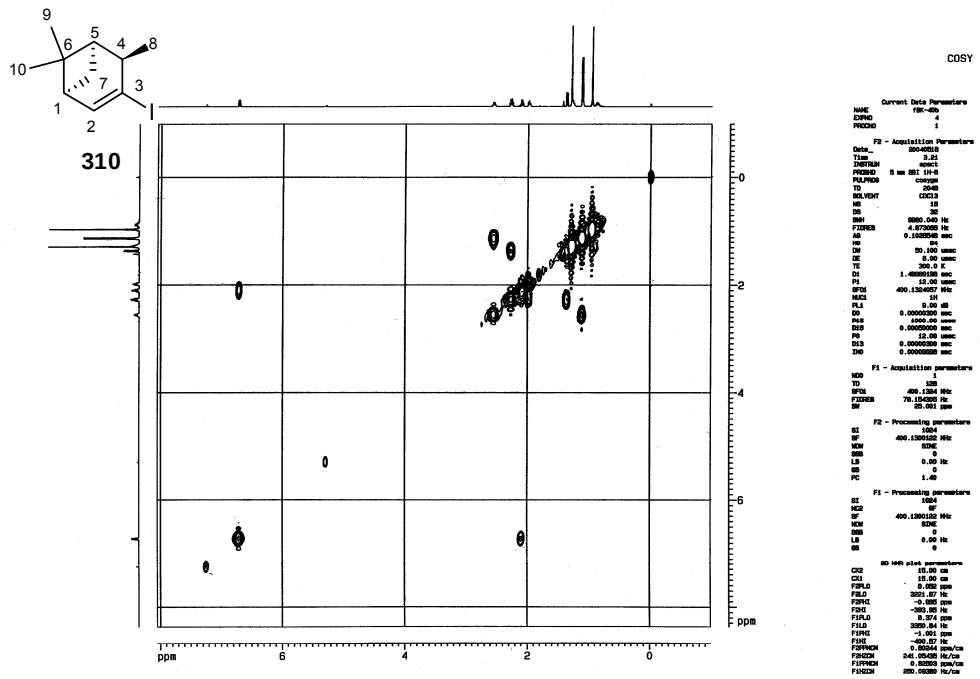


Figure 39: COSY spectrum of **310**

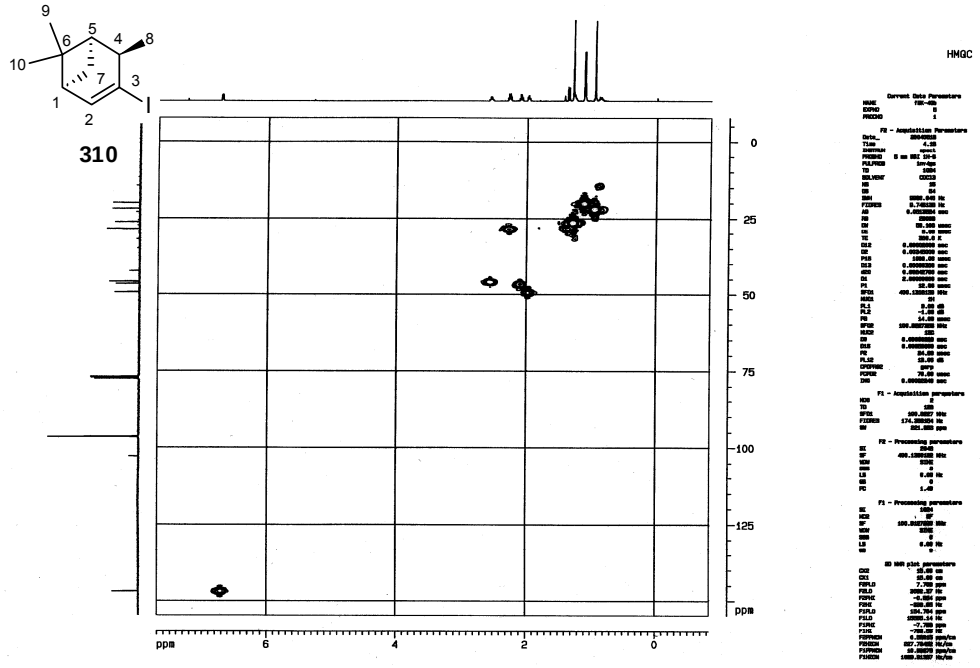


Figure 40: HMQC spectrum of **310**

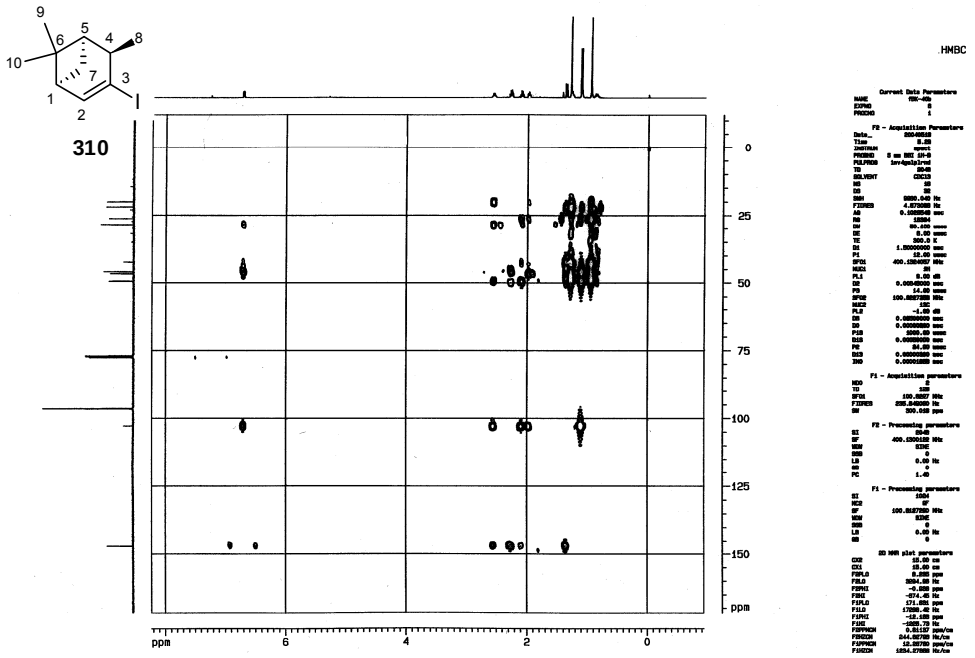


Figure 41: HMBC spectrum of **310**

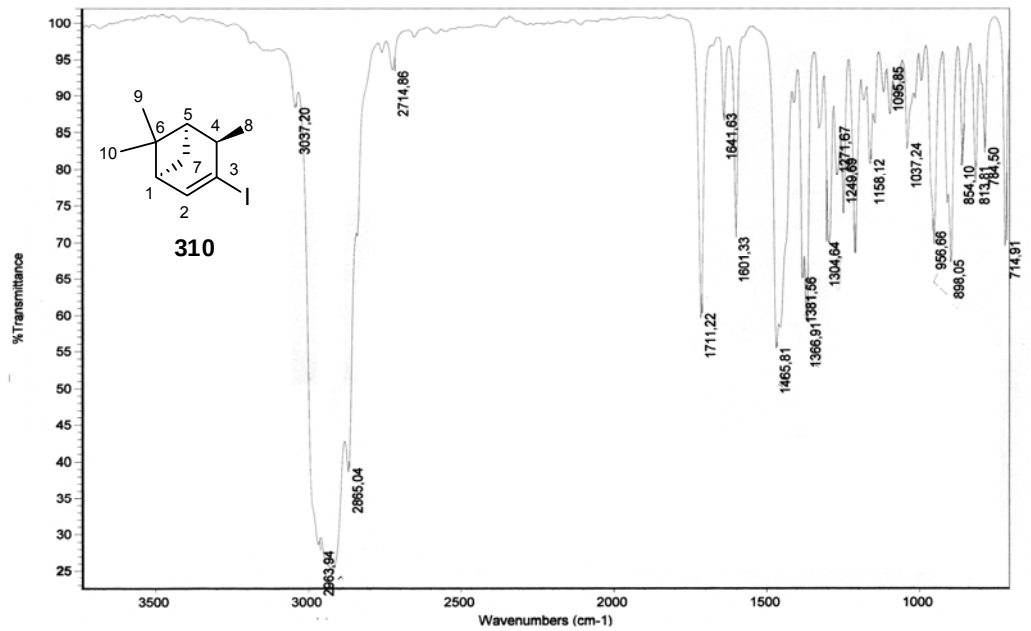
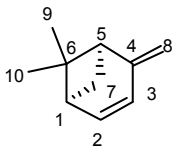


Figure 42: IR spectrum of **310**



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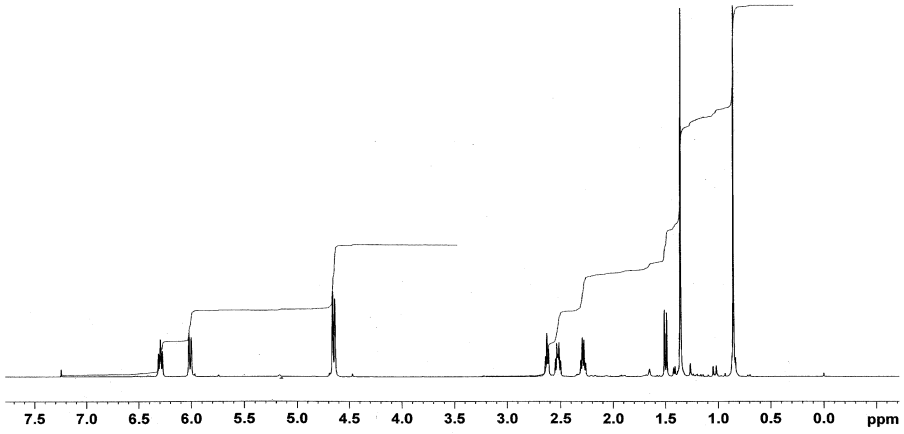
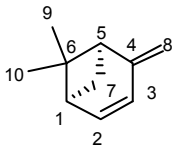


Figure 43: ^{1}H NMR spectrum of **313**



313

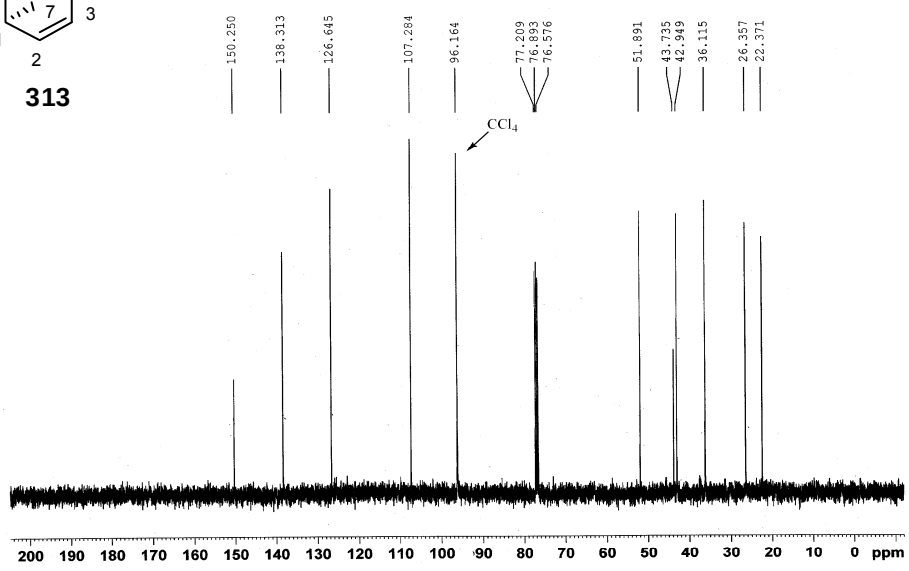


Figure 44: ^{13}C NMR spectrum of **313**

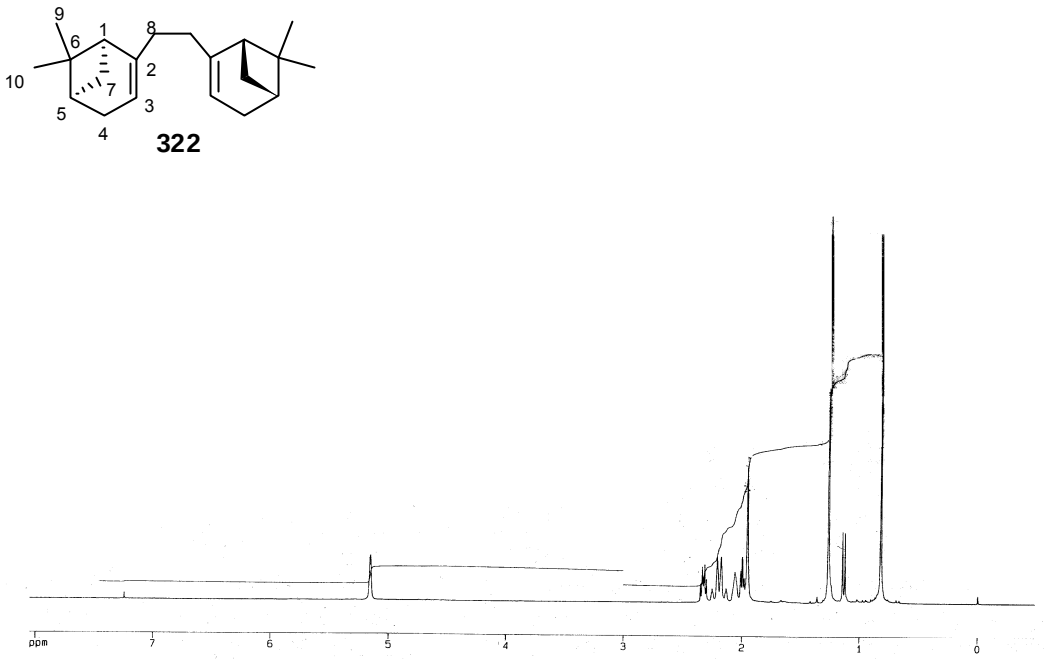


Figure 45: ^{1}H NMR spectrum of **322**

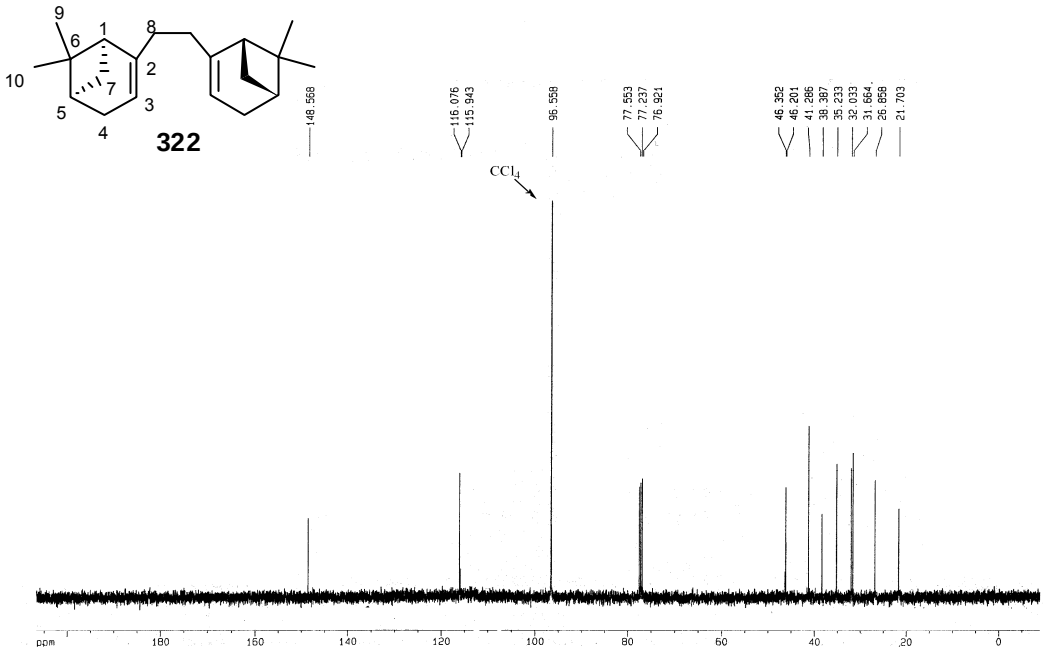


Figure 46: ^{13}C NMR spectrum of **322**

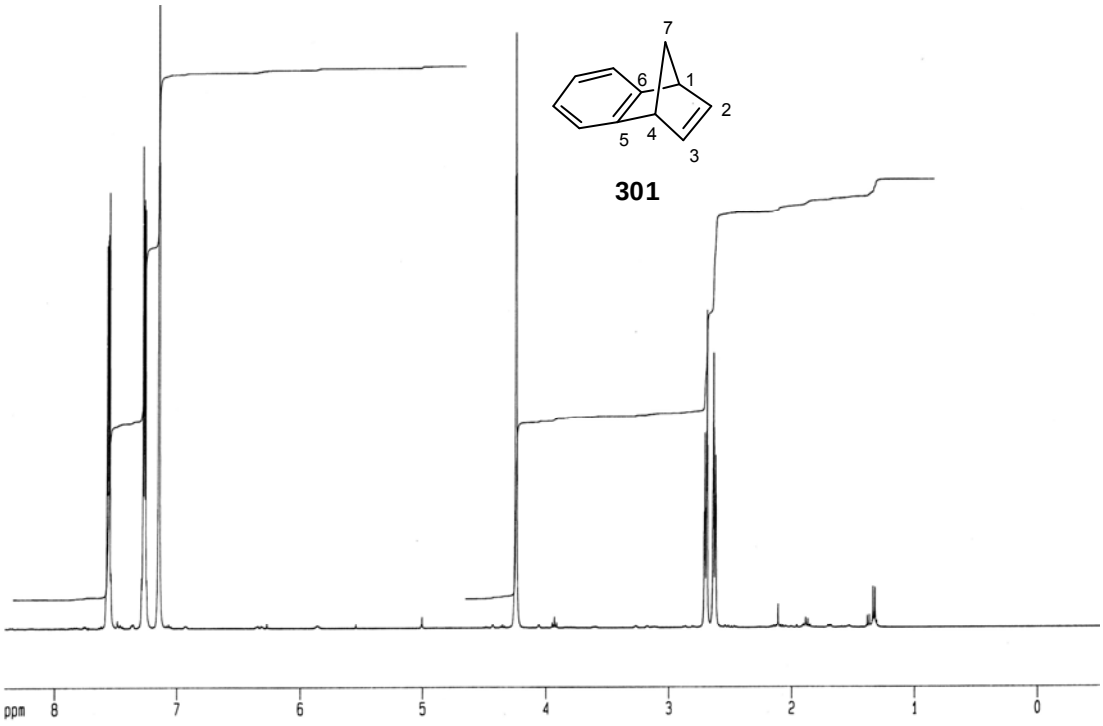


Figure 47: ^{1}H NMR spectrum of **301**

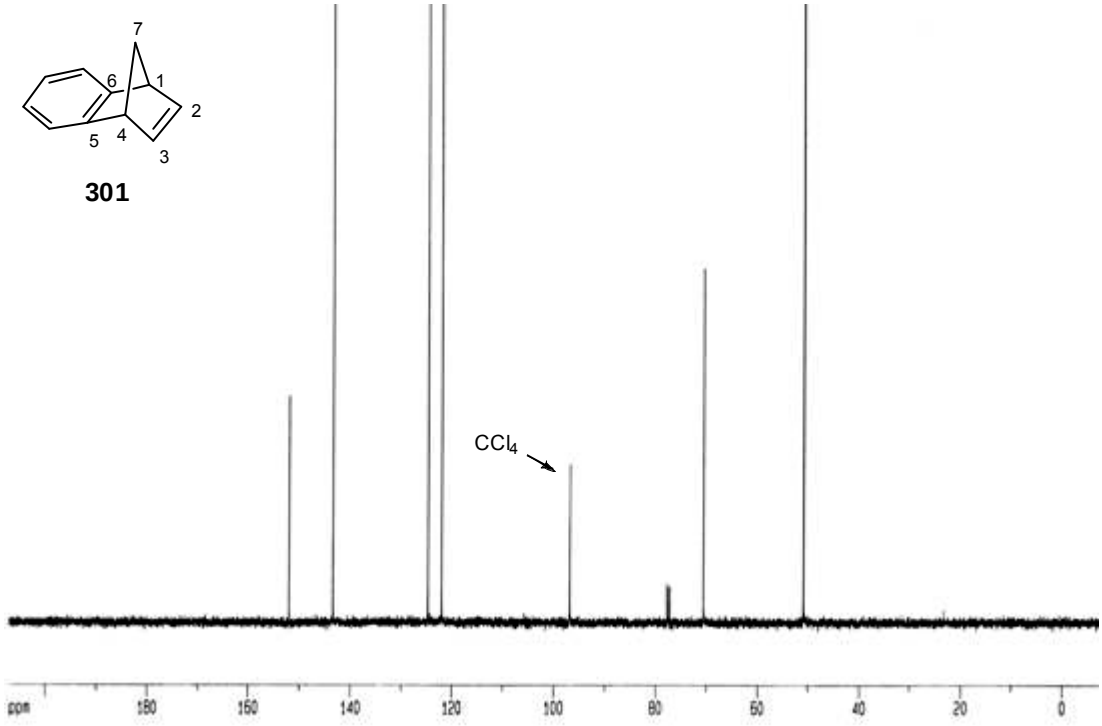
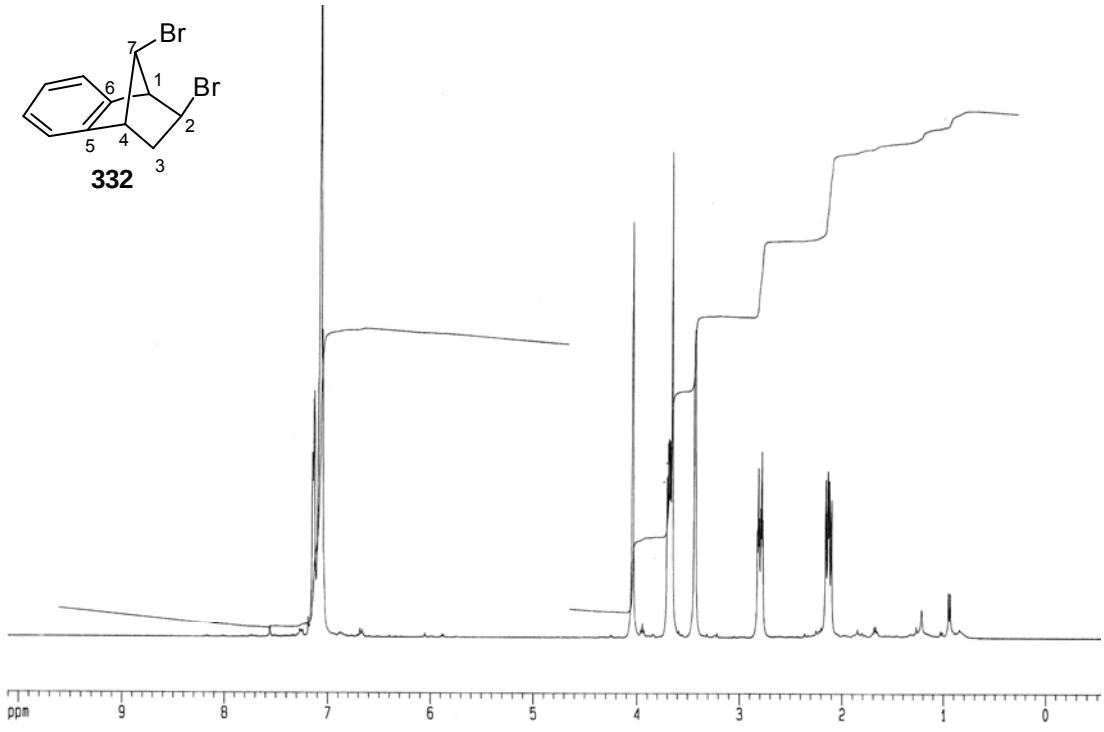


Figure 48: ^{13}C NMR spectrum of **301**



332

Figure 49: ^{1}H NMR spectrum of **332**

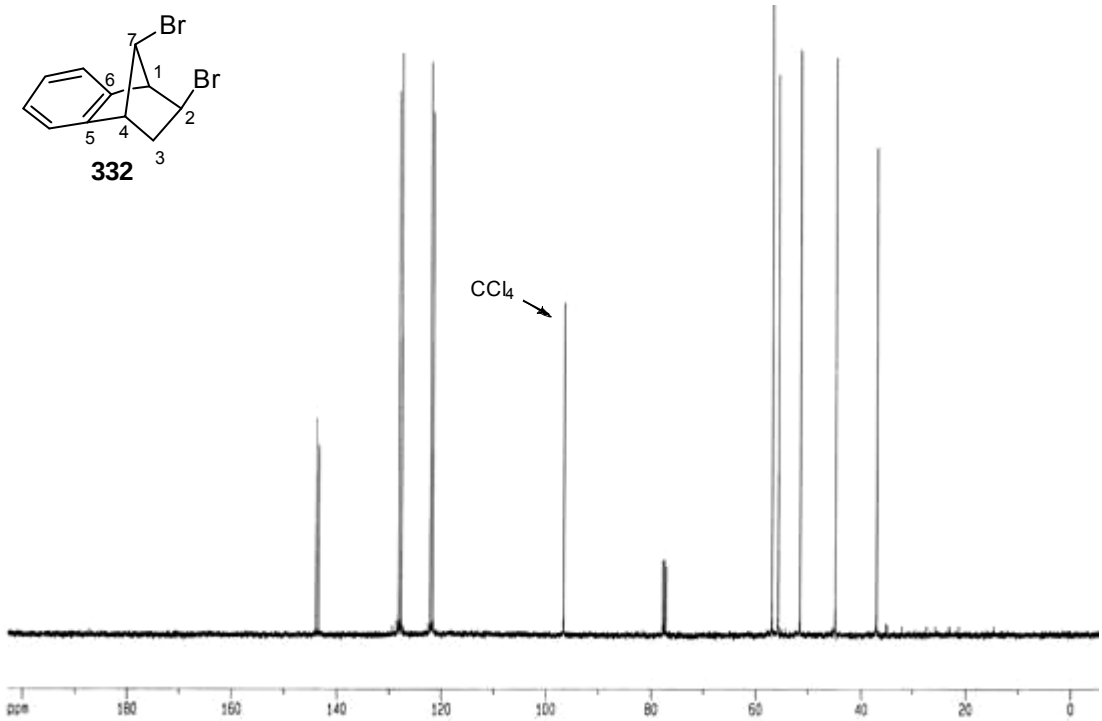


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Figure 50: ^{13}C NMR spectrum of **332**

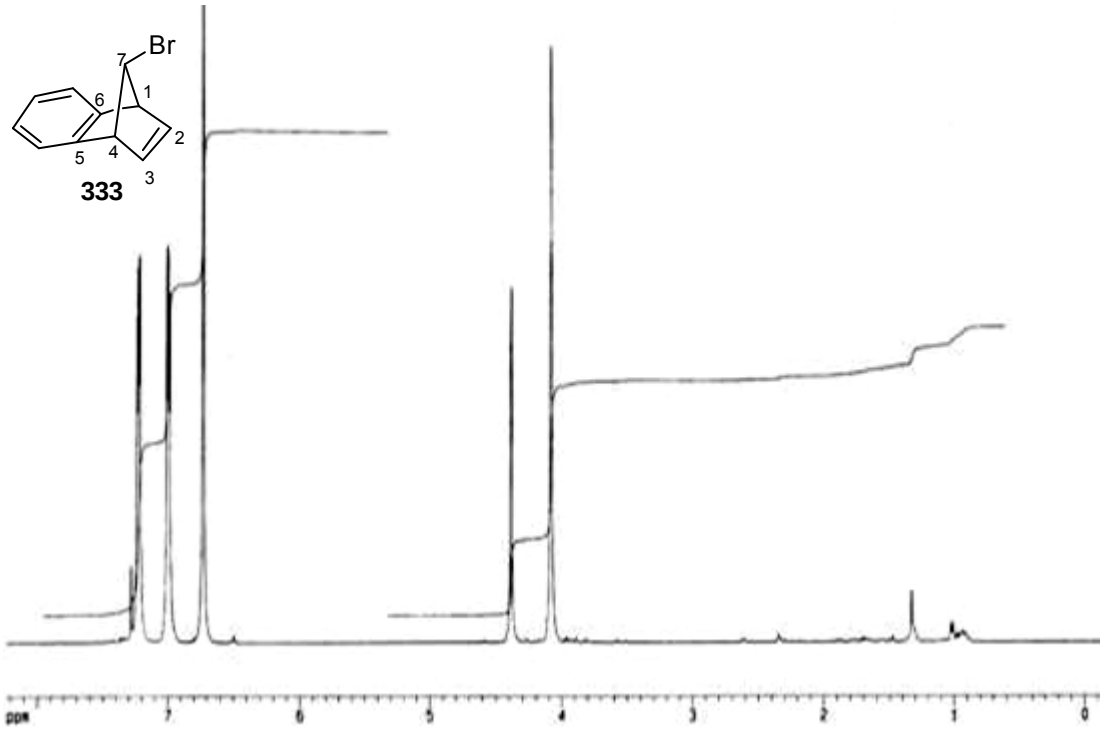


Figure 51: ^{1}H NMR spectrum of **333**

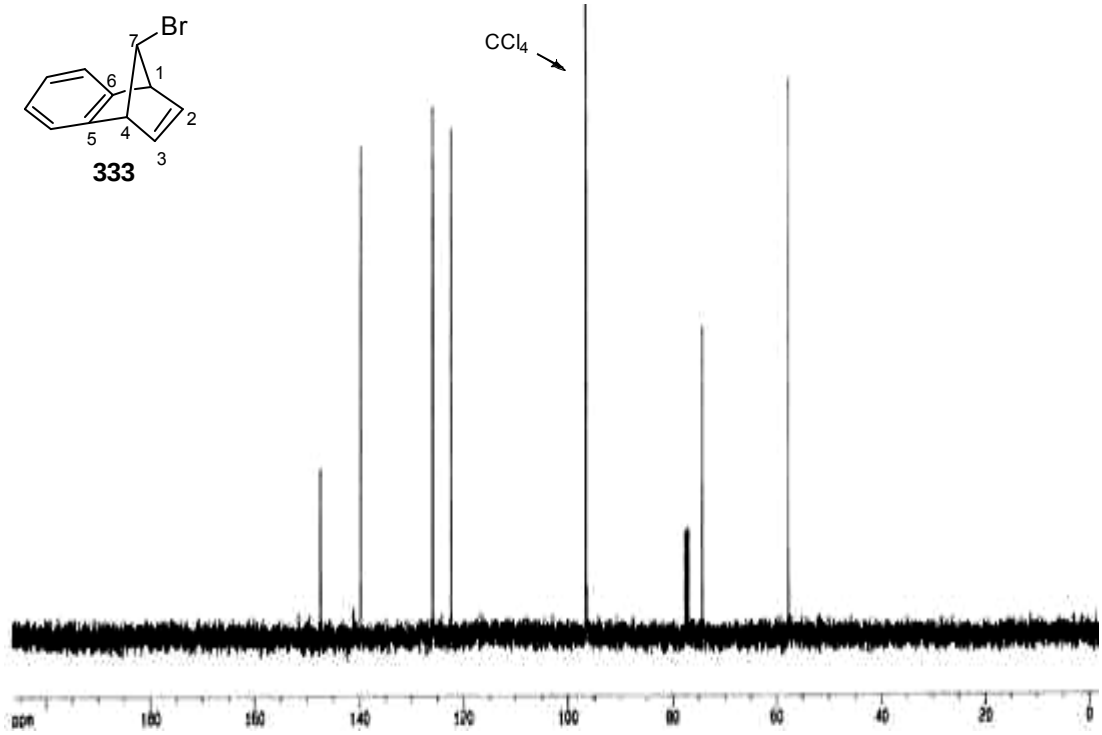


Figure 52: ^{13}C NMR spectrum of **333**

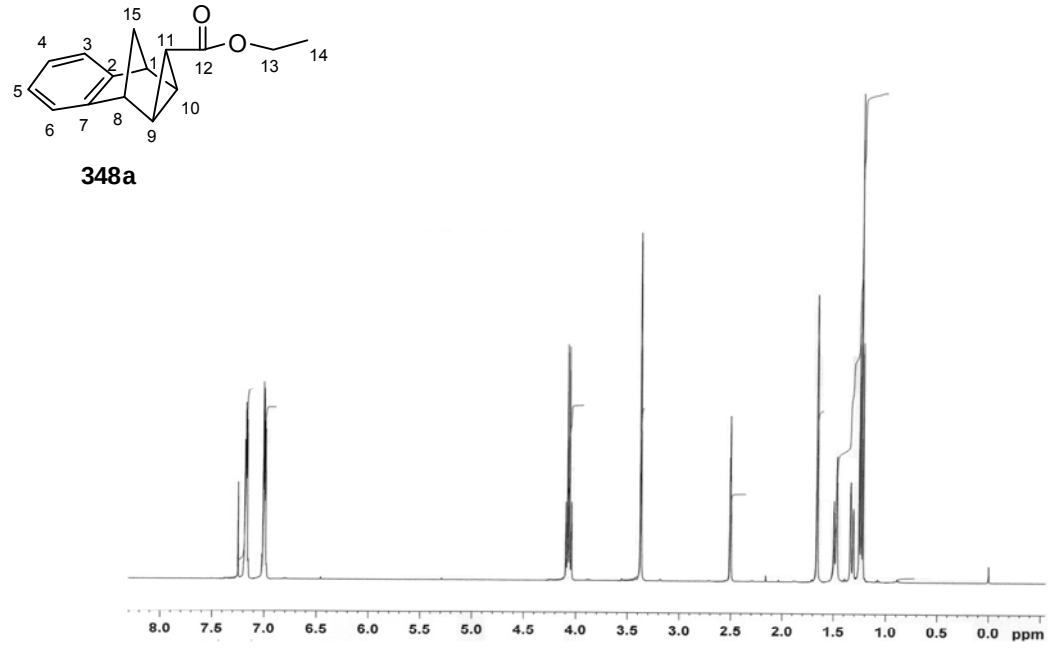


Figure 53: ^{1}H NMR spectrum of **348a**

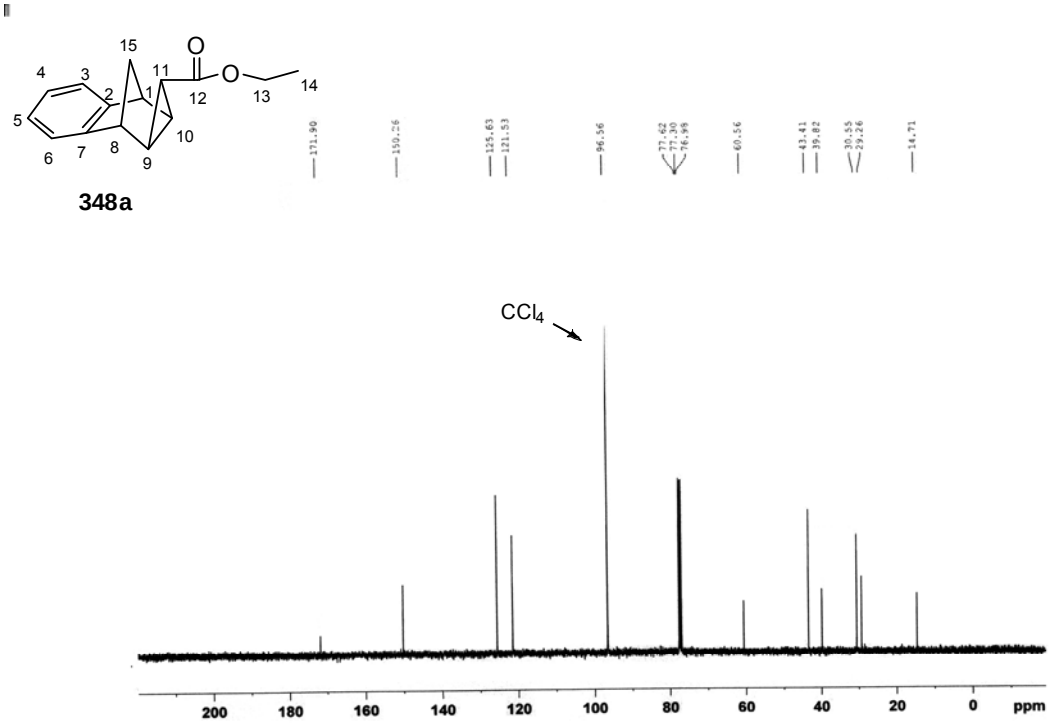


Figure 54: ^{13}C NMR spectrum of **348a**

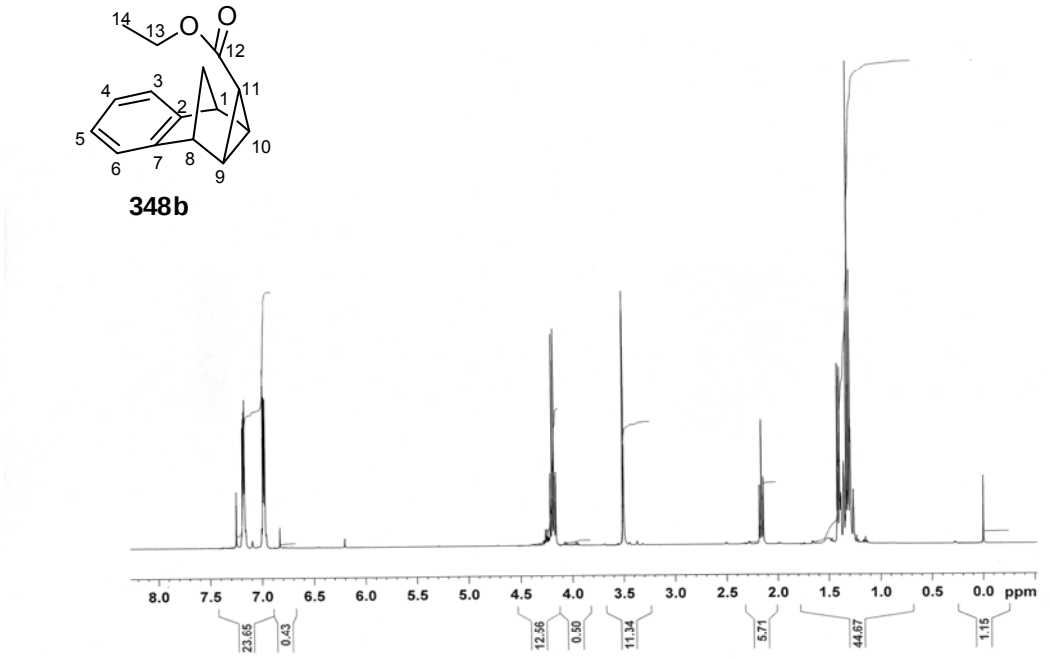


Figure 55: ^{1}H NMR spectrum of **348b**

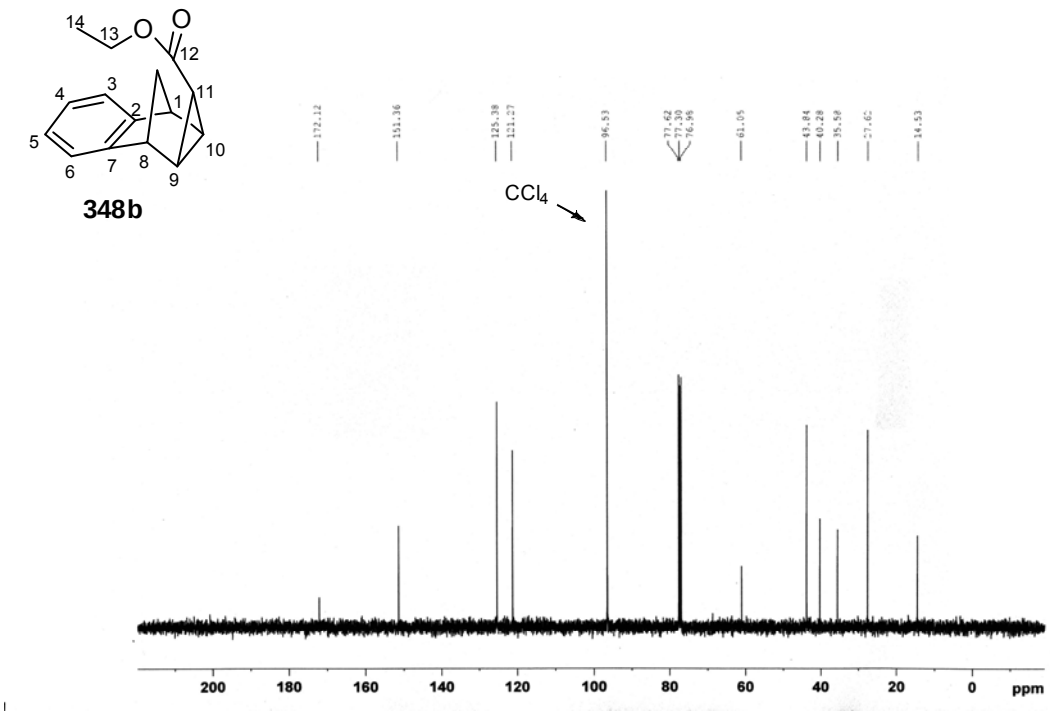


Figure 56: ^{13}C NMR spectrum of **348b**

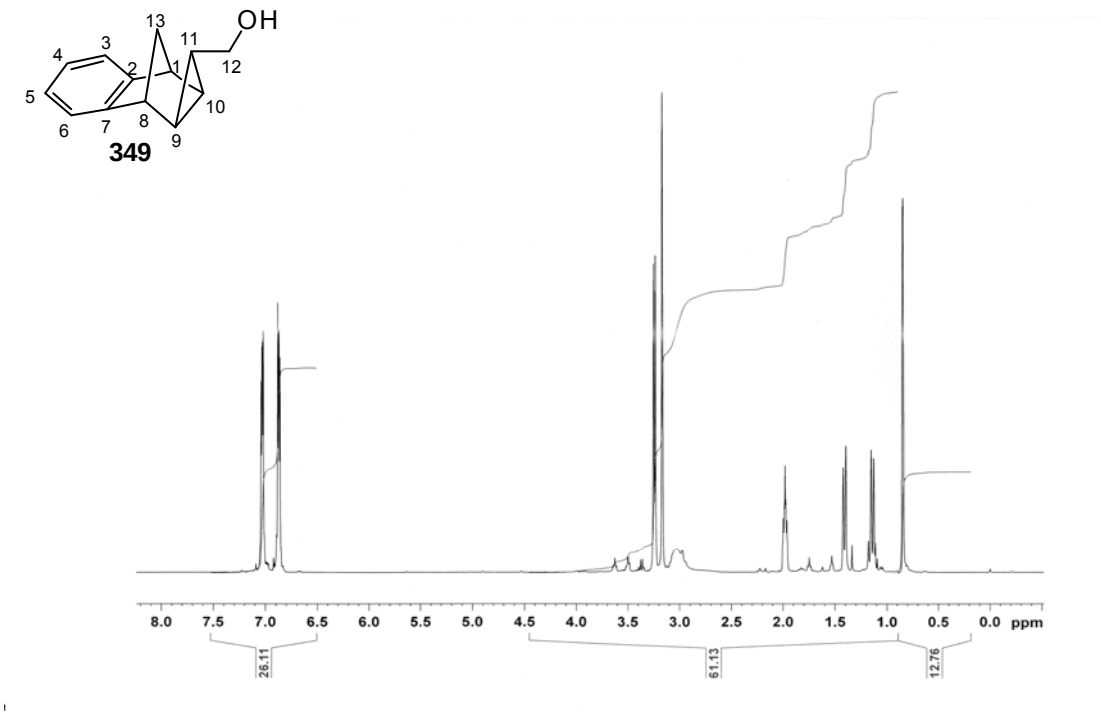


Figure 57: ^{1}H NMR spectrum of **349**

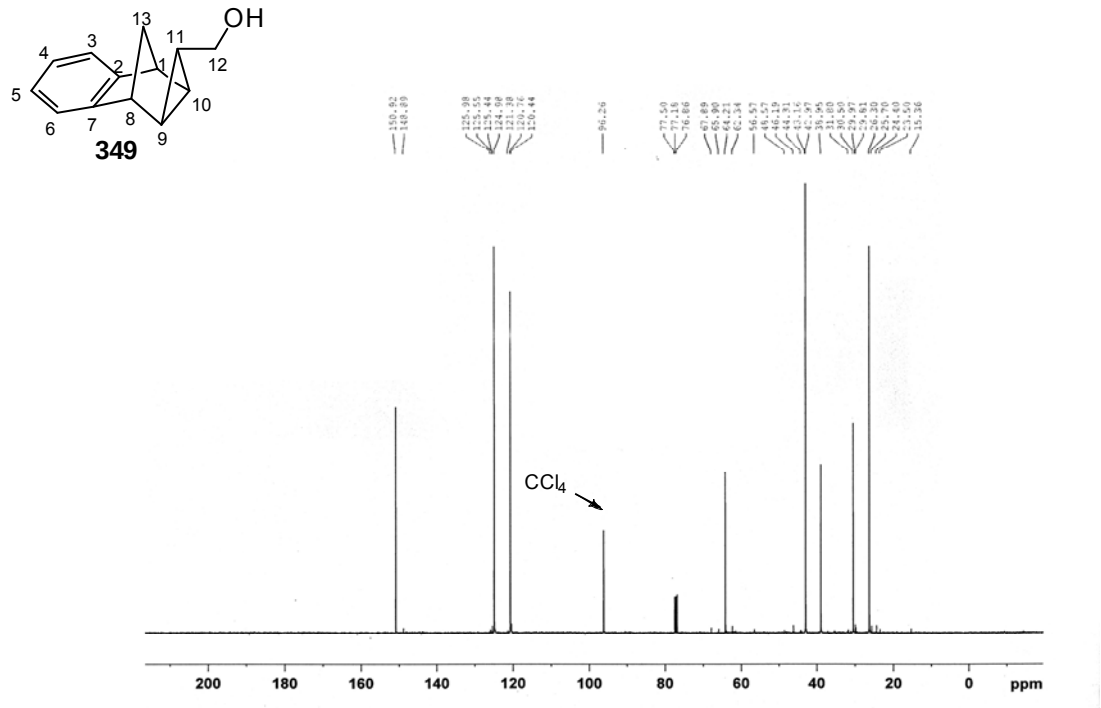


Figure 58: ^{13}C NMR spectrum of **349**

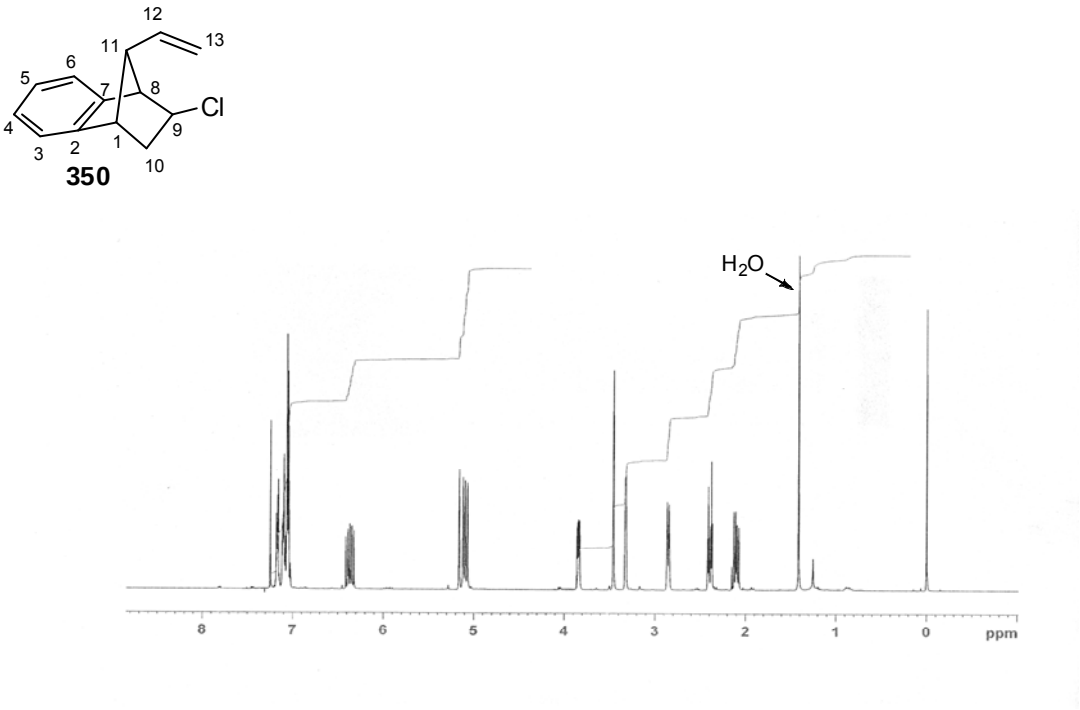


Figure 59: ^{1}H NMR spectrum of **350**

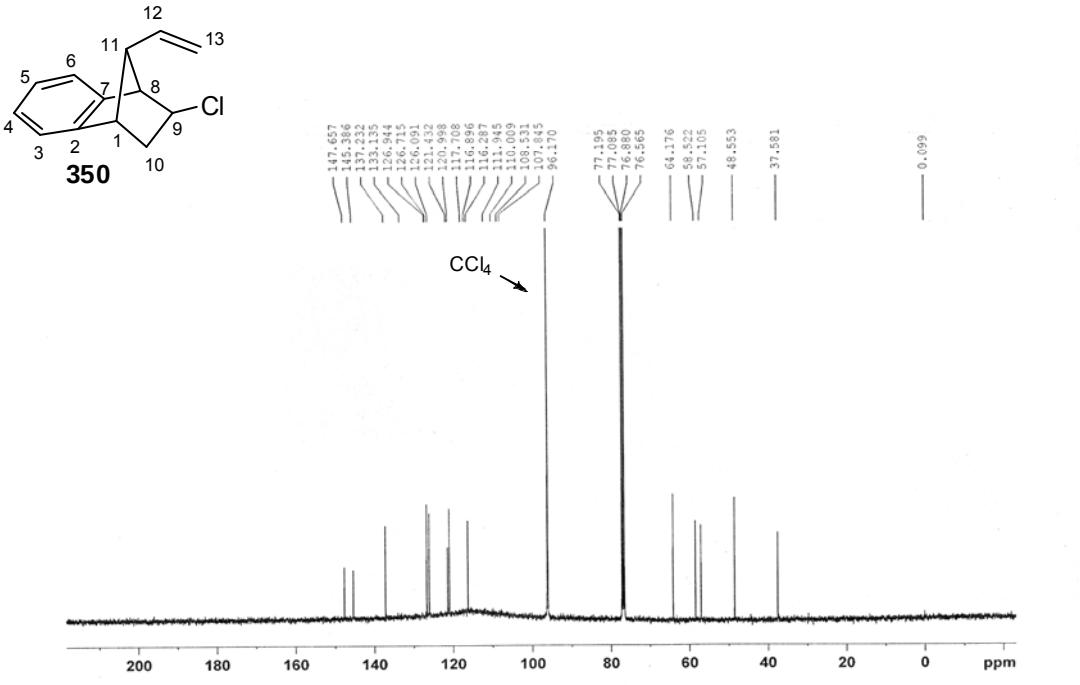
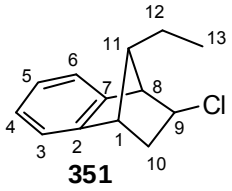


Figure 60: ^{13}C NMR spectrum of **350**



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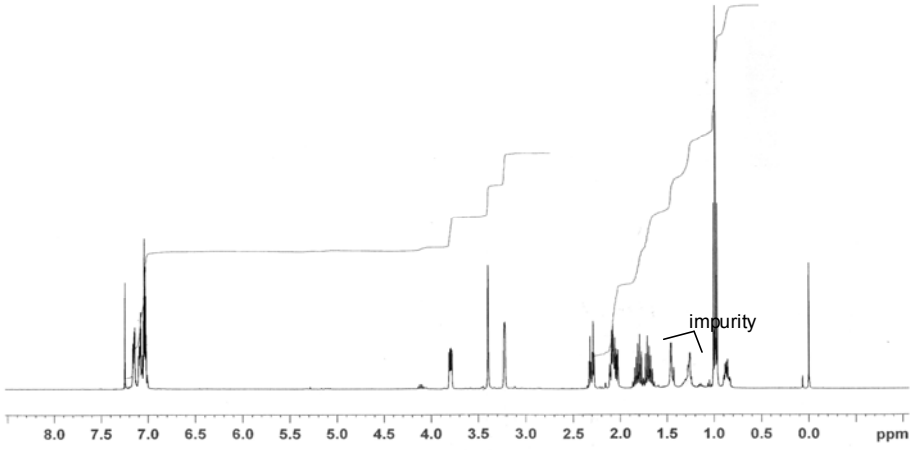
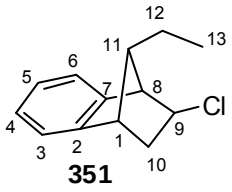


Figure 61: ^{1}H NMR spectrum of **351**



351

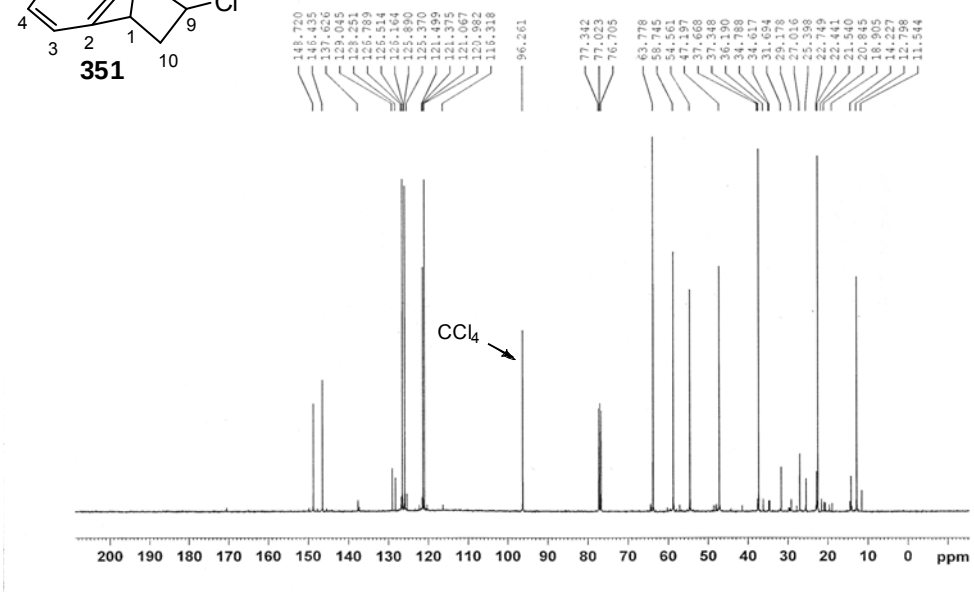


Figure 62: ^{13}C NMR spectrum of **351**

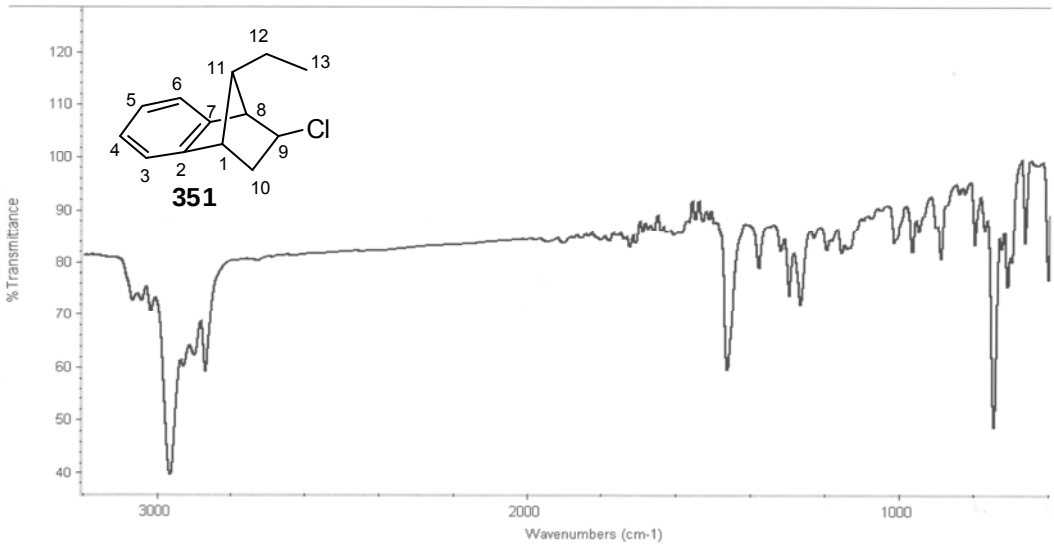
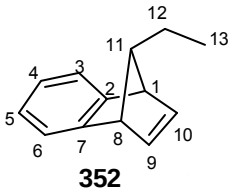


Figure 63: IR spectrum of **351**



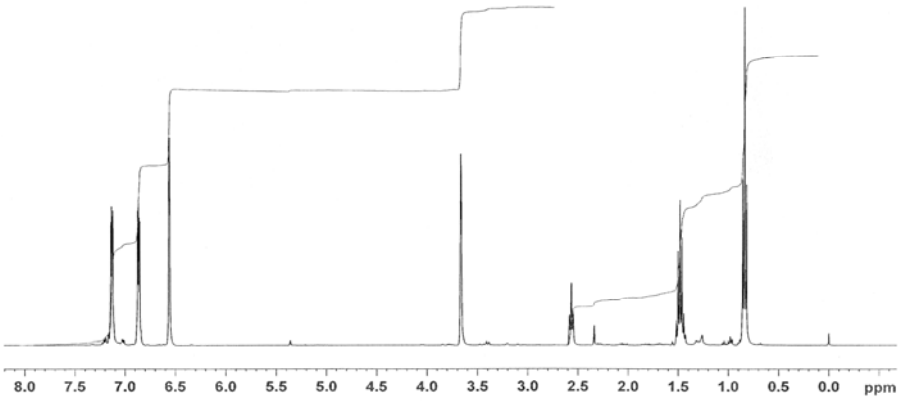


Figure 64: ^{1}H NMR spectrum of **352**

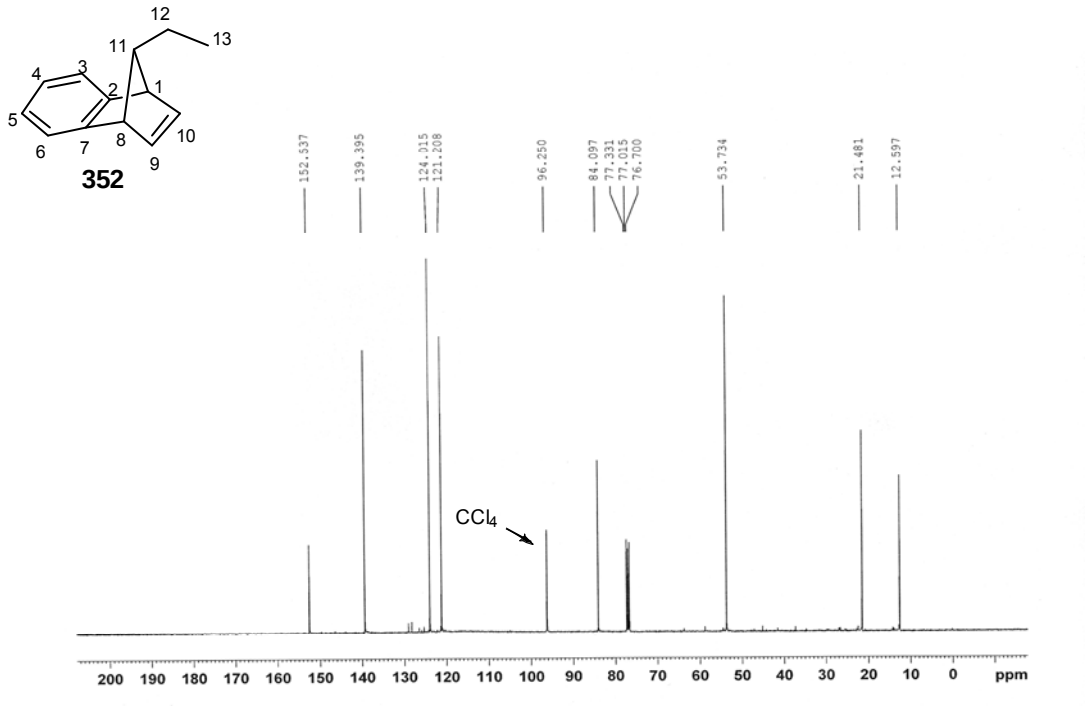


Figure 65: ^{13}C NMR spectrum of **352**

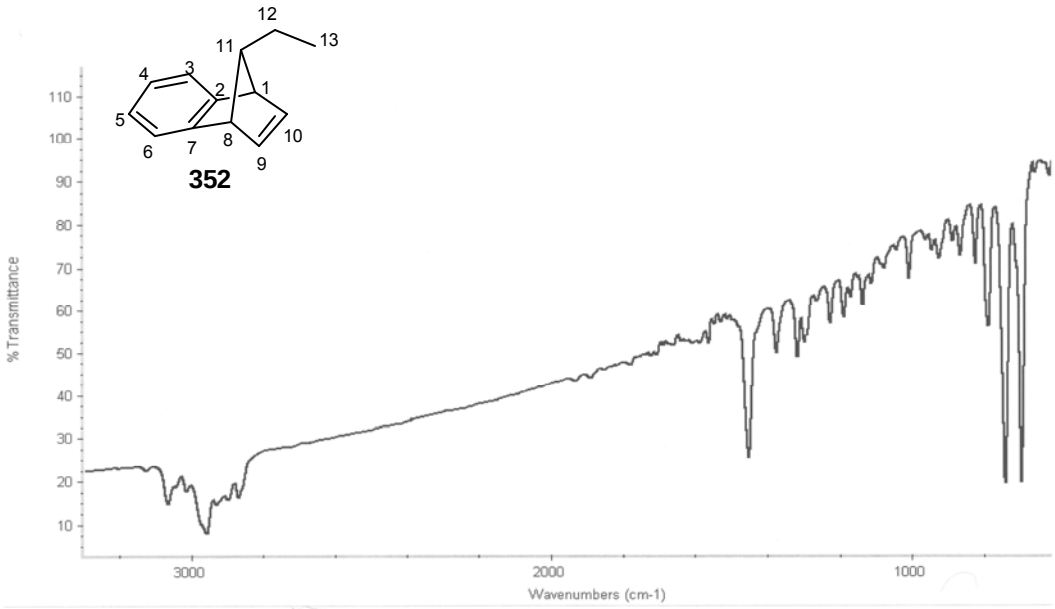


Figure 66: IR spectrum of **352**

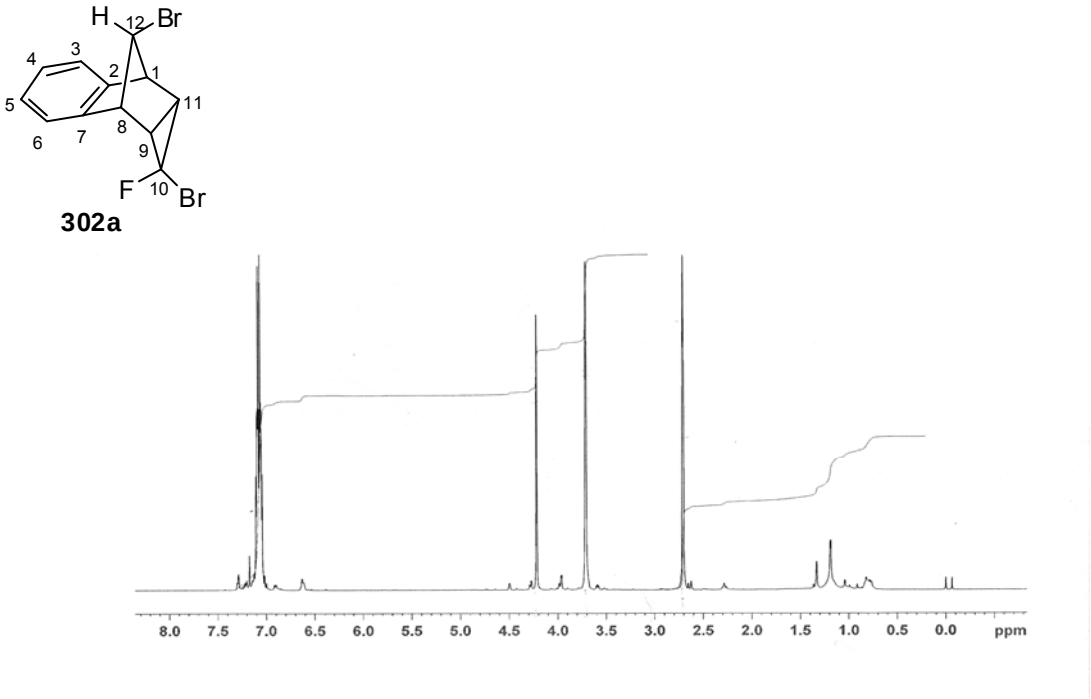


Figure 67: ^{1}H NMR spectrum of **302a**

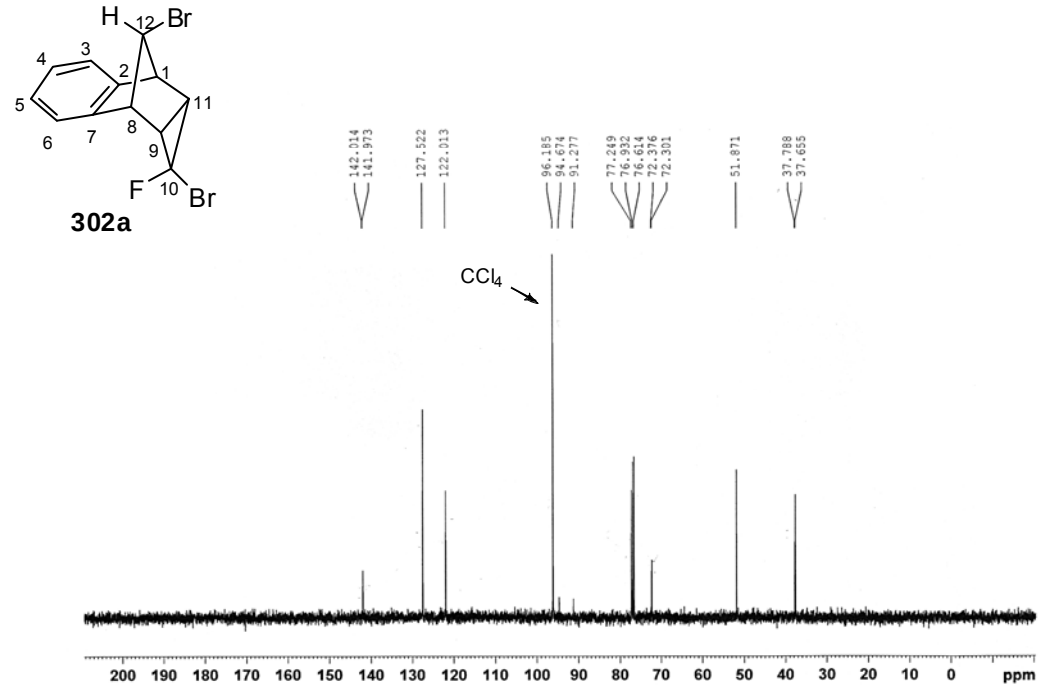


Figure 68: ^{13}C NMR spectrum of **302a**

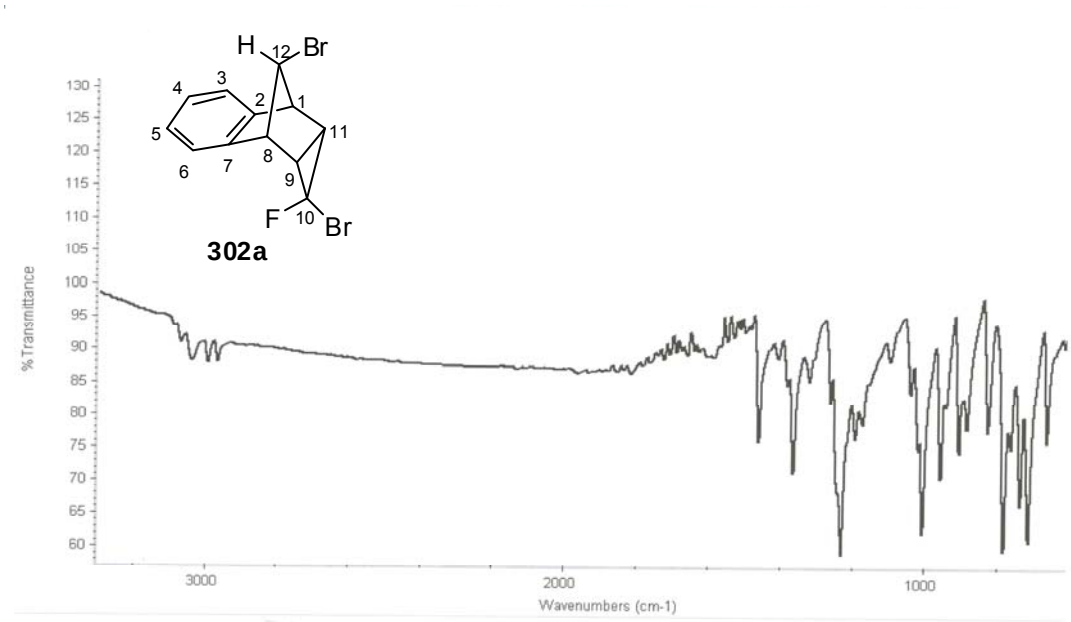


Figure 69: IR spectrum of **302a**

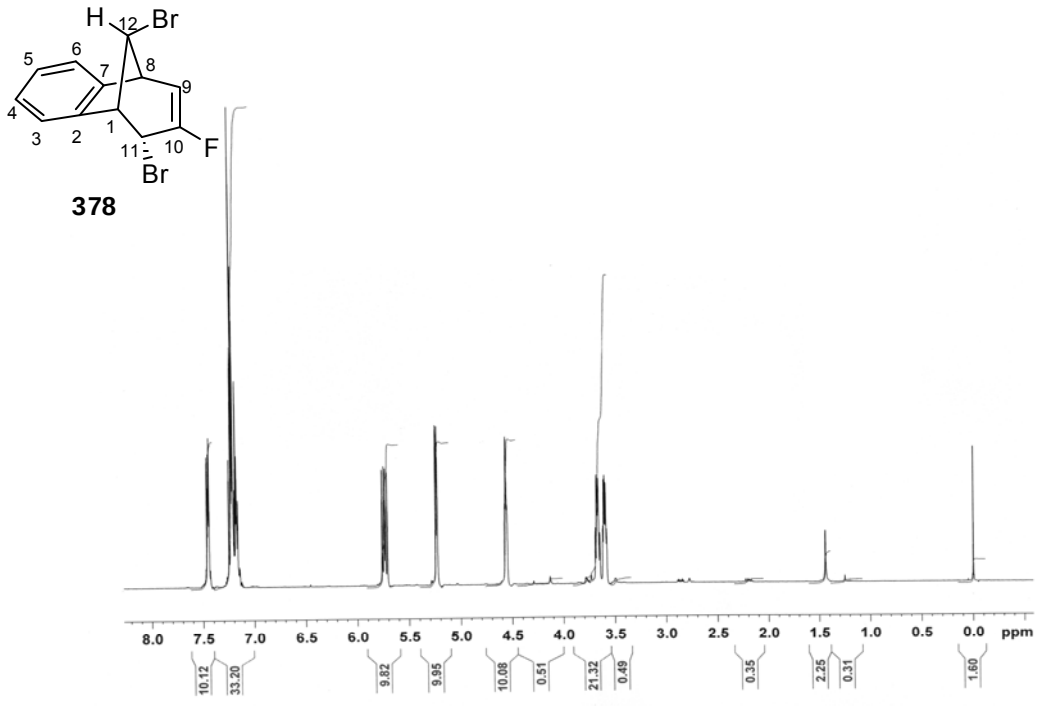


Figure 70: ^{1}H NMR spectrum of **378**

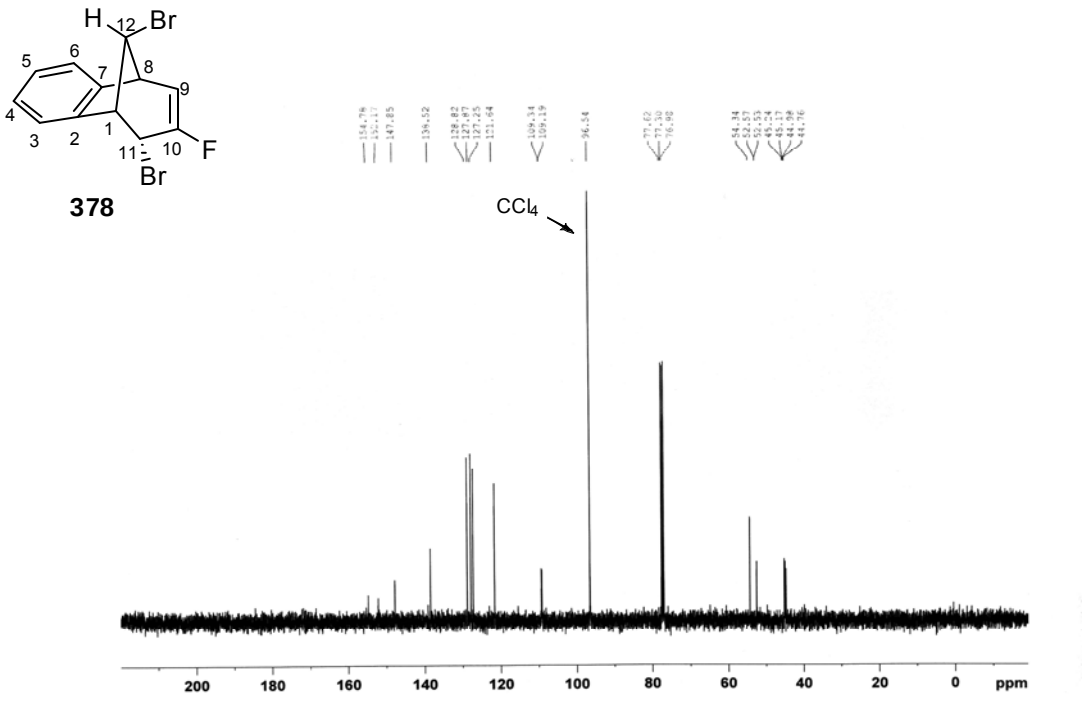


Figure 71: ^{13}C NMR spectrum of **378**

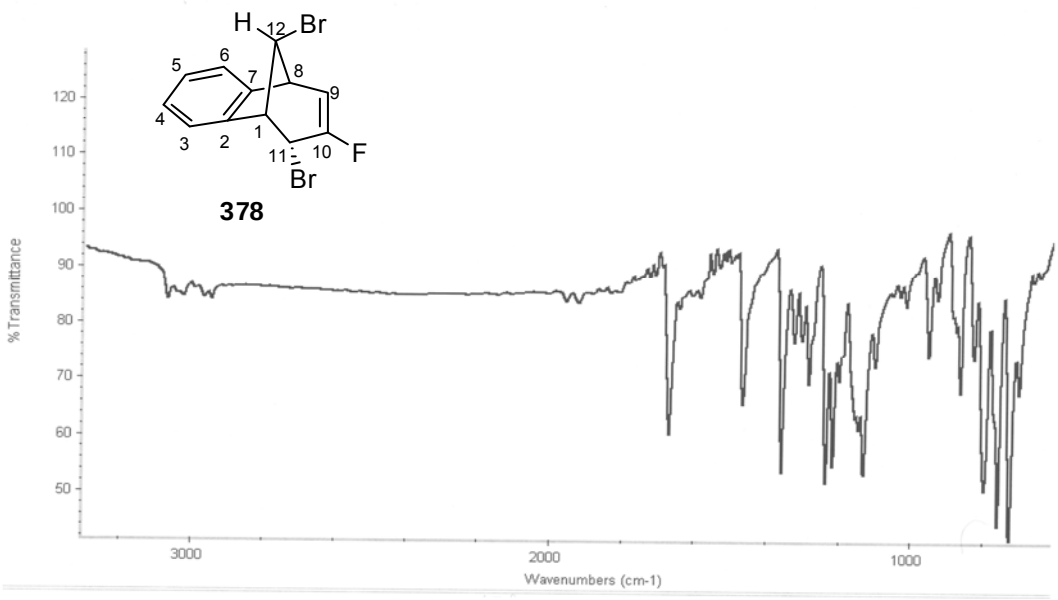


Figure 72: IR spectrum of **378**

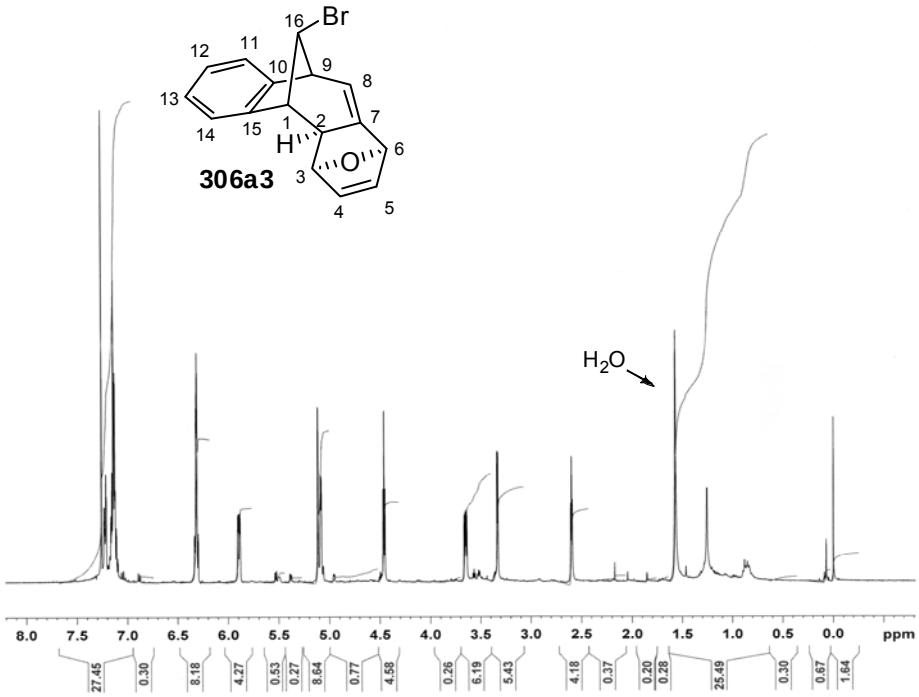


Figure 73: ^{1}H NMR spectrum of **306a3**

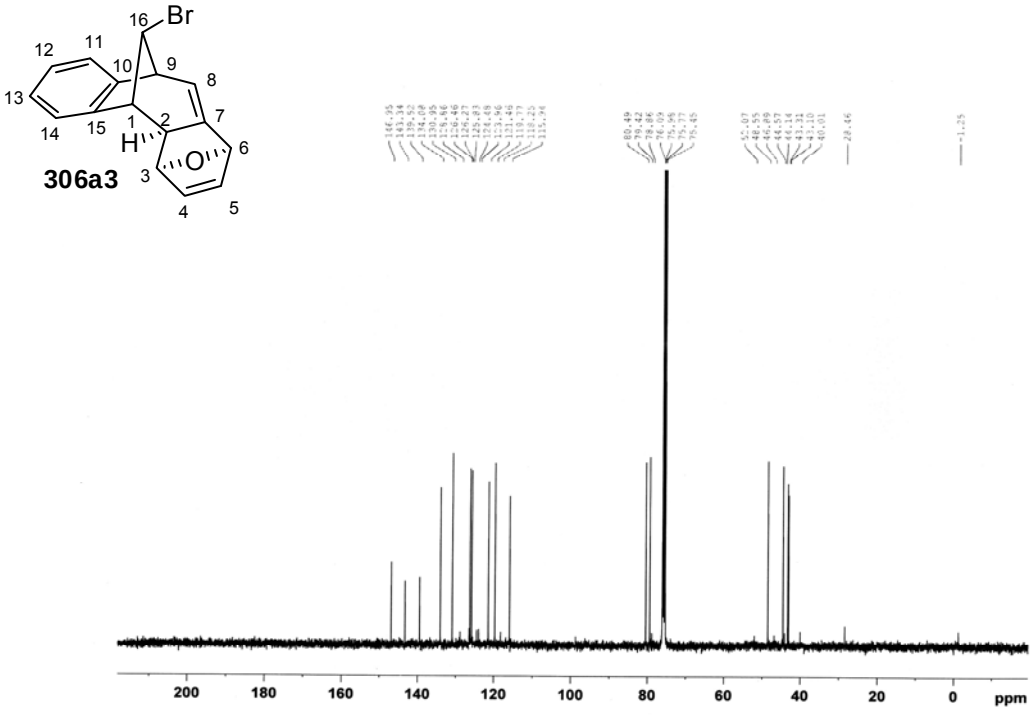


Figure 74: ^{13}C NMR spectrum of **306a3**

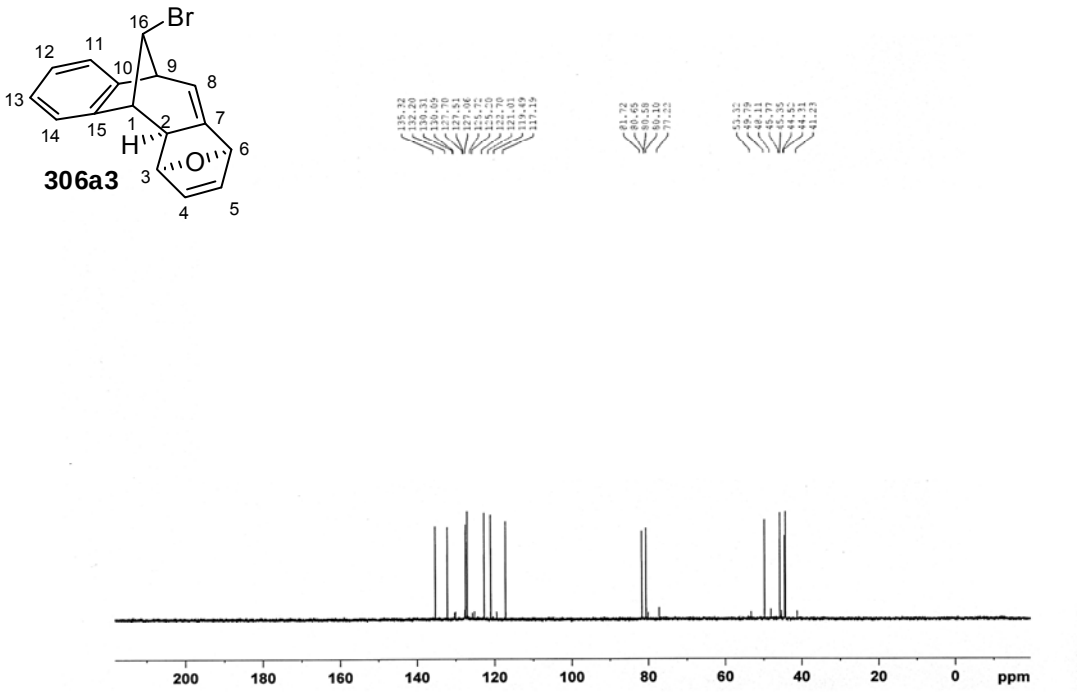


Figure 75: DEPT 90 spectrum of **306a3**

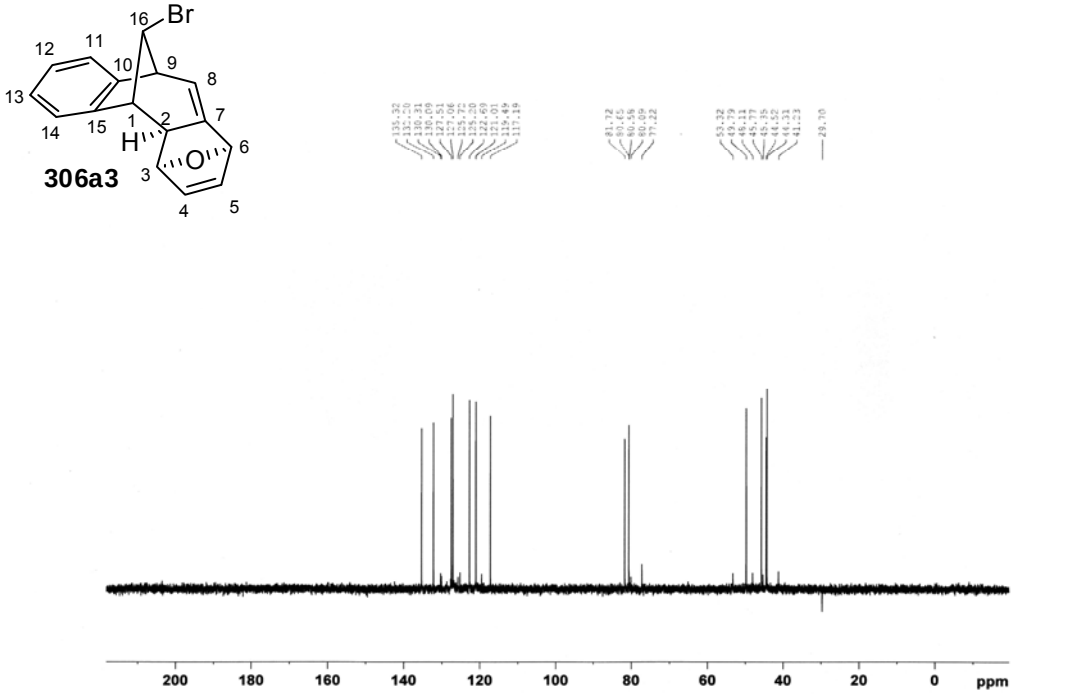


Figure 76: DEPT 135 spectrum of **306a3**

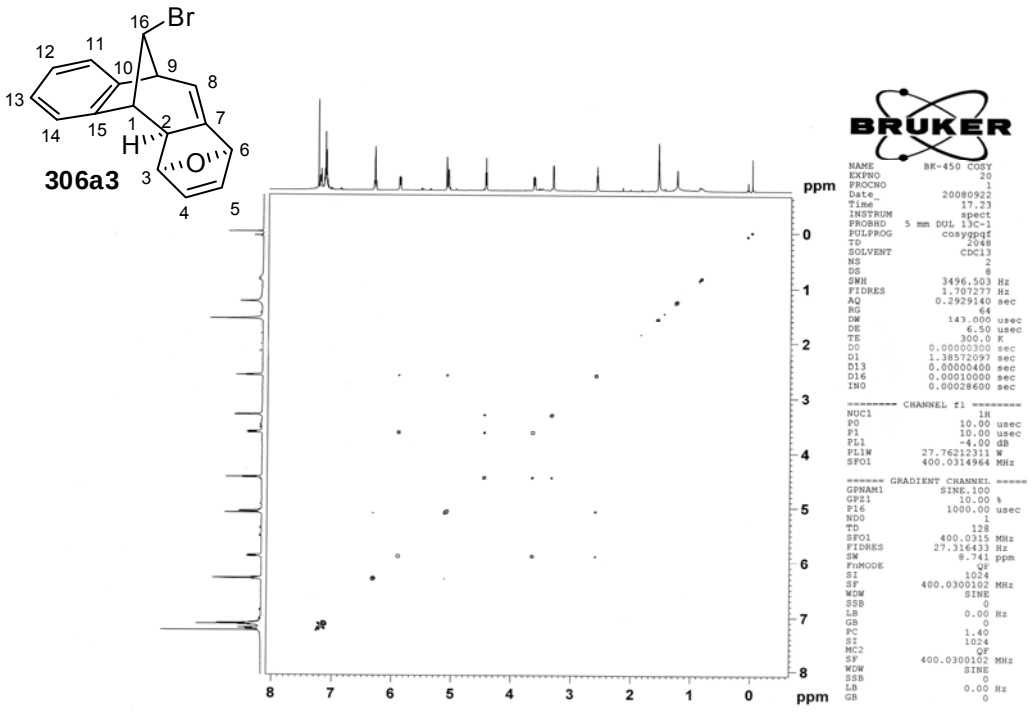


Figure 77: COSY spectrum of **306a3**

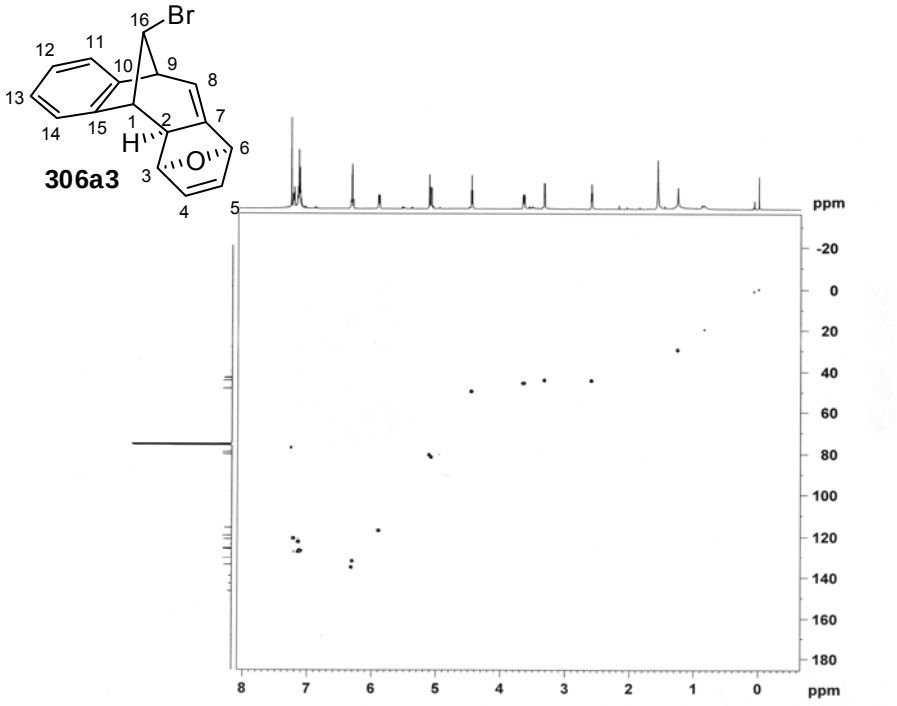


Figure 78: HSQC spectrum of **306a3**

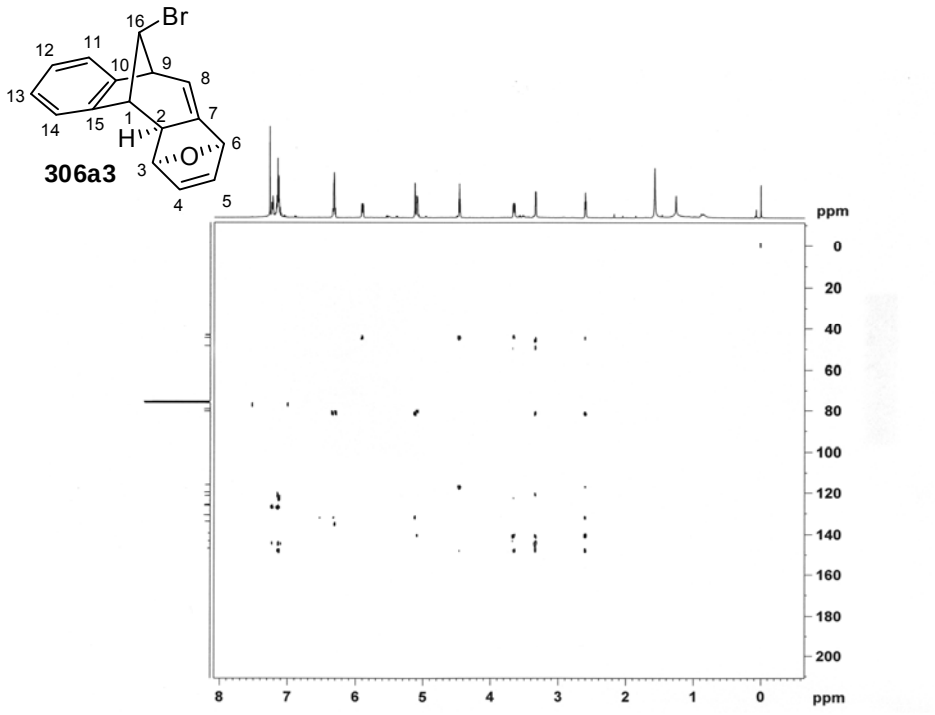


Figure 79: HMBC spectrum of **306a3**

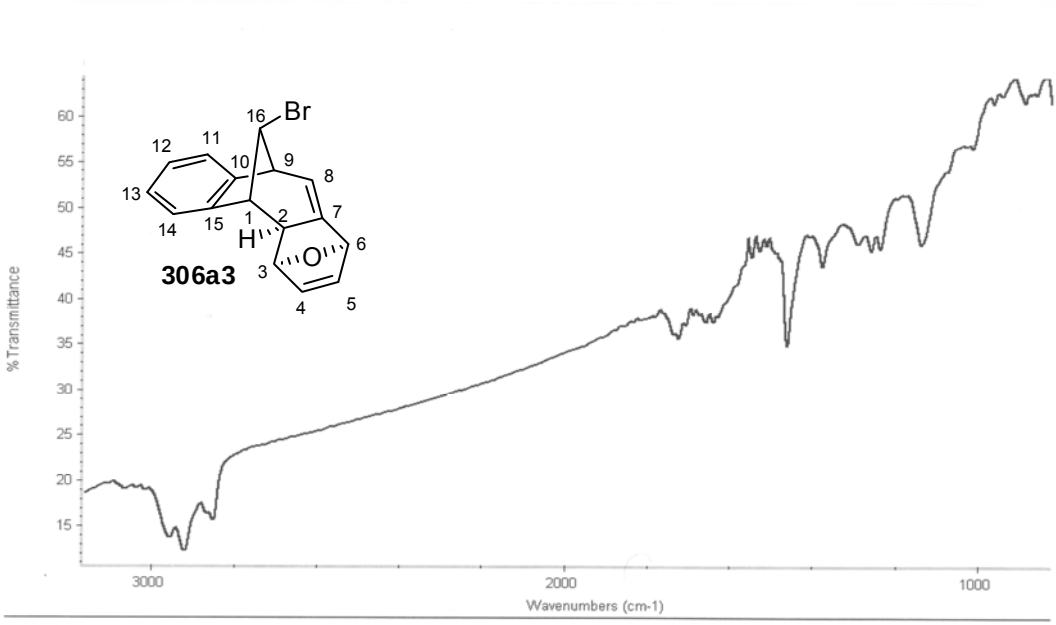


Figure 80: IR spectrum of **306a3**

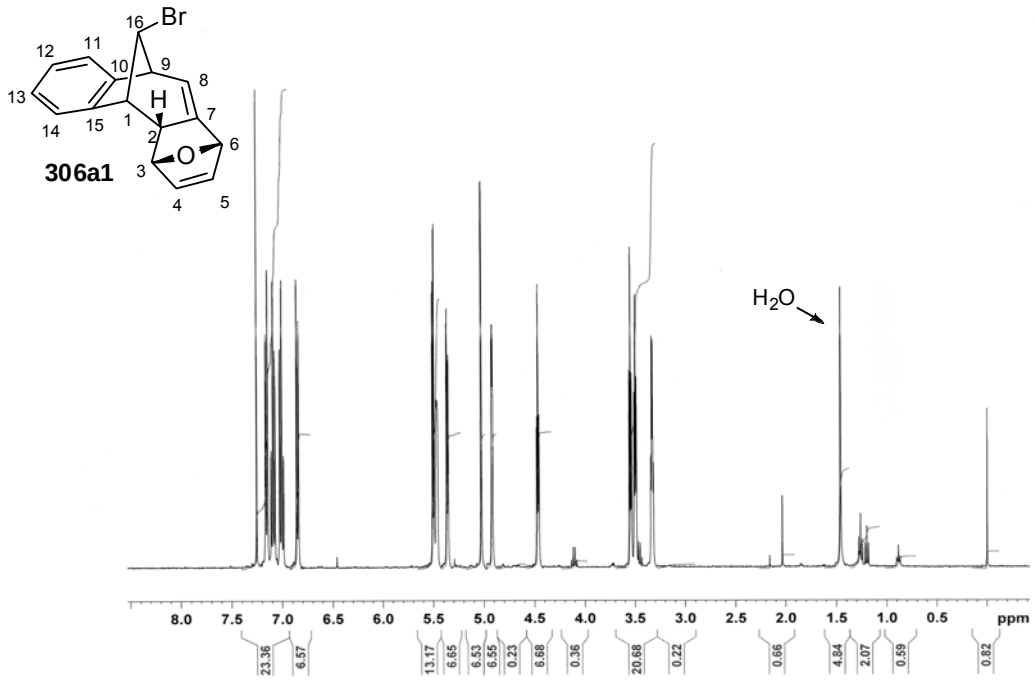


Figure 81: ^{1}H NMR spectrum of **306a1**

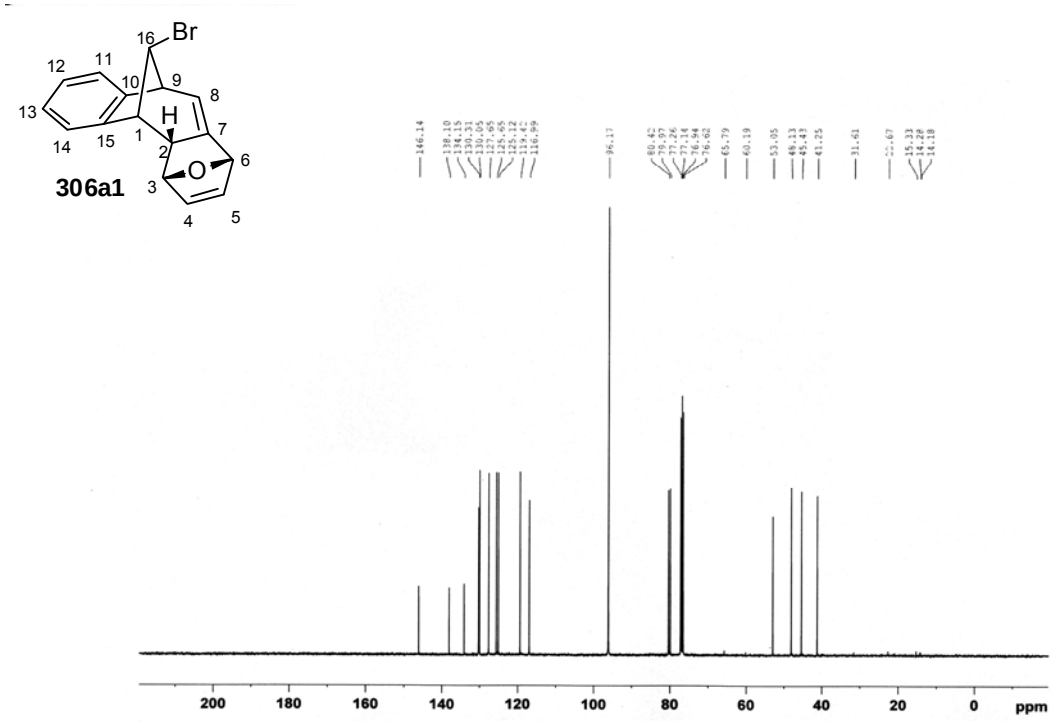


Figure 82: ^{13}C NMR spectrum of **306a1**

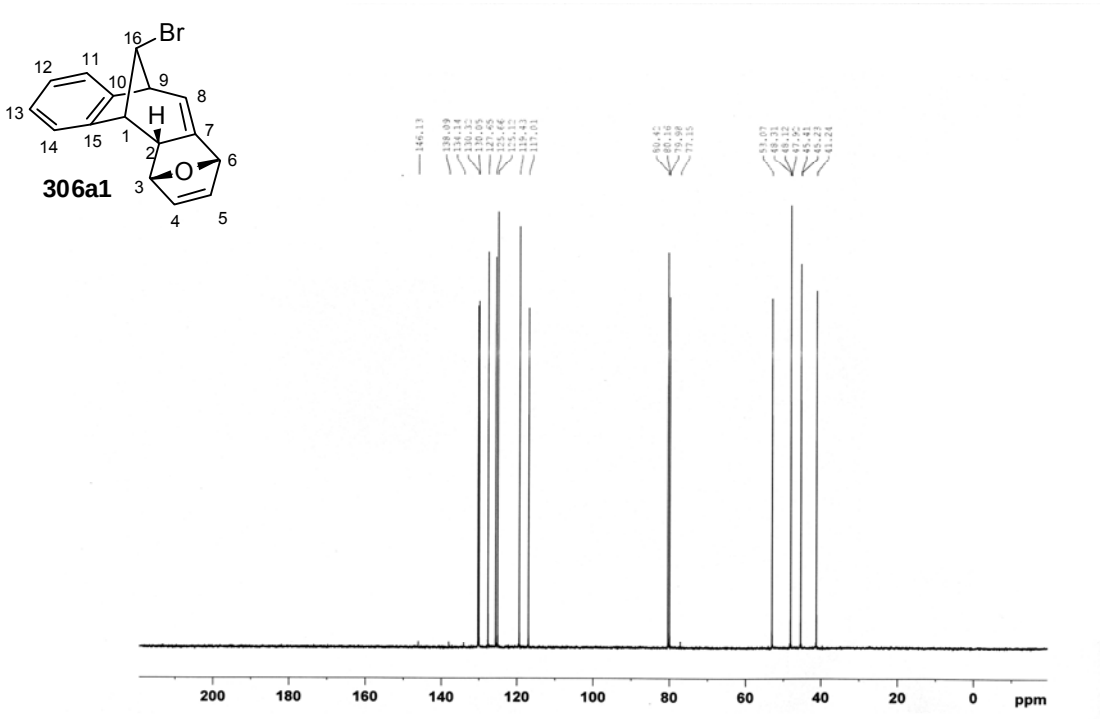


Figure 83: DEPT 90 spectrum of **306a1**

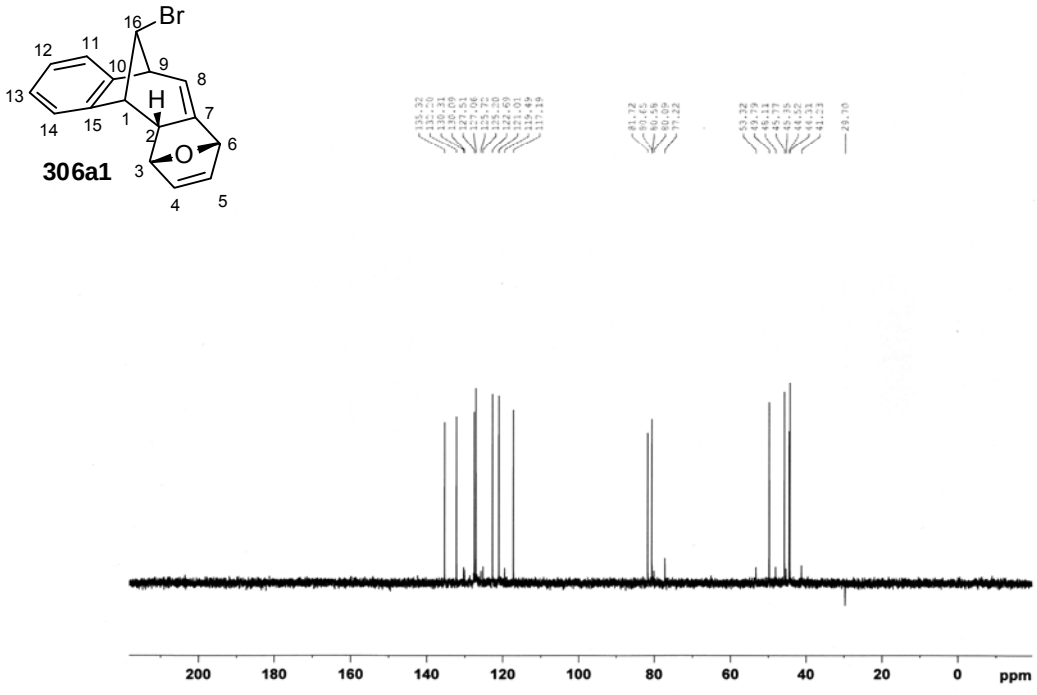


Figure 84: DEPT 135 spectrum of **306a1**

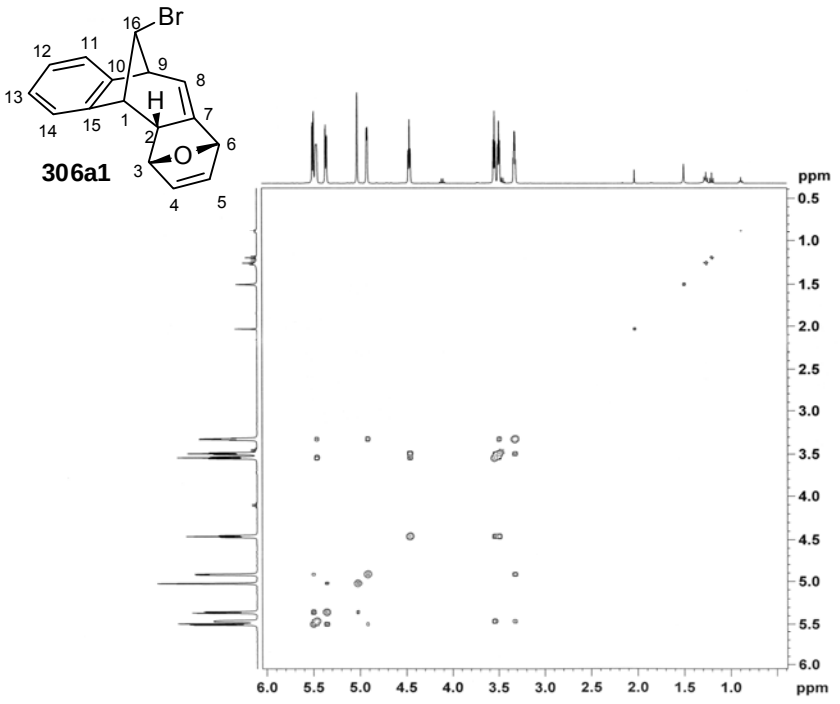


Figure 85: COSY spectrum of **306a1**

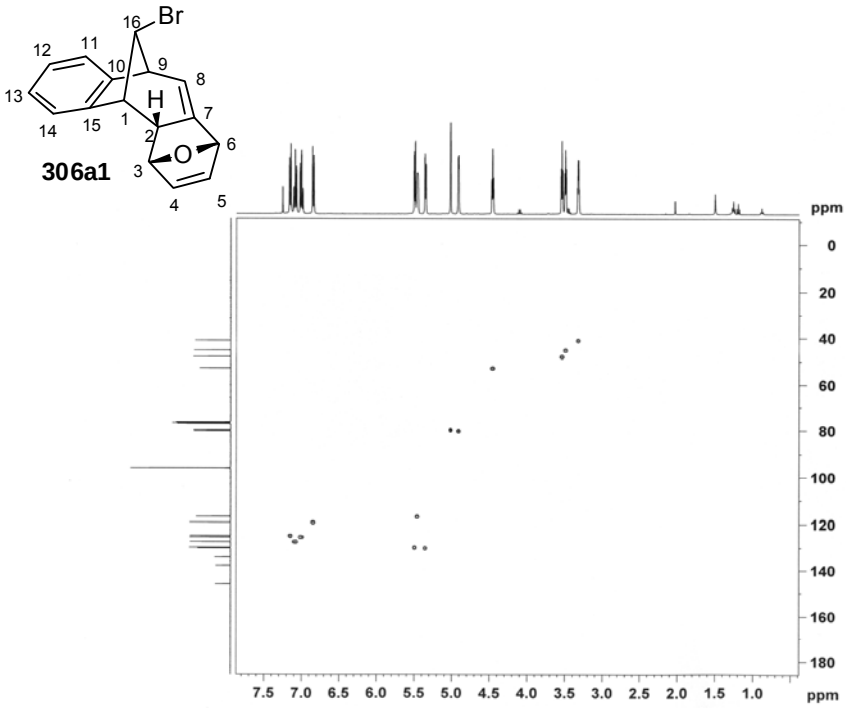


Figure 86: HSQC spectrum of **306a1**

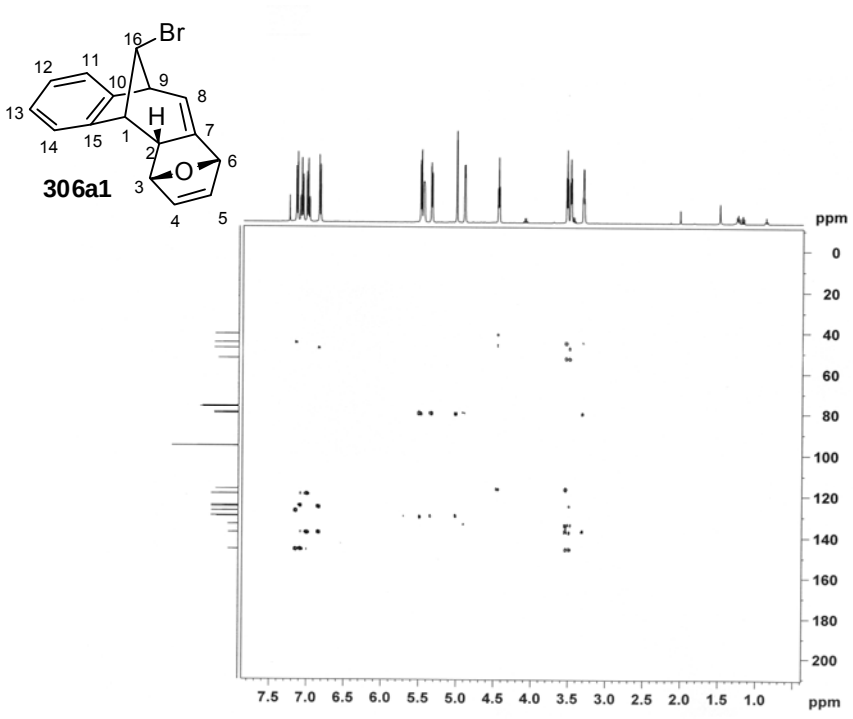


Figure 87: HMBC spectrum of **306a1**

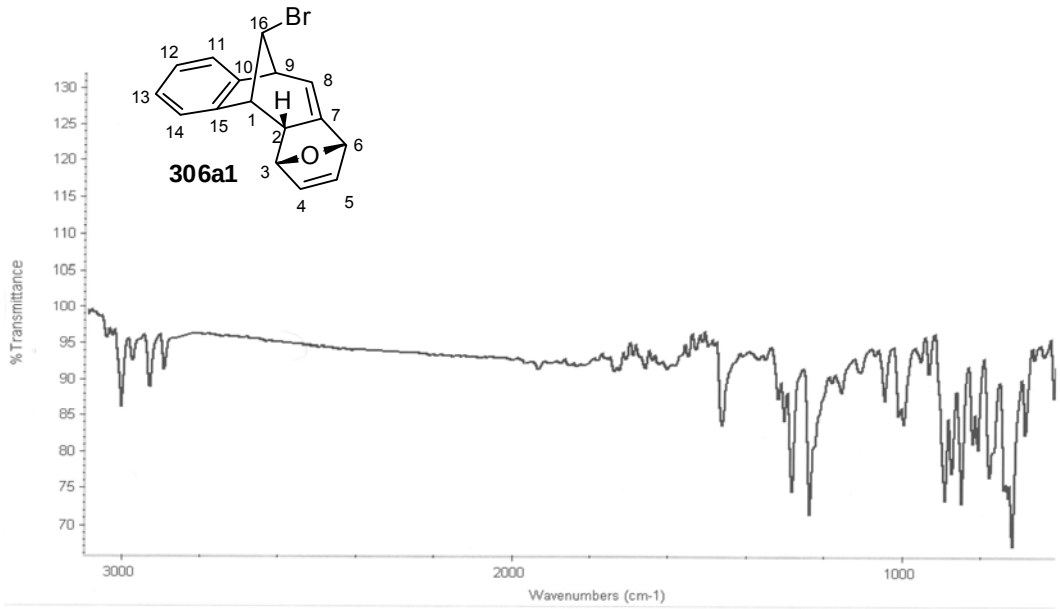


Figure 88: IR spectrum of **306a1**

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Publications

1., Incorporation of an Allene Unit into α-Pinene via β-Elimination, Benan Kilbas, Akin Azizoglu, Metin Balci, *Helv. Chim. Acta*., **2006**, 89, 1449-1456.

2., The Investigation of Endocycloproplidenoids-Cyclopropylidene-Allene Isomerization in the Bicyclic Systems, Benan Kilbas, Akin Azizoglu, Metin Balci, (in preparation).