BICYCLIC STRAINED ALLENES:
INCORPORATION OF AN ALLENE UNIT INTO
ALPHA-PINENE
AND
BENZONORBORNADIENE

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BENAN KILBAŞ

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AND BENZONORBORNADIENE

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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 retarded 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 retarded 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

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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 yılda ilgi konusu olmuştur. Siklik allen sentezi yöntemleri arasında en çok kullanılan yöntemler, Doering-Moore-Skattebol metodu ve β-eliminasyon metodu dur.

Çalışmanın ilk kısmında, β-eliminasyon metodu kullanılarak doğal bir bileşik olan α-pinen içerisindeki organik biriminin oluşturulmasını 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 sırasında oluşan mekanizmalar tartışılmıştır. Yapılan teorik hesaplamalar, reaktif ara ürünün allen \(300\) olduğu ve alkin \(320\) olamayacağını göstermiştir.

To my wife Arife and my son Ömer Yiğit
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<td>AMI</td>
<td>Austin model 1</td>
</tr>
<tr>
<td>B3LYP</td>
<td>Becke 3 parameter functional and Lee, Yang, Parr correlation functional</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>DPIBF</td>
<td>Diphenylisobenzofuran</td>
</tr>
<tr>
<td>GC/MS</td>
<td>Gas chromatography and mass spectrum</td>
</tr>
<tr>
<td>HBr</td>
<td>Hydrogen bromide</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multi-bond coherence</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International union of pure and applied chemistry</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>k</td>
<td>Rate constant</td>
</tr>
<tr>
<td>KOBu</td>
<td>Potassium tert-butoxide</td>
</tr>
<tr>
<td>MCSCF</td>
<td>Multi-configuration self-consistent field</td>
</tr>
<tr>
<td>MeLi</td>
<td>Methylithium</td>
</tr>
<tr>
<td>MNDO</td>
<td>Modified neglect of diatomic overlap</td>
</tr>
<tr>
<td>MPn</td>
<td>Moller Plesset</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase Transfer Catalyst</td>
</tr>
<tr>
<td>TS</td>
<td>Transition structure</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra-violet</td>
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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).

![Diene classes](image)

**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.

![Allene structure](image)

**Figure 2:** Allene structure
As shown in Figure 2, central carbon has sp hybridization and terminal carbons have sp² hybridization. R₁, R₂, C₁ and R₃, R₄, C₃ form two planes, which are orthogonal to each other. C₁-carbon atom forms a double bond with C₂-carbon atom, whereas C₂-carbon atom with C₃-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](image)

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 differentiate allenes from the other types of alkenes by spectroscopic analysis. For instance, in ¹³C-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.](image)

Linear allenes are inherently not “strained”. So they are present in nature. The first authentic naturally occurring 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 mycomycin](image)

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](image)
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].

![Chiral two bromoallenic aliphatic fatty acids](image)

**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 continue 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 sp²-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.

\[ \text{a = Bending angle} \]
\[ \text{b = Torsional angle} \]

**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 20°, 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).

![Diagram of cyclic allenes with angles labeled](image)

**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 °C [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](image)

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. Moreover, 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).
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).

\[
\begin{align*}
11 & \xrightarrow{\text{Na, Ether}} 12 \\
11 & \xrightarrow{\text{KOBu-t}} 14
\end{align*}
\]

Scheme 1

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

\[
\begin{align*}
13 & \xrightarrow{\text{KOBu-t}} 14
\end{align*}
\]

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 highly strained cyclopenta-1,2-diene (5) (Scheme 3). Reaction of 15 with
Bu₄NF 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].
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).

Johnson reviewed that there are much more synthetic methods leading to 4, and some of them are summarized below [15] (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 °C (61%), probably formed by dimerization of bisallyl intermediate 37 (Scheme 7). At 35 °C, the major product was crystalline dimer 36 55% yield.
Johnson and Shakespeare [39] described a new synthetic approach to cyclic allenes 4. Dehydrobromination of 1-bromocyclohexene (27) with KOrBu 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).

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).
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).

Caubère et al. [41,42] treated 40a with sodium amide-sodium tert-butoxide (NaNH₂-NaO₂Bu) 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 NaO₂Bu.
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 KOtBu in DMSO. The highest yield (47%) was obtained in refluxing THF (Scheme 11) [39].

![Scheme 11](image)

The mechanism of this substitution was scrutinized by treatment of 2,6,6-trideutero-1-chloro ([D₃]-4₀a) and 1-iodocyclohexene ([D₃]-4₀c) with KOtBu in DMSO. In the case of [D₃]-4₀a, the products [2,6-D₂]-4₃ and [6,6-D₂]-4₃, which bear the functional group at the same carbon atom as the substrate, on one side and [3,3-D₂]-4₃ on the other resulted in a ratio of 98:2, whereas when using of [D₃]-4₀c this ratio was 66:34. These findings allow the conclusion that the intermediates [1,3-D₂]-4 and [3,3-D₂]-cyclohexyne (44), determining the products, emerge from [D₃]-4₀a and [D₃]-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 semiempirical calculations by Dilon and Underwood (Scheme 12) [44].

![Scheme 12](image)

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 °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](image)
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 cycloadditions 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. Nevertheless, 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](image)

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](image)
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).

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).
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).
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](image)

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 KOrBu. 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.
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).
Cyclohepta-1,2-diene (3) can easily be isolated by β-elimination method, however paradoxically, Doering-Moore-Skattebol 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. Moreover, 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](image)

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](image)

Due to the inexplicity of Doering-Moore-Skattebol 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.
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-dihyronaphthalene 118 afforded the expected addition product 119. The reaction 119 with methyllithium gave not only the insertion product
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 °C) 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).
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).

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).
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.

However, 1-phenylcycloocta-1,2-diene 136 [16] generated by application of the Doering-Moore-Skattebol 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.

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

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).
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).

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$_2$Me$_6$ and [Pd(Ph$_3$)$_4$] in the absence of solvent at 80 °C provides in excellent yield cis and trans-147. These compounds furnish useful doubly functionalized medium-ring cycloalkenes (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 C9 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](image)

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).
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 $\pi$ 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)
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).

In 1981, Firl et al. reported the synthesis of strained ketenimine (176) as a mixture of diastereoisomers [77] (Scheme 43).
Carbodiphospharane (177) was isolated as a crystalline substance. Trithiadiazine (178-179) was also described as a red crystalline substance [78] (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).
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 methylithium. 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 from 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).
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).

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).

Christl et al. [86] reported that the treatment of 3-bromo-2H-chromene (196), dissolved in furan, 2-methylfuran or 2,5-dimethylfuran, with KOTBu, 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).

![](image)

**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).

![](image)

**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](image)

Christl et al. [88] reported that the compound 213 reacts rather readily with KOtBu in the presence of furan, providing the hexahydroepoxyquinolines 214-216, although the yield turned out to be only 13%. On replacement of KOtBu 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(SiMe3)2 as base, the hexahydrocyclobutapyridines 217-219 were obtained in 30% yield in a ratio of ca. 6:2:1 (Scheme 52).

![Scheme 52](image)

More recently, Christl et al. [89] have provided the generation and interception of 221. They treated 220 with KOtBu in [D₈]-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 KOtBu. Probably, the rate of trapping is so fast that, cycloaddition of 221 with furan and styrene can not compete (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 53

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](image)

Moreover, 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 hetereallene 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-Pr₂Net 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).
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)-8aH-682-[1,3]diphosphinino[1,2-d][1,2,4] oxazaphosphole (242) and thus also those of 241 (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).

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[3.2.1.02,7.04,6]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 oligomerization 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 °C with KOtBu 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 KOtBu by enantiopure potassium menthoxide gave rise to optically active products 253. On conducting this experiment at 100 °C, 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 °C 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].

42
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]-cycloaducts 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.

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.

In a clutch of papers Balci 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](image)

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](image)
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).

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).

More recently, Balci 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).

Scheme 66

Sevin and Doğan have focused on the possibilities of intramolecular trapping and fragmentation products of \textit{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\textsuperscript{3,8}]non-4-ene (279) (Scheme 67).
Christl et al. [110] synthesized highly strained tricyclic allene 282 and trapped it with different dienes (Scheme 68).
Okazaki et al. [111] reported a novel tricyclic allene 287, which readily dimerizes or being trapped with DPIBF (Scheme 69).

\[ \text{Scheme 69} \]

Lastly, we conclude this section with the report of Balci et al. in 2004 [112]. This study described an investigation aimed at the incorporation of an allene unit into a natural product, being \(\alpha\)-pinene by DMS method. The application of carbenoid method to \(\alpha\)-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).

\[ \text{Scheme 70} \]
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).
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 KOtBu, 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](image-url)
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 \( IS\-(-)\-\alpha\-pinene (298) \) was preferred as a starting material?

\( \alpha\-Pinene (298), C_{10}H_{14}, \) (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 19\textsuperscript{th} century on \( \alpha\-pinene \) in the literature. However, they were complicated because \( \alpha\-pinene \) readily undergoes molecular rearrangements [117]. Many rearrangements of \( \alpha\-pinene \) 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 \( \alpha\-pinene \) 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.

![Scheme 74](image)

A few years ago, Balc\c{c} \textit{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 \( \alpha\-pinene \) skeleton has a large tendency for the \textit{Wagner-Meerwein} rearrangement, they isolated in all cases the
rearranged dibromides instead of the desired normal addition products. [119-122] (Scheme 75).

![Scheme 75](image)

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 NaBH₄ in THF was added dropwise BF₃.OEt₂ solution which was then pre-cooled and maintained at 0 ºC under nitrogen atmosphere. After a while, the addition of NaOH (3M) and 30% H₂O₂ 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).
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$_2$Cl$_2$ was added to solution of 307 in CH$_2$Cl$_2$ 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$_2$Cl$_2$. 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).

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].
Characterization of \( \text{309} \), was based on \(^1\text{H}\) and \(^{13}\text{C}\) NMR and also GC MS spectral data. According to the GC-MS spectrum, molecular ion peak was 167 for [M+H]\(^+\). \(^1\text{H}\) NMR spectrum of \( \text{309} \) revealed nine sets of proton signals; the broad singlet appears at 4.92 ppm indicated the presence of \( \text{NH}_2 \) protons. There are eighteen lines in \(^{13}\text{C}\)-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 \((1S,5S)-3\text{-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (299b)}\) and \((1S,4R,5R)-3\text{-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (310)}\)

A solution of iodine in 160 mL of THF was added to a mechanically stirred solution of hydrazone derivative (\( \text{309} \)) 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 \( \text{299b} \) and \( \text{310} \) were isolated by vacuum distillation (2:3 ratio, 24.7%). These isomers were separated by column chromatography (100 g silica gel: 0.4 g \( \text{AgNO}_3 \)) eluting with hexane (Scheme 79) [56].

The structure of both isomers have been elucidated on the basis of \(^1\text{H}\) and \(^{13}\text{C}\) NMR and also GC MS spectral data. According to the GC MS spectrum, molecular ion peak was 263 for [M]\(^+\). Differentiation of both isomers was done by the NMR spectra. \(^1\text{H}\) 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 $\beta$-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).

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 \((1S,4R,5R)-3\text{-Iodo-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene (310)}\) with \(t\)-BuOK

In this step, we aimed to generate an allene unit into a natural product \(\alpha\)-pinene, by using \(\beta\)-elimination method. Baird et al. and Waegell et al. [127] tried to incorporate an allene unit into \(\alpha\)-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 \(\alpha\)-pinene (298) with methyllithium exclusively forms also dimerization products (295-297) arising from the initially formed allene moiety (Scheme 81).

![Scheme 81](image)

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 \(\alpha\)-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 °C in a sealed tube using KO\textsubscript{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\textsubscript{t}Bu were employed, 310 was not consumed completely. Approximately 5 equiv. of KO\textsubscript{t}Bu changed the ratio of products.

![Scheme 82](image)

The formation of the ketone 308 may be rationalized according to Scheme 83. Nucleophilic addition of \textit{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\textsuperscript{+} to form the conjugated diene 313.

![Scheme 83](image)
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](image)

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 Et₂O 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](image)
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).*

![Figure 13](image)

**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 ¹H and ¹³C 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 °C), 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

In the first step, the base deprotonates the methyl group (instead of the adjacent CH₂ 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 \( \text{H}^+ \) 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 \( \text{ca. 3.4 kcal/mol} \), the isomer 299b being thermodynamically more stable. At a reaction temperature of 170 °C, 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](image)

The structure of 313 and 322 have been elucidated on the basis of \(^1\text{H}\) and \(^{13}\text{C}\) 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 \( \alpha \)-pinene (298), it has been seen that only one proton deficiency in the \(^1\text{H}\) 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](image)

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.

\[
\text{Cl}_2\text{C–H} + \text{K}^+ \text{OC(CH}_3)_3 \rightarrow \text{Cl}_2\text{C}^\ominus + \text{HOC(CH}_3)_3
\]

**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].

\[
\text{CH}_2\text{BrCl} + \text{C}_4\text{H}_9\text{Li} \overset{-100 ^\circ \text{C}}{\longrightarrow} \text{LiCH}_2\text{Cl} + \text{C}_4\text{H}_9\text{Br}
\]

\[
\text{CH}_2\text{Br}_2 + \text{CH}_3\text{Li} \overset{-80 ^\circ \text{C}}{\longrightarrow} \text{LiCH}_3\text{Br} + \text{CH}_3\text{Br}
\]

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

It is known that, bicyclic olefins 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).
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 \textit{exo}-carbene structure could be optimized in its free carbene form. It also isomerizes to the bicyclic allene during the optimization. Hence, \textit{exo}-carbene is not initial intermediate during the allene formation (\textit{Scheme 91}).

![Scheme 91](image)

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

2.3 REACTION PATH FOR THE SYNTHESIS OF \textit{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](image)

2.3.1 The Synthesis of Benzonorbornadiene (301)

A solution of acetone, anthranilic acid and cyclopentadiene was added to a refluxing solution of \textit{iso-amyl}nitrite 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).
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).
However, the electrophilic addition of bromine to benzonorbornadiene (301) gives rearranged dibromide 332 in quantitative yield at 10 °C, 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 °C was added dropwise a solution of bromine in carbon tetrachloride. 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).

Characterization of 2-exo-7-anti-dibromobenzonorborn-5-ene (332) was based on the 1H and 13C NMR spectral data, which was also consistent with the literature data [122, 138, 139].
2.3.3 The Synthesis of \textit{anti}-7-Bromobenzonorbornadiene (333)

Wilt \textit{et al.} reported that dehydrobromination of 332 in DMSO gives \textit{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 \textit{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).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme96.png}
\end{center}

\textbf{Scheme 96}

Characterization of \textit{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 \textit{anti}-7-Methylbenzonorbornadiene (334)

Wilt and Chenier studied the solvolysis reaction of halogenated benzonorbornadienes extensively [140]. The authors reported that both \textit{syn}- and \textit{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 $\pi$-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.
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).

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).
2.4 REACTION PATH FOR THE SYNTHESIS OF *anti*-12-ETHYL-10-*exo*-BROMO-10-*endo*-FLUOROTRICYCL[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).

2.4.1 Synthesis of *Exo,anti*-10-carboethoxytetracyclo[6.3.1.02,7.08,9]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 °C 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 1H and 13C 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 °C. 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[6.3.1.0$^{2,7}$.0$^{8,9}$]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 $\alpha$-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 chromatography eluting with hexane. The desired vinylic halide 350 were isolated in 74% yield (Scheme 103).

![Scheme 103](image)

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.


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

\[
\begin{align*}
\text{350} & \quad \xrightarrow{\text{H}_2, \text{Pd/C}} \quad \text{351} \\
\text{EtOAc, rt} & 
\end{align*}
\]

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](image)

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 $\pi$ pyramidalization in the literature [143] (Figure 18).

![Figure 18](image)

**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 noticeable \( \pi \)-facial stereoselectivity in addition reactions to carbon double bonds [145]. The degree of pyramidalization is influenced by the electron density of the alkenyl \( \pi \)-bond [146].

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

![Scheme 106](image)

Therefore, their two \( \pi \)-faces of the double bond are chemically non-equivalent and they are attacked by a variety of reagents preferentially from the \textit{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 \textit{exo}-face of the bicyclic alkene to give initially a \textit{gem}-dichlorocyclopropane, which under the reaction conditions usually undergoes ring opening to afford a rearranged, ring expanded dihalide. Kitahonoki \textit{et al.} [150] reported that the reaction involves addition of the carbene to the \textit{exo}-face of benzonorbornadiene (301) to give initially a \textit{gem}-dibromocyclopropane 355, which
under the reaction conditions usually undergoes ring opening to afford a rearranged, ring-expanded dihalide 357 (Scheme 107).

\[ \text{Scheme 107} \]

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 stereocenter 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).

\[ \text{Scheme 108} \]

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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).

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](image)

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 CHBr₂F 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 –CH2CH3 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.

<table>
<thead>
<tr>
<th></th>
<th>C1C2C3H6</th>
<th>C4C3C2H5</th>
<th>C4C3C2H5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>301</strong></td>
<td>-174.79975</td>
<td>-175.12106</td>
<td>-176.17040</td>
</tr>
<tr>
<td><strong>352</strong></td>
<td>174.79923</td>
<td>175.00120</td>
<td>176.06344</td>
</tr>
<tr>
<td><strong>363b</strong></td>
<td>-0.095 / -0.095</td>
<td>-0.095 / -0.095</td>
<td>-0.078 / -0.086</td>
</tr>
</tbody>
</table>

83
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*).

*Figure 20*: Optimized structure of 304b-c and transition structure TS8 (304b => 305b) at B3LYP/6-31G(d)
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 unsuccessful 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).
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 CHBr₂F and sodium hydroxide under phase-transfer conditions, to anti-7-bromobenzonorbornadiene (330) at 50 °C 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 °C, since the yield of products decreases drastically above or below this temperature. Other important point is the selection of suitable phase-transfer catalyst. 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](image-url)
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](image)

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 Methylithium

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](image)

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](image)
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 retarded 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 bromocyclopropyldenoids 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.
The trapping of allene $305a$ with furan may result in the formation of four possible isomers which can be represented as; syn-exo isomer $306a_1$, anti-exo isomer $306a_2$, syn-endo isomer $306a_3$, anti-endo isomer $306a_4$ 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 preferred. 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.

<table>
<thead>
<tr>
<th>Isomer</th>
<th>Energy</th>
<th>ZPVE</th>
<th>Relative Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>306a1</td>
<td>-3264.44365</td>
<td>155.25</td>
<td>0.00</td>
</tr>
<tr>
<td>306a2</td>
<td>-3264.43579</td>
<td>155.17</td>
<td>4.85</td>
</tr>
<tr>
<td>306a3</td>
<td>-3264.43727</td>
<td>155.25</td>
<td>4.01</td>
</tr>
<tr>
<td>306a4</td>
<td>-3264.44227</td>
<td>155.26</td>
<td>0.88</td>
</tr>
</tbody>
</table>

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.
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 H1-H2, H2-H3, H3-H4, H8-H9 protons for 306a1-4 molecules from the geometry optimization at B3LYP/6-31+G(d,p) level.

<table>
<thead>
<tr>
<th></th>
<th>H1-H2</th>
<th>H2-H3</th>
<th>H3-H4</th>
<th>H8-H9</th>
</tr>
</thead>
<tbody>
<tr>
<td>306a1</td>
<td>-56.66 °</td>
<td>51.96 °</td>
<td>32.83 °</td>
<td>-31.27 °</td>
</tr>
<tr>
<td>306a2</td>
<td>90.30 °</td>
<td>-98.52 °</td>
<td>31.91 °</td>
<td>-4.22 °</td>
</tr>
<tr>
<td>306a3</td>
<td>92.10 °</td>
<td>-54.42 °</td>
<td>-33.94 °</td>
<td>-8.29 °</td>
</tr>
<tr>
<td>306a4</td>
<td>-55.90 °</td>
<td>95.93 °</td>
<td>-32.24 °</td>
<td>-35.65 °</td>
</tr>
</tbody>
</table>

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 90°. On the other hand, the vicinal coupling constants increase when the dihedral angle gets closer to 0° and 180°.

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 H2 and H3 protons for 306a1 and 306a3 are approximately 52° and 54.4°, whereas for 306a2 and 306a4 are 98.5° and 95.9° respectively. According to the 1H NMR spectrum of furan adducts, 306a1 and 306a3, H2 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 H2 proton has a definite correlation with H3 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 H1 and H2 protons for 306a1 is approximately -57°, whereas
for 306a3 is approximately 92.1°. According to the 1H NMR spectrum of 306a1, H1 proton appears at 3.50 ppm as a triplet with $J = 4.0$ Hz, and its COSY spectrum confirmed the correlation with H16 and H2. However, from 1H NMR spectrum 306a3, H1 proton appears at 3.33 ppm as a doublet with $J = 3.6$ Hz, and its COSY spectrum only revealed the correlation with H16. Furthermore, dihedral angle between H8 and H9 of 306a3 is nearly -8.3°, whereas for 306a1 is nearly -31.3°. These values indicated that, the coupling constant ($J_{89}$) between H8 and H9 of 306a3 should be much more that of the 306a1. According to the 1H NMR spectrum, coupling constant ($J_{89}$) between H9 and H8 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 continue 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, Balci 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.
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.

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 °C. 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 I₂ in the presence of Et₃N. 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).

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*).

At this point, we were curious about the stability of *endo*-cyclopropylidene 304 that was not discussed before in literature (*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](image-url)
According to the theoretical calculations (B3LYP/6-31G(d)), when –CH\textsubscript{2}CH\textsubscript{3} is accommodated to C-7 carbon atom, surprisingly the pyramidalization of double bond increased respect to the methoxy derivative \textit{363b} (Table 1-Figure 19). As a result, more strained energy and deformation of planarity on double bond prevented carbene addition to compound \textit{352} (Scheme 113).

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

![Scheme 129](image)

After unsuccessful attempt to add a carbene to \textit{anti}-7-ethylbenzonorbornadiene (\textit{352}), we decided to change the substituent located at C-7 carbon atom. For this reason, benzonorbornadiene (\textit{301}) was reacted with bromine to give the rearranged product \textit{332} as described in the literature [122,139]. Elimination of HBr resulted in the formation of \textit{333}, where bromine atom is located in \textit{exo}-position. After that, the corresponding bromofluorocarbene adduct \textit{302a} and the \textit{endo}-bromofluoro ring-opened product \textit{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).
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 retarded to the formation of insertion or any other addition products (*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 ($\delta$) 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$_2$SO$_4$) 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$_3$OEt$_2$ (71.0 g, 0.50 mol) at 0 °C under N$_2$ atmosphere. The mixture was kept 3 h at this temperature. Then, 3M aq. NaOH (167 ml) and 30% H$_2$O$_2$ 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$_2$O, the mixture was extracted with CH$_2$Cl$_2$, the organic phase was washed with saturated aq. NaHCO$_3$ solution and H$_2$O, and dried (Na$_2$SO$_4$). Evaporation of the solvent gave crystalline 307 (71 g, 92%). M.p. 53–55 °C.

307: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_2$Cl$_2$ (800 ml) was added to a solution of 307 (71.0 g, 0.46 mol) in CH$_2$Cl$_2$ (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$_2$O and CH$_2$Cl$_2$. The organic phase was washed with saturated aq. NaHCO$_3$ solution and H$_2$O, and dried (Na$_2$SO$_4$). After the removal of the solvent, the residue was passed over silica gel (70 g), eluting with CH$_2$Cl$_2$, 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$_3$): $\delta$ 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$_3$): $\delta$ 214.0 (-CO carbon), 51.6, 45.4, 45.0, 39.5, 39.3, 34.8, 27.5, 22.3, 17.1.

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4.4 \((1S,2S,3E,5R)-\) and \((1S,2S,3Z,5R)-2,6,6\text{-trimethylbicyclo-[3.1.1]heptan-3-one \text{Hydrazone (309)}}\).

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 H₂O and CHCl₃. The organic phase was washed with saturated aq. NaHCO₃ soln. and H₂O, and dried (K₂CO₃). 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, CDCl₃): \(\delta\) 4.92 (br.s, \(-\text{NH}_2\)), 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, CDCl₃; \(\delta\) (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, CDCl₃; (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 C₁₀H₁₈N₂: C 72.24, H 10.91; found: C 72.06, H 10.82.

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

A solution of I₂ (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 Et₃N (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, H₂O (300 ml) was added, and the mixture was extracted with hexane. The organic phase was washed with saturated aq. NaCl solution and H₂O, dried (Na₂SO₄), 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 chromatography (100 g SiO₂ with 0.4 g AgNO₃; 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$_3$), 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, CDCl$_3$): 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$_2$O was added, and the mixture was extracted with Et$_2$O (3 × 100 ml). The organic phase was washed with saturated aq. NaHCO$_3$ solution and H$_2$O, and dried (Na$_2$SO$_4$). After removal of the solvent, the residue was purified by column chromatography (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$_2$Cl$_2$ 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$_3$), 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 $J = 8.5, 1H, H_7a$), 1.35 (s, 3H, $H_9$), 0.85 (s, 3H, $H_{10}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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$_2$O was added, and the residue was extracted with Et$_2$O (3 × 50 ml). The organic phase was washed with saturated aq. NaHCO$_3$ solution and H$_2$O, and dried (Na$_2$SO$_4$). After removal of the solvent, the residue was purified by column chromatography (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$_3$): $\delta$ 5.18 (br. s, 1H, H$_3$), 2.35 (dt, A-part of AB system, $J = 8.5, 5.6, 1H, H_7$,) 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$_3$): $\delta$ 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 NaHCO₃ solution in 2 liters beaker. After considerable CO₂ evolution, the layers were separated and the aqueous layer extracted with n-hexane two times. The combined hexane layers were washed three times with 150 ml portions of saturated NaHCO₃ solution, twice with saturated NaCl solution, and dried over anhydrous MgSO₄. Removal of the hexane at reduced pressure and distillation through a 10-in. Vigreux column afforded i-amyl alcohol, b.p. 45 °C/10 mm, and 28.50 g benzonorbornadiene (301), b.p. 72-81 °C/10 mm, 40% yield.

301: ¹H NMR (400 MHz, CDCl₃) 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, H₇syn), 2.63 (d, B part of AB system, J = 7.0, 1H, H₇anti), ¹³C NMR (100 MHz, CDCl₃) δ 152.0 (C ₂ and C ₃), 143.5, 124.7, 122.0 (aryl carbons), 70.6 (C₇), 50.9 (C₁ and C₄).

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 °C 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, H₂O was added, and the residue was extracted with hexane (3×50 ml). The organic phase was washed with saturated aq. NaHCO₃ solution and H₂O, and dried (Na₂SO₄). After removal of the solvent, the residue was purified by column chromatography (120 g SiO₂; 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.

\textit{exo,anti-10-Carboethoxytetracyclo}[6.3.1.0^{2,7}.0^{8,9}]dodeca-2,4,6-triene} (348a): ¹H NMR (400 MHz, CDCl₃): 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\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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 °C 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 was dried over Na\(_2\)SO\(_4\). After evaporation of solvent, alcohol 349 was obtained (1.674 g, 9.00 mmol, 90%) as a colorless oily residue.

**exo,anti-10-Hydroxymethyltetracyclo[6.3.1.0\(^2\),7.0\(^8\),9]dodeca-2,4,6-triene** (349): \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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 SOCl₂ (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 SOCl₂ were removed by evaporation. The residue was submitted to column chromatography (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, CDCl₃): δ 7.22 – 7.03 (m, 4H, aromatic), 6.37 (ddd, $J = 17.2, 10.3, 8.3$ Hz, 1H, H₁₂), 5.14 (dd, A part of the AB system, $J = 17.2, 1.6$ Hz, 1H, H₁₃a), 5.05 (d, B-part of the AB system, $J = 10.3$ Hz, 1H, H₁₃b), 3.85 (ddd, $J = 7.8, 3.7, 0.7$ Hz, 1H, H₉), 3.46 (br.s, 1H, H₈), (br.d, $J = 3.3$ Hz, 1H, H₁), 2.86 (d, 8.3 Hz, 1H, H₁₀a), 2.08 (dd, B-part of the AB system, $J = 13.4, 7.8, 1H, H₁₀b$). $^{13}$C NMR (100 MHz, CDCl₃): 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, CDCl₃): δ 7.19 – 7.00 (m, 4H, aromatic), 3.79 (dd, $J = 7.1, 3.8$ Hz, 1H, H₀), 3.40 (br.s, 1H, H₈), 3.22 (br.d, $J = 3.40$ Hz, 1H, H₁), 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$_2$O (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 chromatography 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 carbon tetrachloride cooled to 10 °C was added dropwise a solution of bromine (11.53 g, 72.15 mmol) in 40 ml carbon tetrachloride 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: ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.04 (m, 4H, aryl), 4.04 (s, 1H, H₂), 3.69 (dd, J = 4.7, 7.9, 1H, H₂), 3.66 (s, 1H, H₁), 3.43 (s, 1H, H₄), 2.79 (dt, A-part of AB system, J = 4.2, 13.3, 1H, H₃exo), 2.13 (dd, B-part of AB system, J = 8.0, 13.2, 1H, H₃endo). ¹³C NMR (100 MHz, CDCl₃) 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 MgSO₄. 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: ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 CHBr₃ and 15 g of (84 mmol) SbF₃, 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 % Na₂SO₃ solution until the color of bromine disappeared. Lower organic phase was washed with water, dried over CaCl₂, and distilled carefully to give CHBr₂F 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 ºC 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 thoroughly extracted with methylene chloride, and the combined extracts were washed with water, dried over CaCl₂, and evaporated. Unreacted alkene was recovered by distillation (110-115 ºC / 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 CHBr₂F, 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): ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.02 (AA′BB′ system, 4H, aryl), 4.22 (s, 1H, H₁₂), 3.71 (br.s, 2H, H₁ and H₈), 2.71 (br.s, 2H, H₉ and H₁₁). ¹³C NMR (100 MHz, CDCl₃) 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 (s), 907 (m), 783 (s), 737 (s); Elemental Anal. Calc. for C₁₂H₁₉Br₂F: C, 43.41; H, 2.73. Found: C, 43.43; H, 2.78.
378: colorless crystal (m.p. 76-78 °C): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$F: 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 °C 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 chromatography (120 g SiO$_2$) eluting with CH$_2$Cl$_2$/hexane (8:92) to give 306a1 (85 mg, 20%) and 306a4 (29 mg, 5%) respectively.

$anti$-16-bromo-syn-exo-17-oxapentaacyclo-[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 °C). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_5$), 5.36 (dd, B-part of AB system, $J$ = 5.6, 1.2 Hz, 1H, H$_6$), 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$_3$) $\delta$ 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),
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 °C), $^1$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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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
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
Figure 35: $^1$H NMR spectrum of 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
Figure 43: $^1$H NMR spectrum of 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
Figure 49: $^1$H NMR spectrum of 332

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
Figure 61: $^1$H NMR spectrum of 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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<thead>
<tr>
<th>Degree</th>
<th>Institution</th>
<th>Year of graduation</th>
</tr>
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<tbody>
<tr>
<td>PhD</td>
<td>METU</td>
<td>2009</td>
</tr>
<tr>
<td>BS</td>
<td>Fatih University</td>
<td>2003</td>
</tr>
</tbody>
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Foreign Language

English (fluent)
German (elementary)

Publications
