SYNTHESIS OF CYCLOHEPTADIENE ANNELATED DIHYDROFURANE DERIVATIVES AND DESIGN OF PYRROLO-PYRROLO-PYRAZINES AND α-ALKYLIDYN-γ-BUTYROLACTONES VIA ALKYNE CYCLIZATION

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Owing to fascinating regiochemistry and controversial reaction mechanism, the oxidative free radical cyclization reaction of unsaturated bicyclic endoperoxides is an interesting area. In the first part of the thesis, we reacted various 1,3-dicarbonyl compounds with cycloheptatriene in the presence of Ce(NH₄)₂(NO₃)₆ to obtain dihydrocyclohepta[b]furan derivatives. Then, the formed 1,3-cycloheptadiene unit of dihydrocyclohepta[b]furan derivatives was reacted with singlet oxygen to give the corresponding bicyclic endoperoxides. Bicyclic endoperoxides which include acetyl group were reacted with CoTPP, AuCl₃ and NEt₃. Dihydrocyclohepta[b]furan derivatives were oxidized with SeO₂ to tropone derivatives, biologically interesting molecule.

In the second part of the thesis, a new synthetic method for the synthesis of pyrrolo-pyrrolo-pyrazine derivatives was developed. Firstly, pyrrole was reacted with 2-pyrrolidinone to generate 2,2'-(1'-pyrrolinyl)pyrrole, which was reacted with propargyl bromide derivatives to afford propargylated compounds which were further derivatized via Sonogashira cross coupling reaction. Pd/C-supported cyclization reaction of propargylated compounds and their derivative with Pd/C, afforded pyrrolo-pyrrolo-pyrazine derivatives.

In the last part of the thesis, we examined the reaction of bicyclic endoperoxides with gold salt for the first time. Firstly, we synthesized bicyclic endoperoxide, 2,3-dioxabicyclo[2.2.2]oct-5-ene by the reaction of cyclohexa-1,3-diene with singlet
oxygen. Reaction of unsaturated bicyclic endoperoxide with alkynes in the presence of Au(L)/AgOTf resulted in the formation of α-alkylidene-γ-butyrolacton derivatives.

Keywords: dihydrocyclohepta[b]furans, bicyclic endoperoxides, tropone, pyrrolo-pyrrolo-pyrazines, α-alkylidine-γ-butyrolactons.
ÖZ

SİKLOHEPTADIENE KONDENZE DİHİDROFURAN TÜREVLERİİNİN
SENTEZİ VE PİROLO-PİROLO-PİRAZİNLERİN VE
α-ALKİLİLDİN-γ-BUTİROLAKTONLARIN ALKİN
SİKLİZASYONU İLE TASARIMI

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Oksidatif radikal halkalaştırma reaksiyonu ve doymamış bisiklik endoperoksidlerin etkileyici yerseçimli reaksiyonları ve tartışmalı mekanizmaları nedeniyle ilgi çekici bir alandır. Tezin birinci kısmında, 1,3-dikarbonil bileşiklerini sikloheptatrien ile Ce(NH₄)₂(NO₃)₆ varlığında reaksiyona sokarak dihydrocyclohepta[b]furan türevleri elde edildi. Sonrasında, oluşan 1,3-sikloheptadien birimini singlet oksijen ile reaksiyona sokup ilgili bisiklik endoperoksidler oluşturuldu. Asetil grubu içeren bisiklik endoperoksit CoTPP, AuCl₃ ve NEt₃ ile reaksiyona sokuldu. Dihydrocyclohepta[b]furan türevlerini SeO₂ ile biyolojik olarak ilginç moleküller olan troponlara yükseltgendi.


Tezin son kısmında, bisiklik endoperoksidlerin altın tuzları ile reaksiyonlarını ilk olarak biz araştı. İlk olarak, bisiklik endoperoksid, 2,3-diokzabisiklo[2.2.2]okt-5-en bileşğini siklohekza-1,3-dien singlet oksijen ile reaksiyona sokarak sentezledik.
Doymamış bisiklik endoperoksitlerin Au(L)/AgOTf varlığında alkinlerle reaksiyonu α-alkilidin-γ-butorolakton türevlerinin oluşumuna neden oldu.

This work is dedicated to
My soul mate, lovely wife Zeynep.
My children Sena and Seza
And also to my parents
Veysel and Mukaddes
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LIST OF ABBREVIATIONS

**AIBN**: Azobisisobutyronitrile

**CAN**: Cerium Ammonium Nitrate

**DBU**: 1,8-Diazabicyclo[5.4.0]undec-7-ene

**DIPA**: Diisopropylamine

**L**: Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)

**LDA**: Lithium diisopropylamide

**NBS**: N-Bromosuccinimide

**TBAF**: Tetra-n-butylammonium fluoride

**TBDMS**: tert-Butyldimethylsilyl

**THF**: Tetrahydrofurane

**THP**: Tetrahydropyran

**TPP**: Tetraphenylporphine

**t-Boc**: tert-Butyloxycarbonyl

**PMB**: p-Methoxybenzyl
CHAPTER 1

SYNTHESIS OF CYCLOHEPTADIENE ANNELATED DIHYDROFURANE DERIVATIVES AND STUDIES OF SYNTHETIC POTENTIAL OF THE FORMED COMPOUNDS

1.1 INTRODUCTION

1.1.1. Oxidative Free Radical Cyclization

Free radical cyclization reaction has emerged as an important reaction for the construction of carbon-carbon and carbon-heteroatom bonds in recent years.\(^1\) Especially, metal salts such as Mn(III), Ce(IV), V(V), Co(III), and Cu(II) have been used for radical cyclization reactions. In this group, Mn(OAc)\(_3\) has been used most widely.\(^2\) But, there are two limitation for Mn(OAc)\(_3\); poor solubility in organic solvents and the formation of byproducts especially by intermolecular reactions. This limitation and the other reagents drawbacks show that Ce (IV) reagents are more proper as one-electron oxidant.

Cerrium ammonium nitrate (CAN) is an oxidant discovered by Smith group.\(^3\) CAN exist in pure form and includes cerium atom in the center surrounded by six nitrate groups around. CAN is valuable chemical reactive because it has a low toxicity, ease of handling, experimental simplicity and solubility in a number organic solvent. Furthermore, CAN as an electron oxidant like Mn(OAc)\(_3\) has a large electron potential (+1.61 V). CAN undergoes different oxidative transformation reactions.

Carbon-carbon bond forming reaction in presence of CAN is an important reaction in organic chemistry and they are divided into two classes; intermolecular and intramolecular reactions. Intermolecular carbon-carbon forming reaction in the presence of CAN is widely used by researchers.
Intermolecular reactions of olefins 2 and 3 with dimedon (1) mediated by CAN mainly result in the formation of dihydrofuran and spirodihydrofuran derivatives 4 and 5 as shown in Scheme 1.\(^4\)

![Scheme 1](image)

Addition of acyclic alkene 7 to Meldrum’s acid (6) mediated by CAN gave α-methylene lactone 8.\(^5\) Spirocyclopropyl dihydrofurane derivative 11 was synthesized via the similar procedure (Scheme 2).\(^5\)

![Scheme 2](image)

A procedure for the synthesis of furo-p-quinones 14 as well as o-quinone 15 was developed by the reaction of 2-hydroxynaphthalene-1,4-dione (12) and with cyclopentadiene (13) in the presence of CAN.\(^7\) Furthermore, CAN mediated reaction of t-butyl 2-(2-hydroxytetrahydrofuran-2-yl)acetate(16) with alkene 17 gave tetrahydrofuro[3,2-c]oxepin-4(6H)-one (18) (Scheme 3).\(^8\)
Ce(IV) mediated intramolecular carbon-carbon bond forming reaction was reported for the first time by Hansel et al.\textsuperscript{9} According to the procedure described by Snider et al.\textsuperscript{10} unsaturated silyl enolether 19 underwent oxidative cyclization reaction in the presence of CAN affording tricyclic ketone 21. Citterio et al.\textsuperscript{11} reported the oxidative cyclization of 5-aryl-3-oxo-pentanoic acid ester (22) by CAN leading to 2-hydroxy-1-naphthoic acid ester (24) (Scheme 4).

Takemoto et al.\textsuperscript{12,13} presented that oxaspiro undeconone 26 and cis-fused chlorinated bicyclic ether 28 were obtained in good yields by the reaction of bicyclo[4.1.0]heptyl
sulfide having an hydroxyl group in the side chain 25 and cyclopropyl sulfides of the type 27 with CAN, respectively (Scheme 5).

![Scheme 5](image)

Jamie *et al.* reported CAN mediated intermolecular cyclization to benzene ring. δ-Aryl-β-dicarbonyl 30 can undergo 6-endo cyclization mediated by CAN affording β-tetralone 31. Kim *et al.* reported that 6-endo cyclization reaction of phenethylamide 32 provided dihyroisoquinoline 33 (Scheme 6).

![Scheme 6](image)

In 1971, Trahanovsky *et al.* discovered for the first time, azidonitration reaction in presence of CAN. According to this method, oxidation of olefin 34 in the presence of NaN₃ and CAN provided α-azido-β-nitro alkanes 35. Magnus *et al.* reported that the reaction of triisopropyl silyl enol ether 36 with CAN and sodium azide gave α-azido keton 37. A procedure for the synthesis α-azido ketone 39 starting from styrene (38) and sodium azide was also developed in the presence of CAN (Scheme 7).
CAN is also used as a catalytic oxidant in reactions such as regioselective ring opening and transformation of epoxides into dicarbonyl compounds. Salehi et al. reported the conversion of epoxides to the corresponding \( \beta \)-halohydrines mediated by catalytic amount of CAN (Scheme 8). Iranpoor and coworkers synthesized 1,2-azidoalcohols and by the reaction of with \( \text{NaN}_3 \) in presence of catalytic amount of CAN. CAN and ammonium thiocyanate were used to convert epoxide to thiiranes (Scheme 8).

\[
\text{Scheme 7}
\]

\[
\text{Scheme 8}
\]
CAN is an effective catalyst for using condensation reactions to synthesize diazepine and quinoaxiline derivatives. For example, o-phenyldiamine (46) was reacted with ketone 47 in presence of catalytic amount of CAN to give 1,5-benzodiazepine derivative 48. The reaction of α-hydroxyketone 49 and benzene-1,2-diamine 46 leading to the synthesis of quinoaxiline derivative 50 was also catalyzed by CAN (Scheme 9).

Scheme 9

CAN was also used in organocatalyzed reactions as a single electron oxidant composing transient radical species from enamine. Vinylation of aldehyde, carbo-oxidation of styrene and enantioselective α-enolation are example for this strategy. As a result of these reaction, compound 53, 54 and 56 were obtained, respectively. These reactions are shown in (Scheme 10).
CAN has also been used by several protection and deprotection reactions such as deprotection of acetals, TBDMS, THP, t-Boc, Benzyl, PMB and PMPE groups and protection of benzyl and t-Boc group.

CAN plays an important role in deprotecting acetal groups. Nair et al.\textsuperscript{28} reported that 1.2 equiv. CAN removed acetal groups in 57 and 59 in aqueous methanol (Scheme 11).

![Scheme 11](image)

Singh et al.\textsuperscript{29} employed CAN in methanol for the deprotection of TBDMS ethers 61. Otherwise, C-Si bond was broken with CAN in methanol to obtain β-lactam derivatives 62 (Scheme 12).\textsuperscript{30}

![Scheme 12](image)

Hakemelahi et al.\textsuperscript{31} reported an efficient procedure for removal of t-Boc-group using catalytic amount of CAN in acetonitrile (Scheme 13).

![Scheme 13](image)
Examples of protection method; allylic alcohol 67 and tertiary benzylic alcohol 69 were converted to the corresponding allyl ethers by using a catalytic amount of CAN (Scheme 14).\(^{32}\)

1.1.2 Photogenerated Singlet Oxygen

Photogenerated singlet oxygen (\(^{1}\)O\(_2\)) has been discussed in synthetic organic chemistry since 1924.\(^{33}\) It is a very short lived species in a exited state, but it easily oxidizes carbon-oxygen and heteroatom-oxygen bonds. Bicyclic endoperoxides synthesized by cycloaddition of singlet oxygen to diene systems are important compounds for the chemical and biological transformations. Especially, biochemists and biologists pay particular attention to singlet oxygen because of biochemical role of the photogenarated singlet oxygen such as free radical aging mechanism, cancer inducing mechanism etc.\(^{34,35}\)

1.1.2.1 Generation of Singlet Oxygen

A. Chemical Methods

There are a plenty of laboratory methods to obtain singlet oxygen. These are;

a. Reaction of chlorine with hydrogen peroxide to generate singlet oxygen\(^ {36,37,38}\)
b. Reaction of bromine with hydrogen peroxide to generate singlet oxygen

\[
\text{Br}_2 + H_2O_2 \rightarrow ^1O_2 + 2\text{HBr}
\]

c. Reaction of peracids with hydrogen peroxide

\[
\begin{align*}
2 \text{R} - \text{C} - \text{OOH} & \rightarrow ^1\text{O}_2 + 2\text{R} - \text{C} - \text{OH} \\
\text{R} - \text{C} - \text{OOH} + H_2O_2 & \rightarrow ^1\text{O}_2 + \text{R} - \text{C} - \text{OH} + H_2O
\end{align*}
\]

d. Reaction of nitriles with hydrogen peroxide to generate singlet oxygen

\[
\begin{align*}
\text{RCN} + H_2O_2 & \rightarrow \text{R} - \text{C} - \text{OOH} \\
\text{R} - \text{C} - \text{OOH} + H_2O_2 & \rightarrow ^1\text{O}_2 + \text{R} - \text{C} - \text{NH}_2 + H_2O
\end{align*}
\]

e. Decomposition of triphenyl phosphite ozonide at -35 °C to generate singlet oxygen

\[
(C_6H_5O)_3P \xrightarrow{O_3} (C_6H_5O)_3PO \\
(C_6H_5O)_3P \xrightarrow{-35 °C} ^1\text{O}_2 + (C_6H_5O)_3P=O
\]

f. Decomposition of potassium peroxychromate with water to generate singlet oxygen

\[
4\text{CrO}_8^{3-} + 2H_2O \rightarrow 7 ^1\text{O}_2 + 4\text{CrO}_4^{2-} + 4\text{OH}
\]

g. Decomposition of 9,10-diphenylantracene at high temperatures
B. Photosensitizing Methods

Researchers used different photosensitizers to synthesize singlet oxygen on a laboratory scale. Popular photosensitizers are dyes such as; meso-tetraphenylporphin, rose bengal, eosin Y, methylene blue, toluidine blue etc.

Firstly, singlet oxygen mechanism was examined by Kautsky. This mechanism includes the excitation of a sensitizer with visible light to form corresponding excited single state. After intersystem crossing, the excited triplet state of the sensitizer undergoes an energy transfer with triplet oxygen to generate singlet oxygen and the ground state sensitizer.

\[
\begin{align*}
\text{Sensitizer} \quad \rightarrow & \quad \text{Sensitizer}^* \\
\text{Sensitizer}^* \quad \rightarrow & \quad \text{Sensitizer}^* \\
\text{Sensitizer}^* \quad \rightarrow & \quad \text{Sensitizer} + \text{O}_2
\end{align*}
\]

1.1.2.2 Reactions of Singlet Oxygen

There are three types of singlet oxygen reactions which are cycloaddition reaction, ene reaction and heteroatom oxidation reaction. Cycloaddition of singlet oxygen is divided into two classes; 1,3 dien compounds undergo \([4+2]\) cycloaddition reaction to form cyclic peroxides called as endoperoxides such as and ethylene compounds undergo \([2+2]\) cycloaddition reaction to form dioxetan. Alkenes and phenols, including allylic hydrogen are reacted with singlet oxygen (called ene reaction) to form hydroperoxides and . Singlet oxygen oxidizes sulfides and phosphines to generate sulfoxides and phosphate oxides, respectively. These reactions are called heteroatom oxidation reaction (Scheme 15).
1.1.2.3 Chemical Transformation of Bicyclic Endoperoxides

Diimide reduction is an important reaction for a bicyclic endoperoxide because diimide reduces only the C=C double bond not the peroxide linkage. When catalytic hydrogen is used instead of diimide, double bonds as well as peroxide bond are reduced. Diimide is generated by the reaction of potassium azodicarboxylate and acetic acid. Solomon et al. used diimide reduction to synthesize prostaglandin substructure 85 (Scheme 16).^{42}

There are three types of reduction reactions of bicyclic endoperoxides. These are LiAlH₄, thiourea and catalytic reduction reactions. LiAlH₄ and thiourea are used to generate 2-ene-1,4-diols 87. One the other hand, catalytic reduction is applied to obtain 1,4-diols 88. Thiourea reduction has some advantages compared to catalytic reduction and lithium aluminum hydride reduction. This advantage is that thiourea
reduces only oxygen-oxygen bond and thus preserves other functional groups. For example, reaction of endoperoxide 86 synthesized by addition of singlet oxygen to cyclopentadiene, was reduced by thiourea, to 2-ene-1,4-diols 87. On the other hand, catalytic hydrogenation reaction of endoperoxide 86 generates, 1,4-diols 88 (Scheme 17).

Scheme 17

Endoperoxide 86 was reacted with triphenylphosphine to give unsaturated epoxide 90. Mechanism of triphenylphosphine deoxygenation; trivalent phosphorus atom provides the reductive extrusion of one oxygen atom then ensure the unsaturated epoxide 90 (Scheme 18). 39

Scheme 18

There are two types of decomposition reactions in the thermochemical reaction of endoperoxide 86; loss of molecular oxygen or cleavage of the O-O bond (Scheme 19). 44, 45
Example for loss of molecular oxygen; Wasserman and Larsen studied decompositon of alkyl-substituted naphthalene 1,4-endoperoxides \(94\) to obtain the starting material and singlet oxygen (Scheme 20).\(^{46}\) Thermal fragmentation of bicyclic endoperoxides is an important reaction for singlet oxygen generation.

Example for cleavage of the O-O bond; thermal isomerization of bicyclo[4.2.0]octa-2,4-diene endoperoxide \(95\) in \(\text{CCl}_4\) at 110 °C provides bicyclo[4.2.0]octa-2,4-diene diepoxide \(96\) (Scheme 21).\(^{47}\)

Adam and Erden reported that warming of (1\(R\),4\(S\))-2,3-dioxabicyclo[2.2.1]heptan-7-one \(97\) up to -10 °C gave succinaldehyde \(98\) and carbonmonoxide (Scheme 22).\(^{48}\)
Base catalyzed decomposition of bicyclic endoperoxides is a rearrangement reaction and used to obtain cyclic hydroxy ketones. First base abstracts a hydrogen atom from the bridgehead carbon atom then the rearrangement occurs. For example, 2,3-dioxabicyclo[2.2.1]heptane derivative (99) was reacted with NEt$_3$ and it was converted to cyclic hydroxy ketone 100 (Scheme 23).\cite{48}

![Scheme 23](image)

1.1.3 Troponoids

Troponoids are natural compounds having seven membered aromatic rings, tropone and tropolone. Tropone is not present in the nature, but many natural compounds have tropone in their structures. Troponoids having these skeleton have a wide range of pharmacological activities. Trust et al.\cite{49} studied that tropolidine and tropone posses bactericidal and bacteriostatic activities, but don’t have sporicidal activity against gram positive and gram negative species (Scheme 24).

![Scheme 24](image)

Further studies showed that tropolone for instance benzotropolone and thujaplicins exhibit strong antimicrobial and antifungal activity.\cite{50} According to Inamori groups, tropolones such as β-dolabrin, γ-thuiaplicin showed strong antimicrobial activity (Scheme 25).\cite{51}
To synthesize tropone (106), firstly cycloheptanone (104) was reacted with bromine under acidic condition to give 105, then the adduct was reduced with catalytic hydrogen to give 106. According to the Collington’s method, α-position of cycloheptanone (104) was firstly brominated with bromine. Then the product 107 was reacted with lithium chloride to obtain tropone (106) (Scheme 26).

For a general synthesis for tropolone (110), cycloheptanone (104) was first oxidixed with SeO₂ to α-diketone 108. Bromination of 108 followed by debromination and catalytic reduction resulted in the formation of tropolone (110) (Scheme 27).

Scheme 25

Scheme 26

Scheme 27
Oxidation reaction is used to synthesize tropone (106) and tropolone (110) most widely. Nozoe$^{56}$ and Radlick$^{57}$ oxidized cycloheptatriene (111) to tropone (106) with SeO$_2$ or CrO$_3$ in pyridine. On the other hand, for the synthesis of tropolone (110) Doering et al.$^{58}$ used KMnO$_4$ as oxidation reagent (Scheme 28).

Scheme 28

Cycloaddition reaction is also a method to synthesize tropone or tropolones. Stevens et al.$^{59}$ reported that cycloaddition of dichloroketene (112) to cyclopentadiene afforded cyclobutanone derivative 113. Then the adduct 113 underwent a ring enlargement reaction to form tropolone (110) (Scheme 29).

Scheme 29

Birch, et al.$^{60}$ reduced anisole derivatives 114 to 1-methoxycyclohexa-1,4-diene 115 by the Birch reduction. Addition of dibromocarbene to 1,4-diienes 115 followed by the reaction with aqueous AgNO$_3$ afforded corresponding tropone derivatives 117 (Scheme 30).
Weitz, et al. synthesized benzotropone 120 by a condensation reaction. According to this synthetic pathway, firstly, commercially available phthalaldehyde (118) was reacted with 1,3-acetonedicarboxylates. Condensation product 119 was hydrolyzed to afford benzotropone 120 (Scheme 31).

An alternate pathway to synthesize benzotropone 124 was the reaction of α,α’-dibromo-o-xylene (121) with 1-[(1Z)-1-ethylprop-1-enyl]pyrrolidine (122) to afford desired compound 123. Bromination of 123 followed by dehydrobromination gave benzotropone derivative 124 (Scheme 32).

Balci et al. synthesized benzotropolone (129) using an unusual endoperoxide rearrangement. Firstly, benzotropone (127) was synthesized by the Collington’s method. Then, benzotropone (127) was reacted with singlet oxygen to form benzotropone endoperoxide 128. Thiourea reduction of 134 followed by water elimination gave benzotropolone (129) (Scheme 33).
1.1.4 Aim of the Study

The aim of this part was the synthesis of cycloheptadiene-fused dihydrofurane derivatives and searching further reactions of dihyrofuranes 130. We were interested in the construction of these type of skeletons due to their important mechanistic properties and as well as pharmacological properties. In this project, cyclohepta
triene (111) will be reacted with 1,3-dicarbonyl compounds in the presence of cerium ammonium nitrate to generate dihydrofurane-fused cycloheptadiene 130. The diene system in 130 will be submitted to photoxygenation reaction to obtain endoperoxides 131 and 132. Furthermore, compound 130 will be converted to furan-fused tropone derivatives 133 (Scheme 34).
In addition, we are also interested in the transformation reactions of endoperoxide 131. Firstly, we will examine reaction of endoperoxide 131 with CoTPP to form 134. After that, gold-catalyzed oxidative ring-opening reaction of endoperoxide 131 will be studied to generate 132a. The reaction of endoperoxide 131 with triethyl amine is also planned to form 157.

Scheme 35
1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of Dihydrocyclohepta[b]furan (130)

Commercially available cycloheptatriene (111) was treated with 1,3-diketones 137 in the presence of CAN to obtain dihydrocyclohepta[b]furan derivatives 130. The reaction proceeded cleanly, no side products were formed during this addition reaction (Scheme 36).

Scheme 36

The characterization of compound 130a was performed by using $^1$H and $^{13}$C NMR spectra (Fig 3 and Fig 4 - p. 109-110). In the $^1$H NMR spectrum of compound 130a, the methine proton H-8a resonates as a broad doublet at 5.01 ppm with a coupling constant of $J = 8.7$ Hz. The value of the coupling constant is in agreement with the cis-configuration of the annulated five-membered ring. Furthermore, this peak is a characteristic peak for this kind of compounds. Inspection of the Dreiding models shows that the dihedral angle between the protons H-8 and H-8a is approximately 80-90°. Due to the lack of a coupling between those protons, the doublet splitting arises from the coupling with the neighboring proton H-3a. Olefinic protons for these compounds resonate between 6.21-5.97 ppm. The other methine proton H-3a resonates as a broad triplet at 3.27 ppm due to the coupling with the proton H-8a and one of the methylene protons H-4. The fact that this proton couples only with one of the methylene protons H-4 can be ascribed to the dihedral angels formed between the relevant protons. The other signals in the $^1$H NMR spectrum are in agreement with the proposed structure.
The signal at 193.6 ppm in the $^{13}$C NMR spectrum of 130a belongs to the carbonyl carbon. The olefinic carbon resonances appear at 167.1, 134.6, 129.8, 127.2, 126.9, and 118.2 ppm. There are five aliphatic carbons and they resonate at 84.6, 51.8, 30.0, 29.1 and 15.3 ppm. The NMR spectra of the other derivatives 130b-d were also in agreement with the proposed structures (p. 109-116).

The addition of dicarbonyl compounds is a regiospecific reaction. The radical generated from dicarbonyl compounds 137 can attack two different double bonds (C1-C2 or C3-C4) in cycloheptatriene. The final structure of the compounds 130 shows that the radical exclusively attacks the terminal double bond (C1-C2) in cycloheptatriene. Even in this case there are two different routes for the attacks so that two different products can be formed. The dicarbonyl radical can attack the carbon atom C-1 as well as C-2. In the case of Route A (Scheme 35) the generated carbocation formed after oxidation will be in conjugation with the diene system and will be stabilized. However, in the case of an attack on C-2 carbon atom, the formed carbocation cannot be stabilized. Therefore, the route A will be preferred. Careful examination of the reaction products did not reveal the formation of any trace of compound having the structure 138 (Scheme 37).

![Scheme 37](image)

In the light of this result, we decided to react cycloheptatriene with 3-cyclohexanediomine (139a) and dinedone (139b), with more enolizable characters than acetyl acetone and derivatives to check the generality of this reaction (Scheme 38).
The $^1$H NMR spectrum (Fig 19 - p. 118) of 140a exhibits four olefinic proton signals in the range of 6.5 to 5.6 ppm. The observed coupling constants between the olefinic protons are in the usual range. Additionally, alkoxy methine proton resonates as doublet of doublets of triplets at the 4.90 ppm due to double bond in the α-position and the oxygen atom. Other methine proton for compound 140a resonates as a broad triplet at 3.39 ppm with a coupling constant of $J = 6.3$ Hz. The other signals of $^1$H NMR spectrum were coherent with the proposed structure.

For the compound 140a, in the $^{13}$C NMR spectrum (Fig 20 - p. 118) there are three characteristic groups which are carbonyl group resonating at 197.5 ppm, tertiary carbon atoms appearing at 169.9 and 114.5 ppm and olefinic carbon resonances at 139.1, 129.6, 128.8 and 123.2 ppm. The remaining carbon resonances appear in the aliphatic area at 72.4, 36.7, 28.4, 28.3, 27.4, 20.6 ppm.

The NMR spectra of compounds 141a and 141b looked similar to the NMR spectrum of compounds 130 a-d.

We propose the following mechanism for the formation of these products. CAN firstly abstract acidic proton in a cyclo-1,3-carbonyl compound 139 to form carboxyl methyl radical 142 which adds to double bond of cycloheptatriene (111) to afford new radical 143 on the cycloheptatriene. Oxidation of 143 by CAN results in the formation of 144 that can undergo two different ring closure reaction to form 140 and 141(Scheme 39).
1.2.2 Photooxygenation of the Dihydrocyclohepta[b] (130)

Tetraphenylporphyrin sensitized photooxygenation of dihydrocyclohepta[b]furan derivatives 130 a-d in methylene chloride at room temperature for 15 h produced endoperoxides 131 a-d which are stable at room temperature for many days (Scheme 40).

Comparison of the NMR spectra of the products 131a with those of the starting material shows that one double bond is missing and two new bridgehead protons are formed instead. In the $^1$H NMR spectrum (Fig 35 - p. 126) of 131a olefinic protons resonate as an AB-system. A-part of this systems appears at 6.57 ppm as doublet of doublets ($J = 9.10$ and 7.1 Hz) whereas the B-part resonate at 6.47 ppm as doublet of doublets ($J = 9.10$ and 6.8 Hz). Bridgehead protons of 131a resonate at 5.11 and 4.64 ppm. The other signals of $^1$H NMR spectrum were in agreement with the proposed structure.

In the $^{13}$C NMR spectrum (Fig 36 - p. 126), the carbonyl carbon resonates at 192.6 ppm. Olefinic carbons appear at 168.4, 134.1, 124.3, 118.8 ppm. The other carbon
signals were coherent with the structure. The NMR spectra of the other derivatives were also in agreement with the proposed structures.

When, dihydrocyclohepta[b]furan derivatives 130 were submitted to the photooxygenation reaction under the same reaction conditions; in methylene chloride at room temperature. However the reaction time was increased up to 96 h to give endoperoxide 132 (Scheme 41).

![Scheme 41](image)

Endoperoxide 132a was characterized on the basis of the $^1$H and $^{13}$C NMR spectra, which were in agreement with the proposed structure. There are three olefinic protons in $^1$H NMR spectrum (Fig 51 - p. 134) of 132a. Neighbouring olefinic protons resonate as an AB system. The A-part resonates at 6.73 as broad doublet of triplets ($J = 8.0$ and $0.9$ Hz). The B-part appears at 6.51 as doublet of triplets ($J = 8.7$ and $1.0$ Hz). The other olefinic proton resonates at 7.32 as doublet of triplets ($J = 6.8$ and $1.7$ Hz). Methylenic protons of 132a also resonate as an AB system. A-part resonates at 3.13 ppm as doublet of doublets of triplets with coupling constants of $J = 19.4$, $4.5$ and $2.0$ Hz and B-part resonates at 2.70 ppm as doublet of triplets with coupling constant $J = 19.4$ and $1.3$ Hz. Bridgehead protons resonate as multiplet at 5.02-4.94 ppm.

The $^{13}$C NMR spectrum (Fig 52 - p. 134) of 132a shows ten different signals. The resonance signals at 200.1 and 193.3 ppm belong to two carbonyl groups. Four of the resonances appear in the range of sp$^2$ hybridized carbon atoms, at 146.5, 136.6, 131.8 and 128.5 ppm. Bridgehead carbons signal appear at 75.0 and 72.3 ppm. Aliphatic carbons resonate at 33.2 and 26.6 ppm. The NMR spectra of the other derivatives were also in agreement with the proposed structures.
For this reaction, we proposed the following reaction mechanism. Singlet oxygen first undergoes a [4+2] cycloaddition reaction with the diene unit of cycloheptadiene. We assume, that singlet oxygen undergoes a [2+2] cycloaddition reaction with the double bond present in the five-membered ring during the increased reaction time to form a dioxetane 146. Thermal decomposition of dioxetane unit in 146 gives ester intermediate 147 which undergoes an elimination reaction upon treatment with silica gel to form the final product 132. (Scheme 42).

Scheme 42

1.2.3 SeO₂ Oxidation Reaction for Dihydrocyclohepta[b]furans (133)

Because of the biological importance of tropones and structural suitability of synthesized compounds, we decided to synthesize tropone derivatives. Dihydrocyclohepta[b]furan derivatives 130 were submitted to oxidation reaction with SeO₂. This method includes forceful reaction conditions such as high temperatures. Reaction of 130 with SeO₂ in anisole at 154 °C for 18-20 h provided the corresponding tropone derivatives 133 in acceptable yields (Scheme 43).
Comparison of the $^1$H NMR spectra (Fig 55 - p. 136) of 130a with those of (Fig 62 - p. 139) 133a clearly shows that the resonances of methylene, methine protons in seven-membered ring and the methyl protons attached to the double bond are disappeared. Appearing of olefinic proton resonances in the $^1$H NMR spectrum of 133a, clearly indicates the formation of tropone unit. One of the five olefinic protons resonates at 9.14 ppm as doublet with a coupling constant of $J = 11.2$ Hz. The proton resonance at 7.64 ppm appears as doublet of doublets ($J = 11.2$ and 8.9 Hz). The double bond proton in the five-membered ring resonates as singlet at 7.52 ppm. The other protons appear at 7.54–7.49 ppm as multiplet and 7.36 ppm as doublet of doublets of doublets ($J = 11.5$, 8.5 and 4.0 Hz). Methyl proton resonance appears at 2.58 ppm as singlet.

In the $^{13}$C NMR spectrum (Fig 56 - p. 136), carbonyl carbons resonate at 195.1 and 167.6. The signal of eight olefinic carbons appear in a range of 159.2 to 103.6. Methyl protons group resonate at 30.1 ppm. The NMR spectra of the other derivatives were also in agreement with the proposed structures.

For the formation of this interesting product 133, we propose the following reaction mechanism. In the first step SeO$_2$ undergoes an ene reaction. The allylic seleninic acid 149 formed as an intermediate undergoes a [2,3]-sigmatropic rearrangement to form 150 that may decompose to an allylic alcohol or an allylic carbonyl compounds as shown below. In the case of formation of an allylic alcohol, oxidation may continue to give an $\alpha$,$\beta$-unsaturated carbonyl product.

The methyl group attached to the double bond may also be oxidized to the corresponding carboxylic acid. The decarboxylation at high temperature results in
removal of the methyl group. These two oxidation reactions can take place one after one or at the same time (Scheme 44).

Scheme 44

1.2.4 Reaction of Endoperoxide (130a) with Co-TPP (153 and 134)

To examine the behavior of synthesized endoperoxide 130a against CoTPP, endoperoxide 130a was treated with CoTPP in CH₂Cl₂ at room temperature. Surprisingly, the compound 134 was formed instead of the expected product 154 (Scheme 45).

Careful inspection of the NMR spectra indicated the formation of the epoxide-rings beside the opening the dihydrofurane ring and formation of two new carbonyl groups in compound 134. For this oxidative transformation reaction, the addition of oxygen molecule to the double bond in the five-membered ring is necessary. The mechanism of formation of this product is not clear and will be searched in the future. For purification of 153, silica gel column chromatography was used. We noticed that the ester functionality in 153 was eliminated during purification to give 134 where newly formed double bond is conjugated with the carbonyl group (Scheme 45).
Comparison of the $^1$H NMR spectrum of 131a with those of 153 (Fig 77 - p. 147) showed disappearance of the olefinic proton and bridgehead proton resonances. The epoxide proton resonances were formed instead. Four epoxide protons resonate at 3.50 ppm as a broad triplet ($J = 3.1$ Hz), 3.40 ppm as doublet of doublets ($J = 3.9$ and 2.0 Hz) and other two epoxide protons epoxide signals appear at 3.20-3.11 ppm as multiplet. There are two methine protons in the structure. The methine proton next to the oxygen atom resonates at 5.46 as doublet of doublets with coupling constants of $J = 4.7$ and 2.2 Hz. The other methine proton resonates at 3.78-3.73 ppm as multiplet. In addition to methylene proton resonances at 2.19 ppm as triplet ($J = 6.7$ Hz), two methyl groups resonate at 2.30, 1.99 as singlets.

$^{13}$C NMR spectrum (Fig 78 - p. 147) of 153 includes twelve different signals. Three of them are arising from the carbonyl groups which appear at 197.5, 196.0 and 170.3 ppm. Methine carbons of 153 resonate at 69.5 and 43.3. Epoxide carbons resonate at 58.1, 53.8, 51.6 and 50.4 ppm. Additionally, methylene carbon resonates at 23.5 and two methyl groups appear at 24.0 and 20.8 ppm.

The presence of four epoxide protons and methylenic protons in the $^1$H NMR spectrum (Fig 86 - p. 151) of 134 showed that this part of the molecule was not changed during column chromatography. However, the presence of an olefinic proton resonance at 6.86 ppm as doublet of doublets ($J = 4.2$ and 1.8 Hz) indicated the elimination of the ester group.
\(^{13}\)C NMR spectrum (Fig 87 - p. 152) of \textbf{134} was much more informative. The signal of one of the carbonyl groups was disappeared and the remaining carbon resonances appear at 200.5 ppm and 191.8 ppm. The formation of C=C double bond carbons at 141.5 and 136.5 ppm further confirmed the elimination of the ester group. Four epoxide carbon resonances were found at 52.8, 52.8, 49.7, and 48.1 ppm. Additionally methyl carbon and methylene carbon resonances were observed at 26.8 ppm 22.4 ppm, respectively.

\textbf{1.2.5 \textit{AuCl}_3\text{-Catalyzed Reaction of Endoperoxide (130a)}}

To examine the reaction of endoperoxides with gold salt, we treated compound \textbf{131a} with gold trichloride at the room temperature under the oxygen atmosphere. We expected that endoperoxide unit in \textbf{131a} would undergo some kind of reaction with \textit{Au(Cl)}\textsubscript{3}. However, we noticed that the endoperoxide unit was intact. On the other hand, five-membered ring underwent an oxidative ring-opening reaction to give \textbf{147} (Scheme 46).

For this transformation, we suggest the following reaction mechanism. We assume that the double bond in the five-membered ring is activated with \textit{Au}\textsuperscript{3+} ions upon complexation so that the oxygen can attack this bond and form perepoxide \textbf{156} which has tendency to rearrange to corresponding dioxetane \textbf{146a}. Cleavage of the dioxetane \textbf{146a} will provide dicarbonyl compound \textbf{147}. Elimination of CH\textsubscript{3}COOH group on silica gel may furnish \textbf{132a}. 
The characterization studies of compound 147 were done with the help of $^1$H and $^{13}$C NMR spectra. In the $^{13}$C NMR spectrum (Fig 96 - p. 156) two new carbonyl carbons were formed that resonate at 196.7 and 170.7 ppm the other carbonyl carbon resonates at 197.1 ppm. At the same time two olefinic carbon resonances of dihydrofuran ring disappeared. The other signals of $^{13}$C NMR spectrum were in accordance with the proposed structure.

In the $^1$H NMR spectrum (Fig 95 - p. 156) of 147, two bridgehead protons resonate at 4.95 ppm as triplet of triplets ($J = 6.4$ and 1.0 Hz) and at 4.81 ppm as doublet of triplets ($J = 6.7$ and 1.2 Hz). Olefinic proton resonates as multiplet between 6.56 to 6.45 ppm.

NMR spectra of 132a were discussed above.

1.2.6 Reaction of endoperoxide (130a) with NEt$_3$

It is well established that the unsaturated bicyclic endoperoxides reacts with bases to give the rearranged $\alpha,\beta$-unsaturated enones. For further functionalization, endoperoxide 131a was treated with triethyl amine in dichloromethane at 0 °C. Contrary to our expectation, compound 160 was formed instead of 157 (Scheme 47).

We propose the following mechanism for the formation of compound 160. We assume that the expected product enone 157 is formed in the first step. Then,
triethylamine abstracts the proton from the hydroxyl group generating an alkoxy anion that attacks the β-carbon atom of enone forming an epoxide ring. The formed carbanion can easily be protonated to generate final compound 160 (Scheme 45).

When we compare $^1$H NMR (Fig 35 - p. 126) spectrum of the starting compound 131a with the $^1$H NMR spectrum (Fig 104 - p. 160) of product 160, we observe that bridgehead protons and olefinic protons signals are disappeared and epoxide protons signals are formed instead. Epoxide protons appear as a doublet of doublets of doublets at 4.79 ppm ($J = 8.1$, 5.8, 2.3 Hz) and doublet of doublets at 4.55 ppm ($J = 7.9$, 5.8 Hz). Methine protons signal shows a broad doublet at 5.38 ($J = 2.1$ Hz) and multiplet in the range of 2.76 to 2.71 ppm. The other protons were coherent with the structure.

In the $^{13}$C NMR spectrum (Fig 105 - p. 161), there are two carbonyl carbon signals resonating at 201.9 and 197.3 ppm and two olefinic carbon signals at 169.3 and 104.2 ppm. Epoxide carbon signals appear at 76.7 and 70.9 ppm.
CHAPTER 2

DESIGN OF PYRROLO-PYRROLO-PYRAZINES VIA Pd/C-CATALYZED CYCLIZATION OF N-PROPARGYL PYRROLINYL-PYRROLE DERIVATIVES

2.1 INTRODUCTION

2.1.1 Pyrrole

Pyrrole, from Greek meaning red, is an attractive azaheterocyclic compound. Pyrrole and its derivatives show interesting biological and pharmacological properties such as antitumor, antibacterial, antioxidative, anti-inflammatory, antifungal activities. These properties show that pyrrole is an important pharmaceutical compound. For instance, antrovastatin, marketed name is Lipitor® (1) possesses a cholesterol-lowering properties.

![Pyrrole molecule](image)

Pyrrole ring was used to synthesize non-steroidal anti-inflammatory drugs, which are called tolmetin (Rumatol®) (2) and ketorac (Ketrac®) (3).
Recently, anticancer drugs having pyrrole ring have been used by treatment of cancer diseases. Sunitinib (4) is an important example, this marketing drug, is used for treatment of renal cancer. The other example of synthetic anticancer drug including pyrrole ring is a tallimustine (5).

Optoelectronic materials having pyrrole ring, such as OLED (Organic Light-Emitting Diodes), PLED (Polimeric Light-Emitting Diodes), polypyrrole-latex materials, polypyrrole, hexa(N-pyrrolyl)benzene (6) are important for the material science. In addition to, BODIPY (4,4-difluoro-4-boradipyrrin system) (7) is an important pyrrole derivative used by many scientist because it possesses strong absorption properties in the UV and emit very intense fluorescence.
2.1.2 Pyrazines

Pyrazine (8) is a heterocyclic compound having two nitrogen atoms with a six membered aromatic ring. Compounds including the pyrazine skeleton represent important role in materials science and drug chemistry. In other words, they show a great range of biological activities, such as antihypersensetive, antiarrhythmic, psychotropic, antihypoxic.

Pyrazine is found in many natural products but larger part of natural pyrazines are found in amino acids such as, terezine A (9), barrenzine A and B (10), actinopolymerphol C (11), 2,5-diisopropylpyrazine (12), botryllazine A (13) and botryllazine B (14).

2.1.2.1 The Synthesis of Pyrazines

Cyclocondensation reaction is an important and most common way to synthesize pyrazine ring. Masuda et al. synthesized 2,3-dihydropyrazine 17 by cyclocondensation reaction of 1,2-dicarbonyl compound 15 with 1,2-diaminoethane
Oxidation of 2,3-dihydropyrazine 17 with copper chromite gave pyrazine 18 (Scheme 1).

Darkins et al.\textsuperscript{86} reported that \(N\)-protected 1,2-dicarbonyl compound 19 was condensed with 1,2-diaminoethane to generate dihydropyrazine which is oxidized to pyrazine 20 by \(\text{MnO}_2\) in the presence of KOH (Scheme 2).

1,4-Diazine scaffold 23 was generated by the reaction of bicyclo[2.2.1]hept-5-ene-2,3-dione (21) with 1,2-diaminoethan followed by oxidation in the presence of \(\text{NiO}_2\) (Scheme 3).\textsuperscript{87}

According to a new synthetic methodology developed by Kamitori,\textsuperscript{88} dialkylhydrazone 24 was first reacted with TFAA (trifluoroacetic acid) followed by hydrolysis with \(\text{H}_2\text{SO}_4\) to generate \(\alpha\)-diketohydrate 25 which was condensed with diamines to obtain pyrazine derivative 26 (Scheme 4).
Kano and coworkers demonstrated the direct synthesis of pyrazine by the reaction of diaminomalononitrile 27 with β-keto sulfoxide 28 to form 2,3-dicyanopyrazine 29 (Scheme 5).\textsuperscript{89}

Bradbury \textit{et al.}\textsuperscript{90} synthesized new pyrazinone derivatives 32 starting from 1,2-dicarbonyl compound 30 and α-amino malonamides 31 in the presence of NaOH/NaHSO\textsubscript{3} (Scheme 6).

In 2003, Taylor and coworkers developed a highly efficient and novel route for the synthesis of quinoxaline derivative 35 by a tandem oxidation procedure, where α-hydroxyketone 33 was reacted with 1,2-diamines 34 in presence of MnO\textsubscript{2} (Scheme 7).\textsuperscript{91}
Lindsley et al.\textsuperscript{92} designed a practical and general method under the microwave irradiation conditions to synthesize functionalized pyrazine 38 that are important class of heteroaromatic compounds (Scheme 8).

![Scheme 8](image)

**Scheme 8**

An alternate way to synthesize pyrazine ring is the cyclodimerization of \(\alpha\)-amino carbonyl compounds. Firstly, \(\alpha\)-amino ester 39 undergoes a self-condensation reaction to form 2,5-dihydropyrazine 40. Treatment of 40 with trialkloxonium salt followed by oxidation with DDQ resulted in the formation of 3,6-dialkoxy pyrazadine 41 (Scheme 9).\textsuperscript{93}

![Scheme 9](image)

**Scheme 9**

Meier et al.\textsuperscript{94} reported a new procedure to synthesize trisubstituted 1\(H\)-pyrazine-2-ones. Boc-protected amino acid 43 was treated with \(\alpha\)-aminoalcohol 42 or with \(\alpha\)-amino ketone followed by oxidation with DMP (Dess–Martin periodinane) to obtain coupling adduct 44. Reaction of 44 with HCl in pyridine at 80 °C afforded 1\(H\)-pyrazin-2-one 45 in good yield (Scheme 10).

![Scheme 10](image)

**Scheme 10**
Schulz and coworkers designed a practical and alternative method for the synthesis of pyrazine derivatives via aza-Witting cyclization reaction. Their synthetic strategy includes firstly the formation of α-phosphazinyl ketone 47 starting from α-azidoketone 46 and triphenylphosphine. After that, aza-Witting cyclization reaction of α-phosphazinyl ketone 47 formed dihydropyrazine derivative 48 (Scheme 11).\textsuperscript{95}

![Scheme 11](image)

Janda \textit{et al.}\textsuperscript{96} presented that pyrazine-6-one 51 was obtained in good yields by the reaction of α-diazo-β-ketoester 49 with Boc-protected α-aminoamide 50 mediated by rhodium octanoate catalyst. Pyrazine-6-one 51 was treated with POBr\textsubscript{3} to afford 6-bromopyrazine 52, which was reacted with biphenyl boronic acid under the Suzuki coupling conditions to obtain 6-arylpyrazine 53 (Scheme 12).

![Scheme 12](image)

An interesting and straightforward method for the synthesis of tetrasubstituted pyrazine is the thermal Beckmann rearrangement. Firstly, thermally deprotonated oxime hydrochloride 54 affords the nitrile ylide that undergoes dimerization to give
the dihydropyrazine derivative intermediate. Air oxidation of this intermediate furnishes tetrasubstituted pyrazine 55 (Scheme 13).  

Scheme 13

Büchi et al. showed that α-hydroxyimino ketone 56 reacts with allylamine to give imine derivative 57. Base-catalyzed isomerization of 57 with KO\textsubscript{Bu} followed by O-acylation and finally electrocyclization reaction provides pyrazine derivative 60 (Scheme 14).  

Scheme 14
The another and interesting way to synthesize pyrazine ring is a [4+2] cycloaddition reaction. Sato et al.\textsuperscript{99} benefited this way to synthesize lumuzines (63) starting from 61 and 62 which is an important biological active compound (Scheme 15).

Scheme 15

Recently, Balci et al. reported a new synthetic methodology for the construction of novel pyrazine derivatives using alkyne cyclization reactions.\textsuperscript{100} They synthesized a number of pyrazolo-pyrrolo-pyrazine derivatives 65 by the cyclization of \( N \)-propargyl pyrroles derivatives 64 either by \( \text{AuCl}_3 \)-catalyzed or \( \text{NaH} \) supported reactions (Scheme 16).

Scheme 16

Furthermore, Balci et al. developed a synthetic methodology for pyrazine oxides 67. Oxime derivatives of \( N \)-propargy pyrroles and \( N \)-propargy indols 66 were reacted with \( \text{AuCl}_3 \) to obtain pyrazole or indol fused pyrazine oxides 67 (Scheme 17).\textsuperscript{101}
2.1.3 Aim of the Study

The aim of this part was development of a new synthetic methodology for the synthesis of pyrrolo-pyrrolo-pyrazine derivatives via cyclization of N-propargyl 2,2’-(1’-pyrrolinyl) pyrroles.

Firstly, 2,2’-(1’-pyrrolinyl)-pyrrole (70) should be synthesized starting from pyrrole (69). N-propargyl 2,2’-(1’-pyrrolinyl) pyrrole (71) which is key compound of this study, will be obtained by the reaction of 2,2’-(1’-pyrrolinyl)-pyrrole (70) with propargyl bromide. The Sonogashira cross-coupling reaction of N-propargyl 2,2’-(1’-pyrrolinyl) pyrrole (71) with various aromatic bromides will result in the formation of further substituted derivatives 72 (Scheme 18).

After getting compound 72, we planned aromatization of 72 followed by ring-cyclization reaction to obtain the target compound pyrrolo-pyrrolo-pyrazine derivatives 73 (Scheme 19).
Scheme 19
2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of 2,2'-(1'-pyrrolyl)pyrrole (70)

Firstly, we synthesized starting compound, 2,2'-(1'-pyrrolyl)pyrrole (70). To synthesize this compound, pyrrole (69) was reacted with 2-pyrrolidinone (74) in the presence of phosphoryl chloride. Reaction must be done carefully because polymerization take place very quickly (Scheme 20).

![Scheme 20](image)

There are three pyrrole hydrogens and six methylene hydrogens in the structure of 70. In the $^1$H NMR spectrum (Fig 111 - p. 164) of 70, pyrrole protons resonate at 6.93 ppm as doublet of doublets ($J = 2.4$ and $1.1$ Hz), at 6.54 ppm as doublet of doublets ($J = 3.5$ and $1.1$ Hz), and at 6.21 ppm as doublet of doublets ($J = 3.5$ and $2.4$ Hz). In addition, methylene protons resonate at 4.02 ppm as a broad triplet ($J = 7.0$ Hz), at 2.90 ppm as a triplet of triplets ($J = 8.2$ and $1.4$ Hz) and at 2.00 ppm as a quintet ($J = 8.2$ Hz).

In the $^{13}$C-NMR spectrum (Fig 112 - p. 164) of 70, we observe five olefinic carbons signals resonating at 166.5, 127.8, 122.2, 113.2 and 109.1 ppm. Other remaining signals are arising from the methylene carbons appearing at 60.5, 35.0 and 22.7 ppm.

2.2.2 Synthesis of 1-Prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (71)

To synthesize target molecules, we had to attach propargyl group on the pyrrole nitrogen atom in 70. In order to synthesize compound 71, 2,2'-(1'-pyrrolyl)pyrrole (70) was reacted with propargyl bromide derivatives in the presence of sodium hydride in dry DMF to give the expected propargylated compounds 71 (Scheme 21).
The characterization of compounds 71a and 71b was done on the basis of $^1$H NMR (Fig 113-117 - p. 165-167) and $^{13}$C NMR (Fig 114 118 - p. 165-167) spectra. When we compare the structures of 70 and 71a, compound 71a has an additional methylene group and alkyne group. In the $^1$H NMR spectrum of 71a, this methylene protons resonate at 5.41 ppm as doublet ($J = 2.5$ Hz) due to long range coupling with the alkyne proton. Acetylenic proton appears at 2.37 ppm as triplet ($J = 2.5$ Hz).

The $^{13}$C NMR spectrum shows eleven distinct signals. Acetylenic carbons resonate at 79.3 and 73.1 ppm whereas the olefinic carbons appear at 165.9, 127.3, 125.8, 115.4 and 108.3 ppm. In addition aliphatic carbons resonate at 61.8, 38.3, 36.6, and 21.8.

The NMR spectra of compound 71b is also in agreement with the proposed structure.

2.2.3 Intramolecular Pd/C-catalyzed Cyclization Reaction of N-propargyl Pyrrole-Pyrrolinyl Derivative (71a)

For the synthesis of target molecule 73, first the dihydropyrrole unit should be aromatized followed by cyclization. For aromatization we decided to use Pd/C as catalyst. When compound 71 was reacted with Pd/C in diglyme, surprisingly, the cyclization product 73 was formed. This result was very important because two step reactions were completed in one pot (Scheme 22).

We propose the following mechanism for the formation of compound 73. Pd/C firstly dehydrogenates the methylene protons of pyrrolinyl unit to afford compound 75. The $\pi$ coordination of alkynyl group with Pd produces the alkyne $\pi$ complex. After that, nitrogen atom of pyrrole attacks the activated alkyne $\pi$ complex to occur 6-exo-dig cyclization product 77 followed by isomerization to release the compound 73 (Scheme 22).
Comparison of the $^1$H NMR spectra(Fig 113-137 - p. 165-177) of 71a and 73a show that the resonances of acetylenic proton and methylene protons are disappeared in the NMR spectrum of 73a (Fig 137- p. 177) and a methyl and olefinic proton resonances appeared. Furthermore, methylene protons of pyrrolinyl group also disappeared and pyrrole protons are observed instead. In the $^1$H NMR spectrum of compound 73a, formed olefinic proton of the pyrazine ring resonates at 6.89 ppm as a broad singlet. On the other hand, methyl protons appear as a doublet at 2.35 ppm ($J =1.2$ Hz). Additionally, six pyrrole protons resonate at 6.98, 6.92, 6.56, and 6.42 ppm.

In the $^{13}$C NMR spectrum (Fig 138- p. 177), methyl protons appear at 15.62 ppm. On the other hand, olefinic carbons signals appear at 124.8, 123.9, 118.9, 113.7, 111.9, 111.3, 110.8, 109.1, 99.8, 98.6.

The NMR spectra of compound 73b is similar to the NMR spectra of compound 73a.

2.2.4 Derivatization of Compound 71a with Sonagashira coupling reaction (79)

To test the scope of this cyclization and to show the generality of this reaction, we decided to synthesize compound 79 having aromatic groups attached to the terminal carbon atom of acetylene unit. The most suitable methodology for derivatization of compound 71a was a Sonagashira coupling reaction. There are many variation of Sonogashira cross-coupling reaction in the literature.$^{100, 101}$ We preferred copper-
cocatalyzed Sonogashira coupling reaction which uses Pd catalyst and CuI cocatalyst in dry DMF in the presence of a base.

We applied Sonogashira cross coupling reaction to 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrole (71a) to form 79 by using iodobenzene derivatives 78 (Scheme 23).

![Scheme 23](image)

Comparison of the $^1$H NMR spectra (Fig 113 - p. 165) of (71a) with those of compounds 79 clearly showed that acetylenic proton resonance at 2.37 ppm was missing and benzene protons were formed instead. In the $^1$H NMR spectrum (Fig 121 - p. 169) of 79a benzene protons resonate between 7.38 and 7.20 ppm as multiplet. Pyrrole protons resonate at 7.11 ppm as doublet of doublets ($J = 2.9$ and $1.6$ Hz), 6.46 ppm as doublet of doublets ($J = 3.6$ and $1.6$ Hz), and 6.12 ppm as doublet of doublets ($J = 3.6$ and $2.9$ Hz). Methylene protons (next to the alkyne) resonate at 5.55 ppm as singlet. The other signals were consistent with the proposed structure.

The $^{13}$C NMR spectrum (Fig 122 - p. 169) of 79a show acetylenic carbon resonances at 85.0 and 84.6 ppm. Aliphatic carbons resonate at 61.8, 39.2, 36.6, and 21.9. The other carbon signals are in agreement with the proposed structure.

The NMR spectra of compounds 79b-79d are also in agreement with the proposed structures.

Compounds 79 synthesized via Sonogashira cross coupling reaction were submitted to the cyclization reaction with Pd/C in diglyme under the nitrogen atmosphere to give cyclization products 80 (Scheme 24).
In the $^1$H NMR spectrum (Fig 145 - p. 181) of 80a, the methylene proton resonance appears at 4.05 ppm and olefinic proton resonance at 6.75 ppm clearly indicating that cyclization reaction occurred. Six pyrrole protons resonate at 6.96, 6.91, 6.55 and 6.50 ppm. Benzene protons resonate in a range of 7.37 to 7.28 ppm.

The NMR spectra of compounds 80b-80d are also in agreement with the proposed structure.
CHAPTER 3

THE SYNTHESIS OF α-ALKYLIDYN-γ-BUTYROLACTONES VIA GOLD-CATALYZED CLAISEN REARRANGEMENT

3.1 INTRODUCTION

Syntheses of α-alkylidine-γ-butyrolactone derivatives have drawn the attention of researcher in recent years. The first α-alkylidine-γ-butyrolacton, pyrethrosin (1), was extracted from *Tanacetum cinerariifolium* by Toms in 1891. α-Alkylidine-γ-butyrolactone is a five-membered cyclic ester. Its derivatives show anticancer, antiviral, antibacterial, antiinflammatory activities.

For example, Chang and coworkers reported that Taiwainin A (2) isolated from *Taiwania cryptomeriides* is an interesting molecule to use in the treatment of human tumor inhibition. Kotolactone A (3) extracted from *Cinnamomum ketones*, subamolides D and E (4) extracted from *Cinnamomum subavenium*, were found that these molecule have an activity against colon cancer. The other example of natural compound including α-alkylidine-γ-butyrolactone ring is a Hispitolide A (5), showing activity against HCV (hepatitis C virus).
3.1.1. The Synthesis of α-Alkylidine-γ-Butyrolactones

For the synthesis of substituted α-alkylidine-γ-butyrolactone derivatives, there are many strategic ways which are alkylidenation of γ-butyrolactons, lactonization approach, the Dreiding-Schmidt approach, radical cyclization, Diels-Alder and retro-Diels-Alder reaction, Baeyer-Villiger reaction on cyclobutanones, Pd-catalyzed cross-coupling and tandem intramolecular C-H insertion.

Alkylation of γ-butyrolactons is most commonly used method to synthesize α-methylene-γ-butyrolactons. To synthesize (-)-eriolanin (8) and (-)-eriolangin (9), γ-butyrolacton derivative 6 was reacted with NaH then adduct was treated with paraformaldehyde to give 7 (Scheme 1).\textsuperscript{109}
Lactonization approaches were used to design α-methylene-γ-butyrolactons. In 1999, Ballini et al.\textsuperscript{110} demonstrated the reaction of nitro alkene 10 with enone 11 to give 12. Treatment of adduct 12 with NaBH\textsubscript{4} mediated by Na\textsubscript{2}HPO\textsubscript{4} gave α-alkylidine-γ-butyrolactone 13 (Scheme 2).

Dreiding-Schmidt organometalic method, as the name implies that Dreiding and Schmidt groups improved this method for the first time to synthesize α-methylene-γ-butyrolactones. There are various variations of this reaction. In one of these, Chu et al.\textsuperscript{111} reacted 3-phenylallyl bromine (15) with propanal (14) in the presence of zinc and diiodoethane to afford 3,4-disubstituted-α-methylene-γ-butyrolacton (16) (Scheme 3).
The important pathway to synthesize α-alkylidine-γ-butyrolactons is a radical cyclization method. Bosch et al.\textsuperscript{112} presented that homopropargyl alcohol 17 firstly reacts with phosgene and then with phenylselenol to furnish seleno carbonate 18. Treatment of 18 with AIBN initiated cyclization reaction to form α-arylidine-γ-butyrolacton 19 (Scheme 4).

Thebtaranonth and coworkers synthesized the natural compound xylobovide (22) exhibiting antifungal and antibacterial activity, by a retro-Diels-Alder process. Firstly itaconate-antracene derivative 20 was converted into the bislactone 21 then adduct was submitted to FVP (flash vacuum pyrolysis) to afford xylobovide (22) (Scheme 5).\textsuperscript{113}

An efficient and straightforward way to synthesize γ-butyrolacton is a Baeyer-Villiger oxidation on cyclobutanone derivative 23. Cyclobutanone derivative 23 was
treated with acetic anhydride in pyridine to give the corresponding acetate followed
by the reaction with tert-butyl hydroperoxide to generate γ-butyrolacton derivative
24 (Scheme 6).\textsuperscript{114}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {23};
\node (b) at (3,0) {24};
\node (c) at (0,1) {};\node (d) at (3,1) {};
\draw[->] (a) to node[above] {a. Ac\textsubscript{2}O, Py.} (b);
\draw[->] (b) to node[above] {b. t-BuOOH/NaOH} (a);
\end{tikzpicture}
\end{center}

\textbf{Scheme 6}

Design of α-alkylidine-γ-butyrolactons by tandem intramolecular C-H insertions has
increased dramatically in recent years. For example, Shie and Zhu reported that
treatment of cyclohexyl-α-diazo-α-phosphoryl acetate 25 with Rh\textsubscript{2}(OAc)\textsubscript{4} in DCM
gave the γ-butyrolactone derivative 28 which is an insertion/cyclization products
(Scheme 7).\textsuperscript{115}

\begin{center}
\begin{tikzpicture}
\node (a) at (-2,0) {25};
\node (b) at (-2,1) {};\node (c) at (-2,2) {};
\node (d) at (2,1) {};\node (e) at (2,2) {};
\node (f) at (4,1) {};\node (g) at (4,2) {};
\draw[->] (a) to node[above] {cat. Rh(OAc)} (c);
\draw[->] (c) to node[above] {C-H insertion} (e);
\draw[->] (e) to node[above] {two step} (g);
\end{tikzpicture}
\end{center}

\textbf{Scheme 7}

Pd-catalyzed cross-coupling reaction was developed for the formation of the α-
alkylidine-γ-butyrolactons 31 by Larock\textit{ et al.}\textsuperscript{116} For this, α-iodo acrylic acids 29 was
reacted with 1,3-cyclohexadiene (30) in the presence of Pd(OAc)\textsubscript{2} to generate α-
alkylidine-γ-butyrolacton 31 (Scheme 78).\textsuperscript{116}
3.1.2 Claisen Rearrangement

Claisen Rearrangement discovered by Claisen in 1912\textsuperscript{117} is a [3,3] sigmatropic rearrangement of allyl vinyl ethers which utilize the synthesis of \(\gamma,\delta\)-unsaturated carbonyl compounds (Scheme 9).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.3\textwidth]{claisen_rearrangement.png}};
\end{tikzpicture}
\end{center}

Scheme 9

Bergmann et al.\textsuperscript{118} showed that rearrangement of ethyl cinnamyl oxycrotonate \(\text{36}\) obtained by the reaction of cinamyl alcohol \(\text{34}\) with ethyl-3-ethoxytonate \(\text{35}\), was mediated by \(\text{NH}_4\text{Cl}\) at higher temperature to give the Claisen rearrangement product \(\text{37}\) (Scheme 10).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{bergmann_rearrangement.png}};
\end{tikzpicture}
\end{center}

Scheme 10

Hurd and coworker utilized a new method for designing of the starting material \(\text{39}\). Dialyl dimethylketalts \(\text{38}\) was treated with acid, a methylvinyl allyl ether \(\text{39}\) was formed. Heating of \(\text{39}\) gave \(\gamma,\delta\)-unsaturated carbonyl compound \(\text{40}\) (Scheme 11).\textsuperscript{119}
There are different versions of Claisen rearrangement such as Carroll rearrangement, Eschenmoser rearrangement, Johnson rearrangement, Ireland-Claisen rearrangement, Reformatsky-Claisen rearrangement, thio-Claisen rearrangement, aza-Claisen rearrangement, chelate Claisen Rearangement, diosphenol-Claisen rearrangement, metallo-Claisen rearrangement and retro-Claisen rearrangement.

In 1940, M. F. Carroll showed that thermal rearrangement of allyl acetoacetate 41 first formed 43 that underwent decarboxylation to furnish product 45. Claisen rearrangement followed by a decarboxylation is called as the Carroll rearrangement (Scheme 12).  

In 1964, Eschenmoser observed that the reaction of hydroxy-dimethylcyclohex-2-ene derivative 46 with 1,1-dimethoxy N,N-dimethylethan-1-amine gave an unpredictable product 48. In this reaction, firstly N,O-ketene acetals 47 was formed, which was called as the Eshenmoser rearrangement, followed by the formation of γ,δ-unsaturated amide 48 (Scheme 13).
In 1970, Johnson reported that $\gamma,\delta$-unsaturated ester 51 was formed as a result of the rearrangement of ketene acetal 53, prepared by reaction of trimethoxyethane 49 with allylic alcohol 50 (Scheme 14).\textsuperscript{122}

The Ireland-Claisen rearrangement firstly reported in 1972 afforded the synthesis of $\gamma,\delta$-unsaturated carboxylic acid 57 starting from ester 54. The ester 54 was first converted into the corresponding enolate 55 which was trapped with trimethylsilyl chloride to furnish allyl trimethylsilyl keten acetals 56. Upon heating, compound 56 underwent Claisen rearrangement to give product 57 (Scheme 15).\textsuperscript{123}
Reformatsky-Claisen rearrangement is a thermal rearrangement of a zinc enolate 59 generated by the reaction of a α-bromo ester 58 with zinc dust. Heating of 59 furnished γ,δ-unsaturated zinc carboxylate 60 (Scheme 16).

Kwart and Schwartz reported that thermal rearrangement of allyl phenyl sulfide 61 produced thiol 62 that was not isolated. The intermediate 62 underwent a S_N^2 type reaction with starting sulfide 61 under the same reaction conditions to afford diallyl derivative 63. This methodology is called as thio-Claisen rearrangement (Scheme 17).
Jolidon and Hansen discovered the aza-Claisen rearrangement that is a thermal rearrangement of allyl arylamines \( 65 \). This rearrangement required harsh conditions (200-350 °C) than the other Claisen rearrangements. (Scheme 18).

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{H} \\
\text{1} & \quad \text{2} \\
\text{2} & \quad \text{3} \\
\text{3} & \quad \text{1} \\
\end{align*}
\]

\( 65 \) \[\xrightarrow{\Delta, [3,3]}\] \( 66 \) \[\xrightarrow{\text{NH}_2}\] \( 67 \)

**Scheme 18**

[3,3] sigmatropic rearrangement of a chelate enolate is called as chelate Claisen rearrangement. Reaction of a protected amino acid having an allylic group with \( \text{ZnCl}_2 \) in the presence of LDA results in the formation of the intermediate \( 69 \) that undergoes a Claisen rearrangement to form amino acid \( 70 \) (Scheme 19).

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{N} & \quad \text{Cbz} \\
\text{Zn} & \quad \text{O} \\
\text{3} & \quad \text{2} \\
\text{2} & \quad \text{1} \\
\text{1} & \quad \text{2} \\
\text{3} & \quad \text{1} \\
\end{align*}
\]

\( 68 \) \[\xrightarrow{\text{LDA, ZnCl}_2}\] \( 69 \) \[\xrightarrow{\Delta, [3,3]}\] \( 70 \)

**Scheme 19**

In 1980, Ponaras developed an extremely new method, known as Diosphenol-Claisen rearrangement, for the preparation of diosphenol \( 72 \) affording the thermal rearrangement of allyl ether \( 71 \) at 200 °C (Scheme 20).

\[
\begin{align*}
\text{O} & \quad \text{Me} \\
\text{2} & \quad \text{3} \\
\text{3} & \quad \text{O} \\
\text{1} & \quad \text{2} \\
\text{2} & \quad \text{1} \\
\end{align*}
\]

\( 71 \) \[\xrightarrow{\Delta, [3,3]}\] \( 72 \)

**Scheme 20**

Retro-Claisen rearrangement is a general process for a number of substrates including neighbour quarternary centers when the \( \alpha \)-carbonyl substituent is not an
electron-releasing group For example, Rhoads and Cockroft reported the rearrangement of vinylcyclopropane carboxaldehyde 73 leading to formation of 2,5-dihydrooxepin 74 via retro-Claisen reaction (Scheme 21).

![Scheme 21](image)

Gold-catalyzed sigmatropic rearrangements, especially Claisen rearrangements, have attracted intense research in past few decades. He and coworkers achieved the synthesis of dihydrobenzofurane derivative 77 by using gold-catalyzed Claisen rearrangements (Scheme 22).

![Scheme 22](image)

Important synthetic approach for Gold-catalyzed Claisen rearrangements was reported by Toste and coworkers. In the presence of gold(I) and silylacetylene 78, Claisen rearrangements took place to obtain homoallenic alcohol 79 at room temperature (Scheme 23).

![Scheme 23](image)
According to the proposed mechanism for this reaction, firstly gold(I) catalyst coordinates to the alkyne functionality in 80 to generate more electrophilic alkyne which undergoes rearrangement to form cationic dihydropyran intermediate 82. Removal of gold forms allenic aldehyde 83 (Scheme 23).131

![Scheme 24](image)

Gagnè and coworkers reported that allyl aryl ethers 84 was converted to enones 85 in the presence of gold(I) catalyst and under the mild conditions via Claisen rearrangement reaction (Scheme 24).132

![Scheme 25](image)

According to the proposed mechanism, firstly gold(I) catalyst coordinates the double bond in 87 forming a cationic chair like transition state 88. Removal of gold generates enone 89 (Scheme 25).132
3.1.3 Aim of the Study

This part of this thesis focused on the reaction of bicyclic endoperoxides with gold salt because there is no study on this subject in the literature. Our aim was first to synthesize simple structured endoperoxide derived from cyclohexa-1,3-diene (90). So, cyclohexadiene (92) will be synthesized as reported in the literature starting from cyclohexene (90) by bromination with NBS followed by dehydrobromination to form 91. Reaction of cyclohexa-1,3-diene with singlet oxygen will result in the formation of the key compound named 2,3-dioxabicyclo[2.2.2]oct-5-ene (93) via [4+2] addition reaction (Scheme 26).\(^{133}\)

\[ 
\begin{align*}
\text{90} & \xrightarrow{\text{Br}} \text{91} \xrightarrow{} \text{92} \xrightarrow{} \text{2,3-dioxabicyclo[2.2.2]oct-5-ene (93)}
\end{align*}
\]

Scheme 27
Synthesized simple structured endoperoxide 93 will be reacted with alkynes in the presence of Au(L)/AgOTf. The structures of the formed compounds will be determined and the formation mechanism of the products will be discussed. (Scheme 27).

Scheme 28
3.2 RESULTS AND DISCUSSION

Since there is no study in the literature involving the reaction of endoperoxides with gold salt, we decided to examine this reaction. At the beginning of our work, we wanted to study simple structured endoperoxide. So, we decided to synthesize firstly cyclohexa-1,3-diene and then the bicyclic endoperoxide derived from cyclohexa-1,3-diene.

3.2.1 Synthesis of Cyclohexa-1,3-diene (92)

To afford cyclohexa-1,3-diene (92), cyclohexene (90) was firstly treated with N-bromosuccinimide to generate 3-bromocyclohex-1-ene (91) which was distilled in the presence of quinoline to form the desired compound 92 (Scheme 28). The \(^1\)H NMR spectrum (Fig 161 - p. 189) of compound 92 include three signals. Olefinic protons resonate at 5.82-5.76 and 5.72-5.65 ppm as multiplet. Methylene protons resonate at 2.05 ppm as quasi triplet.

![Scheme 29](image)

3.2.2 Photooxygenation of the Cyclohexa-1,3-diene (92)

Tetraphenylporphyrin sensitized photooxygenation of cyclohexa-1,3-diene (92) in methylene chloride at room temperature for 18 h produced endoperoxide 93 (Scheme 29).

In the \(^1\)H NMR spectrum (Fig 163 - p. 190) of 92, two olefinic protons give multiplet at 6.62-6.57 ppm. Two bridgehead protons resonate at 4.60-4.55 ppm as a broad multiplet. Methylene protons resonate as an AB-systems.
3.2.3 Reaction of Endoperoxide (93) with Alkyne Derivatives in Presence of Au(L)/AgOTf

After synthesis of key compound 93, 2,3-dioxabicyclo[2.2.2]oct-5-ene, we treated endoperoxide 93 with alkyne derivatives 94 in the presence of Au(L)/AgOTf then we obtained new products 95 (Scheme 30).

The structures of 95 a-f were determined by 1D and 2D (DEPT, COSY, HSQC and HMBC) NMR spectral data. In the $^1$H NMR spectrum (Fig 165 - p. 191) of 95a, methine protons H-7a, H-3a and H-3 resonate at 4.64, 2.64-2.61 and 2.26, respectively. Olefinic protons resonate at 5.78 ppm as doublet of doublets of triplets ($J = 9.9, 3.9$ and $1.8$ Hz) and 5.50 ppm as doublet of doublets of doublets ($J = 9.9, 3.7$ and $1.9$ Hz).

In the $^{13}$C NMR spectrum (Fig 166 - p. 192) a new carbonyl carbon was formed which resonates at 178.1 ppm. Furthermore, new formed olefinic carbons resonate at 127.3 and 125.0 ppm, respectively. The other signals of $^{13}$C NMR spectrum were in accordance with the proposed structure.
HMBC spectrum has important correlations supporting the proposed structure. In the HMBC spectrum, we focused on the correlations of methine proton (H-3) with the carbon atoms. As expected, there are correlations between the H-3 and the carbons C-2, C-4, C-7a, C-3a, and C-8 or C-9. These correlations support the proposed structure (Figure 1).

The NMR spectra of the other derivatives 95b-95f were also in agreement with the proposed structures.

![Figure 1: HMBC Spectrum of Compound 95a](image)

For this transformation we suggest the following reaction mechanism. We assume that endoperoxide 93 first undergoes an isomerization reaction to form hydroxyenone 96. We proved that Au(I) salt catalyzes this transformation. We did two different experiments to prove this transformation. Endoperoxide 93 was heated at the reflux temperature of toluene in the presence of Au(L)/AgOTf and in the absence of Au(L)/AgOTf. Hydroxy enone 96 was formed when the experiment was carried out in the presence of Au(L)/AgOTf catalysis. However, epoxy ketone 102 was formed in the absence of Au(L)/AgOTf catalyst (Sheme 32). Hydroxyl group of enone 96 can attack the alkyne complex formed by interaction of alkyne unit with Au1+ to
form an allylvinyl ether 98 as the intermediate. The formed compound 98 has a suitable structure to undergo a [3,3] sigmatropic Claisen rearrangement to form the corresponding γ,δ-unsaturated dicarbonyl compound 99. Ketone carbonyl unit can attack the activated aldehyde carbonyl unit in 100 to generate 101 which has tendency for 1,3-hydrogen shift to form target compound 95 (Scheme 31).

Scheme 32

We tested five different catalyst in our reaction. Unfortunately, there was no reaction when the reaction was conducted with AuCl₃, AuCl, and N-heterocyclic carbene (NHC) complex of Au(I) and AgOTf in toluene. But, reaction with Au(L)/AgOTf gave product 95d after 18 h in 66% yield.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>AuCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
<td>18 h heat</td>
<td>no reaction</td>
</tr>
<tr>
<td>2.</td>
<td>AuCl</td>
<td>toluene</td>
<td>18 h heat</td>
<td>no reaction</td>
</tr>
<tr>
<td>3.</td>
<td>Au(L)</td>
<td>toluene</td>
<td>18 h heat</td>
<td>no reaction</td>
</tr>
<tr>
<td>4.</td>
<td>AgOTf</td>
<td>toluene</td>
<td>18 h heat</td>
<td>no reaction</td>
</tr>
<tr>
<td>5.</td>
<td>Au(L)/AgOTf</td>
<td>toluene</td>
<td>18 h heat</td>
<td>66%</td>
</tr>
</tbody>
</table>

Figure 2: Catalyst Screening on the Cyclization Reaction of 95d
The oxidative free radical cyclization reaction is an important reaction because of fascinating regiochemistry and controversial reaction mechanism. We combined this radical cyclization with photoxygenation reaction and obtained very interesting results in terms of mechanistic studies.

Scheme 1

First we synthesized dihydrocyclohepta[b]furan derivatives 130 by the reaction of cycloheptatriene (111) with various 1,3-dicarbonyl compounds 137. On the other hand, when cycloheptatriene (111) was reacted with cyclic 1,3-diketone 139, we observed two different ring closure products 140 and 141 (Scheme 1).

We performed three different reactions with dihydrocyclohepta[b]furan derivatives 130. Photoxygenation of dihydrocyclohepta[b]furan derivatives 130 gave
endoperoxide derivatives 131. Furthermore, when we increased the reaction time of photooxygenation of dihydrocyclohepta[b]furan derivatives 130, surprisingly, we obtained dicarbonyl compounds 132 where dihydrofuran ring underwent a cleavage reaction. However, the peroxide linkage was intact. Finally, oxidation reaction of dihydrocyclohepta[b]furan derivatives 130 with SeO₂ resulted in the formation of tropone derivatives 133 (Scheme 1).

![Scheme 2]

Endoperoxide 131a was reacted with CoTPP, AuCl₃, and NEt₃. Reaction of endoperoxide 131a with CoTPP afforded bisepoxide 153 where the dihydrofuran ring underwent a ring-opening reaction. On the other hand, reaction of 131a with AuCl₃ in the presence of oxygen caused an oxidative ring-opening reaction of the five-membered ring. The endoperoxide unit was intact against the AuCl₃. Reaction of endoperoxide with triethyl amine afforded compound 160. We assume that the expected product α,β-unsaturated enone 157 was formed as the intermediate which was transformed into 160 under the reaction conditions. Furthermore, we assume that the suitable conformation of this intermediate was responsible for this transformation (Scheme 2).
In the second part, we synthesized pyrrolo-pyrazino-pyrrole derivatives. Pyrazines ring is an important heterocycle compound due to its various biological activities.

In the first step, we synthesized 2,2’-(1’-pyrrolinyl)pyrrole (70) from the reaction of pyrrole (69) and 2-pyrrolidinone (74). Then, 2,2’-(1’-pyrrolinyl)pyrrole (70) was reacted with propargyl bromide derivatives to generate propargylated compounds 71. 1-Prop-2-ynyl-4’,5’-dihydro-1H,3’H-2,2’-bipyrrrole (71a) was derivatized via Sonogashira cross-coupling reaction. Propargylated compounds 71 and their derivatives 79 were reacted with Pd/C to form the target compounds, pyrrolo-pyrazino-pyrrole derivatives 73 and 80 (Scheme 3).

Scheme 3

In the third part, we developed a new methodology for the synthesis of α-alkylidine-γ-butyrolacton derivatives. Endoperoxide 93 was reacted with alkyne derivatives in the presence of Au(L)/AgOTf and we obtained unexpected product, α-alkylidine-γ-butyrolacton derivatives 95. Au\(^{+1}\) plays an important role in this reaction. We assume
that Au$^{+1}$ catalyzes thermal isomerization of endoperoxide 93 to give enone 96 as an intermediate that adds to the activated alkyne unit to form 98. This product 98 contains an allyl vinyl ether which is suitable for a [3,3]-sigmatropic rearrangement to give dicarbonyl compound 99. Cyclization of dicarbonyl compound results in the formation of the final product 95 (Scheme 4).

Scheme 4
CHAPTER 5

EXPERIMENTAL

5.1 General

\(^1\)H-NMR and \(^{13}\)C-NMR spectrums were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in CDCl\(_3\), CD\(_3\)OD, DMSO-\(d_6\), and with TMS as internal reference. Chemical shifts (\(\delta\)) were reported in units parts per million (ppm). Spin multiplicities were specified as singlet (s), broad singlet (bs), doublet (d), broad doublet (bd), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), doublet of doublets of doublets (ddd), triplet (t), triplet of doublets (td), quintet (quint), quasi triplet (quasi t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

HRMS data were recorded by Agilent Technologies, 6224 TOF LC/MS-T1200 Series applying the electrospray technique. GC-MS data were recorded by Agilent Technology 7890A using Agilent J&W GC HP-5MS, 30 m x 0.2500 mm x 0.25 \(\mu\)m (190915-433:325 °C)

Infrared spectra were recorded on a Bruker Platinum ATR FT-IR spectrometer in the range of 600-4000 cm\(^{-1}\).

Melting points were reported by operating Gallenkamp electronic melting point apparatus.

Column chromatography separations were done by using 60-mesh silica gel. Thin layer chromatography (TLC) was performed by using 0.20 mm silica gel 60 F254 aluminum plates.

Names of the compounds were established by using ACD/NMR.
All solvents and chemicals were commercially available and used without further purification.

5.2. 1-[(3aS,8aS)-2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-yl]ethanone (130a)

To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added acetyl aceton 147a (1.00 g, 10 mmol) and then the reaction mixture was cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise in 45 minutes and the solution was stirred for 75 minutes. After completion of reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:4) to give 1-[(3aS,8aS)-2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-yl]ethanone (130a) (1.81 g, 9.52 mmol, 95%) as a colorless oil.

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta: 6.21-6.12 (m, H}_5\text{ and H}_8\text{), 6.05 (ddd, J = 12.0, 5.4, and 1.1 Hz, H}_7\text{), 5.97 (ddd, J = 10.1, 5.4, and 1.2 Hz, H}_6\text{), 5.01 (bd, J = 8.7, H}_8\text{a), 3.27 (bt, J = 10.1 Hz, H}_3\text{a), 2.35-2.29 (m, H}_4\text{), 2.28 (s, CH}_3\text{), 2.24 (s, CH}_3\text{), 2.03 (ddd, J = 16.2, 9.0, 5.3, and 2.0 Hz, H}_4\text{). \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)} \delta 193.6, 167.1, 134.6, 129.8, 127.2, 126.9, 118.2, 84.6, 51.8, 30.0, 29.1, 15.3. IR (ATR, cm\textsuperscript{-1}) 1716, 1609, 1393, 1340, 1217, 1204, 1203, 1066, 1027, 946, 900, 710; HRMS Calcd for (C\textsubscript{12}H\textsubscript{14}O\textsubscript{2}) [M + H]\textsuperscript{+}: 191.1066; Found: 191.1065.\]

5.3 Methyl(3aS,8aS)-2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130b)

To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added methyl acetoacetate 147b (1.16 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was
washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:1) to give methyl (3aS,8aS)-2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130b) (1.78 g, 8.64 mmol, 86%) as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ 6.19-6.11 (m, H₅ and H₈), 6.02 (ddd, J = 11.9, 5.4, and 1.1 Hz, H₇), 5.98-5.93 (m, H₆), 5.03 (bd, J = 8.9 Hz, H₈a), 3.73 (s, O-CH₃), 3.22 (bt, J = 10.1 Hz, H₃a), 2.38 (ddd, J = 13.3, 8.3, and 1.5 Hz, H₄), 2.20 (s, CH₃), 2.03 (dddd, J = 13.3, 9.5, 5.5, and 1.8 Hz, H₄). **13C NMR** (100 MHz, CDCl₃) δ 167.7, 166.1, 134.5, 130.2, 126.9 (2C), 106.6, 84.5, 51.7, 50.7, 29.8, 14.1. **IR (ATR, cm⁻¹)** 3019, 2161, 1980, 1730, 1435, 1279, 1045, 928, 725, 668; **HRMS** Calcd for (C₁₂H₁₄O₃) [M + H]⁺: 207.1015; Found: 207.1006.

### 5.4 Ethyl (3aS,8aS)-2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130c)

To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added ethyl acetoacetate 147c (1.3 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:1) to give ethyl (3aS,8aS)-2-methyl-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130c) (1.63 g, 7.4 mmol, 74%) as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ 6.19-6.11 (m, H₅ and H₈), 6.00 (bdd, J = 11.5 and 5.5 Hz, H₇), 5.95 (bdd, J = 10.1 and 5.5 Hz, H₆), 5.02 (bd, J = 8.9 Hz, H₈a), 4.18 (m, CH₂), 3.22 (bt, J = 10.1 Hz, H₃a), 2.40 (dd, J = 13.2 and 8.3 Hz, H₄), 2.20 (s, CH₃), 2.01 (dt, J = 13.2 and 4.8 Hz, H₄), 1.3 (t, J = 7.1 Hz, CH₃). **13C NMR** (100 MHz, CDCl₃) δ 167.1, 165.4, 134.4, 130.3 126.9, 126.8, 106.7,
To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added ethyl acetoacetate 147d (1.74 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:4) to give methyl (3aS,8aS)-2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130d) (1.81 g, 6.85 mmol, 68%) as a colorless oil.

\[ \text{IR (ATR, cm}^{-1}) \quad 2977, 1690, 1638, 1439, 1380, 1340, 1312, 1199, 1102, 1076, 975, 905, 771; \]

\[ \text{HRMS Calcd for (C}_{13}\text{H}_{16}\text{O}_{3}) [M + H]^+: 221.1172; \text{ Found: 221.1165}. \]

5.5 Methyl (3aS,8aS)-2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130d)

To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added ethyl acetoacetate 147d (1.74 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:4) to give methyl (3aS,8aS)-2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3aH-cyclohepta[b]furan-3-carboxylate (130d) (1.81 g, 6.85 mmol, 68%) as a colorless oil.

\[ \text{IR (ATR, cm}^{-1}) \quad 2977, 1690, 1638, 1439, 1380, 1340, 1312, 1199, 1102, 1076, 975, 905, 771; \]

\[ \text{HRMS Calcd for (C}_{13}\text{H}_{16}\text{O}_{3}) [M + H]^+: 221.1172; \text{ Found: 221.1165}. \]

5.6 (2S,7R)-7,9,10,11-tetrahydro-2,7-methano-1-benzo[8(2H)-one (140a) and (5aR,10aR)-2,3,4,5a,10,10a-hexahydro-1H-benzo[b]cyclohepta[d]furan-1-one (141a)
To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added 1,3-cyclohexanadione (139a) (1.12 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:1) to give (2S,7R)-7,9,10,11-tetrahydro-2,7-methano-1-benzoxonin-8(2H)-one (140a) (0.65 g, 3.2 mmol, 32%) as a light yellow colored solid from CH₂Cl₂/n-hexane, Mp: 71-73 °C and (5aR,10aR)-2,3,4,5a,10,10a-hexahydro-1H-benzo[b]cyclohepta[d]furan-1-one (141a) (0.78 g, 3.86 mmol, 38%) as a light yellow colored solid from CH₂Cl₂/n-hexane, Mp: 87-89 °C.

**1H NMR** (400 MHz, CDCl₃) δ 6.39 (dd, J = 10.7 and 8.7 Hz, H₄), 5.95 (ddd, J = 11.8, 7.3, and 0.6 Hz, H₆), 5.79 (dd, J = 11.8 and 6.3 Hz, H₇), 5.68 (dd, J = 10.7 and 7.3 Hz, H₅), 4.92 (ddt, J = 5.9, 4.2, and 2.0 Hz, H₇a), 3.39 (bt, J = 6.3 Hz, H₃a), 2.32-2.13 (m, 5H), 1.87-1.80 (m). **13C NMR** (100 MHz, CDCl₃) δ 197.5, 169.9, 139.1, 129.6, 128.8, 123.2, 114.5, 72.4, 36.7, 28.4, 28.3, 27.4, 20.6. IR (ATR, cm⁻¹) 3018, 1606, 1386, 1214, 725, 668; HRMS Calcd for (C₁₃H₁₄O₂) [M + H]^+ : 203.1066; Found: 203.1069.

**1H NMR** (400 MHz, CDCl₃) δ 6.16 (m, H₅ and H₈), 5.97 (ddd, J = 11.4, 5.4, and 2.0 Hz, H₇), 5.90 (ddd, J = 10.4, 5.4, and 1.1 Hz, H₆), 5.12 (bd, J = 9.3 Hz, H₈a), 3.37 (bt, J = 9.9 Hz, H₃a), 2.45 (ddd, J = 13.4, 8.2, and 2.1 Hz, H₄), 2.41-2.34 (m, 2H), 2.30-2.24 (m, 2H), 2.0-1.95 (m, 2H), 1.87 (ddd, J = 13.4, 5.0, and 2.1 Hz, H₄). **13C NMR** (100 MHz, CDCl₃) δ 194.2, 175.0, 133.8, 129.2, 126.4, 126.1, 116.2, 86.3, 49.3, 35.7, 28.5, 22.8, 20.6. IR (ATR, cm⁻¹) 1967, 1722, 1615, 1393, 1216, 1066, 725, 668; HRMS Calcd for (C₁₃H₁₄O₂) [M + H]^+ : 203.1066; Found: 203.1061.
To a solution of cycloheptatriene (111) (0.92 g, 10 mmol) in MeOH (50 mL) was added dimedone (139b) (1.4 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:2) to give (2S,7R)-10,10-dimethyl-7,9,10,11-tetrahydro-2,7-methano-1-benzoxonin-8(2H)-one (140b) (0.68 g, 2.95 mmol, 29%) as a light white colored solid from CH₂Cl₂/n-hexane, Mp: 83-85 °C and (5aR,10aR)-3,3-dimethyl-2,3,4,5a,10,10a-hexahydro-1H-benzo[b]cyclohepta[d]furan-1-one (141b) (0.75 g, 3.26 mmol, 32%) as a white colored solid from CH₂Cl₂/n-hexane, Mp: 65-68 °C.

**1H NMR** (400 MHz, CDCl₃) δ 6.44 (bt, J = 10.5 Hz, H₄), 6.0 (dd, J = 11.8 and 6.2 Hz, H₆), 5.87 (dd, J = 11.8 and 6.1 Hz, H₇), 5.77 (dd, J = 11.0 and 6.2 Hz, H₅), 5.03-4.95 (m, H₇a), 3.47 (bt, J = 6.2 Hz, H₃a), 2.28-2.22 (m, CH₂(10), H₈), 2.21-2.18 (m, CH₂(2a)), 1.93 (dd, J = 16.0 and 1.1 Hz, H₅), 1.02 (s, CH₃), 1.0 (s, CH₃). **13C NMR** (100 MHz, CDCl₃) δ 196.7, 168.1, 138.8, 129.3, 129.0, 123.1, 113.0, 72.2, 50.4, 42.1, 31.8, 28.8, 27.9, 27.5, 27.3. **IR** (ATR, cm⁻¹) 2987, 2900, 2834, 2160, 2017, 1977, 1650, 1616, 1378, 1082, 1066, 1056; **HRMS** Calcd for (C₁₅H₁₈O₂) [M + H]⁺: 231.1379; Found: 231.1386.

**1H NMR** (400 MHz, CDCl₃) δ 6.15-6.08 (m, H₅ and H₈), 5.98 (ddd, J = 12.0, 5.4 and 1.7 Hz, H₇), 5.90 (ddd, J = 10.4, 5.4 and 1.1 Hz, H₆), 5.13 (bd, J = 9.1 Hz, H₈a), 3.36 (bt, J = 10.2 Hz, H₃a), 2.45 (ddd, J = 13.4, 8.4 and 2.0 Hz, H₃), 2.23 (s, CH₂(10)), 2.23 (d, J = 10.2 Hz, CH₂(2a)), 1.88 (ddt, J = 13.4, 5.3, and 1.8 Hz, H₄), 1.05 (s, CH₃), 1.02 (s, CH₃). **13C NMR** (100 MHz, CDCl₃) δ 194.2, 175.0, 133.8, 129.2, 126.4, 126.1, 116.2, 86.3, 50.4, 42.1, 31.8, 28.8, 27.9, 27.5, 27.3. **IR** (ATR, cm⁻¹) 2968, 2900, 2834, 2160, 2017, 1977,
1697, 1614, 1455, 1394, 1255, 1049; HRMS Calcd for (C_{13}H_{18}O_{2}) [M + H]^+: 231.1379; Found: 231.1385.

5.8 1-[(3aR,5S,8S,8aR)-2-Methyl-4,8a-dihydro-3aH-5,8-epidioxycyclohepta[b]furan-3-yl]ethanone (131a)

Dihydro cyclohepta[b]furan derivative 130a (0.380 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in CH_{2}Cl_{2} (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (2:1) to give 1-[(3aR,5S,8S,8aR)-2-methyl-4,8a-dihydro-3aH-5,8-epidioxycyclohepta[b]furan-3-yl]ethanone (131a) (0.351 g, 79%) as a colorless oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{) } \delta \text{, } 6.57 (dd, A-part of AB-system, } J = 9.10 \text{ and } 7.1 \text{ Hz, H}_3\text{), } 6.47 (dd, B-part of AB-system, } J = 9.10 \text{ and } 6.8 \text{ Hz, H}_3\text{), } 5.12-5.08 (m, H_{2a})\text{, } 5.07 (bt, } J = 4.9 \text{ Hz, H}_{8a}\text{, } 4.64 (t, } J = 6.8 \text{ Hz, H}_{4a}\text{), } 2.53 (quintet, } J = 6.4 \text{ Hz, H}_{5a}\text{), } 2.11 (ddt, } J = 15.5 \text{ and } 12.8 \text{ Hz, H}_5\text{), } 1.65 (dd, } J = 15.5 \text{ and } 6.7 \text{ Hz, H}_3\text{), } 1.59 (s, CH}_3\text{). \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{) } \delta \text{, } 192.6\text{, } 168.4\text{, } 134.2\text{, } 124.4\text{, } 118.8\text{, } 84.5\text{, } 76.2\text{, } 73.8\text{, } 38.2\text{, } 35.4\text{, } 28.2\text{, } 14.8\text{. IR (ATR, } \text{cm}^{-1}\text{) } 2988\text{, } 2900\text{, } 1732\text{, } 1715\text{, } 1698\text{, } 1624\text{, } 1416\text{, } 1375\text{, } 1229\text{, } 1188\text{, } 1148\text{, } 1065\text{; } 705\text{, } 666\text{, } 641\text{, } 619 \text{ HRMS Calcd for (C}_{12}\text{H}_{14}\text{O}_4\text{) [M + H]}^+: 223.0964; \text{ Found: } 223.0961. \]

5.9 Methyl (3aR,5S,8S,8aR)-2-methyl-4,8a-dihydro-3aH-5,8-epidioxycyclohepta[b]furan-3-carboxylate (131b)

Dihydro cyclohepta[b]furan derivative 130b (0.412 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in CH_{2}Cl_{2} (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give methyl (3aR,5S,8S,8aR)-2-
methyl-4,8a-dihydro-3aH-5,8-epidioxycyclohepta[b]furan-3-carboxylate  \( \text{(131b)} \) (0.365 g, 76%) as a colorless oil.

**1H NMR** (400 MHz, CDCl\(_3\)) \( \delta \) 6.71 (dd, A-part of AB-system, \( J = 9.1 \) and 7.1 Hz, H\(_3\)), 6.42 (ddd, B-part of AB-system, \( J = 9.1, 6.8 \) and 0.9 Hz, H\(_4\)), 5.09 (dt, \( J = 6.5 \) and 2.3 Hz, H\(_{2a}\)), 4.96 (bt, \( J = 6.3 \) Hz, H\(_{4a}\)), 4.66 (dd, \( J = 9.1 \) and 2.8 Hz, H\(_{8a}\)), 3.75 (s, OCH\(_3\)), 3.14 (br, \( J = 9.2 \) Hz, H\(_{5a}\)), 2.70 (ddd, \( J = 14.2, 7.7 \), and 6.4 Hz, H\(_5\)), 2.23 (s, CH\(_3\)), 2.20-2.14 (m, H\(_5\)).

**13C NMR** (100 MHz, CDCl\(_3\)) \( \delta \) 170.2, 166.1, 135.1, 125.5, 107.9, 85.6, 77.2, 74.9, 50.8, 38.7, 36.5, 14.5. IR (ATR, cm\(^{-1}\)) 3023, 2953,
Methyl (3aR,5S,8S,8aR)- 2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3aH-5,8-epidioxycyclohept[a]furan-3-carboxylate (131d)

Dihydro cyclohepta[b]furan derivative 130d (0.530 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in CH₂Cl₂ (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give methyl (3aR,5S,8S,8aR)-2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3aH-5,8-epidioxycyclohept[a]furan-3-carboxylate (131d) (0.394 g, 66%) as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ 6.73 (dd, A-part of AB-system, J = 9.3 and 7.0 Hz, H₃), 6.43 (ddd, B-part of AB-system, J = 9.3, 6.8 and 0.9 Hz, H₄), 5.11 (dt, J = 6.8 and 2.0 Hz, H₈), 4.79 (dd, J = 9.2 and 2.8 Hz, H₈a), 4.70 (bt, J = 6.5 Hz, H₄a), 4.03 (d, A-part of AB-system, J = 16.5 Hz, H₁₂), 3.73 (s, OCH₃), 3.71 (s, OCH₃), 3.50 (d, B-part of AB-system, J = 16.5 Hz, H₁₂), 3.22 (q, J = 8.8 Hz, H₅a), 2.70 (ddd, J = 15.5, 7.7, and 6.5 Hz, H₃), 2.25 (dd, J = 15.5 and 10.5 Hz, H₅). **13C NMR** (100 MHz, CDCl₃) δ 168.6, 165.3, 164.9, 135.2, 125.4, 110.4, 86.3, 77.1, 74.7, 52.4, 51.1, 38.6, 36.3, 34.2. **IR** (ATR, cm⁻¹) 2988, 2900, 2159, 2017, 1978, 1743, 1705, 1632, 1435, 1373, 1327, 1194, 1124, 1053; **HRMS** Calcd for (C₁₄H₁₆O₅) [M + H]^+ : 297.0979; Found: 297.0973.

1-[(1S,5S)-6,7-Dioxabicyclo[3.2.2]nona-2,8-dien-3-yl]propane-1,2-dione (132a)

Dihydro cyclohepta[b]furan derivative 130a (0.380 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in 50 mL of CH₂Cl₂ in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 96 h while the dry oxygen was bubbled through the
solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give 1-[(15,5S)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl]propane-1,2-dione (132a) (0.320 g, 82%) as a colorless oil.

\[ \text{1H NMR} \quad (400 \text{ MHz, CDCl}_3) \delta 7.32 (bd, J = 6.8, H_7), 6.73 (bdt, J = 8.9 and 0.9 Hz, H_3), 6.51 (dt, J = 8.7 and 1.0 Hz, H_4), 5.02-4.94 (m, H_{2a} and H_{4a}), 3.13 (ddd, A-part of AB-system, J = 19.4, 7.04 and 2.0 Hz, H_5), 2.70 (dt, B-part of AB-system, J = 19.4 and 1.3 Hz, H_3), 2.4 (s, CH_3).

\[ \text{13C NMR} \quad (100 \text{ MHz, CDCl}_3) \delta 200.1, 193.3, 146.5, 136.6, 131.8, 128.5, 75.0, 72.3, 33.2, 26.6. \]

\[ \text{IR} \quad (\text{ATR, cm}^{-1}) \quad 2159, 2017, 1978, 1743, 1705, 1632, 1435, 1373, 1327, 1254, 1194, 1124, 1084, 1053, 582; \text{HRMS} \quad \text{Calcd for (C}_{10}\text{H}_{10}\text{O}_4)[M + H]^+: 195.0651; \text{Found:} \quad 195.0658. \]

5.13 Methyl (15,5S)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (132b)

Dihydro cyclohepta[b]furan derivative 130b (0.412 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in 50 mL of CH_2Cl_2 in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 96 h while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give methyl (1S,5S)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (132b) (0.331 g, 78%) as a colorless oil.

\[ \text{1H NMR} \quad (400 \text{ MHz, CDCl}_3) \delta 7.32 (dt, J = 6.8 and 1.6 Hz, H_7), 6.73 (bddd, J = 8.6 and 1.1 Hz, H_3), 6.51 (ddd, J = 8.6, 7.4 and 1.0 Hz, H_4), 5.02-4.95 (m, H_{2a} and H_{4a}), 3.90 (s, OCH_3), 3.14 (ddd, A-part of AB-system, J = 19.3, 4.5 and 1.8 Hz, H_3), 2.74 (dt, B-part of AB-system, J = 19.3 and 1.3 Hz, H_3). \]

\[ \text{13C NMR} \quad (100 \text{ MHz, CDCl}_3) \delta 193.2, 187.6, 146.6, 137.8, 131.6, 128.6, 74.9, 72.2, 52.8, 33.0. \]

\[ \text{IR} \quad (\text{ATR, cm}^{-1}) \quad 2988, 2900, 2833, 2159, 2017, 1977, 1867, 1688, 1680, 1540, 1521, 1457. \]
5.14 Ethyl (1S,5S)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (132c)
Dihydro cyclohepta[b]furan derivative 130c (0.440 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in 50 mL of CH₂Cl₂ in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 96 h while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give ethyl (1S,5S)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (132c) (0.312 g, 69%) as a colorless oil.

![132c](image)

**1H NMR** (400 MHz, CDCl₃) δ 7.30 (d, J = 6.7 Hz, H₇), 6.73 (bt, J = 8.8, H₃), 6.51 (bt, J = 8.6 Hz, H₄), 5.05-4.95 (m, H₂a and H₄a), 4.35 (dd, J= 7.2 and 2.0 Hz, CH₂(11)), 3.14 (ddd, A-part of AB-system, J = 19.4, 4.9 and 1.9 Hz, H₅), 2.73 (dd, B-part of AB-system, J = 19.4 and 1.9 Hz, H₃), 1.37 (t, J = 7.2 Hz, CH₃). **13C NMR** (100 MHz, CDCl₃) δ 188.0, 163.4, 146.4, 137.8, 131.6, 128.6, 74.9, 72.2, 74.9, 72.2, 62.4, 33.0, 14.1. **IR** (ATR, cm⁻¹) 2988, 2900, 2160, 2030, 1978, 1769, 1716, 1682, 1594, 1540, 1476, 1424, 1267, 1148, 1215, 1066;

5.15 3-Acetyl-4H-cyclohepta[b]furan-4-one (133a)
To a solution of dihydro cyclohepta[b]furan derivative 130a (0.380 g, 2 mmol) in anisole (15 mL) was added SeO₂ (0.888 g, 8 mmol) and the reaction mixture was heated at the reflux temperature for 18 h. After completion of the reaction, the mixture was cooled, filtered and evaporated. The residue was chromatographed on silica gel (45 g), eluting with ethyl acetate/hexane (4:1) to give 3-acetyl-4H-cyclohepta[b]furan-4-one (133a) (0.276 g, 73%) as a light yellow colored solid from CH₂Cl₂/n-hexane, Mp: 87-89 °C.
1H NMR (400 MHz, CDCl₃) δ 9.14 (d, J = 11.2 Hz, H₅), 7.64 (dd, J = 11.2 and 8.9 Hz, H₆), 7.54-7.49 (m, H₈), 7.52 (s, H₂), 7.36 (ddd, J = 11.5, 8.5 and 4.0 Hz, H₇), 2.58 (s, CH₃).

13C NMR (100 MHz, CDCl₃) δ 195.1, 167.6, 159.2, 153.3, 140.8, 136.5, 135.0, 131.7, 120.1, 103.6, 30.1. IR (ATR, cm⁻¹) 2988, 2900, 2558, 2017, 1977, 1760, 1732, 1657, 1480, 1468, 1416, 1263.1066; HRMS Calcd for (C₁₁H₈O₃) [M + H]^+: 189.0546; Found: 189.0551.

5.16 Methyl 4-oxo-4H-cyclohepta[b]furan-3-carboxylate (133b)

To a solution of dihydro cyclohepta[b]furan derivative 130b (0.412 g, 2 mmol) in anisole (15 mL) was added SeO₂ (0.888 g, 8 mmol) and the reaction mixture was heated at the reflux temperature for 20 h. After the completion of the reaction, the mixture was cooled, filtered and evaporated. The residue was chromatographed on silica gel (45 g), eluting with ethyl acetate/hexane (1:2) to give methyl 4-oxo-4H-cyclohepta[b]furan-3-carboxylate (133b) (0.307 g, 75%) as a light yellow colored solid from CH₂Cl₂/n-hexane, Mp: 84-86 °C.

1H NMR (400 MHz, CDCl₃) δ 8.88 (d, J = 11.3 Hz, H₅), 7.65 (dd, J = 11.3 and 8.5 Hz, H₆), 7.53-7.49 (m, H₈), 7.50 (s, H₂), 7.36 (ddt, J = 12.5, 8.2 and 4.4 Hz, H₇), 3.95 (s, OCH₃). 13C NMR (100 MHz, CDCl₃) δ 165.3, 164.0, 158.7, 154.8, 139.7, 136.1, 134.1, 130.8, 119.3, 96.5, 51.8. IR (ATR, cm⁻¹) 2988, 2900, 2159, 1770, 1747, 1715, 1697, 1537, 1478, 1440, 1268, 1211, 1147, 1065; HRMS Calcd for (C₁₁H₈O₄) [M + H]^+: 205.0495; Found: 205.0502.

5.17 Ethyl 4-oxo-4H-cyclohepta[b]furan-3-carboxylate (133c)

To a solution of dihydro cyclohepta[b]furan derivative 130c (0.440 g, 2 mmol) in anisole (15 mL) was added SeO₂ (0.888 g, 8 mmol) and the reaction mixture was heated at the reflux temperature for 20 h. After the completion of the reaction, the mixture was cooled, filtered and evaporated. The residue was chromatographed on silica gel (45 g), eluting with ethyl acetate/hexane (1:2) to give ethyl 4-oxo-4H-
cyclohepta[b]furan-3-carboxylate (133c) (0.293 g, 67%) as a light yellow colored solid from CH$_2$Cl$_2$/n-hexane, Mp: 91-93 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.85 (d, $J = 11.3$ Hz, H$_5$), 7.62 (dd, $J = 11.3$ and 8.2 Hz, H$_6$), 7.50-7.45 (m, H$_8$), 7.47 (s, H$_2$), 7.36 (ddd, $J = 12.5$, 8.2 and 4.4 Hz, H$_7$), 4.40 (q, $J = 7.1$ Hz, CH$_2$), 1.40 (t, $J = 7.1$ Hz, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.2, 163.6, 158.7, 154.6, 139.4, 135.9, 133.8, 130.7, 118.9, 77.2, 60.7, 14.4. IR (ATR, cm$^{-1}$) 2987, 2900, 2558, 2159, 2017, 1977, 1771, 1732, 1748, 1688, 1681, 1507, 1488, 1473, 1267, 1208, 1065; HRMS Calcd for (C$_{12}$H$_{10}$O$_4$) [M + H]$^+$: 219.0651; Found: 219.0658.

5.18 1-[(1R,2S,4S,8R)-3,9-Dioxatricyclo[6.1.0.0$^{2,4}$]non-6-yl]propane-1,2-dione-5yl acetate (153) and 1-[(1R,2S,4S,8R)-3,9-dioxatricyclo[6.1.0.0$^{2,4}$]non-5-en-6-yl]propane-1,2-dione (134)

To a stirred solution of 0.22 g (1.0 mmol) endoperoxide (131a) in 10 mL of CH$_2$Cl$_2$ at room temperature was added 14.0 mg (0.02 mmol) of CoTPP. The resulting mixture was stirred for 3 h, and the solvent was evaporated to give 1-[(1R,2S,4S,8R)-3,9-dioxatricyclo[6.1.0.0$^{2,4}$]non-6-yl]propane-1,2-dione-5yl acetate (153) (0.195 g, 76%) as a white colored solid Mp: 62-64 °C. When (153) was chromatographed on silica gel (25 g), eluting with ethyl acetate/hexane (1:1) the compound 1-[(1R,2S,4S,8R)-3,9-dioxatricyclo[6.1.0.0$^{2,4}$]non-5-en-6-yl]propane-1,2-dione (134) (0.141 g, 72%) was formed as a light yellow colored oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.46 (dd, $J = 4.7$ and 2.2 Hz, H$_3$), 3.78-3.73 (m, H$_4$), 3.5 (bt $J = 3.1$, Hz, H$_{2a}$), 3.40 (dd, $J = 3.9$ and 2.0 Hz, H$_{1a}$), 3.20-3.17 (m, H$_3a$), 3.16-3.11 (m, H$_5a$), 2.30 (s, CH$_3$), 2.19 (t, $J = 6.7$ Hz, CH$_2$), 1.99 (s, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 197.5, 196.0, 170.3, 69.5, 58.1, 53.8, 51.6, 50.4, 43.3, 24.0, 23.5, 20.8. IR (ATR, cm$^{-1}$) 2988, 2900, 1685, 1637, 1438, 1356, 1333, 1314, 1305, 1299, 1223, 1192, 1161, 1119, 1089, 1039, 1023, 983, 891, 839, 700, 666, 617; HRMS Calcd for (C$_{12}$H$_{14}$O$_6$) [M + H]$^+$: 255.0824; Found: 255.0885.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.86 (dd, $J = 4.2$ and 1.8 Hz, H$_3$), 3.75 (dd, , $J = 4.2$ and 2.3 Hz, H$_{2a}$), 3.62 (t, $J = 4.2$ Hz, H$_{3a}$), 3.17 (dd, $J = 4.1$ and 2.3 Hz, H$_{1a}$), 3.13
(d, J = 6.4 Hz, H₅), 3.01 (ddd, J = 6.4, 4.1 and 2.0 Hz, \( H_{5a} \)), 2.85 (ddd, J = 8.6, 6.4 and 1.79 Hz, H₃), 2.30 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 200.5, 191.8, 114.5, 136.5, 52.8, 52.7, 49.7, 48.1, 26.8, 22.4. IR (ATR, cm⁻¹) 3019, 1715, 1621, 1396, 1214, 1044, 928, 750, 668, 627;

HRMS Calcd for (C₁₀H₁₀O₄) [M + H]⁺: 195.0613; Found: 195.0659.

5.19 \((1R,2R,3S,5R)-3\)-Pyruvoyl-6,7-dioxabicyclo[3.2.2]non-8-en-2-yl acetate (147)

To a stirred solution of 0.22 g (1.0 mmol) endoperoxide (131a) in 5 mL of CH₃Cl at room temperature under an oxygen atmosphere. The resulting mixture was stirred for 24 h, and the solvent was evaporated to give compound (1R,2R,3S,5R)-3-pyruvoyl-6,7-dioxabicyclo[3.2.2]non-8-en-2-yl acetate (147) (0.213 g, 83%) as a white colored solid Mp: 60-62 °C. When 147 was chromatographed on silica gel, eluting with ethyl acetate/hexane gave 132a.

¹H NMR (400 MHz, CDCl₃) δ 6.56-6.45 (m, H₃ and H₄), 5.32 (dt, J = 4.8 and 1.0 Hz, H₇), 4.95 (tt, J = 6.4 and 1.0 Hz, H₂a), 4.81 (dt, J = 6.7 and 1.2 Hz, H₄a), 3.69 (dt, J = 12.6 and 4.8 Hz, H₆), 2.55 (dd, J = 15.6 and 12.6 Hz, H₅), 2.25 (s, CH₃), 1.99 (s, CH₃), 1.95-1.87 (m, H₅). ¹³C NMR (100 MHz, CDCl₃) δ 197.1, 196.7, 170.7, 131.9, 126.9, 75.2, 75.1, 72.7, 42.0, 28.8, 23.6, 20.7. IR (ATR, cm⁻¹) 2988, 2900, 2884, 1716, 1507, 1405, 1216, 1074, 1066, 1057, 1027, 1016, 891, 668, 625, 601.; HRMS Calcd for (C₁₂H₁₄O₆) [M + H]⁺: 255.0824; Found: 255.0890.

5.20 \((1aS,7bS)-5\)-acetyl-6-methyl-1a,2,4,4a,7a,7b-hexahydro-3H-oxireno[6,7]cyclohepta[1,2-b]furan-3-one (160):

A solution of triethylamine (45 mg, 0.44 mmol) in 25 mL of CHCl₃ was added to a stirred solution of 0.22 g (1.0 mmol) endoperoxide (131a) in 50 mL of CHCl₃ at 0 °C dropwise over 15 min. The resulting mixture was stirred for 8 h at room temperature, and the solvent was evaporated to give compound \((1aS,7bS)-5\)-acetyl-6-methyl-1a,2,4,4a,7a,7b-hexahydro-3H-oxireno[6,7]cyclohepta[1,2-b]furan-3-one (160) (0.181 g, 81%) as a yellow colored solid from EtOAc/n-hexane, Mp: 85-87 °C.
**1H NMR** (400 MHz, CDCl₃) δ 5.38 (d, J = 2.1 Hz, H₇a), 4.79 (dt, J = 5.5 and 2.3 Hz, H₁a), 4.55 (dd, J = 7.8 and 5.8 Hz, H₂a), 3.13 (ddd, J = 16.1, 7.9 and 1.2 Hz, H₂), 2.84-2.78 (m, H₂ and CH₂(4)), 2.76-2.71 (m, H₄a), 2.09 (s, CH₃), 1.43 (s, CH₃). **13C NMR** (100 MHz, CDCl₃) δ 2019, 197.3, 169.3, 104.2, 76.7, 72.6, 70.9, 45.0, 44.0, 42.5, 19.9, 15.1.

### 5.21 2,2'-(1'-Pyrrolinyl)pyrrole (70)

Phosphoryl chloride (4.2 mL, 45.0 mmol) was added over a period of 1 h to pyrrole (15.6 mL, 225 mmol) under nitrogen and cooled in an ice bath. To that solution, 2-pyrrolidinone (74) (3.9 mL, 51.0 mmol) was added over a period of 2 h under nitrogen and cooled in an ice bath. After the addition was complete, the viscous, amber solution was allowed to warm to room temperature. CHCl₃ (25 mL) was added and the solution was transferred to a flask containing water (100 mL) and sodium acetate (40.0 g) cooled in an ice bath. The pH of the turbid, orange solution was adjusted to ~10 with aq KOH (~20 mL, 10 M). The organic layer was separated and saved. The aqueous layer was extracted three times with CHCl₃ (~25 mL). The organic extracts were combined with the saved organic layer, and extracted five times with aq. HCl (50 mL, 0.5 M). The pH of each aq. extract was adjusted to ~10 with aq KOH (10 M) to produce a yellow/orange precipitate. The aq. extracts with the precipitate were combined and extracted four times with CHCl₃ (100 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated to dryness to afford a light orange waxy solid. Crude product 70 was purified by sublimation at 80 °C (100 mTorr) to afford 4.7 g of a white powder. Crystallization from ethanol afforded (70) as white crystals (3.6 g, 66%), Mp 162-163 °C.

**1H NMR** (400 MHz, CDCl₃) δ 6.93 (dd, J = 2.4 and 1.1 Hz, H₅), 6.54 (dd, J = 3.5 and 1.1 Hz, H₃), 6.21 (dd, J = 3.5 and 2.4 Hz, H₄), 4.02 (bt, J = 7.0, Hz, CH₂(8)), 2.90 (tt, J = 8.2, 1.4 Hz, CH₂(10)), 2.00 (quintet, J = 8.2 Hz, CH₂(9)). **13C NMR** (100 MHz, CDCl₃) δ 166.5, 127.8, 122.2, 113.2, 109.1, 60.5, 35.0, 22.7.
5.22 1-Prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (71a)

To a solution of 2,2'-(1'‐pyrrolinyl)pyrrole (70) (0.201 g, 1.5 mmol) in dry DMF (5 mL) was added NaH (0.040 g, 1.7 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 0.5 h. To this solution was added propargyl bromide (0.178 g, 1.5 mmol) drop wise, and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (controlled by TLC), water (5 mL) was added, and the solution was extracted with ethyl acetate 6 times. The combined organic extracts were dried over MgSO₄. The solvent was evaporated to give the crude product, which was purified by column chromatography eluting with EtOAc/hexane (1:4) to give final product 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (71a) (0.201 g, 77%) as a light yellow colored oil.

1H NMR (400 MHz, CDCl₃) δ 7.06 (bddd, J = 2.5 and 1.6 Hz, H₂), 6.50 (dd, J = 3.6 and 1.6 Hz, H₃), 6.17 (dd, J = 3.6 and 2.5 Hz, H₄), 5.41 (d, J = 2.5 Hz, CH₂(11)), 4.01 (t, J = 7.2 Hz, CH₂(8)), 2.86 (tt, J = 8.0, 1.4 Hz, CH₂(10)), 2.37 (t, J = 2.5 Hz, H₁₃), 1.87 (quintet, J = 7.7 Hz, CH₂(9)). 13C NMR (100 MHz, CDCl₃) δ 165.9, 127.3, 125.8, 115.4, 108.3, 79.3, 73.1, 61.8, 38.3, 36.6, 21.8. IR (ATR, cm⁻¹) 3001, 2944, 2292, 2252, 1441,1375, 1038, 918, 749; HRMS Calcd for (C₁₁H₁₂N₂) [M + H]+: 173.1073; Found: 173.1081.

5.23 1-But-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (71b)

To a solution of 2,2'-(1'-pyrrolinyl)pyrrole (70) (0.201 g, 1.5 mmol) in dry DMF (5 mL) was added NaH (0.040 g, 1.7 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 0.5 h. To this solution was added propargyl bromide (0.200 g, 1.5 mmol) drop wise, and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (controlled by TLC), water (5 mL) was added, and the solution was extracted with ethyl acetate 6 times. The combined organic extracts were dried over MgSO₄. The solvent was evaporated to give the crude product, which was purified by column chromatography eluting with EtOAc/hexane (1:4) to give final product 1-but-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (71b) (0.177 g, 63%) as a light yellow colored oil.
1H NMR (400 MHz, CDCl3) δ 7.10 (bdd, J = 2.8 and 1.6 Hz, H5), 6.51 (dd, J = 3.8 and 1.6 Hz, H3), 6.17 (dd, J = 3.6 and 2.8 Hz, H4), 5.32 (q, J = 2.5 Hz, CH2(11)), 4.00 (tt, J = 7.2 and 1.6 Hz, CH2(10)), 2.88 (tt, J = 7.2 and 1.6 Hz, CH2(10)), 1.89 (quintet, J = 7.3 Hz, CH2(9)), 1.84 (t, J = 2.5 Hz, CH3).

13C NMR (100 MHz, CDCl3) δ 165.9, 127.1, 125.9, 115.2, 107.9, 74.5, 61.9, 38.7, 36.6, 21.9, 3.7. IR (ATR, cm⁻¹) 3164, 3001, 2292, 2253, 1443, 1375, 1039, 918, 749; HRMS Calcd for (C11H12N2) [M + H]+: 187.1223; Found: 187.1223.

5.24 1-(3-Phenylprop-2-ynyl)-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (79a)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh3 (90.0 mg, 0.34 mmol), and Pd(OAc)2 (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (71a) (0.190 g, 1.1 mmol), iodobenzene (0.245 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 3 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-(3-phenylprop-2-ynyl)-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (79a) (0.240 g, 87%) as a light yellow colored oil.

1H NMR (400 MHz, CDCl3) δ 7.37–7.33 (m, arom, 2H), 7.23-7.20 (m, arom, 3H), 7.11 (dd, J = 2.9 and 1.6 Hz, H5), 6.46 (dd, J = 3.6 and 1.6 Hz, H3), 6.12 (dd, J = 3.6 and 2.9 Hz, H4), 5.55 (s, CH2(11)), 3.95 (tt, J = 7.2 and 1.3 Hz, CH2(8)), 2.82 (tt, J = 7.2 and 1.6 Hz, CH2(10)), 1.82 (quintet, J = 7.2 Hz, CH2(9)). 13C NMR (100 MHz, CDCl3) δ 166.0, 131.8, 128.4, 128.3, 127.3, 125.9, 122.8, 115.3, 108.1, 85.0, 84.6, 61.8, 39.2, 36.6, 21.9. IR (ATR, cm⁻¹) 3164, 3001, 2292, 2253, 1443, 1375, 1039, 918, 749; HRMS Calcd for (C17H16N2) [M + H]+: 249.1386; Found: 249.1397.
5.25 1-[3-(4-Methylphenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79b)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh₃ (90.0 mg, 0.34 mmol), and Pd(OAc)₂ (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (71a) (0.190 g, 1.1 mmol), 4-iodotoluene (0.261 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 4 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-[3-(4-methylphenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79b) (0.215 g, 74%) as a light yellow colored oil.

1H NMR (400 MHz, CDCl₃) δ 7.34-7.29 (A-part of AA'BB'-system, arom, 2H), 7.19 (bdd, J = 2.9 and 1.6 Hz, H₅), 7.11-7.06 (B-part of AA'BB'-system, arom, 2H), 6.52 (dd, J = 3.7 and 1.6 Hz, H₃), 6.19 (dd, J = 3.6 and 2.9 Hz, H₄), 5.61 (s, CH₂(11)), 4.02 (tt, J = 7.2 and 1.7 Hz, CH₂(8)), 2.88 (tt, J = 7.5 and 1.6 Hz, CH₂(10)), 2.32 (s, CH₃), 1.88 (quintet, J = 7.6 Hz, CH₂(9)).

13C NMR (100 MHz, CDCl₃) δ 166.0, 138.5, 131.7, 129.0, 127.3, 125.9, 119.7, 115.3, 108.0, 85.1, 83.8, 61.8, 39.2, 36.6, 21.9, 21.5. IR (ATR, cm⁻¹) 3001, 2293, 2253, 1632, 1507, 1441, 1375, 1039, 918, 749, 668; HRMS Calcd for (C₁₈H₁₈N₂) [M + H]⁺: 263.1542; Found: 263.1560.

5.26 1-[3-(4-Methoxyphenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79c)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh₃ (90.0 mg, 0.34 mmol), and Pd(OAc)₂ (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (71a) (0.190 g, 1.1 mmol), 4-iodoanisole (0.281 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 3 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-[3-(4-methoxyphenyl)prop-2-ynyl]-
4',5'-dihydro-1H,3'H-2,2'-bipyrrole (79c) (0.237 g, 77%) as a light yellow colored oil.

\[
\text{\textbf{1H NMR} (400 MHz, CDCl}_3\text{)} \delta 7.37 \text{ (quasi d, } J = 8.8 \text{ Hz, arom, 2H), } 7.19 \text{ (bddd, } J = 2.6 \text{ and 1.7 Hz, H}_5\text{), } 6.82 \text{ (quasi d, } J = 8.8 \text{ Hz, arom, 2H), } 6.53 \text{ (dd, } J = 3.7 \text{ and 1.7 Hz, H}_3\text{), } 6.19 \text{ (dd, } J = 3.7 \text{ and 2.6 Hz, H}_4\text{), } 5.60 \text{ (s, CH}_2(11)\text{), } 4.03 \text{ (tt, } J = 7.2 \text{ and 1.6 Hz, CH}_2(8)\text{), } 3.80 \text{ (s, OCH}_3\text{), } 2.89 \text{ (tt, } J = 7.6 \text{ and 1.6 Hz, CH}_2(10)\text{), } 1.90 \text{ (quintet, } J = 7.6 \text{ Hz, CH}_2(9)\text{).}
\]

\[
\text{\textbf{13C NMR} (100 MHz, CDCl}_3\text{)} \delta 166.0, 159.7, 133.2, 127.3, 125.9, 115.3, 114.9, 113.9, 108.0, 84.9, 83.1, 61.8, 55.3, 39.3, 36.7, 21.9. \]

\[
\text{IR (ATR, cm}^{-1}\text{)} 3164, 3001, 2292, 2253, 1443, 1038, 918, 749; \text{HRMS Calcd for (C}_{18}\text{H}_{18}\text{N}_2\text{O} [M + H]^+: 279.1491; Found: 279.1497.}
\]

5.27 1-[3-(4-Chlorophenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (79d)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh\textsubscript{3} (90.0 mg, 0.34 mmol), and Pd(OAc)	extsubscript{2} (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (71a) (0.190 g, 1.1 mmol), 1-chloro-4-iodobenzene (0.286 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 3 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-[3-(4-chlorophenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrole (79d) (0.201 g, 78%) as a light yellow colored oil.

\[
\text{\textbf{1H NMR} (400 MHz, CDCl}_3\text{)} \delta 7.37-7.27 \text{ (m, arom, 5H), } 7.14 \text{ (dd, } J = 2.8 \text{ and 1.7 Hz, H}_5\text{), } 6.54 \text{ (dd, } J = 3.7 \text{ and 1.7 Hz, H}_3\text{), } 6.20 \text{ (dd, } J = 3.7 \text{ and 2.8 Hz, H}_4\text{), } 5.63 \text{ (s, CH}_2(11)\text{), } 4.03 \text{ (tt, } J = 7.3 \text{ and 1.6 Hz, CH}_2(8)\text{), } 2.90 \text{ (tt, } J = 7.3 \text{ and 1.6 Hz, CH}_2(10)\text{), } 1.91 \text{ (quintet, } J = 7.3 \text{ Hz, CH}_2(9)\text{).}
\]

\[
\text{\textbf{13C NMR} (100 MHz, CDCl}_3\text{)} \delta 165.9, 131.7, 128.3, 128.2, 127.3, 125.9, 122.7, 115.2, 108.0, 84.9, 84.5, 61.8, 39.2, 36.6, 21.9. \text{IR (ATR, cm}^{-1}\text{)} 3164, 3000,
5.28 5-Methyldipyrryrolo[1,2-a:2',1'-c]pyrazine (73a)

To a 50 mL flask equipped with a condenser was added 1-prop-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (71a) (0.172 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-Methyldipyrryrolo[1,2-a:2',1'-c]pyrazine (73a) (0.135 g, 79%) as a yellow colored solid from EtOAc/n-hexane, Mp: 123-125 °C.

\[ 1^H \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 6.98 \ (bd, J = 2.1 \text{ Hz, } H_8), \ 6.92 \ (bd, J = 2.1 \text{ Hz, } H_3), \ 6.90-6.88 \ (m, H_6), \ 6.56 \ (d, J = 2.1 \text{ Hz, } H_1 \text{ and } H_{10}), \ 6.47 \ (d, J = 2.1 \text{ Hz, } H_2 \text{ and } H_9), \ 2.35 \ (d, J = 1.2 \text{ Hz, } \text{CH}_3). \ 1^C \text{NMR} \ (100 \text{ MHz, CDCl}_3) \delta \ 124.8, \ 123.9, \ 118.9, \ 113.6, \ 111.9, \ 111.3, \ 110.8, \ 109.1, \ 99.8, \ 98.6, \ 15.6. \ \text{IR} \ (\text{ATR, cm}^{-1}), \ 3164, \ 3000, \ 2292, \ 2253, \ 1632, \ 1442, \ 1375, \ 1039, \ 918, \ 749; \ \text{HRMS} \ \text{Calcd for} \ (\text{C}_{11}\text{H}_{10}\text{N}_2) \ [M + H]^+ : 171.0916; \ \text{Found:} \ 171.0918. \]

5.29 5-Ethyldipyrryrolo[1,2-a:2',1'-c]pyrazine (73b)

To a 50 mL flask equipped with a condenser was added 1-but-2-ynyl-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (71b) (0.186 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-
ethylidipyrrrolo[1,2-α:2',1'-c]pyrazine (73b) (0.130 g, 70%) as a yellow colored solid from EtOAc/n-hexane, Mp: 127-129 °C.

1H NMR (400 MHz, CDCl3) δ 7.05 (bt, J = 2.2 Hz, H8), 6.97 (dd, J = 2.5, 1.6 Hz, H3), 6.92 (bs, H6), 6.57-6.55 (m, H1 and H10), 6.51-6.47 (m, H2 and H9), 2.77 (dq, J = 7.4 and 1.2 Hz, CH2), 1.38 (t, J = 7.4 Hz, CH3).

13C NMR (100 MHz, CDCl3) δ 124.8, 124.4, 123.9, 113.8, 111.6, 111.3, 110.9, 108.0, 99.6, 98.5, 22.5, 11.2. IR (ATR, cm⁻¹) 3164, 3001, 2944, 2292, 2252, 1632, 1443, 1375, 1038, 918, 749; HRMS Calcd for (C12H12N2) [M + H]^+: 185.1073; Found: 185.1078.

5.30 5-Benzylidipyrrrolo[1,2-α:2',1'-c]pyrazine (80a)

To a 50 mL flask equipped with a condenser was added 1-(3-phenylprop-2-ynyl)-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79a) (0.248 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-benzylidipyrrrolo[1,2-α:2',1'-c]pyrazine (80a) (0.185 g, 75%) as a yellow colored solid from EtOAc/n-hexane, Mp: 125-127 °C.

1H NMR (400 MHz, CDCl3) δ 7.37-7.28 (m, arom, 5H), 6.96 (dd, J = 2.8 and 1.4 Hz, H6), 6.91 (bt, J = 2.2 Hz, H3), 6.75 (bs, H6), 6.55 (dd, J = 3.7 and 1.4 Hz, H10), 6.51-6.47 (m, H1, H2 and H9), 4.05 (s, CH2). 13C NMR (100 MHz, CDCl3) δ 135.8, 128.9, 128.8, 127.2, 124.8, 123.9, 121.9, 114.0, 112.4, 111.3, 111.2, 110.7, 99.7, 98.7, 35.9. IR (ATR, cm⁻¹) 3164, 3001, 2292, 2252, 1443, 1375, 1039, 918, 749; HRMS Calcd for (C17H14N2) [M + H]^+: 247.1229; Found: 247.1241.

5.31 5-(4-Methylbenzyl)dipyrrrolo[1,2-α:2',1'-c]pyrazine (80b)
To a 50 mL flask equipped with a condenser was added product 1-[3-(4-
methylphenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79b) (0.262 g, 1.0
mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to
continuously bubble through the solution. The solution was warmed to a few degrees
below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025
mmol) was added then the resulting mixture was heated at the reflux temperature for
17h. After complete conversion (monitored by TLC) solvent was evaporated, and the
residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to
give pure product 5-(4-methylbenzyl)dipyrrolo[1,2-a:2',1'-c]pyrazine (80b) (0.167 g,
64%) as a yellow colored solid from EtOAc/n-hexane, Mp: 145-147 °C.

1H NMR (400 MHz, CDCl3) δ 7.20-7.14 (AA'BB' system, arom, 4H), 6.97 (dd, J = 2.8 and 1.4 Hz, H8),
6.92 (bt, J = 2.2, H3), 6.75 (bs, H6), 6.55 (dd, J = 3.7 and 1.4 Hz, H10), 6.51-6.47 (m, H1, H2 and H9), 4.02 (s,
CH2), 2.35 (s, CH3). 13C NMR (100 MHz, CDCl3) δ
136.8, 132.7, 129.5, 128.7, 124.8, 123.9, 122.1, 114.0,
112.3, 111.3, 111.1, 110.6, 99.7, 98.6, 35.5, 21.1. IR (ATR, cm−1) 3164, 3001, 2292,
2253, 1442, 1375, 1038, 918, 749; HRMS Calcd for (C18H16N2) [M + H]+: 261.1386; Found: 261.1401.

5.32 5-(4-Methoxybenzyl)dipyrrolo[1,2-a:2',1'-c]pyrazine (80c)

To a 50 mL flask equipped with a condenser was added product 1-[3-(4-
methoxyphenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79c) (0.278 g, 1.0
mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to
continuously bubble through the solution. The solution was warmed to a few degrees
below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025
mmol) was added then the resulting mixture was heated at the reflux temperature for
16 h. After complete conversion (monitored by TLC) solvent was evaporated, and the
residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to
give pure product 5-(4-methoxybenzyl)dipyrrolo[1,2-a:2',1'-c]pyrazine (80c)
(0.171 g, 62%) as a light green colored viscous oil.
\[
\text{\bf{H NMR}} \quad (400 \text{ MHz, CDCl}_3) \ \delta \ 7.14 \ (\text{quasi d, } J = 8.5 \text{ Hz, arom, 2H}), 6.90 \ (\text{dd, } J = 2.8, 1.4 \text{ Hz, } H_8), 6.84 \ (\text{bt, } J = 2.0 \text{ Hz, } H_5), 6.81 \ (\text{quasi d, } J = 8.5 \text{ Hz, arom, 2H}), 6.65 \ (\text{bs, } H_6), 6.48 \ (\text{dd, } J = 3.7 \text{ and } 1.3 \text{ Hz, } H_{10}), 6.44-6.39 \ (\text{m, } H_1, H_2 \text{ and } H_9), 3.92 \ (\text{s, } CH_2), 3.74 \ (\text{s, } CH_3).
\]

\[ \text{\bf{13C NMR}} \quad (100 \text{ MHz, CDCl}_3) \ \delta \ 158.8, 129.9, 127.7, 124.8, 123.9, 114.3, 114.0, 112.3, 111.3, 111.1, 110.6, 99.7, 98.6, 55.3, 35.0. \]

\[
\text{IR} \quad (\text{ATR, cm}^{-1}) \ 3164, 3001, 2292, 2253, 1443, 1375, 1038, 918, 749; \ 
\text{HRMS} \ 
\text{Calcd for (C}_{18}\text{H}_{16}\text{N}_2\text{O}) \ [\text{M + H}]^+ : 277.1335; \ 
\text{Found: } 277.1340.
\]

5.33 5-(4-Chlorobenzyl)dipyrrolo[1,2-a:2',1'-c]pyrazine (80d)

To a 50 mL flask equipped with a condenser was added product 1-[3-(4-chlorophenyl)prop-2-ynyl]-4',5'-dihydro-1H,3'H-2,2'-bipyrrrole (79d) (0.282 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then was the resulting mixture heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-(4-chlorobenzyl)dipyrrolo[1,2-a:2',1'-c]pyrazine (80d) (0.175 g, 62%) as a yellow colored solid form EtOAc/n-hexane, Mp:137-138.

\[ \text{\bf{H NMR}} \quad (400 \text{ MHz, CDCl}_3) \ \delta \ 7.32 \ (\text{quasi d, } J = 8.3 \text{ Hz, arom, 2H}), 7.24 \ (\text{quasi d, } J = 8.3 \text{ Hz, arom, 2H}), 6.93 \ (\text{bt, } J = 1.8 \text{ Hz, } H_8), 6.90 \ (\text{dd, } J = 2.4 \text{ and } 1.4 \text{ Hz } H_5), 6.78 \ (\text{bs, } H_6), 6.57-6.54 \ (\text{m, } H_{10}), 6.53-6.48 \ (\text{m, } H_1, H_2 \text{ and } H_9), 4.03 \ (\text{s, } CH_2). \ 
\text{\bf{13C NMR}} \quad (100 \text{ MHz, CDCl}_3) \ \delta \ 134.4, 133.1, 130.1, 129.1, 124.7, 123.8, 121.3, 114.1, 112.5, 111.5, 111.4, 110.8, 99.9, 98.9, 35.3. \ 
\text{IR} \quad (\text{ATR, cm}^{-1}) \ 3164, 3001, 2292, 2253, 1443, 1375, 1039, 918, 749; \ 
\text{HRMS} \ 
\text{Calcd for (C}_{19}\text{H}_{15}\text{N}_2\text{Cl}) \ [\text{M + H}]^+ : 281.0767; \ 
\text{Found: } 281.0862.
\]

5.34 Cyclohexa-1,3-diene (92)
A mixture of 156 mL of cyclohexene (88) (127.0 g, 1.55 mol) and N-bromosuccinimide (55.0 g, 0.31 mol) was heated at the reflux temperature for 3h in a round-bottomed flask with a condenser and drying tube. After complete conversion, reaction mixture was filtered into a one round-bottomed flask. Filtrate was evaporated and the residual yellowish oil was purified by vacuum distillation to give 3-bromocyclohex-1-ene (89) (209.0 g, 84%). Liquid distilled between T = 51-52 °C. (10 torr) 3-Bromocyclohexene (209.0 g, 1.30 mol) (89) and 386 mL of quinoline (422.0 g, 3.27 mol) were added into a round-bottomed flask attached with distilling equipment ending with an oil bubbler. Oil bath was set to maximum power to avoid precipitation. The colorless cyclohexa-1,3-diene (90) (88.4 g, 85%) distilled between T = 80-82 °C.\(^{133}\)

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 5.82-5.76 (m, A part of AB system, H}_2\text{ and H}_3\text{), 5.72-5.65 (m, B part of AB system, H}_1\text{ and H}_4\text{), 6.93 (bt, J = 1.8 Hz, CH}_2(5)\text{ and CH}_2(6)\text{)}. \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \delta 124.2 (2C) 22.4 (2C), 20.1 (2C). \]

54.35 2,3-Dioxabicyclo[2.2.2]oct-5-ene (93)

Cyclohexa-1,3-diene (92) (1 g, 1.25 mol) and a catalytic amount of tetraphenylporphine (TPP) (30 mg) was dissolved in 100 mL of CH\(_2\)Cl\(_2\) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 18 h while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (65 g), eluting with ethyl acetate/hexane (1:1) to give 2,3-Dioxabicyclo[2.2.2]oct-5-ene (93) (1.26 g, 90%) as a colorless oil.\(^{134}\)

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 6.60 (t, J=4.3, H}_2\text{ and H}_3\text{), 4.56 (bs, H}_1\text{ and H}_4\text{), 2.17 (AA' part of AA'BB' system, CH}_2(6)\text{), 1.41 (BB' part of AA'BB' system, CH}_2(5)\text{). C NMR (100 MHz, CDCl}_3\text{)} \delta 131.6 (2C) 70.2 (2C), 21.1 (2C). \]

5.36 3-Butyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95a)
To a solution of 2,3-Dioxabicyclo[2.2.2]oct-5-ene (93) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added 1-hexyne (0.082 g, 1 mmol) and the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) reaction mixture was filtered and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-butyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95a) (0.119 g, 61%) as a colorless oil.

1H NMR (400 MHz, CDCl3) δ 5.78 (ddt, J = 9.9, 3.9 and 1.8 Hz, H5), 5.50 (ddd, J = 9.9, 3.7 and 1.9 Hz, H4), 4.64 (td, J = 6.5 and 4.6 Hz, H7a), 2.64-2.61 (m, H3a), 2.26 (dt, J = 8.1 and 6.0 Hz, H3), 2.17-2.07 (m, H6), 2.01-1.91 (m, H6), 1.82 (ddt, J = 9.3, 6.6 and 2.3 Hz, CH2(8)), 1.78-1.70 (m, H7), 1.60-1.53 (m, H7), 1.43-1.35 (m, CH2(9)), 1.33-1.25 (m, CH2(10)), 0.89 (t, J=7.3 Hz, CH3). 13C NMR (100 MHz, CDCl3) δ 178.1, 127.3, 125.0, 75.2, 45.8, 39.4, 28.8, 28.5, 24.2, 21.5, 19.4, 12.8. IR (ATR, cm⁻¹) 3019, 2931, 2858, 2394, 2196, 2025, 1763, 1467, 1214, 1175, 1028, 667; HRMS Calcd for (C12H18O2) [M + H]+: 195.1379; Found: 195.1374.

5.37 3-Propyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95b)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (93) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added 1-pentyne (0.068 g, 1 mmol) and was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) reaction mixture was filtered and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-propyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95b) (0.115 g, 63%) as a colorless viscous oil.

1H NMR (400 MHz, CDCl3) δ 5.86 (ddt, J = 9.9, 3.7 and 1.8 Hz, H5), 5.57 (ddd, J = 9.8, 3.4 and 1.7 Hz, H4), 4.71 (dd, J = 11.2 and 6.5 Hz, H7a), 2.70 (m, H3a), 2.34 (dt, J= 7.8 and 6.1 Hz, H3), 2.24-2.14 (m, H6), 2.08-1.98 (m, H6), 1.93-1.86 (m, CH2(8)),
1.79 (ddt, \( J = 15.0, 8.4 \) and 5.6, Hz, \( H_7 \)), 1.66-1.59 (m, \( H_7 \)), 1.55-1.47 (m, CH\(_{2(9)}\)), 0.96 (t, \( J=7.3 \) Hz, CH\(_3\)). \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 179.1, 128.4, 126.0, 76.2, 46.6, 40.4, 32.2, 25.2, 20.5, 20.4, 13.9. IR (ATR, cm\(^{-1}\)) 3019, 2900, 1688, 1393, 1214, 1047, 928, 750, 668, 582; HRMS Calcd for (C\(_{11}H_{16}O_2\)) [M + H]\(^+\): 181.1223; Found: 181.1215.

5.38 Methyl 2-oxo-2,3,3a,6,7,7a-hexahydro-1-benzofuran-3-carboxylate (95c)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (93) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added ethyl propiolate (0.098 g, 1 mmol) and was heated at the reflux temperature for 14 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give methyl 2-oxo-2,3,3a,6,7,7a-hexahydro-1-benzofuran-3-carboxylate (95c) (0.120 g, 57%) as a colorless viscous oil.

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.87 (bdt, \( J = 10.2 \) and 1.2 Hz, \( H_5 \)), 5.45 (bdt, \( J = 10.2 \) and 1.8 Hz, \( H_4 \)), 4.88 (dt, \( J = 6.1 \) and 3.4 Hz, \( H_{7a} \)), 4.20 (q, \( J = 7.2 \) Hz, CH\(_{2(8)}\)), 3.31-3.27 (m, \( H_{3a} \)), 2.18-2.10 (m, \( H_3 \) and \( H_6 \)), 2.02-1.91 (m, \( H_6 \) and \( H_7 \)), 1.85-1.74 (m, \( H_7 \)), 1.25 (t, \( J = 7.2 \) Hz, CH\(_3\)). \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.6, 167.3, 129.8, 124.1, 77.5, 62.3, 53.6, 39.0, 24.7, 19.5, 14.1. IR (ATR, cm\(^{-1}\)) 3018, 2900, 2399, 1730, 1516, 1399, 1214, 1047, 928, 750, 668; HRMS Calcd for (C\(_{11}H_{14}O_4\)) [M + H]\(^+\): 211.0964; Found: 211.0973.

5.39 3-Phenyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95d)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (93) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added phenylacetylene (0.102 g, 1 mmol) and was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethylacetate/hexane (1:2) to give
3-phenyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95d) (0.141 g, 66%) as a light yellow colored oil.

\[^{1}H\text{ NMR}\ (400\text{ MHz, CDCl}_{3})\ \delta\ 7.30-7.20\ (m, 3H, arom.),\ 7.17-7.13\ (m, 2H, arom.),\ 5.82\ (dt, J = 10.2\ and\ 5.9\ Hz, H_{5}),\ 4.88\ (ddd, J = 10.4, 2.7\ and\ 1.5\ Hz, H_{4}),\ 4.81\ (bs, H_{7a}),\ 4.11\ (d, J = 8.0, H_{5}),\ 3.18-3.11\ (m, H_{3a}),\ 2.30-2.21\ (m, H_{7}),\ 2.20\ (m, H_{6})\ 1.95\ (dt, J = 17.7\ and\ 5.7, Hz, H_{6}),\ 1.65\ (ddddd, J = 17.0, 11.9, 6.2\ and\ 2.0\ Hz, H_{7})\ .\ ^{13}C\text{ NMR}\ (100\text{ MHz, CDCl}_{3})\ \delta\ 175.5, 132.3, 128.9, 128.6, 127.3, 126.5, 121.5, 75.2, 50.8, 39.8, 23.4, 17.6.\ \text{IR}\ (\text{ATR, cm}^{-1})\ 3018, 2987, 2900, 1770, 1393, 1214, 1066, 929, 750, 668, 626, 589;\ \text{HRMS}\ \text{Calcd for (C}_{14}H_{14}O_{2})\ [M + H]^{+}: 215.1066;\ \text{Found: 215.1065}.\]

5.40 3-(4-Ethylphenyl)-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95e)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (93) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added 1-ethyl-4-ethynylbenzene (0.130 g, 1 mmol) and was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-(4-ethylphenyl)-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95e) (0.135 g, 56%) as a light yellow colored oil.

\[^{1}H\text{ NMR}\ (400\text{ MHz, CDCl}_{3})\ \delta\ 7.18\ (quasi\ d, J = 8.2\ Hz, 2H, arom.),\ 7.13\ (quasi\ d, J = 8.2\ Hz, 2H, arom.),\ 5.80\ (dt, J = 10.0\ and\ 5.7\ Hz, H_{5}),\ 4.99\ (ddt, J = 10.0\ and\ 3.0\ Hz, H_{4}),\ 4.86\ (bs, H_{7a}),\ 4.15\ (d, J = 8.1\ Hz, H_{3}),\ 3.23-3.15\ (m, H_{3a}),\ 2.64\ (q, J = 7.7\ Hz, CH_{2(12)}),\ 2.35-2.28\ (m, H_{7}),\ 2.27-2.19\ (m, H_{6}),\ 2.01\ (dt, J = 17.5\ and\ 4.0\ Hz, H_{6}),\ 1.72\ (ddddd, J = 17.0, 11.9, 6.3, 2.0\ Hz, H_{7}),\ 1.23 (t, J = 7.7\ Hz, CH_{3}).\ ^{13}C\text{ NMR}\ (100\text{ MHz, CDCl}_{3})\ \delta\ 176.8, 143.5, 129.9, 129.5, 127.9, 124.3, 122.7, 76.1, 51.5, 40.8, 28.5, 24.5, 18.6, 15.5.\ \text{IR}\ (\text{ATR, cm}^{-1})\ 3019, 2965, 2162, 1979, 1770, 1516, 1214, 1038, 929, 750, 626, 581;\ \text{HRMS}\ \text{Calcd for (C}_{16}H_{16}O_{2})\ [M + H]^{+}: 243.1379;\ \text{Found: 243.1384}.\]
To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (93) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added cyclopropylacetylene (0.066 g, 1 mmol) and was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-cyclopropyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3H)-one (95f) (0.121 g, 67%) as a colorless viscous oil.

**1H NMR** (400 MHz, CDCl₃) δ 5.85 (ddt, J = 9.8, 3.9 and 1.9 Hz, H₅), 5.58 (ddd, J = 9.8, 3.7 and 1.8 Hz, H₄), 4.77 (dt, J = 11.0 and 6.2 Hz, H₇), 2.70-2.60 (m, H₃a), 2.23-2.13 (m, H₆), 2.07-1.99 (m, H₆), 1.92-1.85 (m, H₃ and H₇), 1.85-1.81 (m, H₇), 0.99 (ddt, J = 13.1, 8.3 and 4.8 Hz, H₃), 0.67 (ddt, J = 13.8, 9.1 and 4.9 Hz, H₉), 0.58 (ddt, J = 13.5, 8.1, 4.5 Hz, H₁₀), 0.48 (dt, J = 9.5 and 4.9 Hz, H₀), 0.35 (dt, J=9.4 and 4.7 Hz, H₁₀). **13C NMR** (100 MHz, CDCl₃) δ 177.9, 128.3, 125.9, 76.3, 50.9, 41.5, 25.1, 20.3, 11.5, 3.4, 2.8. **IR** (ATR, cm⁻¹) 2988, 2900, 1766, 1405, 1393, 1216, 1066, 1057, 1027, 870, 750, 668; **HRMS** Calcd for (C₁₁H₁₄O₂) [M + H]⁺: 179.1066; Found: 179.1068.
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APPENDICIES

A. SPECTRAL DATA

Figure 3 \( ^1 \text{H NMR} \) Spectrum of Compound 130a in CDCl\(_3\)
**Figure 4** $^{13}$C NMR Spectrum of Compound 130a in CDCl$_3$

**Figure 5** IR Spectrum of Compound 130a
Figure 6 HRMS Spectrum of Compound 130a

Figure 7 $^1$H NMR Spectrum of Compound 130b in CDCl$_3$
Figure 8 $^{13}$C NMR Spectrum of Compound 130b in CDCl$_3$

Figure 9 IR Spectrum of Compound 130b
Figure 10 HRMS Spectrum of Compound 130b

Figure 11 $^1$H NMR Spectrum of Compound 130c in CDCl$_3$
Figure 12 $^{13}$C NMR Spectrum of Compound 130c in CDCl$_3$

Figure 13 IR Spectrum of Compound 130c
Figure 14 HRMS Spectrum of Compound 130c

Figure 15 $^1$H NMR Spectrum of Compound 130d in CDCl$_3$
Figure 16 $^{13}$C NMR Spectrum of Compound 130d in CDCl$_3$

Figure 17 IR Spectrum of Compound 130d
Figure 18 HRMS Spectrum of Compound 130d

Figure 19 $^1$H NMR Spectrum of Compound 140a in CDCl$_3$
Figure 20 $^{13}$C NMR Spectrum of Compound 140a in CDCl$_3$

Figure 21 IR Spectrum of Compound 140a
Figure 22 HRMS Spectrum of Compound 140a

Figure 23 $^1$H NMR Spectrum of Compound 141a in CDCl$_3$
Figure 24 $^{13}$C NMR Spectrum of Compound 141a in CDCl$_3$

Figure 25 IR Spectrum of Compound 141a
Figure 26 HRMS Spectrum of Compound 141a

Figure 27 $^1$H NMR Spectrum of Compound 140b in CDCl$_3$
Figure 28 $^{13}$C NMR Spectrum of Compound 140b in CDCl$_3$

Figure 29 IR Spectrum of Compound 140b
Figure 30 HRMS Spectrum of Compound 140b

Figure 31 $^1$H NMR Spectrum of Compound 141b in CDCl$_3$
**Figure 32** $^{13}$C NMR Spectrum of Compound 141b in CDCl$_3$

**Figure 33** IR Spectrum of Compound 141b
Figure 34 HRMS Spectrum of Compound 141b

Figure 35 $^1$H NMR Spectrum of Compound 131a in CDCl$_3$
Figure 36 $^{13}$C NMR Spectrum of Compound 131a in CDCl$_3$

Figure 37 IR Spectrum of Compound 131a
Figure 38 HRMS Spectrum of Compound 131a

Figure 39 $^1$H NMR Spectrum of Compound 131b in CDCl$_3$
Figure 40 $^{13}$C NMR Spectrum of Compound 131b in CDCl$_3$

Figure 41 IR Spectrum of Compound 131b
Figure 42 HRMS Spectrum of Compound 131b

Figure 43 $^1$H NMR Spectrum of Compound 131c in CDCl$_3$
**Figure 44** $^{13}$C NMR Spectrum of Compound 131c in CDCl$_3$

**Figure 45** IR Spectrum of Compound 131c
**Figure 46** HRMS Spectrum of Compound 131c

**Figure 47** $^1$H NMR Spectrum of Compound 131d in CDCl$_3$
Figure 48 $^{13}$C NMR Spectrum of Compound 131d in CDCl$_3$  

Figure 49 IR Spectrum of Compound 131d
Figure 50 HRMS Spectrum of Compound 131d

Figure 51 $^1$H NMR Spectrum of Compound 132a in CDCl$_3$
Figure 52 $^{13}$C NMR Spectrum of Compound 132a in CDCl$_3$

Figure 53 IR Spectrum of Compound 132a
Figure 54 HRMS Spectrum of Compound 132a

Figure 55 $^1$H NMR Spectrum of Compound 132b in CDCl$_3$
Figure 56 $^{13}$C NMR Spectrum of Compound 132b in CDCl$_3$

Figure 57 IR Spectrum of Compound 132b
Figure 58 HRMS Spectrum of Compound 132b

Figure 59 $^1$H NMR Spectrum of Compound 132c in CDCl$_3$
Figure 60 $^{13}$C NMR Spectrum of Compound 132c in CDCl$_3$

Figure 61 IR Spectrum of Compound 132c
Figure 62 $^1$H NMR Spectrum of Compound 133a in CDCl$_3$

Figure 63 $^{13}$C NMR Spectrum of Compound 133a in CDCl$_3$
Figure 64 HSQC Spectrum of Compound 133a in CDCl₃

Figure 65 COSY Spectrum of Compound 133a in CDCl₃
Figure 66 HMBC Spectrum of Compound 133a in CDCl$_3$

Figure 67 IR Spectrum of Compound 133a
Figure 68 HRMS Spectrum of Compound 133a

Figure 69 $^1$H NMR Spectrum of Compound 133b in CDCl$_3$
Figure 70 $^{13}$C NMR Spectrum of Compound 133b in CDCl$_3$

Figure 71 IR Spectrum of Compound 133b
Figure 72 HRMS Spectrum of Compound 133b

Figure 73 $^1$H NMR Spectrum of Compound 133c in CDCl$_3$
Figure 74 $^{13}$C NMR Spectrum of Compound 133c in CDCl$_3$

Figure 75 IR Spectrum of Compound 133c
Figure 76 HRMS Spectrum of Compound 133c

Figure 77 $^1$H NMR Spectrum of Compound 153 in CDCl$_3$
Figure 78 $^{13}$C NMR Spectrum of Compound 153 in CDCl$_3$

Figure 79 DEPT90 Spectrum of Compound 153 in CDCl$_3$
Figure 80 DEPT135 Spectrum of Compound 153 in CDCl$_3$

Figure 81 HSQC Spectrum of Compound 153 in CDCl$_3$
Figure 82 COSY Spectrum of Compound 153 in CDCl₃

Figure 83 HMBC Spectrum of Compound 153 in CDCl₃
Figure 84 IR Spectrum of Compound 153

Figure 85 HRMS Spectrum of Compound 153
Figure 86 $^1$H NMR Spectrum of Compound 134 in CDCl$_3$

Figure 87 $^{13}$C NMR Spectrum of Compound 134 in CDCl$_3$
Figure 88 DEPT90 Spectrum of Compound 134 in CDCl₃

Figure 89 DEPT135 Spectrum of Compound 134 in CDCl₃
Figure 90 HSQC Spectrum of Compound 134 in CDCl₃

Figure 91 COSY Spectrum of Compound 134 in CDCl₃
Figure 92 HMBC Spectrum of Compound 134 in CDCl₃

Figure 93 IR Spectrum of Compound 134
Figure 94 HRMS Spectrum of Compound 134

Figure 95 $^1$H NMR Spectrum of Compound 147 in CDCl$_3$
Figure 96 $^{13}$C NMR Spectrum of Compound 147 in CDCl$_3$

Figure 97 DEPT90 Spectrum of Compound 147 in CDCl$_3$
Figure 98 DEPT135 Spectrum of Compound 147 in CDCl₃

Figure 99 HSQC Spectrum of Compound 147 in CDCl₃
Figure 100 COSY Spectrum of Compound 147 in CDCl₃

Figure 101 HMBC Spectrum of Compound 147 in CDCl₃
Figure 102 IR Spectrum of Compound 147

Figure 103 HRMS Spectrum of Compound 147
Figure 104 $^1$H NMR Spectrum of Compound 160 in CDCl₃

Figure 105 $^{13}$C NMR Spectrum of Compound 160 in CDCl₃
Figure 106 DEPT90 Spectrum of Compound 160 in CDCl₃

Figure 107 DEPT135 Spectrum of Compound 160 in CDCl₃
Figure 108 HSQC Spectrum of Compound 160 in CDCl$_3$

Figure 109 COSY Spectrum of Compound 160 in CDCl$_3$
Figure 110 HMBC Spectrum of Compound 160 in CDCl₃

Figure 111 ¹H NMR Spectrum of Compound 70 in CDCl₃
Figure 112 $^{13}$C NMR Spectrum of Compound 70 in CDCl$_3$

Figure 113 $^1$H NMR Spectrum of Compound 71a in CDCl$_3$
**Figure 114** $^{13}$C NMR Spectrum of Compound 71a in CDCl$_3$

**Figure 115** IR Spectrum of Compound 71a
Figure 116 HRMS Spectrum of Compound 71a

Figure 117 $^1$H NMR Spectrum of Compound 71b in CDCl$_3$
Figure 118 $^{13}$C NMR Spectrum of Compound 71b in CDCl$_3$

Figure 119 IR Spectrum of Compound 71b
Figure 120 HRMS Spectrum of Compound 71b

Figure 121 $^1$H NMR Spectrum of Compound 79a in CDCl$_3$
Figure 122 $^{13}$C NMR Spectrum of Compound 79a in CDCl$_3$

Figure 123 IR Spectrum of Compound 79a
Figure 124 HRMS Spectrum of Compound 79a

Figure 125 $^1$H NMR Spectrum of Compound 79b in CDCl$_3$
Figure 126 $^{13}$C NMR Spectrum of Compound 79b in CDCl$_3$

Figure 127 IR Spectrum of Compound 79b
Figure 128 HRMS Spectrum of Compound 79b

Figure 129 $^1$H NMR Spectrum of Compound 79c in CDCl$_3$
Figure 130 $^{13}$C NMR Spectrum of Compound 79c in CDCl$_3$

Figure 131 IR Spectrum of Compound 79c
Figure 132 HRMS Spectrum of Compound 79c

Figure 133 $^1$H NMR Spectrum of Compound 79d in CDCl$_3$
Figure 134 $^{13}$C NMR Spectrum of Compound 79d in CDCl$_3$

Figure 135 IR Spectrum of Compound 79d
Figure 136 HRMS Spectrum of Compound 79d

Figure 137 $^1$H NMR Spectrum of Compound 73a in CDCl$_3$
Figure 138 $^{13}$C NMR Spectrum of Compound 73a in CDCl$_3$

Figure 139 IR Spectrum of Compound 73a
Figure 140 HRMS Spectrum of Compound 73a

Figure 141 $^1$H NMR Spectrum of Compound 73b in CDCl$_3$
Figure 142 $^{13}$C NMR Spectrum of Compound 73b in CDCl$_3$

Figure 143 IR Spectrum of Compound 73b
Figure 144 HRMS Spectrum of Compound 73b

Figure 145 $^1$H NMR Spectrum of Compound 80a in CDCl$_3$
Figure 146 $^{13}$C NMR Spectrum of Compound 80a in CDCl$_3$

Figure 147 IR Spectrum of Compound 80a
Figure 148 HRMS Spectrum of Compound 80a

Figure 149 $^1$H NMR Spectrum of Compound 80b in CDCl$_3$
Figure 150 $^{13}$C NMR Spectrum of Compound 80b in CDCl$_3$

Figure 151 IR Spectrum of Compound 80b
Figure 152 HRMS Spectrum of Compound 80b

Figure 153 $^1$H NMR Spectrum of Compound 80c in CDCl$_3$
Figure 154 $^{13}$C NMR Spectrum of Compound 80c in CDCl$_3$

Figure 155 IR Spectrum of Compound 80c
Figure 156 HRMS Spectrum of Compound 80c

Figure 157 $^1$H NMR Spectrum of Compound 80d in CDCl$_3$
Figure 158 $^{13}$C NMR Spectrum of Compound 80d in CDCl$_3$

Figure 159 IR Spectrum of Compound 80d
Figure 160 HRMS Spectrum of Compound 80d

Figure 161 $^1H$ NMR Spectrum of Compound 92 in CDCl$_3$
Figure 162 $^{13}$C NMR Spectrum of Compound 92 in CDCl$_3$

Figure 163 $^1$H NMR Spectrum of Compound 93 in CDCl$_3$
Figure 164 $^{13}$C NMR Spectrum of Compound 93 in CDCl$_3$

Figure 165 $^1$H NMR Spectrum of Compound 95a in CDCl$_3$
Figure 166 $^{13}$C NMR Spectrum of Compound 95a in CDCl$_3$

Figure 167 DEPT90 Spectrum of Compound 95a in CDCl$_3$
Figure 168 DEPT135 Spectrum of Compound 95a in CDCl₃

Figure 169 HSQC Spectrum of Compound 95a in CDCl₃
Figure 170 COSY Spectrum of Compound 95a in CDCl₃

Figure 171 HMBC Spectrum of Compound 95a in CDCl₃
Figure 172 IR Spectrum of Compound 95a

Figure 173 HRMS Spectrum of Compound 95a
Figure 174 $^1$H NMR Spectrum of Compound 95b in CDCl$_3$

Figure 175 $^{13}$C NMR Spectrum of Compound 95b in CDCl$_3$
Figure 176 IR Spectrum of Compound 95b

Figure 177 HRMS Spectrum of Compound 95b
Figure 178 $^1$H NMR Spectrum of Compound 95c in CDCl$_3$

Figure 179 $^{13}$C NMR Spectrum of Compound 95c in CDCl$_3$
Figure 180 IR Spectrum of Compound 95c

Figure 181 HRMS Spectrum of Compound 95c
Figure 182 $^1$H NMR Spectrum of Compound 95d in CDCl$_3$

Figure 183 $^{13}$C NMR Spectrum of Compound 95d in CDCl$_3$
Figure 184 IR Spectrum of Compound 95d

Figure 185 HRMS Spectrum of Compound 95d
Figure 186 \(^1\)H NMR Spectrum of Compound 95e in CDCl\(_3\)

Figure 187 \(^{13}\)C NMR Spectrum of Compound 95e in CDCl\(_3\)
Figure 188 IR Spectrum of Compound 95e

Figure 189 HRMS Spectrum of Compound 95e
Figure 190 $^1$H NMR Spectrum of Compound 95f in CDCl$_3$

Figure 191 $^{13}$C NMR Spectrum of Compound 95f in CDCl$_3$
Figure 192 IR Spectrum of Compound 95f

Figure 193 HRMS Spectrum of Compound 95f
CURRICULUM VITAE

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Marital Status: Married
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Education

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Foreign Language

English (fluent)

Work Experience

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<td>Research and Teaching Assistant</td>
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Publications


**National Conference Proceeding**

1. Akbaş, E., Aslanoğlu, F., Sönmez, M., Bazı 5-benzoil-1,2,3,4-tetrahidro-2-tiyoksopirimidin Türevlerinin Sentezi, XX. Ulusal Kimya Kongresi, OKP-61, Kayseri, Türkiye, 4-8 Eylül 2006.


3. Aslanoğlu F., Sudemen B., Balç M., Mn(OAc)3 ve Seryum Amonyum Nitrat Varlığında Sikloheptatrienin 1,3 Dikabonil Bileşikleriyle Reaksiyonlarının İncelenmesi, XXV. Ulusal Kimya Kongresi, Erzurum, Türkiye, 27 Temmuz-2 Eylül 2011.