SYNTHESIS OF FERROCENYLIDENE CYCLOPENTENEDIONES

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MUSTAFA KÖKTÜRK

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Approval of the Graduate School of Natural and Applied Sciences

_____
Prof. Dr. Canan Özgen
Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

_____
Prof. Dr. Hüseyin İşçi
Head of the Department

This is to certify that we have read this thesis and in our opinion it is full adequate, in scope and quality, as a thesis for the degree of Master of Science.

_____
Assoc. Prof. Dr. Metin Zora
Supervisor

Examining Committee Members

Prof.Dr. Bekir Peynircioğlu	(METU, CHEM)	_____
Assoc.Prof.Dr. Metin Zora	(METU, CHEM)	_____
Prof.Dr. Engin U. Akkaya	(METU, CHEM)	_____
Prof.Dr. Fatma Sevin Düz	(Hacettepe U., CHEM)	_____
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Name, Last name: Mustafa Köktürk

Signature :

ABSTRACT

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Köktürk, Mustafa

M.S., Department of Chemistry

Supervisor: Assoc. Prof. Dr. Metin Zora

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2-Arylidine-4-cyclopentene-1,3-diones are known to be antitumor agents. Incorporation of the essential structures of such compounds with a ferrocene moiety instead of an aryl group could provide subtances with enhanced antitumor activities since some ferrocene derivatives have already proved to be active against a number of tumors. Thus, we have investigated the squarate-based synthesis of 2-ferrocenylidene-4-cyclopentene-1,3-diones. Upon thermolysis, 4-hydroxy-4-ferrocenylethynyl-2-cyclobutenones, prepared from 3-cyclobutene-1,2-diones and lithioethynylferrocene, produced exclusively 2-ferrocenylidene-4-cyclopentene-1,3-diones. In some cases, ferrocenyl quinone derivatives are obtained in very minor amounts. Moreover, the heating of a mixture of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones and silica gel in oven at 120 ^{o}C without using any solvent provided the same type of products. More importantly, the stirring of a solution of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenone (**37A-C**) derivatives in ethyl acetate at the room temperature yielded the same type products, as well. It appears that 4-hydroxy-4-ferrocenylethynyl-2-cyclobutenones are more reactive than corresponding phenyl analogs.

For the formation of ferrocenyl-substituted cyclopentenediones, a mechanism involving first electrocyclic ring opening of ferrocenylethynyl-substituted cyclobutenones to corresponding ketene intermediate and then ring closure, has been proposed. The exclusive formation of cyclopentenediones is attributed to the radical stabilizing ability of the ferrocenyl moiety during the course of the reaction.

Keywords: Ferrocene, Ferrocenylidenecyclopentenedione, Quinone, Cyclobutenedione, Cyclobutenone, Electrocyclization.

ÖZ

FERROSENİLİDEN SİKLOPENTENDİON TÜREVLERİNİN SENTEZİ

Köktürk, Mustafa
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Doç. Dr. Metin Zora

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2-Ariliden-4-siklopenten-1,3-dionlar antitümör ajanları olarak biliniyor. Bu bileşiklerde aril grubu yerine ferrosenin bulunması, bileşiklerin antitümör aktivitesinin artmasını sağlayabilir çünkü bir takım ferrosen türevlerinin bazı tümörlere karşı aktif olduğu daha önce tespit edilmiştir. Bu nedenle, 2-ferroseniliden-4 siklopenten-1,3-dionların squarat bazlı sentezini gerçekleştirdik. Termolizle, 3-siklobuten-1,2-dionlardan ve lityoetinilferrosenden hazırlanan 4-hidroksi-4-ferroseniletinil-2-siklobutenonlar, spesifik olarak 2-ferroseniliden-4-siklopenten-1,3-dionları oluşturdu. Bazı durumlarda ise, ferrosenil kinon türevleri çok az miktarda elde edildi. Ayrıca, 4-hidroksi-4-ferroseniletinil-2-siklobutenon ve silikajel karışımının 120 ^{o}C de solvent kullanılmaksızın ısıtılması aynı tip ürünleri oluşturdu. Daha da önemlisi, 4-hidroksi-4-ferroseniletinil-2-siklobutenon (**37A-C**) türevlerinin etil asetat içinde, oda sıcaklığında karıştırılması da aynı tür ürünleri oluşturdu. Buradan, 4-hidroksi-4-ferroseniletinil-2-siklobutenonların fenil analoglarından daha reaktif oldukları görülmektedir.

Ferroseniliden substitute siklopentendionların oluşumu, önce alkinil substitute siklobütenonun ketene elektrosiklik halka açılımı ve daha sonra halka kapanmasını içeren bir mekanizma ile açıklanmıştır. 2-ferrosenilidene-4-siklopenten-1,3-dion türevlerinin oluşumu ferrosenil grubunun radikal stabilize etme özelliğinden kaynaklanmaktadır.

Anahtar Kelimeler: Ferrosen, Ferrosenilidensiklopentendion, Kinon, Siklobütendion, Siklobütenon, Elektrosiklik Halka Açılması..

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To My Family

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LIST OF ABBREVIATIONS

bp	boiling point
br	broad (spectral)
Bu	butyl
^{o}C	degrees Celcius
Cp	cyclopentadienyl ligand
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
Et	ethyl
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
i-Pr	isopropyl
J	coupling constant
m	multiplet (spectral)
Me	methyl
mL	milliliter(s)
mHz	megahertz
min	minutes
mmol	millimole(s)
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
Pr	propyl
q	quartet

R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography

CHAPTER 1

INTRODUCTION

Study of carbon compounds by all means is simply and most commonly defined as organic chemistry [1-6]. With the developments in science, organic chemistry is considered as a separate branch at the beginning of nineteenth century. Humans have used organic compounds for thousands of years since organic chemistry touches the daily lives. Today organic chemistry is a broad field which intersects with such diverse areas as biology, medicine and pharmacology, polymer, agriculture and petroleum engineering [1-6].

Organometallic chemistry is one of the most active areas of chemical research in recent years. The importance of organometallic compounds, both in organic syntheses and mechanistic studies, and in preparing metal derivatives of unusual structure, attracts the attention of every chemist [7].

The history of organometallic chemistry falls rather naturally into three 50-year periods, the start of each period being signaled by a far-reaching discovery in preparative chemistry. The first period was started by the synthesis of zinc alkyls by Edward Frankland in 1849 [8] and the following extension of the preparative methodology to alkyls of mercury, lead, antimony, bismuth, aluminum, silicon, and germanium. The second period began in 1900 with the discovery of the formation of organomagnesium halides directly from the organic halide and the metal by Victor Grignard. Finally, the third period of development, the most dramatic and remarkable of all, can be dated as beginning in the early 1950s with the dual discoveries of ferrocene [9].

In fact, the latter half of the 20th century witnessed a tremendous development of organometallic chemistry. The pace of the development of organometallic chemistry initiated by the discovery of ferrocene was spurred by another unexpected discovery by Ziegler [10]. His discovery came out of his fundamental studies on the reactions of organolithium and aluminum compounds. The discovery of the Ziegler catalyst was followed closely by the remarkable development in coordination polymerization by Natta. Ziegler and Natta opened a new field of coordination polymerization to let us realize that we were at the start of the bursting development of polymer chemistry using transition-metal complexes as catalysts. On the other hand, the chemistry of low-valent transition-metal complexes attracted the attention of various researchers. Low-valent late transition-metal complexes that gave particularly strong impacts were Vaska's complex, $IrCl(CO)(PPh_3)_2$ [11], and Wilkinson's complex $RhCl(PPh_3)_3$ and $Pd(PPh_3)_4$. Important organometallic terms such as oxidative addition and reductive elimination [l2] were proposed in those days and have been accepted widely as important concepts since then [13]. In the last three decades, organometallic chemistry has grown more rapidly in scope than have the classical divisions of the chemistry.

Organometallic chemistry is closely related to the neighboring fields as well, which include organic chemistry, polymer synthesis, materials science, and heterogeneous catalysis. Thus, the results obtained in organometallic chemistry can have an impact on these neighboring fields. Those who are working in the neighboring fields can pick up the fruits developed in the fertile land of organometallic chemistry [13].

The metallocenes are relatively old organometallic complexes that were discovered as early as 1951. First compound discovered was ferrocene, a simple complex consisting of an iron center and two cyclopentadienyl (Cp) rings surrounding the metal. The term metallocene was used to describe any complex with a metal center and Cp ligands surrounding it. Presently, the term is used to describe a wide variety of organometallic complexes including those with altered structures such as substituted Cp rings and bridging atoms.

With 18 valance electrons, ferrocene (**1**) is the most stable member of metallocene series. This orange solid, which has melting point of 173 °C, is insoluble in water, sublimes readily in air and is not attacked by air or water. It undergoes typical electrophilic substitution reactions such as Vilsmeier formylation, mercuration, alkylation and Friedel-Crafts acylation [14]. Some basic reactions of ferrocene are shown in Figure 1.

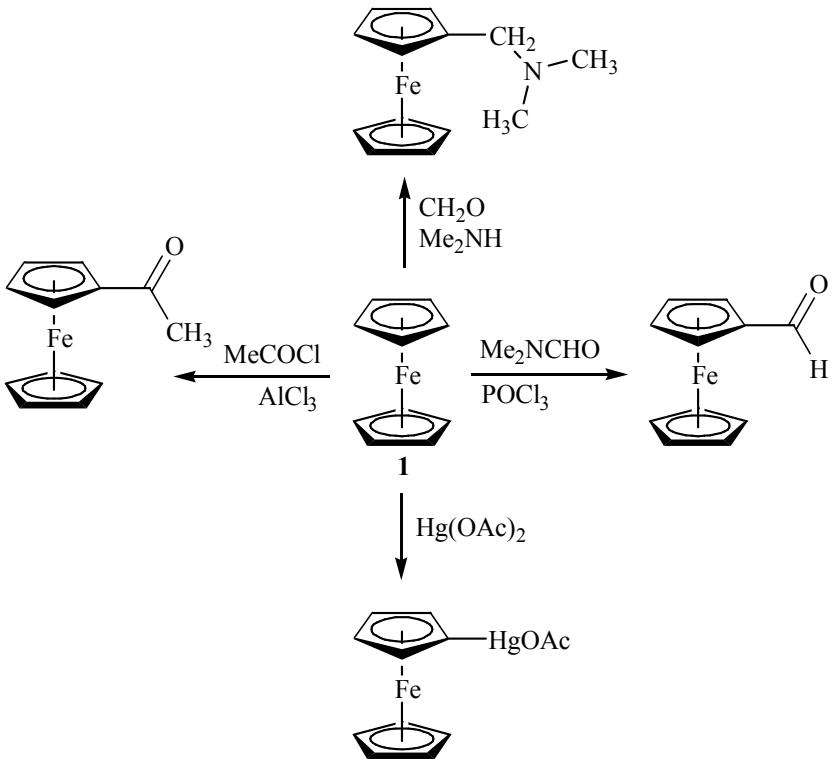


Figure 1. Some typical electrophilic substitution reactions of ferrocene

The synthesis of ferrocene was accomplished by Kealy and Pauson [15] and independently by Miller, Tebboth and Tremanie [16] at the end of 1951. Both groups prepared a 'traditional' structure as a δ complex. In the spring of 1952, Wilkinson, Rosenblum, Whiting and Woodward proposed an aromatic sandwich structure for ferrocene [17]. In the same period, Fischer and Prab derived the same sandwich structure for ferrocene from X-ray experiments [18]. This breakthrough opened a new area of the field of organometallic chemistry and let the Nobel prize for Wilkinson and Fischer in 1973.

More than fifty years after its discovery, ferrocene still enjoys a great deal of interest from scientists in many areas of research. Due to its high stability and the well-established methods for its incorporation into more complex structures, ferrocene has become a versatile compound for enormous number of synthesis and research areas.

The use of metal complexes capable of enhancing the activity of biological compounds has become a vibrant and growing area [19]. Inorganic platinum complexes, of which the archtype is cis-platin have a well established status as effective antitumorial agents, despite a relatively narrow therapeutic range [20]. This breakthrough led to research on organometallic compounds of various metals for antitumorial applications. Of these the metallocene derivatives have given encouraging results [21]. Ferrocene is ideal for use in drug design because of low toxicity of the molecule containing a ferrocenyl moiety and the ease of substitution of conventional phenyl or heteroaromatic group with ferrocene moiety [22]. Moreover, ferrocene containing compounds often show unexpected and/or enhanced biological activity.

Tamoxifen (TAM), a non-steroidal anti-estrogen, has been shown to provide effective treatment in breast cancer cells (Figure 2). It has been found that there are actually two forms of estrogen receptors, α form (ER α) and also a β form (ER β) both implicated in breast cancer [23-24]. Tamoxifen is only effective on approximately 60% of tumors, those classified as receptor α. It also causes resistance over the long term and has undesirable side effects [25]. A ferrocene-hydroxytamoxifen analogue, hydroxyferrocifen, (*Z*)-[(Et)(Fc)C=C(*p*-C_6H_4-OH)(*p*-C_6H_4-O-CH_2-CH_2-NMe_2], in which a phenyl ring is replaced by a ferrocenyl (Fc) group has shown to be active against both ER α and ER β estrogen receptors (Figure 2) [26]. Bioassay tests showed that ferrocifen derivatives exhibit strong activity against breast cancer cells that are mediated by both. Importantly, ferrocene derivatives act via mechanisms different from those of cisplatin, *cis*-[$PtCl_2(NH_3)_2$], and thus may lend themselves to treatment of a wider range of cancers. Thus, in recent years, considerable effort has been devoted to the synthesis of new ferrocene derivatives since the properly functionalized ferrocene derivatives could be potential antitumor substances.

Chloroquine (CQ) is a compound used as antimalarial agent (Figure 2), but plasmodium parasites are becoming increasingly resistant to CQ and other traditional drugs for malaria [27]. Ferrocene chloroquine analoque, ferroquine, has been produced by Brocard and coworkers, which is much more safe and effective [28]. After insertion of ferrocenyl group, the molecule induced great changes in molecular properties such as solubility and lipophilicity (Figure 2) [29].

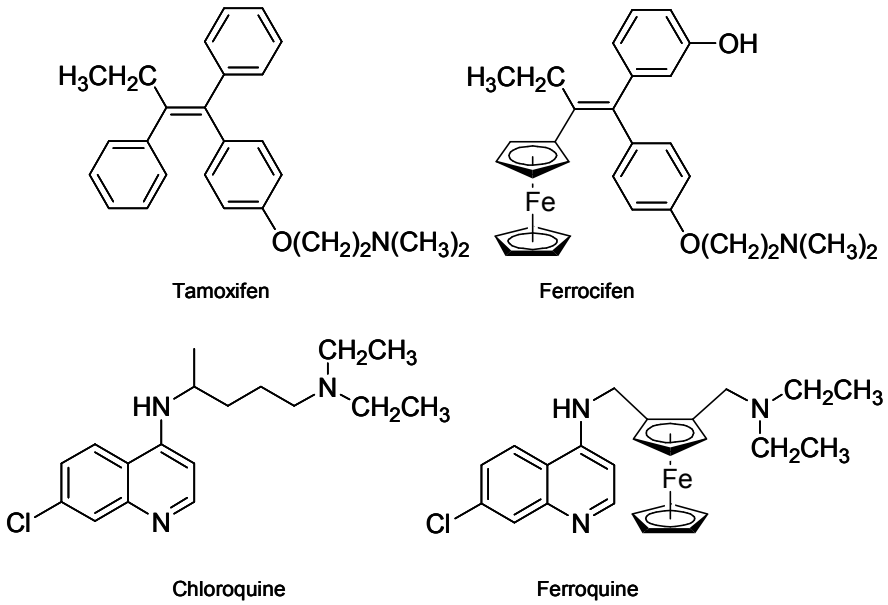
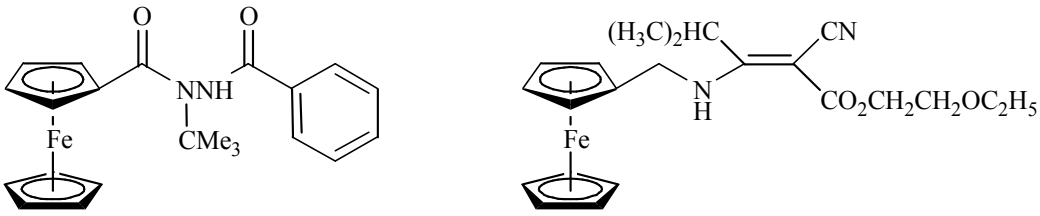


Figure 2. Ferrocenyl derivatives of two biologically active compounds

Recently a range of ferrocenyl amine-platinum(II) complexes with cyclometallated ferrocenyl ring have been reported. This kind of molecules exhibit strong activity against cis-platin resistant cells tested on mouse P-338 leukomia [30].

Biological activity of ferrocene derivatives has a wide application area. In a search of new insect growth regulator, ferrocenyl acylhydrazines showed excellent larwacidal activities [31]. Cyanoacrylates, which are a kind of herbicide, shows excellent activity when the replacement of the phenyl with ferrocenyl group is occurred (Figure 3) [32].



Acylhydrazine Cyanoacrylate

Figure 3. Ferrocenyl derivatives of biologically active compounds used in industry

The biological activity of ferrocene derivatives is attributed to the liphophilic property of ferrocene. It can easily cross cellular membranes [30]. Another important aspect is the fact that ferrocene can be readily oxidized to ferrocenium ion. The neutral, uncharged compound loses an electron, thereby converting to its one electron oxidation product, the ferrocenium ion. Holding an unpaired electron in one of the two non-bonding orbitals, the cation represents a free-radical species of appreciable stability. With free-radical processes abundant in the biological world, it is not surprising that the ferrocene/ferrocenium system has become a hot subject for researchers in the biochemical and biomedical disciplines.

In addition to pharmaceutical area, ferrocene has wide application in many fields. Ferrocene is used in supramolecular chemistry as magnetic materials and liquid crystals, in organometallic catalysis [33] and as oil additives [34].

On the other hand for many years, cyclobutenediones and cyclobutenones were studied as theoretically interesting molecules without any obvious potential use in the design of complex organic molecules [35]. Within the last 20 years this situation began to change since a variety of simple methods have been developed that allow the conversion cyclobutenediones and cyclobutenones into highly functionalized cyclopentenedione and quinone derivatives [36].

Mechanistically, one of the most interesting rearrangements of cyclobutenones is the ring expansion of 4-alkynyl-4-hydroxy-2-cyclobutenones (**4**) to 2-alkylidene-4-cyclopenten-1,3-diones (**7**) and/or 1,4-benzoquinones (**6**) (Figure 4) [37]. During the study of unsaturated ketenes, Moore explored the themolysis of **2** and discovered this novel rearrangement [37-38]. These are unique reactions since the intermediate enynyketenes **3** undergo ring closure to the previously unknown diradical intermediates **4** and/or **5** and these proceed to their respective products *via* a process involving migration of the R_4 group. The outcome of the reaction is dependent on the nature of alkyne substituent (R_3). In general, ring closure of **3** to the five membered ring diradical **5** competes with the generation of the six membered ring diradical **4** when the alkyne substituent (R_3) is a radical stabilizing group. A site of conjugated unsaturation or a heteroatom bearing a nonbonding electron pair tend to favor cyclopentenedione formation.

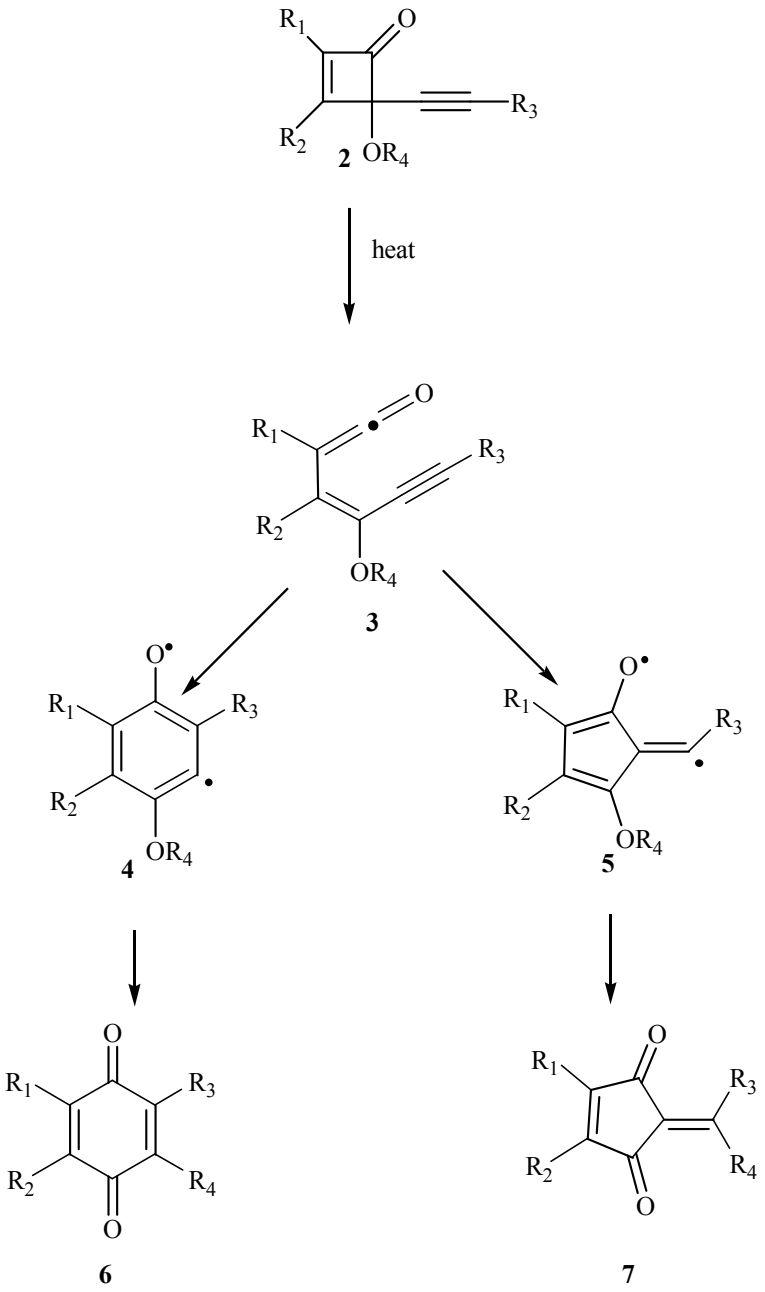
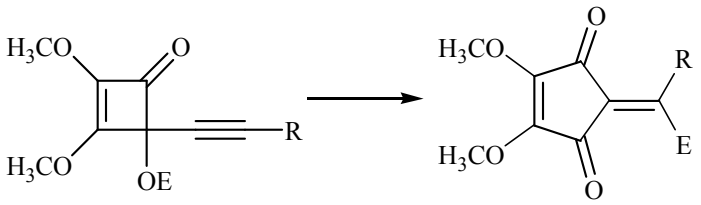


Figure 4. Thermal rearrangement of 4-alkynyl-4-hydroxy-2-cyclobutenones.

As mentioned above when the alkyne moiety is substituted with a group capable of radical stabilization as in **8a-c** the reaction proceeds to give mostly the cyclopentenediones **9a-c** (Figure 5) [37b]. These results are best explained by the generalized mechanism represented in Figure 4. Clearly, the direct stabilization of vinyl radical center by the adjacent R_3 substituent favors the formation of five-membered ring compound **7** over the formation of six membered ring compound **6**.



8 **9**

	R	E	%yield
a	$CO_2C_2H_5$	$Si(CH_3)_3$	33
b	$CO_2C_2H_5$	H	66
c	C_6H_5	H	46

Figure 5. Cyclopentenedione formation with radical stabilizing substituents

An alternative, organometallic based route to alkylidenecyclopentenediones from 4-alkynyl-4-hydroxy-2-cyclobutenones has also been reported (Figure 6) [39-40]. This palladium induced ring expansion provides a general route and the rearrangement proceeds with high stereoselectivity for the formation of five-membered ring compound. Treatment of **10** with 10 mol% palladium trifluoroacetate gave **11,** which was further converted to **12** upon treatment with NBS. Analogously, the benzocyclobutenone ketals **13** was converted to **14**. The mild condition of the palladium induced ring expansion reactions has allowed a number of highly functionalized compounds to be prepared [36].

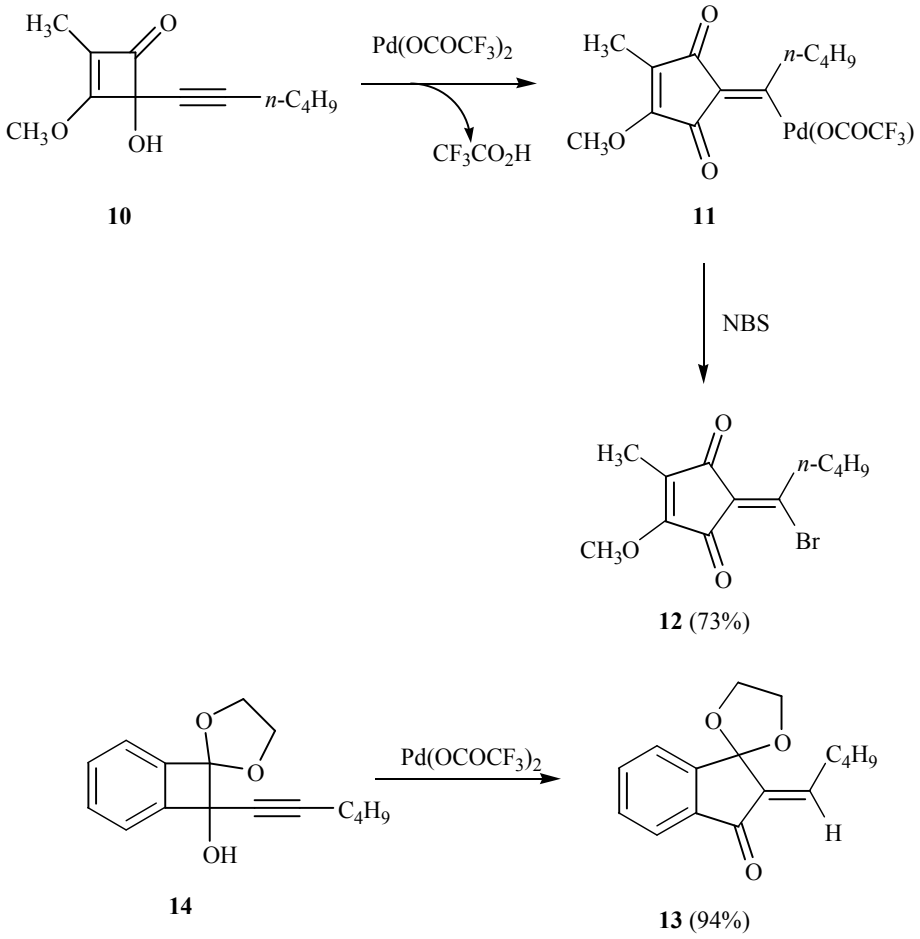


Figure 6. Palladium catalyzed cyclopentenedione formation

An interesting example for the conversion of alkynylcyclobutenones to cyclopentenedione is illustrated for **15** (R = H and $Si(CH_3)_3$) (Figure 7). As expected, the trimethylsiloxy derivative rearranges to give cyclopentenedione **16** along with a small amount of benzoquinone. However, for the sterically less hindered 4-hydroxy derivative, the Diels-Alder dimer **17** was realized as the main product (Figure 7).

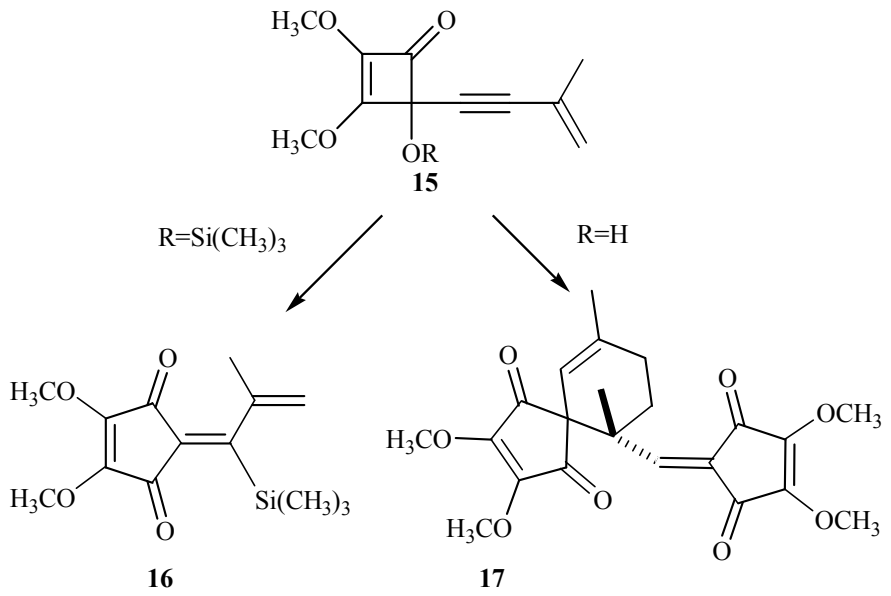


Figure 7. Example for cyclobutenone to cyclopentenedione rearrangement

In literature, there are only few methodologies for preparation of 2-alkylidene-4-cyclopentene-1,3-dione derivatives such as **21**. One synthetic method is depicted in Figure 8. Dihydroxycyclopentene **18** is oxidized to 4-cyclopentene-1,3-dione derivative **19**. Upon treatment with the corresponding aldehyde **20,** alkylidenecyclopentenedione derivatives **21** are obtained (Figure 8) [41].

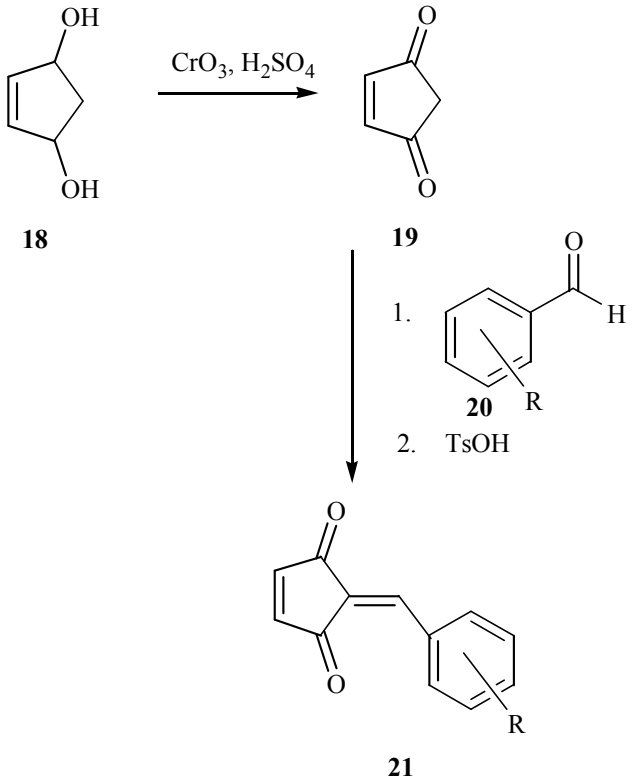


Figure 8. Synthesis of substituted alkylidenecyclopentenediones starting from dihydroxycyclopentene

Many of the cyclobutenone ring expansions have been employed as key steps in the synthesis of variety of natural products and related compounds. Abikoviromycin, is an antiviral and antifungal antibiotics isolated from culture broths of *Strepmyces abikoensis, sterptomyces rubescenns,* and *streptomyces abikoensis* (Figure 11) [42]. In terms of biological activity, abikoviromycin have attracted the attention of both synthetic and medicinal chemists but it is highly unstable and readily polymerizes when not in dilute solution. Benzoabiko-viromycin **24**, a more stable unnatural analog showing significant *in vitro* activity against five tumor cell lines, was synthesized by a route involving the ring expansion of 4-alkynylcyclobutenones (Figure 9) [43]. The key ring expansion step is the palladium catalyzed ring expansion of benzocyclobutenone ketal **22** that proceeded stereoselectively to give **23** as an E/Z mixture of stereoisomers. This mixture was then subjected to eight additional steps to give **24** as a 1:1 mixture of E and Z isomers.

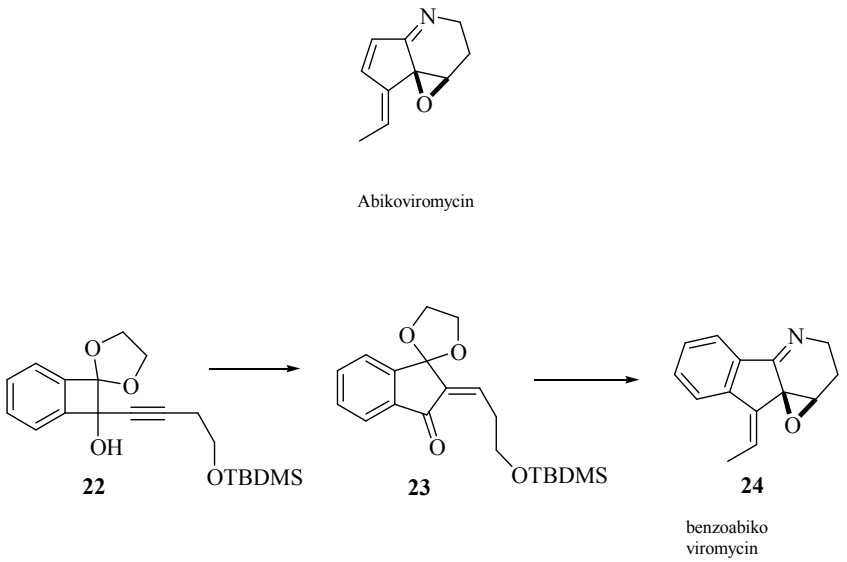


Figure 9. Schematic synthesis of benzoabikoviromycin (**24**)

The potent biological activity of alkylidenecyclopentenedione derivatives directed scientist for research on these compounds. Recent studies on piperacene, a tropical family that comprises many pharmaceutically important plants, useful as bioproducer of essential oils, revealed two new natural cyclopentenedione derivatives which are shown in Figure 10 [44].

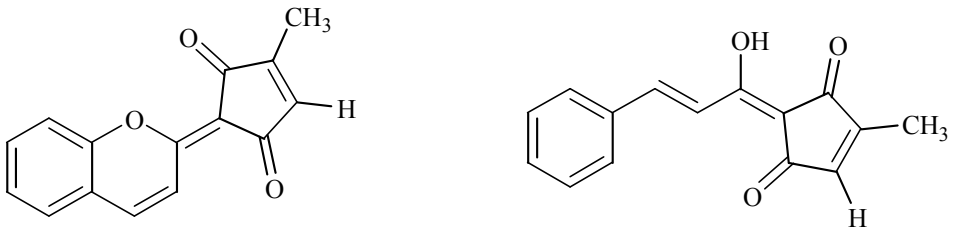


Figure 10. Two new naturally occuring cyclopentenedione derivatives

As previously mentioned, 4-alkynyl-4-hydroxy-2-cyclobutenones (**2**) are the main starting materials for 2-alkylidene-4-cyclopentene-1,3-diones (**7**). 4-Alkynylcyclobutenones can be synthesized from squaric acid (**25**) through corresponding cyclobutenediones. Squaric acid (**25**) has received much attention from the synthetic point of view as a precursor of substituted cyclobutenones and cyclobutenediones, which can be transformed into highly important ring systems such as quinone [45], phenols [45], cyclopentenediones [46], butenolides [47], polyquinanes [48], and various heterocycles [49]. In order to perform such transformations, a general, efficient and selective derivatization of squaric acid is a prerequisite. Therefore, a number of feasible methods were established based on the 1,2-addition of organolithiums [50] and palladium-catalyzed cross coupling of organotins [51].

Cyclobutenediones can be prepared from squaric acid according to known literature procedures [48 a,b]. The synthetic sequences are shown in the Figure 11. First, squaric acid (**25**) is converted to diisopropyl squarate (**26A**) by refluxing **25** in diisoproyl alcohol and with continuous removal of the resulting water. Cyclobutenediones are then obtained by treating diisopropyl squarate (**26A**), a crystalline ester of squaric acid, with organolithium nucleophiles followed by hydrolysis with HCl, as shown in Figure 11. Standard acid catalyzed hydrolysis allows the isopropyl group of **27** to be replaced with an alkyl substituent.

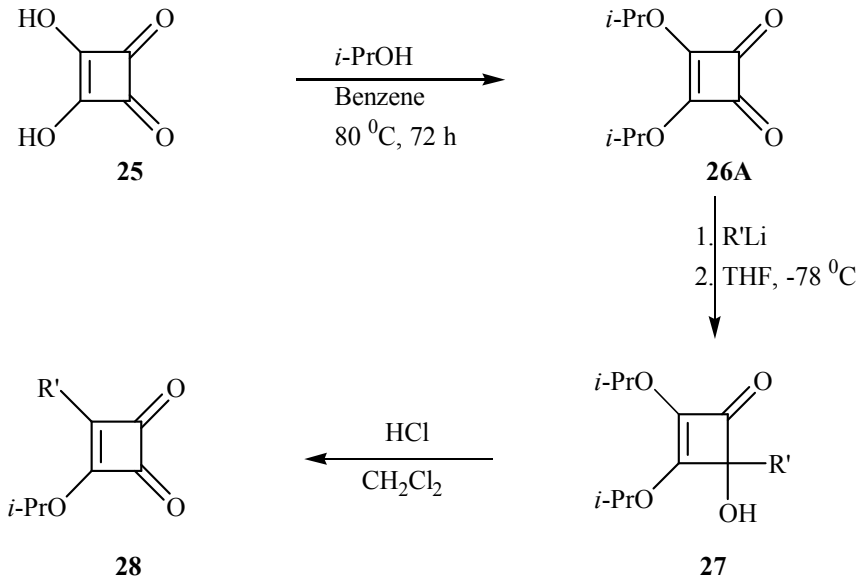


Figure 11. Synthesis of mono-substituted cyclobutenediones from squaric acid.

Differently disubstituted cyclobutenediones **31** are available by the sequential addition of two different organolithium reagents to diisopropyl squarate (**26A**), as depicted in Figure 12 [50 a,b]. Addition of organolithium nucleophile to diisopropyl squarate (**26A**) gives isolable 1,2-adduct, which is then protected as *tert*-butyldimethylsilyl ether **29**. Addition of second organolithium reagent to cyclobutenone **29**, followed by acidic hydrolysis, provides differently disubstituted cyclobutenediones **31** (Figure 12).

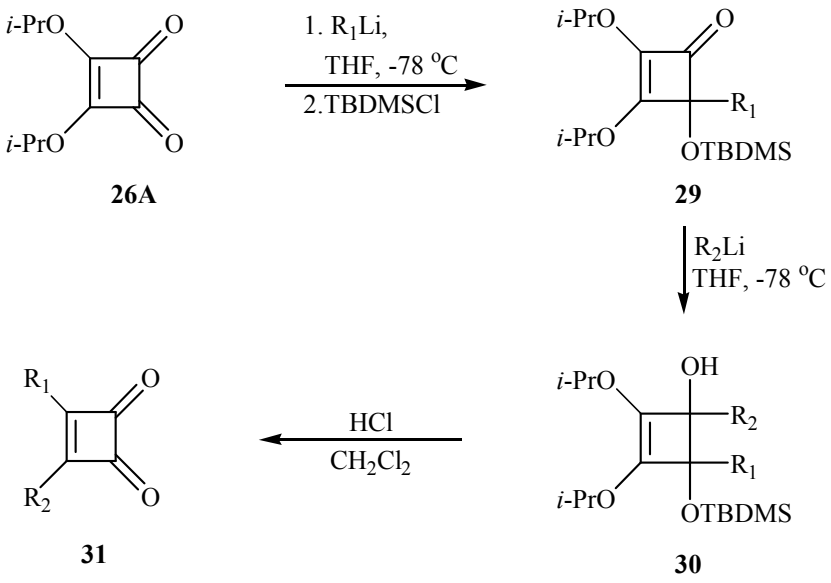


Figure 12. Synthesis of differently disubstituted cyclobutenediones from squaric acid

The incorporation of the essential structural features of alkylidene-cyclopentenediones with a ferrocene moiety could provide new derivatives with enhanced antitumor and biological activities. We were surprised that there has been very limited study of the ferrocenyl-substituted alkylidenecyclo-pentenediones. As part of our general involvement in ferrocene containing potential pharmaceuticals, we have investigated the thermolysis reaction of 4-ferrocenylethynyl-4-hydroxy-2-cycobutenones (**32**), affording 2-ferrocenylidene-4-cyclopentene-1,3-diones (**33** and/or **34**) and/or ferrocenyl quinones (**35**) (Figure 13). Although this methodology is known, it has not been utilized for the synthesis of ferrocenyl-substituted alkylidenecyclopentenediones, presumably due to scare availability of the starting materials containing ferrocenyl moiety.

In this thesis, the results concerning the scope, limitations and mechanism for the formation of 2-ferrcenylidene-4-cyclopentene-1,3-diones (**33** and/or **34**) and/or ferrocenyl quinones (**35**) are discussed.

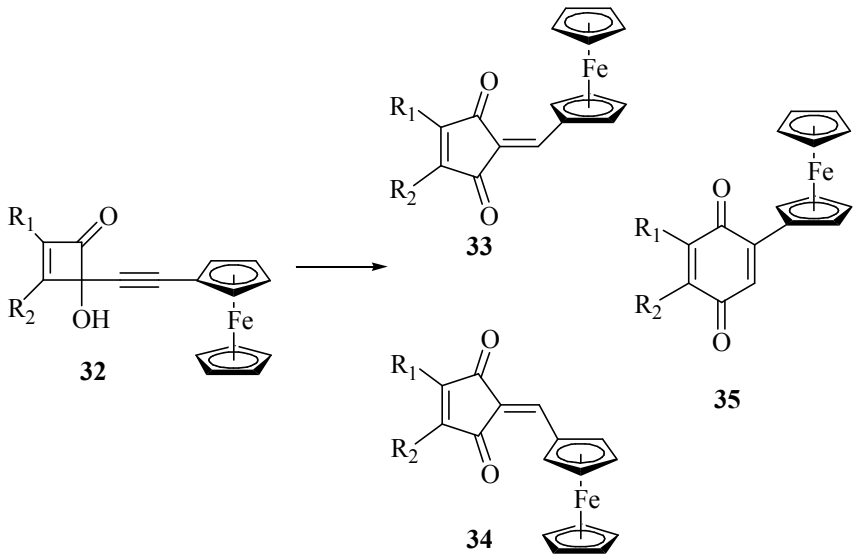


Figure 13. Thermal rearrangement of 4-ferrocenylethynyl-4-hyroxy-2-cyclobutenones

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of Ethynylferrocene.

Ethynylferrocene (**38**) was synthesized from ferrocene (**1**) in three steps according to known literature procedures [52]. Initially, acetylferrocene (**36**) was synthesized from ferrocene via Friedel-Crafts acylation reaction in CH_2Cl_2 at 0 ºC in the presence of aluminum chloride and acetylchloride (Figure 14). Then acetylferrocene (**36**) was treated with phosphorus oxychloride in *N,N*-dimethylformamide. Addition of sodium acetate at 0 ºC followed by water quenching led to the formation of (2-formyl-1-chlorovinyl)ferrocene (**37**). Finally, ethynylferrocene (**38**) was obtained by refluxing a mixture of **37** and sodium hydroxide in dioxane for 30 minutes (Figure 14).

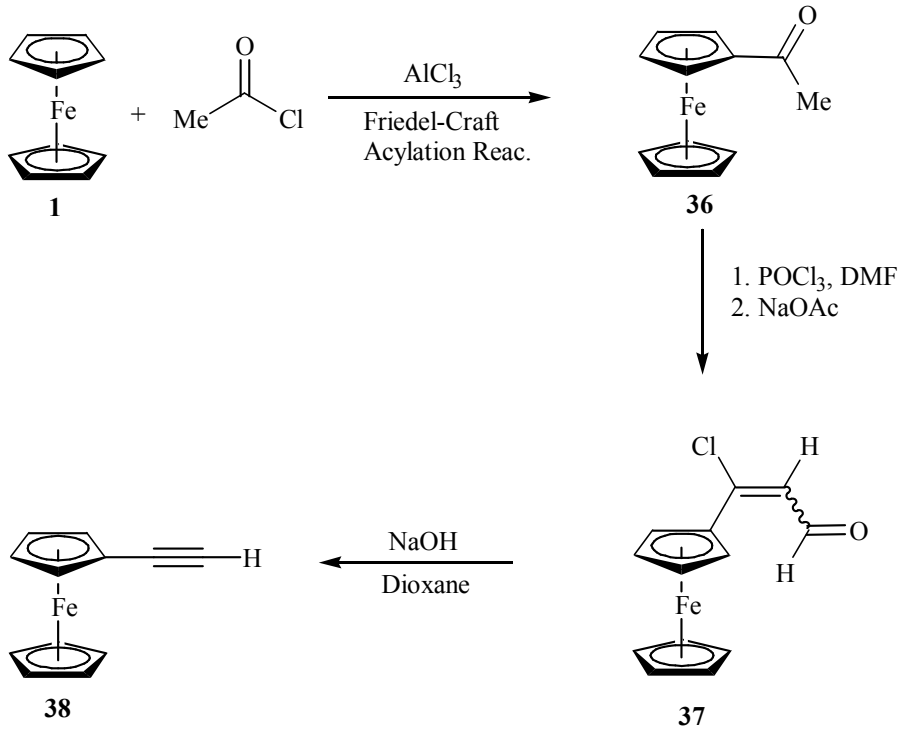


Figure 14. Synthesis of ethynylferrocene (**38**).

2.2. Synthesis of Cyclobutenedione Derivatives

Second starting materials, cyclobutenedione derivatives, were prepared starting from squaric acid with known literature procedures [50a,b]. Squaric acid (**25**) was refluxed in isopropyl alcohol and benzene for 72 hours with continuous removal of the water by using a Dean-Stark apparatus to produce diisopropyl squarate(**26A**) (Figure 15).

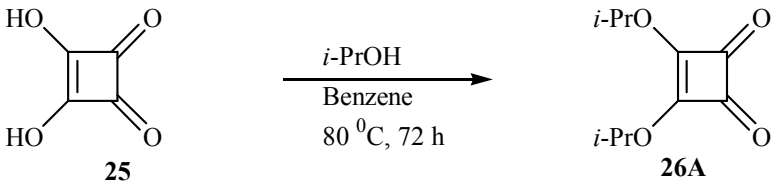
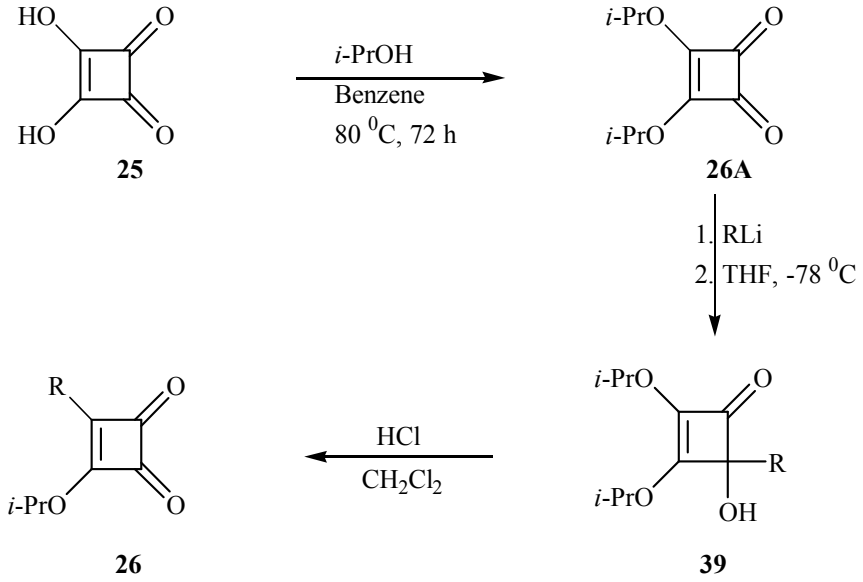


Figure 15. Synthesis of diisopropyl squarate (**26A**).

Diisopropyl squarate **26A** was then used in the preparation of methyl, phenyl-substituted cyclobutenedione derivatives **26B**,**C** (Table 1). For this purpose, diisopropyl squarate (**26A**) was first treated with corresponding organolithium reagent (MeLi or PhLi) in THF at -78 ºC, leading the formation of 4-alkyl/aryl-4-hydroxy-2-cyclobutenones **39B,C**. Subsequently, hydrolysis of cyclobutenones **39B,C** with HCl in CH_2Cl_2 at room temperature gave the corresponding cyclobutenediones **29B,C** [50a,b] (Table 1).

Table 1. Synthesis of methyl- and phenyl-substituted cyclobutenedione derivatives (**26B-C**).



Entry[a]	R	39 (% Yield)	26 (% Yield)
B	Me	85	87
C	Ph	84	90

[a]Entry letters define the R group for compounds **26** and **39**.

Dimethyl-substituted cyclobutenedione **26D** was also prepared starting from diisopropyl squarate (**26A**) In the first step, **26A** was treated with MeLi in THF at -78 ºC. Then excess chlorotrimethylsilane (TMSCl) was added to the resulting mixture for the protection of hydroxyl group to produce **40**. Second addition of MeLi at -78 ºC afforded alcohol **41**. Then, **41** was hydrolized with HCl in CH_2Cl_2 to afford dimethylcyclobutenedione (**26D**) (Figure 16) [50b].

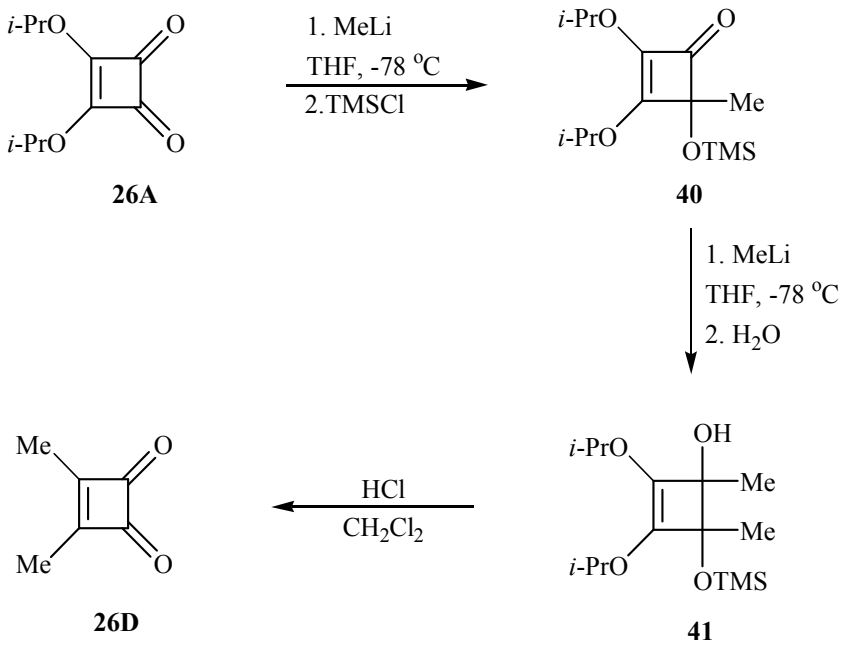


Figure 16. Synthesis of dimethylcyclobutenedione (**26D**)

Diphenyl-substituted cyclobutenedione **26E** was synthesized starting from squaric acid (**25**) via Fridel-Crafts acylation (Figure 17) [53]. Firstly, dichloro-substituted cyclobutenedione **42** was prepared with addition of thionyl chloride in the presence of catalytic amount of DMF. Then, the treatment of the resulting mixture with dry benzene in the presence of aluminium chloride afforded the diphenyl-substituted cyclobutenedione **26E** (Figure 17) [53] .

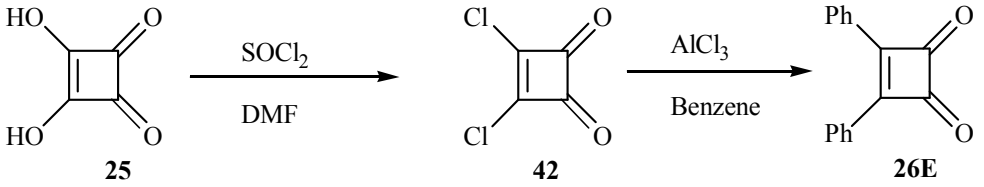


Figure 17. Synthesis of diphenycyclobutenedione (**26E**).

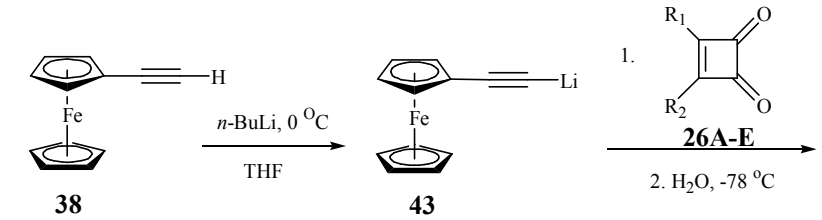
2.3. Synthesis of 4-Ferrocenylethynyl-4-hydroxy-2-cyclobutenones.

First of all, ethynylferrocene was treated with *n*-BuLi at 0 ^{o}C in THF to produce *in situ* lithioethynylferrocene, which was reacted with cyclobutenediones **26A-E** at -78 ^{o}C for 3 h to afford corresponding 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenone derivatives. It should be noted that we examined the reaction in different reaction conditions and the best results were obtained with molar ratio of 1:1.1 cyclobutenedione **26** and ethynylferrocene (**38**), respectively. Results are summarized in Table 2.

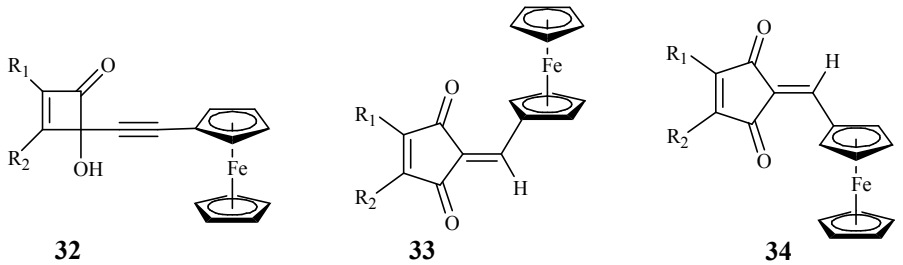
As seen in Entries C and E, cyclobutenones **32C** and **32E** was found to be so reactive or unstable during the flash column chromatography, and they were converted to corresponding compounds **33C** and **33E**, respectively, or decomposed. Probably the acidity of silica gel accelerated these conversions. Especially for phenyl-substituted alcohols **32C**,**E**, this conversion was very rapid. In addition, the isolated alcohols **32C**,**E** directly turned to a black bulk during the evaporation of the solvent in rotary evaporator. That's why; as will be discussed in the next part, these compounds were not isolated and immediately thermolyzed in dioxane to corresponding rearranged products.

Notably, methyl-substituted alcohols **32B,D** were insoluble in hexane and they were obtained in pure form by filtration after dissolving crude product in hexane. Less conversion to five membered ring is achieved by this method during the isolation of alcohols. The ease of isolating these derivatives in high yields without rearrangement allowed us to have their NMR spectra of highly pure samples.

Table 2. Synthesis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones



38 **43**



32 **33** **34**

Entry[a]	R_1	R_2	32 (% Yield)	33 (% Yield)	34 (% Yield)
A	*i*-PrO	*i*-PrO	65	5	--
B	Me	*i*-PrO	34	19	9
C	Ph	*i*-PrO	*b*	35	--
D	Me	Me	38	22	--
E	Ph	Ph	*c*	37	--

[a] Entry letters define the R_1 and R_2 groups for compounds **32**, **33** and **34**.

[b] This product was so reactive that it could not be isolated and immediately converted to compound **33C** or decomposed during the flash column chromatography.

[c] This product was so reactive that it could not be isolated and immediately converted to compound **33E** or decomposed during the flash column chromatography.

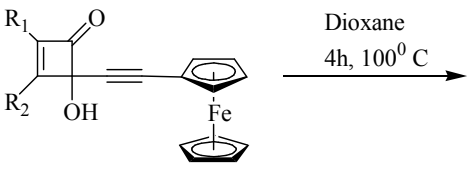
2.4. Thermolysis of 4-Ferrocenylethynyl-4-hydroxy-2-cyclobutenones

We have demonstrated that thermolysis of alcohols **32A-E** afforded ferrocenylidenecyclopentenediones **33A-E** as major products along with the varying amounts of isomer **34B** and benzoquinones **35A-C** as very minor products. First of all, thermolysis of cyclobutenone **32A** was tried in refluxing THF but this reaction produced the expected product **33A** in 30 % yield. Finally, it was found that the optimal condition for the reaction requires thermolysis in dioxane at 100 ^{o}C for a period of 4 h. Under this condition, the reaction of **32A** afforded compounds **33A** and **35A** in 70 and 2 % yields, respectively (Table 3, Entry 1).

In addition, inspired from the transformation of some alcohols to corresponding cyclopentenediones during flash column chromatography, we also heated a mixture of alcohols **32** and silica gel at 120 ^{o}C for 5 min without any solvent, giving corresponding products in good yields as depicted in Table 3. Moreover, as illustrated in Table 3, the stirring of cyclobutenones in ethyl acetate at the room temperature provides the corresponding products.

The result for the methyl isopropoxy derivative **32B** is noteworthy since it provided three products, 61% major cyclopentenedione isomer **33B**, 3 % minor isomer **34B** and 4 % benzoquinone **35B** (Table 3, Entry 4). However, minor isomer **34B** formed in 32 % yield by heating with silica gel in oven (Table 3, Entry 5). This result was not surprising when we consider the previous studies since E/Z equilibration of cyclopentenedione isomers with the treatment of silica gel was reported by Moore and his coworkers [37b].

Table 3. Thermolysis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones



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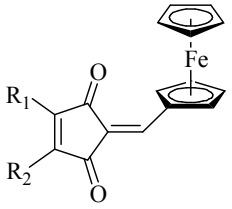

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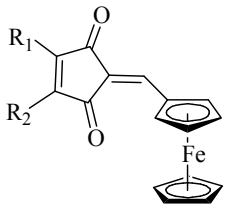

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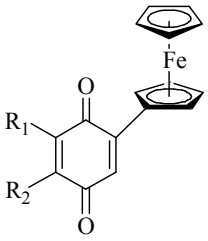

35

Entry	Starting Material[a]	R_1	R_2	Reaction Condition	33 (%)	34 (%)	35 (%)
1	**32A**	*i*-PrO	*i*-PrO	Dioxane, 100 °C	70	--	2
2	**32A**	*i*-PrO	*i*-PrO	SiO_2, 125 °C	67	--	--
3	**32A**	*i*-PrO	*i*-PrO	SiO_2, EtOAc, rt	34	--	--
4	**32B**	Me	*i*-PrO	Dioxane, 100 °C	61	3	4
5	**32B**	Me	*i*-PrO	SiO_2, 125 °C	45	32	--
6	**32B**	Me	*i*-PrO	SiO_2, EtOAc, rt	51	6	--

[a] Letter in starting material number defines R_1 and R_2 groups for compounds **33**, **34** and **35**.

Table 3 (Continued). Thermolysis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones

Entry	Starting Material[a]	R_1	R_2	Reaction Condition	33 (%)	34 (%)	35 (%)
7	**32C**[b]	Ph	*i*-PrO	Dioxane, 100 °C	53[c]	--	--
8	**32C**[b]	Ph	*i*-PrO	SiO_2, EtOAc, rt	56[c]	--	--
9	**32D**	Me	Me	Dioxane, 100 °C	55	--	8
10	**32D**	Me	Me	SiO_2, 125 °C	71	--	5
11	**32D**	Me	Me	SiO_2, EtOAc, rt	74	--	8
12	**32E**[d]	Ph	Ph	Dioxane, 100 °C	58[e]	--	--
13	**32E**[d]	Ph	Ph	SiO_2, EtOAc, rt	45[e]	--	--

[a] Letter in starting material number defines R_1 and R_2 groups for compounds **33**, **34** and **35**.

[b] Crude starting material **32C** obtained according to Table 2 was used.

[c] Overall yield from cyclobutenedione **26C**.

[d] Crude starting material **32E** obtained according to Table 2 was used.

[e] Overall yield from cyclobutenedione **26E**.

When dimethylcyclobutenone **32D** was thermolyzed, 55% and 71% yields of compound **33D** were obtained by reflux in dioxane, and heating with silica gel in oven, respectively (Table 3, Entries 9 and 10). Quinone **35D** formation between 5 and 8 % yields were observed during the SiO_2 treatment whereas the other cyclobutenone derivatives did not produce even the trace amount of quinone with SiO_2.

An interesting rearrangement was observed in the phenyl-substituted alcohols **32C**,**E**. Isomerization was expected for **32C** but neither of the reaction routes produced other isomer. Our result is an evident of how the substituents on the cyclobutenedione ring affect the resulting product. Besides, the rapid rearrangement of the phenyl-substituted alcohols did not let any formation of quinone because **32C** and **32E** rearranged even during the extraction process. That's why; yields are given from the starting materials cyclobutenediones **26C**,**E**. These results are nicely in accord with the previous studies of Moore [37b]. Phenyl substitution on the cyclobutenone ring system favors the formation of cyclopentenedione product as a single product, particularly if there is a radical stabilizing group attached to alkyne moeity.

The selectivity of this rearrangement to give either benzoquinones **35** or cyclopentenediones **33** is significantly influenced by the substituent of alkyne moeity in that radical stabilizing groups e.g. phenyl, $-CO_2C_2H_5$ tend to favor cyclopentenedione formation [37b]. When substituent becomes more and more capable of stabilizing an adjacent radical site, cyclopentenedione diradical intermediate becomes favored [37b].

Quantitative ability of aromatic ferrocenyl group to stabilize free radicals were reported [54-55]. The study on the rearrangement of methylene cyclopropene **44** showed that ferrocenyl group is a very effective radical stabilizing group (Figure 18). In this reaction, aromatic radical stabilizing ability of the groups increase the rate of the rearrangement. The ferrocenyl substituted system rearranges somewhat faster than the phenyl analogue (k_{rel} for ferrocenyl group **45b** is 1.6 whereas 1.0 for phenyl group **45a**).

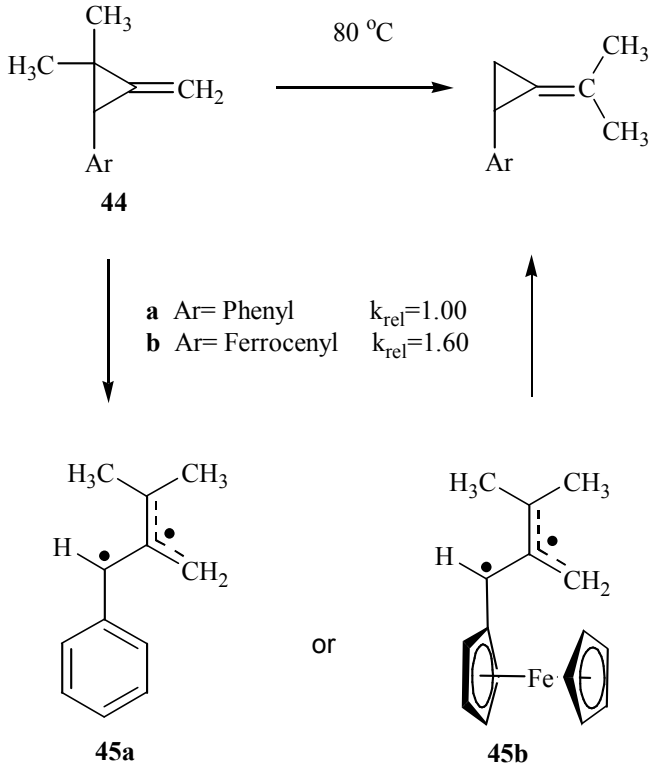

Figure 18. Experimental methylenecyclopropane rearrangement

According to computational studies [54-55], ferrocenyl group stabilizes radicals by a delocalization mechanism where significant spin is placed on the Fe atom, i.e., there is major contribution from a η^4 form (Figure 19). Due to the good radical stabilizing ability of ferrocene, cyclopentenediones formed as major or single products.

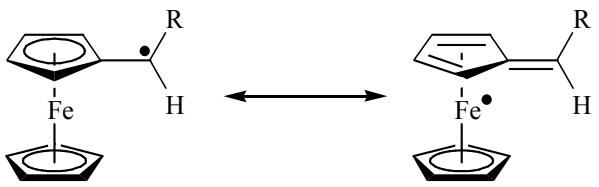

Figure 19. Spin delocalization of ferrocene radical

2.5. Mechanism

It is well known that in the case of 4-alkynyl groups of cyclobutenones are substituted with an alkyl group or a proton, ring expansion reaction to six membered ring occurs after thermolysis [37,56]. When the alkyne moeity is substituted with a group capable of radical stabilization the reaction proceeds to give at least in part the cyclopentenediones. The mechanistic approach to the formation of ferrocenylidene cyclopentenediones **33** is depicted in Figure 20.

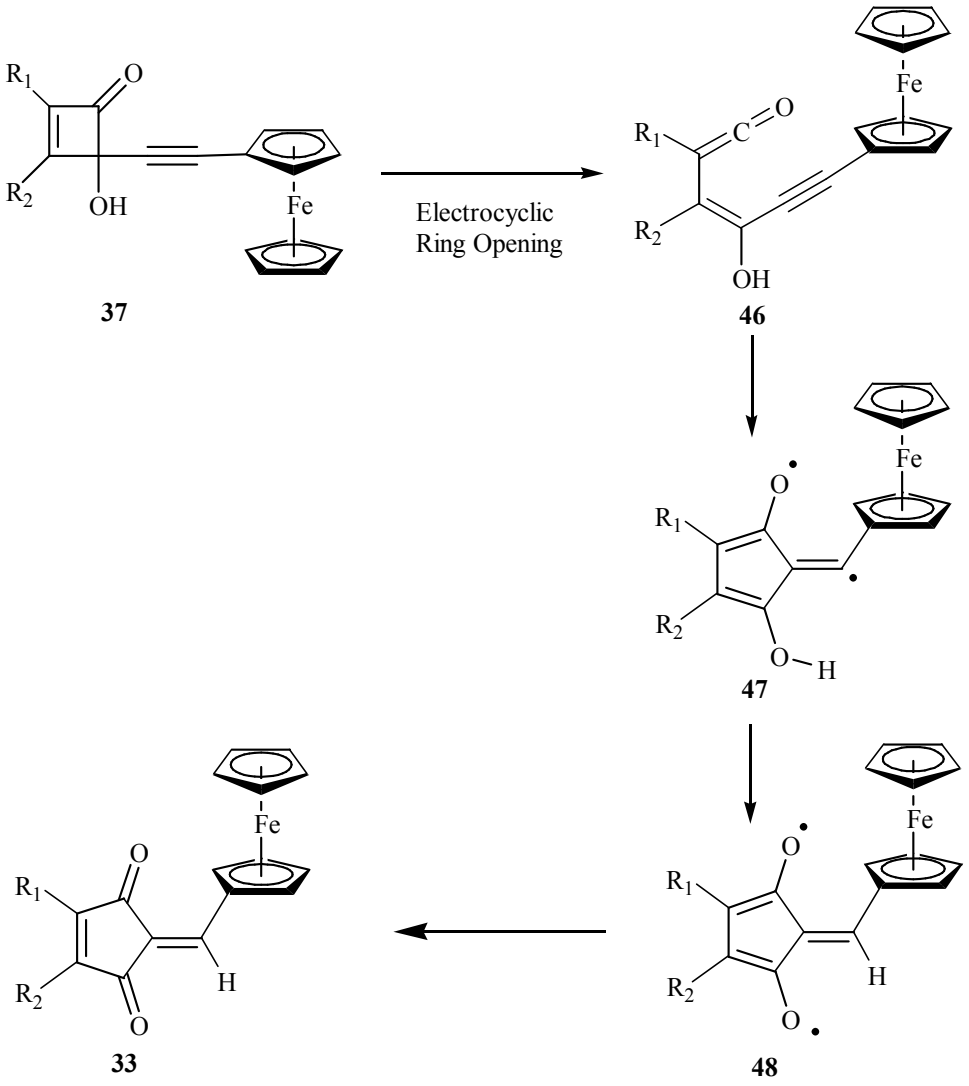

Figure 20. Formation mechanism of cyclopentenediones

The rearrangement mechanism for the formation of cyclopentenediones **33** is a unique reaction. During the reflux in dioxane, electrocyclic ring opening and the corresponding enynyl ketene **46** formation occurs. Intermediate represented by **46** is of particular interest. If the intermediate **46** undergoes to [4+2] ring closure, strained cyclic allene formation is expected. Cyclic allenes in rings with less than nine members cannot attain their preferred linear geometry. Especially, for six membered rings, strain is extremely high, so radical ring closure of the conjugate ketene takes place and molecule find relief by reorganizing to diradical form **47**.

As mentioned before, the outcome of the reaction is significantly influenced by the substituent on the alkyne moeity. During the ring closure, radical stays outside the ring system and tend to favor cyclopentenediones when a radical stabilizing group is substituted to alkyne. The mechanistic question why reaction provides cyclopentenediones is explained by the radical stabilizing ability of ferrocene. After the intermolecular H migration in diradical intermediate **48** forms and then it proceeds to form cyclopentenediones **33.**

Stereochemistry of similar cyclopentenediones have been determined by Moore and coworkers (Figure 21) (37b). During the thermolysis of **49**, only **50** was obtained as the kinetic product and equilibration with the other isomer **51** was established with treatment of silica gel. Regioselective addition of MeLi to phenyl ethoxy substituted isomers give compounds **52** and **53**, respectively (Figure 21). The configuration was established with their ^{1}H-NMR spectra. The deshielding anisotropy effect of carbonyl group of the *E* isomer **53** make the vinyl hydrogen give resonance in more downfield compared to *Z* isomer **52** in ^{1}H-NMR [39]. Confirmation assignments have been done with NOE studies.

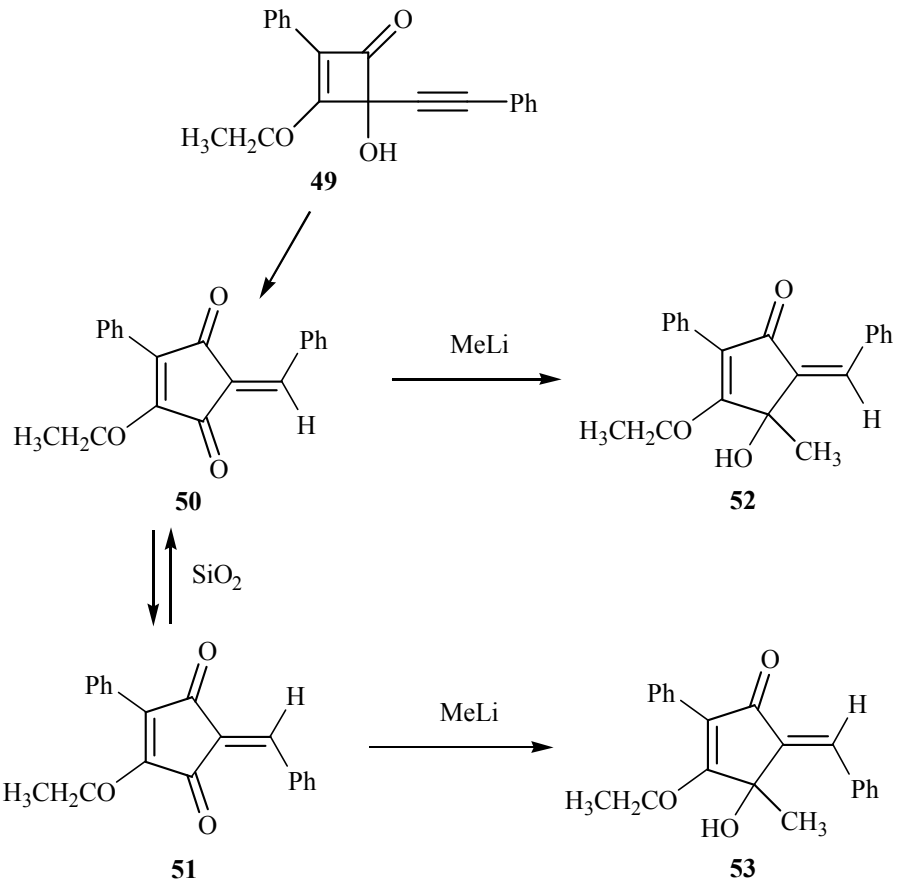

Figure 21. Stereochemical studies of cyclopentenediones

Although its formation is only a byproduct, the mechanism for the formation of ferrocenyl quinones **35** is also noteworthy (Figure 22). After the formation of enynyl ketene **46**, radical ring closure occurs in a way that the radical stays on the ring system and six-membered diradical **54** forms. After the intramolecular migration of hydrogen atom in the diradical intermediate, quinones **35** are obtained as green oils.

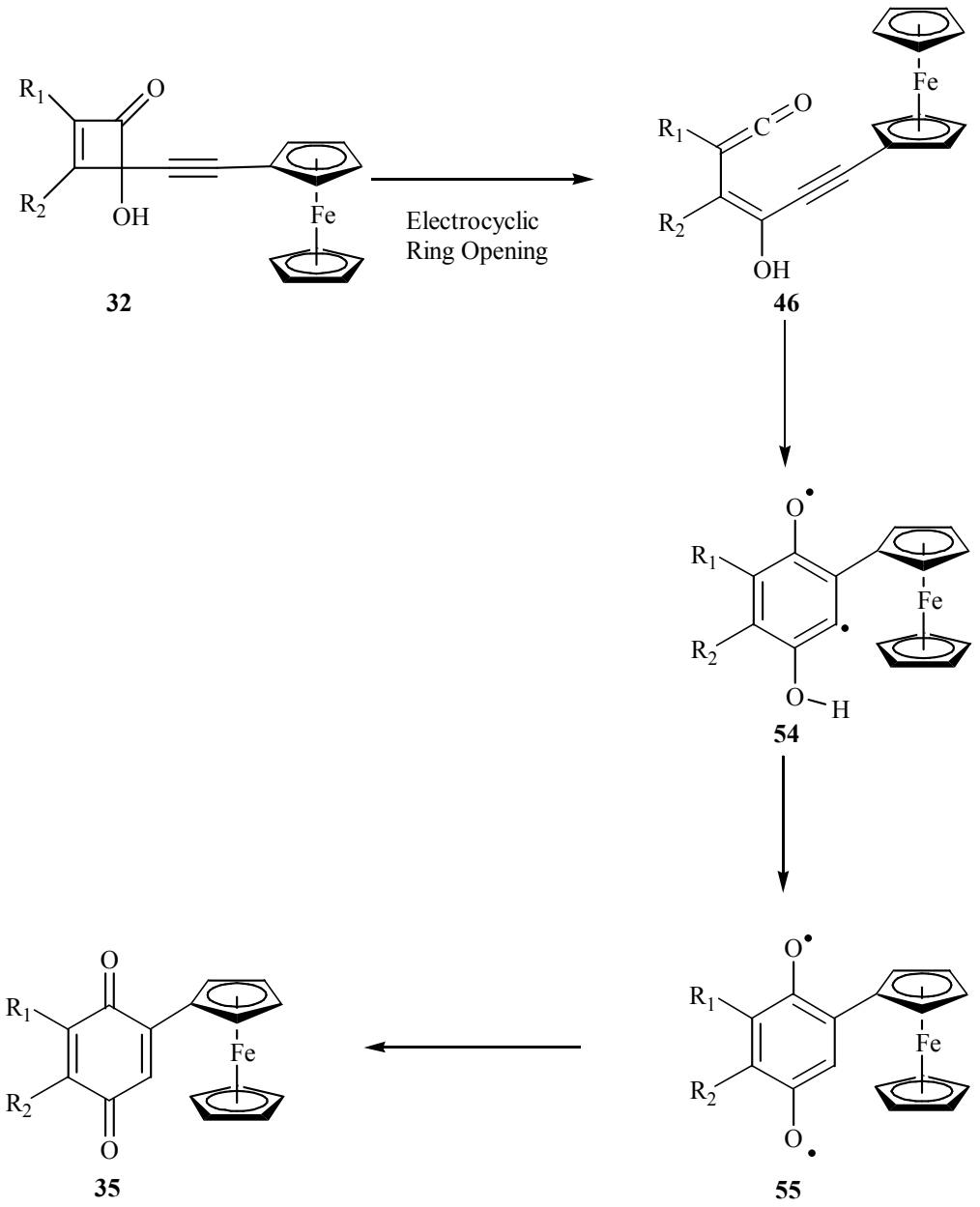

Figure 22. Formation mechanism of benzoquinones

Since methylisopropoxycyclobutenone **32D** afforded all the possible reaction products, their ^{1}H and ^{13}C NMR spectra reveal the characteristics of the products.

The structure elucidation of cyclopentendiones was primarily based on their ^{1}H and ^{13}C NMR spectra. For instance, in **33D**, The proton signals at δ 5.61 (septet, J = 6.1 Hz) and 1.36 (d, J = 6.1 Hz), which were related to carbon signals at δ 74.5 and 23.6 ppm, reveal the presence of isopropoxy group. Signals on δ 5.21, 4.60 and 4.15 ppm belongs to the ferrocenyl group, which appears at δ 74.5, 73.8 and 70.5 ppm in ^{13}C-NMR spectrum. It should be noted that the carbon peaks of ferrocenyl CH and isopropoxy CH signals overlap at δ 74.5 ppm according to HMQC spectrum. Ferrocenyl ipso carbon gives resonance at δ 76.3 ppm. The remaining methyl group substituted to cyclobutenedione ring gives resonance at δ 1.93 ppm. Two carbonyl carbons (δ 191 and 189.5 ppm) are also evident. As expected, in HMBC spectrum, the vinylic hydrogen peak at δ 7.25 ppm gives a two-bond coupling ($^{2}J_{CH}$) with the carbon (122.6 ppm) between carbonyl carbons and a three-bond coupling ($^{3}J_{CH}$) with the carbonyl carbons (189.5 and 191.0 ppm). Both cyclopentenedione isomers **33D** and **34D** show very similar spectra except the vinyl proton giving resonance at δ 7.25 ppm for **33D** and at δ 7.39 ppm for **34D**.

For cyclopentenedione derivative **33D**, the proton attached to the *β*-carbon atom gives chemical shift at δ 7.20 ppm where it is at δ 6.75 ppm for quinone **38D**. The delocalization between exocyclic C-C double bond and carbonyl group is doubled in cyclopentenedione system. This causes the exocyclic vinyl hydrogen to be more positive compared to that in quinone. Because the electron density on this proton is less, it gives resonance in more downfield (Figure 23). This evidence is further supported with the ferrocenyl hydrogens which appear at δ 5.21 and 4.92 ppm for cyclopentenedione **33D** and quinone **35D**, respectively.

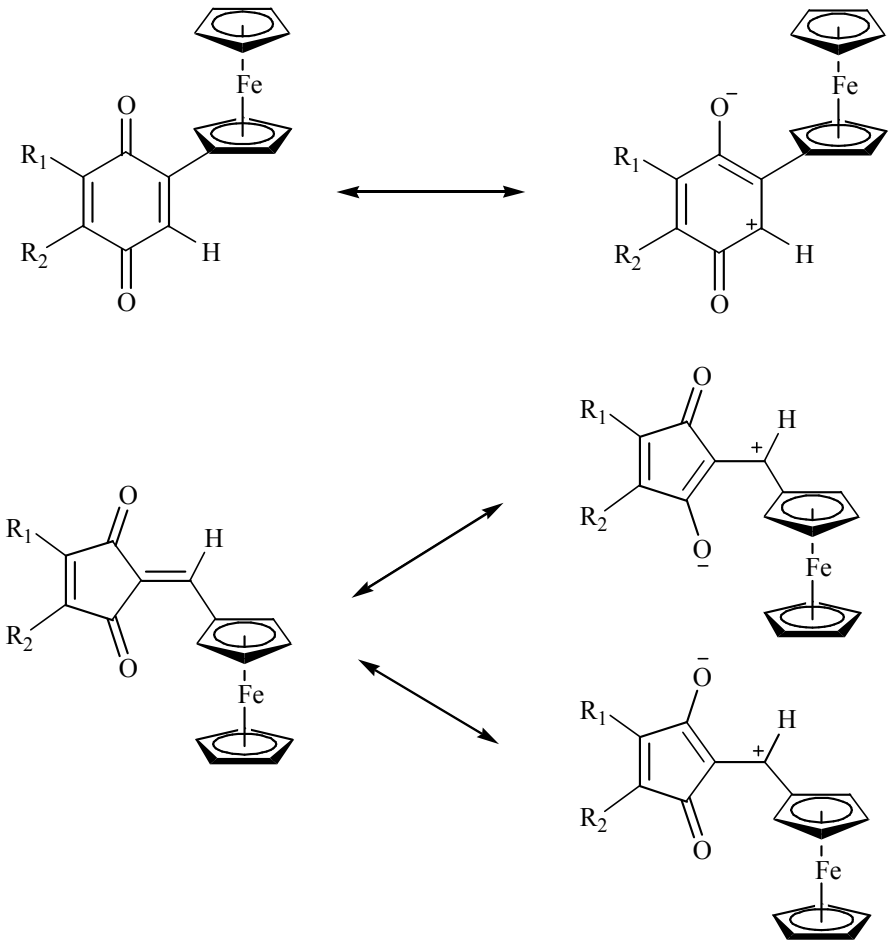

Figure 23. Delocalization of double bond in benzoquinones **35** and cyclopentenediones **33**.

Another evidence for the exact structures of these two cyclopentenedione products was obtained by mass spectroscopy. The MS (FAB) analysis of **33D** showed molecular peaks at *m/z* 364 ([M]+). However, in addition to [M]+ peaks,. quinones showed peaks which corresponds to [M+2] ion, resulting from the hydroquinone formation from quinones under mass conditions. Similar situation was not observed for cyclopentenediones.

CHAPTER 3

CONCLUSION

We have investigated the synthesis of ferrocenyl-substituted 2-alkylidene-4-cyclopentene-1,3-diones (**33** and/or **34**) starting from squaric acid (**25**). For this purpose, ethynylferrocene was first prepared and then converted to 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenone derivatives (**37A-E**) by a series of reactions. The thermolysis of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (**37A-E**) in dioxane at 100 ^{o}C afforded 2-ferrocenylidene-4-cyclopentene1,3-diones (**33A-E**) as major or single products. In some cases, the isomer of **34B**, i.e. **36B,** and/or benzoquinones **35A-C** formed as very minor products.

We have also shown that the heating of a mixture of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenones (**37A-C**) and silica gel in oven at 120 ^{o}C without using any solvent provided the same type products. More importantly, the stirring of a solution of 4-ferrocenylethynyl-4-hydroxy-2-cyclobutenone (**37A-C**) derivatives in ethyl acetate at the room temperature yielded the same type products, as well.

The formation of 2-ferrocenylidene-4-cyclopentene1,3-dione derivatives (**33A-E**) as major or single products was attributed due to the radical stabilizing ability of ferrocenyl group.

CHAPTER 4

EXPERIMENTAL

General Consideration. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Brucker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in a parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in hertz(Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C-NMR information is given in parenthesis as C, CH, CH_2, CH_3. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Band positions are repoted in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Mass spectra (MS) were obtained on a Micromass UK Platform-II spectrometer using electron impact (EI); *m/e* values are reported, followed by the relative intensity in parantheses. Flash column chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230-400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF, and dioxane were distilled from sodium/benzophenone kettle. The inert atmosphere is created by slight positive pressure (ca. 0.1 psi) of argon.

4.1. Synthesis of acetylferrocene (36).

Ferrocene (**1**) (2.0 g, 0.011 mol) was added to a round-bottomed flask and dissolved with stirring in dry dichloromethane (9 mL). To the resultant dark orange/red solution, acetyl chloride (0.9 g, 0.012 mol) was added, then flask was immersed in an ice-water bath at 0-5 °C. Aluminium chloride (1.44 g, 0.011 mol) was added in approximately 10 portions to the reaction mixture, allowing approximately 2 min between each addition. Then the reaction was stirred for 2 h during which time the ice-water bath was allowed to warm to room temperature. After this period of time, the solution was recooled by placing it in a fresh ice-water bath. Reaction mixture was hydrolyzed by the slow addition of 4 x 0.5 mL portions of cold water. Then a further 3.0 mL of cold water was added more rapidly. The mixture was transferred to separating funnel and the organic (lower) phase was separated. The aqueous phase was extracted with two 10 mL portions of dichloromethane. The organic extracts were combined and washed with 2.5 mL of saturated aqueous sodium chloride solution. Then organic solution was dried over sodium sulfate and the solvent was removed on a rotary evaporator Final purification was achieved by flash chromatography on silica gel using 9:1 as eluent and single fraction was assigned as acetylferrocene (**36**) as a red/orange solid (1.96 g, 80%)

36: ^{1}H-NMR ($CDCl_3$): δ 2.40 (s, 3 H), 4.21 (s, 5 H), 4.51 (s, 2 H), 4.78 (s, 2 H). The spectral data are in agreement with those reported previously for this compound [52].

4.2. Synthesis of (2-formyl-1-chlorovinyl)ferrocene (37).

A dry two necked flask, equipped with a pressure equalizing dropping funnel is charged with acetylferrocene (**36**) (2.28 g, 0.01 mol) and *N,N*-dimethylformamide (DMF) (2.5 mL, 0.032 mol) the system was flushed under argon and cooled to 0 °C, and the brown reaction mixture was stirred for several minutes. Separately, in a 25 ml flask DMF (2.5 mL, 0.032 mol) was added, flushed under argon, cooled to 0 °C and agitated by hand during the cautious addition of phosphorus oxychloride (2.5 mL, 0.027 mol). The resulting viscous, red complex was transferred to the dropping funnel and added to mixture of acetylferrocene and DMF dropwise over 30 min. The mixture was stirred at 0°C for 2 h during which time the color of the reaction mixture changed from dark brown to olive and ultimately to deep blue. A 7.5 mL portion of diethyl ether was added, and the viscous mixture was stirred vigorously for several minutes. With continued ice cooling, sodium acetate trihydrate (11.6 g, 0.085 mol) was cautiously added to the reaction mixture in one portion followed by cautious addition of 1 mL of water with vigorous stirring. The ice bath was removed whereupon the organic layer undergone a striking color change from colorless to ruby red indicating the formation of the formyl derivative. After 1 h, an additional 1 mL of ether was added, and stirring was continued for 3 h at room temperature to ensure complete quenching. The reaction mixture was transferred to a separatory funnel with ether and water and mixed thoroughly, and the organic phase was separated. The aqueous phase was extracted several times with 10 mL portions of ether. The combined organic phases were carefully washed twice with 10 mL portions of saturated aqueous sodium bicarbonate solution and then with 10 mL of water. The organic phase was dried over sodium sulfate, filtered, and concentrated using a rotary evaporator affording (2-formyl-1-chlorovinyl)ferrocene (**37**) as deep purple crystals after drying under high vacuum (2.56 g, 93%).

37: ^{1}H-NMR ($CDCl_3$): δ 4.24 (s, 5 H), 4.57 (s, 2 H), 4.75 (s, 2 H), 6.40 (d, 1 H), 10.09 (d, 1 H). The spectral data are in agreement with those reported previously for this compound [52].

4.3. Synthesis of ethynylferrocene (38).

(2-formyl-1-chlorovinyl)ferrocene (**37**) (2.6 g, 9.5 mmol) and of anhydrous 1,4-dioxane (30 mL) were placed into a dry, two-necked, round-bottomed flask, equipped with a reflux condenser, and was flushed with argon. Then the apparatus was placed in an oil bath. The reaction mixture was heated to reflux and after 5 min at reflux, 25 mL of a boiling 1 N solution of sodium hydroxide (a 2.5-fold excess) was cautiously added as rapidly as possible in one portion, and the mixture was heated at reflux for another 25 min. The oil bath was removed and the reaction mixture was allowed to cool to room temperature. The reaction mixture was poured into ice and neutralized with 1 N hydrochloric acid. After transferring to a separately funnel, the aqueous mixture was extracted five times with 10 mL of hexane. After the combined organic extracts were successively washed twice with 10 mL portions of saturated aqueous sodium bicarbonate solution and water, the organic phase was dried over sodium sulfate, filtered, and concentrated using a rotary evaporator affording an orange residue of crude ethynylferrocene. The crude product was purified by flash chromatography with elution by hexane. Concentration of the fractions containing the product and drying under high vacuum afforded pure ethynylferrocene (**38**) which crystallized as an orange solid (1.48 g, 74%).

38: ^{1}H-NMR ($CDCl_3$): δ 2.71 (s, 1 H), 4.19 (s, 2 H), 4.21 (s, 5 H), 4.46 (s, 2 H). The spectral data are in agreement with those reported previously for this compound [52].

4.4. 3,4-Diisopropoxy-3-cyclobutene-1,2-dione (Diisopropyl squarate) (26A).

3,4-dihydroxy-3-cyclobutene-1,2-dione (Squaric acid) (**25**) (20.00 g, 175.40 mmol) was sluried in 100 mL of 1:1 benzene/2-propanol in a round-bottomed flask equipped with a Dean-Stark apparatus. The suspension was heated to reflux with continuous removal of the azeotrope over a period of 72 h. As the azeotrope was removed, 1:1 benzene/2-propanol was replenished. The reaction mixture was cooled to room temperature, and the solvents were removed on a rotary evaporator. The resulting oil was dissolved in diethyl ether (350 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 20 mL) and once with saturated aqueous sodium chloride solution (20 mL). After drying over sodium sulfate, the solvent was removed on a rotary evaporator. The resulting viscous oil (R_f = 0.30 in 4:1 hexane/ethyl acetate) gave crystals of diisopropyl squarate (**26A**) after standing overnight under argon (mp. 43-44 ^{o}C, 30.74 g, 88.4%). The product was pure according to TLC and ^{1}H-NMR.

26A: ^{1}H-NMR ($CDCl_3$): δ 5.35 (septet. 2 H, J = 6.1 Hz), 1.46 (d, 12H, J = 6.1 Hz); IR (CCl_4): 2986(w), 1809 (m), 1736 (s), 1606 (vs), 1468 (w), 1406 (vs), 1388 (s), 1377(m), 1331 (m), 1102 (s) cm^{-1}. The spectral data are in agreement with those reported previously for this compound [50b].

4.5. General procedure 1. Synthesis of hydroxycyclobutenones (39B,C).

To a solution of diisopropyl squarate (26A) (25.25 mmol) in THF (50 ml) at -78 °C under argon was added the corresponding organolithium reagent (30.30 mmol). The reaction mixture was stirred for 3 h at -78 °C, and then quenched by water (20 ml) at -78 °C. The mixture was diluted with diethyl ether (250 ml), and the organic layers were seperaetd. The aqueous layerwas extracted with diethyl ether (2 x 50 ml). The combined organic layers were dried over sodium sulfate, and the solvents were removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.5.1. 4-Hydroxy-2,3-diisopropoxy-4-methyl-2-cyclobuten-1-one (39B).

General procedure 1 was followed using diisopropyl squarate (**26A**) (5.00 g, 25.25 mmol), methyllithium (17.9 ml 1.7 M diethyl ether solution, 30.30 mmol). A single fraction was collected and assigned as compound **39B** (5.07 g, 94%)

39B: ^{1}H-NMR ($CDCl_3$): δ 4.89 (septet. 1 H, *J* = 6.0 Hz), 4.87 (septet, 1H, *J* = 6.0 Hz), 2.60 (s, 1H), 1.50 (s, 3H), 1.41 (d, 3H, *J* = 6.0 Hz), 1.39 (d, 3H, *J* = 6.0 Hz), 1.29 (d, 3H, *J* = 6.0 Hz), 1.26 (d, 3H, *J* = 6.0 Hz); IR (neat): 3400 (br), 2990 (m), 1770 (s), 1625 (vs), 1390 (m), 1340 (m). The spectral data are in agreement with those reported previously for this compound [51b].

4.5.2. 4-Hydroxy-2,3-diisopropoxy-4-phenyl-2-cyclobuten-1-one(39C).

General procedure 1 was followed using diisopropyl squarate (**26A**) (5.00 g, 25.25 mmol), phenyllithium (16.8 ml 1.7 M diethyl ether solution, 30.30 mmol). A single fraction was collected and assigned as compound **39C** (5.9 g, 85%).

39C ^{1}H-NMR ($CDCl_3$): δ 7.56-7.51 (m, 2H), 7.40-7.29 (m, 3H), 4.96 (septet. 1 H, *J* = 6.0 Hz), 4.91 (septet, 1H, *J* = 6.0 Hz), 2.81 (s, 1H), 1.41 (d, 3H, *J* = 6.0 Hz), 1.35 (d, 3H, *J* = 6.0 Hz), 1.34 (d, 3H, *J* = 6.0 Hz), 1.30 (d, 3H, *J* = 6.0 Hz); IR (neat): 3570 (br), 2980 (m), 1768 (vs), 1620 (vs), 1318 (m). The spectral data are in agreement with those reported previously for this compound [51b].

4.6. General procedure 2. Synthesis of cyclobutenediones (26B,C).

Cyclobutenone derivative **39** was dissolved in dichloromethane (50 ml) and concentrated HCl (4 drops, ca 0.20 ml) was added. The mixture was stirred at room temperature for 30 min (The progress of the reaction was monitored by routine TLC for disappearance of the starting compound). The reaction mixture was then diluted with saturated sodium bicarbonate solution (20 ml) and the layers were separated. The organic layer was washed with water (2 x 10 ml). and the aqueous layer was extracted with dichloromethane (2 x 50 ml). Combined organic layers were dried over sodium sulfate. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.6.1 3-Isopropoxy-4-methyl-3-cyclobutene-1,2-dione (26B).

General Procedure 2 was followed using cyclobutenone **39B** (5.07 g, 23.69 mmol). After chromatographic purification, a single fraction (R_f = 0.26 in 4:1 hexane/ethyl acetate) was isolated and identified as compound **26B** (3.36 g, 92 %)

26B: ^{1}H-NMR ($CDCl_3$): δ 5.40 (septet, 1H, *J* = 6.0 Hz), 2.22 (s, 3H), 1.48 (d, 6H,); IR (neat): 2985 (vw), 2359 (vw), 1799 (vs), 1750 (vs), 1597 (vs), 1399 (s), 1331 (m), 1098 (m), 1072 (w), 977 (vw), 897 (vw), 730 (w) cm^{-1}. The spectral data are in agreement with those reported previously for this compound [50b].

4.6.2. 3-Isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (26C).

General Procedure 2 was followed using cyclobutenone **39C** (5.92 g, 21.45 mmol). After chromatographic purification, a single fraction (R_f = 0.20 in 9:1 hexane/ethyl acetate) was isolated and identified as compound **26C** (4.12 g, 89 %).

26C: ^{1}H-NMR ($CDCl_3$): δ 8.10-8.00 (m, 2H), 7.60-7.45 (m, 3H), 5.63 (septet, 1H, *J* = 6.0 Hz), 1.57 (d, 6H, *J* = 6.0 Hz); IR (CH_2Cl_2): 2986 (m), 1781 (vs), 1749 (vs), 1603 (vs), 1586 (vs), 1494 (s), 1397 (vs), 1342 (s), 1268 (s), 1086 (vs), 1016 (s), 905 (s), 777 (m), 692 (s) cm^{-1}. The spectral data are in agreement with those reported previously for this compound [50b].

4.6.3. 4-(Trimethylsiloxy)-2,3-bis(1-methylethoxy)-4-methylcyclobut-2-en-1-one (40).

To a solution of diisopropyl squarate(**26A**) (2.5 g, 12.62 mmol) in THF (25 ml) at -78 ºC under argon was added *via* syringe methyllithium (10.1 ml 1.5 M diethyl ether solution, 15.15 mmol) over a period of 15 min. The reaction mixture was stirred for 3 h at -78 ºC, and then allowed to come to room temperature and chlorotrimethylsilane (3.2 ml, 25.24 mmol) was added into the solution. The resulting solution was stirred for 1 h at this temperature and diluted with ether (150 ml). The layers were separated and the aqueous layer was extracted with ether (2 x 50 ml). the combined organic layers were dried over sodium sulfate, and the solvent was removed on rotary evaporator. final purification was achieved by column chromatography on aluminum oxide using 9:1 hexane/ethyl acetate as the eluent. A single fraction (R_f = 0.43 in 9:1 hexane/ethyl acetate) was isolated and identified as compound **40** (2.41 g, 67 %).

40: ^{1}H-NMR ($CDCl_3$): δ 4.79 (septet, 1H, *J* = 6.1 Hz), 1.36 (s, 3H), 1.34 (d, 3H, *J* = 6.3 Hz), 1.32 (d, 3H, *J* = 6.3 Hz), 1.21 (d, 3H, *J* = 6.1 Hz) d, 1.18 (3H, *J* = 6.1 Hz), 0.07 (s, 9H); ^{13}C-NMR ($CDCl_3$): δ 185.8 (C), 167.5 (C), 129.1 (C), 83.1 (C), 75.2 (CH), 71.7 (CH), 21.5 (CH_3), 21.4 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 19.5 (CH_3), 0.29 (CH_3); IR (CH_2Cl_2): 2980 (m), 2933 (w), 1768 (m), 1625 (vs), 1465 (w), 1385 (m), 1322 (s), 1251 (m), 1142 (m), 1100 (m), 1036 (w), 995 (s), 924 (m), 910 (m), 865 (w), 845 (w) cm^{-1}.

4.6.4. 3,4-Dimethylcyclobut-3-ene-1,2-dione (26D).

Solution of compound **40** (2.41 g, 8.42 mmol)in THF (25 ml) at -78 ºC under argon was treated dropwise methyllithium(6.73 ml 1.5 M diethyl ether solution, 10.1 mmol). Reaction was complete in 3 h and was quenched at -78 ºC. The aqueous phase was extracted with ether (3 x 50 ml) and combined extracts were dried over sodium sulfate. The solvent was removed on rotary evaporator and the crude oil was dissolved in CH_2Cl_2 (20 ml) and treated with 4 drops of concentrated HCl. The mixture was stirred at room temperature for 30 min (the progress of the reaction was monitored by routine TLC for the disappearance of the starting compound). The reaction mixture was then diluted with saturated sodium bicarbonate solution (20 ml), and the aqueous layer was extracted with dichloromethane (2 x 50 ml). Combined organic layers were dried over sodium sulfate. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent (R_f = 0.23 in 4:1 hexane/ethyl acetate) was isolated and identified as compound **26D** (0.47 g, 51 %).

26D: ^{1}H-NMR ($CDCl_3$): δ 2.31 (s, 6H); ^{13}C-NMR ($CDCl_3$): δ 200.2 (C), 199.7 (C), 11.3 (CH_3); IR (CH_2Cl_2): 1774 (vs), 1606 (vs), 1428 (w), 1383 (m), 1307 (m), 1179 (w), 1106 (w), 1017 (m), 908 (w), 682 (w) cm^{-1}.

4.6.5. 3,4-Diphenyl-3-cyclobuten-1,2-dione (26E).

A mixture of squaric acid (**25**) (3.04 g, 26.6 mmol), thionyl chloride (6.42 mL, 54 mmol), and DMF (catalytic amount), was placed into a two necked round bottom flask and refluxed for 2.5 hours. To the reaction mixture, benzene (20 ml) and $AlCl_3$ (8.50g, 63.8 mmol) were added and the mixture was stirred for 45 h at room temperature. The mixture was poured into water and extracted with diethyl ether (2 x 150 ml). the combined organic layers were dried over sodium sulfate, and the solvents were removed on rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent. A single fraction (R_f = 0.35 in 9:1 hexane/ethyl acetate) was isolated and identified as compound **26E.**

26E: ^{1}H-NMR ($CDCl_3$): δ 8.02 (d, 4H, *J* = 7.5 Hz), 7.56-7.47 (m, 6H). The spectral data are in agreement with those reported previously for this compound [53].

4.7. General Procedure 3. Reaction of ethynyl ferrocene (36) with cyclobutanediones (26A-E).

To a solution of cyclobutenedione derivative **26** (1 mmol) in THF (15 ml) at -78^o C under argon was added ferrocenyl ethynyl lithium (**43**) (1.1 mmol), which was prepared *in situ* by reacting *n*-butyllithium and ethynyl ferrocene (**36**). The reaction mixture was stirred at -78^0 C for 3 h and then quenched with water (5 ml) at -78^0 C. The mixture was allowed to warm to room temperatureand diluted with ether (50 ml). The layers were seperated and the aqueous layer was extracted with ether (2 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvents were removed on rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate followed by 4:1 hexane/ethyl acetate as eluent.

4.7.1 4-hydroxy-2,3-diisopropoxy-4-ferrocenylethynyl-2-cyclobutenone (32A).

General Procedure 3 was followed using cyclobutenedione **26A** (200 mg,1 mmol) and ferrocenyl ethynyl lithium, which was prepared *in situ* by reacting ethynyl ferrocene (0.25 g, 1.2 mmol) in THF (15 ml) and *n*-butyllithium (0.45 mL of a 2.5 M of hexane-ether solution, 1.1 mmol) at 0^0 C.After chromatographic purification two fractions were isolated. First fraction (R_f =0.40 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione **(33A)** (20 mg, 5 %). The second fraction (R_f =0.30 in 4:1 hexane/ethyl acetate) was isolated and assigned as compound **32A** (265 mg, 65%).

32A: ^{1}H NMR ($CDCl_3$): δ 5.01 (septet, 1 H, *J*=6.1 Hz), 4.87 (septet, 1H, *J*=6.1 Hz), 4.41 (s, 2 H), 4.17 (s, 7H), 3.10 (br s, 1 H), 1.45 (d, 3H, *J*=6.1 Hz), 1.43 (d, 3H, *J*=6.1 Hz), 1.29 (d, 3H, *J*=6.1 Hz), 1.28 (d, 3H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 181.0 (C), 164.8 (C), 134.3 (C), 88.3 (C), 80.0 (C), 79.7 (C), 78.2 (CH), 74.5 (CH), 72.0 (CH), 70.4 (CH), 69.3 (CH), 63.9(C), 23.1(CH_3), 22.9(CH_3); IR (CH_2Cl_2): 3358 (w), 3323 (br), 2975 (m), 2928 (m), 2223 (w), 1773 (s), 1627 (vs), 1458 (w), 1388 (s), 1322 (s), 1261 (s), 1096 (s) cm^{-1}; MS (FAB): 409 ($[M+1H]^+$, 55), 408 ($[M]^+$, 100), 395 (11), 324 (19), 311 (6), 213 (18), 199 (7), 137 (17), 136 (16), 43 (11), 41 (9); HRMS (FAB): Calc. for $C_{22}H_{24}FeO_4$: 408.1034. Found: 408.1024.

33A: ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 4.91, 5.50 (septet, 1 H, *J*=6.2 Hz), 5.44 (septet, 1 H, *J*=6.2 Hz), 5.14 (pseudo t, 2H), 4.56 (pseudo t, 2H), 4.13 (s, 5H), 1.36 (d, 6H, *J*=6.2 Hz), 1.34 (d, 6H, *J*=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 186.1 (C), 150.9 (C), 147.1 (C), 139.0 (CH), 121.6 (C), 76.2 (C), 75.1 (CH), 74.9 (CH), 74.2 (CH), 73.4 (CH), 70.4 (CH), 23.4 (CH_3), 23.4 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1668 (vs), 1620 (vs), 1461 (vw), 1377 (m), 1305 (s), 1102 (s), 1029 (s) cm^{-1}; MS (FAB): 409 ($[M+1H]^+$, 36), 408 ($[M]^+$, 75), 367 (12), 366 (9), 324 (41), 301 (27), 259 (100), 186 (9), 135 (10), 121 (8), 103 (18), 85 (18), 45 (34); HRMS (FAB): Calc. for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1035.

4.7.2 4-hydroxy-3-isopropoxy-2-methyl-4-ferrocenylethynyl-2-cyclobutenone(32B).

General procedure 3 was followed using cyclobutenedione **26B** (155 mg, 1 mmol) and ferrocenyl ethynl lithium, which was prepared *in situ* by reacting ethynyl ferrocene (0.25 g, 1.2 mmol) in THF (15 ml) and (*n*-butyllithium (0.45 mL of a 2.5 M of hexane-ether solution, 1.1 mmol) at 0^{o} C.After chromatographic purification three fractios were isolated. The first fraction (R_f =0.58 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione **(33B)** (69 mg, 19 %). Second fraction (R_f =0.45 in 9:1 hexane/ethyl acetate) was isolated and assigned as compound **34B** (33 mg, 9 %)**.** Third fraction (R_f =0,25 in 4:1 hexane/ethyl acetate) was isolated and assigned as compound **32B** (124 mg, 34 %).

32B: ^{1}H NMR ($CDCl_3$): δ 5.08 (septet, 1 H, *J*=6.1 Hz), 4.40 (s, 2 H), 4.17 (s, 7H), 3.34 (s, 1 H), 1.68 (s, 3H), 1.50 (d, 3H, *J*=6.1 Hz), 1.46 (d, 3H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.6 (C), 180.3 (C), 124.9 (C), 89.4 (C), 84.2 (C), 79.9 (C), 77.7 (CH), 72.0 (CH), 70.4 (CH), 69.4 (CH), 63.8 (C), 23.4 (CH_3), 23.1 (CH_3), 7.0 (CH_3); IR (CH_2Cl_2): 3559 (w), 3308 (br), 2976 (w), 2926 (vw), 2223 (w), 1764 (s), 1623 (vs), 1463 (vw), 1397 (s), 1312 (s), 1097 (s) cm^{-1}; MS (FAB): 365 ($[M+1H]^+$, 81), 364 ($[M]^+$, 87), 347 (82), 322 (100), 305 (25), 295 (16), 257 (96), 255 (13), 210 (11), 183 (6), 157 (8), 121 (20), 85 (9); HRMS (FAB): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775.

33B: ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H), 5.61 (septet, 1 H, *J*=6.1 Hz), 5.21 (s, 2H), 4.60 (s, 2 H), 4.15 (s, 5H), 1.93 (s, 3H), 1.36 (d, 6H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 191.0 (C), 189.5 (C), 163.8 (C), 140.7 (CH), 134.7 (C), 122.6 (C), 76.1 (C), 74.5 (CH)(Fc CH and isopropoxy CH overlaps), 73.8 (CH), 70.5 (CH), 23.7 (CH_3), 7.6 (CH_3); IR (CH_2Cl_2): 2980(vw) , 1712 (w), 1668 (vs), 1605 (vs), 1492 (w), 1376 (vs), 1319 (m), 1247 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 365 ($[M+1H]^+$, 73), 364 ($[M]^+$, 100), 322 (35), 299 (16), 257 (100), 155 (12), 119 (26), 85 (30); HRMS (FAB): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775

34B: ^{1}H NMR ($CDCl_3$): δ 7.39 (s, 1H), 5.58 (septet, 1 H, *J*=6.1 Hz), 5.20 (s, 2H), 4.64 (s, 2 H), 4.18 (s, 5H), 1.97 (s, 3H), 1.40 (d, 6H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 192.3 (C), 188.0 (C), 166.3 (C), 141.0 (CH), 130.0 (C), 122.2 (C), 76.2 (C), 74.6 (CH), 74.4 (CH), 73.8 (CH), 70.5 (CH), 23.6 (CH_3), 7.5 (CH_3).

4.7.3 4-Hydroxy-3-isopropoxy-2-phenyl-4-ferrocenylethynyl-2-cyclobutenone (32C).

General Procedure 3 was followed using cyclobutenedione **26C** (216 mg,1 mmol) and ferrocenyl ethynyl lithium, which was prepared *in situ* by reacting ethynyl ferrocene (0.25 g, 1.2 mmol) in THF (15 ml) and *n*-butyllithium (0.45 mL of a 2.5 M of hexane-ether solution, 1.1 mmol) at 0^0 C) to yield **32C** (R_f =0.23 in 4:1 hexane/ethyl acetate). After the removal of the solvent on a rotary evaporator, the crude product obtained was found to be very reactive and immediately converted to compound **33C** (see **4.8.3**).

4.7.4 4-hydroxy-2,3-dimethyl-4-ferrocenylethynyl-2-cyclobutenone (32D).

General procedure 3 was followed using cyclobutenedione **26D** (110 mg,1 mmol) and ferrocenyl ethynl lithium, which was prepared *in situ* by reacting ethynyl ferrocene (0.25 g, 1.2 mmol) in THF (15 ml) and (*n*-butyllithium (0.45 mL of a 2.5 M of hexane-ether solution, 1.1 mmol) at 0^0 C. After chromatographic purification two fractions were isolated. The first fraction (R_f =0.49 in 4:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione **(33D)** (70 mg, 22 %). The second fraction (R_f =0.17 in 4:1 hexane/ethyl acetate) was isolated and assigned as compound **32D** (122 mg, 38 %).

32D: ^{1}H NMR ($CDCl_3$): δ 4.39 (s, 2H), 4.18 (s, 2H), 4.16 (s, 5H), 2.58(s,1H), 2.20 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.8 (C), 177.2 (C), 151.1 (C), 89.2 (C), 87.1 (C), 80.4 (C), 72.0 (CH), 70.6 (CH), 69.4 (CH), 63.9 (C), 10.9 (CH_3), 8.4 (CH_3); IR (CH_2Cl_2): 3568 (w), 3392 (br), 3099 (vw), 2960 (vw), 2219 (m), 1765 (vs), 1637 (s), 1432 (w), 1380 (w), 1303 (w), 1259 (w), 1176 (w), 1099 (m) cm^{-1}; MS (FAB): 321 ([M+1H]$^+$, 68), 320 ([M]$^+$, 100), 303 (76), 275 (50), 255 (90), 253 (11), 183 (10), 155 (14), 121 (13), 115 (4), 85 (5); HRMS (FAB): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489.

33D: ^{1}H NMR ($CDCl_3$): δ 7.40 (s, 1H), 5.24 (pseudo t, 2H, J = 1.7 Hz), 4.64 (pseudo t, 2H, J = 1.7 Hz), 4.13 (s, 5H), 2.02 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 194.7 (C), 193.5 (C), 154.0 (C), 150.2 (C), 142.8 (CH), 121.1 (C), 76.0 (C), 74.6 (CH), 74.1 (CH), 70.6 (CH), 9.6 (CH_3), 9.6 (CH_3); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1604 (vs), 1492 (w), 1376 (vs), 1326 (s), 1248 (m), 1126 (s), 1088 (s), 1023 (s) cm^{-1}; MS (FAB): 321 ([M+1H]$^+$, 51), 320 ([M]$^+$, 100), 256 (23), 255 (84), 149 (14), 121(9), 85 (9), 69 (6); HRMS (FAB): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0514

4.7.5 4-Hydroxy- 2,3- diphenyl-4-ferrocenylethynyl-cyclobut-2-enone (32E)

General procedure 3 was followed using cyclobutenedione **26E** (234 mg,1 mmol) and ferrocenyl ethynl lithium which was prepared *in situ* by reacting ethynyl ferrocene (0.25 g, 1.2 mmol) in THF (15 ml) and (*n*-butyllithium (0.45 mL of a 2.5 M of hexane-ether solution, 1.1 mmol) at 0^0 C to yield **32E** (R_f =0.24 in 4:1 hexane/ethyl acetate). After the removal of the solvent on a rotary evaporator, the crude product obtained was found to be very reactive and immediately converted to compound **33E** (see **4.8.5**).

4.8. General Procedure 4: Ring Enlargement Reactions of 32A-E (Method 1)

A dioxane (15 ml) solution of alcohol **32A-E** (0.50 mmol) was heated to reflux under argon for a period of 4 h. The mixture was allowed to cool to room temperature and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel 9:1 hexane/ ethyl acetate as eluent.

4.8.1 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione (33A).

General procedure 4 was followed using alcohol **32A** (204 mg, 0.5 mmol). After chromatographic purification two fractions were isolated. The first fraction (R_f =0.41 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2,3-diisopropoxy-5-ferrocenyl-[1,4] benzoquione **(35A)** (4 mg, 2 %) The second fraction (R_f =0.40 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione **(33A)** (142 mg, 70 %).

33A: Spectral data are given in **3.7.1**

35A: ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.91 (s, 2H), 4.89 (septet, 1 H, *J*=6.2 Hz), 4.74 (septet, 1 H, *J*=6.2 Hz), 4.57 (s, 2H), 4.13 (s, 5H), 1.33 (d, 6H, *J*=6.2 Hz), 1.31 (d, 6H, *J*=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 184.8 (C), 184.0 (C), 147.2 (C), 145.8 (C), 125.5 (CH), 76.3 (C), 76.2(CH), 72.5(CH), 70.9 (CH), 70.1 (CH), 23.1 (CH_3), 23.0 (CH_3) two tertiary carbons match with each other; IR (CH_2Cl_2): 2975 (w), 2928 (vw), 1637 (s), 1567 (s), 1453 (w), 1378 (w), 1261 (vs), 1181(m), 1101 (s), 1049 (w) cm^{-1}; MS (FAB): 410 ($[M+2H]^+$, 100), 409 ($[M+1H]^+$, 14), 408 ($[M]^+$, 16), 368 (18), 325 (23), 291 (29), 259 (24), 213 (17), 186 (8), 121 (8); HRMS (FAB, $[M]^+$): Calc. for $C_{22}H_{24}FeO_4$: 408.1024. Found: 408.1015; HRMS (FAB, $[M+2H]^+$): Calc. for $C_{22}H_{26}FeO_4$: 410.1180. Found: 410.1199.

4.8.2 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (33B).

General procedure 4 was followed using alcohol **32B** (182 mg, 0.5 mmol). After chromatographic purification three fractions were isolated. The first fraction (R_f =0.59 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-isopropoxy-3-methyl-5-ferrocenyl-[1,4] benzoquione **(35B)** (7 mg, 4 %). The second fraction (R_f =0.58 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione **(33B)** (111 mg, 61 %). Third fraction (R_f =0.45 in 9:1 hexane/ethyl acetate) was isolated and assigned as compound **34B** (5 mg, 3 %).

33B: Spectral data are given in **3.7.2**

34B: Spectral data are given in **3.7.2**

35B: ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1H), 4.92 (s, 2H), 4.92 (septet, 1 H, *J*=6.1 Hz), 4.58 (s, 2 H), 4.12 (s, 5H), 1.96 (s, 3H), 1.31 (d, 6H, *J*=6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 187.7 (C), 183.5 (C), 154.8 (C), 148.8 (C), 131.0 (C), 126.0 (CH), 76.6 (C), 76.3 (CH), 72.5 (CH), 70.9 (CH), 70.30 (CH), 23.4 (CH_3), 9.9 (CH_3); IR (CH_2Cl_2):2975 (vw), 2928 (vw), 1646 (vs), 1580 (vs), 1453 (vw), 1378 (w), 1317 (vw), 1256 (s), 1181 (vs), 1096 (s), 1016 (m) cm^{-1}; MS (FAB): 366 ($[M+2H]^+$, 75), 365 ($[M+1H]^+$, 68), 364 ($[M]^+$, 100), 323 (27), 322 (19), 257 (45), 229 (9), 186 (3), 149 (6), 121 (6), 85 (4); HRMS (FAB, $[M]^+$): Calc. for $C_{20}H_{20}FeO_3$: 364.0762. Found: 364.0775; HRMS (FAB, $[M+2H]^+$): Calc. for $C_{20}H_{22}FeO_3$: 366.0918. Found: 366.0912.

4.8.3 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione (33C).

General procedure 4 was followed without purification of **32C**. After chromatographic purification a single fraction (R_f =0.48 in 4:1 hexane/ethyl acetate) was isolated as 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione (**33C**) (226 mg, 53 % from **26C**).

33C: ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 2H, *J* = 7.2 Hz), 7.45-7.35 (m, 4H), 5.91 (s, 1H, *J* = 6.1 Hz), 5.27 (pseudo t, 2H, *J* = 1.7 Hz), 4.65 (pseudo t, 2H, , *J* = 1.7 Hz), 4.15 (s, 5H), 1.41 (d, 6H, , *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 189.6 (C), 189.4 (C), 162.7 (C), 142.3 (CH), 132.1 (C), 130.0 (CH), 129.4 (CH), 128.5 (CH), 122.7 (C), 76.1 (C), 75.7 (CH), 74.9 (CH), 74.1 (CH), 70.6 (CH), 23.8 (CH_3) two of the tertiary carbons match with each other; IR (CH_2Cl_2): 2982 (vw), 1712 (w), 1668 (vs), 1617 (s), 1593 (m), 1491 (vw), 1376 (m), 1322 (w), 1268 (m), 1126 (w), 1088 (w), 1023 (m) cm^{-1}; MS (FAB): 427 ($[M+1H]^+$, 87), 426 ($[M]^+$, 100), 384 (47), 361 (12), 320 (30), 319 (91), 245 (4), 189 (4), 149 (4), 121 (5), 85 (4); HRMS (FAB): Calc. for $C_{25}H_{22}FeO_3$: 426.0918. Found: 426.0908.

4.8.4 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione (33D).

General procedure 4 was followed using alcohol **32D** (160 mg, 0.5 mmol). After chromatographic purification two fractions were isolated. The first fraction (R_f =0.53 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2,3-dimethyl-5-ferrocenyl-[1,4] benzoquione (**35D)** (13 mg, 8 %). The second fraction (R_f =0.49 in 4:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione **(33D)** (88 mg, 55 %).

33D: Spectral data are given in **3.7.4**

35D: ^{1}H NMR ($CDCl_3$): δ 6.80 (s, 1H), 4.91 (s, 2H), 4.55 (s, 2H), 4.11 (s, 5H), 1.94 (s, 3H), 1.93 (s, 3H); IR (CH_2Cl_2): 3680 (w), 3586 (vw), 2919 (w), 1641 (vs), 1623 (s), 1585 (s), 1453 (w), 1378 (w), 1317 (m), 1247 (s), 1030 (m) cm^{-1}; MS (FAB): 322 ([M+2H]$^+$, 72), 321 ([M+1H]$^+$, 88), 320 ([M]$^+$, 100), 287 (5), 255 (42), 253 (4), 209 (4), 177 (4), 155 (14), 119 (24), 85 (23); HRMS (FAB, [M]$^+$): Calc. for $C_{18}H_{16}FeO_2$: 320.0500. Found: 320.0489; HRMS (FAB, [M+2H]$^+$): Calc. for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0667.

4.8.5 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione (33E)

General procedure 4 was followed without purification of **32E**. After chromatographic purification a single fraction (R_f =0.42 in 4:1 hexane/ethyl acetate) was isolated as 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione **(33E)** (258 mg, 58 % from **26E**).

33E: ^{1}H NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.46-7.40 (m, 4H), 7.38-7.31 (m, 6H), 5.34 (s, 2H), 4.72 (s, 2H), 4.21 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 193.2 (C), 192.0 (C), 151.0 (C), 147.5 (C), 146.2 (CH), 130.6 (CH), 130.5 (CH), 130.3 (C), 130.1 (C), 130.0 (CH), 128.8 (CH), 76.2 (C), 75.1 (CH), 74.8 (CH), 70.8 (CH); IR (CH_2Cl_2): 2982 (w), 2933 (vw), 1712 (w), 1668 (vs), 1616 (vs), 1606 (vs), 1492 (w), 1376 (vs), 1326 (m), 1248 (w), 1127 (m), 1088 (s), 1024 (s) cm^{-1}; MS (FAB): 446 ($[M+2H]^+$, 39), 445 ($[M+1H]^+$, 100), 444 ($[M]^+$, 81), 379 (67), 377 (9), 323 (6), 279 (5), 202 (5), 135 (8), 119 (15), 85 (13); HRMS (FAB, $[M]^+$): Calc. for $C_{28}H_{20}FeO_2$: 444.0813. Found: 444.0825; HRMS (FAB, $[M+1H]^+$): Calc. for $C_{28}H_{21}FeO_2$: 445.0891. Found: 445.0914.

4.9 General Procedure 5: Ring Enlargement Reactions of 32 A,B,D (Method 2).

A mixture of silica gel (0.5 g) and alcohol **32A,B,D** (0.10 mmol) were heated in oven at 125^0 C for 5 minutes. The resulting mixture was cooled to room temperature and directly purified by flash chromatography on silica gel 9:1 hexane/ ethyl acetate as eluent.

4.9.1 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione (33A).

General procedure 5 (Method 2) was followed using alcohol **32A** (41 mg, 0.1 mmol). After chromatographic purification a single fraction (R_f =0.40 in 9:1 hexane/ethyl acetate) was isolated as 2-ferocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione **(33A)** (27 mg, 67 %).

4.9.2 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione(33B).

General procedure 5 (Method 2) was followed using alcohol **32B** (36 mg, 0.1 mmol). After chromatographic purification two fractions were isolated. The first fraction (R_f =0.58 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione **(33B)** (16 mg, 45 %). Second fraction (R_f =0.45 in 9:1 hexane/ethyl acetate) was isolated and assigned as compound **34B** (12 mg, 32 %).

4.9.3 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione (33D).

General procedure 5 (method 2) was followed using alcohol **32D** (32 mg, 0.1 mmol). After chromatographic purification two fractions were isolated. The first fraction (R_f =0.53 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2,3-dimethyl-5-ferrocenyl-[1,4] benzoquione **(35D)** (2 mg, 5 %).The second fraction (R_f =0.49 in 4:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione **(33D)** (23 mg, 71 %).

4.10 General Procedure 6: Ring Enlargement Reactions of 32 A-E (Method 3).

A mixture of silica gel (0.5 g) and alcohol **32A-E** (0.25 mmol) in ethyl acetate (10 ml) were stirred at room temperature and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel 9:1 hexane/ ethyl acetate as eluent.

4.10.1 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione (33A).

General procedure 6 (method 3) was followed for 48 h, using alcohol **32A** (41 mg, 0.1 mmol). After chromatographic purification a single fraction (R_f =0.40 in 9:1 hexane/ethyl acetate) was isolated as 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione **(33A)** (14 mg, 34 %).

4.10.2 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (33B).

General procedure 6 (method 3) was followed for 48 h, using alcohol **32B** (36 mg, 0.1 mmol). After chromatographic purification two fractions were isolated. The first fraction (R_f =0.58 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione **(33B)** (18 mg, 51 %). Second fraction (R_f =0.45 in 9:1 hexane/ethyl acetate) was isolated and assigned as compound **34B** (2 mg, 6 %).

4.10.3 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione (33C).

General procedure 6 (method 3) was followed for 24 h without purification of **32C**. After chromatographic purification a single fraction (R_f =0.48 in 4:1 hexane/ethyl acetate) was isolated as 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione **(33C)** (239 mg, 56 % from **26C**).

4.10.4 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione (33D).

General procedure 6 (method 3) was followed for 48 h, using alcohol **32D** (32 mg, 0.1 mmol). After chromatographic purification two fractions were isolated. The first fraction (R_f =0.53 in 9:1 hexane/ethyl acetate) was isolated and assigned as 2,3-dimethyl-5-ferrocenyl-[1,4] benzoquione (**35D)** (3 mg, 8 %). The second fraction (R_f =0.49 in 4:1 hexane/ethyl acetate) was isolated and assigned as 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione **(33D)** (24 mg, 74 %).

4.10.5 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione (33E).

General procedure 6 (method 3) was followed for 24 h, without purification of **32E**. After chromatographic purification a single fraction (R_f =0.42 in 4:1 hexane/ethyl acetate) was isolated as 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione **(33 E)** (200 mg, 45 % from **26E**).

REFERENCES

1 Solomons, T. W. G.; Fryhle, C. B. *Organic Chemistry*, 7th Ed., Wiley: New York, **2000**.

2 McMurry, J. *Organic Chemistry*, 5th Ed., Brooks/Cole: New York, **2000**.

3 Jones, M. *Organic Chemistry*, 2nd Ed., W. W. Norton & Company: New York, **2000**.

4 Volthard, K. P. C.; Schore, N. E. *Organic Chemistry*, 3rd Ed., Freeman: New York, **1999**.

5 Wade, L. G. *Organic Chemistry*, 2nd Ed., Prentice Hall: New Jersey, **1999**.

6 Bruice, P. Y. *Organic Chemistry*, 2nd Ed., Prentice Hall: New Jersey, **1998**.

7 Eisch, J. J. *Chemistry of Organometallic Compounds*, Macmillan Company: New York, **1967**.

8 Frankland, E. *Ann. Chem. Pharm.* **1849**, *71*, 177.

9 Eisch, J. J. *Organometallics* **2002**, *21*, 5439.

10 Ziegler, K.; Holtzkamp, E.; Breil, H; Martin H. *Angew. Chem*. **1955**, *67*, 541.

11 Vaska, L. *Acc. Chem. Res*. **1968,** *1*, 335.

12 (a) Colhnan, J. P. *Acc. Chem. Res*. **1968**, *1*, 136; (b) Halpem, J. *Acc. Chem. Res*. **1970**, 386; (c) Collman, J. P.; Roper, W. R. *Adv. Organomet. Chem*. **1968**, *1*, 753.

13 Yamamoto, A. *Journal of Organometallic Chemistry* **2000**, *600*, 159.

14 Little, W. F.; Scott, A. *Comprehensive Organometallic Chemistry*, Academic: New York, **1963**, *1*, 133.

15 Kealy, T. J.; Pauson, P. L. *Nature* **1951**, *168*, 1039.

16 Miller, S. A.; Tebboth, J. A.; Tremaine J. F. *J. Chem. Soc*. **1952**, 632.

17 Wilkinson, G.; Rosenblum, M.; Whiting, M.C.; Woodward R. B. *J. Am. Chem. Soc.* **1952**, *72*, 2125.

18 Fischer, E. O.; Prab, W. *Z. Naturforsch* **1952**, *7*, 377.

19 G. Jaouen, A.; Vessie`res, I. S.; Butler, H. *Acc. Chem. Res,* **1993**, *26*, 361.

20 (a) Guo, Z.; Sadler, P. J. *Angew. Chem. Int. Ed. Engl.* **1999,** *38*, 1512; (b) Heim, M. E.; Keppler, B. K. *Metal Complexes in Cancer Chemotherapy*, VCH: Weinheim, **1993**; (c) Rosenberg, B. *Interdisciplinary Sci. Rev*. **1978**, *3*, 134.

21 Kopf-Maier, P.;. Keppler, B. K. *Metal Complexes in Cancer Chemotherapy*, VCH: Weinheim, **1993**, 259.

22 (a) Nakagawa, Y. ; Smagghe, G.; Kugimiya, S. *Pestic. Sci.* **1999**, *55*, 909; (b) Simionescu, C. R.; Lixandru, T.; Scutaru, D.; Vata**,** M. *J. Organomet. Chem.* **1985**, *292*, 269; (c) Molina, P.; Tarraga, A.; Lopez, J. L.; Martinez, J. C.; *J. Organomet. Chem.* **1999,** *584*, 147; (d) Top, S.; Tang, J.; Vessieres, A.; Carrez, D.; Prorot, C.; Jaouen, G. *J. Chem. Soc. Chem. Commun.* **1996**, 955; (e) Motohashi, N.; Meyer, R.; Gollapudi, S. R.; Bhattiprolu, K.R. *J. Organomet. Chem*. **1990**, *398*, 205.

23 Gustafsson, J. *J. Endocr.* **1999**, *163*, 379.

24 Paech, K.; Webb, P.; Kuiper, G.G.J.M.; Nilsson, S.; Gustafsson, J. A.; Kushner, P. J.; Scanlan, T. S. *Science* **1997**, *277*, 1568.

25 K. Dhingra, *Invest. New Drugs* **1999**, *17*, 285.

26 a) Top, S.; Vessie`res, A.; Cabestaing, C.; Laios, I.; Leclercq, G.; Provot, C.; Jaouen, G. *Journal of Organometallic Chemistry* **2001,** 637; b) R.H. Fish, G. Jaouen *Organometallics* **2003**, *22*, 2166-2177.

27 a) WHO. *Weekly Epidemiol. Rep*. **1996**, *3*, 17; b) WHO. *Weekly Epidemiol. Rep*. **1996**, *4*, 25.

28 Biot, C.; Glorian, G.; Maciejevski, L.A.; Brocard, J. *J. Med.. Chem*. **1997**, *40*, 3715.

29 Biot, C.; Delhaes, L.; Abessolo, H.; Domarle, O.; Maciejewski, L. A.; Mortuaire, M.; Delcourt, P.; Deloron, P.; Camus, D.; Dive, D.; Brocard, J.S. *Journal of Organometallic Chemistry* **1999**, *589*, 59.

30 Mason, R.W.; McGrouther, K.; Ranatunge-Bandarage, P.R.R.; Robinson, B.H.; Simpson, J. *Appl. Organometal. Chem.* **1999,** *13*, 163.

31 Rungiu H.; Qingmin W. *J. Organometallic Chem* **2001**, *637-639*, 94-98.

32 Huikai, S.; Qingmin, W.; Runqiu, H.; Heng, L.; Yonghong, L. *J. Organometallic Chem.* **2002**, *655*, 182.

33 Togni, A.; Hayashi, T.; Eds. *Ferrocenes,* VCH: Weinheim, Germany, **1995**.

34 Kajdas, C.; Domoniak, M.; Firkowski, A.; Dýbrowski, J. R.; Misterkiewicz, B. *Tribochemistry of Some Ferrocene Derivative. ASLE Trans.* **1983**, *26*, 21.

35 (a) West R., *Oxocarbons*, Academic Press: New York, **1980**; (b) Schmidt, A. H.; Ried, W. *Synthesis* **1978**, 1; (c) Knorr, H.; Ried, W. *Synthesis* **1978**, 649; (d) Schmidt, A. H.; Ried W. *Synthesis* **1978**, 869.

36 Liebeskind, L. S. *Tetrahedron*, **1989**, *45*, 3053.

37 (a) Karlson, J. O., Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc*. **1985**, *107*, 3392; (b) Foland, L.D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. T.; Patil, S.; Moore, H.W. *J. Am. Chem. Soc*. **1989,** *111*, 975; (c) Perri, S.T.; Foland, L. D.; Moore, H. W. *Tetrahedron Lett.* **1988**, 5681.

38 (a) Perri, S. T.; Foland, L. D.; Decker, O. H.; Moore, H. W. *J.Org. Chem*. **1986**, *51*, 3067; (b) Decker, O. H.; Moore, H.W. *J.Org. Chem* **1987**, *52*, 1174.

39 Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J.Am. Chem. Soc*. **1987**, *109*, 7908.

40 Liebeskind, L. S.; Chidabbaram, R.; Mitchell, D.; Foster, B. S. *Pure Appl.Chem*. **1988**, *60*, 27.

41 Inayama, S.; Mamoto, K.; Shibata, T. *J. Med. Chem*. **1976**, *19*, 433.

42 Onda, M.; Konda, Y.; Narimatsu, Y.; Tanaka, H.; Awaya, J.; Omura, S. *Chem. Pharm. Bull*. **1974**, *22*, 2916.

43 Mitchell, D.; Liebeskind, L. S. *J.Am. Chem. Soc*. **1990**, *112*, 291.

44 Facundo, V. A.; Sa, L. A.; Silva, S. A. F.; Morias, S. M.; Matos, C. R. R.; Braz-Filho, R. *J. Braz. Chem. Soc.* **2004**, *15*, 140.

45 (a) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412; (b) Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 6101; (c) Liu, H.; Gayo, L. M.; Sullivan, R. W.; Choi, A. V. H.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 3284; (d) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 3274; (e) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.

46 (a) Zora, M.; Yucel, B.; Peynircioglu, N. B. *J. Organomet. Chem.* **2002**, *656*, 11; (b) Zora, M.; Herndon, J. W. *J. Org. Chem.* **1994**, *59*, 688; (c) Bohnbrun, A.; Libeskind, L. S. *J. Org. Chem.* **1994**, *59*, 1149; (d) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron Lett.* **1995**, *36*, 5539.

47 (a) Moore, H. W.; Foland, L. D.; Perri, S. T. *Tetrahedron Lett.* **1988**, *29*, 3529; (b) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1994**, *50*, 7783; (c) Moore, H. W.; Lee, K. H. *J. Org. Chem.* **1995**, *60*, 735; (d) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Am. Chem. Soc.* **1995**, *117*, 9653.

48 (a) Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189; (b) Paquettte, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 1451; (c) Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799; (d) Wilson, P. D.; Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1351; (e) Santora, V. J.; Moore, H. W. *J. Am. Chem. Soc.* **1995**, *117*, 8486.

49 (a) Yerxa, B. R.; Moore, H. W. *Tetrahedron Lett.* **1992**, *33*, 7811; (b) Liebeskind, L. S.; Wang, J. *Tetrahedron* **1993**, *49*, 5461; (c) Brichler, A.G.; Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 7737; (d) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550.

50 (a) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland; L. D.; Moore; H. W. *J. Org. Chem.* **1988**, *53*, 2477; (b) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482; (c) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350; (d) Gayo, L. M.; Winters, P. M.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896.

51 (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359; (b) Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543; (c) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942; (d) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048.

52 Gibson, E. S. *Transition Metals in Organic Chemistry,* Oxford University Press: Oxford, **1997**.

53 Yang, C. N.; Jeong, J. K.; Choi, S. J.; Rhee, T. H.; Suh, D. H. *Macromol. Rapid Commun.* **1999**, *20*, 586.

54 Creary, X. *Organic Letters* **2000**, *2*, 2069.

55 Creary, X.; Mehrsheikh-Mohammadi, M.E., McDonald, S. *J. Org. Chem*. **1989**, *54*, 2904.

56 (a) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990,** *112*, 8612; (b) Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Letters* **1991,** *32*, 5681.

APPENDIX A

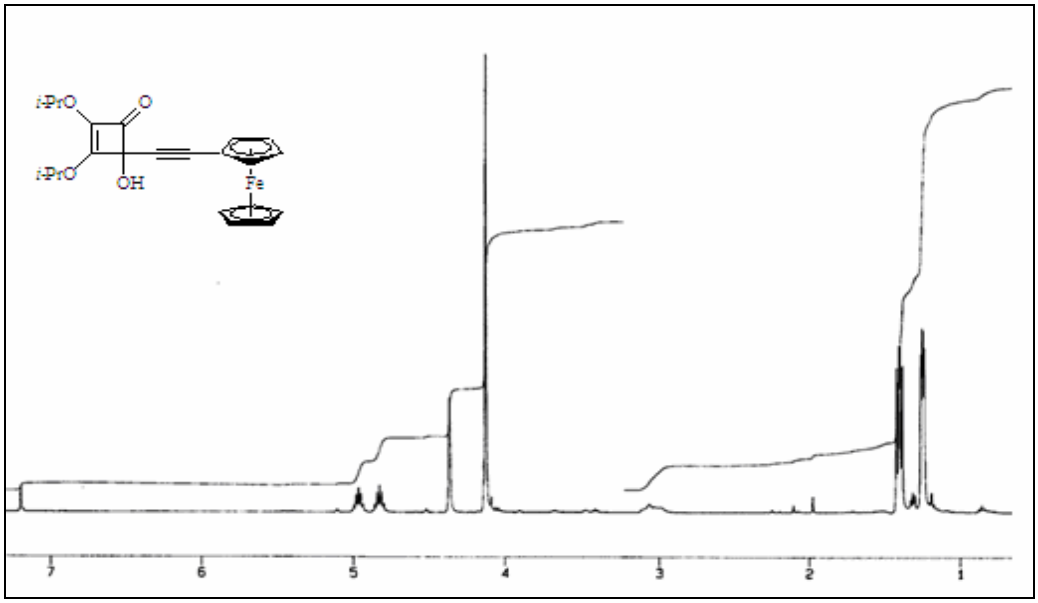

Figure A1. ^{1}H-NMR Spectrum (400MHz) of 4-hydroxy-2,3-diisopropoxy-4-ferrocenylethynyl-2-cyclobutenone (**32A**)

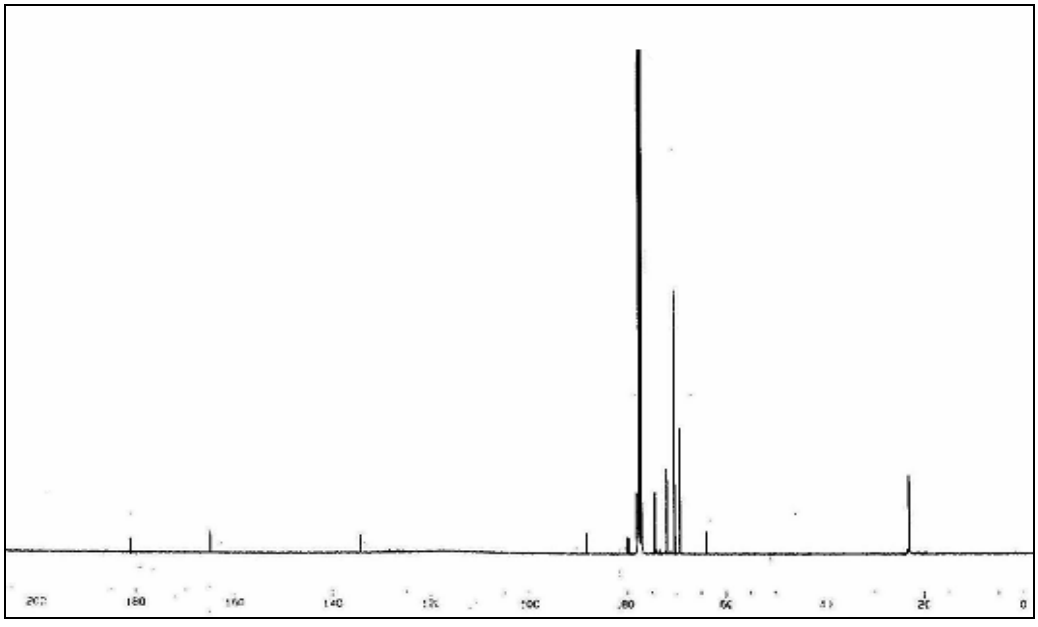

Figure A2. ^{13}C-NMR Spectrum (400MHz) of 4-hydroxy-2,3-diisopropoxy-4-ferrocenylethynyl-2-cyclobutenone (**32A**)

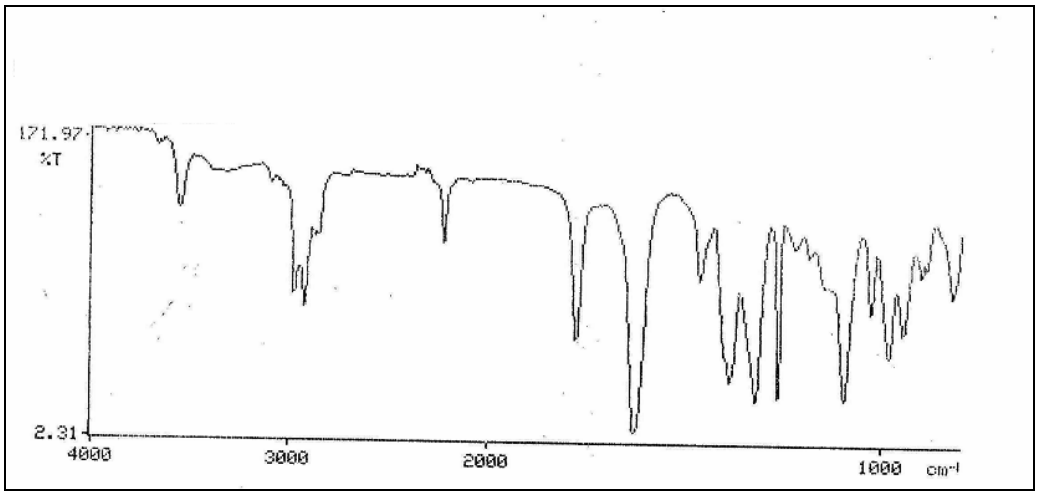

Figure A3. IR Spectrum of 4-hydroxy-2,3-diisopropoxy-4-ferrocenylethynyl-2-cyclobutenone (**32A**)

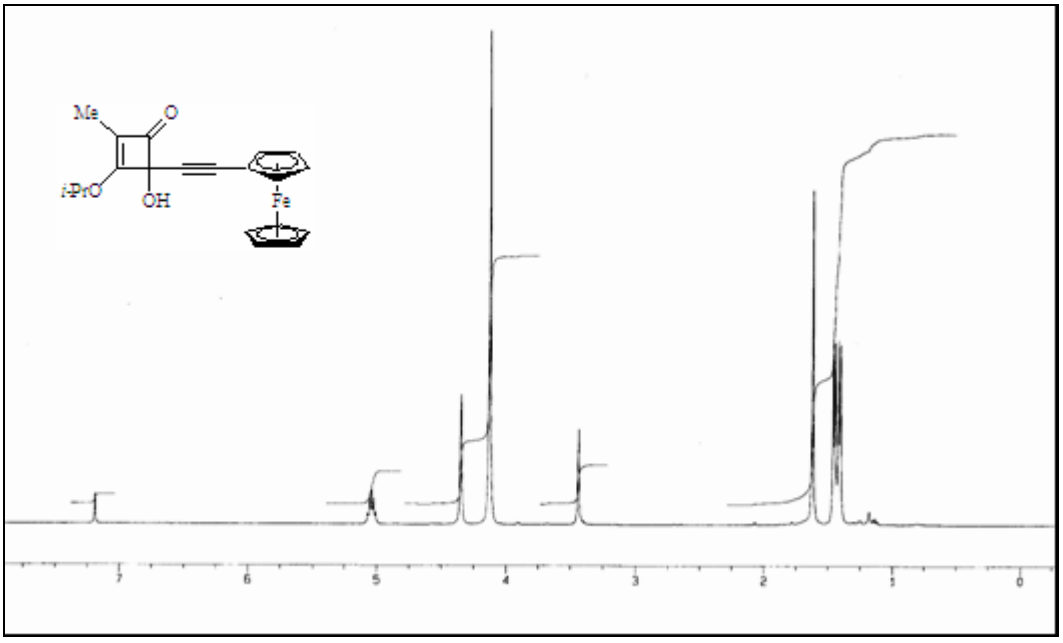

Figure A4. ^{1}H-NMR Spectrum (400MHz) of 4-hydroxy-3-isopropoxy-2-methyl-4-ferrocenylethynyl-2-cyclobutenone(**32B**)

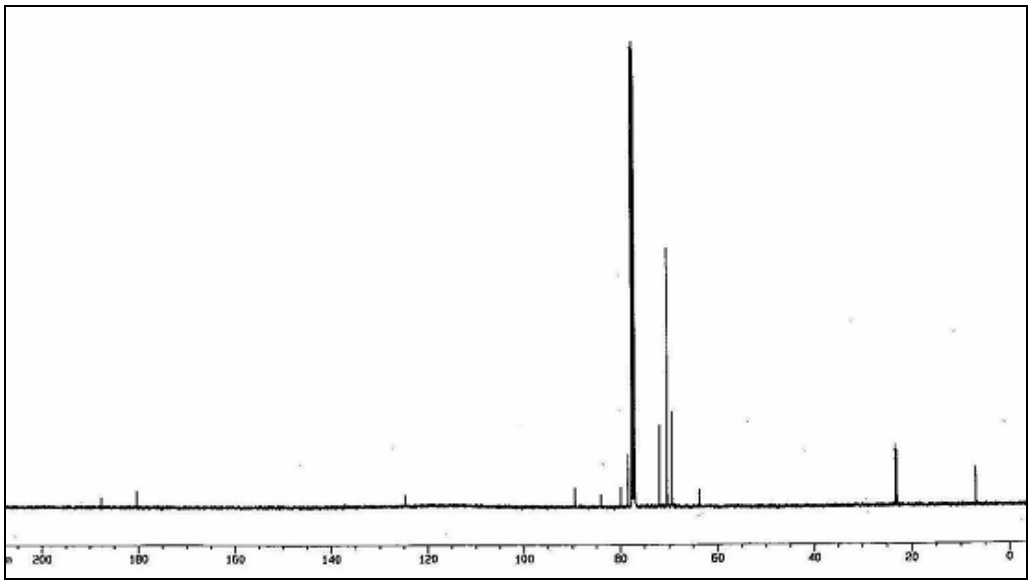

Figure A5. ^{13}C-NMR Spectrum (400MHz) of 4-hydroxy-3-isopropoxy-2-methyl-4-ferrocenylethynyl-2-cyclobutenone(**32B**)

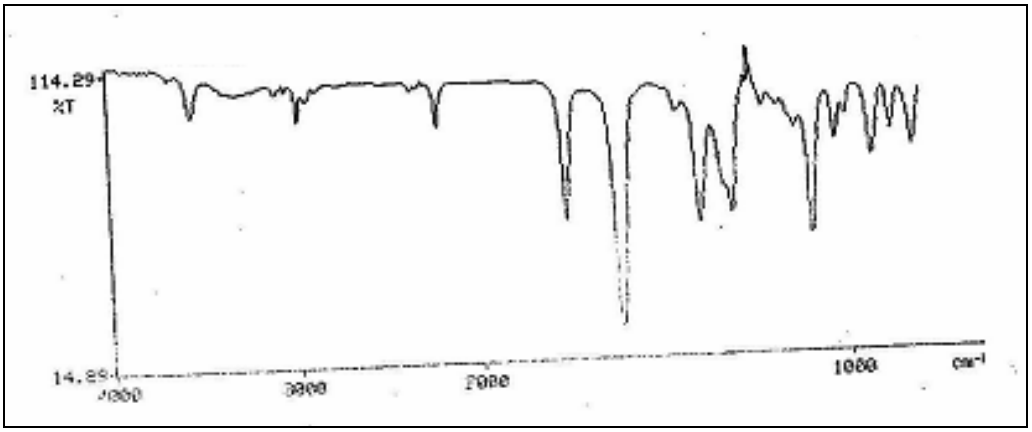

Figure A6. IR Spectrum of 4-hydroxy-3-isopropoxy-2-methyl-4-ferrocenylethynyl-2-cyclobutenone(**32B**)

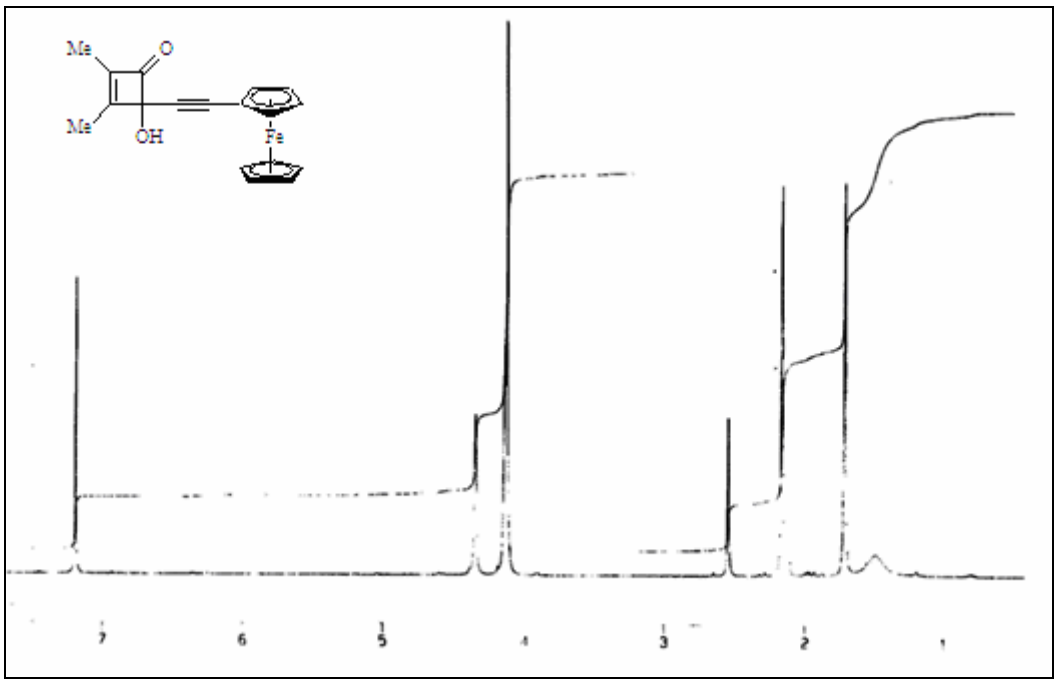

Figure A7. ^{1}H-NMR Spectrum (400MHz) of 4-hydroxy-2,3-dimethyl-4-ferrocenylethynyl-2-cyclobutenone (**32D**)

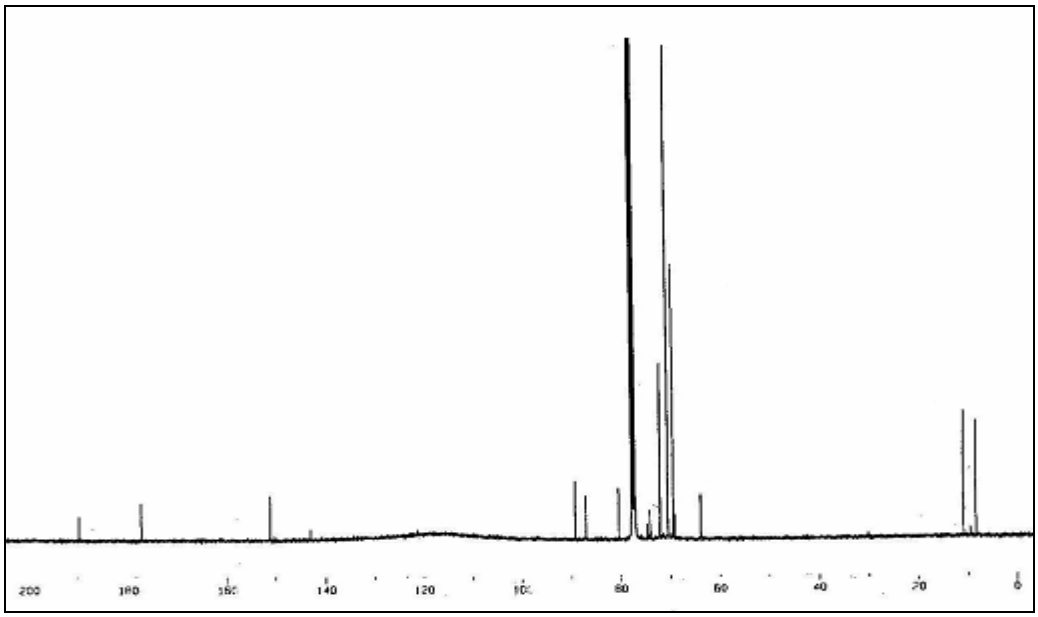

Figure A8. ^{13}C-NMR Spectrum (400MHz) of 4-hydroxy-2,3-dimethyl-4-ferrocenylethynyl-2-cyclobutenone (**32D**)

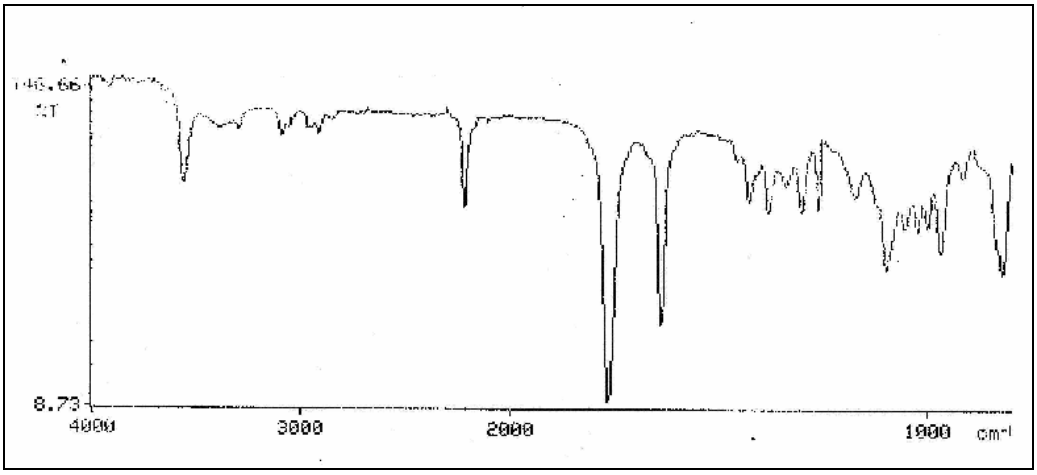

Figure A9. IR Spectrum of 4-hydroxy-2,3-dimethyl-4-ferrocenylethynyl-2-cyclobutenone (**32D**)

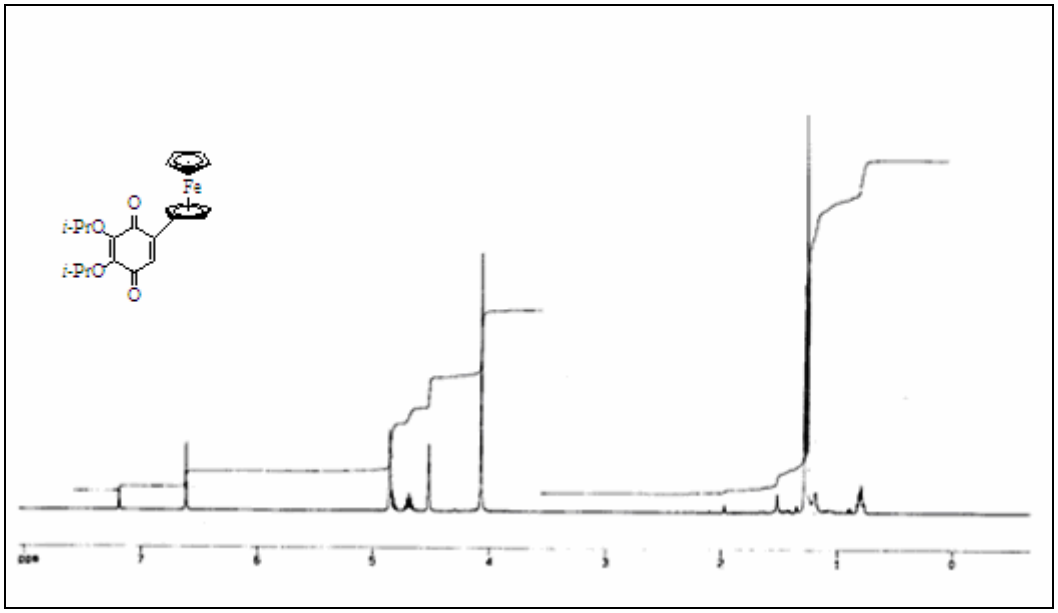

Figure A10. ^{1}H-NMR Spectrum (400MHz) of 2,3-diisopropoxy-5-ferrocenyl-[1,4]-benzoquione (**35A)**

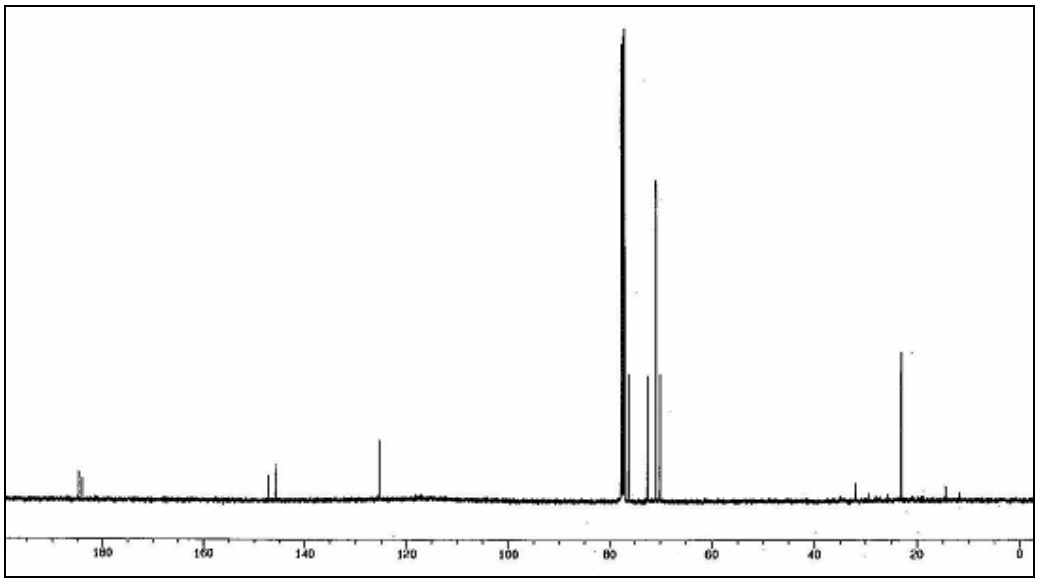

Figure A11. ^{13}C-NMR Spectrum (400MHz) of 2,3-diisopropoxy-5-ferrocenyl-[1,4]-benzoquione (**35A)**

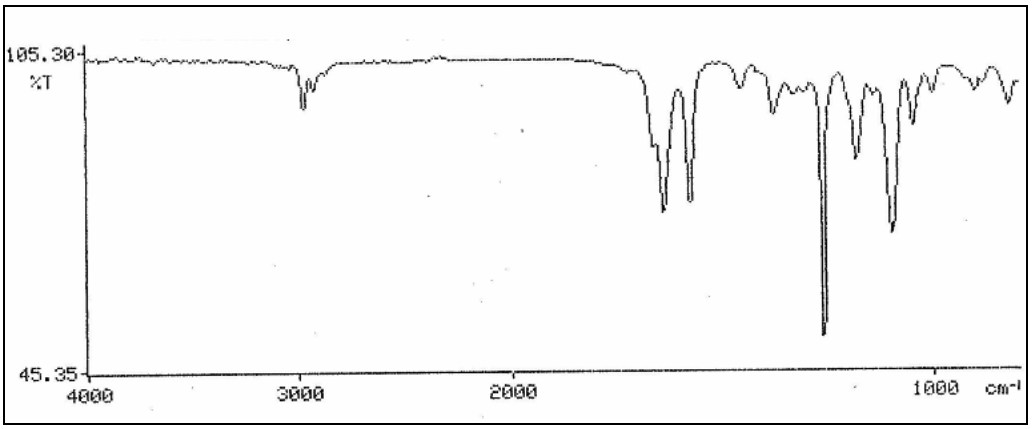

Figure A12. IR Spectrum of 2,3-diisopropoxy-5-ferrocenyl-[1,4]-benzoquione (**35A)**

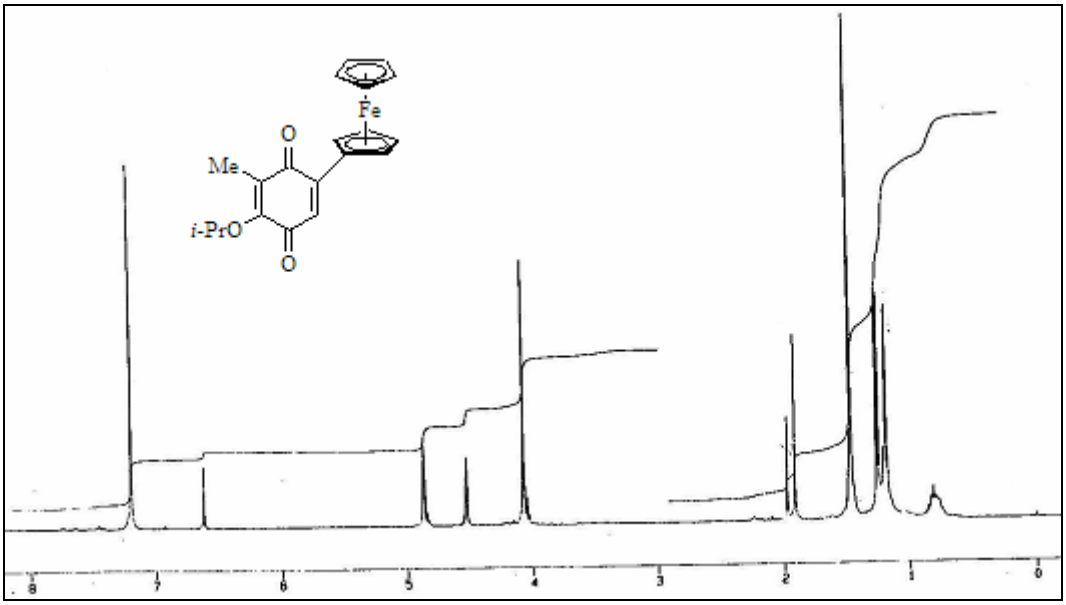

Figure A13. ^{1}H-NMR Spectrum (400MHz) of 2-isopropoxy-3-methyl-5-ferrocenyl-[1,4]-benzoquione (**35B)**

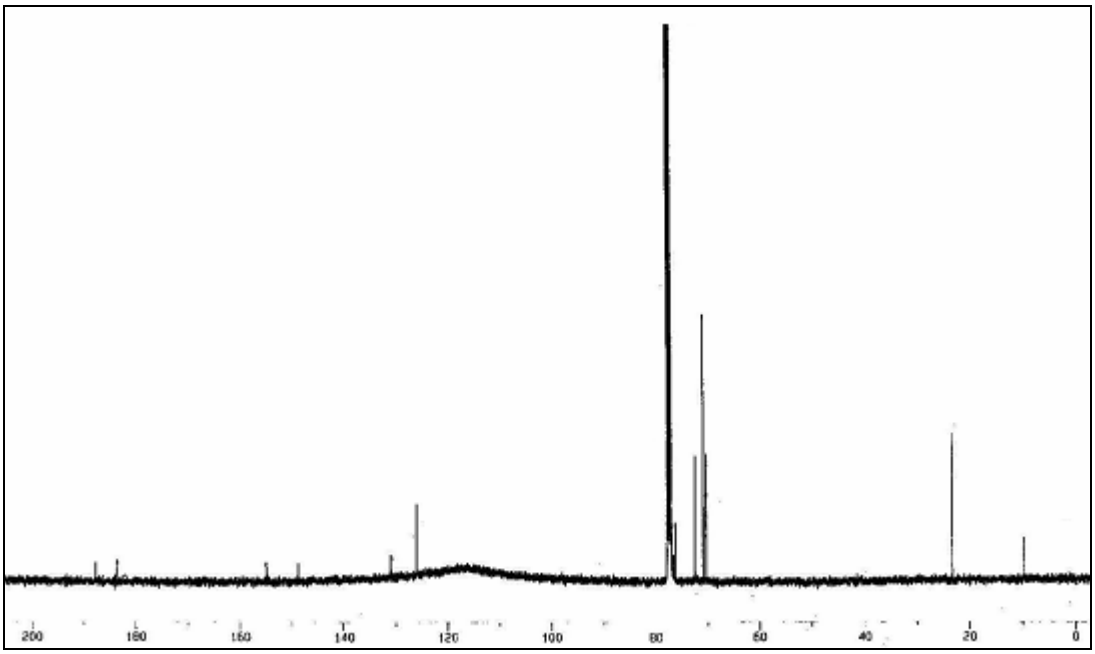

Figure A14. ^{13}C-NMR Spectrum (400MHz) of 2-isopropoxy-3-methyl-5-ferrocenyl-[1,4]-benzoquione (**35B)**

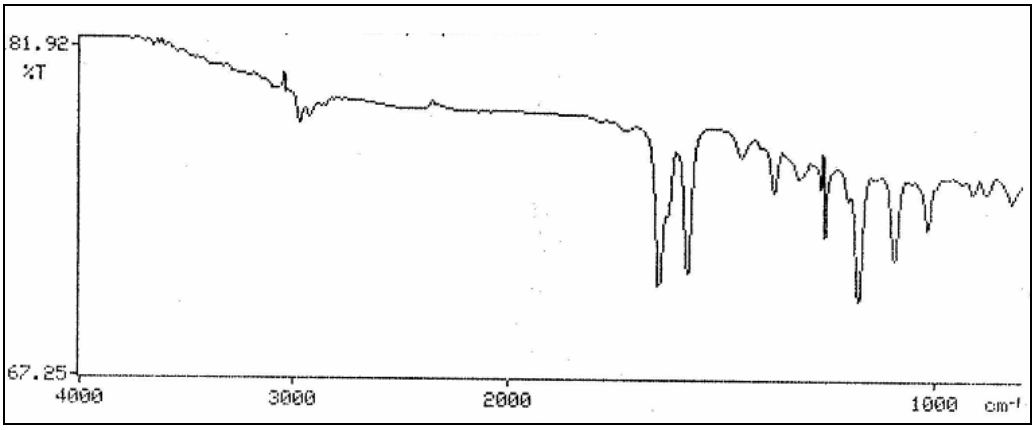

Figure A15. IR Spectrum of 2-isopropoxy-3-methyl-5-ferrocenyl-[1,4]-benzoquione (**35B)**

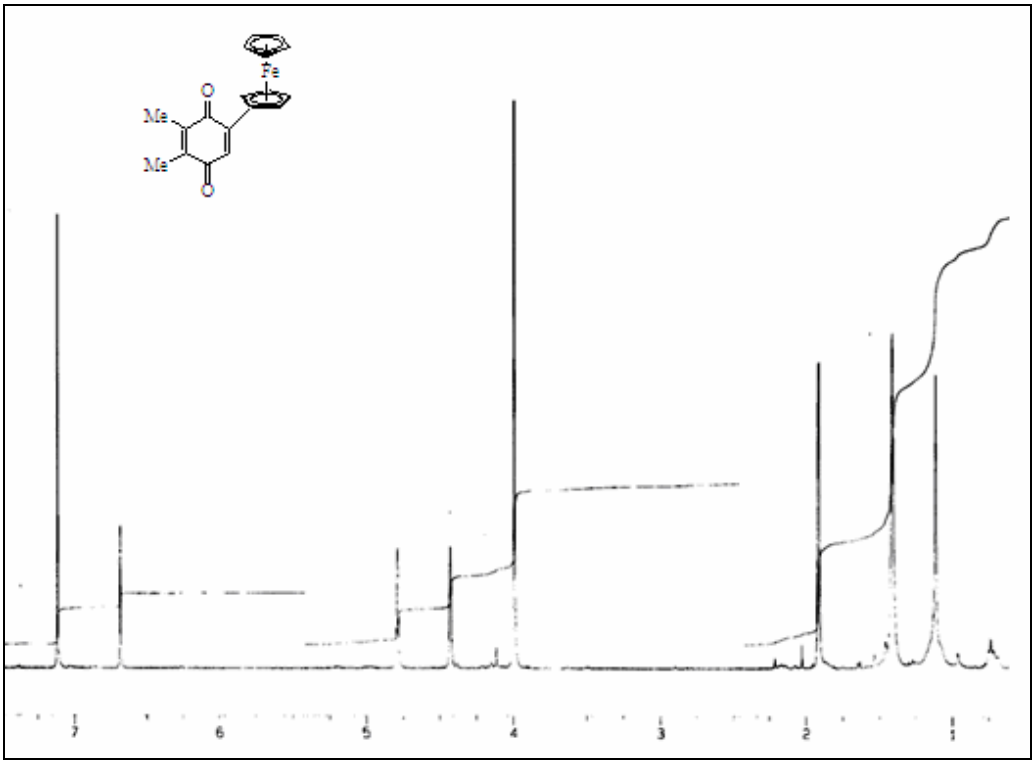

Figure A16. [1]H-NMR Spectrum (400MHz) of 2,3-dimethyl-5-ferrocenyl-[1,4]-benzoquione (**35D**)

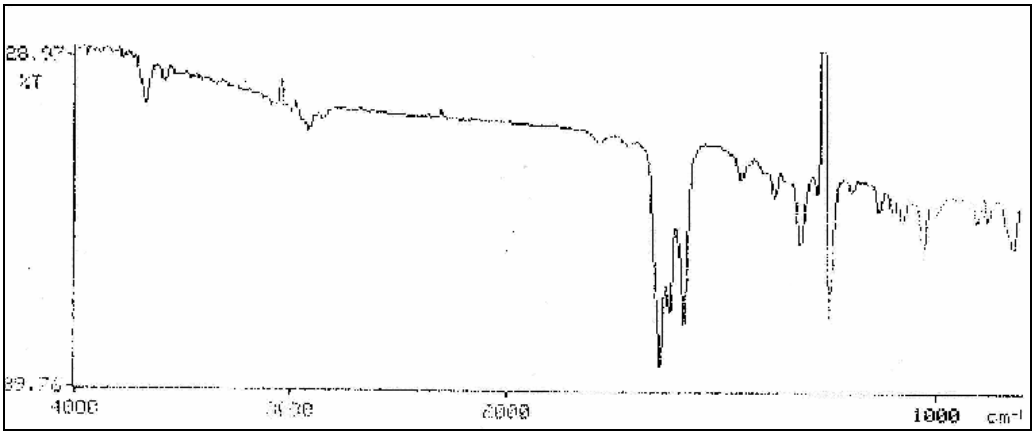

Figure A17. IR Spectrum of 2,3-dimethyl-5-ferrocenyl-[1,4]-benzoquione (**35D**)

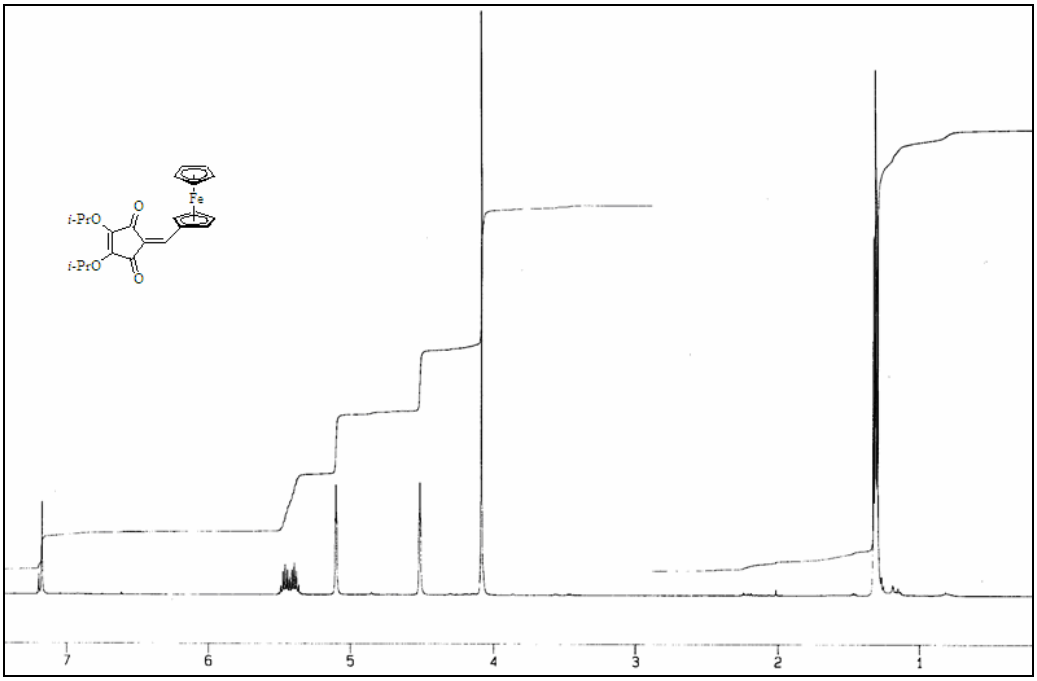

Figure A18. ^{1}H-NMR Spectrum (400MHz) of 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione (**33A**)

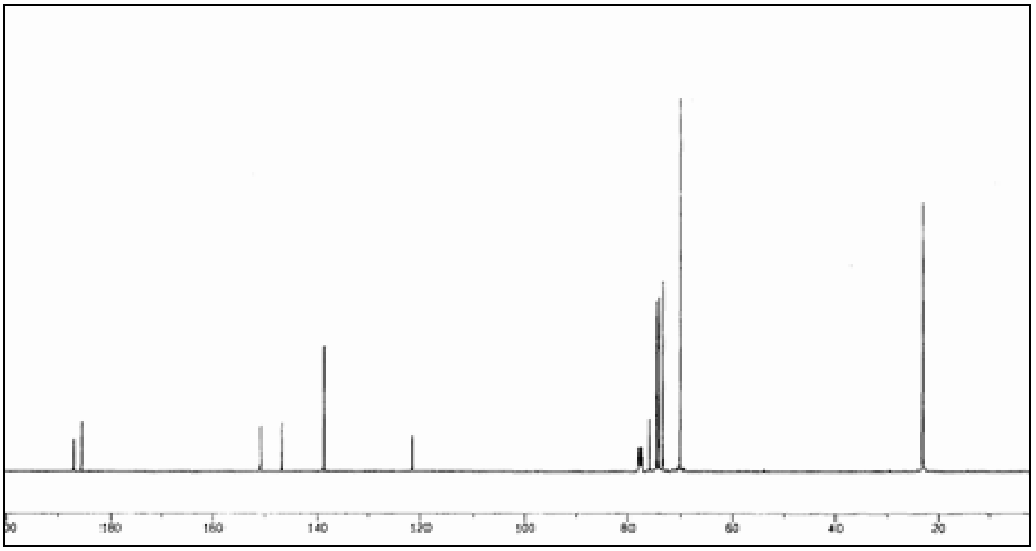

Figure A19. ^{13}C-NMR Spectrum (400MHz) of 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione (**33A**)

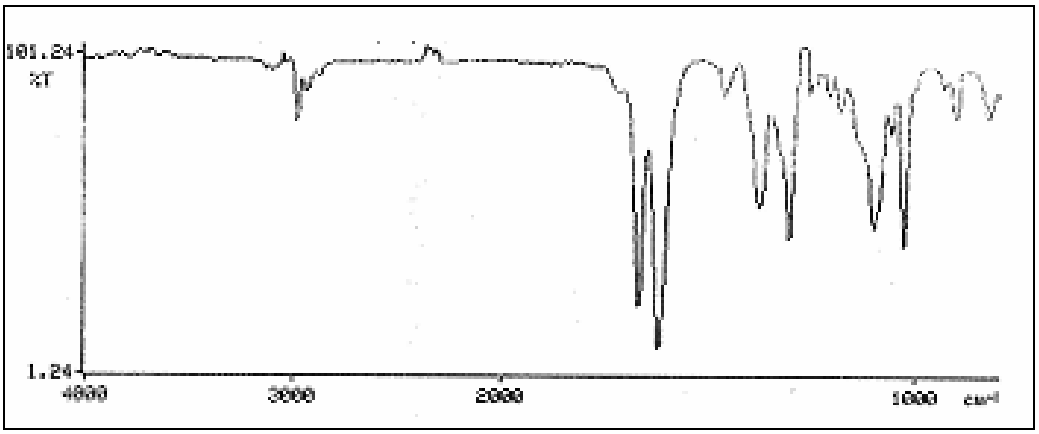

Figure A20. IR Spectrum of 2-ferrocenylidene-4,5-diisopropoxy-cyclopent-4-ene-1,3-dione (**33A**)

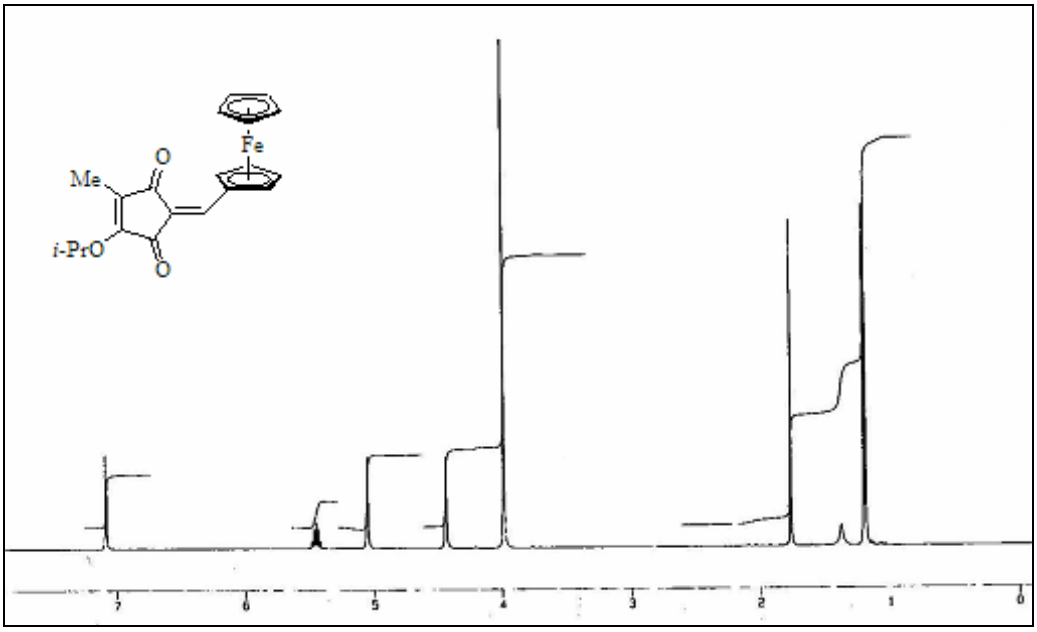

Figure A21. ^{1}H-NMR Spectrum (400MHz) of 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (**33B-**Major isomer)

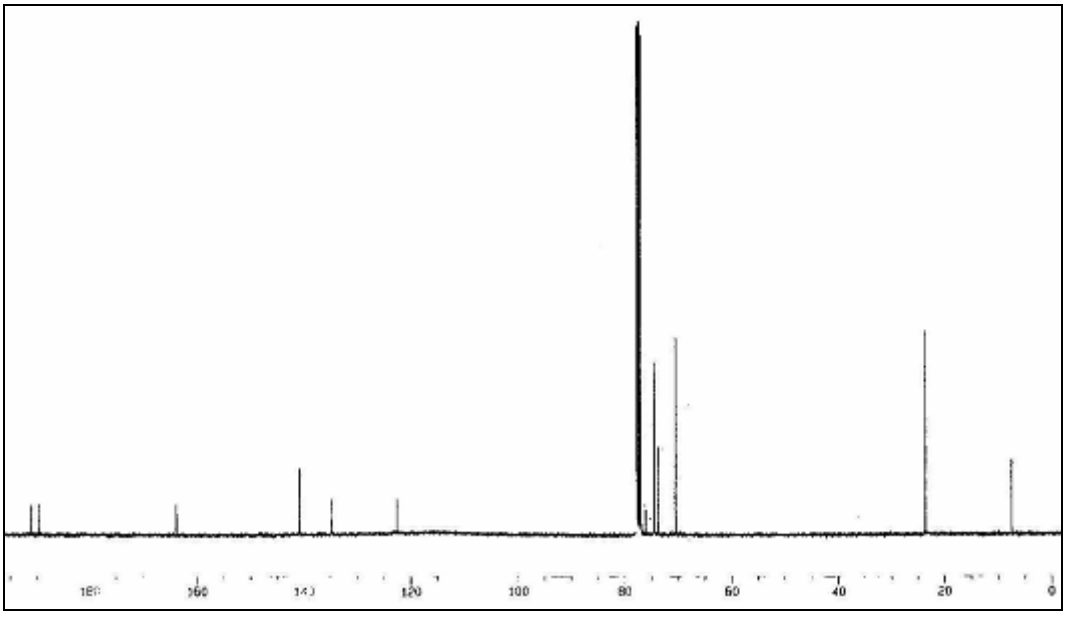

Figure A22. ^{13}C-NMR Spectrum (400MHz) of 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (**33B-**Major isomer)

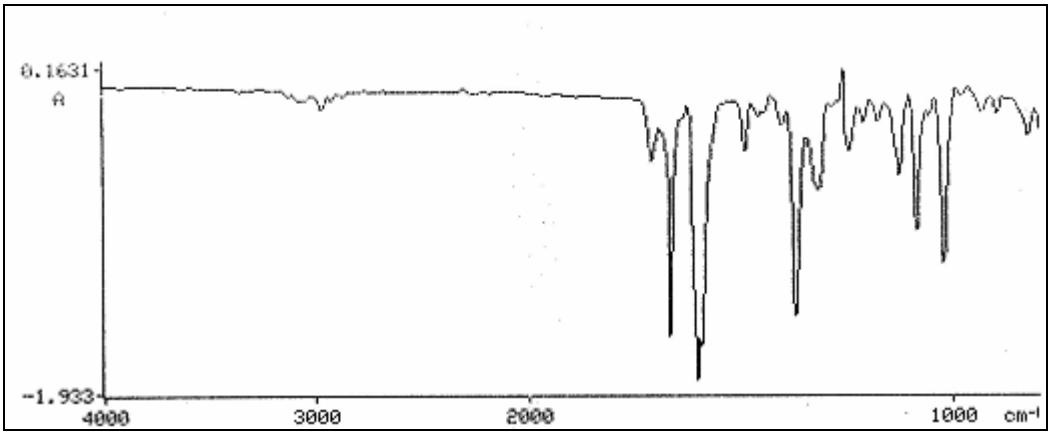

Figure A23. IR Spectrum of 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (**33B-**Major isomer)

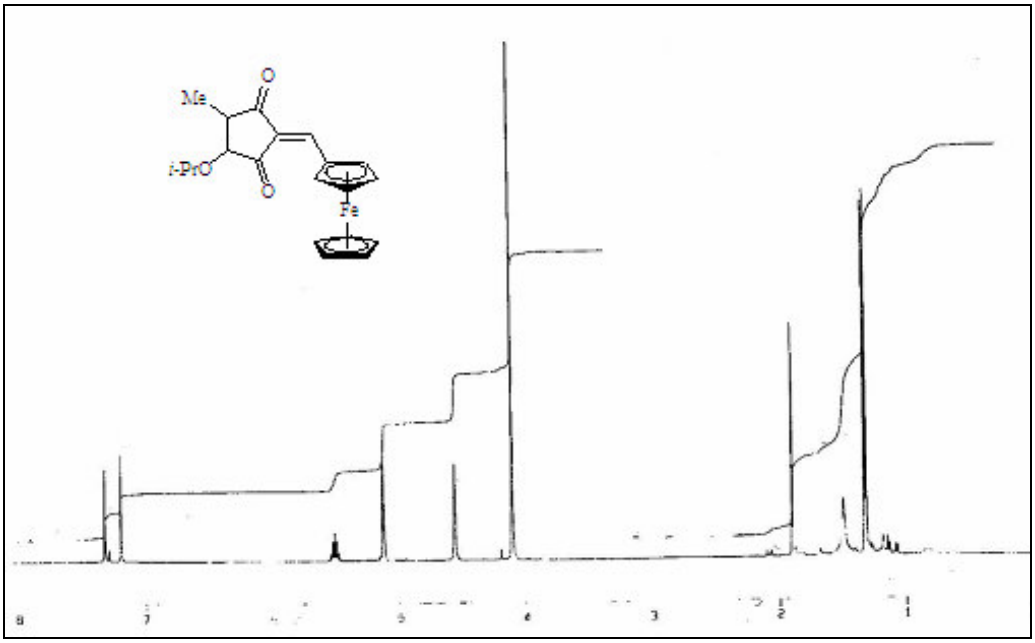

Figure A24. [1]H-NMR Spectrum (400MHz) of 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (**34B-**Minor isomer)

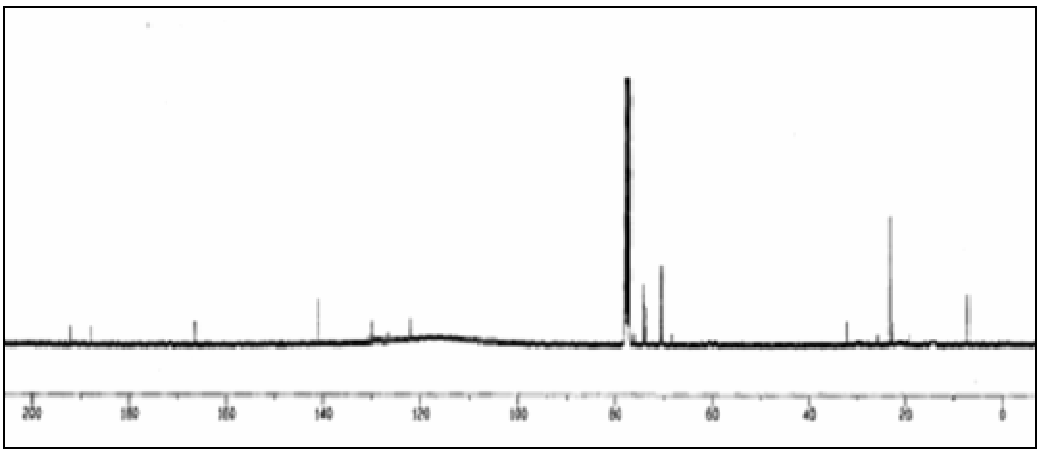

Figure A25. ^{13}C-NMR Spectrum (400MHz) of 2-ferrocenylidene-4-isopropoxy-5-methyl-cyclopent-4-ene-1,3-dione (**34B-**Minor Isomer)

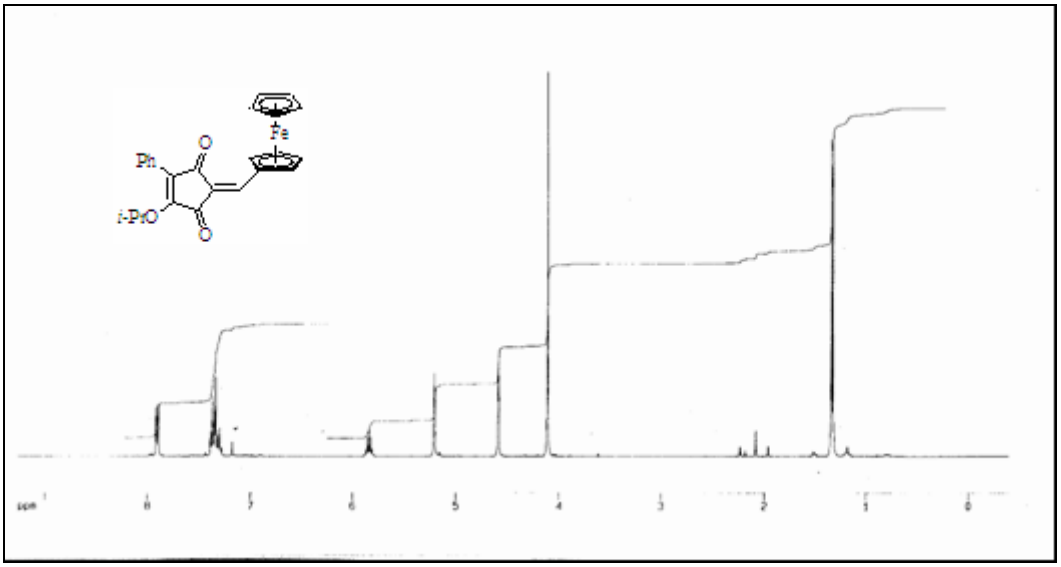

Figure A26. ^{1}H-NMR Spectrum (400MHz) of 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione (**33C**)

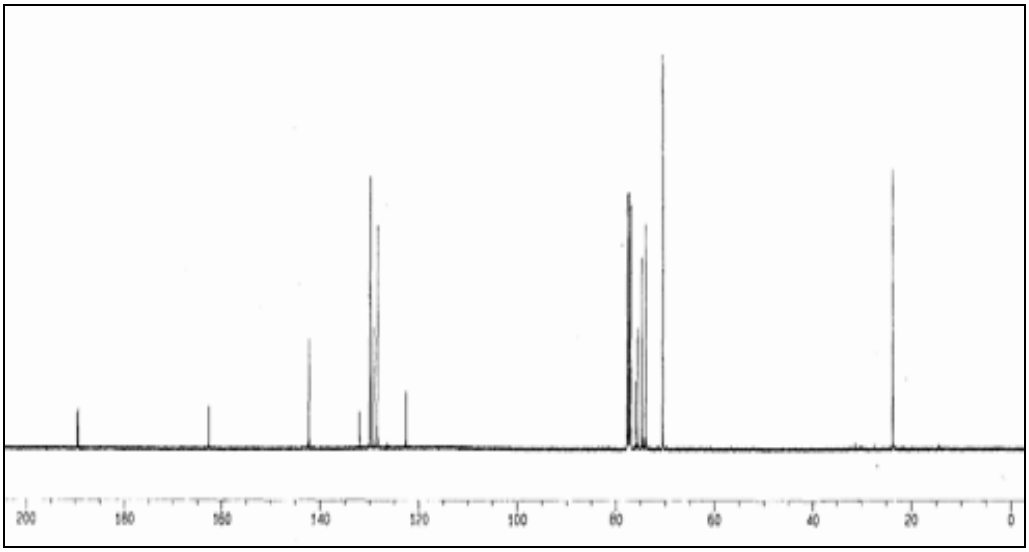

Figure A27. ^{13}C-NMR Spectrum (400MHz) of 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione (**33C**)

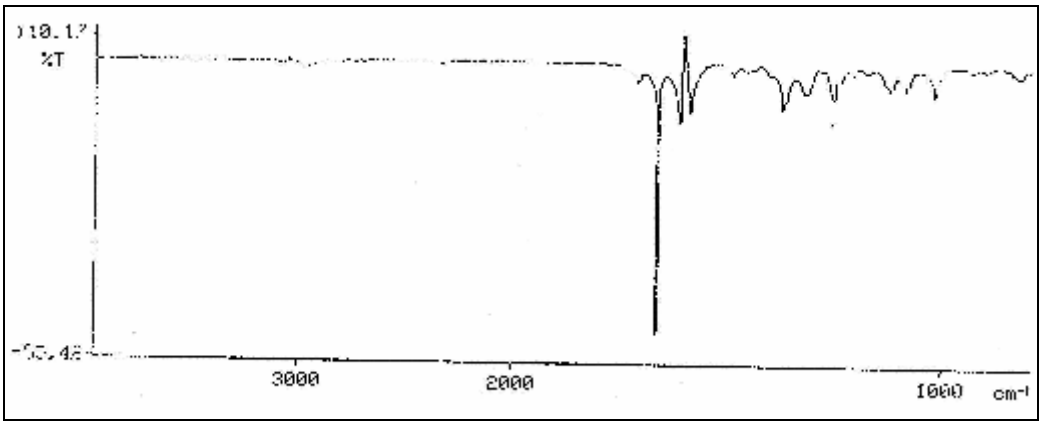

Figure A28. IR Spectrum of 2-ferrocenylidene-4-isopropoxy-5-phenyl-cyclopent-4-ene-1,3-dione (**33C**)

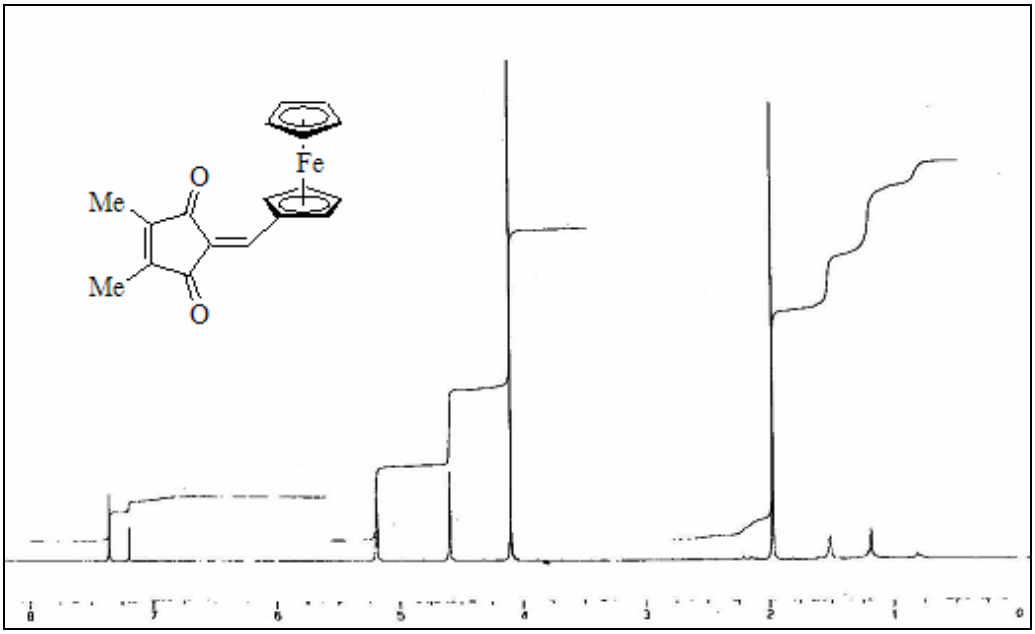

Figure A29. ^{1}H-NMR Spectrum (400MHz) of 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione (**33D**)

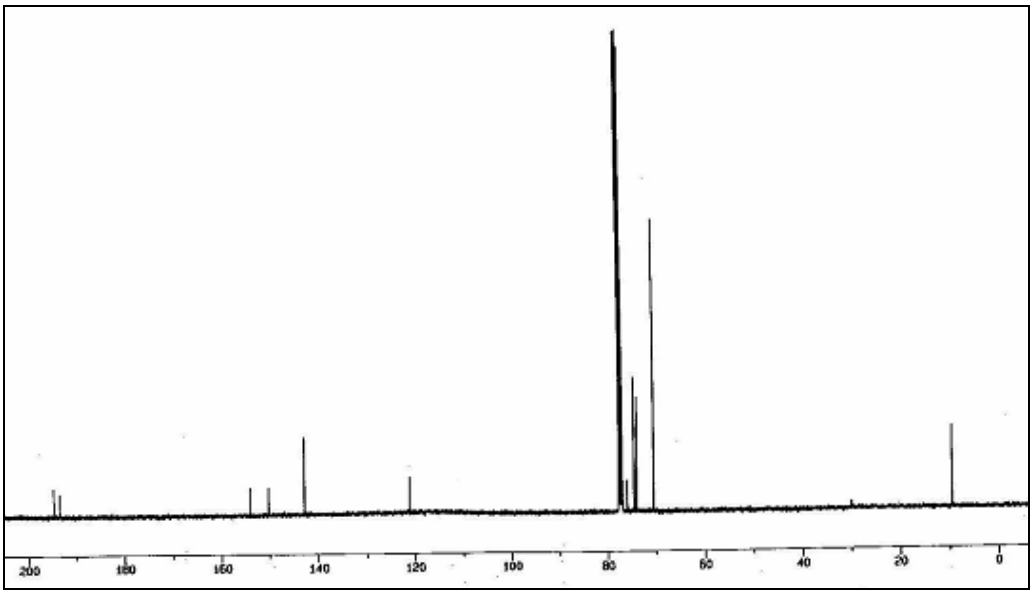

Figure A30. ^{13}C-NMR Spectrum (400MHz) of 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione (**33D**)

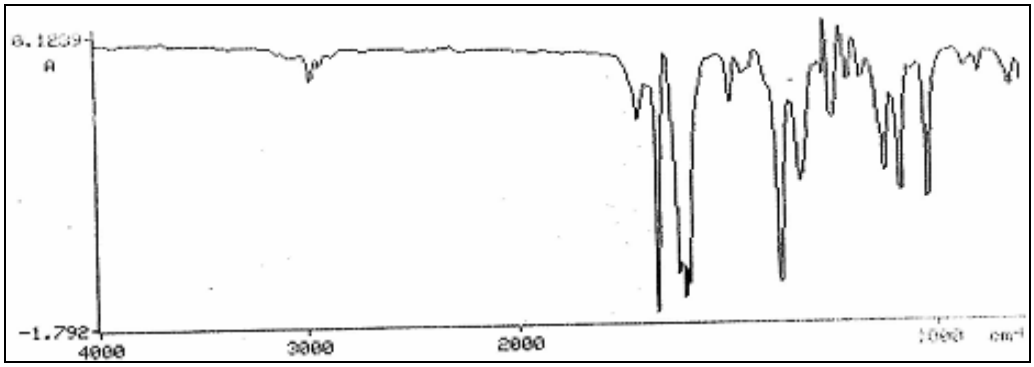

Figure A31. IR Spectrum of 2-ferrocenylidene-4,5-dimethyl-cyclopent-4-ene-1,3-dione (**33D**)

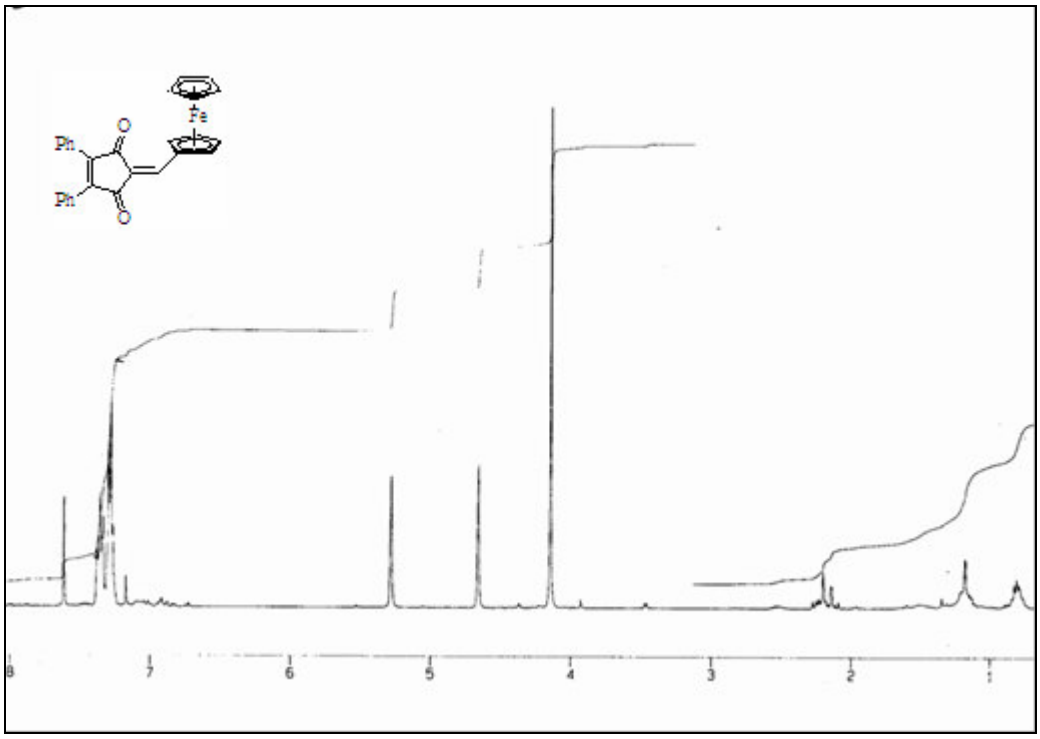

Figure A32. ^{1}H-NMR Spectrum (400MHz) of 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione (**33E**)

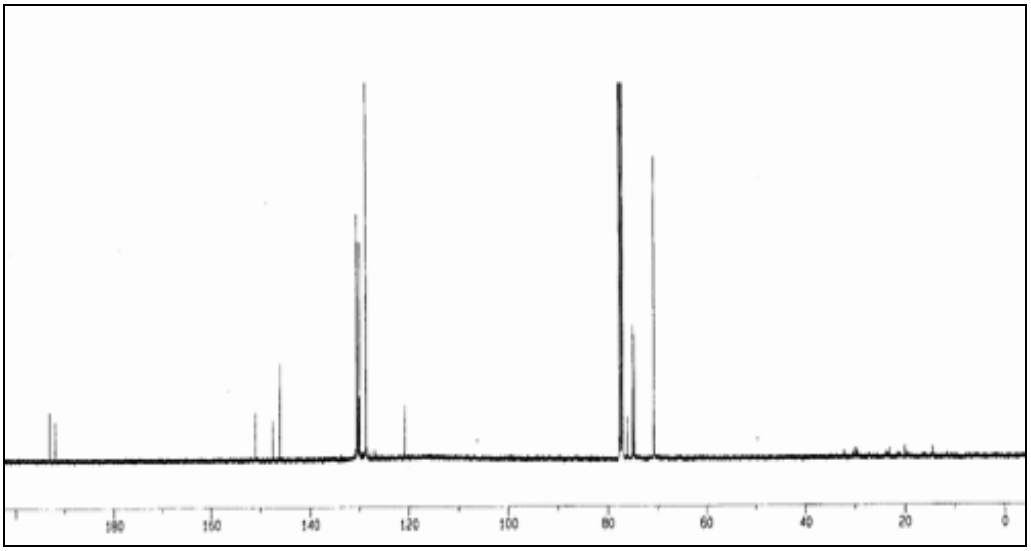

Figure A33. ^{13}C-NMR Spectrum (400MHz) of 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione (**33E**)

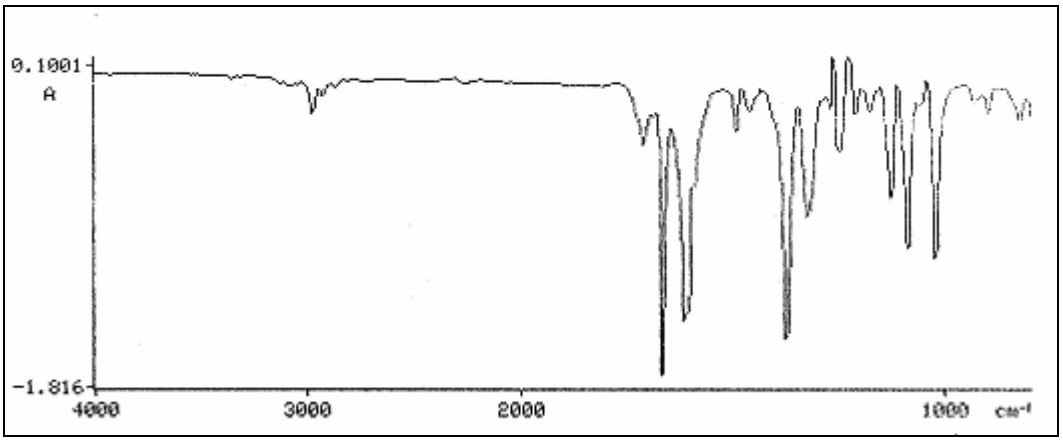

Figure A34. IR Spectrum of 2-ferrocenylidene-4,5-diphenyl-cyclopent-4-ene-1,3-dione (**33E**)