SYNTHESIS OF FERROCENYL CYCLOPENTENONES

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

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Tülay Aslı Tumay

ABSTRACT

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Construction of highly functionalized five-membered rings via cycloaddition reaction of cyclopropylcarbene-chromium complex with alkynes has become a very active area of research in recent years by virtue of their presence in antitumour natural products. Also with the finding that ferrocene derivatives are active against various tumours, considerable interest has been devoted to the synthesis of new ferrocene derivatives since properly functionalized ferrocene derivatives could be potential antitumour substances. So, the incorporation of the essential structural features of cyclopentenones with a ferrocene moiety could provide compounds with enhanced antitumour activities. For this purpose, we have investigated the reaction between cyclopropylcarbene-chromium complex and ferrocenyl alkynes.

The reaction of cyclopropylcarbene-chromium complex with ferrocenyl alkynes afforded α-hydroxycyclopentenones in a one-pot process, whereas the same reaction with alkynes gave cyclopentenones as major products.

Interestingly, water addition was observed instead of reduction according to the previously proposed mechanism. This is a different result than those in literature.

The reaction was regioselective both with terminal ferrocenyl alkynes and internal unsymmetrical ferrocenyl alkynes. The products obtained were those where the sterically larger alkyne substituent, ferrocene, was α to the carbonyl group.

Keywords: Cyclopentenones, α-hydroxycyclopentenones, cyclopropylcarbene-chromium complex, metal carbene complex, Fischer carbene complex, ferrocene, ferrocenyl alkynes

ÖZ

FERROSENİL SİKLOPENTENONLARIN SENTEZİ

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

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Antitümör özelliğine sahip doğal ürünlerde bulunması nedeniyle, son derece işlevselleştirilmiş beşli halkaların siklopropilkarben-krom kompleksinin alkinlerle tepkimesi yoluyla elde edilmesi son yıllarda çok aktif bir araştırma alanı haline gelmiştir. Ayrıca ferrosen türevlerinin antitümör aktivite özelliklerinin bulunmasından sonra da, yapılarında ferrosen içeren maddelerin sentezi büyük bir önem kazanmıştır. Siklopentenon yapısını bir ferrosen birimiyle birleştirmek maddenin antitümör özelliğini arttırabilir düşüncesiyle, bu çalışmada siklopropilkarben-krom kompleksinin ferrosenil alkinlerle tepkimesi incelenmiştir.

Siklopropilkarben-krom kompleksinin alkinlerle tepkimesi ana ürün olarak siklopentenonları verirken, bu çalışmada ferrosenil alkinlerle tepkimesi sonucunda tek bir proseste α-hidroksisiklopentenonlar elde edilmiştir. İlginç olarak, daha önce önerilen reaksiyon mekanizmasında son basamakta gerçekleşen indirgenmenin yerini bu reaksiyonda su katılması almıştır. Bu sonuç literatürdeki sonuçlardan farklıdır, ve ilk defa gözlemlenmiştir.

Tepkime kullanılan ferrosenil alkinler açısından bölgesel seçicilik göstermektedir. Oluşan ürünlerde yapıca büyük olan ferrosen sübstitüenti karbonil grubuna α pozisyonundadır.

Anahtar Kelimeler: Siklopentenon, α-hidroksisiklopentenon, siklopropilkarben-krom kompleksi, metal karben kompleksi, Fischer karben kompleksi, ferrosen, ferrosenil alkin

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Finally, I would like to thank to my labmates and Organic Research Group members for their cooperation and friendship whenever I need.

To my mother Güler Tumay

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br	broad (spectral)
Bn	benzyl
Bu	butyl
°C	degrees Celcius
Cp	cyclopentadienyl ligand
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
dd	doublet of doublet (spectral)
EI	electron impact
Et	ethyl
Fc	ferrocenyl
FT	fourier transform
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant
m	medium (spectral)
m	multiplet (spectral)
Me	methyl
MHz	megahertz
min	minutes
mL	milliliter(s)
mmol	millimole(s)
MS	mass spectrum

NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
s	strong (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
vs	very strong (spectral)
vw	very weak (spectral)
w	weak

CHAPTER 1

INTRODUCTION

Organic chemistry is simply defined as the chemistry of the compounds of carbon. Carbon compounds are in everywhere in our life. Deoxyribonucleic acids (DNAs), ribonucleic acids (RNAs), proteins, carbohydrates, lipids, enzymes and hormones in our body are all organic compounds. We are not only composed largely of organic compounds, but also we are surrounded by them. The gasoline that propels our automobiles, the clothing materials such as wool, cotton, nylon or polyester, are all made of carbon compounds. Most of the medicines that we use are also organic. So we can say that we are living in an age of organic chemistry.

In the beginning of the nineteenth century, organic chemistry was considered as a separate branch of chemical science. Today it is a broad field, which intersects with diverse areas such as biology, pharmacology, medicine, agriculture and polymer chemistry [1-4].

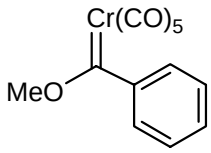
One of the most attractive areas of chemical research in recent years has been the field of organometallic chemistry, which is the study of those compounds containing direct carbon-metal linkages. This field combines aspects of organic chemistry and inorganic chemistry and has led to many important applications in synthetic organic chemistry [5-7].

Following the discovery of Grignard reagent at the turn of the century, organometallic reagents have played a major role in organic synthesis. Today,

they are often used in laboratories for multistep synthesis as well as in industrial scale for the production of commercial products [8].

The application of transition metal compounds to the field of organic synthesis can be in two ways. They can be used in both catalytic and stoichiometric amounts. Catalysis is a highly active area of organometallic chemistry, and many methods have been used on an industrial scale, such as Ziegler-Natta polymerization [9], Monsanto's acetic acid process [10], Wacker process [11], asymmetric hydrogenation [12] and many others [13]. On the other hand, stoichiometric reactions are often preferred on a laboratory scale since they can offer an opportunity to effect chemical conversions, which are difficult to perform using conventional methods of organic chemistry.

Transition metal carbene complexes are among the most important organometallic compounds. They are the compounds in which a divalent carbon is bound to a transition metal. Since the discovery of the first stable carbene complex **1** by Fischer and Maasböl in 1964 (Figure 1) [14], they have proven to be extremely valuable building blocks in synthetic organic chemistry [15].



1

Figure 1. Phenyl methoxy carbene complex **1**

Metal carbene complexes are generally divided into two classes, which are 'Fischer-type' carbene complexes and 'Schrock-type' carbene complexes, according to the chemical behaviour of the carbene carbon [16,17]. Fischer-type carbene complexes contain a low oxidation state late-transition metal from Group

VI to VIII and the carbene carbon has an electrophilic character. So, these complexes behave as electrophiles [18]. On the other hand, Schrock-type carbene complexes have typically nucleophilic carbene carbon and contain early-transition metals in higher oxidation states. In this case, the carbene behaves as a nucleophile [19].

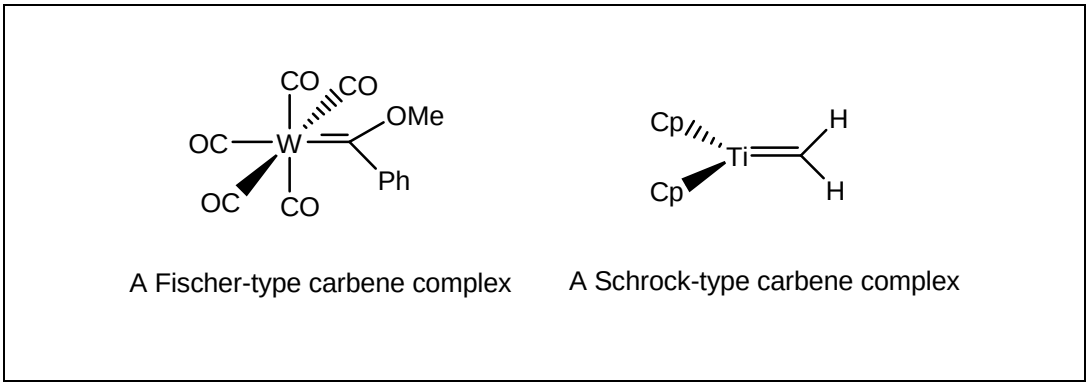


Figure 2. Schematic representation of metal carbene complexes

In Fischer-type carbene complexes, the metal is stabilized by π-acceptor ligands such as carbon monoxide and the electron-deficient carbene carbon is stabilized by π-donor substituents like OCH_3 and $N(CH_3)_2$ (Figure 3). The strong electron-withdrawing power of the $Cr(CO)_5$ moiety makes the carbene carbon electrophilic, and the α-protons of this carbon highly acidic [20]. So, alkyl carbene complexes are deprotonated by bases easily and the resulting metal enolates are usually very reactive to undergo bond formation with electrophilic reagents allowing the preparation of a wide range of new complexes [21]. General reactivity of these complexes is shown in Figure 3.

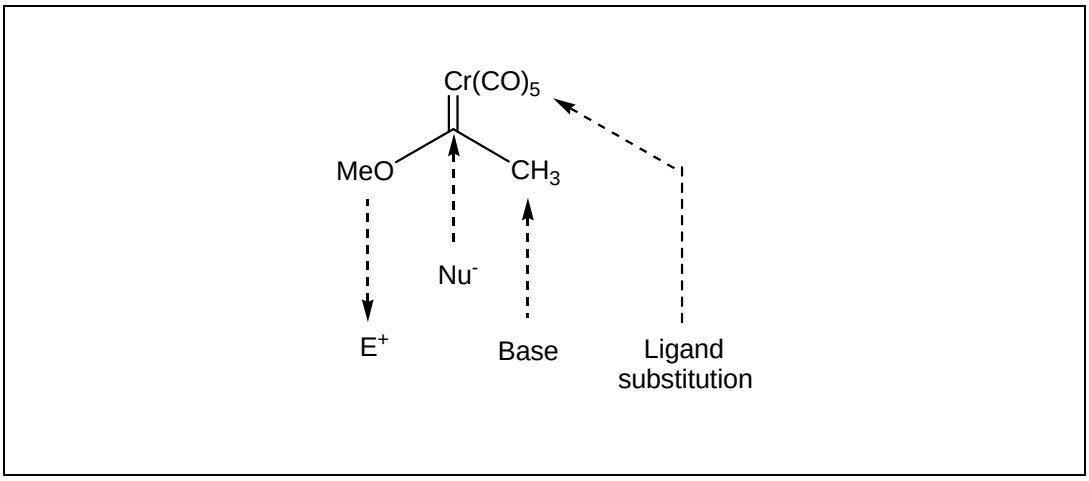


Figure 3. The general reactivity of Fischer-type carbene complexes

There is a rich and varied reaction chemistry of transition metal carbene complexes and at the moment the potential for applications to synthetic organic chemistry seems greater for the Fischer-type carbene complexes than for the Schrock-type carbene complexes. The heteroatom-stabilized Fischer carbene complexes are convenient to use in that they are generally crystalline solids that are handleable in air, can endure temperatures of 100 °C or more, are stable to mild aqueous acids and bases and are soluble in organic solvents to the point where most can be rapidly eluted from silica gel with hexane. Despite their solubility in hexane, Fischer carbene complexes such as **1** have large dipole moments and the carbene carbon displays marked electrophilic behaviour.

The first transition metal carbene complex to be prepared was the phenyl methoxy carbene complex **1** by Fischer in 1964 [14]. His original procedure involves the addition of phenyllithium to chromium hexacarbonyl followed by the alkylation as depicted in Figure 4.

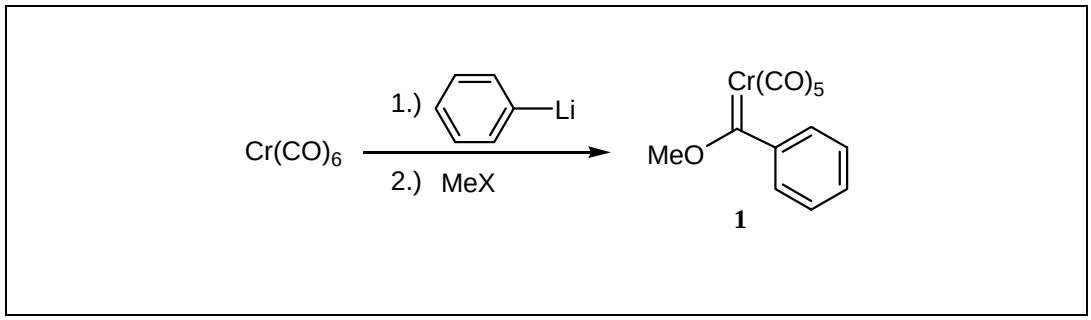


Figure 4. Original procedure of the synthesis of first carbene complex **1**

Fischer's method is still the most commonly used method for the preparation of Fischer-type carbene complexes, and the reaction can be generalized as shown in Figure 5. Treatment of metal carbonyls with organolithium compounds gives the lithiated intermediates. Since these organolithium compounds have proven to be very good nucleophiles, even at low temperatures they react rapidly and give good yields. The neutral alkoxycarbene complexes can be obtained directly from the lithium metal acylates by treatment with strong alkylating agents such as methyl triflate or trimethyloxonium salts. These methylating reagents give better yields when compared with less reactive electrophiles such as methyl iodide, because the formers contain better leaving groups [22,23].

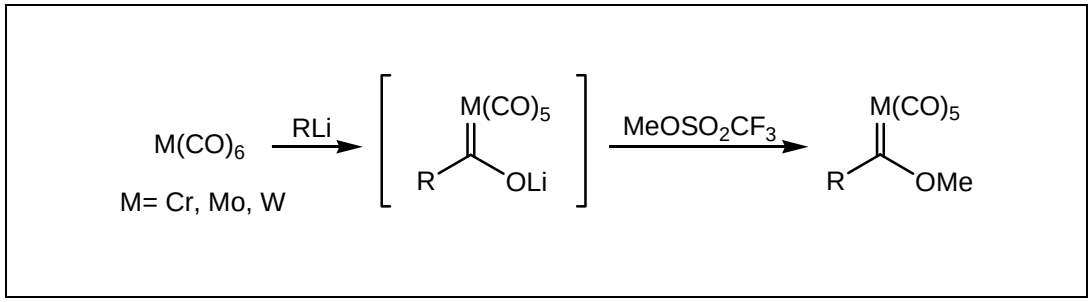


Figure 5. General synthesis of Fischer carbene complexes

The yields of metal carbene complexes by this method are good to excellent and can be prepared on an open-ended scale since most complexes are solid and purification can be accomplished by crystallization. Most of the carbene

complexes can be handled in the presence of air so; they can also be purified on silica gel. The sensitivity of these complexes to air increases with temperature. An inert atmosphere is employed for the reactions that are carried out above room temperature [22].

The chemistry of Fischer-type carbene complexes is a fascinating area both in terms of the variety of reaction types that can be attained and the possibility of the construction of a large variety of highly functionalized structures through several patterns of reactivity [15]. One of the main reasons for the high versatility and often unexpected behavior of Fischer carbene complexes relies on the possibility of incorporation of carbonyl ligands along the reaction pathway, depending on the reaction conditions [24]. Due to these versatile features, these reagents and reactive intermediates are playing an increasing role in the development of new bond-forming reactions that lead to substantial increases in molecular complexity from simple substrates in a single operation [25].

Depending on the nature of the reagents and the reaction conditions, Fischer carbene complexes can lead to the formation of diverse array of products including phenols, cyclopentenones, indenes, furans, furanones, cyclobutenones, vinylketenes and cyclohexadienones [16].

In spite of that many studies highlight the formation of rings of various sizes such as cyclopropane [26], cyclobutane [27], cyclopentane [28], and cycloheptane [29] rings, the most famous and intensely studied reaction of Fischer carbene complexes is by far the coupling of α,β-unsaturated carbene complexes with alkynes, a process commonly known as the Dötz reaction or benzannulation reaction (Figure 6) [16, 30].

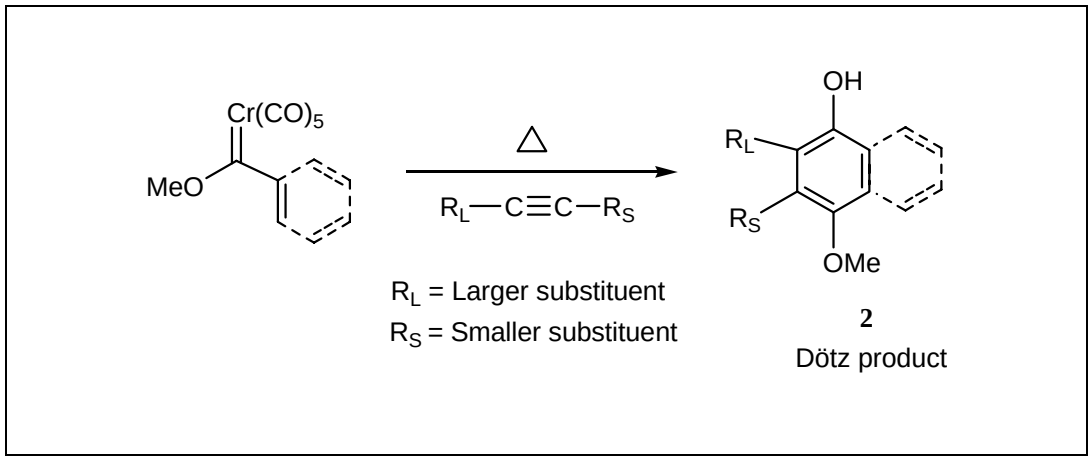


Figure 6. Dötz benzannulation reaction

Dötz benzannulation reaction is a [3+2+1] cyclization between an alkenyl or aryl carbene and an alkyne to form an aromatic ring where three carbon atoms of the α,β-unsaturated carbene ligand, the two acetylenic carbons and a carbonyl ligand from chromium are joined together in the coordination sphere of the metal. The major product of the reaction is a phenol or a naphtol derivative, when the starting material is an alkenyl or an aryl carbene complex, respectively [31]. The mechanism of the reaction is demonstrated in Figure 7.

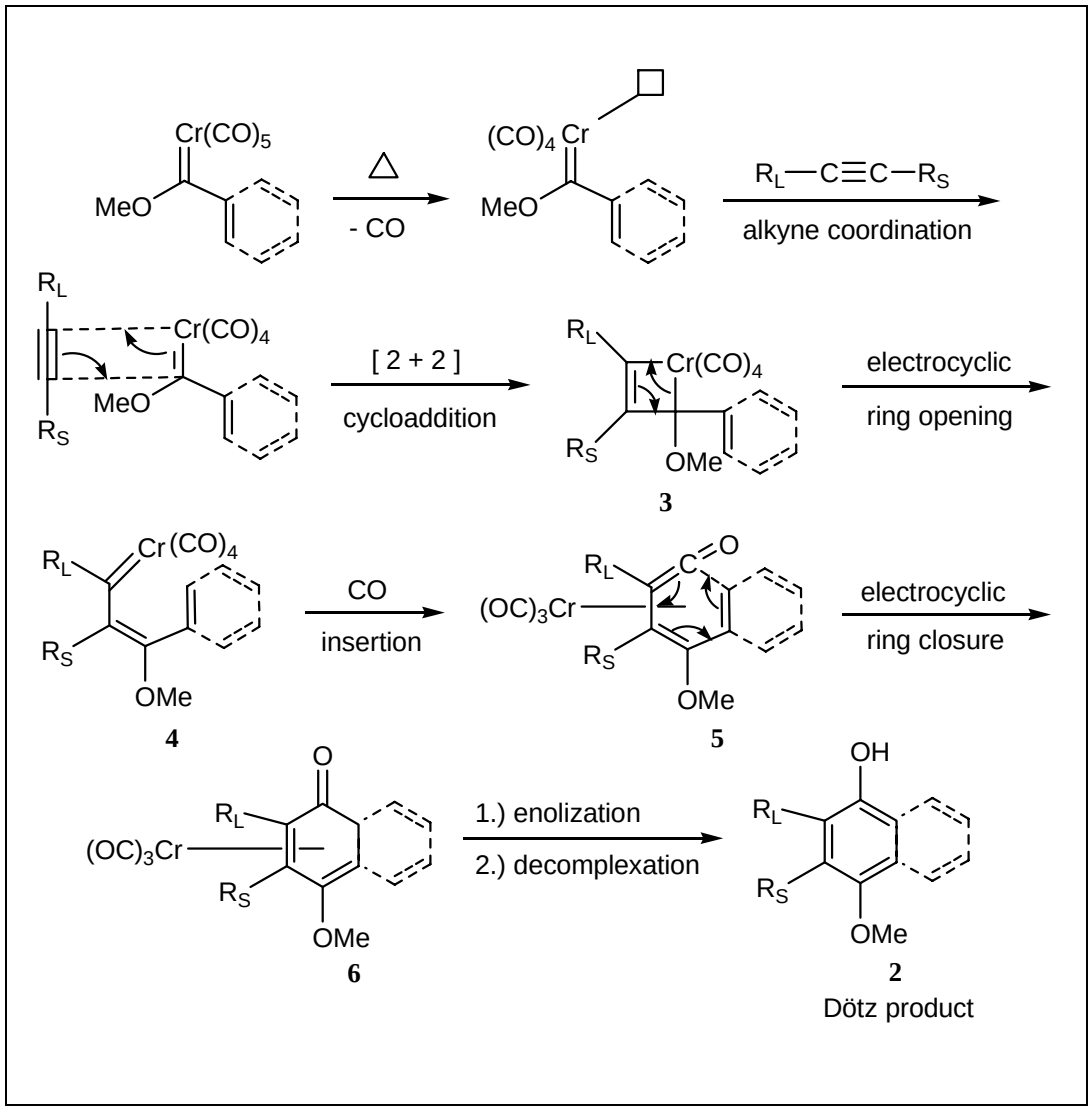


Figure 7. Mechanism of the Dötz reaction

As indicated in Figure 7, the reaction begins with a thermal loss of one carbonyl ligand from the carbene to generate a vacant coordination site on metal. Coordination of the alkyne followed by a [2+2] cycloaddition reaction between the alkyne and the metal-carbon double bond gives the metallacyclobutene **3**. Then this compound goes through an electrocyclic ring opening reaction, which produces the metallahexatriene intermediate **4**. Subsequent carbonyl insertion generates the metal bound vinyl ketene **5**. Then an electrocyclic ring closure occurs forming the intermediate **6**. Enolization followed by the decomplexation of $Cr(CO)_3$ produces the Dötz product **2**.

The benzannulation reaction takes place in a regioselective way and is governed by steric factors. The predominant isomer has the sterically larger substituent of the alkyne adjacent to the free hydroxyl group of the phenol or naphtol derivative [32,33].

Dötz benzannulation reaction is the cornerstone of the synthetic chemistry of Fischer carbene complexes and also it is the most useful reaction for the synthesis of natural products and bioactive compounds such as vitamin K, vitamin E, naphthoquinone antibiotic nanaomycin, effective antitumour agent daunomycinone, and potential antiatherosclerotic agent khellin (Figure 8) [34,35].

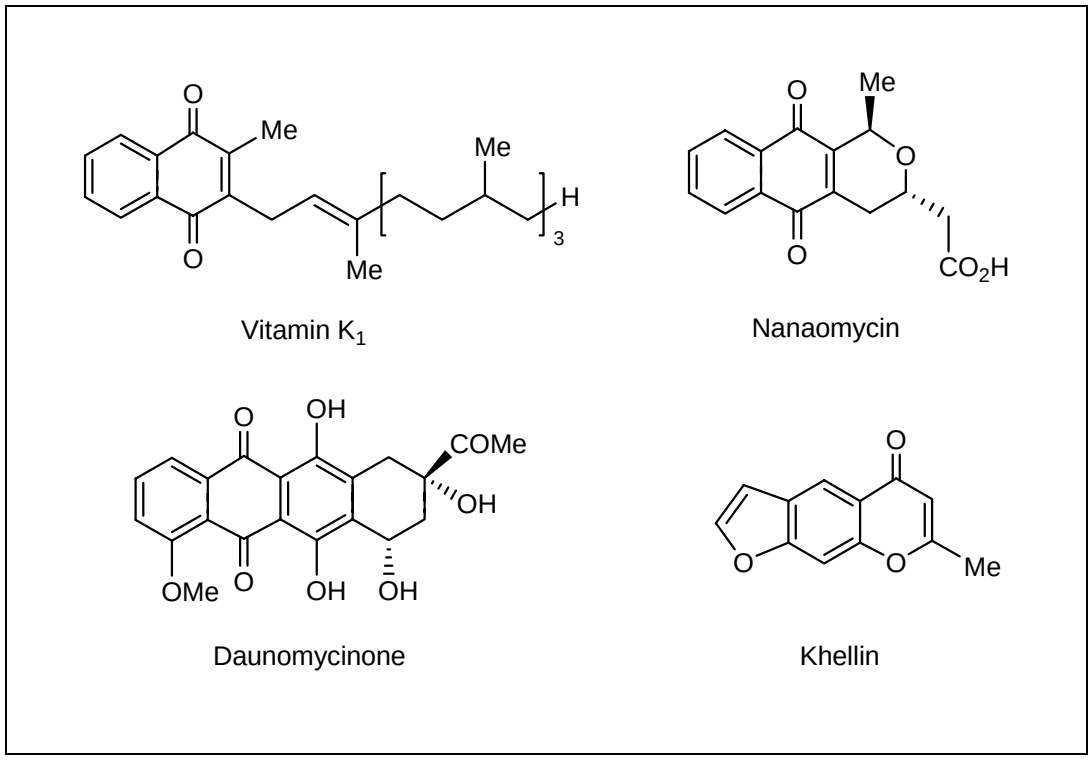


Figure 8. Examples of natural products and bioactive compounds synthesized by Dötz reaction

As can be seen, a wide array of products can be synthesized by Dötz reaction. It has many steps, each of which can be diverted along other pathways,

leading to other products. For example, when cyclopropylcarbenes are subjected to the typical Dötz reaction, totally unexpected products result [36].

Treatment of cyclopropylcarbene complexes with alkynes lead to seven-membered carbocycles **8**, on the basis of a mechanism analogous to the proposed for the Dötz benzannulation but incorporating the cyclopropyl ring opening. However, only molybdenum and tungsten carbene complexes undergo this [4+2+1] cyclization to produce a seven-membered ring product (Figure 9). On the other hand, with chromium carbene complexes a different process takes place, leading to cyclopentenones **10** as main reaction products in moderate to good yields (Figure 9).

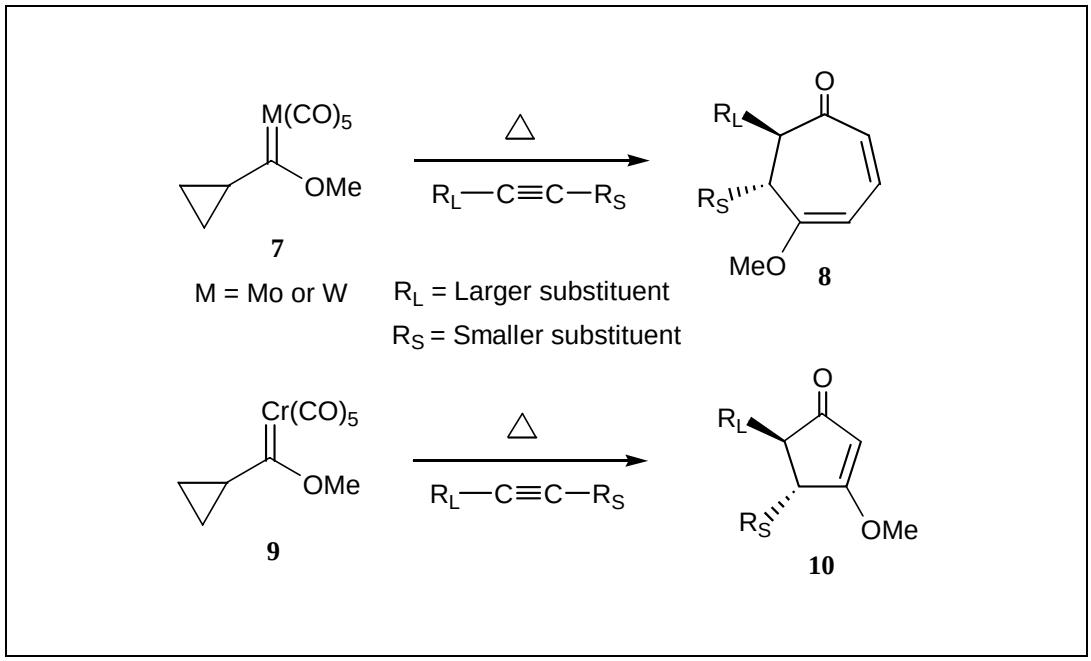


Figure 9. Reactions of cyclopropylcarbene complexes

Cyclopentenones are not only key building blocks for organic synthesis, but many possess interesting biological properties in their own right. The cyclopentenone ring structure is present in a wide range of important natural products such as jasmones [37] and pentenomycins [38], in bioactive compounds such as prostaglandins [39], and in interesting drug targets such as

cyclopentanoid antibiotics. Furthermore, the cyclopentenone structural unit is a very useful building block for the synthesis of other biologically active compounds composed of cyclopentane units, due to the versatility of the α,β-unsaturated carbonyl functionality [40].

For some time, prostaglandins (PGs) have attracted considerable attention, as they play an important role in the human body, controlling a wide variety of physiological responses [41]. More recently, studies on the biological activities of the so-called 'cyclopentenone PGs' have revealed that these compounds are potent bioactive molecules and have been shown to possess anticancer, antiviral and anti-inflammatory activity [42]. Indeed recent reviews on the subject reflect the explosion of interest from biological and chemical research laboratories working in this area [43].

The α,β-unsaturated carbonyl group is clearly key to many of the biological actions of the cyclopentenone PGs because other PGs, devoid of this functionality, do not possess such a comparable range of biological activities. This has been confirmed in model studies, where cyclopenten-2-one has shown significant biological activity, whilst related compounds, cyclopentanone and cyclopentene, were unreactive [44].

Cyclopentenone PGs, such as Δ^7-PG-A_1 **11** and its methyl ester **12**, display significant antitumour activity (Figure 10) [45]. 13,14-Dihydro-15-deoxy-Δ^7-PG-A_1 methyl ester **13** (TEI 9826) is active *in vivo* against *cis*-platin-resistant tumours and is undergoing clinical trials (Figure 10) [46].

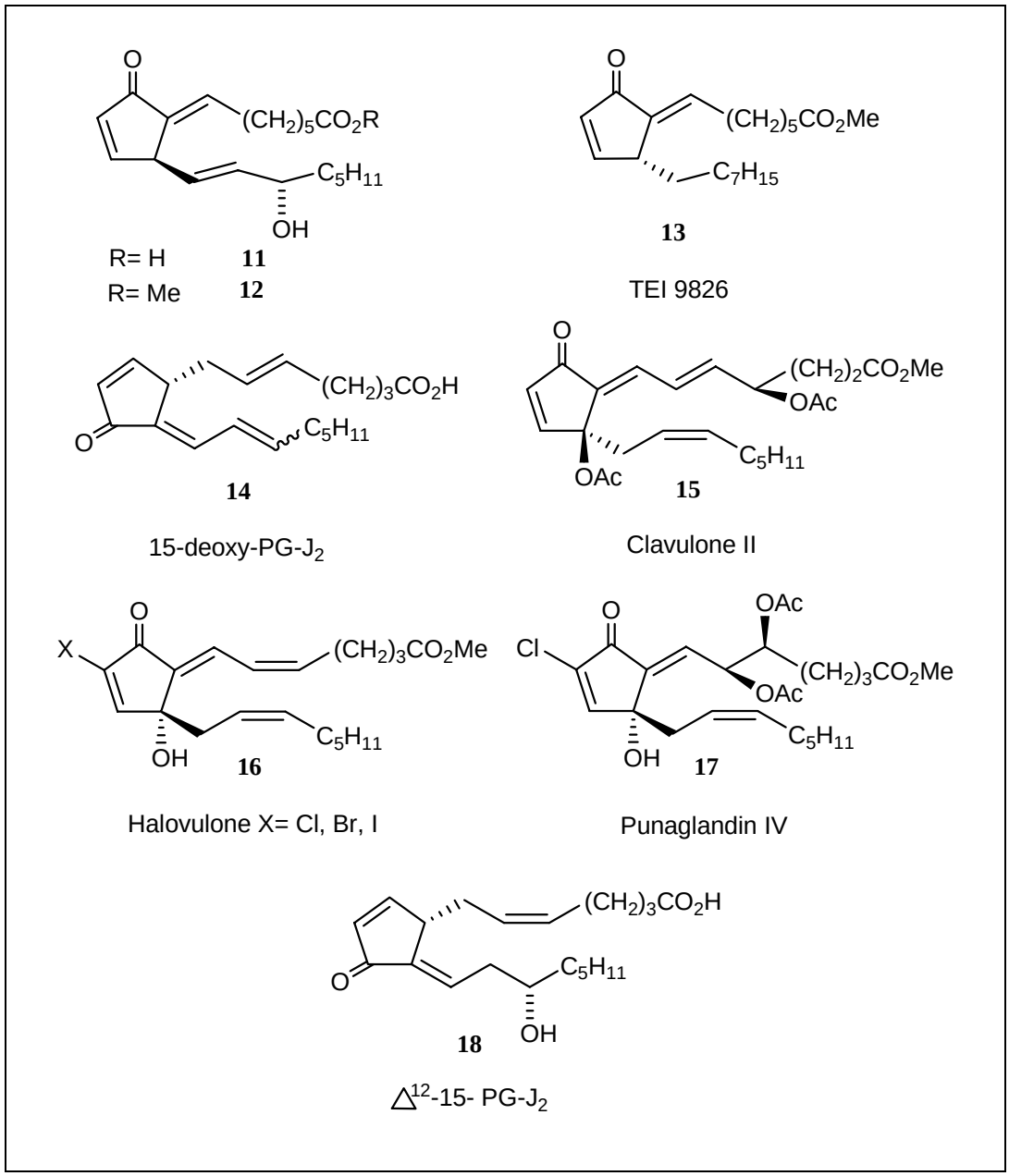


Figure 10. Biologically important cyclopentenone derivatives

The PG-As and PG-Js have also been reported to inhibit a wide range of viruses, including influenza virus [47] and human immunodeficiency virus (HIV) [48]. Additionally, $\Delta^{12,14}$-15-deoxy-PG-J_2 **14** has been found to be a potent anti-inflammatory agent, which may open the way to a novel class of non-steroidal-based anti-inflammatory [49] and antiviral drugs (Figure 10) [50].

Marine prostaglandins such as clavulone II **15** [51], naturally halogenated halovulone **16** [52] and punaglandin IV **17** [53] isolated from corals have also cyclopentenone structures (Figure 10). Their cytotoxic and antitumour activities [54] have been demonstrated both *in vitro* and *in vivo*. Δ^{12}-15-PG-J_2 **18** is a mammalian-derived antitumour prostaglandin (Figure 10) [55]. It exerts potent action via direct interaction with putative nuclear proteins, resulting in breast cancer cell arrest and growth inhibition, cell differentiation, induction of cellular defence mechanisms against viral inflection, modulation of gene and protein functions [56].

The broad spectrum of biological activity of this type of compounds has prompted an extensive search for development of new methods of their preparation. One of the most extensively studied procedures for forming cyclopentenones is the Pauson-Khand reaction (Figure 11), which consists of a [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide, promoted by octacarbonyldicobalt (0), resulting in the formation of cyclopentenones [57, 58]. This powerful method does, however, suffer from certain deficiencies, including poor regioselectivity in the incorporation of the olefin and modest yield in reactions of unstrained or hindered olefins, as well as internal alkynes.

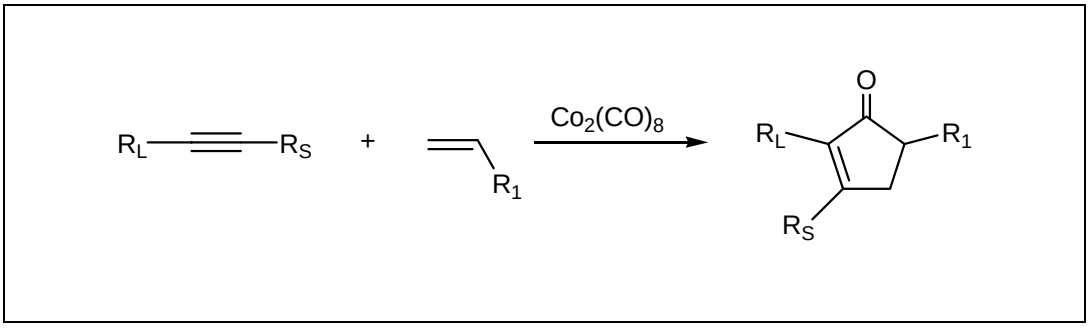


Figure 11. Pauson-Khand reaction

On the other hand, since the discovery of ferrocene (**19**) in the 1950s by G. Wilkinson, R. B. Woodward and E. O. Fischer [59], the fascinating structural properties of ferrocene and its derivatives have been the subject of increasing interest in all fields of organometallic chemistry.

Ferrocene, an orange crystalline diamagnetic solid, is one of the most common and well-known organometallic compounds [60]. It is a simple complex consisting of an iron center and two cyclopentadienyl (Cp) rings surrounding the metal. Ferrocene, with its 18 valence electrons, is also one of the most stable member of the metallocenes. It is thermally stable and tolerant to oxygen and moisture [61].

Ferrocene is easily transformed to the blue, paramagnetic, ferrocenium ion **20** by such mild one-electron oxidizing agents as ferric salts, silver (I), halogens, nitric acid, and even sulfuric acid (Figure 12) [62].

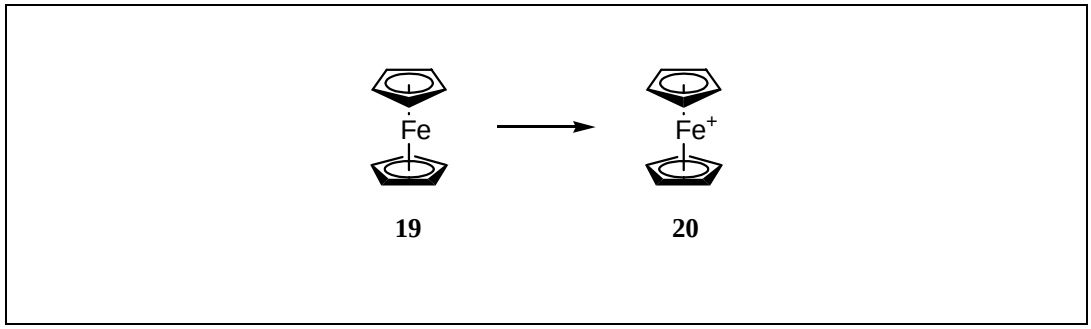


Figure 12. Ferrocenium ion

Ferrocene has a rich aromatic chemistry as long as one-electron oxidizing agents are not employed. The cyclopentadienyl ring in ferrocene carries a partial negative charge and is susceptible to electrophilic substitution reactions. For example, ferrocene very readily undergoes Friedel-Crafts acylation and alkylation, Vilsmeir formylation, dimethylaminomethylation, and mercuration (Figure 13). Ferrocene is 10^6 more reactive than benzene toward Friedel-Crafts acylation. Thus, it is easy to introduce various donor groups to the ferrocene skeleton. The mercury derivatives are useful in the preparation of haloferrocenes [62].

Ferrocene and its derivatives play an important role in many fields of chemistry. For example, numerous ferrocene derivatives, or their complexes, are

used as catalysts for asymmetric synthesis of a wide number of optically active organic compounds [63,64].

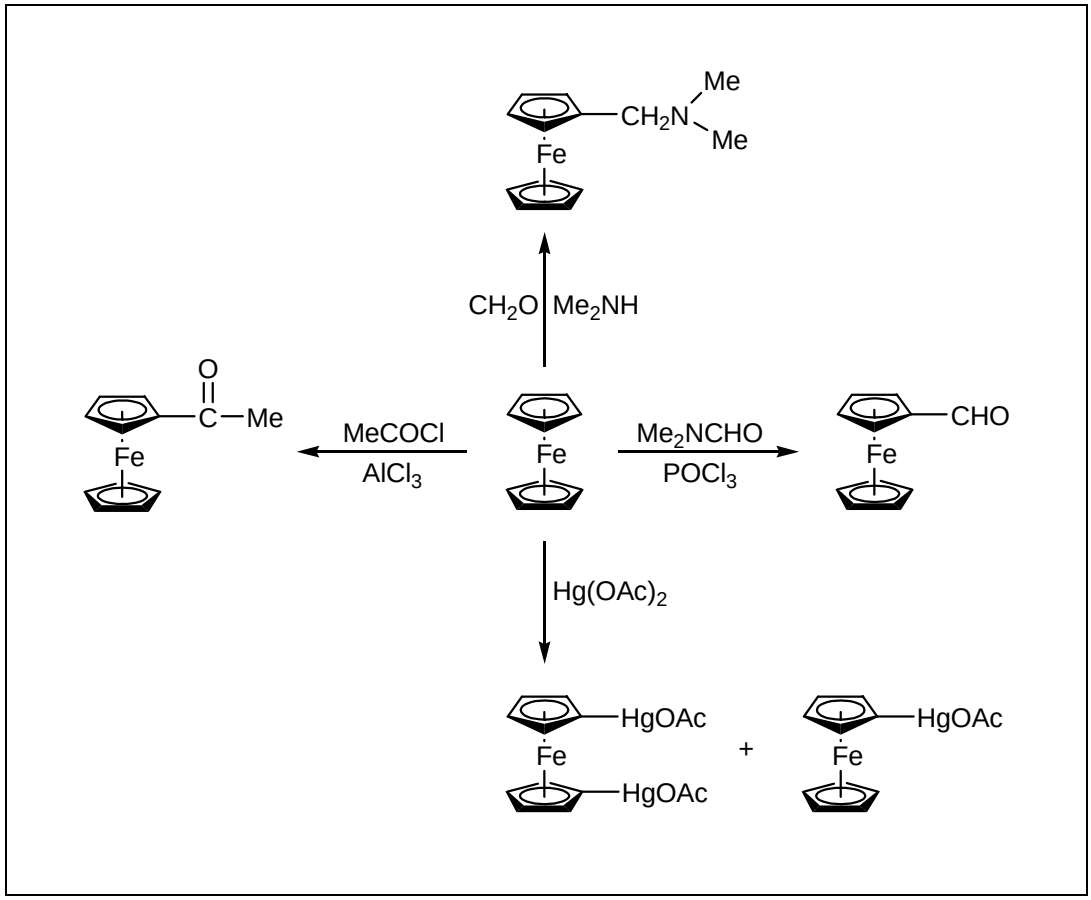


Figure 13. Typical electrophilic substitution reactions of ferrocene

On the other hand, as other transition metal complexes ferrocene derivatives have attracted the interest to themselves in medicine and other biological areas [65,66] after the first successful application of the '*cis*-platin', i.e. *cis*-$[PtCl_2(NH_3)_2]$ as an antitumour agent [67].

Ferrocenium salts have proved to be particularly active against a number of various animal and human tumours [66]. Ferrocene itself is insoluble in water and does not exhibit any antitumour activity. Even if it is solubilized in water using heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (dmβ-CD), it does not show any tumour inhibitory effect [68], but ferrocenium salts, in which the central iron

atom has a +3 charge, have antitumour activity against a number of tumours [66,68]. Although the excellent solubility of salts in water, caused by their ionic character, proves to be propitious for applications in biological systems, the inhibitory activity of ferrocenium salts is independent of the water solubility. The only factor that makes these ferrocenium salts active against tumours is the +3 oxidation state of the central iron [68].

Tamoxifen **21** is the most powerful drug still used in the treatment of breast cancer today. It has an inhibitory effect against breast cancer cells [69]. But it works only hormone-dependently, which means that it has an antitumour activity against only on hormone-dependent cancer cells. Jaouen and his coworkers have prepared a ferrocene analogue of hydroxytamoxifen **22** by replacing the phenyl group by a ferrocene moiety. Resulting hydroxyferrocifens **24** have shown to be active against both hormone-dependent and hormone-independent breast cancer cells (Figure 14) [70].

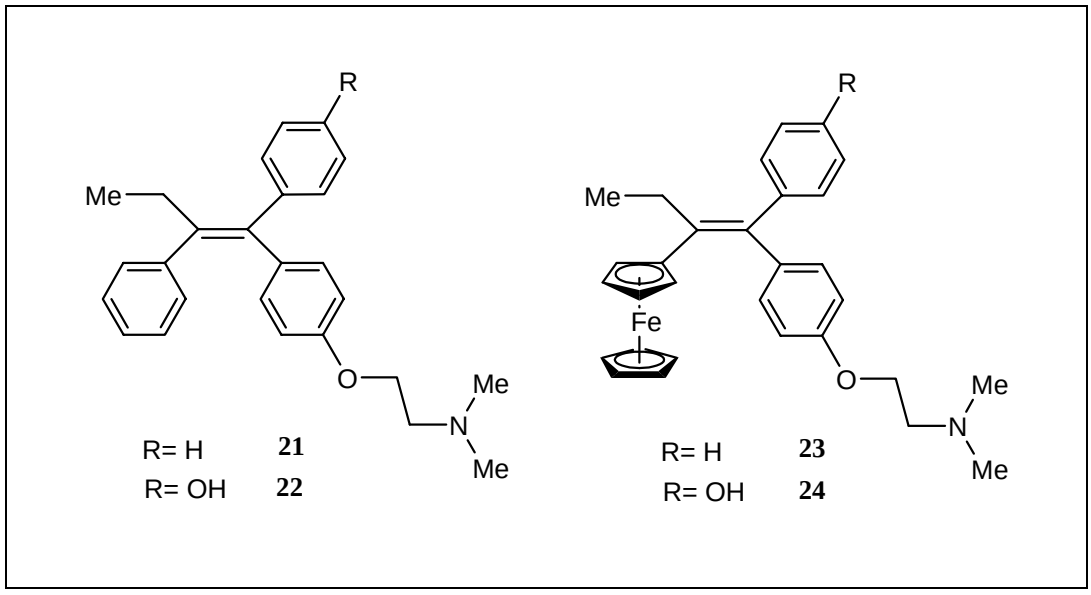


Figure 14. Tamoxifen and ferrocifen

Ferrocene derivatives are also active against malaria parasite. Chloroquine is one of the drugs used in the treatment of this disease. But unfortunately, malaria parasites have gained resistance to these drugs almost all over the world

[71]. Brocard and his coworkers inserted a ferrocenyl group into the side chain of the chloroquine, thus producing a hybrid compound called ferroquine [72]. It is reported that the resulted ferroquine is much more safe and effective in mice, as well as non-mutagenic (Figure 15) [73].

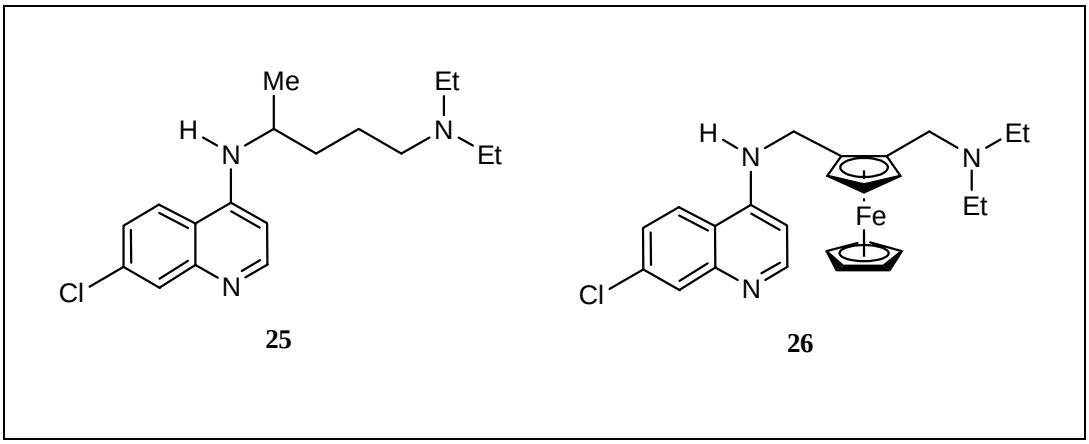


Figure 15. Chloroquine and ferroquine

The successful attempts made on tamoxifen and chloroquine were promising. Thus, in recent years, considerable interest has been devoted to the synthesis of new ferrocene derivatives since the properly functionalized ferrocene derivatives; particularly their ferrocenium salt forms could be potential antitumour substances [74].

As mentioned previously, cyclopentenones are important structures possessing biological activity. This apparent importance of cyclopentenones and the discovery that ferrocene derivatives are effective against various kinds of tumours brings to mind that the combination of the structural aspects of cyclopentenones with a ferrocene moiety could furnish compounds with enhanced antitumour activities.

Thus, we have investigated the reaction of cyclopropylcarbene-chromium complexes with ferrocenyl alkynes in order to synthesize the ferrocenyl-

substituted cyclopentenones (Figure 16). In this study, the scope, limitations and the mechanism of this reaction are discussed.

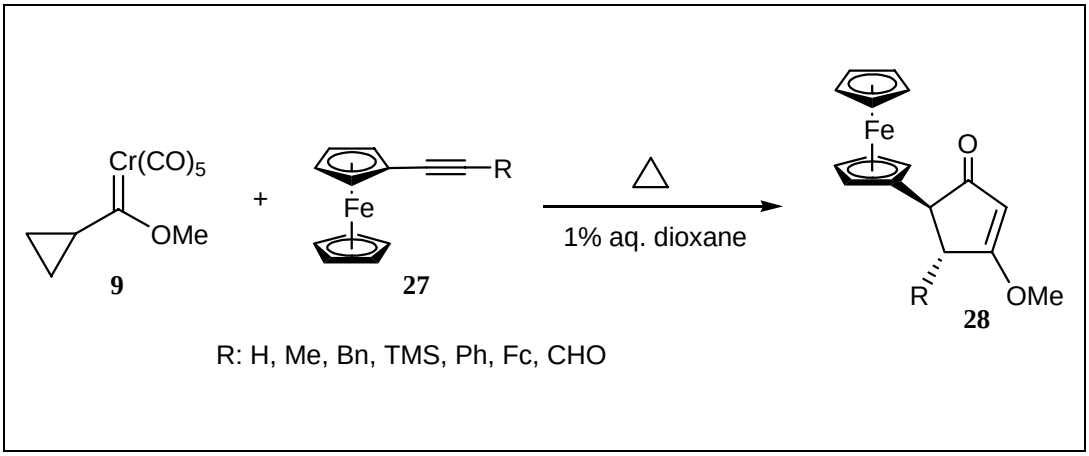


Figure 16. Reaction of cyclopropylcarbene-chromium complex **9** with ferrocenyl alkynes **27**

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of Carbene Complex and Ferrocenyl Alkynes

In this work, the starting materials, cyclopropylcarbene-chromium complex **9** and the ferrocenyl-substituted alkynes **27**, were first synthesized.

2.1.1. Synthesis of Cyclopropylcarbene-Chromium Complex 9

In order to synthesize ferrocenyl-substituted cyclopentenone derivatives **28** by using the reaction between cyclopropylcarbene-chromium complex **9** and ferrocenyl alkynes **27**, first of all, complex **9** was synthesized (Figure 17) [75]. For this purpose, cyclopropylbromide (**29**) was treated with *tert*-butyllithium (*t*-BuLi) in dry tetrahydrofuran (THF) at –78 °C to produce the lithiated intermediate **30**, which was then directly added to a suspension of chromium hexacarbonyl in THF at –78 °C to afford lithium metal enolate. Treatment of this enolate with methyl triflate produced the desired cyclopropyl(methoxy)carbene chromium (0) complex (**9**).

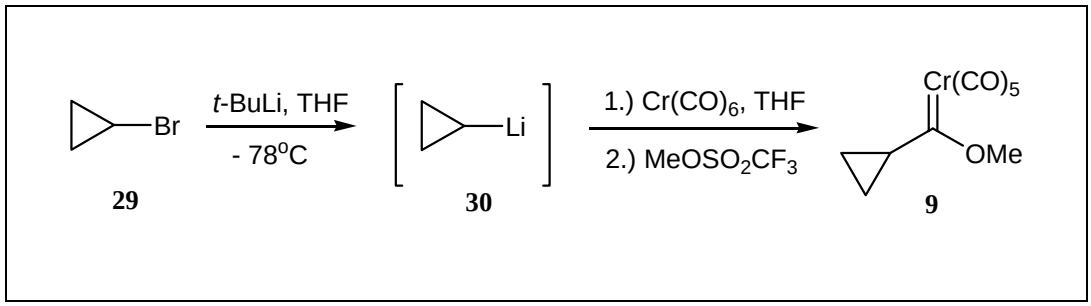


Figure 17. Synthesis of cyclopropylcarbene-chromium complex **9**

2.1.2. Synthesis of Ferrocenyl Alkynes 27

Ferrocenyl alkyne derivatives **27** were prepared starting from ethynylferrocene (**27A**). So, in the first phase of the study, ethynylferrocene (**27A**) was synthesized in three steps according to literature procedures (Figure 18) [76,77]. Initially, acetylferrocene (**31**) was synthesized starting from ferrocene (**19**) according to the Friedel-Crafts acylation reaction in dichloromethane (CH_2Cl_2) at 0 ºC in the presence of acetyl chloride and aluminium chloride. Then, acetylferrocene (**31**) was treated with phosphorus oxychloride in *N*,*N*-dimethylformamide (DMF), followed by the addition of sodium acetate at 0 ºC. The resulted product, (2-formyl-1-chlorovinyl)ferrocene (**32**), was then refluxed in dioxane in the presence of sodium hydroxide to give ethynylferrocene (**27A**).

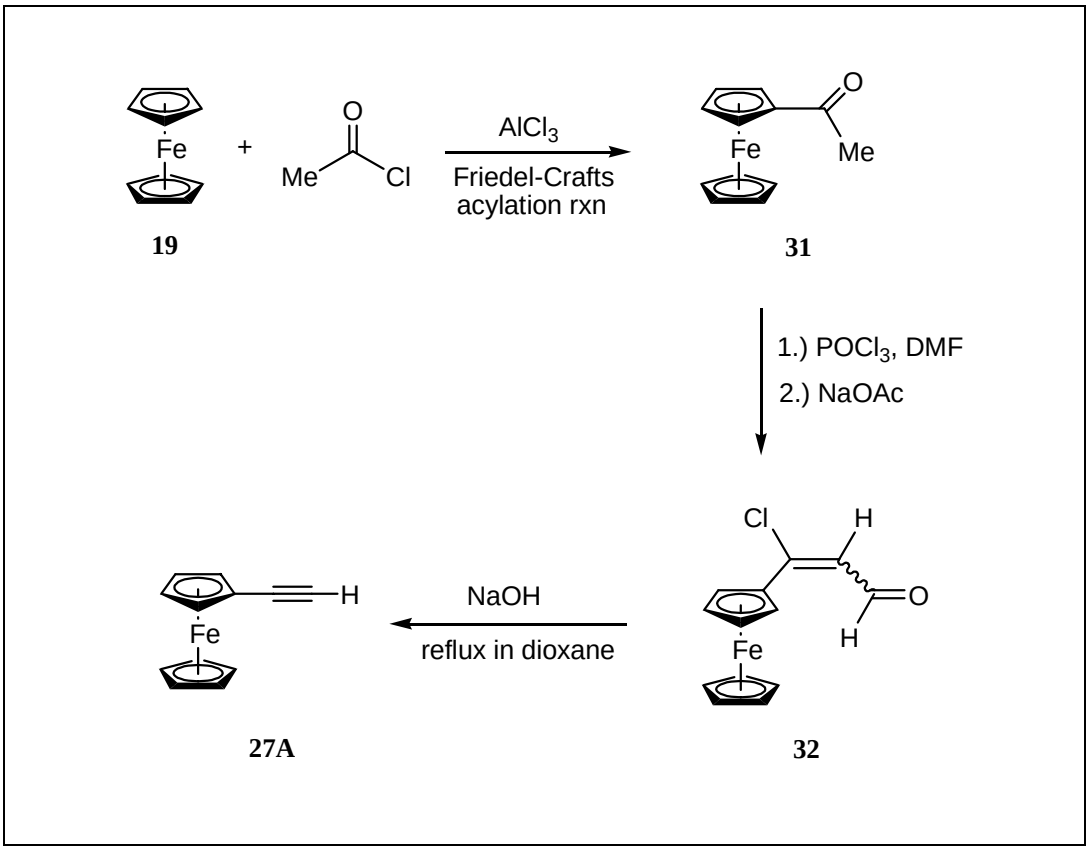


Figure 18. Synthesis of ethynylferrocene (**27A**)

Methyl, benzyl, trimethylsilyl and aldehyde-substituted ferrocenyl alkynes **27B-D,G** were synthesized by using the same method starting from ethynylferrocene (**27A**) (Figure 19) [78]. For this purpose, ethynylferrocene was treated with *n*-butyllithium (*n*-BuLi) in dry THF at –78 °C to produce the lithiated intermediate **33**. After stirring the solution for 1 h, the addition of methyl iodide, benzyl bromide, trimethylsilyl chloride and DMF at –78 °C generated the desired ferrocenylpropyne (**27B**), 1-ferrocenyl-3-phenylprop-1-yne (**27C**), (2-ferrocenylethynyl)trimethylsilane (**27D**) and ferrocenyl(formyl)acetylene (**27G**), respectively.

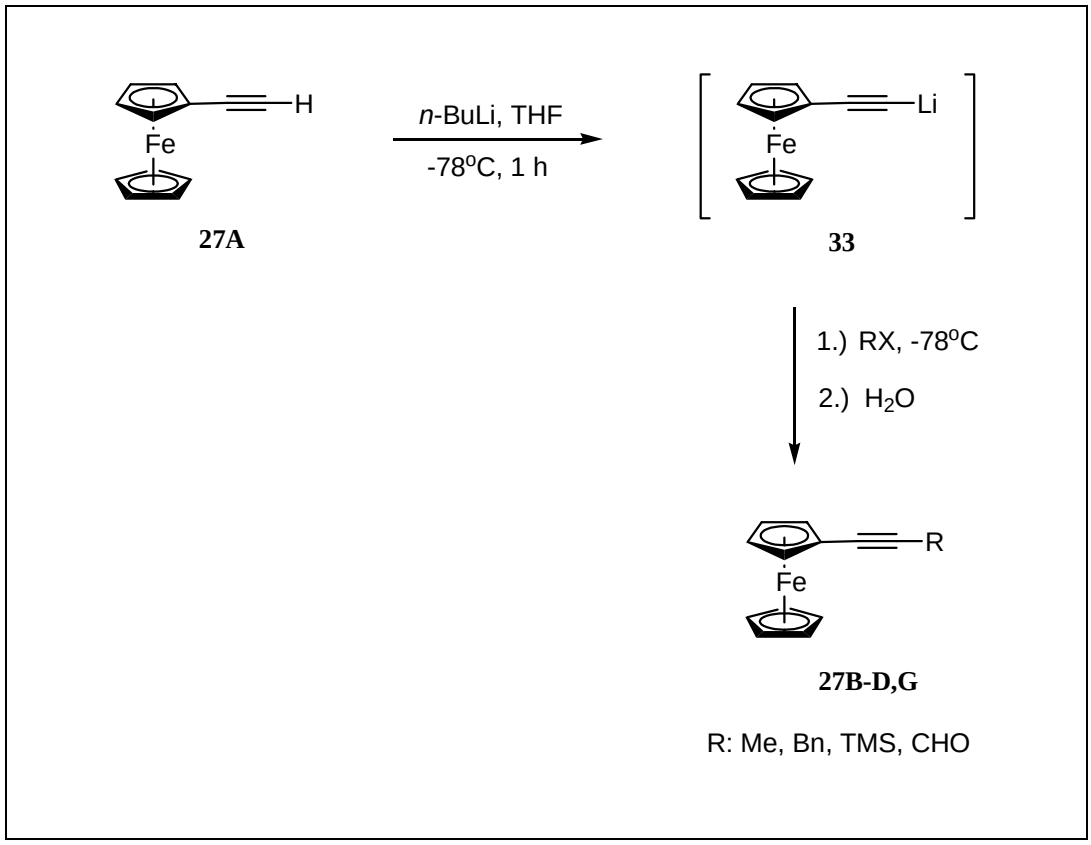


Figure 19. Synthesis of ferrocenyl alkynes **27B-D,G**

Phenyl-substituted ferrocenyl alkyne **27E** was synthesized according to a literature procedure again starting from ethynylferrocene (**27A**) (Figure 20) [79]. Addition of iodobenzene to ethynylferrocene (**27A**) and refluxing them in DMF for 16 h in the presence of copper iodide, triphenyl phosphine and potassium carbonate produced the desired 1-ferrocenyl-2-phenylethyne (**27E**).

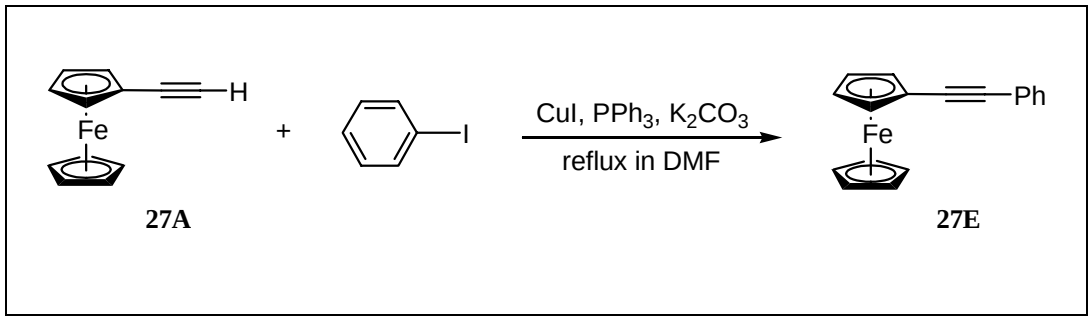


Figure 20. Synthesis of 1-ferrocenyl-2-phenylethyne (**27E**)

Diferrocenylethyne (**27F**) was synthesized according to a literature procedure (Figure 21) [80]. Refluxing a solution of methyl-substituted ferrocenyl alkyne **27B**, molybdenum hexacarbonyl and 2-fluorophenol in chlorobenzene for 2 h gave the product **27F**.

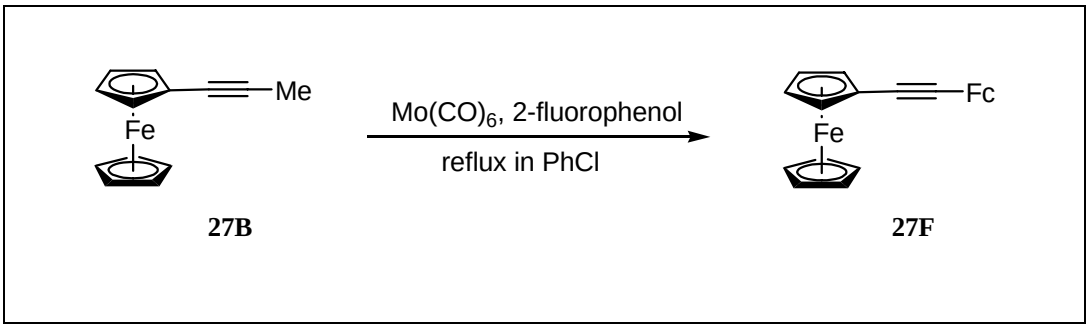


Figure 21. Synthesis of diferrocenylethyne (**27F**)

Yields of the ferrocenyl alkyne derivatives **27** were illustrated in Table 1. As seen in Table 1, the yields were quite good. The best yield for the synthesis of ferrocenyl alkynes was obtained for the methyl-substituted alkyne **27B** whereas the lowest yield was obtained for the diferrocenylethyne (**27F**).

Table 1. Yields of ferrocenyl alkynes **27**

R	H **27A**	Me **27B**	Bn **27C**	TMS **27D**	Ph **27E**	Fc **27F**	CHO **27G**
Yield (%)	75	96	56	84	47	26	93

2.2. Reaction of Cyclopropyl(Methoxy)Carbene Chromium (0) Complex (9) with Ferrocenyl Alkynes (27): Scope and Limitations

After synthesizing these ferrocenyl alkyne derivatives **27**, we have investigated their reactions with cyclopropylcarbene-chromium complex **9**.

Reactions were carried out by adding a solution of alkyne and carbene to a refluxing 1% aqueous dioxane solution over a period of 2 h, and reflux was continued for a period of 6 h. The reason of using high-dilution conditions generated by the slow addition of a solution of the carbene complex and the alkyne to a refluxing aqueous dioxane over a period of 2 h, is for the prevention of polymerization of the alkyne by keeping it at low concentration.

The reaction products were isolated by flash column chromatography and all products isolated from these reactions were characterized by means of NMR, IR and HRMS. Preliminary results of this study were summarized in Figure 22.

Yields of the products that were obtained from the coupling of cyclopropyl(methoxy)carbene chromium (0) complex (**9**) with ferrocenyl-substituted alkynes **27** were depicted in Table 2.

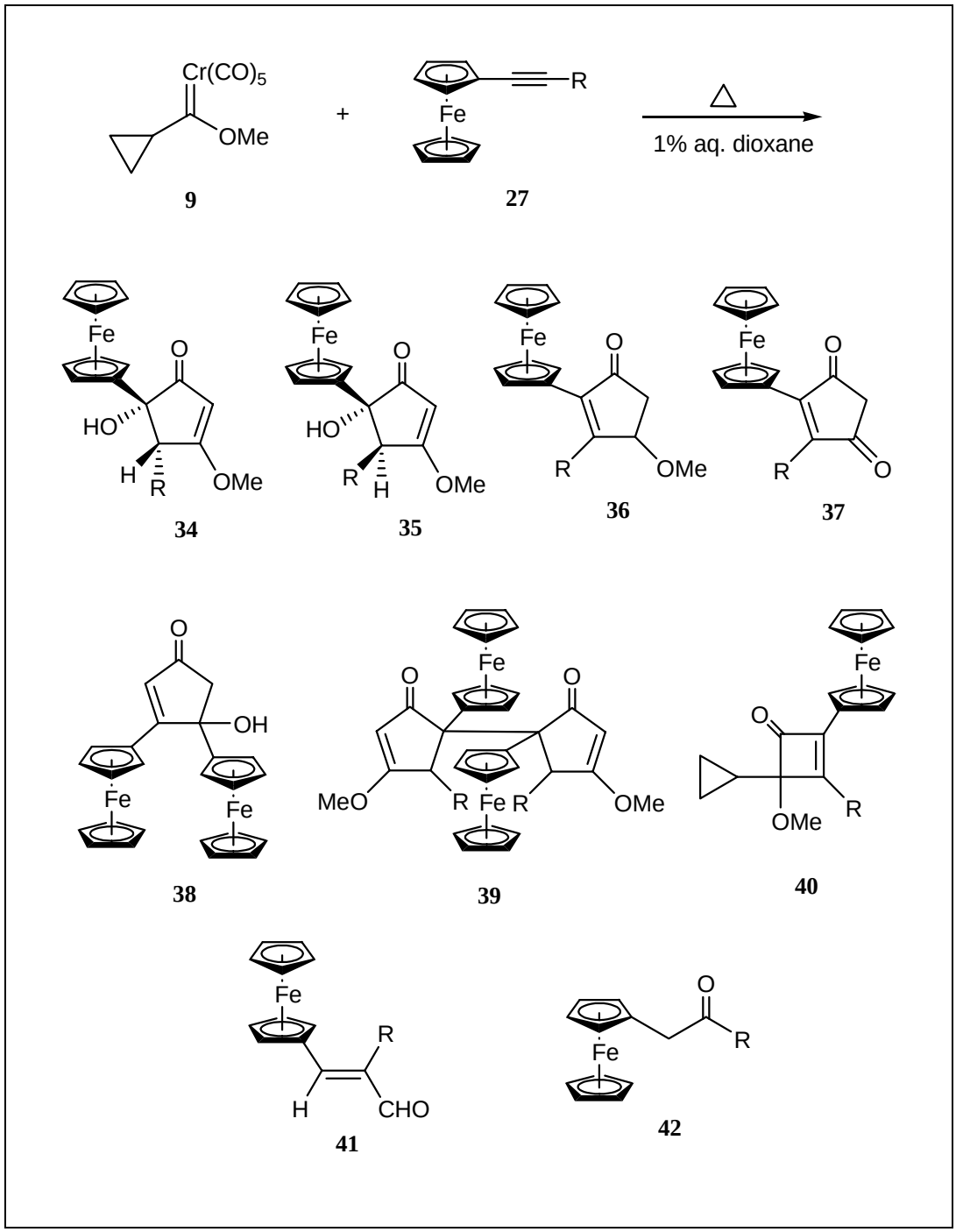


Figure 22. Products from the reaction of cyclopropylcarbene-chromium complex **9** with ferrocenyl alkynes **27**

Table 2. Yields of the products from reaction of cyclopropylcarbene-chromium complex **9** with ferrocenyl alkynes **27**

Entry	Alkyne	R	Products (yield %)
A	**27A**	H	**34A** (45) + **38** (6)
B	**27B**	Me	**34B** (36) + **35B** (16) + **36B** (17) + **39B** (4) + **41B** (6) + **42B** (17)
C	**27C**	Bn	**34C** (16) + **37C** (30) + **42C** (27)
D	**27D**	TMS	**34A** (26)
E	**27E**	Ph	**34E** (31) + **36E** (5) + **37E** (20) + **42E** (35)
F	**27F**	Fc	**34F** (18) + **36F** (9) + **37F** (32) + **40F** (7)
G	**27G**	CHO	–

As can be seen in Table 2, the reaction is general for a wide variety of alkynes. We have demonstrated that the reactions of cyclopropylcarbene-chromium complex **9** with ferrocenyl alkynes **27** give thermodynamically more stable *trans*-α-hydroxy ferrocenyl cyclopentenones **34** as the major product of these coupling reactions in most cases.

With monosubstituted alkyne **27A** (Table 2, Entry A), the only regioisomer obtained was that in which ferrocene moiety of the alkyne was α to the carbonyl group in the product **34A**. When a large excess of ethynylferrocene (**27A**) was used, cyclopentenone such as **38** was obtained as a side product in low yield, which might have resulted from a Reppe-type coupling of the alkyne with CO (Figure 23) [81].

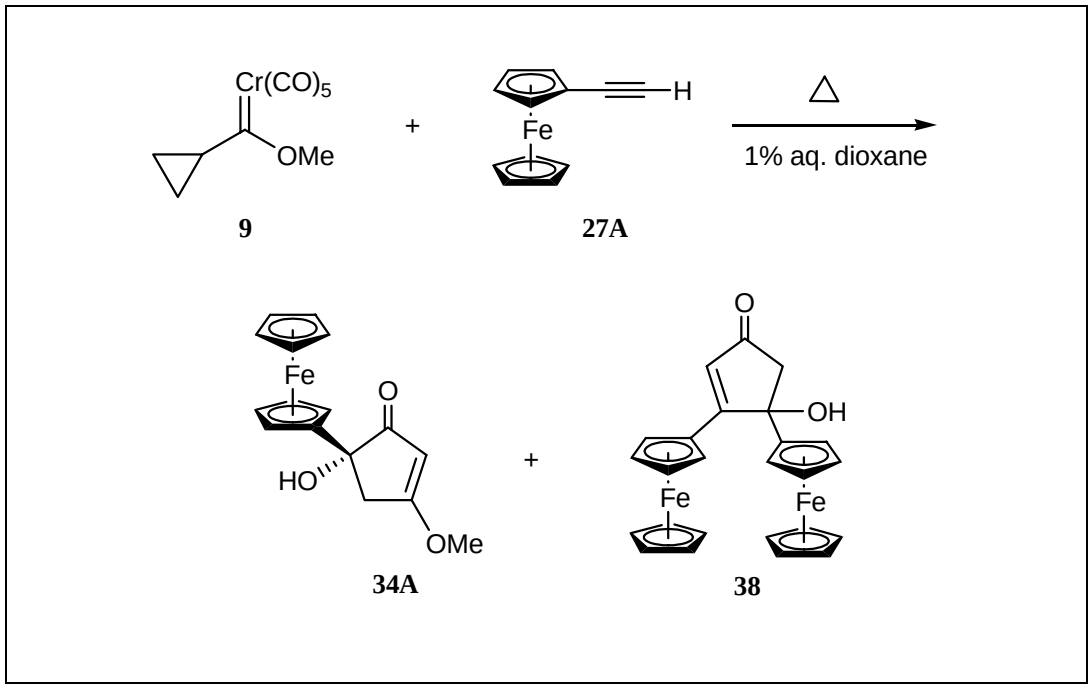


Figure 23. Reaction of carbene complex **9** with terminal alkyne **27A**

The reaction was regioselective when the unsymmetrically-disubstituted alkynes were employed. The products obtained were those where the sterically larger substituent, ferrocene, was α to the carbonyl group. So, we can conclude that the reaction appears to proceed in a way such that the larger substituent will end up α to the carbonyl group in the final product. This result is also in agreement with the regioselectivity observed in the Dötz reaction [32].

According to these results, we can conclude that the reaction is regioselective both with terminal ferrocenyl alkynes and disubstituted unsymmetrical ferrocenyl alkynes, and can be used for synthetic purposes.

The products in Table 2 vary according to the substitution pattern of the alkyne. The reaction process is tolerant of a variety of substitution patterns within the terminating alkyne. The *cis*-α-hydroxy ferrocenyl cyclopentenone **35** was obtained only from the reaction of methyl-substituted ferrocenyl alkyne **27B** (Table 2, Entry B). But the *trans* isomer provides a higher yield of cyclopentenone than the *cis* isomer. A possible problem with the *cis* isomer is

failure to obtain the desired conformation (*cis*) for the electrocyclic ring closure that is shown in Figure 25. *Cis* isomer is the kinetic product from the cyclopentadienone reduction process.

The cyclopentenones **36** were also obtained from the reaction of carbene complex **9** with methyl-substituted ferrocenyl alkyne **27B**, phenyl-substituted ferrocenyl alkyne **27E** and diferrocenylethyne (**27F**) (Table 2, Entry B,E,F). After the reduction of the double bond adjacent to the methoxy group in the cyclopentadienone intermediate, these cyclopentenones were yielded.

Oxidation of the methoxy group in cyclopentenones **36** in the presence of water and chromium (0) byproducts gives cyclopentenediones **37** (Table 2, Entry C,E,F). These products were isolated from the reactions with alkynes **27C**, **27E** and **27F**.

Products **39** and **41** were also obtained as byproducts from the reaction with ferrocenypropyne **27B** (Table 2, Entry B). On the other hand, ferrocenyl ketones **42** were obtained in some cases with quite good yields as a result of water addition to the ferrocenyl alkynes **27**.

The reaction of (2-ferrocenylethynyl)trimethylsilane (**27D**) (Table 2, Entry D) with carbene complex **9** led to α-hydroxycyclopentenone **34A**. Protiodesilylation of compound **34D** could lead to **34A** since trimethylsilyl group is capable of being hydrolyzed in aqueous reaction medium (Figure 24).

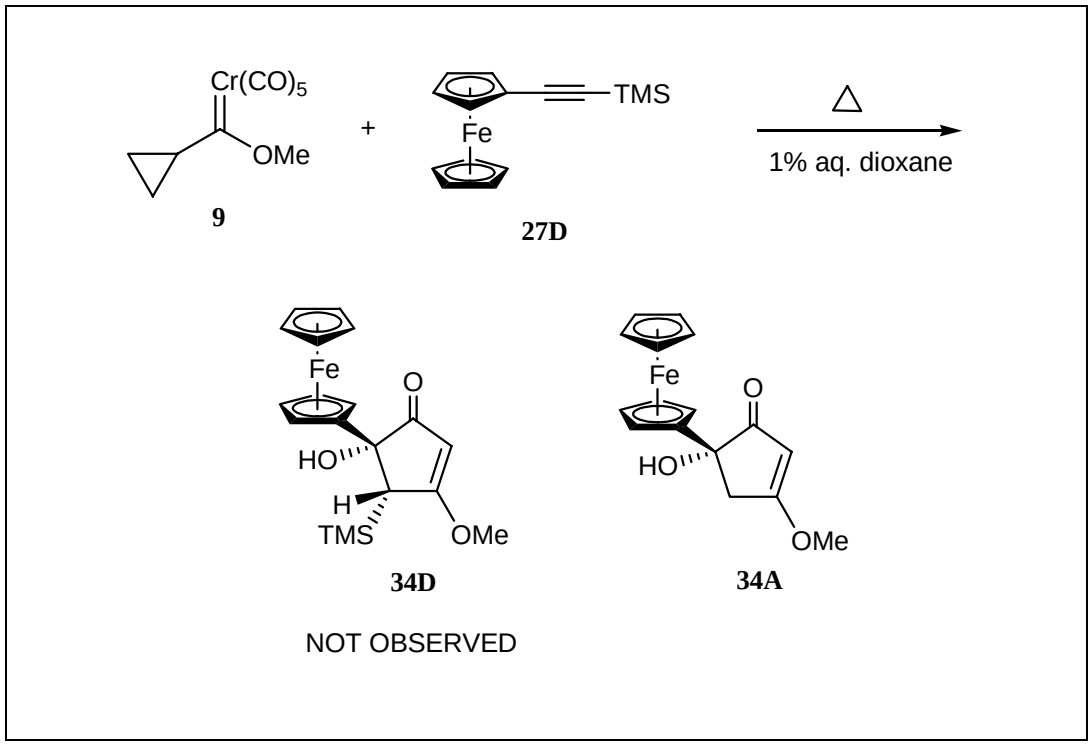


Figure 24. Protiodesilylation in the reaction of carbene complex **9** with (2-ferrocenylethynyl)trimethylsilane (**27D**)

The five membered ring forming reaction did not proceed using the electron-deficient alkyne, ferrocenyl(formyl)acetylene (**27G**) (Table 2, Entry G). It is also known that alkynes of this type often exhibit abnormal behavior in reactions with Fischer carbene complexes [82].

2.3. Mechanism

The reaction mechanism proposed for the synthesis of β-methoxycyclopentenones from the coupling of cyclopropylcarbene-chromium complex **9** and alkynes was depicted in Figure 25. It is similar to the mechanism for the Dötz reaction, which was shown in Figure 7.

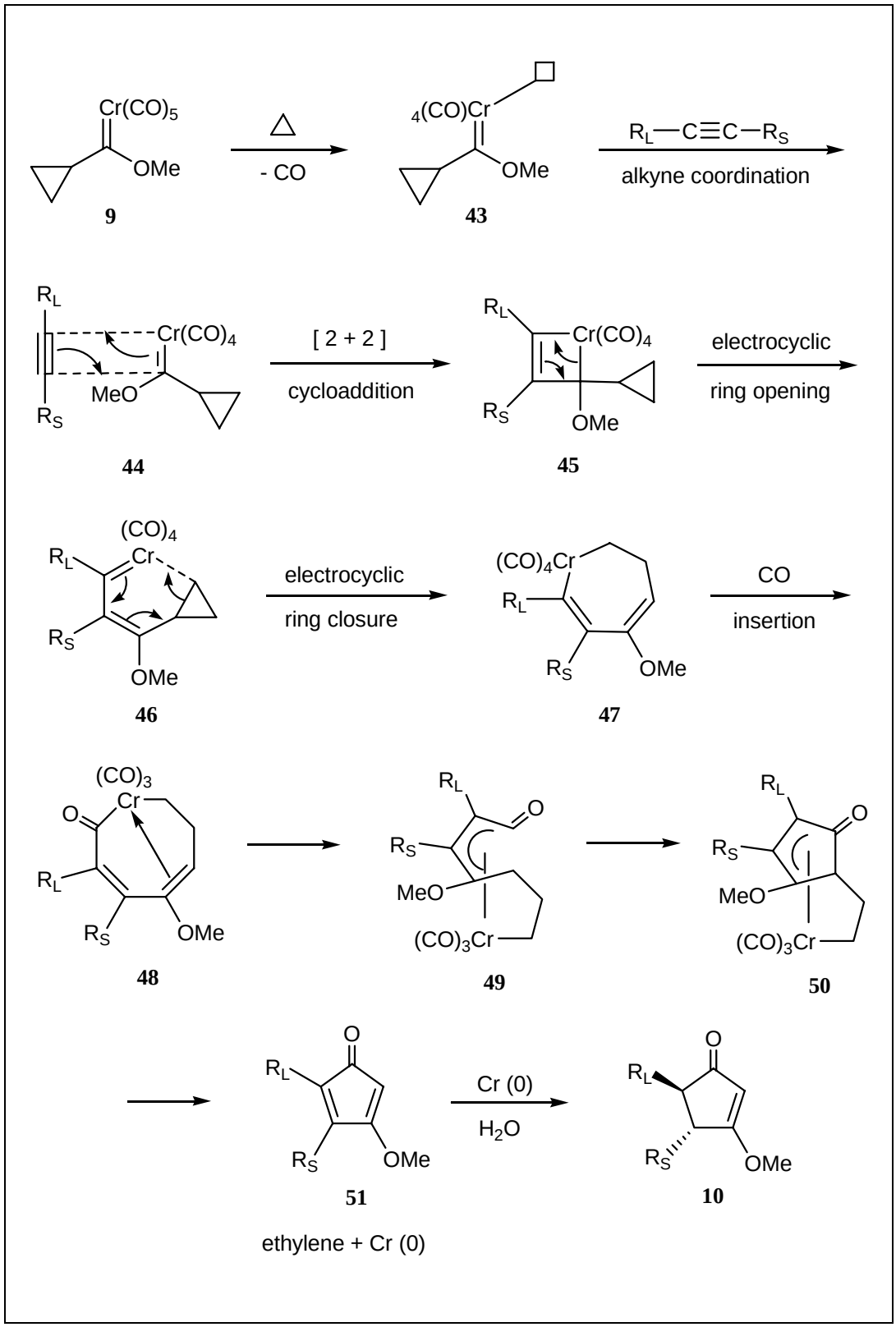


Figure 25. Mechanism for the formation of cyclopentenones

Upon heating, the mechanism begins with the thermal loss of one carbonyl ligand from carbene **9** to generate a vacant coordination site. Then, alkyne coordinates to the carbene complex **43**. After the coordination of alkyne, a [2 + 2] cycloaddition reaction occurs, which goes through the metallacyclobutene intermediate **45**. Then, this metallacyclobutene goes under an electrocyclic ring opening reaction, yielding a vinylcarbene intermediate **46** according to the mechanism of Dötz. Next, the 'sp^2' like cyclopropane ring opens as if it were an olefin by a 1,5-alkyl shift to give the metallacycloheptadienone complex **47**. CO insertion then occurs to give the metallacyclooctadienone complex **48**. This complex undergoes an alkene insertion to give the pentadienyl complex **49**, and a ring closure yields the metallacyclopentane **50**. After a fragmentation with the loss of ethylene it gives the cyclopentadienone intermediate **51**. Since this intermediate is very unstable, it undergoes a reduction with chromium (0) and water. The yielded product is the cyclopentenone derivative **10**.

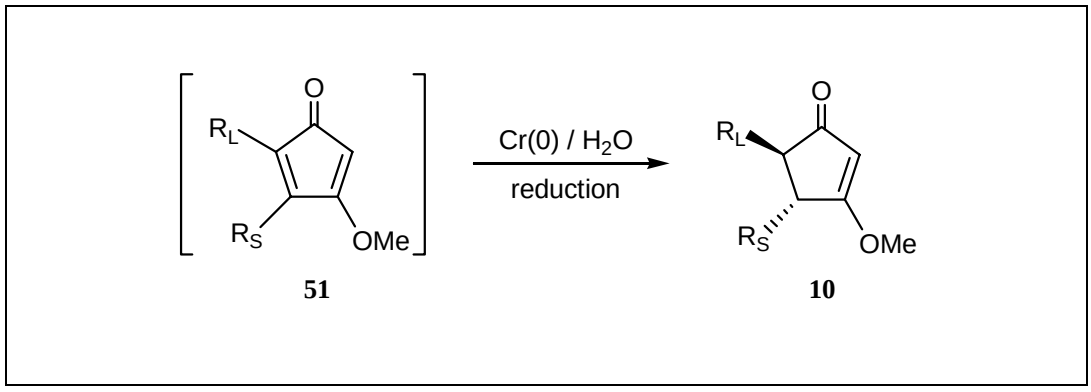
The overall reaction is represented by this [4 + 2 + 1 – 2] cycloaddition reaction. Carbons of cyclopropyl ring and carbene carbon, totally four carbons coming from the carbene complex, meet with the two carbons of the alkyne and one carbonyl carbon arising from a CO ligand of the carbene complex. Then two carbons belonging to ethylene are lost as two-carbon fragment.

As it is seen from Figure 25, the reaction was proposed to proceed via formation of a highly unstable cyclopentadienone intermediate **51**, which was reduced to the corresponding *trans* isomer of cyclopentenone **10**. In the course of the reaction, two protons are provided by the water as the hydrogen source. Chromium (0) oxidizes to chromium (III) and these results suggest that the overall reaction involves an oxidation-reduction process to the observed cyclopentenone derivatives **10**.

The reaction mechanism of our study is somehow different than the mechanism proposed by Herndon et al [36]. Because instead of *trans*-cyclopentenones, which are usually the major products of these reactions, we

obtained *trans*-α-hydroxycyclopentenones in our study. The difference is the presence of a hydroxy group in α position of the carbonyl group. We proposed that the reaction mechanism is the same until to the last step since the formation of cyclobutenones such as **40** as minor byproducts supports the intermediacy of metallacyclobutenes **45** and vinylcarbenes **46**. However, in the last step of the reaction, the presence of ferrocene presumably favors the water addition instead of the reduction of the cyclopentadienone intermediate **51**.

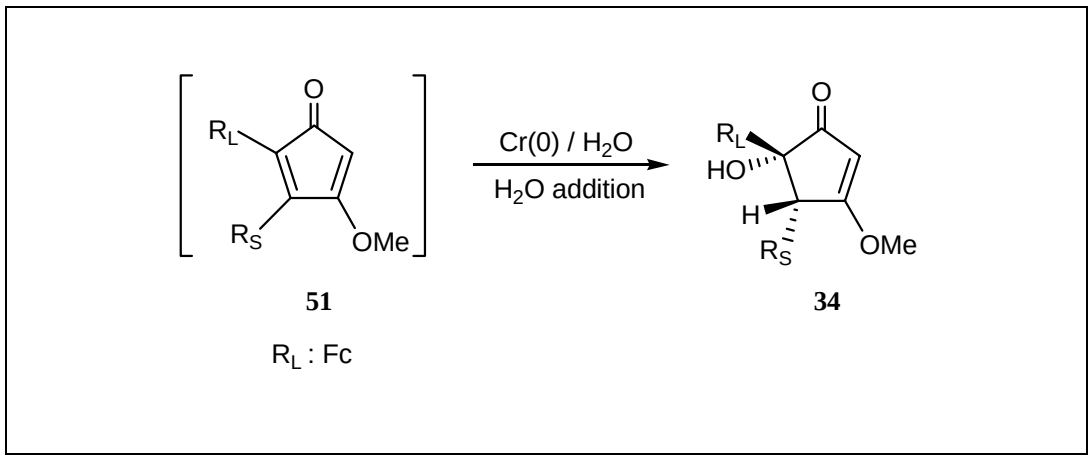
In literature:



51 **10**

Figure 26. Last step of the [4 + 2 + 1 – 2] cycloaddition reaction

In our study:



51 **34**

R_L : Fc

Figure 27. Last step of the reaction in our study

This result was observed for the first time in literature. And in order to confirm this interesting result, we made a controlling experiment by investigating the reaction of cyclopropylcarbene-chromium complex **9** with diphenylacetylene in the presence of ferrocene (**19**). As we expected, we obtained the *trans*-α-hydroxycyclopentenone **34H**, not the *trans*-cyclopentenone derivative **10** (Figure 28).

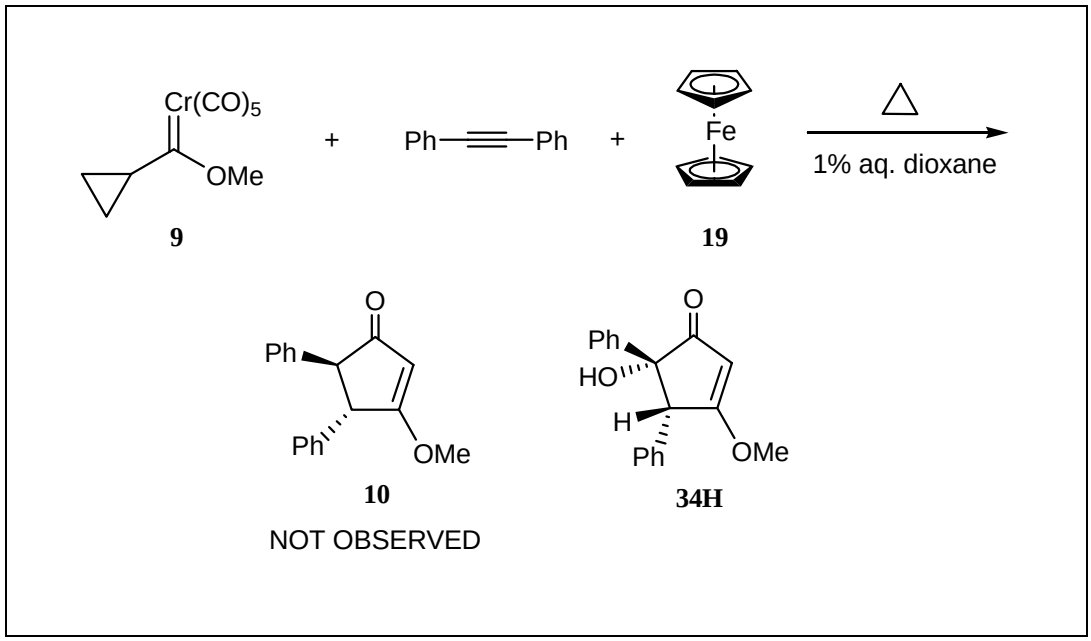


Figure 28. Controlling experiment by the reaction of carbene complex **9** with diphenylacetylene in the presence of ferrocene **19**

After getting these results, we could say that the presence of iron and/or ferrocene in the medium favors the water addition instead of reduction of the unstable cyclopentadienone intermediate **51** in the last step of the reaction. The formation of ferrocenyl ketones **42** as the result of water addition to ferrocenyl alkynes **27** also supports our proposal for the mechanism in the formation of α-hydroxy ferrocenyl cyclopentenones **34**.

As mentioned at the beginning, all products isolated from these reactions were characterized by means of NMR, IR and HRMS. As a representative

compound, the structure of compound **34B** was also analyzed by X-ray single crystal analysis as depicted in Figure 29.

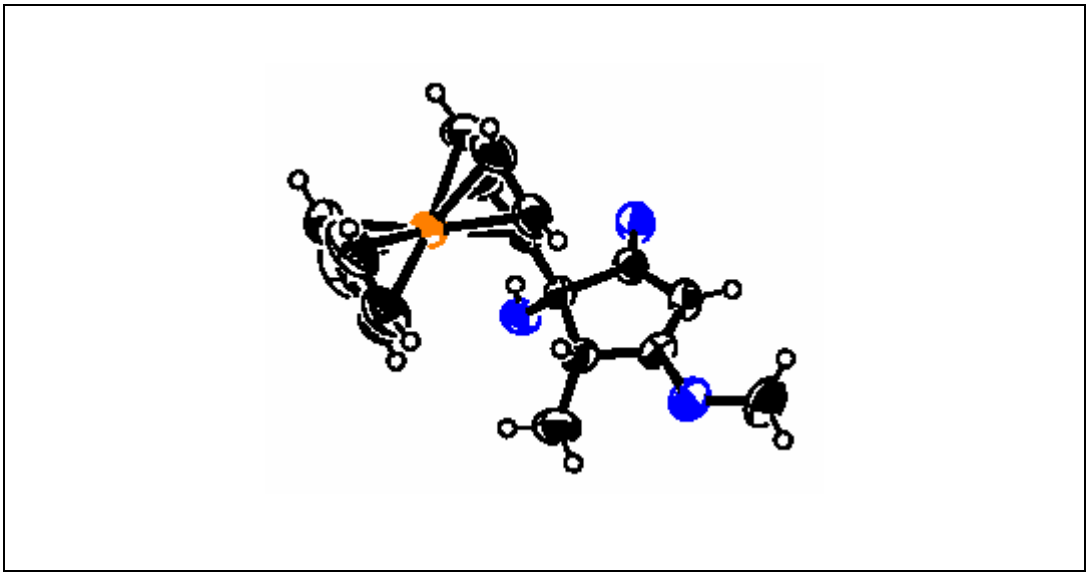


Figure 29. ORTEP crystal structure of compound **34B**

CHAPTER 3

CONCLUSION

We have shown that the reaction between cyclopropylcarbene-chromium complex **9** and ferrocenyl alkynes **27** affords α-hydroxycyclopentenones as major products whereas the same reaction with alkynes produces cyclopentenone derivatives. The presence of iron and/or ferrocene moiety favors the water addition to cyclopentadienone intermediate **51** during the course of the reaction. This result has been obtained for the first time in literature.

The thermodynamically more stable α-hydroxycyclopentenone **34** is usually the major product and the original alkyne substituents have the *trans* stereochemistry in the product.

The reaction is regioselective which is governed by steric effects of the alkyne substituents. In our study, the larger substituent, ferrocene, ends up α to the carbonyl group.

The reaction works well with a variety of alkynes, but the reaction did not proceed with electron-deficient alkynes such as ferrocenyl(formyl)acetylene (**27G**).

In conclusion, synthesis of ferrocenyl-substituted cyclopentenones via coupling of cyclopropylcarbene-chromium complex **9** with ferrocenyl alkynes **27** in a one-pot synthesis was performed successfully. Additionally, the effect of iron and/or ferrocene moiety for the formation of α-hydroxycyclopentenones in this method was found for the first time in literature.

CHAPTER 4

EXPERIMENTAL

General Consideration. Nuclear Magnetic Resonance spectra (^{1}H and ^{13}C) were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in 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), dd (doublet of doublet), m (multiplet). ^{13}C-NMR information is given in paranthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as follows: 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 parentheses. Routine 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. Dioxane, THF, and hexane were distilled under argon from sodium and benzophenone. All reactions were carried out under an atmosphere of argon.

4.1. Synthesis of Carbene Complex 9. To a solution of cyclopropyl bromide (0.8 mL, 10.0 mmol) under argon at –78 °C in THF was added by syringe *t*-BuLi (9.1 mL, 2.2 M, 20.0 mmol) over a period of 15 min. This solution was stirred at –78 °C for a period of 30 min, and then transferred by cannula to a suspension of chromium hexacarbonyl (2.2 g, 10.0 mmol) in THF at 0 °C. This mixture was warmed to room temperature and was allowed to stir for 1 h. The reaction mixture was cooled to 0 °C, and methyl fluorosulfonate (3.4 mL, 30.0 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 20 min. After the extraction with diethyl ether, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution and water, the organic layer was dried with magnesium sulfate. Final purification was achieved by flash chromatography on silica gel using pure hexane as the eluent. The product was isolated as a yellow fraction with 74 % yield and assigned as cyclopropyl(methoxy)carbene chromium (0) complex (**9**).

Cyclopropyl(methoxy)carbene chromium (0) complex (9): ^{1}H NMR ($CDCl_3$): δ 4.65 (s, 3H), 3.46 (m, 1H), 1.36 (m, 2H), 1.18 (m, 2H). The spectral data were in agreement with those reported previously for this compound [75].

4.2. Synthesis of Acetylferrocene (31). Ferrocene (**19**) (10.0 g, 54 mmol) was dissolved with stirring in 45 mL of dry CH_2Cl_2 under argon. To the resultant dark orange/red solution acetyl chloride (4.6 g, 59 mmol) was added and flask was immersed in an ice-water bath at 0-5 °C. On the other hand, anhydrous aluminum chloride (7.2 g, 54 mmol) was weighed out in a glass beaker and added in approximately 10 portions to the reaction mixture, allowing approximately 2 min between each addition for heat exchange. The reaction mixture was stirred for 2 h during which time the ice-water bath was allowed to warm to room temperature. After this period of time, placing it in a fresh ice-water bath recooled the solution. The reaction mixture was hydrolyzed by the slow addition of 4 x 2.5 mL portions of cold water. Then a further 15 mL of cold water was added more rapidly. The mixture was extracted with CH_2Cl_2, and organic extracts were washed with 5 % sodium hydroxide solution followed by saturated aqueous

sodium chloride solution. Then organic phase was dried over magnesium sulfate. Final purification was achieved by flash chromatography on silica gel using hexane:ethyl acetate (9:1) as the eluent. The product was isolated as an orange fraction with 80 % yield and assigned as acetylferrocene (**31**).

Acetylferrocene (31): ^{1}H-NMR ($CDCl_3$): δ 4.78 (s, 2 H), 4.51 (s, 2 H), 4.21 (s, 5 H), 2.40 (s, 3 H). The spectral data were in agreement with those reported previously for this compound [76].

4.3. Synthesis of (2-Formyl-1-chlorovinyl)ferrocene (32). Acetylferrocene (**31**) (2.3 g, 10 mmol) and DMF (2.5 mL, 32 mmol) were added into a two-necked, round-bottom flask equipped with a dropping funnel, and cooled to 0 °C by means of an ice bath under argon. The brown reaction mixture was stirred well for several minutes. Separately, into a small round-bottom flask DMF (2.5 mL, 32 mmol) was added and cooled in crushed ice and agitated by hand during the cautious addition of phosphorus oxychloride (2.5 mL, 27 mmol). The resulting viscous complex was transferred to the dropping funnel and added to the reaction mixture of acetylferrocene (**31**) and DMF dropwise over 30 min. After complete addition, 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. Then 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, 85 mmol) 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 extracted with ether, and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulfate. Removing solvent using a

rotary evaporator afforded (2-formyl-1-chlorovinyl)ferrocene (**32**) with 93 % yield as deep purple crystals after drying under high vacuum.

(2-Formyl-1-chlorovinyl)ferrocene (32): ^{1}H-NMR ($CDCl_3$): δ 10.09 (d, 1 H, J = 6.7), 6.40 (d, 1 H, J = 6.7), 4.75 (s, 2 H), 4.57 (s, 2 H), 4.24 (s, 5 H). The spectral data were in agreement with those reported previously for this compound [77].

4.4. Synthesis of Ethynylferrocene (27A). (2-formyl-1-chlorovinyl)ferrocene (**32**) (2.6 g, 9.5 mmol) and 30 mL of anhydrous 1,4-dioxane were placed into a two-necked, round-bottom flask, equipped with a reflux condenser. The reaction mixture was heated to reflux under argon. 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. Then the reaction mixture was allowed to cool to room temperature and cautiously poured into ice and neutralized with 1 N hydrochloric acid. The reaction mixture was extracted with hexane, and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulfate. Final purification was achieved by flash chromatography on silica gel using hexane as the eluent. The product was isolated as an orange fraction with 75 % yield and assigned as ethynylferrocene (**27A**).

Ethynylferrocene (27A): ^{1}H-NMR ($CDCl_3$): δ 4.45 (s, 2 H), 4.20 (s, 5 H), 4.18 (s, 2 H), 2.70 (s, 1 H). The spectral data were in agreement with those reported previously for this compound [77].

4.5. General Procedure I. Synthesis of Ferrocenyl Alkynes 27B-D,G. A solution of *n*-BuLi (1.1 equiv.) in hexane was added slowly to ethynylferrocene (**27A**) (1.0 equiv.) in 30 mL of THF at –78 °C under argon. The resulting mixture was stirred for 30 min at –78 °C. After this period of time, an excess of corresponding alkyl halide (4.2 equiv.) was added to the mixture. Then the solution was brought to room temperature and stirred for an additional 1 h. After

hydrolysis with water at 0 °C, the reaction mixture was extracted with proper organic solvent. After washing with water and and removal of solvent, the residue was purified by flash chromatography.

4.6. Synthesis of Ferrocenylpropyne (27B). General Procedure I was followed using a solution of *n*-BuLi (1.3 mL, 1.6 M, 2 mmol) in hexane, ethynylferrocene (**27A**) (400 mg, 1.9 mmol) and an excess of MeI (0.5 mL, 8 mmol). Extraction was performed by using CH_2Cl_2 as the solvent and final purification was achieved by flash chromatography on silica gel using pure hexane as the eluent. The product was isolated as an orange fraction with 96 % yield and assigned as ferrocenylpropyne (**27B**).

Ferrocenylpropyne (27B): ^{1}H-NMR ($CDCl_3$): δ 4.35 (s, 2 H), 4.25 (s, 2H), 4.20 (s, 5H), 1.95 (s, 3H). The spectral data were in agreement with those reported previously for this compound [78].

4.7. Synthesis of 1-Ferrocenyl-3-phenylprop-1-yne (27C). General Procedure I was followed using a solution of *n*-BuLi (1.3 mL, 1.6 M, 2 mmol) in hexane, ethynylferrocene (**27A**) (400 mg, 1.9 mmol) and an excess of BnBr (0.9 mL, 8 mmol). Extraction was performed by using CH_2Cl_2 as the solvent and final purification was achieved by flash chromatography on silica gel using pure hexane as the eluent. The product was isolated as an orange fraction with 56 % yield and assigned as 1-ferrocenyl-3-phenylprop-1-yne (**27C**).

1-Ferrocenyl-3-phenylprop-1-yne (27C): ^{1}H-NMR ($CDCl_3$): δ 7.40-7.38 (m, 2H), 7.34-7.30 (m, 3H), 4.39 (s, 2H), 4.19 (s, 5H), 4.15 (s, 2H), 3.71 (s, 2H). The spectral data were in agreement with those reported previously for this compound.

4.8. Synthesis of (2-Ferrocenylethynyl)trimethylsilane (27D). General Procedure I was followed using a solution of *n*-BuLi (1.3 mL, 1.6 M, 2 mmol) in hexane, ethynylferrocene (**27A**) (400 mg, 1.9 mmol) and an excess of TMSCl

(1.0 mL, 8 mmol). Extraction was performed by using CH_2Cl_2 as the solvent and final purification was achieved by flash chromatography on silica gel using pure hexane as the eluent. The product was isolated as an orange fraction with 84 % yield and assigned as (2-ferrocenylethynyl)trimethylsilane (**27D**).

(2-Ferrocenylethynyl)trimethylsilane (27D): ^{1}H-NMR ($CDCl_3$): δ 4.41 (s, 2H), 4.17 (s, 5H), 4.15 (s, 2H), 0.19 (s, 9H). The spectral data were in agreement with those reported previously for this compound.

4.9. Synthesis of Ferrocenyl(formyl)acetylene (27G). General Procedure I was followed using a solution of *n*-BuLi (3.2 mL, 1.6 M, 5 mmol) in hexane, ethynylferrocene (**27A**) (1.0 g, 4.8 mmol) and an excess of DMF (1.0 mL, 13 mmol). After the addition of DMF, the solution was stirred for 1 h at –78 °C and then it was brought to room temperature. The solution was poured over 50 mL of an ice-water mixture containing 5 mL of conc. HCl. After it was neutralised with $NaHCO_3$, extraction was performed by using diethyl ether as the solvent, and final purification was achieved by flash chromatography on silica gel using pure hexane as the eluent. The product was isolated as a red fraction with 93 % yield and assigned as ferrocenyl(formyl)acetylene (**27G**).

Ferrocenyl(formyl)acetylene (27G): ^{1}H-NMR ($CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H). The spectral data were in agreement with those reported previously for this compound [78].

4.10. Synthesis of 1-Ferrocenyl-2-phenylethyne (27E). To a mixture of CuI (23 mg, 0.12 mmol), PPh_3 (62 mg, 0.24 mmol), K_2CO_3 (493 mg, 3.57 mmol), and DMF (4.8 mL), were added iodobenzene (0.3 mL, 2.38 mmol) and ethynylferrocene (**27A**) (500 mg, 2.38 mmol) under argon. The resulting mixture was refluxed at 120 °C for 16 h. After the solution was allowed to cool to room temperature, it was extracted with ether and washed with water. The organic phase was dried over magnesium sulfate. Final purification was achieved by flash chromatography on silica gel using pure hexane as the eluent. The product was

isolated as an orange fraction with 47 % yield and assigned as 1-ferrocenyl-2-phenylethyne (**27E**).

1-Ferrocenyl-2-phenylethyne (27E): ^{1}H-NMR ($CDCl_3$): δ 7.46-7.40 (m, 2H), 7.26-7.19 (m, 3H), 4.43 (s, 2H), 4.16 (s, 5H), 4.14 (s, 2H). The spectral data were in agreement with those reported previously for this compound.

4.11. Synthesis of Diferrocenylethyne (27F). A solution of ferrocenylpropyne (**27B**) (430 mg, 1.920 mmol), $Mo(CO)_6$ (25 mg, 0.096 mmol), and 2-fluorophenol (0.176 mL, 1.920 mmol) in 35 mL of chlorobenzene was heated to reflux for 2 h using a heating mantle under argon. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel using hexane as the eluent. The product was isolated as an orange fraction with 26 % yield and assigned as diferrocenylethyne (**27F**).

Diferrocenylethyne (27F): ^{1}H-NMR ($CDCl_3$): δ 4.43 (s, 2H), 4.20 (s, 5H), 4.18 (s, 2H). The spectral data were in agreement with those reported previously for this compound.

4.12. General Procedure II. Reaction of Ferrocenyl Alkynes 27 with Cyclopropylcarbene-Chromium Complex 9. To a two-necked round-bottom flask equipped with a reflux condenser and dropping funnel, under argon, was added 20 mL of 1% aqueous dioxane solution. The dioxane solution was heated to reflux. Separately, a solution of 1 equiv. of carbene complex **9** (0.1 M) and 1.5 equiv. of the ferrocenyl alkyne **27** in dioxane was prepared and transferred to the dropping funnel by cannula. Then this carbene solution was added to the refluxing solution through dropping funnel over a period of 2 h. After the addition was complete, the mixture was allowed to reflux for an additional period of 6 h. The mixture was then allowed to cool to room temperature, and the solvent was removed on a rotary evaporator. Final purification was achieved through flash chromatography on silica gel.

4.13. Reaction of Ethynylferrocene (27A) with Carbene Complex 9 (Table 1, Entry A). General Procedure II was followed using ethynylferrocene (**27A**) (200 mg, 0.952 mmol) and cyclopropylcarbene-chromium complex **9** (175 mg, 0.635 mmol). After chromatographic purification, 2 fractions were isolated and identified as (*R*)-5-hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (**34A**) with 45 % yield and 4-hydroxy-3,4-diferrocenylcyclopent-2-enone (**38**) with 6 % yield.

(*R*)-5-Hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (34A): ^{1}H-NMR ($CDCl_3$): δ 5.29 (s, 1H), 4.28 (s, 1H), 4.19 (s, 8H), 3.89 (s, 3H), 3.08 (d, 1H, J = 17.4 Hz), 2.97 (d, 1H, J = 17.4 Hz), 2.82 (s, 1H); IR (CH_2Cl_2): 3053 (s), 2982 (m), 2682 (vw), 2302 (w), 1599 (vw), 1402 (m), 1270 (vs), 896 (m), 733 (br) cm^{-1}; MS (EI): 312 (M^+, 100), 294, 247, 229, 213, 185, 169, 145, 129, 121, 56; HRMS (EI): calcd for $C_{16}H_{16}{}^{56}FeO_3$: 312.0449, found 312.0452.

4-Hydroxy-3,4-diferrocenylcyclopent-2-enone (38): ^{1}H-NMR ($CDCl_3$): δ 6.07 (s, 1H), 4.70 (s, 1H), 4.69 (s, 1H), 4.61 (s, 1H), 4.46 (s, 1H), 4.43 (s, 1H), 4.25 (s, 7H), 4.00 (s, 1H), 3.96 (s, 5H), 3.37 (d, 1H, J = 17.7 Hz), 2.99 (d, 1H, J = 17.7 Hz), 2.67 (s, 1H); IR (CH_2Cl_2): 3052 (s), 2981 (m), 2685 (vw), 2306 (w), 1686 (w), 1583 (w), 1426 (m), 1268 (vs), 899 (m), 741 (br) cm^{-1}; MS (EI): 466 (M^+, 100), 450, 383, 328, 300, 233, 186, 178, 152, 121; HRMS (EI): calcd for $C_{25}H_{22}{}^{56}Fe_2O_2$: 466.0319, found 466.0320.

4.14. Reaction of Ferrocenylpropyne (27B) with Carbene Complex 9 (Table 1, Entry B). General Procedure II was followed using ferrocenylpropyne (**27B**) (240 mg, 1.071 mmol) and cyclopropylcarbene-chromium complex **9** (197 mg, 0.714 mmol). After chromatographic purification, 6 fractions were isolated and identified as (4*R*,5*R*)-5-hydroxy-3-methoxy-4-methyl-5-ferrocenylcyclopent-2-enone (**34B**) with 36 % yield, (4*S*,5*R*)-5-hydroxy-3-methoxy-4-methyl-5-ferrocenylcyclopent-2-enone (**35B**) with 16 % yield, 4-methoxy-3-methyl-2 ferrocenylcyclopent-2-enone (**36B**) with 17 % yield, 3-methoxy-5-(3-methoxy-2-methyl-5-oxo-1-ferrocenylcyclopent-3-enyl)-4-methyl-5-ferrocenylcyclopent-2-

enone (**39B**) with 4 % yield, (*E*)-2-methyl-3-ferrocenylacrylaldehyde (**41B**) with 6 % yield and 1-ferrocenylpropan-2-one (**42B**) with 17 % yield.

(4*R*,5*R*)-5-Hydroxy-3-methoxy-4-methyl-5-ferrocenylcyclopent-2-enone (34B): ^{1}H-NMR ($CDCl_3$): δ 5.21 (s, 1H), 4.20 (s, 1H), 4.18 (s, 5H), 4.15 (s, 1H), 4.14 (s, 1H), 4.13 (s, 1H), 3.87 (s, 3H), 3.13 (q, 1H, *J* = 7.3 Hz), 2.76 (s, 1H), 1.27 (d, 3H, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 203.7 (C), 192.4 (C), 99.1 (CH), 92.7 (C), 77.2 (C), 68.9 (CH), 68.4 (CH), 68.3 (CH), 66.2 (CH), 65.9 (CH), 58.7 (CH_3), 48.0 (CH), 13.7 (CH_3); IR (CH_2Cl_2): 3056 (w), 2983 (vw), 2298 (vw), 1691 (vw), 1582 (w), 1418 (vw), 1270 (vs), 892 (w), 744 (br) cm^{-1}; MS (EI): 326 (M^+, 100), 308, 261, 243, 213, 186, 185, 149, 129, 84; HRMS (EI): calcd for $C_{17}H_{18}{}^{56}FeO_3$: 326.0605, found 326.0602.

(4*S*,5*R*)-5-Hydroxy-3-methoxy-4-methyl-5-ferrocenylcyclopent-2-enone (35B): ^{1}H-NMR ($CDCl_3$): δ 5.30 (s, 1H), 4.33 (s, 5H), 4.30 (s, 1H), 4.18 (s, 1H), 4.16 (s, 1H), 3.81 (s, 3H), 3.75 (s, 1H), 3.06 (q, 1H, *J* = 7.3 Hz), 2.98 (s, 1H), 0.74 (d, 3H, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 203.5 (C), 189.3 (C), 100.5 (CH), 80.4 (C), 77.2 (C), 69.6 (CH), 69.4 (CH), 67.9 (CH), 67.8 (CH), 66.4 (CH), 58.5 (CH_3), 46.8 (CH), 12.0 (CH_3); IR (CH_2Cl_2): 3052 (m), 2981 (w), 1700 (m), 1591 (s), 1463 (vw), 1354 (w), 1268 (vs), 1104 (vw), 896 (vw), 819 (vw), 746 (br) cm^{-1}; MS (EI): 326 (M^+, 100), 308, 262, 261, 243, 213, 185, 131, 113, 78; HRMS (EI): calcd for $C_{17}H_{18}{}^{56}FeO_3$: 326.0605, found 326.0607.

4-Methoxy-3-methyl-2-ferrocenylcyclopent-2-enone (36B): ^{1}H-NMR ($CDCl_3$): δ 4.79 (s, 1H), 4.69 (s, 1H), 4.30 (s, 2H), 4.27 (dd, 1H, *J* = 2.1, 6 Hz), 4.08 (s, 5H), 3.40 (s, 3H), 2.69 (dd, 1H, *J* = 6, 18 Hz), 2.39 (dd, 1H, *J* = 2.1, 18 Hz), 2.21 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 202.9 (C), 164.3 (C), 139.0 (C), 79.9 (CH), 74.8 (C), 69.4 (CH), 68.9 (CH), 68.6(CH), 56.9 (CH_3), 41.1 (CH_2), 15.6 (CH_3); IR (CH_2Cl_2): 3053 (s), 2981 (m), 2683 (vw), 2300 (w), 1703 (w), 1414 (m), 1267 (vs), 1097 (vw), 896 (m), 755 (br) cm^{-1}; MS (EI): 310 (M^+, 100), 279, 258, 227, 212, 186, 163, 129, 121, 91, 55; HRMS (EI): calcd for $C_{17}H_{18}{}^{56}FeO_2$: 310.0656, found 310.0659.

3-Methoxy-5-(3-methoxy-2-methyl-5-oxo-1-ferrocenylcyclopent-3-enyl)-4-methyl-5-ferrocenylcyclopent-2-enone (39B): ^{1}H-NMR ($CDCl_3$): δ 4.78 (s, 1H), 4.75 (s, 1H), 4.35 (s, 1H), 4.34 (s, 1H), 4.11 (s, 5H), 3.16 (s, 3H), 2.62 (d, 1H, *J* = 18.9 Hz), 2.40 (d, 1H, *J* = 18.9 Hz), 2.20 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 202.0 (C), 163.9 (C), 142.2 (C), 87.6 (C), 74.1 (C), 69.8 (CH), 69.4 (CH), 69.3 (CH), 69.2 (CH), 68.4 (CH), 50.9 (CH_3), 40.8 (CH_2), 15.6 (CH_3); IR (CH_2Cl_2): 3054 (w), 2989 (vw), 2365 (vw, br), 1704 (w), 1423 (vw), 1273 (vs), 1105 (vw), 896 (vw), 749 (br) cm^{-1}; MS (EI): 618 (M^+, 100), 556, 492, 310, 309, 294, 229, 199, 159, 121, 77; HRMS (EI): calcd for $C_{34}H_{34}{}^{56}Fe_2O_4$: 618.1156, found 618.1153.

(*E*)-2-Methyl-3-ferrocenylacrylaldehyde (41B): ^{1}H-NMR ($CDCl_3$): δ 9.44 (s, 1H), 7.07 (s, 1H), 4.59 (t, 2H, *J* = 1.8 Hz), 4.48 (t, 2H, *J* = 1.8 Hz), 4.14 (s, 5H), 1.91 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 194.5 (CH), 151.4 (CH), 134.8 (C), 72.0 (C), 71.4 (CH), 71.1 (CH), 69.7 (CH), 10.6 (CH_3); IR (CH_2Cl_2): 3052 (s), 2976 (m), 2682 (vw), 2411 (vw), 2307 (w), 1669 (w), 1616 (w), 1420 (m), 1259 (vs), 896 (m), 751 (br) cm^{-1}; MS (EI): 254 (M^+, 100), 242, 226, 213, 189, 185, 160, 134, 121, 81; HRMS (EI): calcd for $C_{14}H_{14}{}^{56}FeO$: 254.0394, found 254.0394.

1-Ferrocenylpropan-2-one (42B): ^{1}H-NMR ($CDCl_3$): δ 5.04 (s, 2H), 4.58 (s, 2H), 4.13 (s, 5H), 2.93 (s, 2H), 2.11 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 199.5 (C), 77.2 (C), 71.7 (CH), 70.5 (CH), 70.0 (CH), 41.8 (CH_2), 10.5 (CH_3). The spectral data were in agreement with those reported previously for this compound.

4.15. Reaction of 1-Ferrocenyl-3-phenylprop-1-yne (27C) with Carbene Complex 9 (Table 1, Entry C). General Procedure II was followed using 1-ferrocenyl-3-phenylprop-1-yne (**27C**) (280 mg, 0.933 mmol) and cyclopropylcarbene-chromium complex **9** (172 mg, 0.622 mmol). After chromatographic purification, 3 fractions were isolated and identified as (4*R*,5*R*)-4-benzyl-5-hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (**34C**) with 16 % yield, 4-benzyl-5-ferrocenylcyclopent-4-ene-1,3-dione (**37C**) with 30 % yield and 1-ferrocenyl-3-phenylpropan-2-one (**42C**) with 27 % yield.

(4*R*,5*R*)-4-Benzyl-5-hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (34C): ^{1}H-NMR ($CDCl_3$): δ 7.36-7.26 (m, 3H), 7.22-7.10 (m, 2H), 5.20 (s, 1H), 4.13 (s, 3H), 4.10 (s, 5H), 4.01 (s, 1H), 3.82 (s, 3H), 3.36 (dd, 1H, *J* = 4.4, 7.8 Hz), 3.12 (dd, 1H, *J* = 7.8, 13.8 Hz), 2.97 (dd, 1H, *J* = 4.4, 13.8 Hz), 2.76 (s, 1H); IR (CH_2Cl_2): 3050 (s), 2977 (m), 2685 (vw), 2303 (w), 1699 (vw), 1591 (w), 1420 (m), 1267 (vs), 898 (m), 746 (br) cm^{-1}; MS (EI): 402 (M^+, 100), 384, 337, 319, 311, 246, 228, 213, 189, 170, 121, 91; HRMS (EI): calcd for $C_{23}H_{22}{}^{56}FeO_3$: 402.0918, found 402.0916.

4-Benzyl-5-ferrocenylcyclopent-4-ene-1,3-dione (37C): ^{1}H-NMR ($CDCl_3$): δ 7.33-7.18 (m, 5H), 4.97 (s, 2H), 4.55 (s, 2H), 4.02 (s, 5H), 3.96 (s, 2H), 3.02 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 199.4 (C), 199.2 (C), 136.8 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 126.7 (CH), 157.7 (C), 151.2 (C), 72.7 (CH), 71.7 (C), 70.8 (CH), 70.1 (CH), 42.1 (CH_2); IR (CH_2Cl_2): 3050 (vw), 1692 (w), 1600 (vw), 1273 (vs), 748 (br) cm^{-1}.

1-Ferrocenyl-3-phenylpropan-2-one (42C): ^{1}H-NMR ($CDCl_3$): δ 7.34-7.30 (m, 2H), 7.24-7.18 (m, 3H), 4.98 (s, 2H), 4.56 (s, 2H), 4.03 (s, 5H), 3.97 (s, 2H), 3.02 (s, 2H). The spectral data were in agreement with those reported previously for this compound.

4.16. Reaction of (2-Ferrocenylethynyl)trimethylsilane (27D) with Carbene Complex 9 (Table 1, Entry D). General Procedure II was followed using (2-ferrocenylethynyl)trimethylsilane (**27D**) (150 mg, 0.532 mmol) and cyclopropylcarbene-chromium complex **9** (98 mg, 0.355 mmol). After chromatographic purification, a single fraction was isolated and identified as (*R*)-5-hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (**34A**) with 26 % yield.

4.17. Reaction of 1-Ferrocenyl-2-phenylethyne (27E) with Carbene Complex 9 (Table 1, Entry E). General Procedure II was followed using 1-ferrocenyl-2-phenylethyne (**27E**) (200 mg, 0.699 mmol) and cyclopropylcarbene-chromium complex **9** (129 mg, 0.466 mmol). After chromatographic purification, 4 fractions were isolated and assigned as compounds (4*R*,5*R*)-4-phenyl-5-hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (**34E**) with 31 % yield, 4-methoxy-3-phenyl-2-ferrocenylcyclopent-2-enone (**36E**) with 5 % yield, 4-phenyl-5-ferrocenylcyclopent-4-ene-1,3-dione (**37E**) with 20 % yield and 1-phenyl-2-ferrocenylethanone (**42E**) with 35 % yield.

(4*R*,5*R*)-4-Phenyl-5-hydroxy-3-methoxy-5-ferrocenylcyclopent-2-enone (34E): ^{1}H-NMR ($CDCl_3$): δ 7.11-6.99 (m, 3H), 6.71 (d, 2H, *J* = 6.7 Hz), 5.55 (s, 1H), 4.30 (s, 1H), 4.24 (s, 5H), 3.96 (s, 1H), 3.83 (s, 3H), 3.76 (s, 1H), 3.73 (s, 1H), 3.50 (s, 1H), 3.12 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 203.0 (C), 186.8 (C), 135.3 (C), 129.4 (CH), 127.6 (CH), 126.9 (CH), 102.8 (CH), 91.1 (C), 81.9 (C), 68.8 (CH), 68.4 (CH), 67.6 (CH), 67.3 (CH), 66.3 (CH), 58.9 (CH), 58.6 (CH_3); IR (CH_2Cl_2): 3056 (s), 2987 (w), 2681 (vw), 2303 (w), 1704 (s), 1597 (s), 1421 (m), 1354 (m), 1267 (vs), 1171 (w), 1020 (w), 902 (m), 825 (m), 748 (br) cm^{-1}; MS (EI): 388 (M^+, 100), 372, 323, 305, 234, 213, 178, 175, 165, 121, 93; HRMS (EI): calcd for $C_{22}H_{20}{}^{56}FeO_3$: 388.0762, found 388.0761.

4-Methoxy-3-phenyl-2-ferrocenylcyclopent-2-enone (36E): ^{1}H-NMR ($CDCl_3$): δ 7.45-7.35 (m, 5H), 4.89 (d, 1H, *J* = 5.9 Hz), 4.58 (s, 1H), 4.39 (s, 1H), 4.34 (s, 1H), 4.26 (s, 1H), 4.09 (s, 5H), 3.47 (s, 3H), 2.80 (dd, 1H, *J* = 5.9, 18.2 Hz), 2.57 (d, 1H, *J* = 18.2 Hz); IR (CH_2Cl_2): 3050 (s), 2982 (m), 2679 (vw), 2307 (w), 1420 (m), 1273 (vs), 901 (m), 751 (br); MS (EI): 372 (M^+, 100), 356, 342, 291, 277, 249, 191, 165, 149, 121; HRMS (EI): calcd for $C_{22}H_{20}{}^{56}FeO_2$: 372.0813, found 372.0816.

4-Phenyl-5-ferrocenylcyclopent-4-ene-1,3-dione (37E): ^{1}H-NMR ($CDCl_3$): δ 7.45-7.24 (m, 5H), 4.69 (s, 2H), 4.48 (s, 2H), 4.10 (s, 5H), 3.15 (s, 2H).

1-Phenyl-2-ferrocenylethanone (42E): ^{1}H-NMR ($CDCl_3$): δ 7.46-7.38 (m, 3H), 7.36-7.33 (m, 2H), 4.68 (s, 2H), 4.49 (s, 2H), 4.09 (s, 5H), 3.12 (s, 2H). The spectral data were in agreement with those reported previously for this compound.

4.18. Reaction of Diferrocenylethyne (27F) with Carbene Complex 9 (Table 1, Entry F). General Procedure II was followed using diferrocenylethyne (**27F**) (230 mg, 0.584 mmol) and cyclopropylcarbene-chromium complex **9** (107 mg, 0.389 mmol). After chromatographic purification, 4 fractions were isolated and identified as (4*R*,5*R*)-5-hydroxy-3-methoxy-4,5-diferrocenylcyclopent-2-enone (**34F**) with 18 % yield, 4-methoxy-2,3-diferrocenylcyclopent-2-enone (**36F**) 9 % yield, 4,5-diferrocenylcyclopent-4-ene-1,3-dione (**37F**) with 32 % yield and 4-cyclopropyl-4-methoxy-2,3-diferrocenylcyclobut-2-enone (**40F**) with 7 % yield.

(4*R*,5*R*)-5-Hydroxy-3-methoxy-4,5-diferrocenylcyclopent-2-enone (34F): ^{1}H-NMR ($CDCl_3$): δ 5.37 (s, 1H), 4.30 (s, 1H), 4.25 (s, 7H), 4.20 (s, 7H), 4.14 (s, 1H), 3.99 (s, 1H), 3.98 (s, 3H), 3.88 (s, 1H), 2.74 (s, 1H), 2.13 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 202.6 (C), 187.7 (C), 101.2 (CH), 93.4 (C), 84.5 (C), 78.9 (C), 69.4 (CH), 69.3 (CH), 68.6 (CH), 68.4 (CH), 68.0 (CH), 66.8 (CH), 66.7 (CH), 66.1 (CH), 58.6 (CH_3), 54.6 (CH); IR (CH_2Cl_2): 3055 (s), 2983 (m), 2682 (vw), 2301 (w), 1423 (m), 1270 (vs), 898 (m), 762 (br) cm^{-1}; MS (EI): 496 (M^+, 100), 496, 478, 358, 293, 283, 248, 213, 199, 129, 121; HRMS (EI): calcd for $C_{26}H_{24}{}^{56}Fe_2O_3$: 496.0424, found 496.0426.

4-Methoxy-2,3-diferrocenylcyclopent-2-enone (36F): ^{1}H-NMR ($CDCl_3$): δ 4.90 (s, 2H), 4.85 (d, 1H, *J* = 5.5 Hz), 4.55 (s, 1H), 4.46 (s, 2H), 4.43 (s, 1H), 4.37 (s, 1H), 4.25 (s, 1H), 4.14 (s, 5H), 4.08 (s, 5H), 3.45 (s, 3H), 2.69 (dd, 1H, *J* = 5.5, 18.2 Hz), 2.51 (d, 1H, *J* = 18.2 Hz); IR (CH_2Cl_2): 3051 (s), 2983 (m), 2683 (vw), 2306 (w), 1702 (w), 1420 (m), 1270 (vs), 899 (m), 748 (br) cm^{-1}; MS (EI): 480 (M^+, 100), 478, 415, 355, 328, 300, 263, 240, 235, 178, 121; HRMS (EI): calcd for $C_{26}H_{24}{}^{56}Fe_2O_2$: 480.0475, found 480.0474.

4,5-Diferrocenylcyclopent-4-ene-1,3-dione (37F): ^{1}H-NMR ($CDCl_3$): δ 4.79 (s, 4H), 4.47 (s, 4H), 4.06 (s, 10H), 3.03 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 197.6 (C), 152.2 (C), 73.5 (C), 71.1 (CH), 70.5 (CH), 70.3 (CH), 43.2 (CH_2); IR (CH_2Cl_2): 3050 (s), 2985 (m), 2301 (w), 1725 (m), 1690 (s), 1574 (w), 1475 (m), 1417 (m), 1381 (w), 1311 (w), 1275 (vs), 1211 (w), 1156 (vw), 1108 (w), 902 (m), 825 (w), 748 (br) cm^{-1}; MS (EI): 464 (M^+, 100), 399, 396, 341, 277, 232, 186, 165, 152, 121; HRMS (EI): calcd for $C_{25}H_{20}{}^{56}Fe_2O_2$: 464.0162, found 464.0159.

4-Cyclopropyl-4-methoxy-2,3-diferrocenylcyclobut-2-enone (40F): ^{1}H-NMR ($CDCl_3$): δ 5.02 (s, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.64 (s, 1H), 4.62 (s, 1H), 4.40 (s, 1H), 4.39 (s, 1H), 4.30 (s, 5H), 4.18 (s, 5H), 4.06 (s, 1H), 3.28 (s, 3H), 1.44 (m, 1H), 0.85 (m, 2H), 0.71 (m, 1H), 0.63 (m, 1H), 0.39 (m, 1H); IR (CH_2Cl_2): 3054 (vw), 1743 (w), 1695 (vw), 1606 (vw), 1483 (vw), 1261 (vs), 1103 (vw), 916 (vw), 821 (vw), 755 (br) cm^{-1}; MS (EI): 506 (M^+, 100), 478, 464, 410, 397, 354, 305, 281, 253, 232, 202, 186, 121; HRMS (EI): calcd for $C_{28}H_{26}{}^{56}Fe_2O_2$: 506.0632, found 506.0634.

4.19. Reaction of Ferrocenyl(formyl)acetylene (27G) with Carbene Complex 9 (Table 1, Entry G). General Procedure II was followed using ferrocenyl(formyl)acetylene (**27G**) (170 mg, 0.714 mmol) and carbene complex **9** (131 mg, 0.476 mmol). The reaction did not proceed using this electron-deficient alkyne and it failed to produce any of cyclopentenones.

4.20. Data Collection for X-Ray Crystal Structure Analysis. X-Ray crystal structure analysis of compound **34B** was performed at Ondokuz Mayıs University, Department of Physics, by using the Stoe IPDS-II diffractometer. Data collection: *X-AREA* [83]; cell refinement: *X-AREA*; data reduction: *X-RED32* [83]; program(s) used to solve structure: *SHELXS97* [84]; program(s) used to refine structure: *SHELXL97* [85]; molecular graphics: *ORTEP-3* [86], *CAMERON* [87] and *PLUTON* [88]; software used to prepare material for publication: WinGX [89].

REFERENCES

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

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

[3] Wade, L. G. *Organic Chemistry*, 4th Ed., Prentice Hall: New Jersey, 1999.

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

[5] Hart, H.; Hart D. J.; Craine, L. E. *Organic Chemistry*, 9th Ed., Houghton Muflin: New York, 1995.

[6] Eisch, J. J. *The Chemistry of Organometallic Compounds*, The Macmillan Company: New York, 1967.

[7] Elschenbroich, Ch.; Salzer, A. *Organometallics*, 2nd Ed., VCH Publishers Inc.: New York, 1992.

[8] (a) Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*, Pergamon: New York, 1982. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books: California, 1987.

[9] (a) Ziegler, K. *Adv. Organomet. Chem.* **1968**, *6*, 1. (b) Sinn, H.; Kaminsky, W. *Adv. Organomet. Chem.* **1980**, *18*, 99.

[10] Forster, D. *Adv. Organomet. Chem.* **1977**, *17*, 255.

[11] Baeckvall, J. E.; Akermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

[12] (a) Kagan, H. B. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (b) Halpern, J. *Pure Appl. Chem.* **1983**, *55*, 99. (c) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (d) Brunner, H. *J. Organomet. Chem.* **1986**, *300*, 39.

[13] Hermann, W. A. *Comm. Inorg. Chem.* **1988**, *7*, 73.

[14] Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.

[15] Recent reviews about Fischer carbene complexes: (a) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271. (b) de Meijere, A. *Pure Appl. Chem.* **1996**, *68*, 61. (c) Aumann, R.; Nienaber, H. *Adv. Organomet. Chem.* **1997**, *41*, 163. (d) Wulff, W. D. *Organometallics* **1998**, *17*, 3116. (e) Aumann, R.; Göttker-Schnetmann, I.; Fröhlich, R.; Meyer, O. *Eur. J. Org. Chem.* **1999**, 2545. (f) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257. (g) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3964. (h) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591. (i) Barluenga, J.; Fañanás, F. J. *Tetrahedron* **2000**, *56*, 4597. (j) Aumann, R. *Eur. J. Org. Chem.* **2000**, 17. (k) Dötz, K. H.; Jakel, C.; Haase, W. C. *J. Organomet. Chem.* **2001**, *617-618*, 119. (l) Barluenga, J.; Flórez, J.; Fañanás, F. J. *J. Organomet. Chem.* **2001**, *624*, 5. (m) Barluenga, J.; Santamaria, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259. (n) Strassner, T. *Top. Organomet. Chem.* **2004**, *13*, 1. (o) Barluenga, J.; Rodríguez, F.; Fañanás, F. J.; Flórez, J. *Top. Organomet. Chem.* **2004**, *13*, 59.

[16] Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587.

[17] Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.

[18] (a) Fischer, E. O. *Angew. Chem.* **1974**, *86*, 651. (b) Fischer, E. O. *J. Organomet. Chem.* **1976**, *14*, 1.

[19] (a) Schrock, R. R. *Acc. Chem. Res.* **1979**, *12*, 98. (b) Schrock, R. R. *J. Organomet. Chem.* **1986**, *300*, 249.

[20] (a) Casey, C. P.; Anderson, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 1230. (b) Gandler, J. R.; Bernasconi, C. F.; Sun, W. *Organometallics* **1989**, *8*, 2282.

[21] Schubert, U. In *The Chemistry of the Metal-Carbon Bonds;* Hartley, F. R.; Patai, S., Eds.; Wiley: Chichester, 1982, p. 233.

[22] (a) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (b) Wulff, W. D. In *Advances in Metal-Organic Chemistry;* Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989, Vol. 1. (c) Wulff, W. D. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, 1991, Vol. 5.

[23] Wulff, W. D. In *Comprehensive Organometallic Chemistry II;* Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York, 1995, Vol. 12, p. 469.

[24] Most recent review about Fischer carbene complexes: Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539.

[25] (a) Tietze, L. F.; Beifuβ, U. *Angew. Chem.* **1993**, *32*, 137. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem.* **1994**, *106*, 2473. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

[26] (a) Brookhart, M. S.; Studebaker, W. D. *Chem. Rev.* **1987**, *87*, 411. (b) Barluenga, J.; Fernández-Acebes, A.; Trabanco, A. A.; Flórez, *J. J. Am. Chem.* Soc. **1997**, *119*, 7591.

[27] Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

[28] (a) Hoffmann, M.; Buchert, M.; Reissig, H. U. *Chem. Eur. J.* **1999**, *5*, 876. (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Brillet, C.; García-Granda, S.; Piñera-Nicolás, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516. (c) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257.

[29] (a) Wulff, W. D.; Yang, D. C.; Murray, C. K. *J. Am. Chem. Soc.* **1988**, *110*, 2653. (b) Harvey, D. F.; Grenzer, M. E.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994**, *116*, 6719. (c) Barluenga, J.; Aznar, F.; Martín, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1995**, *117*, 9419.

[30] (a) Dötz, K. H. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 644.

[31] (a) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (b) Minatti, A.; Dötz, K. H. *Top. Organomet. Chem.* **2004**, *13*, 123.

[32] Dötz, K. H.; Mühlemeier, J.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187.

[33] Wulff, W. D.; Tang, P. C.; McCallum, J. St. *J. Am. Chem. Soc.* **1981**, *103*, 7677.

[34] (a) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *209*, C4. (b) Dötz, K. H.; Pruskil, I.; Mühlemeier, J. *Chem. Ber.* **1982**, *115*, 1278. (c) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850. (d) Dötz, K. H.; Kuhn, W. *Angew Chem.* **1983**, *95*, 750. (e) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.*

1983, *105*, 2034. (f) Wulff, W. D.; Xu, Y.-C. *J. Am. Chem. Soc.* **1988**, *110*, 2312. (g) Yamashita, A.; Toy, A.; Scahill, T. A. *J. Org. Chem.* **1989**, *54*, 3625.

[35] (a) Dötz, K. H.; Popall, M. *Tetrahedron* **1985**, *41*, 5797. (b) Yamashita, A. *J. Am. Chem. Soc.* **1985**, *107*, 5823. (c) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803. (d) Yamashita, A.; Toy, A.; Ghazal, N. B.; Muchmore, C. R. *J. Org. Chem.* **1989**, *54*, 4481. (e) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1990**, *55*, 1919.

[36] (a) Herndon, J. W.; Tumer, S. U.; Schnatter, W. F. K. *J. Am. Chem. Soc.* **1988**, *110*, 3334. (b) Herndon, J. W.; Tumer, S. U. *Tetrahedron Lett.* **1989**, *30*, 295. (c) Herndon, J. W.; Chatterjee, G.; Patel, P. P.; Matasi, J. J.; Tumer, S. U.; Harp, J. J.; Reid, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 7808. (d) Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394. (e) Herndon, J. W.; Hill, D. K.; McMullen, L. A. *Tetrahedron Lett.* **1995**, *36*, 5687. (f) Herndon, J. W.; Patel, P. P. *Tetrahedron Lett.* **1997**, *38*, 59.

[37] For leading references to jasmone and its derivatives, see: (a) Fràter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633. (b) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genêt, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992.

[38] Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2000**, *41*, 4291.

[39] For reviews, see: (a) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455. (b) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44. (c) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185.

[40] For the most recent review, see: Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873.

[41] (a) Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed.* **1984**, *23*, 847. (b) Noyori, R.; Koyano, H.; Mori, M.; Hirata, R.; Shiga, Y.; Kokura, T.; Suzuki, M. *Pure Appl. Chem.* **1994**, *66*, 1999.

[42] (a) Morimoto, R. I.; Santoro, M. G. *Nature Biotechnol.* **1988**, *16*, 833. (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185. (c) Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans. I* **2002**, 1735. (d) Santoro, M. G.; Rossi, A.; Amici, C. *EMBO J.* **2003**, *22*, 2552.

[43] (a) Ross, A.; Kapachi, P.; Natoli, G.; Takahashi, T.; Chen, Y.; Karin, N. *Nature* **2000**, *403*, 103. (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185. (c) Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 1735.

[44] Bui, T.; Straus, D. S. *Biochem. Biophys. Acta* **1998**, *31*, 1397.

[45] (a) Kato, T.; Fukushima, M.; Kurozumi, S.; Noyori, R. *Cancer Res.* **1986**, *46*, 3538. (b) Fukushima, M.; Kato, T.; Narumiya, S.; Mizushima, Y.; Sasaki, H.; Terashima, Y.; Nishiyama, Y.; Santoro, M. G.; *Adv. Prostagland., Thromboxane Leukotriene Res.* **1989**, *19*, 415. (c) Fukushima, M.; Takeuchi, Y.; Kishimoto, S.; Yamashita, S.; Uetsuki, K.; Shirakawa, S.; Suzuki, M.; Furuta, K.; Noyori, R.; Sasaki, H.; Kikuchi, Y.; Kita, T.; Yamori, T.; Sawada, J.; Kojima, M.; Hazato, A.; Kurozumi, S. *Anticancer. Drugs.* **2001**, *12*, 221.

[46] (a) Sasaki, M.; Niimi, S.; Akiyama, M.; Tanaka, T.; Hazato, A.; Kurozumi, S.; Fukushima, S.; Fukushima, M. *Cancer Res.* **1999**, *59*, 3919. (b) Fukushima, S.; Kishimoto, S.; Takeuchi, Y.; Fukushima, M. *Adv. Drug Deliv. Rev.* **2000**, *45*, 65.

[47] Conti, G.; Portincasa, P.; Visalli, S.; Chezzi, C. *Virus Res.* **2001**, *75*, 43.

[48] Rozero, C.; Caratolli, A.; de Marco, A.; Amici, C.; Giorgi, C.; Santoro, M. G. *J. Clin. Invest.* **1996**, *97*, 1975.

[49] (a) Harris, S. G.; Phipps, R. P. *Eur. J. Immunol.* **2001**, *31*, 1098. (b) Cernuda-Morollon, E.; Pineda-Molina, E.; Canada, F. J.; Perez-Sala, D. *J. Biol. Chem.* **2001**, *276*, 35530. (c) Rovin, B. H.; Lu, L.; Cosio, A. *J. Am. Soc. Nephrol.* **2001**, *12*, 1659.

[50] (a) Rossi, A.; Elia, G.; Santoro, M. G. *Proc. Natl. Acad. Sci.* USA **1997**, *94*, 746. (b) Amici, C.; Belardo, G.; Rossi, A.; Santoro, M. G. *J. Biol. Chem.* **2001**, *276*, 28739.

[51] (a) Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Akutsu, H.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1982**, *23*, 5331. (b) Kikuchi, H.; Tsukitani,Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171. (c) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *Tetrahedron Lett.* **1985**, *26*, 5787.

[52] (a) Iguchi, K.; Yamada, Y.; Kikuchi, H.; Tsukitami,Y. *Tetrahedron Lett.* **1983**, *24*, 4433. (b) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4375.

[53] (a) Baker, B. J.; Okuda, R. K.; Yu, P. T. K.; Scheuer, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 2976. (b) Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B. J.; Scheuer, P. J.; Noyori, R. *J. Org. Chem.* **1988**, *53*, 286.

[54] (a) Fukushima, M. *Prostaglandins Leucotrienes Essent. Fatty Acids* **1992**, *47*, 1. (b) Negishi, M.; Koizumi, T.; Ichikawa, A. J. *Lipid Mediators*, **1995**, *12*, 443.

[55] (a) Fukushima, M. *Eicosanoids* **1990**, *3*, 189. (b) Sasaki, H.; Fukushima, M. *Anti- Cancer Drugs* **1994**, *5*, 131.

[56] (a) Tanikawa, M.; Yamada, K.; Tominaga, K.; Morizaki, H.; Kaneko, Y.; Ikeda, K.; Suzuki, M.; Kiho, T.; Tomokiyo, K.; Furuta, K.; Noyori, R.; Nakanishi, M. *J. Biol. Chem.* **1998**, *273*, 18522. (b) Hsiang, C.-H.; Straus, D. *Oncogene* **2002**, *21*, 2212.

[57] For reviews, see : (a) Schore, N. E. *Org. React.* **1991**, *40*, 1. (b) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297. (c) Brummond, K. M. ; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263.

[58] Recent reviews about the Pauson- Khand reaction: (a) Geis, O.; Schmalz, H. G. *Angew. Chem. Int. Ed.* **1988**, *37*, 911. (b) Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: Berlin, 1999, Vol. II, p. 491. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (d) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589. (e) Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1800.

[59] Wilkinson, G. *J. Organomet. Chem.* **1975**, *100*, 273.

[60] Keally, T. J.; Pauson, P. L. *Nature* **1951**, *168*, 1039.

[61] Bochmann, M. *Organometallic II, Complexes with Transition Metal-Carbon π-Bonds*, 2nd Ed., Oxford University: Oxford, 1994.

[62] Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books: Oxford University, 1980.

[63] Togni, A.; Hayashi, T. *Ferrocenes: Homogenous Catalysts. Organic Synthesis, Material Science,* VCH: Weinheim, 1995; and citations therein.

[64] Taudien, S.; Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1995**, *36*, 3513; and citations therein.

[65] (a) Köpf-Maier, P.; Köpf, H. *Chem. Rev.* **1987**, *87*, 1137. (b) Keppler, B. *Metal Complexes in Cancer Chemotherapy*, VCH: New York, 1993. (c) Köpf-Maier, P. *J. Clin. Pharmacol.* **1994**, *47*, 1.

[66] (a) Köpf-Maier, P.; Köpf, H.; Neuse, E. W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 456. (b) Köpf-Maier, P.; Köpf, H.; Neuse, E. W. *Cancer Res. Clin. Oncol.* **1984**, *108*, 336. (c) Köpf-Maier, P. *Naturforsch Sect. C: Biosci* **1985**, *40*, 843.

[67] Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385.

[68] Osella, D.; Ferrali, M.; Zanello, P.; Laschi, F.; Fontani, M.; Nervi, C.; Cavigiolio, G. *Inorg, Chim. Acta* **2000**, *306*, 42; and citations therein.

[69] Jaouen, G.; Vessieres, A.; Butler, I. *Acc. Chem. Res.* **1993**, *26*, 361.

[70] Vessieres, A.; Top, S.; Cabestaing, C.; Laios, I.; Leclercq, G.; Provot, C.; Jaouen, G. *J. Organomet. Chem.* **2001**, *637-639*, 500.

[71] (a) WHO. *Weekly Epidemiol. Rep.* **1996**, *3*, 17. (b) WHO. *Weekly Epidemiol. Rep.* **1996**, *4*, 25. (c) WHO. *Weekly Epidemiol. Rep.* **1996**, *5*, 37.

[72] Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. *J. Med. Chem.* **1997**, *40*, 3715.

[73] Domrle, O.; Blampain, G.; Agnaniet H.; Nzadiyabi, T.; Lebibi, J.; Brocard, J. *Antimicrob. Agents and Chemother.* **1998**, *42*, 540.

[74] For the recent examples, see: (a) Osello, D.; Gobetto, R.; Nervi, C.; Ravera, M.; D'Amato, R.; Russo, M. V. *Inorg. Chem. Commun.* **1998**, *1*, 239. (b) Thomas, J. L.; Howarth, J.; Hanlon, K.; McGuirk, D. *Tetrahedron Lett.* **2000**, *41*, 413. (c) Georgopoulou, A. S.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J.; Horrocks, B. R.; Houlton, A. *J. Chem. Soc. Dalton Trans.* **2000**, 2969. (d) Bonini, B. F.; Femoni, C.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **2001**, 1092. (e) Howarth, J.; Hanlon, K. *Tetrahedron Lett.* **2001**, *42*, 751.

[75] Connor, J. A.; Jones, E. M. *J. Chem. Soc., Dalton Trans.* **1973**, 2119.

[76] Gibson, S. E. *Transition Metals in Organic Synthesis*, Oxford University Press: Oxford, 1997.

[77] Polin, J.; Schottenberger, H.; Anderson, B.; Martin, S. F. *Org. Synt.* **1995**, *73*, 262.

[78] Doisneau, G.; Balavoine, G.; Fillebeen-Khan, T. *J. Organomet. Chem.* **1992**, *425*, 113.

[79] Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.

[80] Sashuk, V.; Ignatowska, J.; Grela, K. *J. Org. Chem.* **2004**, *69*, 7748.

[81] Yamashita, A.; Timko, J. M.; Watt, W. *Tetrahedron Lett.* **1988**, *29*, 2513.

[82] Yamashita, A.; Scahill, T. A. *Tetrahedron Lett.* **1982**, *23*, 3765.

[83] Stoe & Cie *X-AREA* (Version 1.18) and *X-RED32* (Version 1.04), Stoe & Cie, Darmstadt, Germany, 2002.

[84] Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467.

[85] Sheldrick, G. M. *SHELXL97*, University of Göttingen, Germany, 1997.

[86] Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.

[87] Watkin, D. M.; Pearce, L.; Prout, C. K. *CAMERON*, Chemical Crystallography Laboratory, Oxford, England, 1993.

[88] Spek, A. L. *PLATON*, University of Utrecht, The Netherlands, 1998.

[89] Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837.

APPENDIX

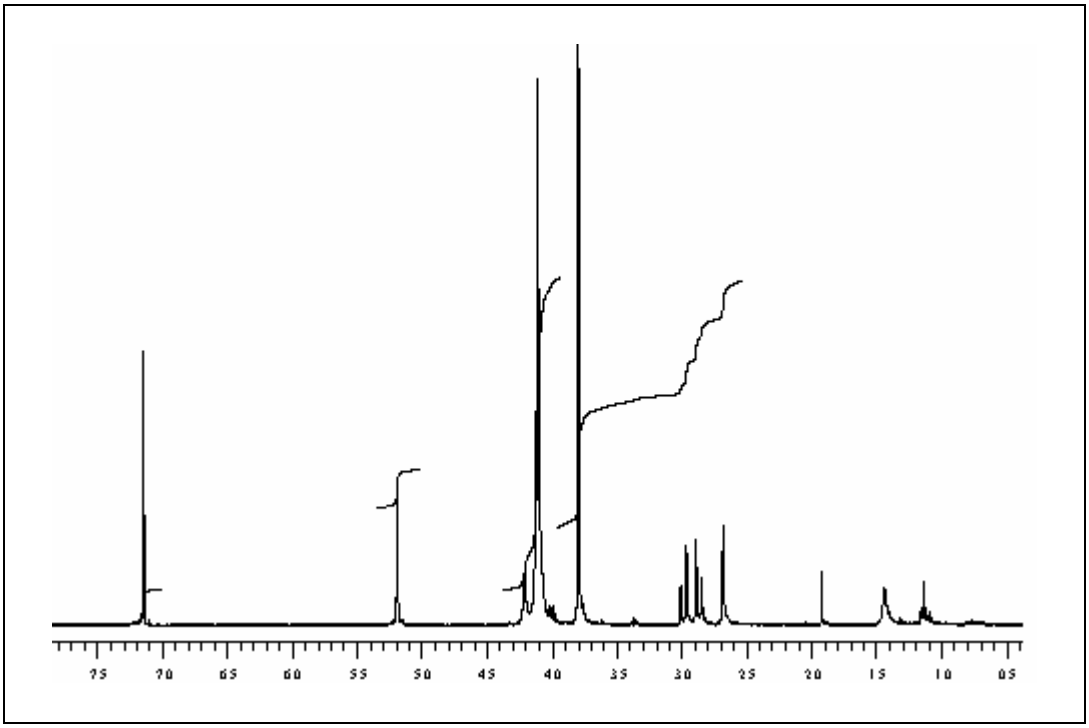


Figure A1. ^{1}H-NMR Spectrum of compound **34A**

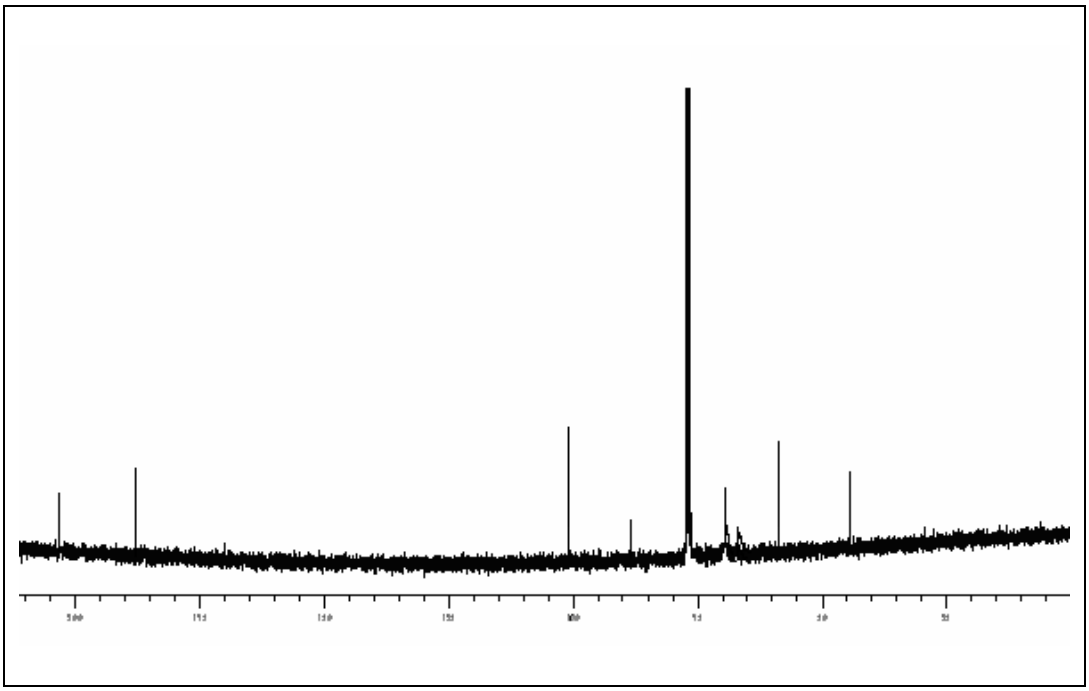


Figure A2. ^{13}C-NMR Spectrum of compound **34A**

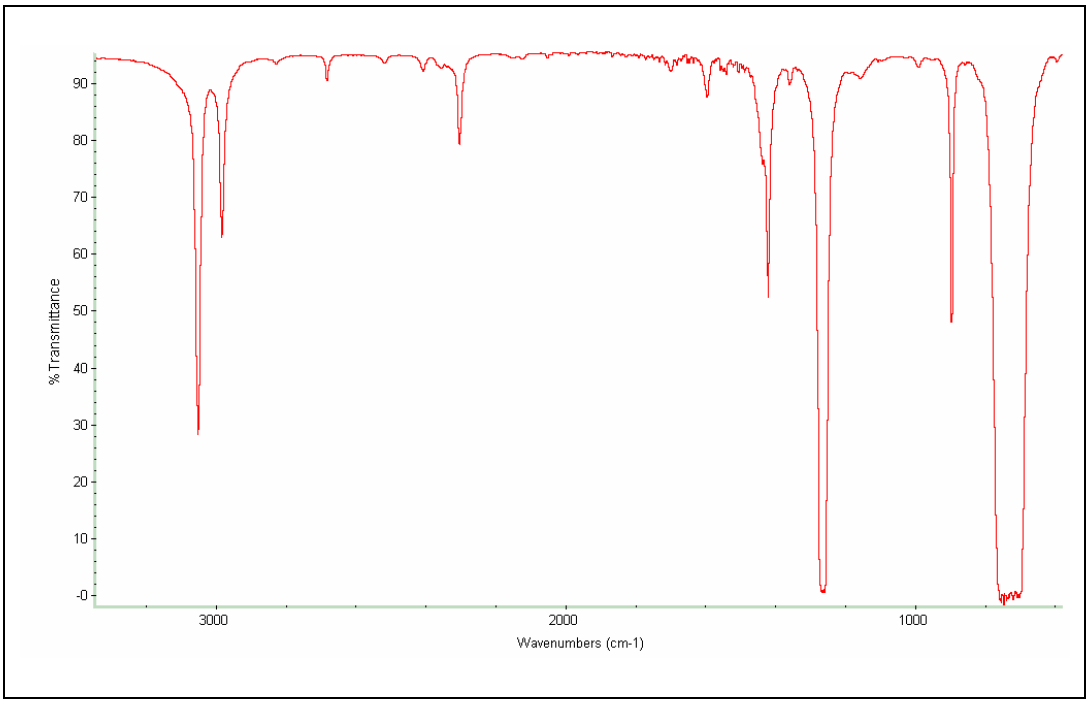


Figure A3. FT-IR Spectrum of compound **34A**

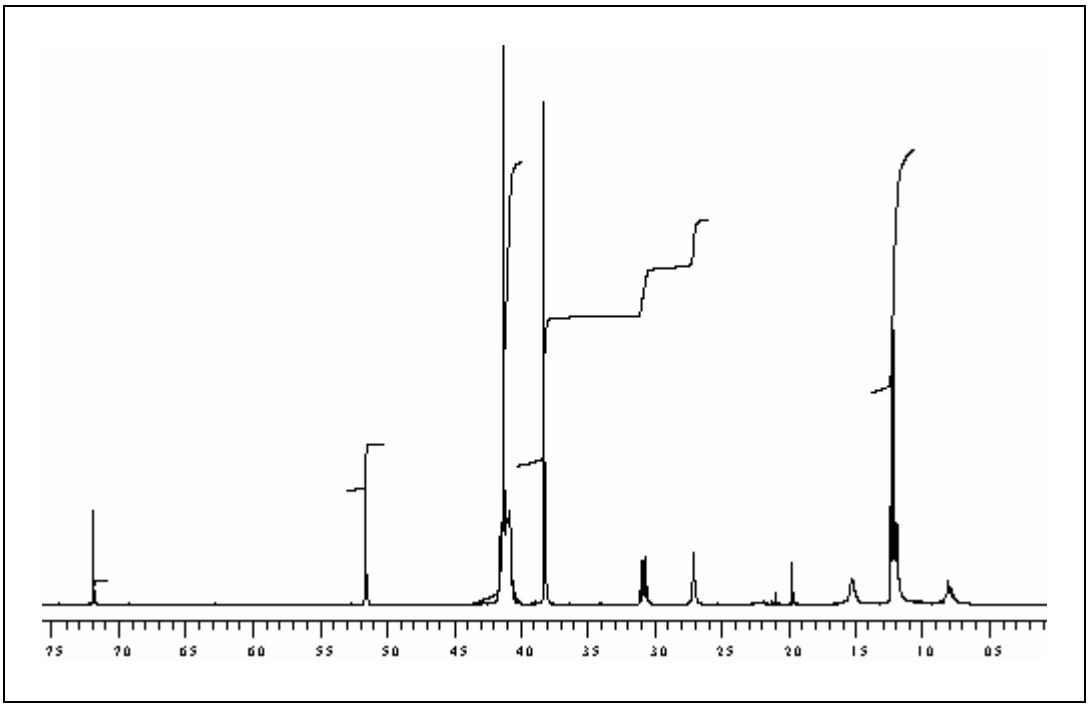


Figure A4. ^{1}H-NMR Spectrum of compound **34B**

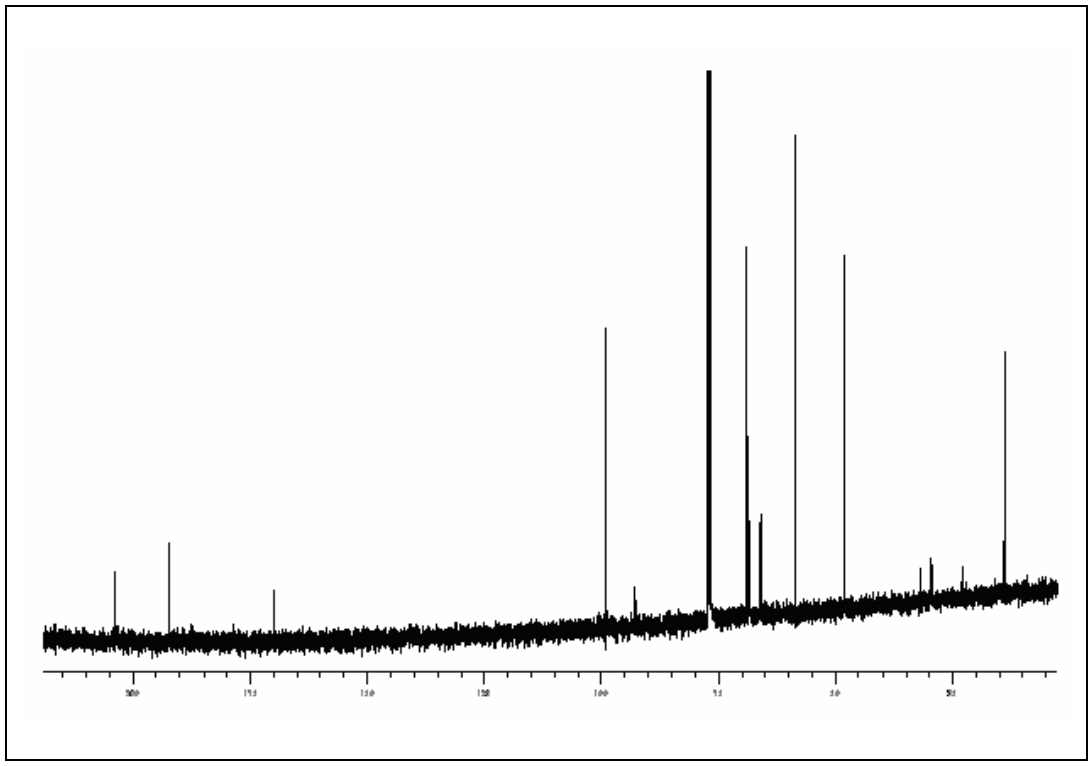


Figure A5. ^{13}C-NMR Spectrum of compound **34B**

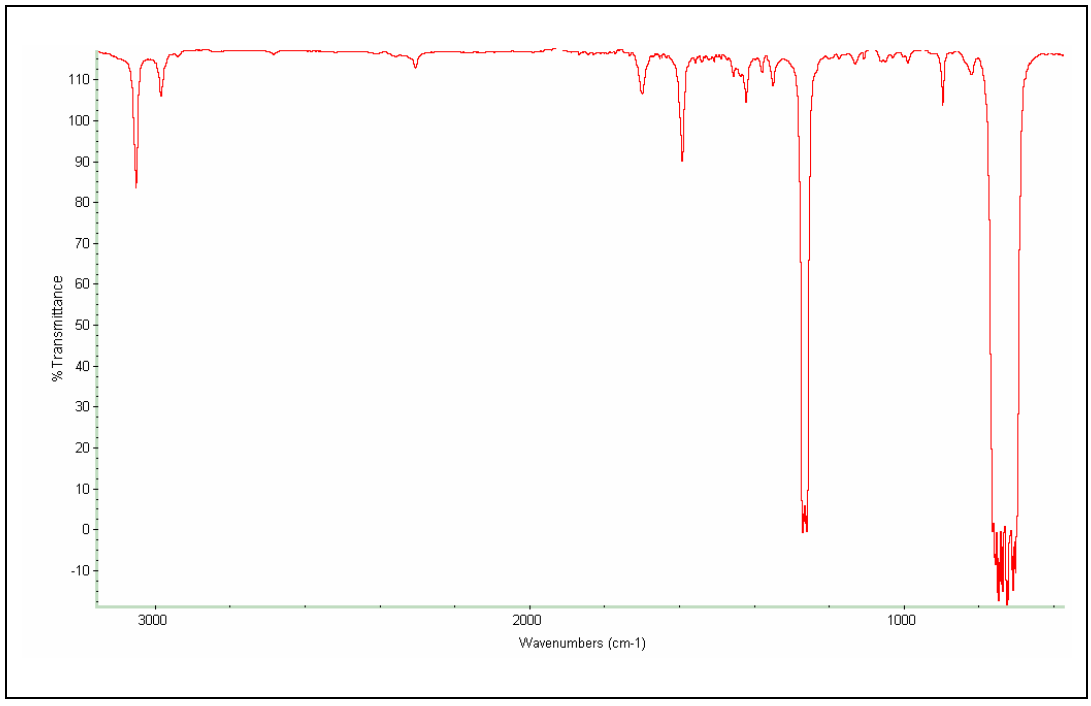


Figure A6. FT-IR Spectrum of compound **34B**

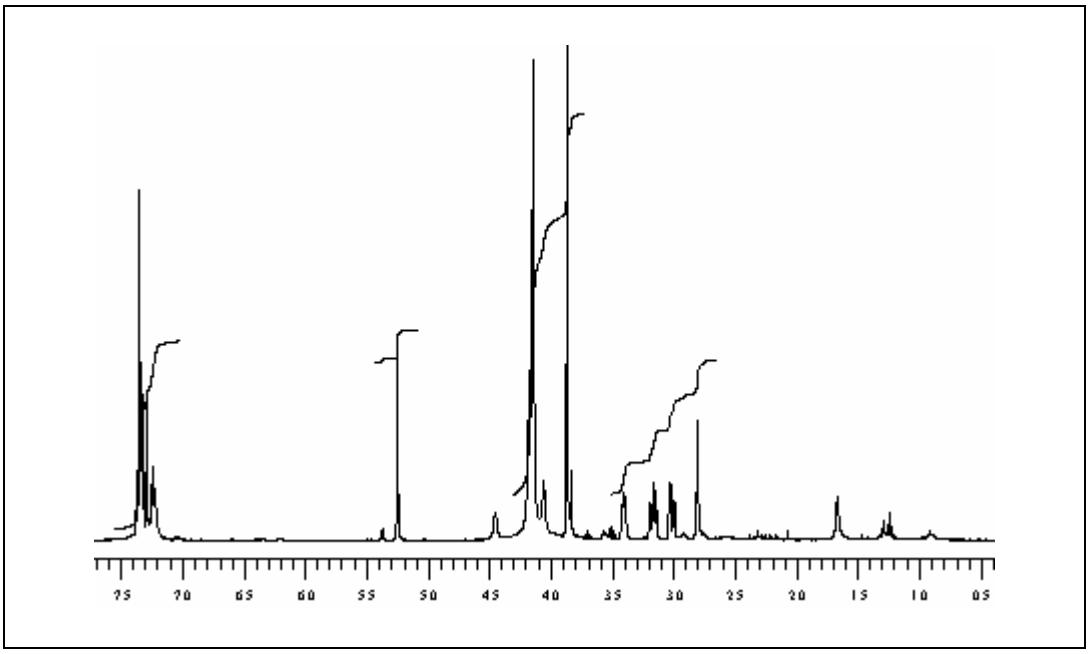


Figure A7. ^{1}H-NMR Spectrum of compound **34C**

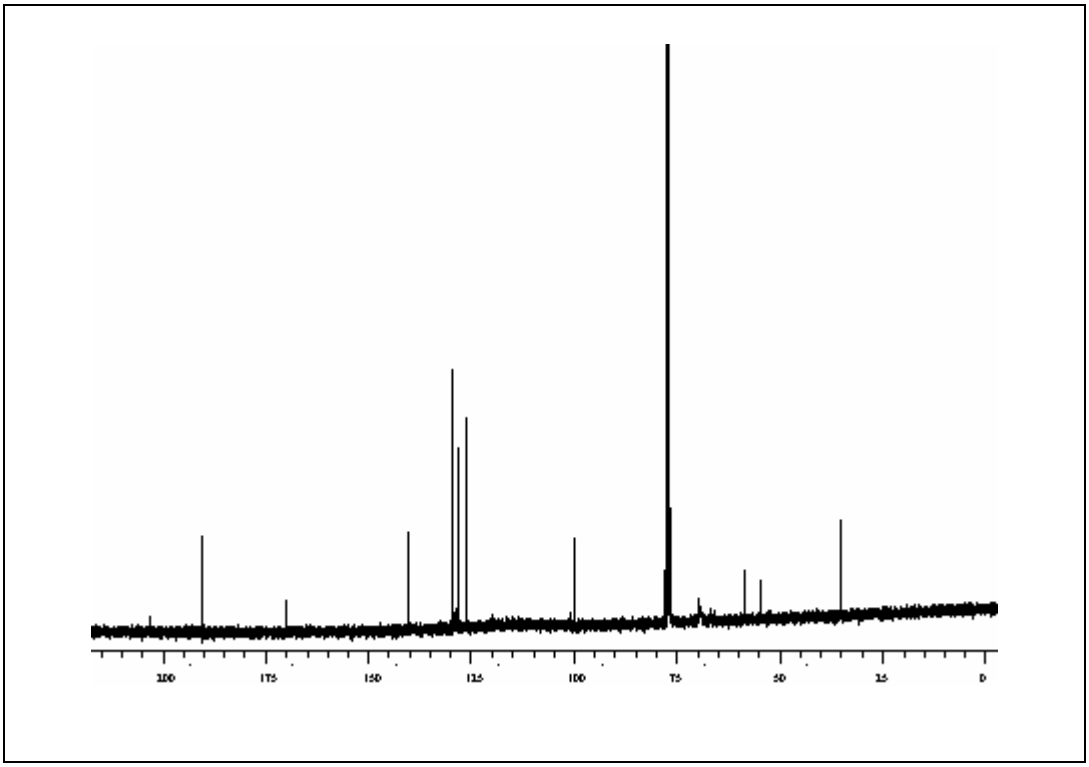


Figure A8. ^{13}C-NMR Spectrum of compound **34C**

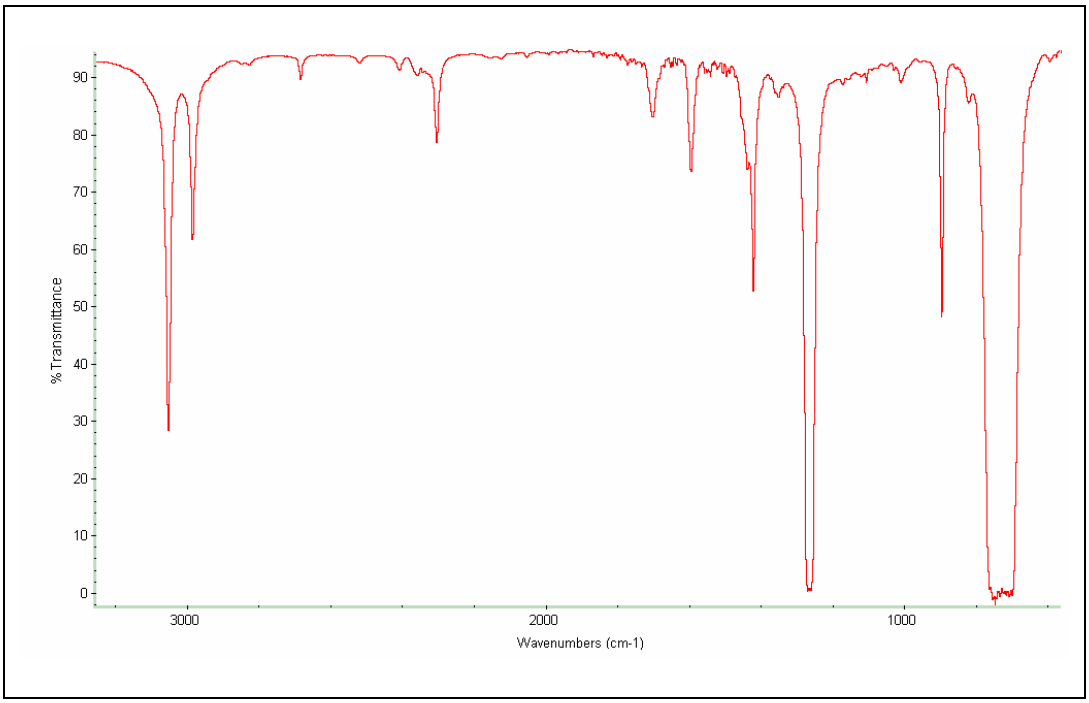


Figure A9. FT-IR Spectrum of compound **34C**

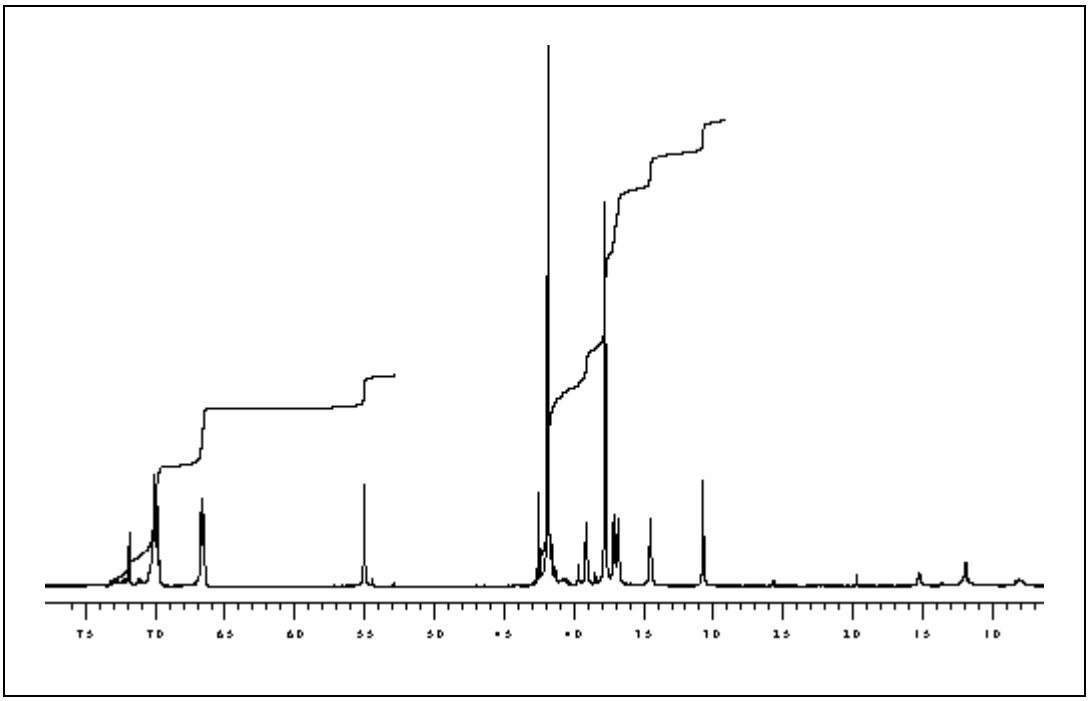


Figure A10. ^{1}H-NMR Spectrum of compound **34E**

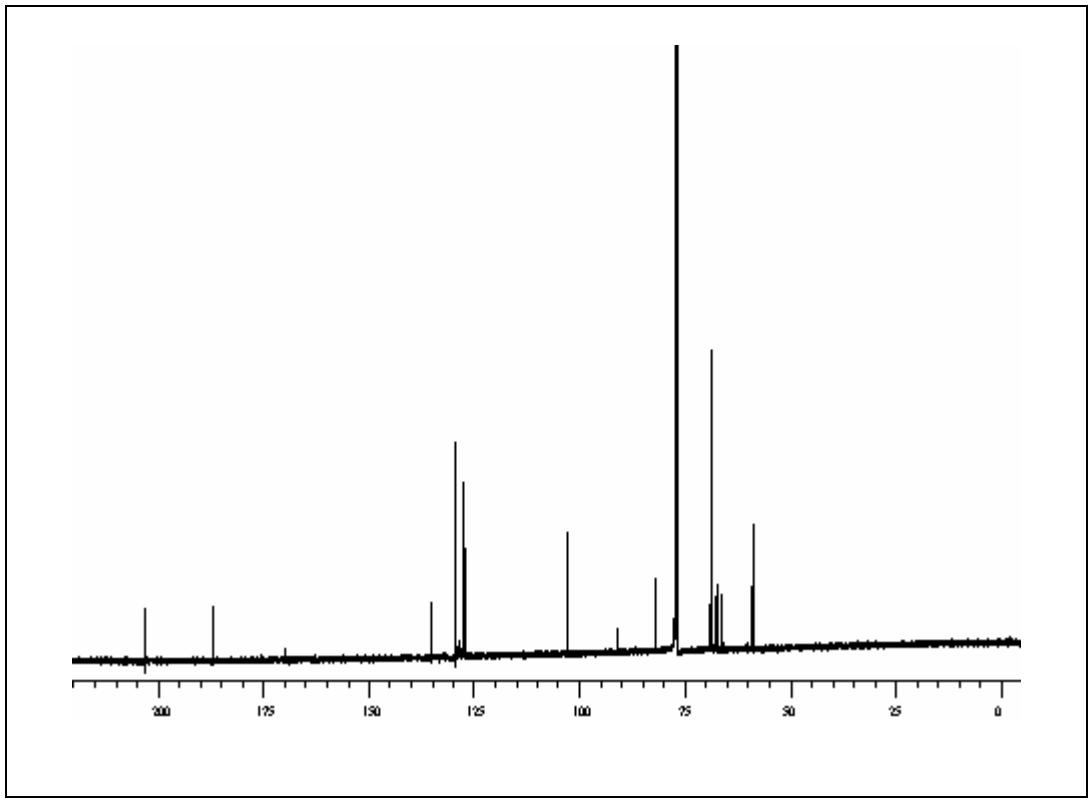


Figure A11. ^{13}C-NMR Spectrum of compound **34E**

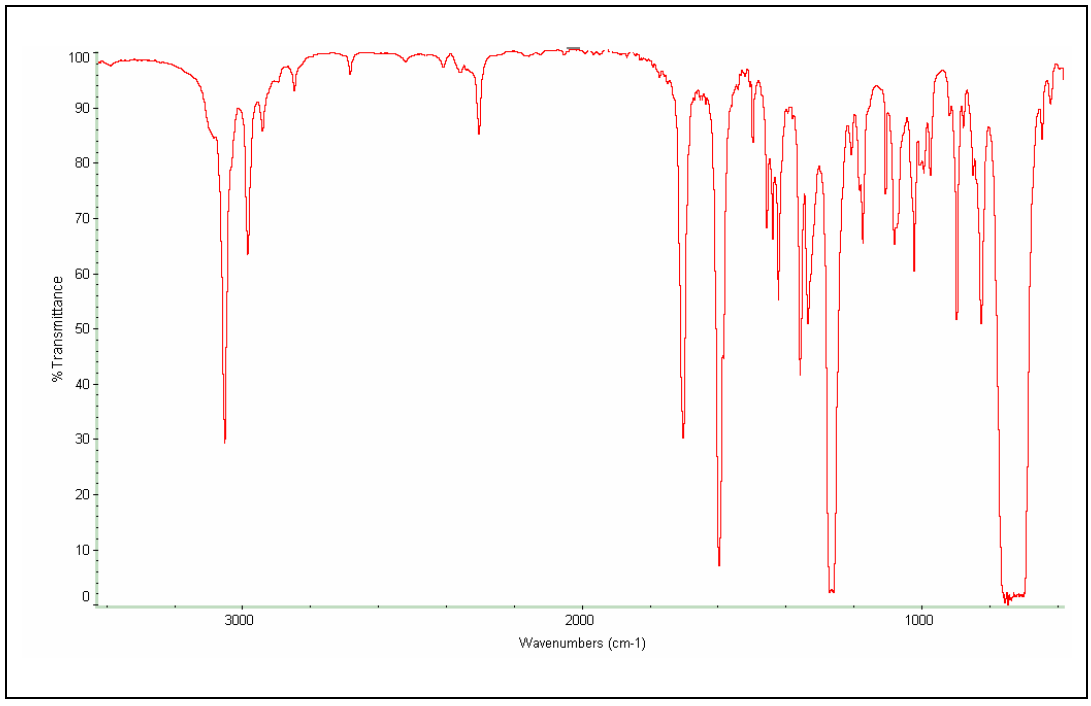


Figure A12. FT-IR Spectrum of compound **34E**

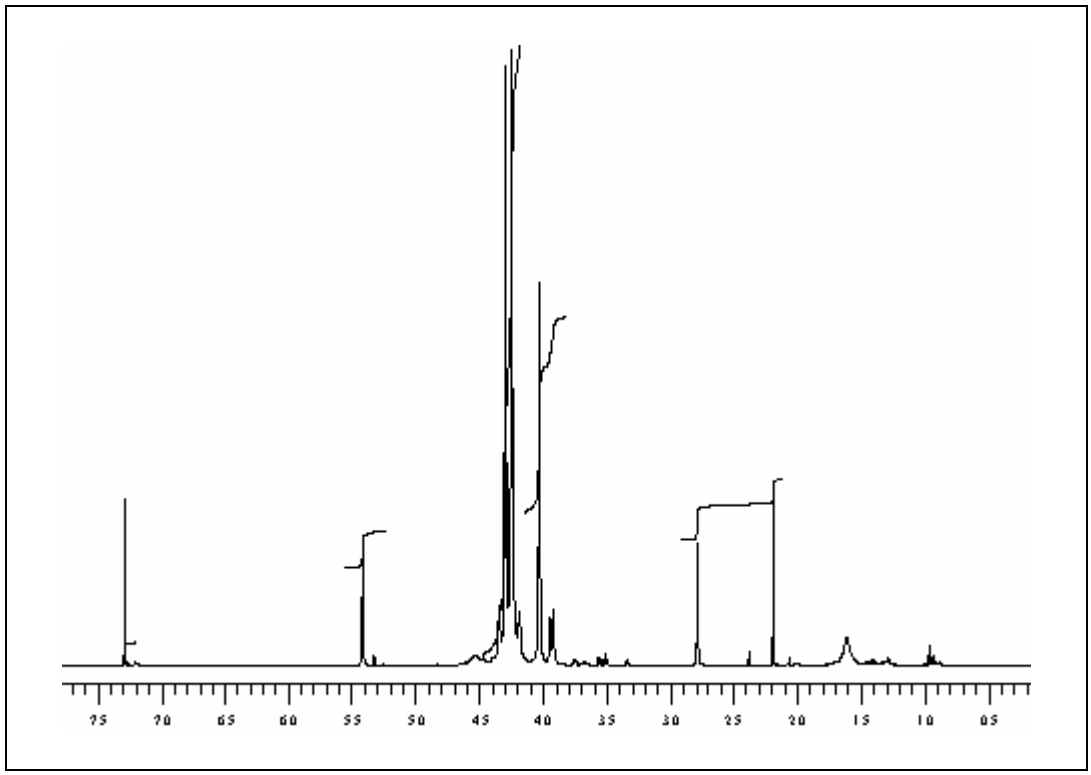


Figure A13. ^{1}H-NMR Spectrum of compound **34F**

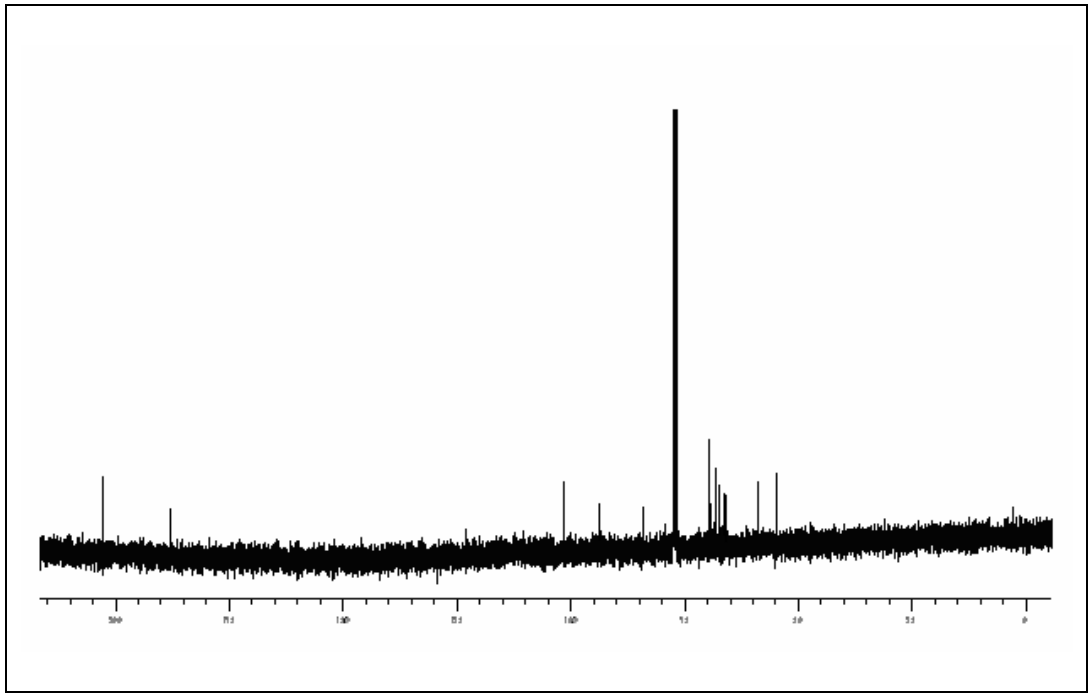


Figure A14. ^{13}C-NMR Spectrum of compound **34F**

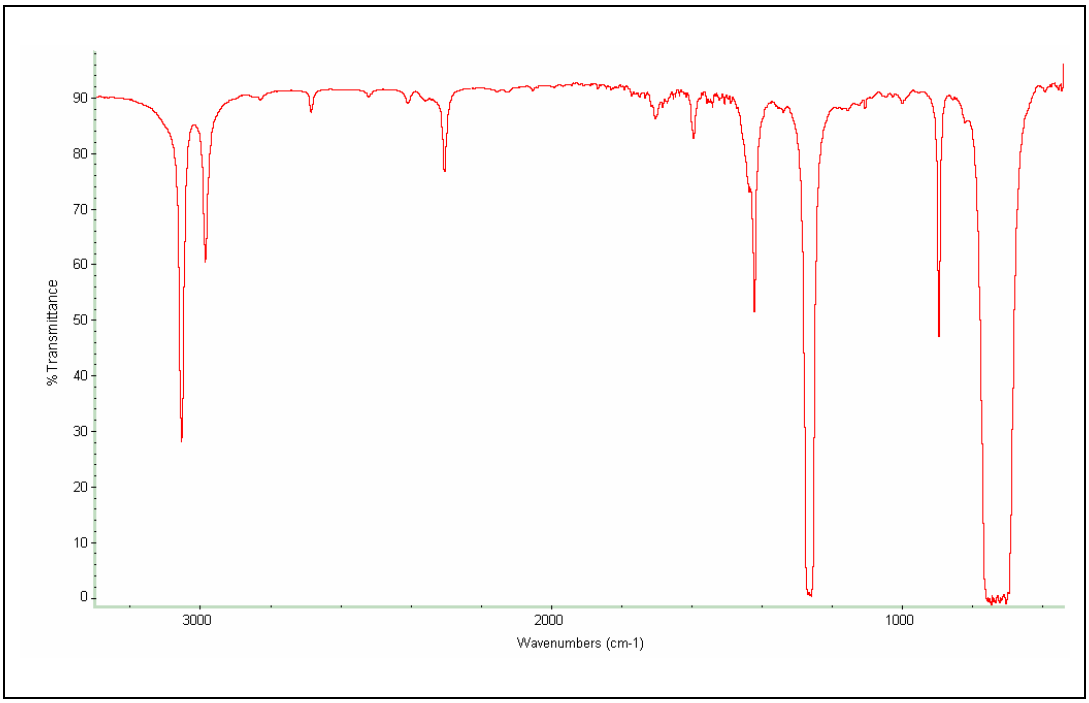


Figure A15. FT-IR Spectrum of compound **34F**

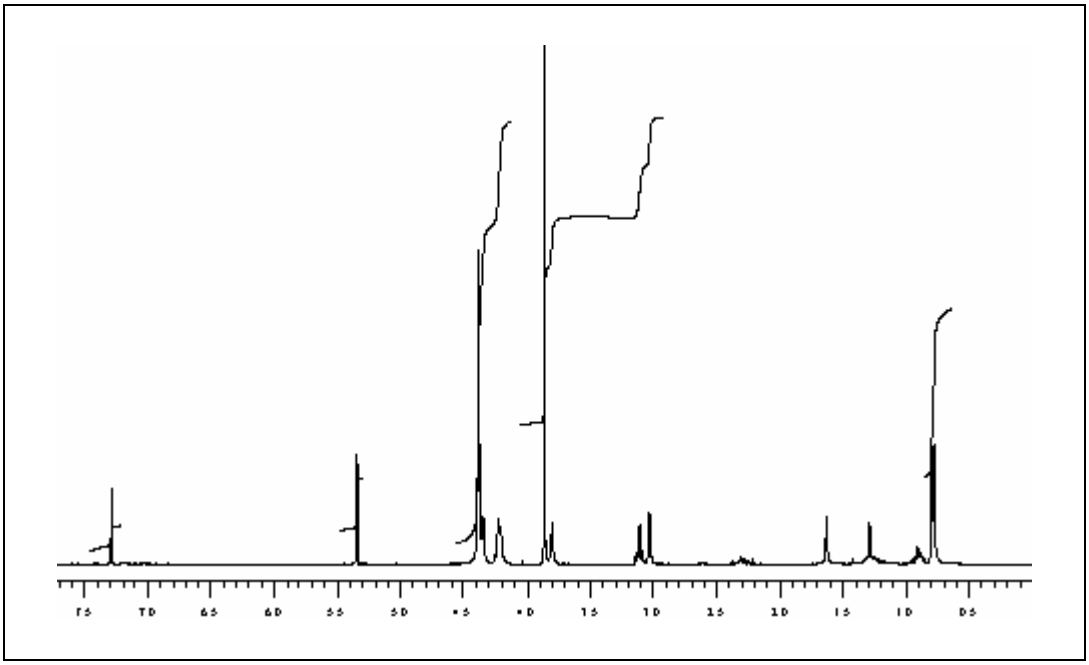


Figure A16. ^{1}H-NMR Spectrum of compound **35B**

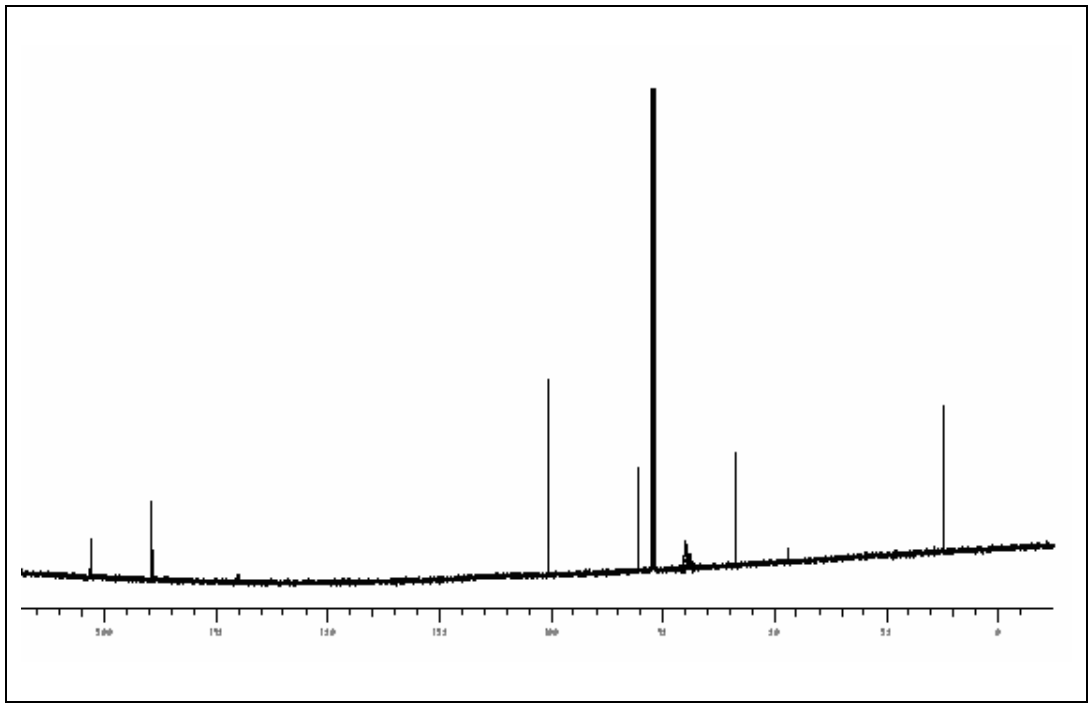


Figure A17. ^{13}C-NMR Spectrum of compound **35B**

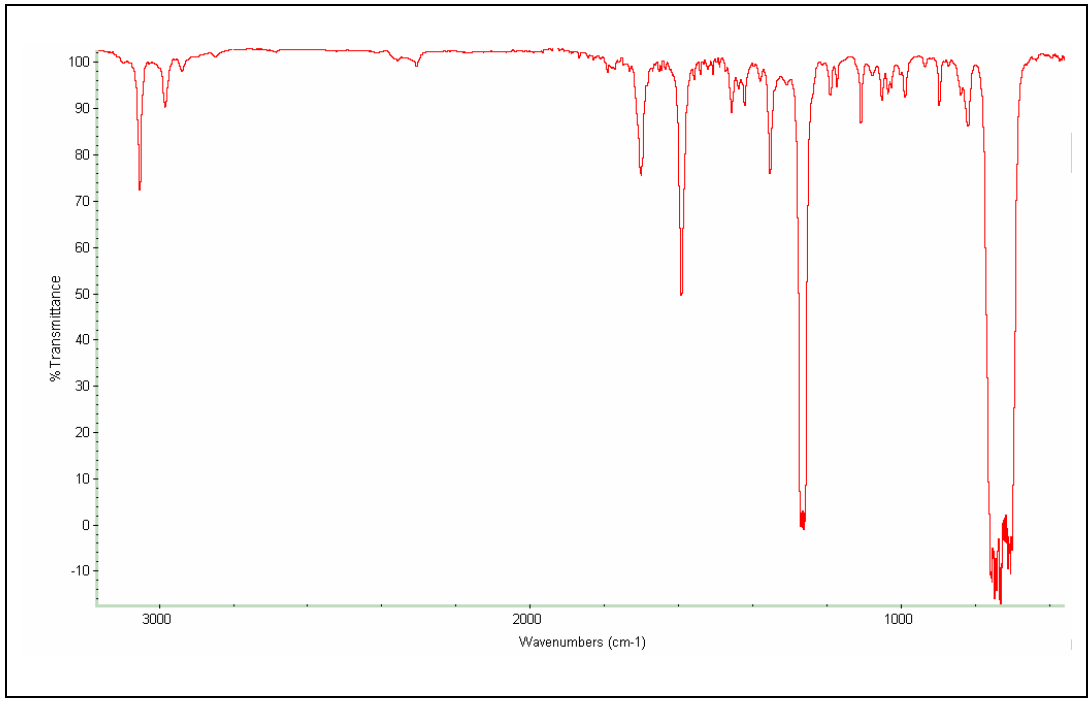


Figure A18. FT-IR Spectrum of compound **35B**

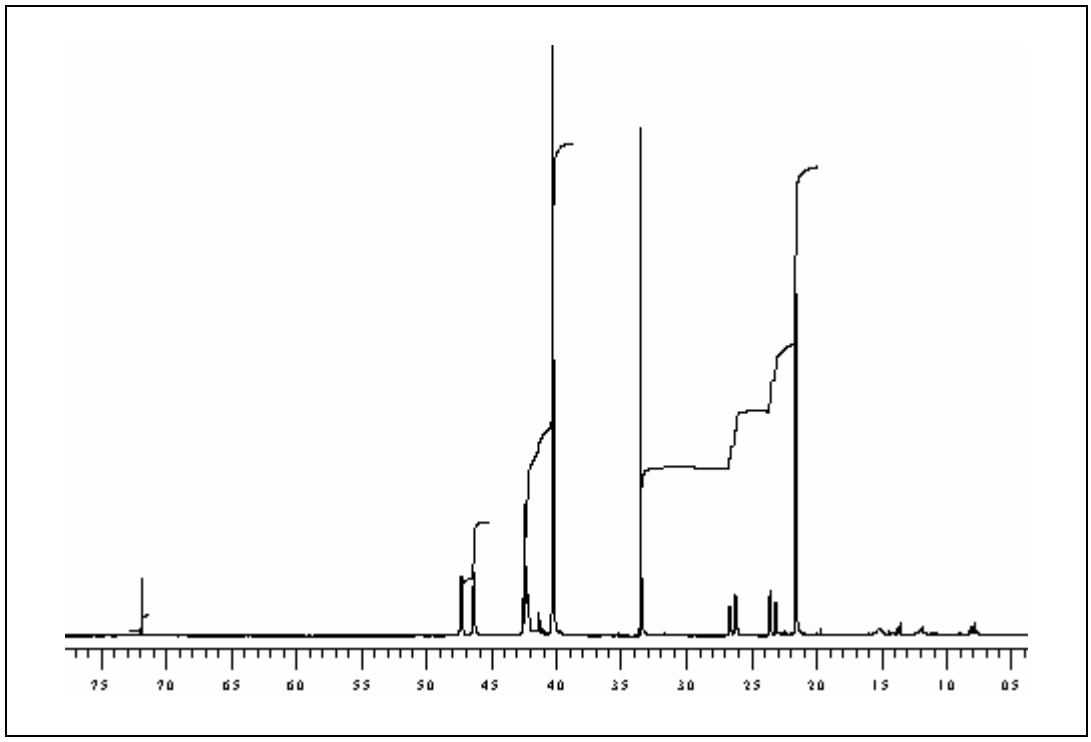


Figure A19. ^{1}H-NMR Spectrum of compound **36B**

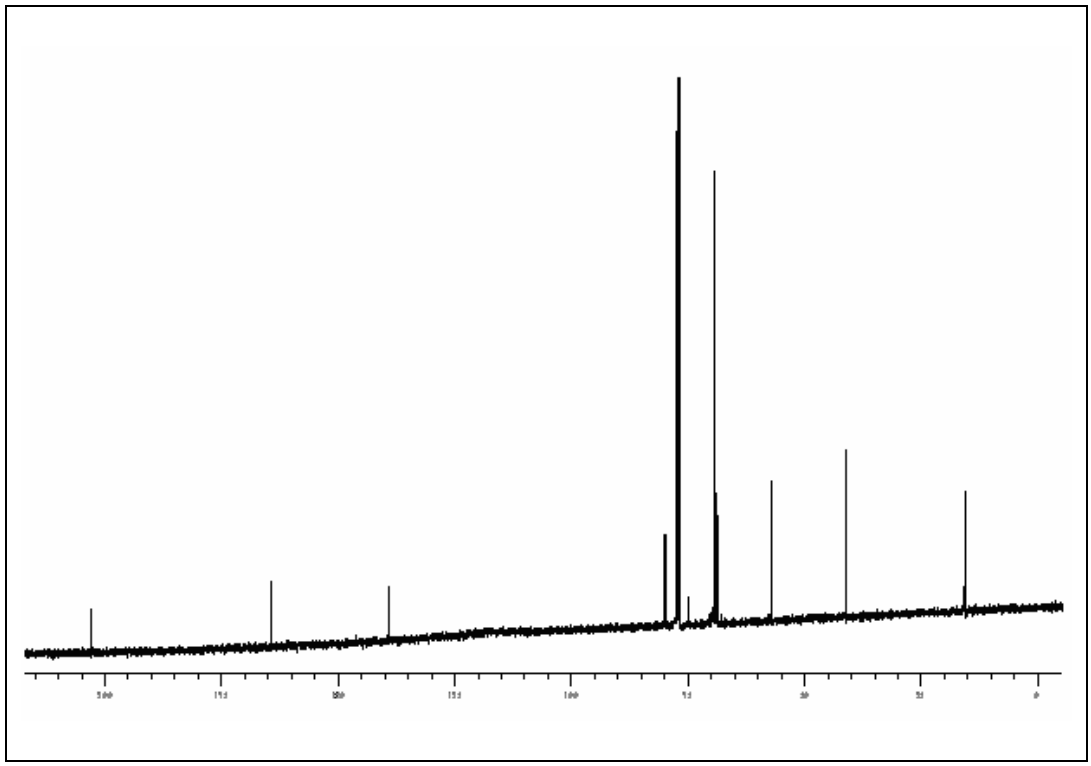


Figure A20. ^{13}C-NMR Spectrum of compound **36B**

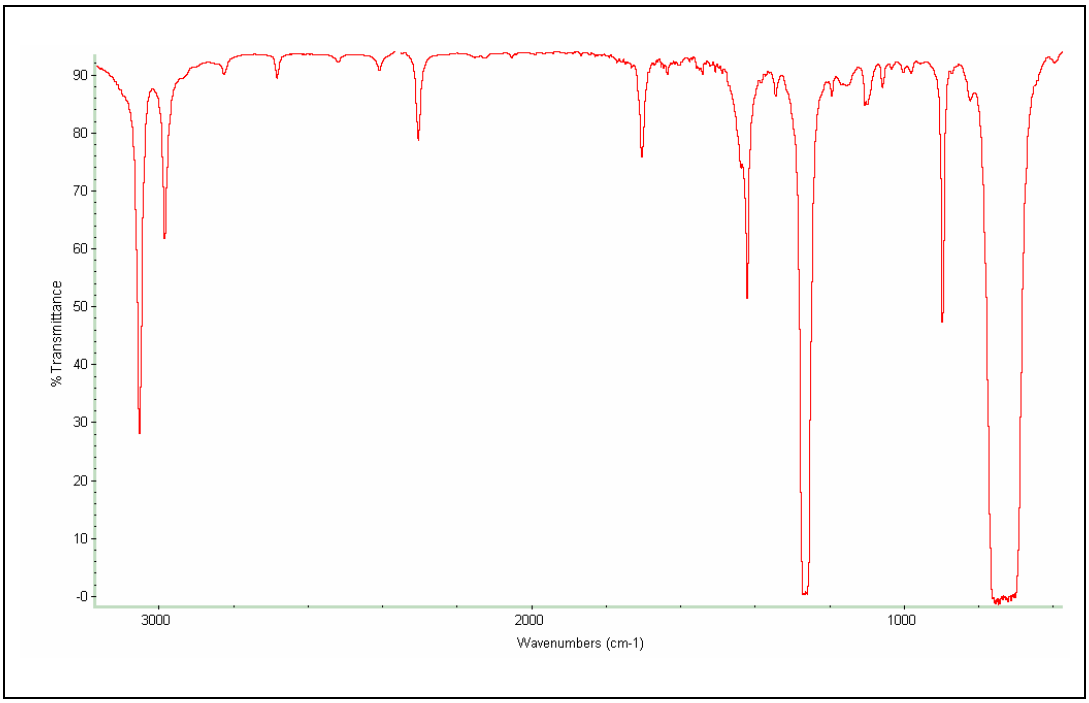


Figure A21. FT-IR Spectrum of compound **36B**

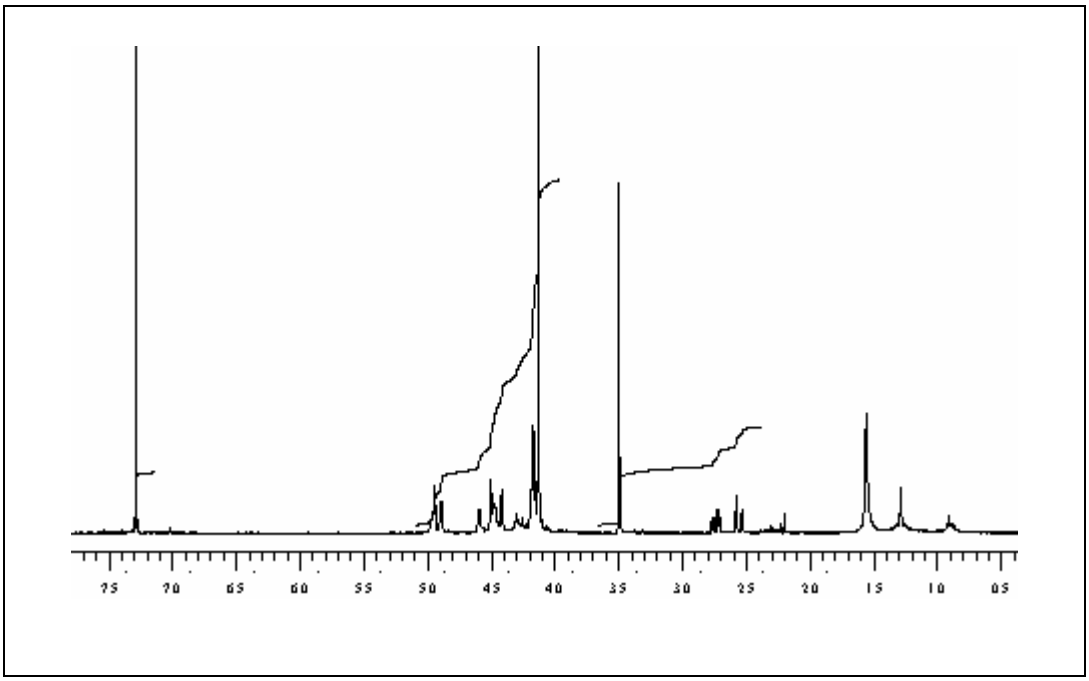


Figure A22. ^{1}H-NMR Spectrum of compound **36F**

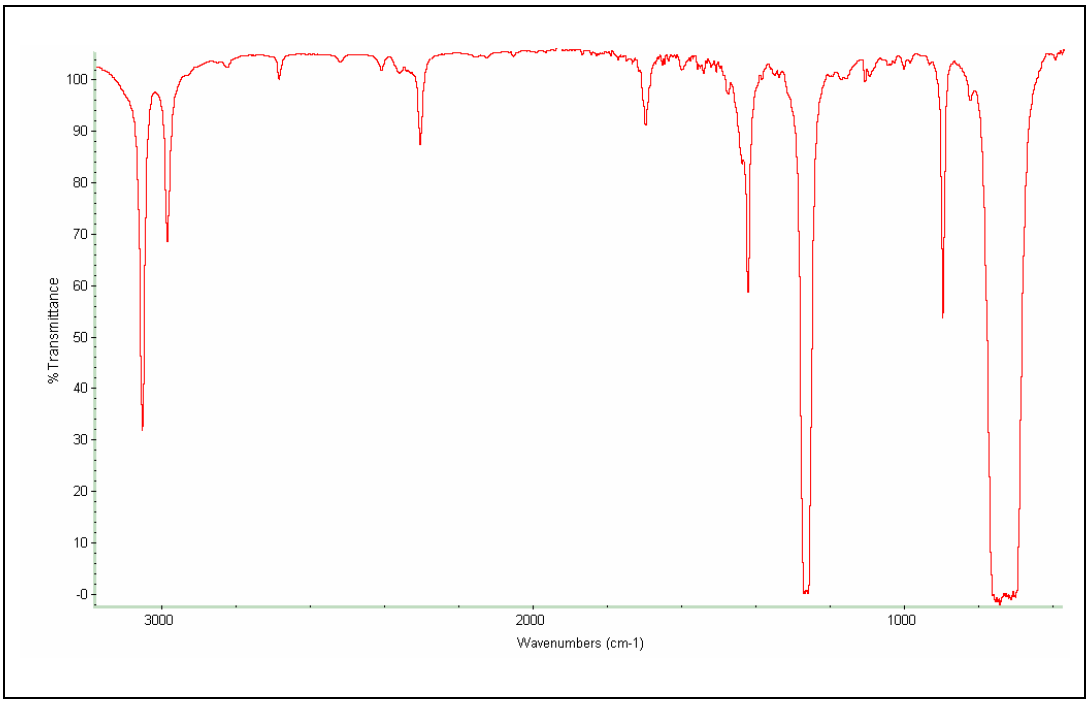


Figure A23. FT-IR Spectrum of compound **36F**

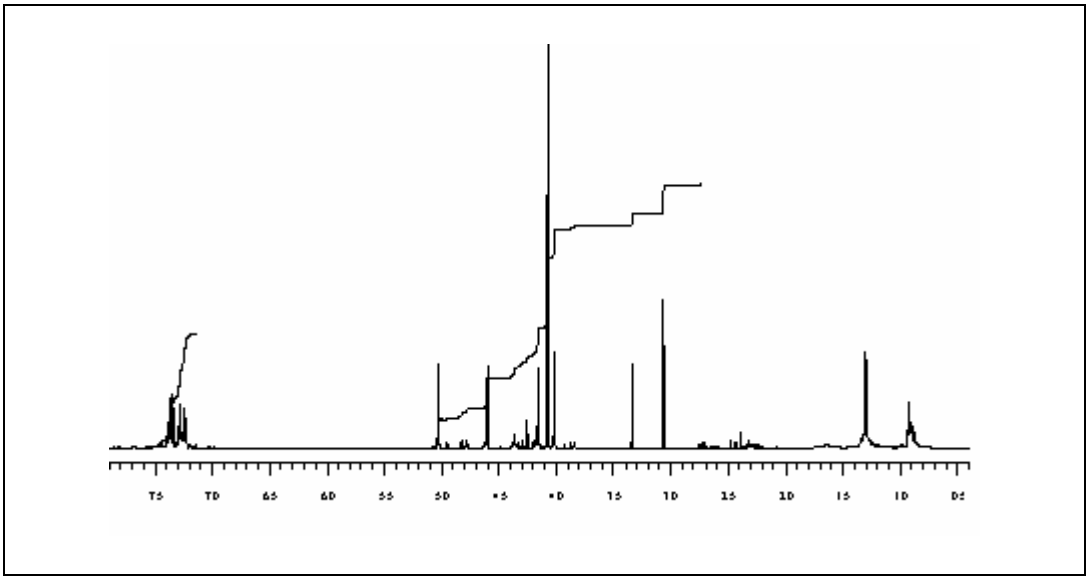


Figure A24. ^{1}H-NMR Spectrum of compound **37C**

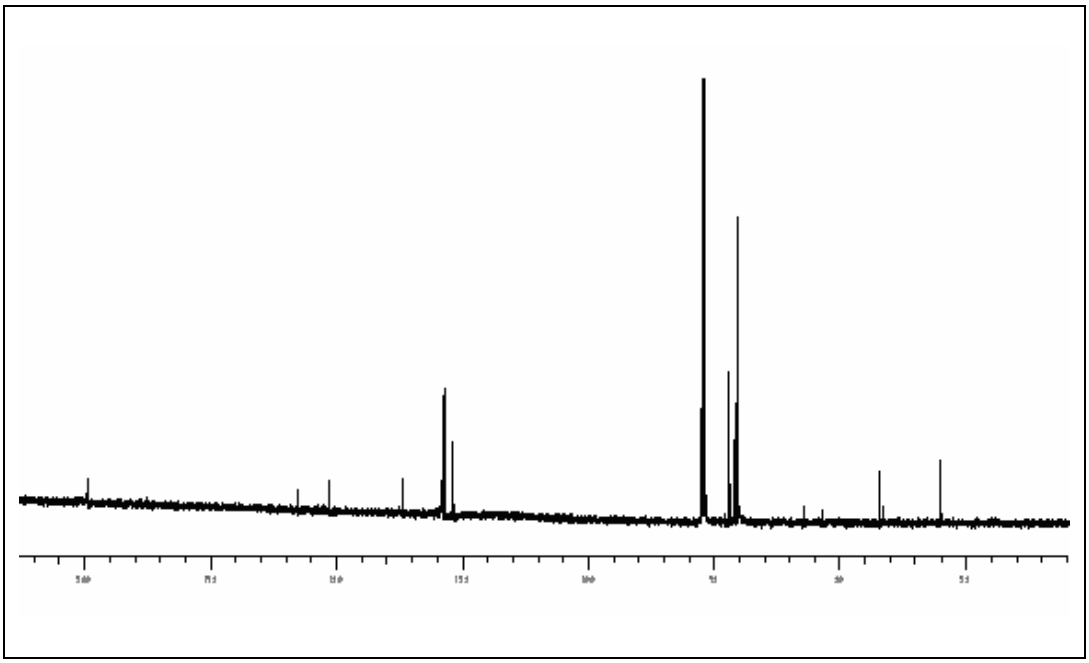


Figure A25. ^{13}C-NMR Spectrum of compound **37C**

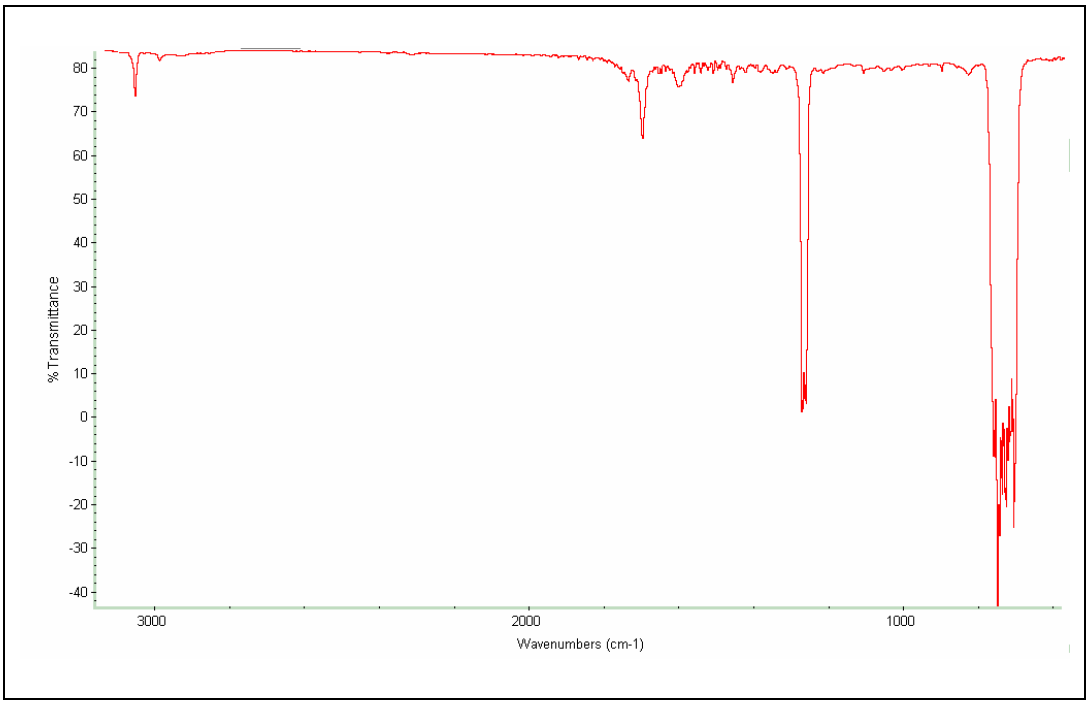


Figure A26. FT-IR Spectrum of compound **37C**

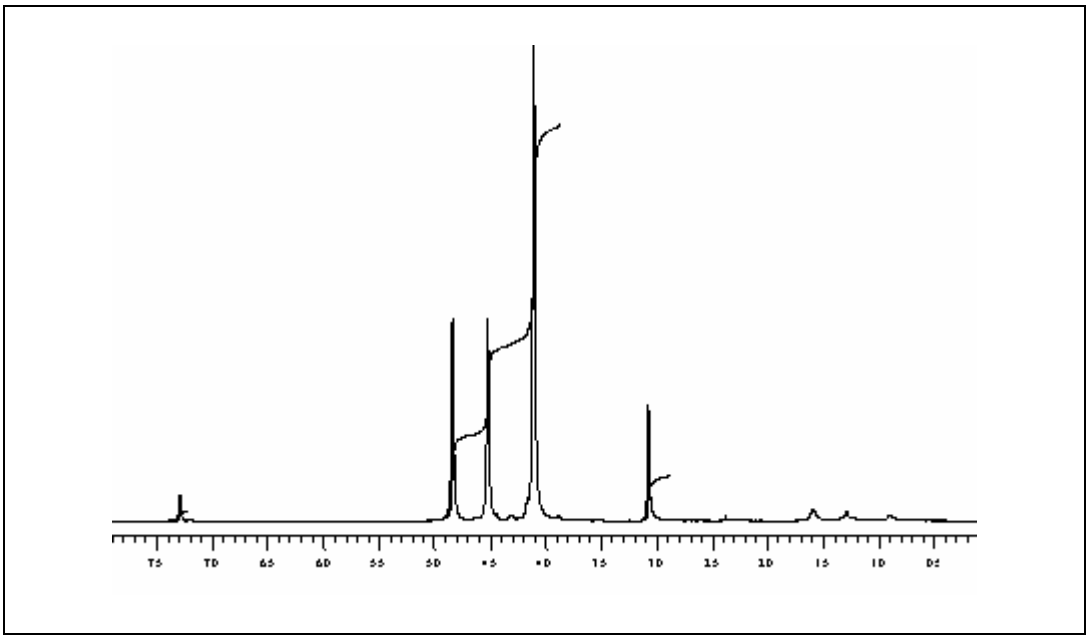


Figure A27. ^{1}H-NMR Spectrum of compound **37F**

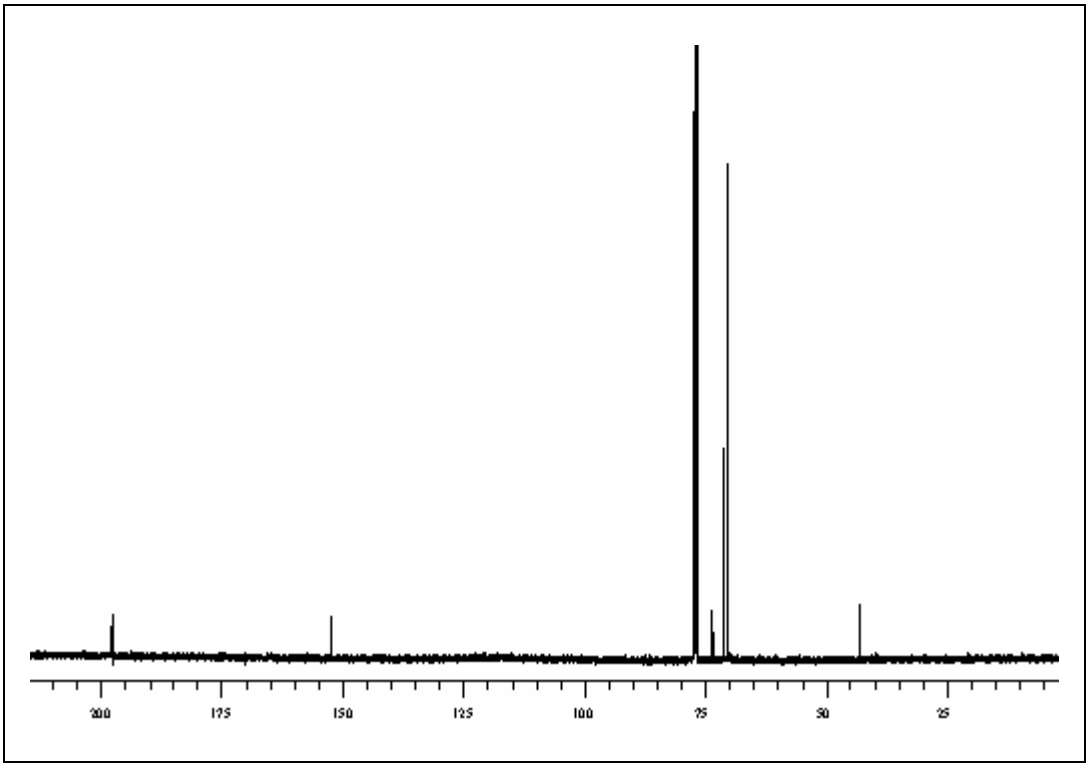


Figure A28. ^{13}C-NMR Spectrum of compound **37F**

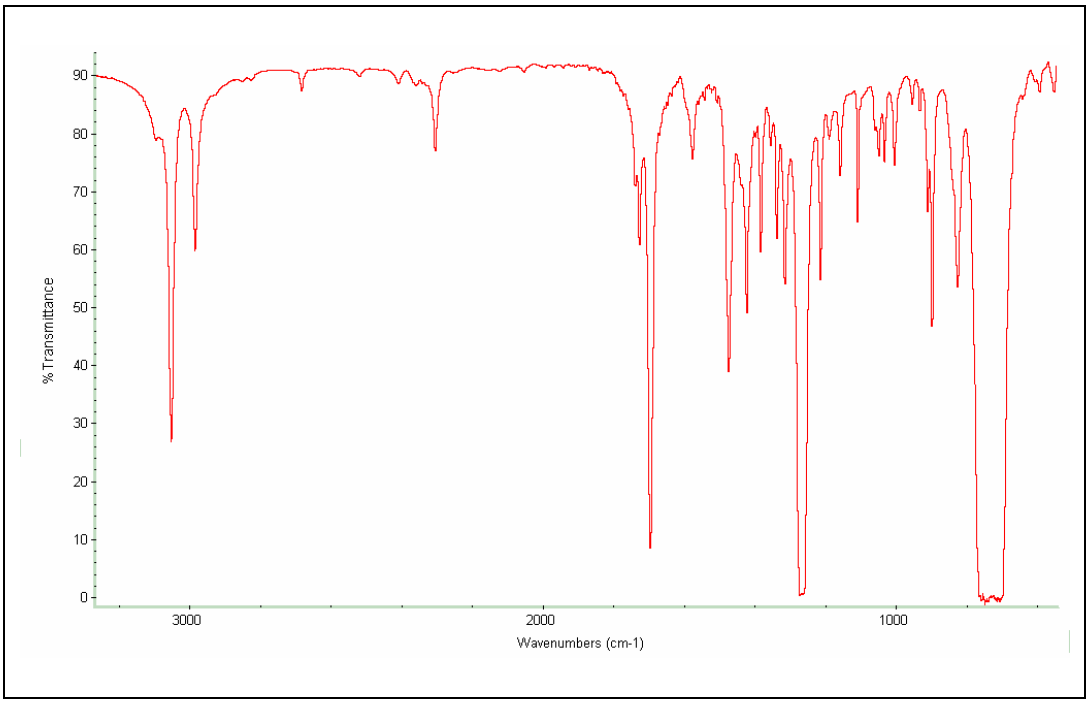


Figure A29. FT-IR Spectrum of compound **37F**

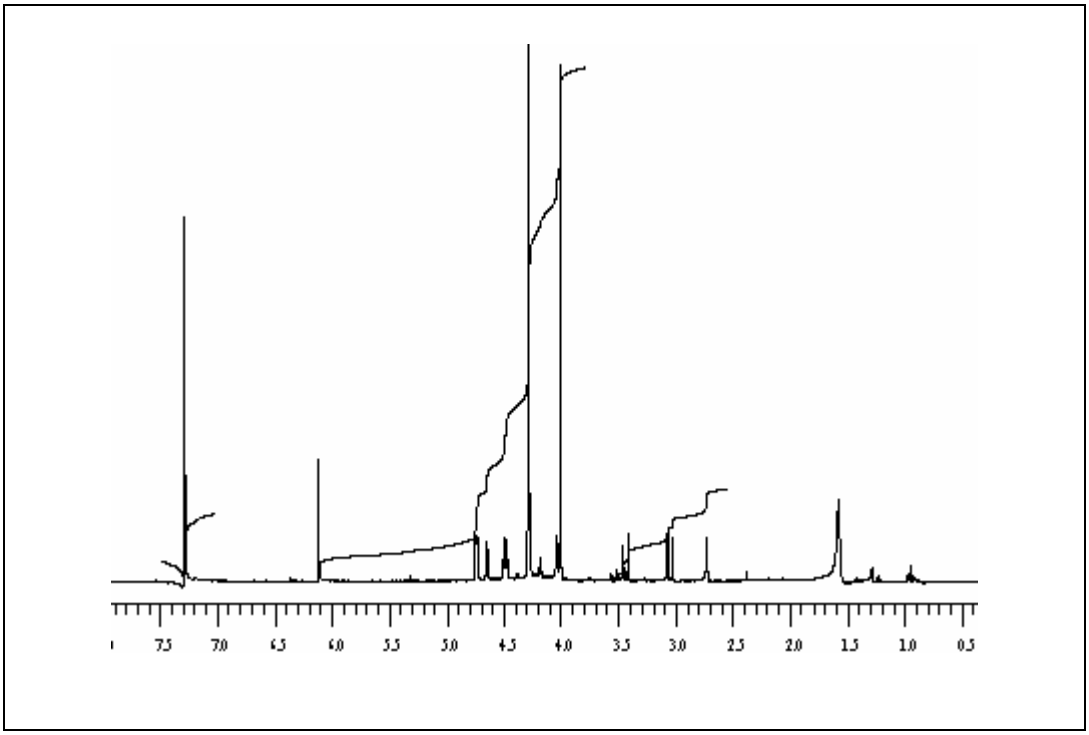


Figure A30. ^{1}H-NMR Spectrum of compound **38**

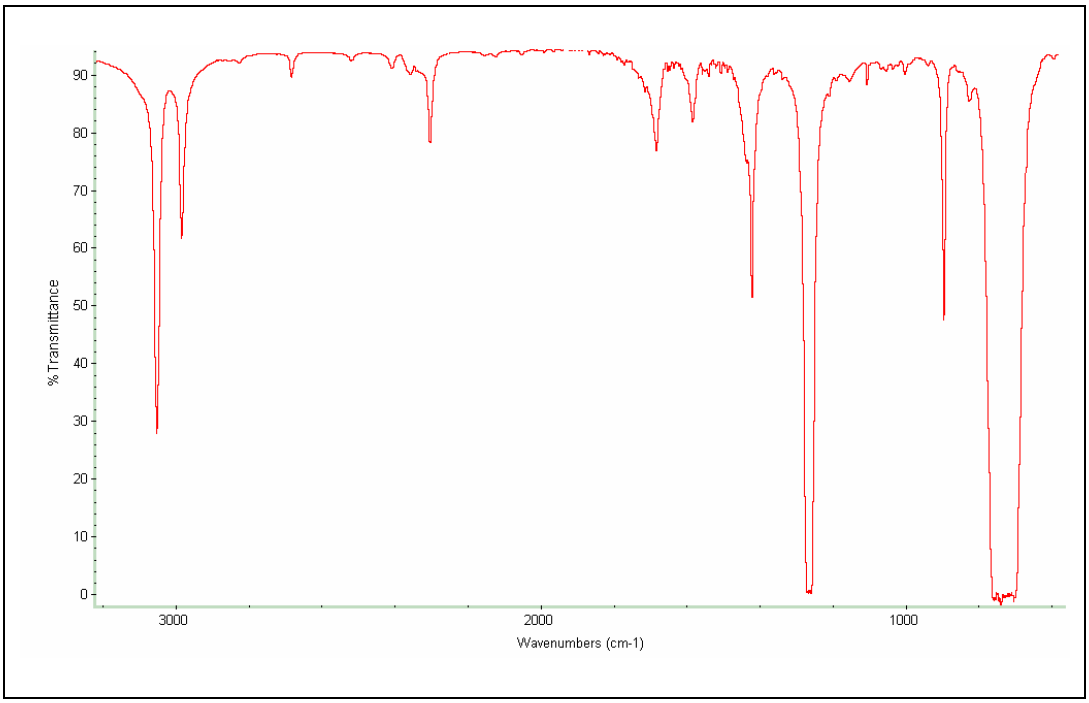


Figure A31. FT-IR Spectrum of compound **38**

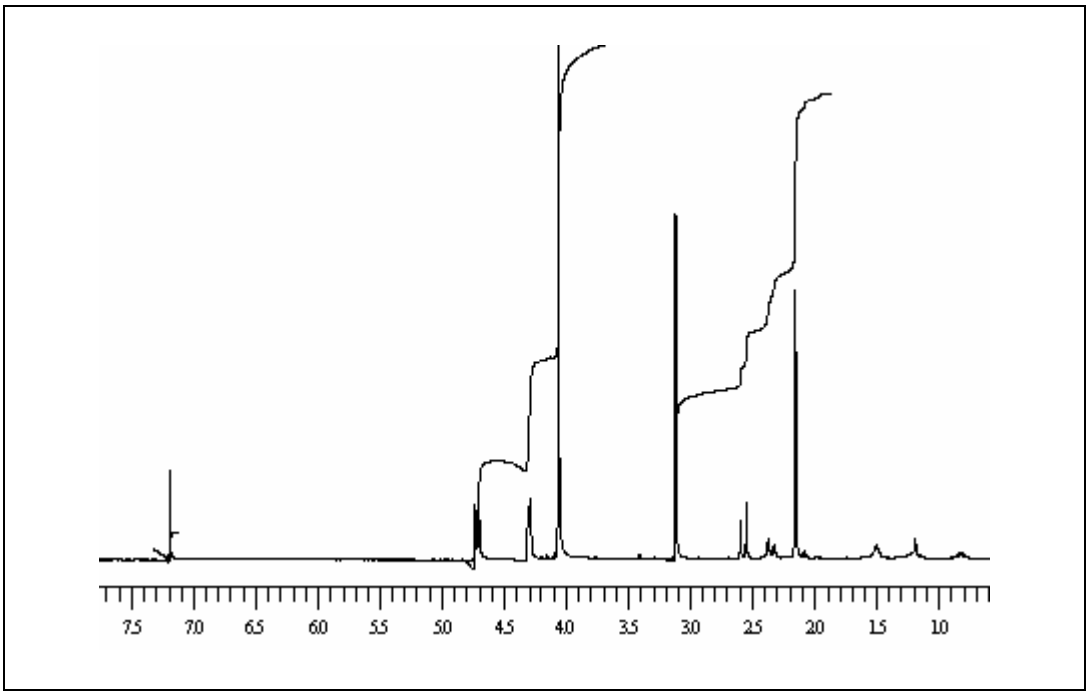


Figure A32. ^{1}H-NMR Spectrum of compound **39B**

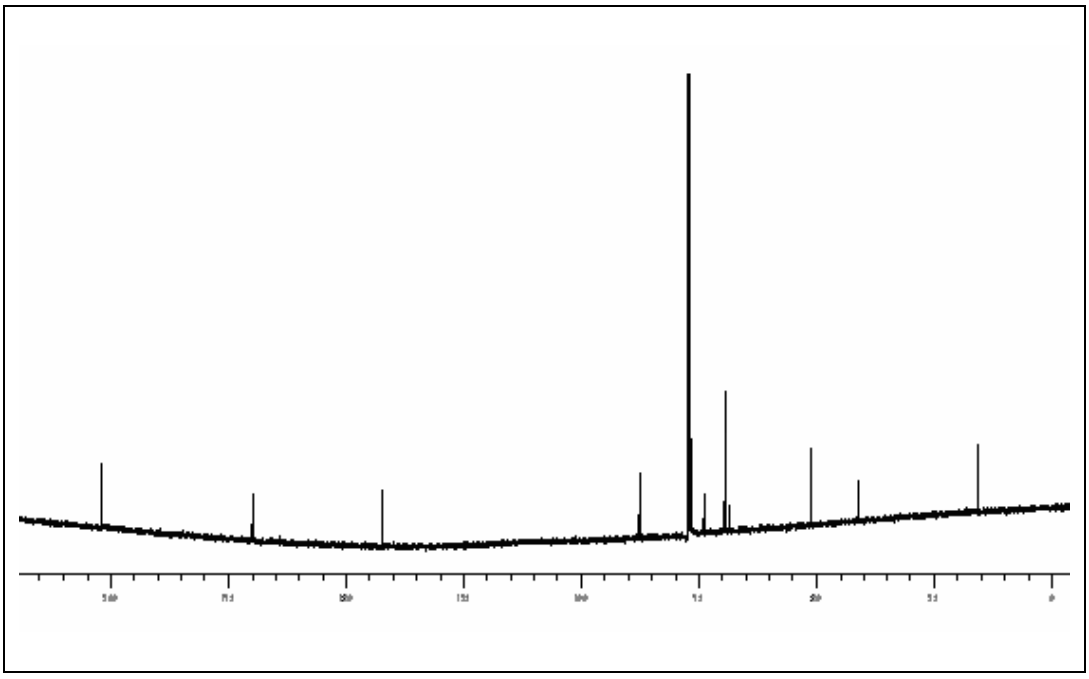


Figure A33. ^{13}C-NMR Spectrum of compound **39B**

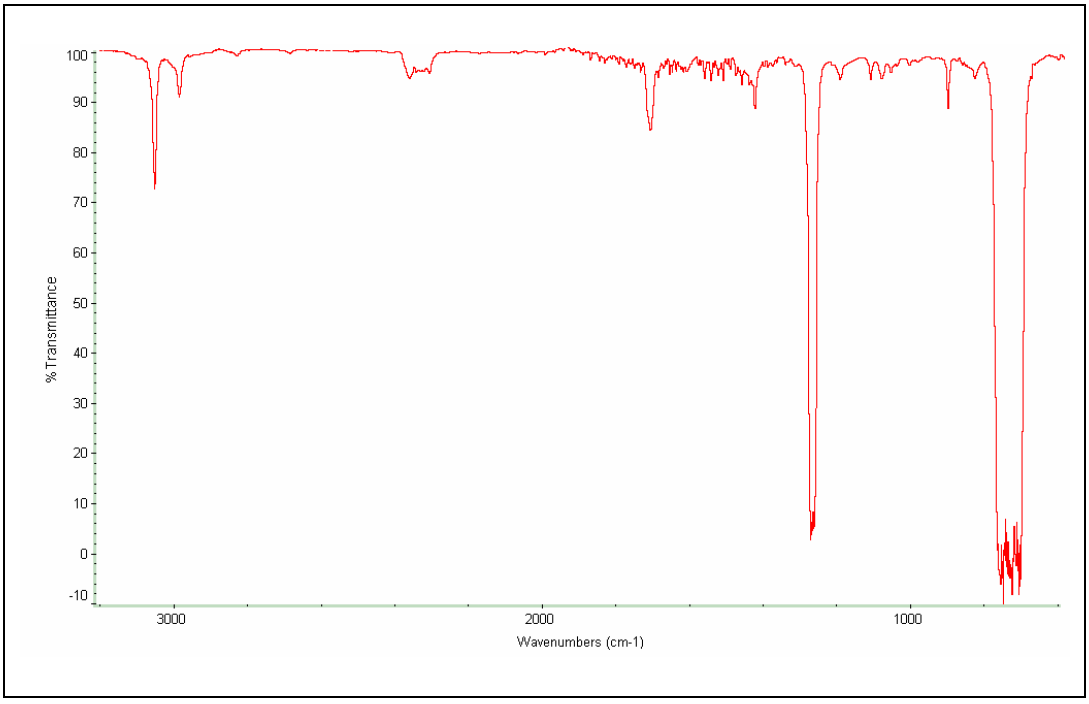


Figure A34. FT-IR Spectrum of compound **39B**

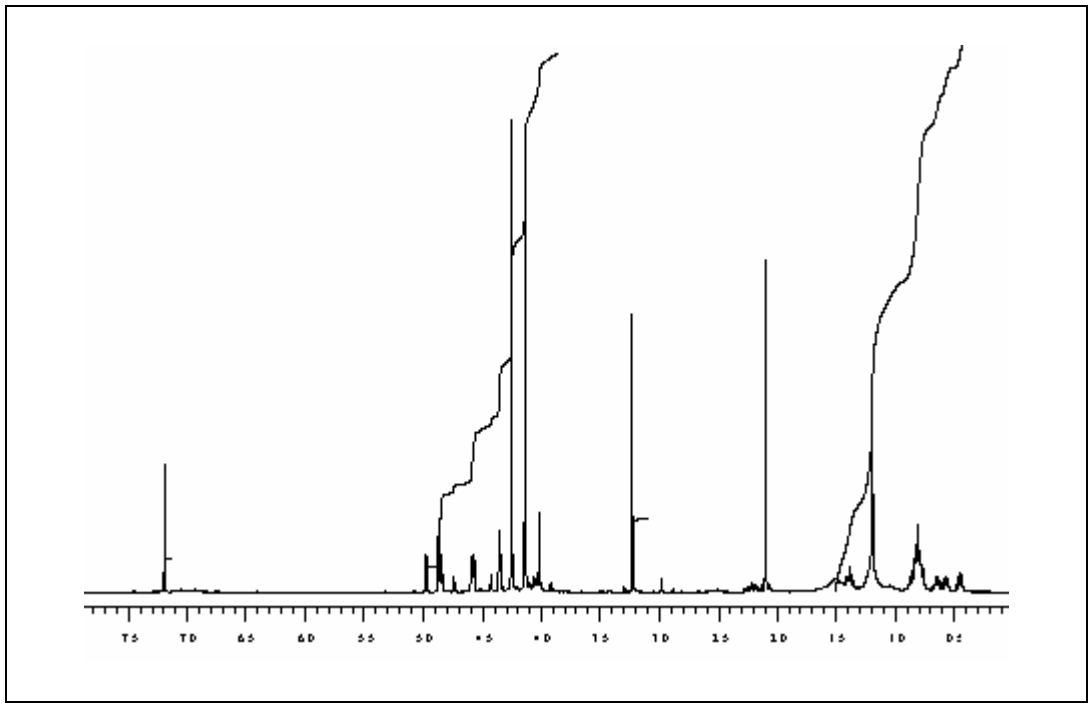


Figure A35. ^{1}H-NMR Spectrum of compound **40F**

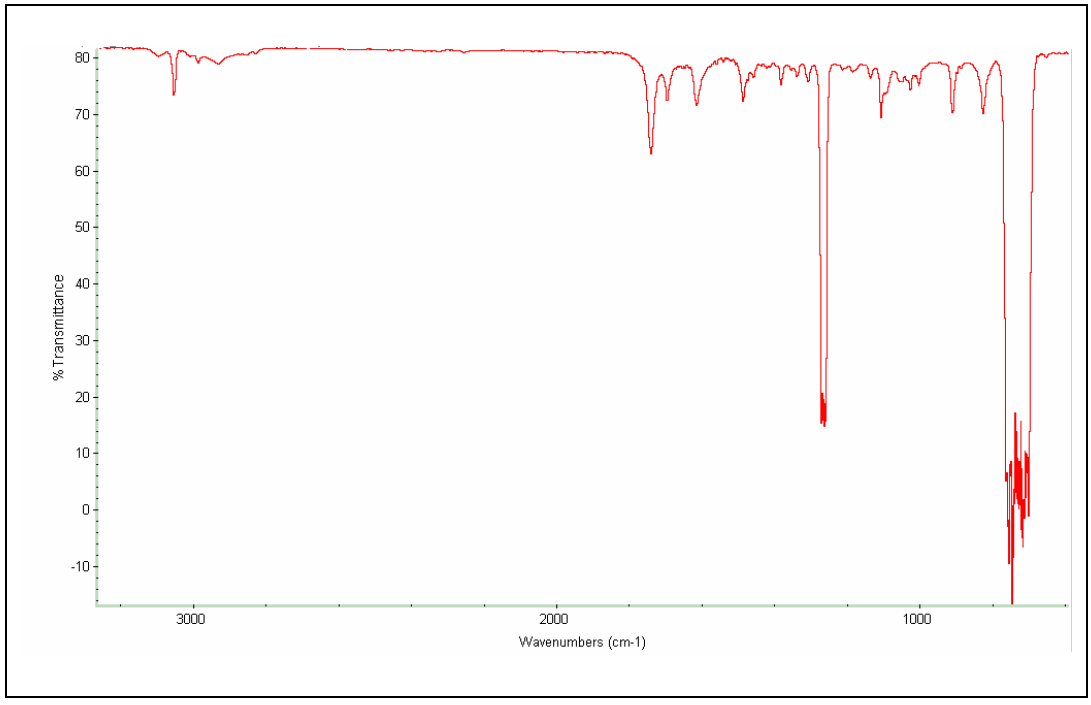


Figure A36. FT-IR Spectrum of compound **40F**

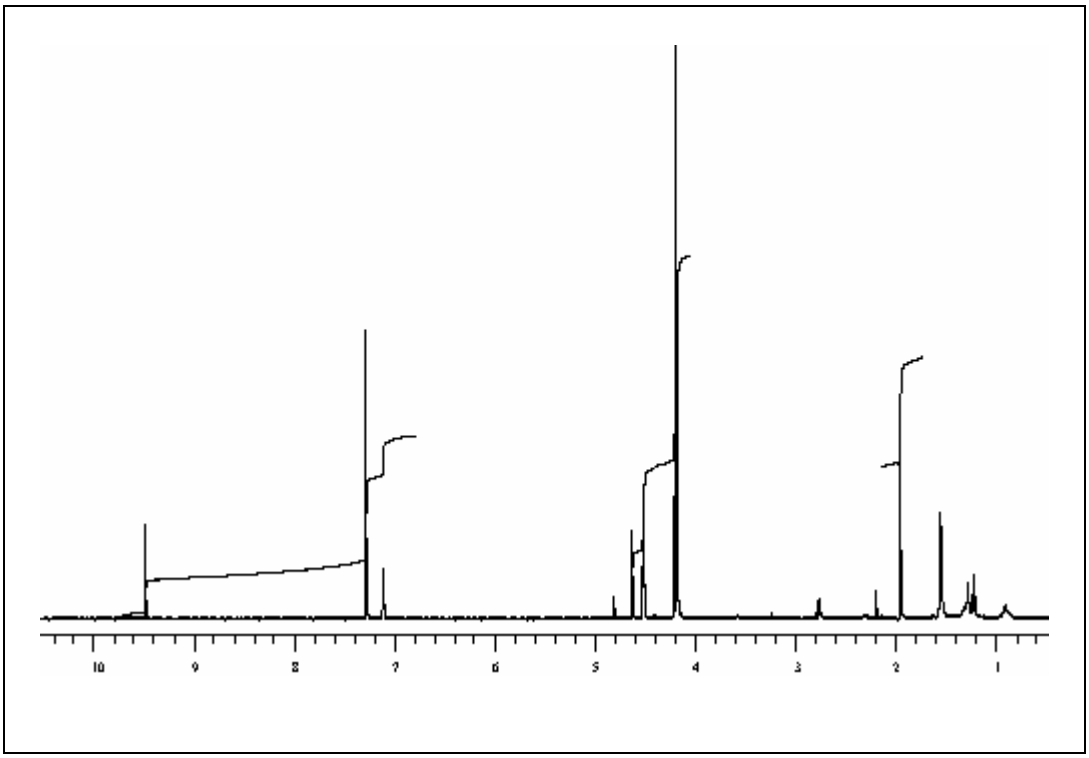


Figure A37. ^{1}H-NMR Spectrum of compound **41B**

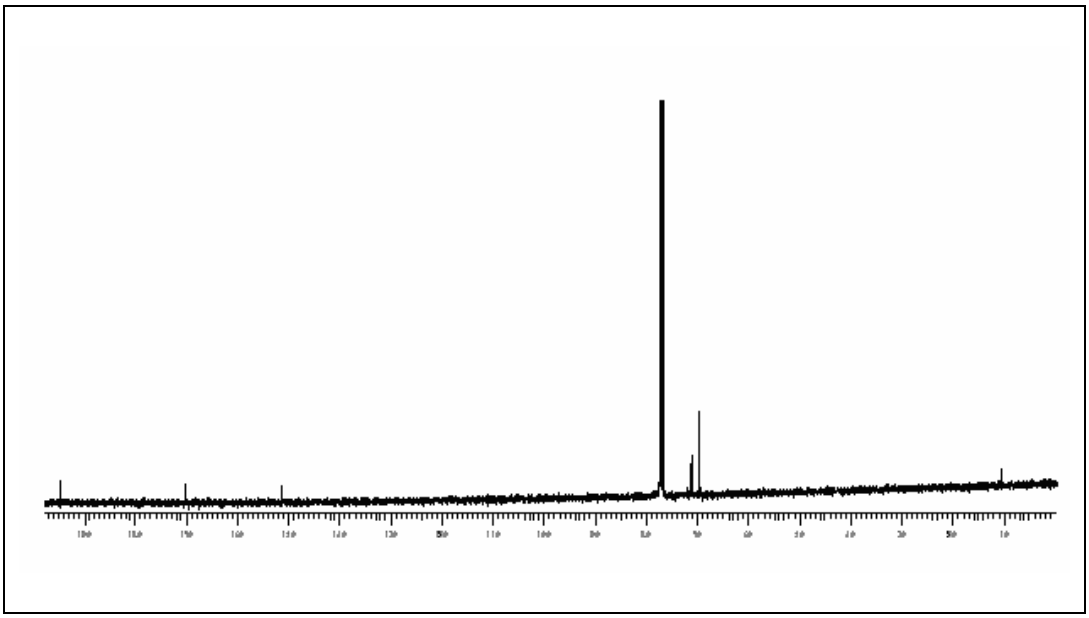


Figure A38. ^{13}C-NMR Spectrum of compound **41B**

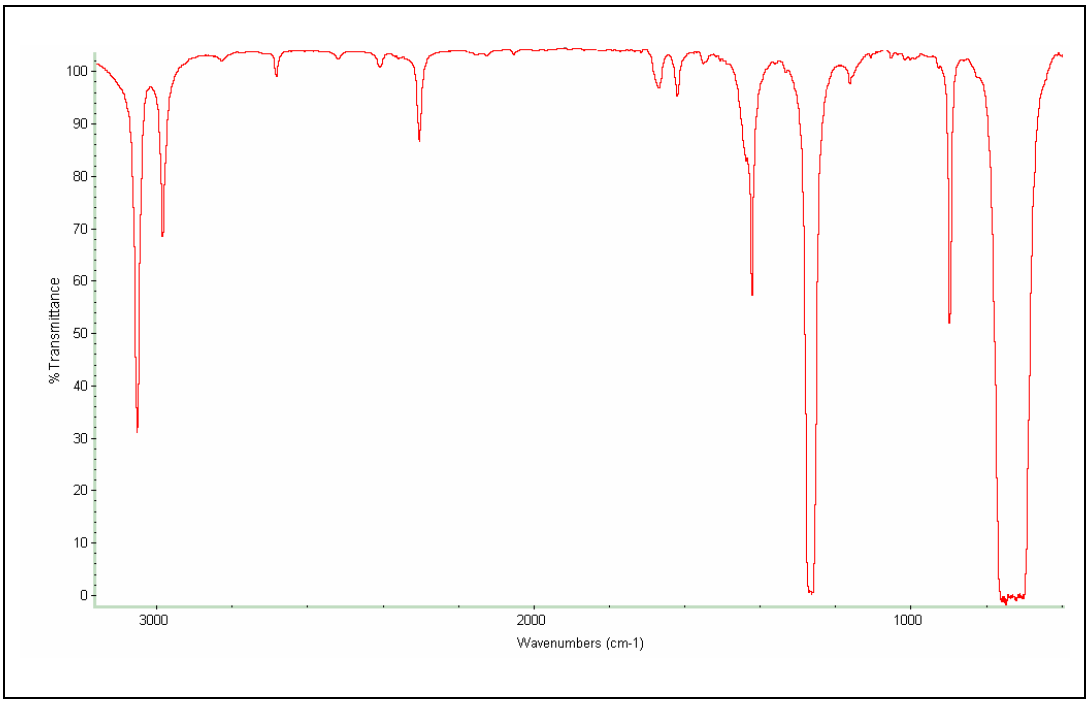


Figure A39. FT-IR Spectrum of compound **41B**