REINVESTIGATION OF THE SYNTHETIC AND MECHANISTIC ASPECTS OF MANGANESE(III) ACETATE MEDIATED REACTIONS

SYNTHESIS OF 1,2,4-TRISUBSTITUTED PYRROLES VIA AMINATION / ANNULATION REACTIONS OF CHLOROENONES WITH CHIRAL AMINE COMPOUNDS

A. ÇİĞDEM İĞDİR

AUGUST 2006

REINVESTIGATION OF THE SYNTHETIC AND MECHANISTIC ASPECTS OF MANGANESE(III) ACETATE MEDIATED REACTIONS

SYNTHESIS OF 1,2,4-TRISUBSTITUTED PYRROLES VIA AMINATION/ANNULATION REACTIONS OF CHLOROENONES WITH CHIRAL AMINE COMPOUNDS

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY
A. ÇİĞDEM İĞDİR

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

AUGUST 2006

Approval of the Graduate School of Natural and Applied Science

Prof. Dr. Canan Özgen
Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Doctor of Philosophy.

Prof. Dr. Hüseyin İşçi
Head of Department

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

Prof. Dr. Ayhan S. Demir
Supervisor

Examining Committee Members

Prof. Dr. Bekir Peynircioğlu (METU, CHEM)
Prof. Dr. Ayhan S. Demir (METU, CHEM)
Prof. Dr. Canan Ünaleroğlu (Hacettepe, CHEM)
Prof. Dr. Engin U. Akkaya (METU, CHEM)
Assoc. Prof. Dr. Nezire Saygılı (Hacettepe, Pharm)

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name: A. Çiğdem İğdir

Signature :

ABSTRACT

REINVESTIGATION OF THE SYNTHETIC AND MECHANISTIC ASPECTS OF MANGANESE(III) ACETATE MEDIATED REACTIONS

SYNTHESIS OF 1,2,4-TRISUBSTITUTED PYRROLES VIA AMINATION / ANNULATION REACTIONS OF CHLOROENONES WITH CHIRAL AMINE COMPOUNDS

A. Çiğdem İğdir
Ph.D., Department of Chemistry
Supervisor: Prof. Dr. Ayhan S. Demir

August 2006, 240 pages

The first part of the thesis presents the reinvestigation of the synthetic and mechanistic aspects of manganese (III) acetate mediated reactions. The main concern about this subject was to perform α'- acetoxylation reactions of enones and saturated systems in shorter reactions times and higher yields than the ones known in literature reproducibly. Although successful α'-acetoxylation of a great variety of substrates have been reported so far, there are some problems associated with the use of $Mn(OAc)_3$. Considering that there are not many simple methods for the direct acetoxylation of enones, optimization of $Mn(OAc)_3$ mediated α'-acetoxylation of enones and reaching its maximum potential has a great importance from a synthetic and economical point of view.

In the second part of the thesis, 1,2,4-trisubstituted pyrrole derivatives were the target molecules to be synthesized. Although there are quite a number of methods available for the synthesis of pyrroles, most of them involve multistep synthetic operations which lower the overall yield. There are limited reports on the preparation of the enantiomers of pyrrole derivatives having **1-N** directly linked to the stereogenic center. Thus, developing a new synthetic method for the efficient preparation of polysubstituted pyrroles without racemization still remains an attractive goal.

Keywords: manganese (III) acetate, α'-acetoxylation, enones, saturated systems, 1,2,4, trisubstituted pyrrole derivatives, chloroenones.

ÖZ

MANGAN(III) ASETAT EŞLİĞİNDEKİ REAKSİYONLARIN SENTETİK VE MEKANİSTİK AÇIDAN YENİDEN İNCELENMESİ

KLOROENONLAR İLE KİRAL AMİNLERİN AMİNASYON / ANULASYON REAKSİYONU SONUCU 1,2,4-TRİSÜBSTİTÜE PİROLLERİN SENTEZLENMESİ

A. Çiğdem İğdir
Doktora, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Ağustos 2006, 240 sayfa

Bu tezin birinci bölümü, mangan(III) asetat eşliğindeki reaksiyonların, sentetik ve mekanistik yönlerden yeniden incelenmesini kapsar. Çalışmadaki temel amaç, enonların ve doymuş sistemlerin α'-asetoksileme reaksiyonlarını, literatürde bilinen yöntemlerden daha kısa sürede ve daha yüksek verimlerle, tekrarlanabilir şekilde gerçekleştirmektir. Çok çeşitli substratların α'-asetoksileme reaksiyonları yayınlanmış olmasına rağmen, $Mn(OAc)_3$ kullanımıyla ilgili problemler hala mevcuttur. Enonların asetoksilenmesi için basit metotların bulunmamasını göz önünde bulundurulduğunda, $Mn(OAc)_3$ eşleniğindeki α'-asetoksileme reaksiyonlarının optimize edilerek sentetik ve ekonomik açıdan maksimum potansiyele ulaştırılması önemini korumaktadır.

Tezin ikinci bölümünde, 1,2,4-trisübstitüe pirol türevlerinin sentezlenmesi hedef olarak seçilmiştir. Pirol sentezi için oldukça fazla metot bulunmasına rağmen, bunların çoğu toplam verimin düşmesine neden olan birçok basamaktan oluşmaktadır. Pirolün azotunun stereo merkeze doğrudan bağlı olduğu kiral pirol türevlerinin sentezi için çok az metot mevcuttur. Kiral polisübstitüe pirol türevlerinin rasematlaşmadan sentezlenmesi için yeni bir sentez metodunun geliştirilmesi hala önemli bir hedef olarak bulunmaktadır.

Anahtar kelimeler: Mangan(III) asetat, α'-asetoksileme, enonlar, doymuş sistemler, 1,2,4-trisübstitüe pirol türevleri, kloroenonlar.

To my family

ACKNOWLEDGEMENT

I would like to express my sincere appreciation to my mentor Prof. Dr. Ayhan S. Demir for his continuing skillful guidance, support and encouragement throughout the course of this work with great patience. It has been a great honor for me to work with him for eleven years.

I would like to express my deep gratitude to Ömer Reis for his sincere friendship and for his cooperation in the first part of this thesis.

I would like to thank Batuhan Günay for his help in the second part of this thesis.

I wish to express my special thanks to Peruze Ayhan, Engin Turkut, Şehriban Barış and Gülizar Sağlam for their help in preparing this thesis in its final shape.

In addition, I would like to thank Zuhal Gerçek for her great friendship, encouragement and help whenever I need.

I would like to thank Fatoş Doğanel Polat for her kind help for our routine NMR analysis.

Finally, my special appreciation and great gratitude is devoted to my parents for their love, encouragement and patience.

TABLE OF CONTENTS

CHAPTER

CHAPTER 1

INTRODUCTION

1.1 Metal Oxidants in Organic Chemistry

The elaboration of redox methods for the generation of radicals by the help of transition metal salts and their oxides has become a powerful impulse for the development of free-radical chemistry in the past two decades. The reactions, mediated by Mn^{3+}, Co^{3+}, Cu^{2+}, Fe^{3+}, Ag^{2+}, Pb^{4+}, Ce^{4+}, Mn^{4+}, V^{5+}, Ag^{+}, Cu^{+}, Fe^{2+}, and Cr^{2+} are the most widely explored [1-5]. In comparison with traditional methods of radical generation [3, 5, 6], redox initiators demonstrate remarkable regioselectivity, especially efficient with polyfunctional organic compounds. Furthermore, new types of radicals, unachievable by traditional approaches, may be successfully generated. The main difference is the dual role that the metal oxidants play in the reactions: first, one-electron oxidation of a carbonyl compound, producing an educt radical and, second, the oxidative interaction with the intermediate adduct radical, formed by addition of educt radical to the substrate. This is why the synthetic result of metal-mediated reactions significantly differs from that of peroxide- or light-initiated processes. Correspondingly, the terminology used reflects the difference in the essence, i.e. “mediated” or “induced” for metal-participation reactions and “induced” for non-metal, traditional ones.

Among metal oxidants, a unique place is occupied by manganese (III) acetate, the history of which, as an effective mediator for the interaction of unsaturated systems with carbonyl compounds, originates from the Bush and Finkbeiner [7] and Heiba and Dessau [8] studies. In the past three decades, multidimensional extension of this reaction has taken place, providing a number of novel accesses to different classes of organic compounds, as well as bringing an improved understanding of the nature of the process [9].

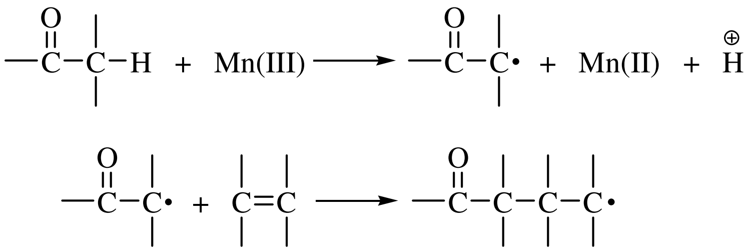
1.2 Reactions with Manganese (III) Acetate

1.2.1 General Knowledge on Manganese(III) Acetate

Oxidations with manganese (III) acetate can be broadly divided into two classes:

1. Direct inner- or outer-sphere one-electron oxidation of the substrate after formation of an inner- or outer-sphere substrate-Mn(III) complex. Often subsequent oxidation of an intermediate radical is product determining. Numerous examples can be found in oxidations of alcohols, amino- and thio-compounds, carboxylic acids, and certain aromatics.
2. Indirect oxidation of the substrate after formation of an intermediate adduct free radical from interaction of manganese (III) acetate and an enolizable compound and subsequent addition or substitution of this radical to the substrate. Most examples here refer to aromatic substitution and oxidative addition of enolizable compounds to unsaturated systems.

The essential sequence of addition reactions of compounds, mostly bearing a hydrogen atom alpha to a carbonyl group, to olefinic and aromatic unsaturated systems in the presence of manganese (III) acetate is given in Scheme 1.



Scheme 1

The fate of the primary adduct radical strongly depends on reaction conditions and the nature of the substrate. Substances that are less reactive to common oxidants are more interesting since here the unique properties of manganese (III) acetate as a free radical generator can be more fully exploited.

Mn(III) bears many similarities with respect to a given substrate class with other one-electron oxidants like Co(III), Ce(IV), and some two-electron oxidants like Tl(III) and Pb(IV). It is often observed that owing to its lower reactivity, higher selectivities can be obtained with manganese (III) acetate as compared with other oxidizing agents. Many of these reactions proceed according to the simplified scheme shown below (Scheme 2).

$$\text{Mn(III)} + \text{substrate} \longrightarrow \text{intermediate radical} + \text{Mn(II)}$$

$$\text{Mn(III)} + \text{intermediate R}\bullet \longrightarrow \text{product} + \text{Mn(II)}$$

Scheme 2

Complications may arise in the presence of water since water induces disproportionation of trivalent manganese into Mn(IV) and Mn(II) and alternative two-electron oxidations by Mn(IV) may take place [2].

1.3 Synthesis and Properties of Manganese (III) Acetate

Although a great amount of work has been done using manganese (III) acetate as an oxidizing agent, relatively little is known of the compound itself. Basically two forms are to be distinguished:

1. The hydrated form, which conforms with a molecular formula $Mn(OAc)_3.2H_2O$, color cinnamon brown, easy to prepare reproducibly.
2. The anhydrous form, color dark brown, difficult to prepare reproducibly, molecular formula variable.

Since many oxidations with manganese (III) species are known to be influenced by small amounts of water, the latter form is preferred by many workers, especially for kinetic work [2]. Moreover, small amounts of water cause disproportionation of Mn(III) acetate in glacial acetic acid. In acetic acid-water mixtures containing large amounts of water, manganese (III) acetate hydrolyzes slowly to mixtures $Mn(OH)_3$ and MnO_2. [10]. Both the hydrated and anhydrous forms have been made in various ways. Many workers introduced special modifications, which certainly have affected the chemical composition and reactivity of the anhydrous form. In Table 1, the most important routes to manganese (III) acetate are given.

Table 1. Routes to Manganese (III) Acetate

Reactants	**Oxidizing agent**	**Product**	**Reference**
$Mn(OAc)_2.4H_2O$, HOAc	$KMnO_4$	Dihydrate	11,12
$Mn(NO_3)_2.6H_2O$, Ac_2O	HNO_3	Anhydrous	13,14
$Mn(OAc)_2$, HOAc, Ac_2O	$KMnO_4$	Anhydrous	15-17
$Mn(OAc)_2$	O_3	Anhydrous	16
$Mn(OAc)_2.4\ H_2O$	Anodic oxidation	Dihydrate	18
$Mn(OAc)_2.4\ H_2O$	Cl_2	Dihydrate	19
$Mn(OAc)_2$, Et_3N, HOAc	O_2	Dihydrate	20
$Mn(OAc)_2$, ketone	O_2	Anhydrous	21

The solubility of manganese (III) acetate in acetic acid depends on the synthetic procedure used and the water content of the acetic acid. The compound should be dissolved by gentle heating. Table 2 gives some pertinent results.

Table 2. Solubility of Manganese (III) Acetate in Acetic Acid-Water Mixtures

Manganese (III) Acetate	**HOAc**	**g/L dissolved (^{o}C)**	**Reference**
Anhydrous	100%	10 (25)	15
Anhydrous	100%	3 (25)	16
Anhydrous	98%	150 (25)	16
Anhydrous	90%	Zero	16
Dihydrate	100%	160 (25)	16
Dihydrate	99%	Very low	16

Since the dihydrate dissolves poorly in water containing acetic acid, the anhydrous form is soluble in such systems only in a very limited range.

1.3.1 Anhydrous Manganese (III) Acetate

Hessel [16] has studied the synthesis and chemical constitution of manganese (III) acetate in detail. He has found that the chemical constitution of anhydrous manganese (III) acetate conforms to the experimental formula $Mn_3(CH_3COO)_8OH$ or $[Mn_3O(CH_3COO)_6.CH_3COO)^-$. When the compound is properly washed and recrystallized, this empirical formula is independent of the chemical route followed, viz., oxidation with $KMnO_4$, Pb(IV) acetate or O_3 of manganese (II) acetate or treating $Mn(NO_3)_2.6H_2O$ with acetic anhydride. In the literature treated by Hessel and also in later work, the anhydrous form is usually indicated as $Mn(OAc)_3$. This is certainly erroneous and mostly due to improper analytical procedures. A disadvantage of Hessel's purification method is that the anhydrous manganese (III) acetate is treated with water. The route developed by Vaerman [21], although claiming the production of $Mn(OAc)_3$, in fact produces acetic acid-formic acid mixed complexes of Mn(III) when acetone is used as a ketone. Formic acid formed by the autooxidation from the ketone, is bound by both Mn(II) and Mn(III) acetate. These mixed acetate-formate complexes are less soluble in the medium used than manganese (III) acetate proper.

The crystal structure of anhydrous manganese (III) acetate was studied by Hessel and Romers [16, 22]. These authors assume a linear polymer with empirical formula $[Mn_3O(OAc)_6.AcOH.OAc]_n$. In the monomer unit, three manganese are connected by three pairs of acetate bridges and form an equilateral triangle with an oxygen atom in its center. Acetic acid molecules and acetate bridges between the monomer units complete the distorted octahedral coordination of the manganese atoms.

In solution, a molecular weight of 640±75 is found [16] and as best representation the following structure is proposed:

$$[Mn_3O(OAc)_6.3AcOH]^+ [OAc]^-$$

Here the octahedral coordination of the manganese atoms in the trinuclear complex is completed by three acetic acid molecules.

Anhydrous manganese (III) acetate dissolves slowly in most solvents at room temperature. It can be dissolved in many solvents without appreciable reduction by gentle warming. Examples are ethanol, pyridine, and to some extent benzene and chloroform. It reacts at relatively low temperatures (70^oC) with enolizable solvents such as acetone or methyl ethyl ketone, but is less reactive with simple esters like ethyl acetate. It is hardly soluble in acetonitrile and petroleum ether and decomposes in water. It exchanges acetate for carboxylic acid when dissolved in such acids [2].

1.3.2 Manganese (III) Acetate Dihydrate

The preparation of manganese (III) acetate dihydrate was first described by Christensen in 1883 [11] and later elaborated in more detail [12]. It has been prepared by oxidation of manganese (II) acetate tetrahydrate by potassium permanganate [11, 12, 23], chlorine [19], and anodic oxidation [18].

The chemical constitution of the dihydrate comes close to $Mn(OAc)_3.2H_2O$ [16, 23] The solubility of the dihydrate in common solvents is similar to that of the anhydrous form.

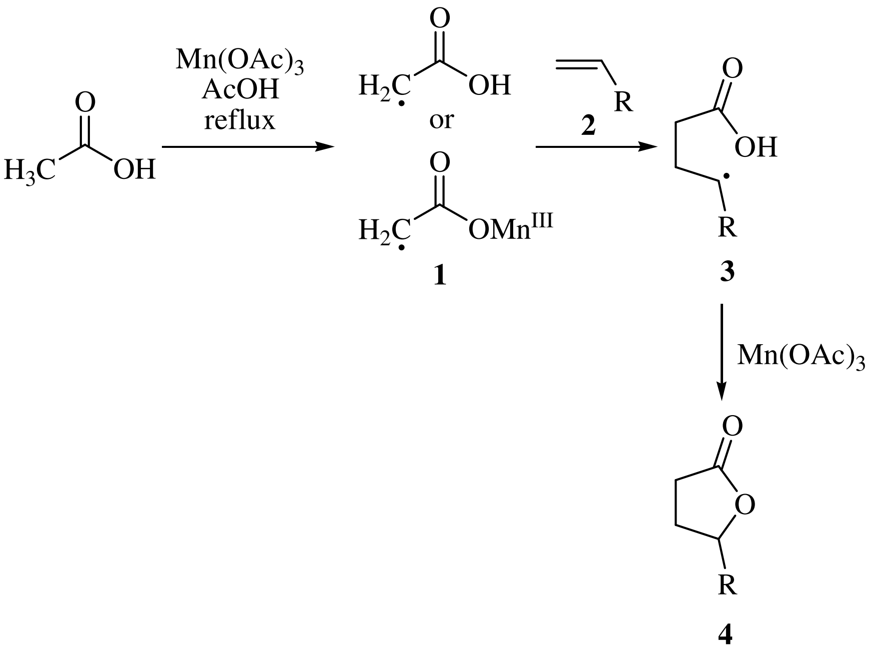
1.4 Oxidative Addition Reactions of Acids to Olefinic Unsaturated Systems

One of the more outstanding reactions initiated by manganese (III) acetate found by Bush and Finkbeiner [7] and Heiba and Dessau [8] is the oxidative addition of carboxylic acids to olefins leading to γ-butyrolactones. This reaction has been proven to be generally applicable, as exemplified by many workers, although lactones are not always major products.

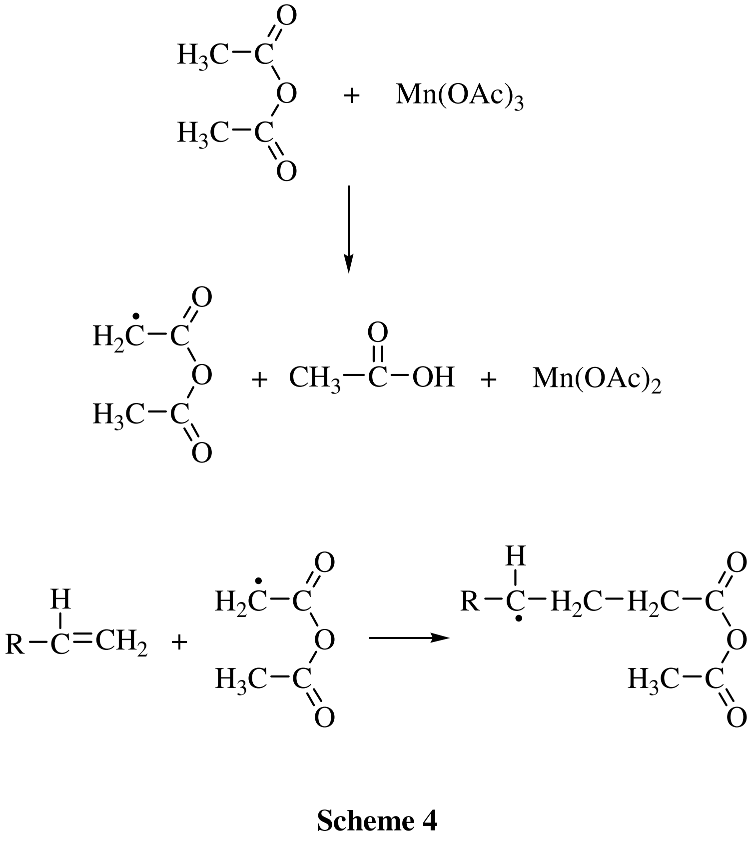
Heating the one-electron oxidant $Mn(OAc)_3$ in acetic acid at reflux (115°C) generates the carboxymethyl radical **1**. This adds to alkenes **2** to give a radical **3**, which is oxidized by a second equivalent of $Mn(OAc)_3$ to give a γ-lactone **4** (Scheme 3).

This sequence of steps generates a radical oxidatively from acetic acid, efficiently forms a carbon-carbon bond, and produces a synthetically useful γ-lactone by oxidation of the carbon-centered radical. Unfortunately, Mn(III)-based oxidative cyclization of unsaturated acids is not possible, since the optimal solvent for this reaction, acetic acid, will be oxidized preferentially [24].

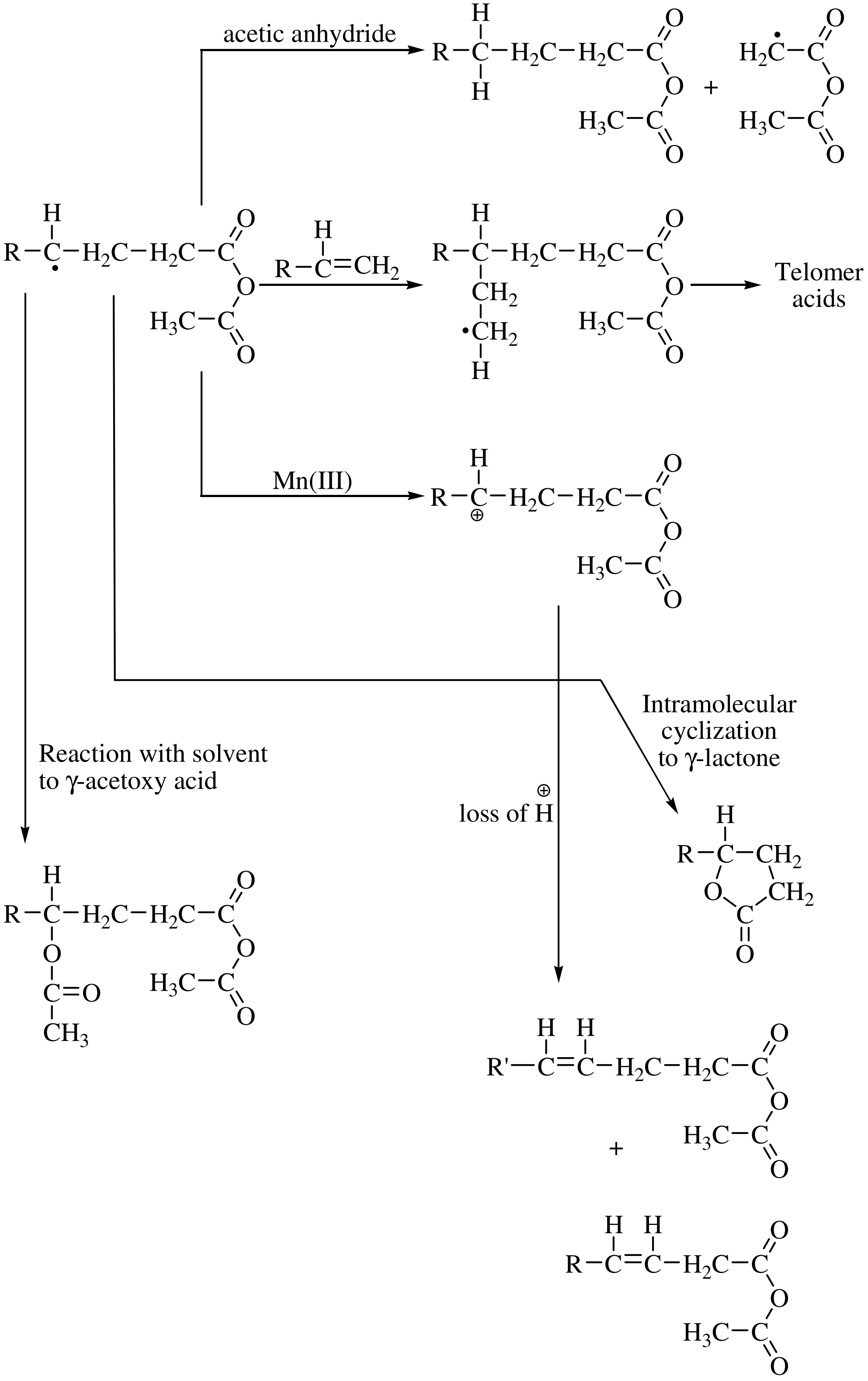
The course of the reaction and the formation of other major products depend largely on the nature of the substrate olefin, reacting acid, and on reaction conditions. There is now general agreement on the mechanism of this reaction together with its main side reactions. The major reactions involved in the Mn(III) acetate initiated addition of acetic acid to an α-olefin in acetic anhydride-acetic acid mixtures are given in Scheme 4 and 5 [25].



Scheme 3



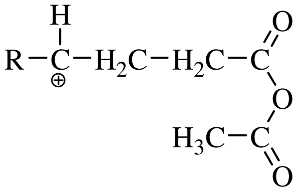
Scheme 4


acetic anhydride
$R-CH=CH_2$
Telomer acids
Mn(III)
Reaction with solvent to γ-acetoxy acid
loss of $H^{\oplus}$
Intramolecular cyclization to γ-lactone

Scheme 5

From these mechanistic schemes, the following basic requirements for oxidative addition can be drawn:

1. Direct generation of carboxyalkyl radicals. In the free acids this is largely limited to acetic, propionic and readily enolizable acids like cyanoacetic acid [26] the major competing reaction being formation of carboxyl radicals RCOO$^\cdot$. In the presence of excess anhydride, carboxyalkyl radical formation is favored and a larger variety of acids can be used [25, 27].
2. No oxidation of the primary formed carboxyalkyl radical. In the respect groups, increasing the electron density on carbon α to the carbonyl group increase the propensity of carboxyalkyl oxidation by Mn(III).
3. Rapid addition of the carboxyalkyl radical to the olefin. The reactivity of various olefins towards the carboxymethyl radical was studied by Heiba [26] and is found to be governed by the stability of the intermediate adduct radical and steric considerations. McQuillin and Wood [28] found evidence that some carboxyalkyl radicals may add reversibly to olefins. Slow addition may lead to competing reactions such as allylic hydrogen abstraction.
4. Rapid oxidation of the intermediate adduct radical to carbenium ion **5**. This is favored by a high Mn(III) concentration, high acid concentration, and high acetate concentration. The structure of the carbenium ion will determine whether lactonization or elimination of a proton to form a new unsaturated carboxylic acid will predominate. Moreover, with excess anhydride, formation of γ-acetoxyacid will compete strongly with ring-closure of the anhydride to a γ-lactone.

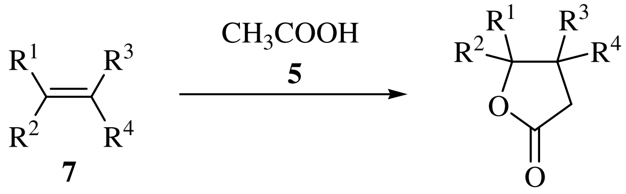


$R-\overset{H}{\underset{\oplus}{C}}-H_2C-H_2C-C(=O)-O-C(=O)-CH_3$

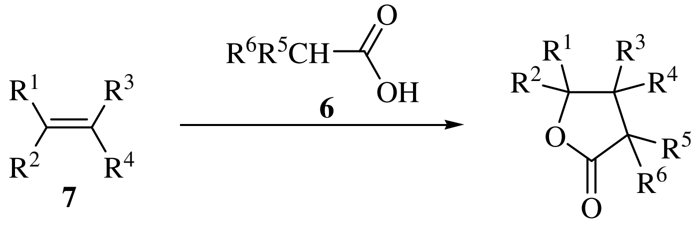
5

> Also this step is sensitive to small amounts of Cu present, [29, 30] which leads to mixtures of γ- and δ-unsaturated carboxylic acids. Low manganese (III) concentrations may lead to a chain transfer reaction of the intermediate adduct radical with the solvent [25, 31] resulting in saturated carboxylic acids. When under these conditions high olefin concentrations are applied, telomer and polymer products are formed [25].

Since so many parameters control effective lactone production, a large variety of reaction conditions is known in the literature. Three main media are put into practice: acetic acid-potassium acetate or sodium acetate mixtures [8]; acetic anhydride-acetic acid mixtures [7]; acetic anhydride-acetic acid-potassium acetate or sodium acetate mixtures [32]. Each may be used in its own right, depending largely on structural constraints of the substrate olefin. Oxidative addition of acetic acid **5** and other acids (notably propionic and cyanoacetic) **6** to simple olefins **7** is given in Scheme 6 and 7 respectively.



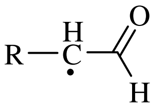
Scheme 6



Scheme 7

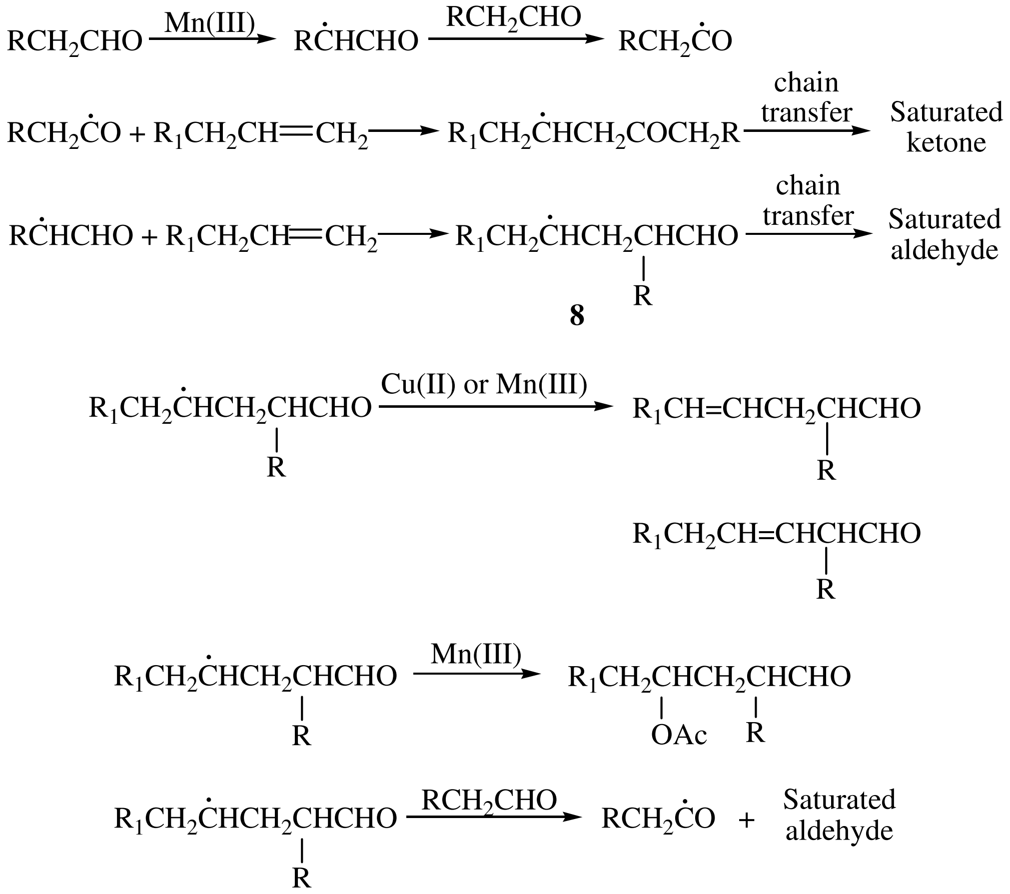
1.5 Mn(III) Acetate-Initiated Addition of Aldehydes to Olefinic Unsaturated Systems

Most free radical additions of aldehydes to olefins yield ketones as main products. Thus the peroxide, γ-radiation, and oxygen initiated addition of aldehydes to 1-alkenes provide a convenient method for the synthesis of ketones. The acyl radical R–Ç=O is believed to be formed as an intermediate in these systems. In the presence of manganese (III) acetate, a free radical addition of aldehydes to olefins is also observed. However, depending on reaction conditions, both the expected ketones and rather unexpected aldehydes can be formed. The primary intermediate from the interaction of manganese (III) acetate and the aldehyde is the formylalkyl radical **7** [33].



7

Formation of acyl radicals R–Ç=O by chain transfer can be largely suppressed by working at high manganese (III) acetate concentrations and by addition of small amounts of Cu(II) acetate [34]. In the latter case, unsaturated aldehydes are formed. In the absence of polar solvents like acetic acid, manganese (III) acetate concentration is low and ketones are formed in high yields [35, 36]. The most important reaction sequences are given in Scheme 8. Since the formation of ketones is largely suppressed by addition of Cu(II) and at high Mn(III) concentrations, acyl radicals are most probably mainly formed via chain transfer of intermediate adduct radical (compound **8** in Scheme 8) with aldehyde rather than chain transfer of formylalkyl radicals with aldehyde.



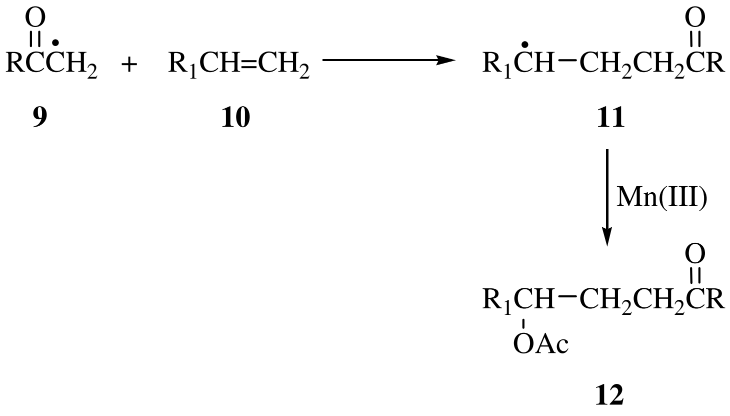
Scheme 8

1.6 Mn(III) Acetate-Initiated Addition of Ketones to Olefinic Unsaturated Systems

Organic peroxides and γ-radiation have been used to initiate the radical addition of ketones to olefins, although surprisingly little on such reactions is reported in the literature. The one-electron oxidation of enolizable ketones by manganese (III) acetate has offered a new and convenient method for the generation of α-oxo alkyl radicals [37, 38] useful in a number of synthetic routes to saturated and unsaturated ketones, substituted dihydrofurans, tetralones, and diketones. Although yields in most cases are only moderate, this reaction may still be the method of choice when the substrate olefins and ketones are readily available. Reactions have been performed with a great variety of ketones and olefins. The reactions are generally accelerated by addition of acetic acid, although product patterns may change. In the presence of Cu(II) acetate, unsaturated adducts are formed.

1.6.1 Formation of Higher Saturated, Unsaturated and Acetoxyketones

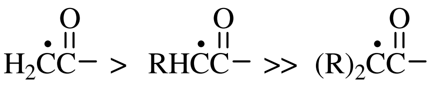
In the presence of manganese (III) acetate, simple ketones **9** like acetone, methylethylketone, cyclic ketones, α- and β-diketones like pyruvic ester, and acetylacetone can be added readily to a variety of olefins **10** like α-olefins, styrene, isobutylene, hydroxy-functional olefins, and 1-alkynes. In the absence of added acetic acid, the reaction is relatively slow and yields mainly saturated adducts **11**. When acetic acid is added in low amounts and the reaction is performed at higher temperatures, much of the manganese (III) acetate goes in solution and oxidizes the ketone-adduct radical. Thus under such conditions, large amounts of acetoxyketones **12** will be formed together with unsaturated ketones (Scheme 9).



Scheme 9

When saturated adducts are the products of choice and a fast reaction is wanted, such reactions can best be performed by slowly adding manganese (III) acetate, to obviate oxidation products, and olefin, to suppress telomerization to the ketone.

The effect of the structure of α-oxo-alkyl-radical on rate of addition to unsaturated systems was clearly demonstrated by Vinogradov [39], primary radicals **13** adding more readily on alkenes and alkynes than secondary **14** and tertiary radicals **15**.

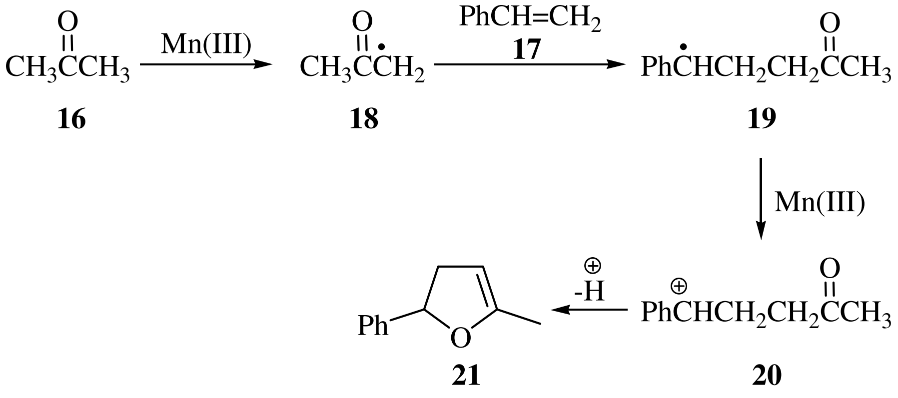


$$H_2\dot{C}\overset{\overset{O}{\|}}{C}- \;>\; RH\dot{C}\overset{\overset{O}{\|}}{C}- \;\gg\; (R)_2\dot{C}\overset{\overset{O}{\|}}{C}-$$

13 **14** **15**

1.6.2 Formation of Dihydrofurans

In the presence of manganese (III) acetate, dihydrofurans may be formed in high yield from readily enolizable ketones **16** and olefins **17**. The reaction proceeds via addition of α-oxoalkyl radicals **18** to the olefin, oxidation of the intermediate adduct radical **19** to a carbenium ion **20**, and subsequent cyclization of this carbenium ion to the dihydrofuran **21** (Scheme 10).



Scheme 10

From this scheme, it can be rationalized that higher yields can be obtained with:

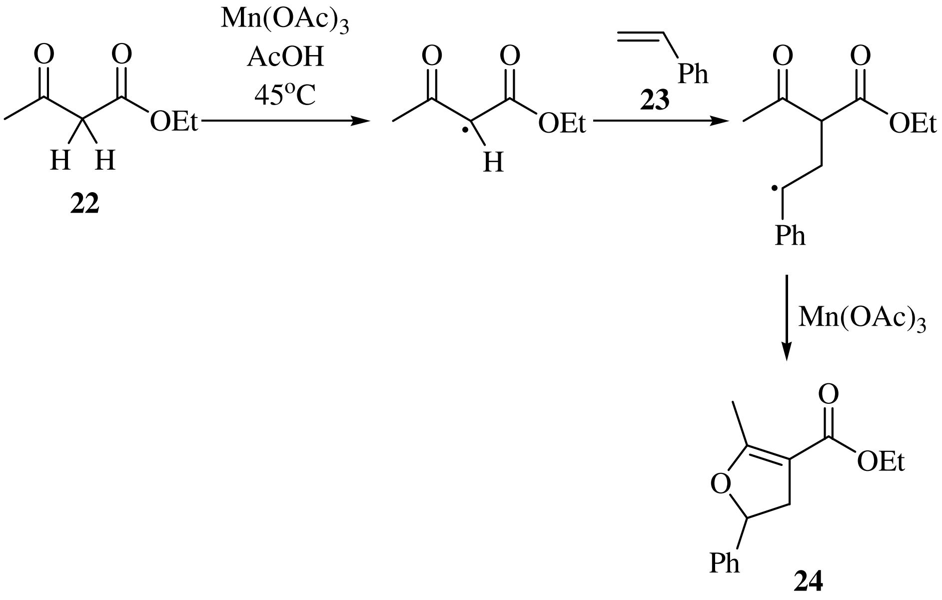
1. Readily oxidizable ketones like β-diketones.
2. Olefins with a vinylidene structure like α-methylstyrene and isobutylene.

Side products to be expected from this reaction are:

1. Saturated ketones, obtained by chain transfer from the intermediate adduct radical when this is less readily oxidized.
2. Unsaturated ketones and γ-acetoxy ketones, obtained from the intermediate carbenium ion when ring closure competes with H^+ elimination and acetoxylation by the solvent.

The reaction products with terminal olefins in all cases have consisted of only one isomer. The corresponding reactions of Tl(III) and Pb(IV) acetate have reportedly led to other isomers or mixtures of isomers [24] and probably via ionic mechanisms.

Heiba and Dessau have reported in 1974 that β-keto esters and related dicarbonyl compounds are oxidized to radicals at 25-70°C in acetic acid [24]. The application of Mn(III) to oxidative free-radical cyclizations was investigated initially by Corey, Fristad, and Snider. Corey and Kang have reported the oxidative cyclization of unsaturated β-keto acids in 1984 [40]. In 1985, Snider [41] has described the oxidative cyclization of unsaturated β-keto esters [42] and Fristad has surveyed the cyclization of unsaturated malonic and cyanoacetic acids [43]. For instance, oxidation of ethyl acetoacetate **22** in the presence of styrene **23** affords a dihydrofuran **24** which was reported by Heiba *et.al.* (Scheme 11) [24].



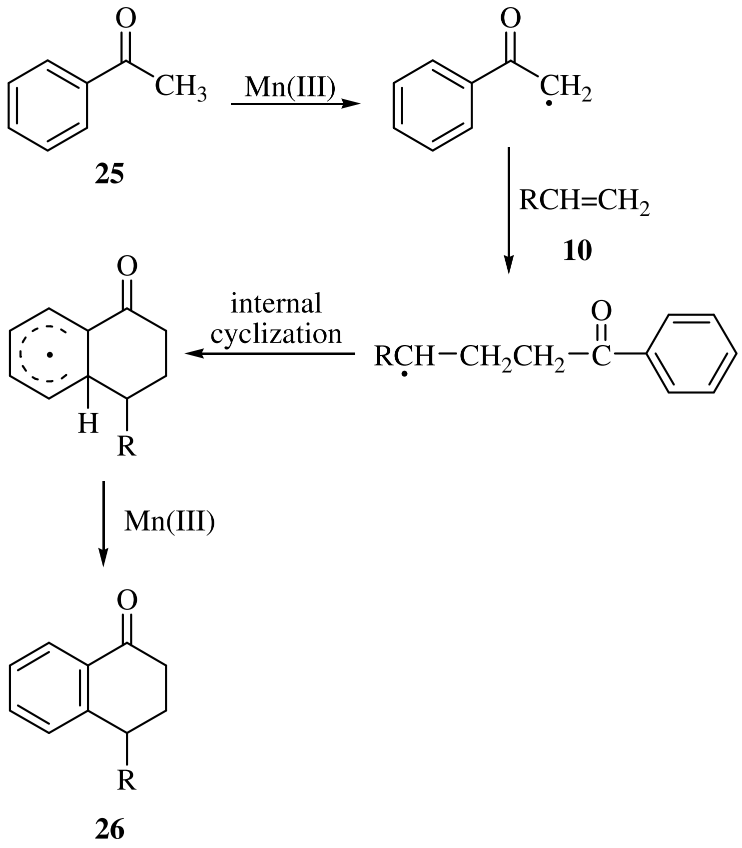
Scheme 11

1.6.3 Formation of Tetralones

When an aromatic ketone such as acetophenone **25** is reacted with an olefin **10** in the presence of manganese (III) acetate, α-tetralones **26** can be formed according to Scheme 12 [44].

It follows from this reaction scheme that side products to be expected are:

1. Saturated linear ketones derived from chain transfer of the intermediate adduct radical; these can be suppressed by working at low acetophenone concentrations.
2. Unsaturated linear ketones and linear keto acetates from oxidation of the intermediate adduct radical.

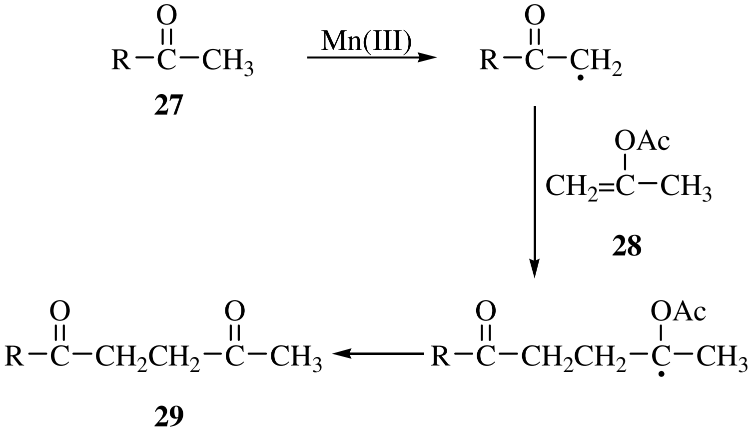


Scheme 12

1.6.4 Formation of 1,4-Diketones

Enol acetates as unsaturated substrates have been used in reactions with aliphatic [45] and terpenoic [46] ketones, resulting in access to 1,4-diketones, key intermediates in cyclopentenone synthesis.

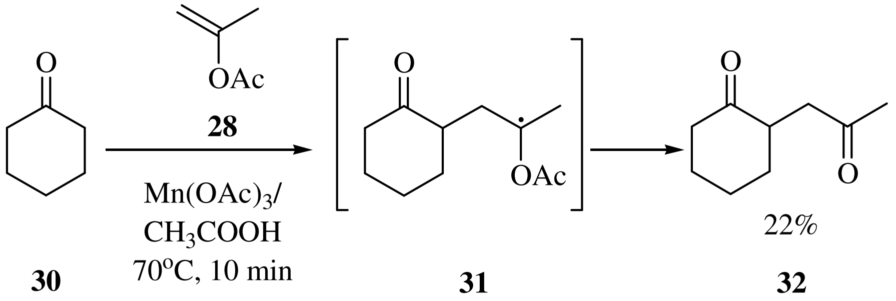
When a ketone **27** is reacted with isopropenyl acetate **28** in the presence of manganese (III) acetate, the predominant nonpolymeric reaction product formed is a 1,4- diketone **29** according to Scheme 13 [45].



Scheme 13

Although yields are only moderate, reportedly due to polymerization of isopropenylacetate, this route offers a single step preparation of 1,4-diketones from readily available reagents, and is much more selective than peroxide initiated reactions [46].

The addition of cyclohexanone **30** to isopropenyl acetate **28** results initially in adduct radical –an intermediate, formed by the addition of educt radical across the multiple bond of a substrate- **31**, which stabilizes by β-elimination of an acetyl group forming 1,4-diketone **32** (Scheme 14) [9].

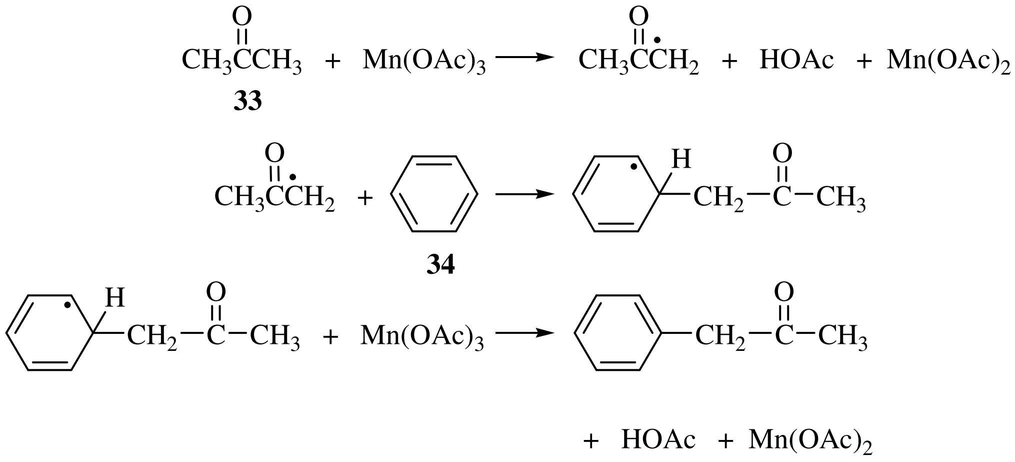


Scheme 14

1.7 Aromatic Substitution Reactions

A number of methods have been reported for aromatic substitution reactions by radicals generated by manganese (III) acetate. Yields of these oxidative reactions largely depend on reaction conditions, structure of intermediate radicals, substrate, and the presence or absence of polar solvents like acetic acid. In many examples, yields of pure compounds are differently extracted from the original work. However, even when the yields are low, the products are obtained in one single step from simple compounds whereas alternative synthetic methods for many examples require multistep procedures.

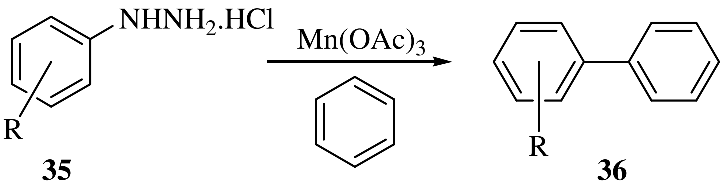
The substitution reactions of this type require two equivalents of manganese (III) acetate as exemplified by the following reaction scheme for the substitution of acetone **33** to benzene **34** (Scheme 15).



Scheme 15

1.8 $Mn(OAc)_3$ Mediated Biaryl Coupling Reactions

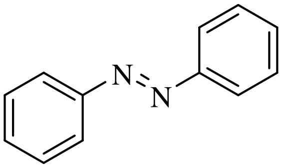
C-C bond-forming reactions leading to biaryls are very important because this approach is the key step in the synthesis of many natural and unnatural biaryls. There are various biaryl coupling methods, and the applications of these methods are reviewed comprehensively in the literature. A common method for the synthesis of simple unsymmetrical biaryls is the generation of aryl radicals in the presence of aromatic solvents. Although the product range of this approach is somewhat limited, it provides an easy access to a variety of unsymmetrical biaryls. Demir *et.al.* have recently shown that arylhydrazines **35** can be efficiently oxidized by manganese(III) acetate to produce aryl radicals that afford biaryls **36** in benzene with very good yields as shown in Scheme 16 [47].



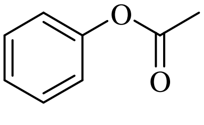
35 **36**

Scheme 16

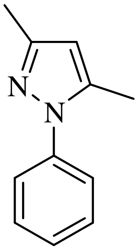
Manganese(III) acetate bears many similarities, with respect to a given substrate class, with other one-electron oxidants like Co(III) and Ce(IV), and some two-electron oxidants like Pb(IV). For comparison, phenylhydrazine was treated with cerium(II) ammonium nitrate (CAN), Co(III) acetylacetonate and Pb(IV) acetate under similar conditions in Demir *et.al*'s study. Reaction of phenylhydrazine with Pb(IV) acetate gave two major products: biphenyl **36** and azobenzene **37** (5:1) and a trace amount of phenyl acetate **38**. The reaction of phenylhydrazine with Co(III) acetylacetonate gave two major products: biphenyl **36** and pyrazole derivative **39** (3:1 respectively). Treatment of phenylhydrazine with CAN furnished a mixture of products. The major fractions were identified as biphenyl **36** and azobenzene **37** (3:2 respectively). In addition to these compounds, complex mixtures of terphenyl isomers and azobenzene derivatives of biphenyls were detected by GC-MS. The isolated yields of products were very low and in all cases there were unidentifiable products.



37



38



39

Mn(III) acetate is more selective and effective than Co(III), Ce(IV) and Pb(IV). Selectivities can be attributed to the slow formation of radicals with Mn(III) acetate. Co(III), Ce(IV) and Pb(IV) compounds are more powerful oxidants, and therefore less selective.

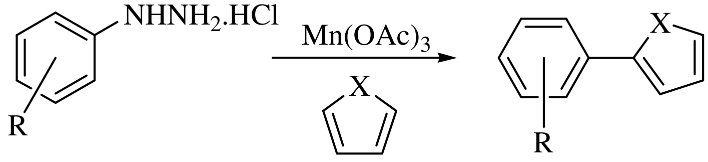
In the oxidation of monoarylhydrazines with several oxidizing agents, the observed products have been explained in terms of a generated phenyldiimide and its subsequent breakdown. A similar mechanism that is proposed for Pb(IV) acetate and Cu(II) is probably operating during the reaction, which is outlined in Scheme 17 [41, 48].

$$\begin{aligned}
\mathrm{ArNHNH_2} + \mathrm{Mn(III)} &\longrightarrow (\mathrm{ArNHNH_2})^{\bullet\oplus} + \mathrm{Mn(II)} \\
(\mathrm{ArNHNH_2})^{\bullet\oplus} &\longrightarrow (\mathrm{ArNHNH})^{\bullet} + \mathrm{H}^{\oplus} \\
(\mathrm{ArNHNH})^{\bullet} + \mathrm{Mn(III)} &\longrightarrow (\mathrm{ArNHNH})^{\oplus} + \mathrm{Mn(II)} \\
(\mathrm{ArNHNH})^{\oplus} &\longrightarrow \mathrm{ArN{=}NH} + \mathrm{H}^{\oplus} \\
\mathrm{ArN{=}NH} &\longrightarrow \mathrm{Ar}^{\bullet} + \mathrm{N_2} + \mathrm{H}^{\oplus}
\end{aligned}$$

Scheme 17

This study has shown that it is possible to oxidize arylhydrazines with Mn(III) acetate in benzene to form the corresponding phenyl-substituted benzene derivatives in good yield; access to biaryls works selectively, and coupling occurs where hydrazine departs. Using substituted benzenes as solvents furnishes isomeric mixtures of the corresponding biaryls.

Although the reaction is very efficient in benzene, Demir *et.al.* have also shown that it generally produces the corresponding heterobiaryls from arylhydrazines **35** in furan **40** and thiophene **41** with moderate to good yields (Scheme 18) [49].

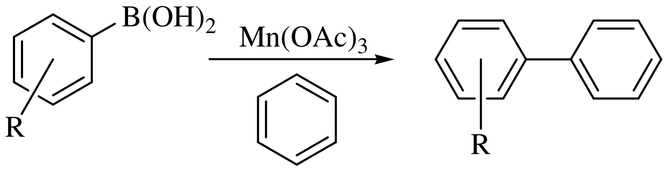


35

40 X=O
41 X=S

Scheme 18

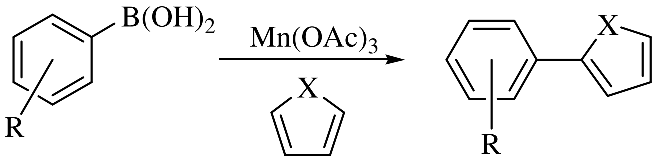
This drawback of arylhydrazines prompted the same group to find a more suitable substrate as the source of aryl radicals. A suitable candidate for this reaction should be much more reactive than arylhydrazinium salts under the reaction conditions yet stable enough to handle easily and not prone to side reactions. It is known that arylboronic acids decompose to aryl radicals in the presence of some oxidants [50]. Arylboronic acids are widely used as the organometallic counterpart in the Suzuki reaction. They are stable under atmospheric and aqueous conditions such that Suzuki coupling can be carried out with aqueous organic solvents. Therefore, Demir *et.al.* decided to investigate the oxidation of arylboronic acids with manganese(III) acetate in aromatic solvents and reported the synthesis of a variety of unsymmetrical biaryls **36** with in situ generated aryl radicals from arylboronic acids **42** with manganese (III) acetate as shown in Scheme 19 [51].



42 **36**

Scheme 19

The yields were generally better than those from similar reactions reported previously. This had shown that arylboronic acids are suitable substrates for the generation of aryl radicals. This study has shown that a variety of radicals can be generated from the corresponding arylboronic acids. In the presence of organic solvents, these radicals afford the monosubstituted biaryls with yields generally higher than those from similar previously reported reactions. Reactions in benzene gave higher yields than those in furan **43** or thiophene **44**; the former was better in terms of yield (Scheme 20).



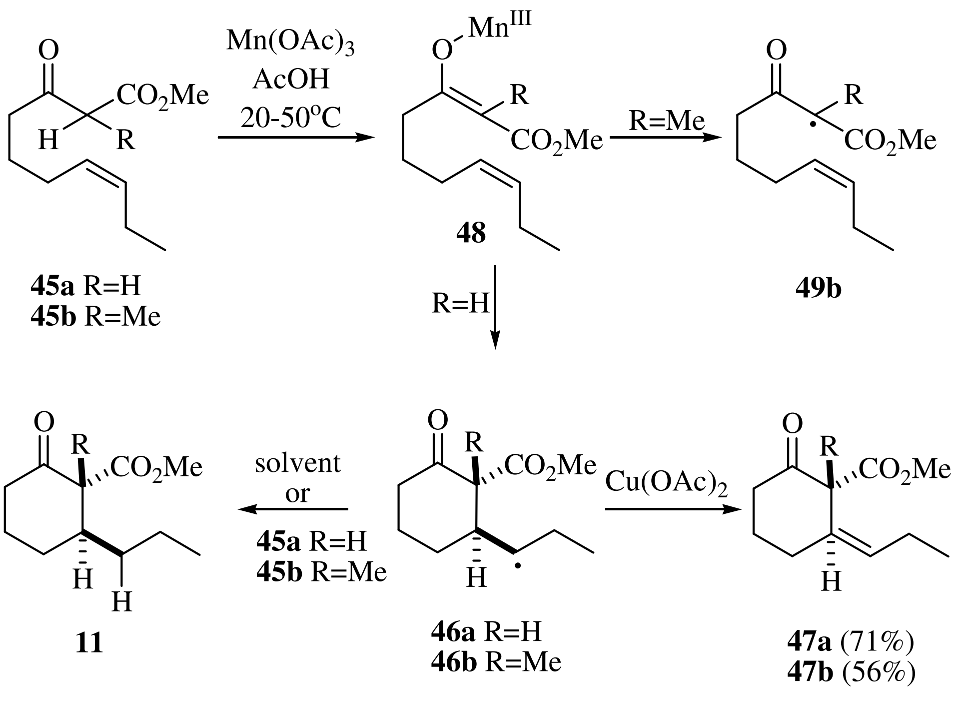
42

43 X = O
44 X = S

Scheme 20

1.9 Tandem Oxidative Cyclizations with Various Mn(III) Reagents and $Cu(OAc)_2$

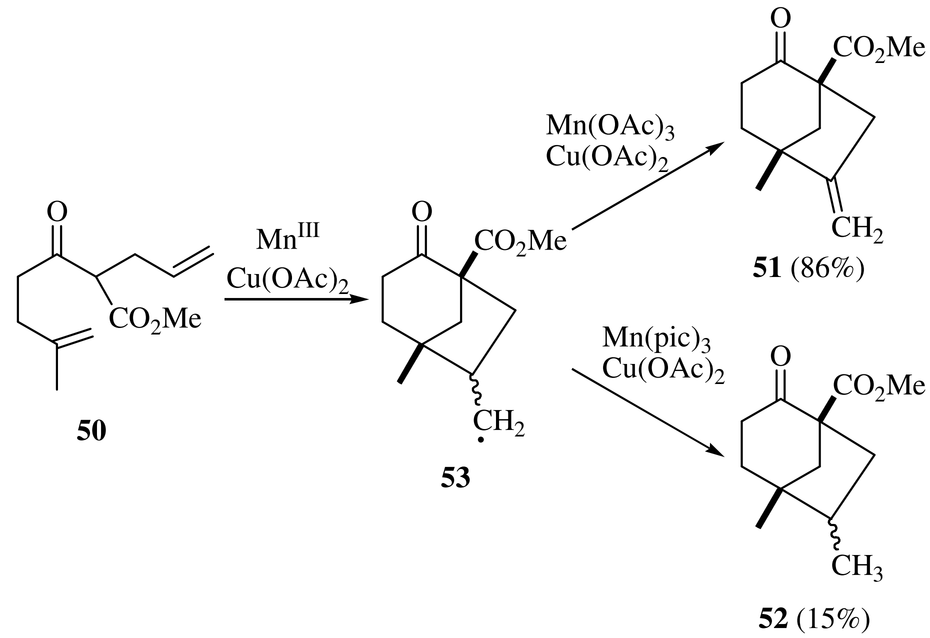
The Mn(III)-based oxidative free-radical cyclization of **45a** and **45b** serves to introduce the factors that need to be understood to use these reactions in synthesis. Oxidative cyclization of β-keto ester **45a** with $Mn(OAc)_3$ affords a complex mixture of products. Primary and secondary radicals, such as **46a** and **46b**, are not oxidized by Mn(III). Heiba and Dessau have found that $Cu(OAc)_2$ oxidizes secondary radicals 350 times faster that $Mn(OAc)_3$ does and that the two reagents can be used together [38, 44]. Oxidative cyclization of **45a** with 2 equiv of $Mn(OAc)_3$ and 0.1-1 equiv of $Cu(OAc)_2$ in acetic acid affords 71% of **47a**. $Cu(OAc)_2$ reacts with radical **46a** to give a Cu(III) intermediate that undergoes oxidative elimination to give **47a** [52, 53]. A similar oxidative cyclization of **45b** affords 56% of **47b** as the major product (Scheme 21).



Scheme 21

The first step in the reaction is the loss of a proton to give the Mn(III) enolate **48**. The next step of the reaction could involve cyclization of the unsaturated Mn(III) enolate **48** to give cyclic radical **46a**. This is the operative pathway for R=H. Alternatively, loss of Mn(II) could give the Mn-free free radical **49b**. This is the operative pathway for R=Me. Cyclization of **49b** from the conformation shown gives radical **46b** stereo- and regiospecifically. Finally, Cu(II) oxidation of **46a** and **46b** gives **47a** and **47b** regio- and stereospecifically.

Snider *et.al.* have examined the tandem oxidative cyclization of **50** with various Mn(III) reagents and $Cu(OAc)_2$ [54]. Oxidative cyclization with $Mn(OAc)_3$ and $Cu(OAc)_2$ affords 86% of **51** and 0% of **52**, while use of $Mn(pic)_3$ and $Cu(OAc)_2$ leads to 0% of **51** and 15% of **52**. A series of control experiments established that the most likely explanation for this observation is that $Mn(pic)_2$, but not $Mn(OAc)_2$, reacts with the bicyclic radical **53** more rapidly than $Cu(OAc)_2$ does. This illustrates a general feature of oxidative radical cyclizations. A one-electron oxidant, e.g., Mn(III), Cu(II), Ce(IV), etc., is needed for both the generation of the acyclic radical and oxidation of the cyclic radical. Furthermore, the lower valent metal salt produced in these oxidations must not react rapidly with any of the radical intermediates. $Mn(pic)_3$ does not meet these requirements, since $Mn(pic)_2$ reacts with the cyclic radical more rapidly than $Cu(OAc)_2$ does; the alkyl $Mn(pic)_2$ intermediate produced in this reaction apparently abstracts a hydrogen giving reduced products such as **52** (Scheme 22).

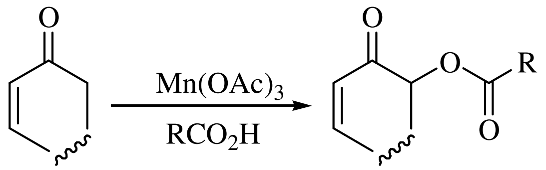


Scheme 22

Acetylacetonatomanganese (III) (Mn(acac)$_3$) and MnF$_3$ are other readily available Mn(III) reagents. Mn(acac)$_3$ has been extensively used for oxidative coupling of phenols [55]. While both are suitable for oxidative radical cyclizations, they appear to offer no advantages over Mn(OAc)$_3$.2H$_2$O [54].

1.10 Mn(III) Acetate Mediated Oxidation of α,β-Unsaturated Ketones

The oxidation of α,β-unsaturated ketones **54** with manganese (III) acetate provided an efficient synthesis of α′-acetoxy-α,β-unsaturated ketones **55** (R′=CH$_3$), and the oxidation of **54** using manganese (III) acetate in the presence of an excess of a manganese (II) carboxylate or a carboxylic acid provided a general synthesis of α′-acyloxy-α,β-unsaturated ketones **55** (Scheme 23).



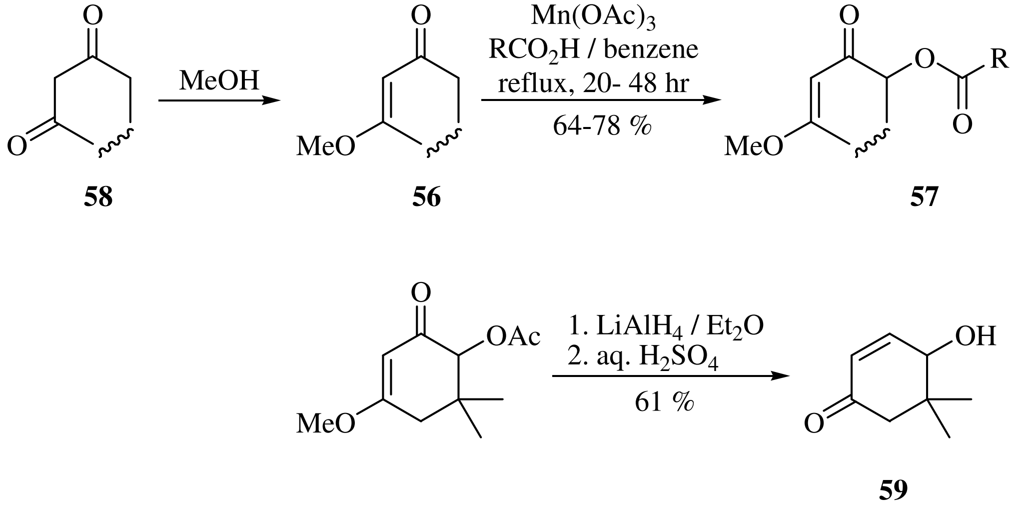
54 **55**

Scheme 23

Demir *et.al.* [56-61] have comprehensively developed the α′-oxidation of enones to α′-acyloxyenones discovered by Hunter [62]. During the course of this work they have found that a wide variety of manganese (III) carboxylates could be prepared from Mn(OAc)$_3$ and the carboxylic acid *in situ* and used for α′-acyloxylation of enones and aryl alkyl ketones [56-61]. The utility of these manganese(III) carboxylates in oxidative free-radical cyclizations has not been examined.

Demir *et.al.* [57] have reported the extension of the oxidation process discovered by Hunter [62] to cyclic β-alkoxy-α,β-unsaturated ketones **56**, which exhibits the same regiochemical preference for oxidation at the α′-position to afford the α′-acyloxy-β-alkoxy-α,β-unsaturated ketones **57** in good yield (Scheme 24). These α′-acyloxy-β-alkoxy-α,β-unsaturated ketones **57** are useful intermediates in the synthesis of natural products [63-71], and general procedures for the synthesis of **55** are either not available or involve multiple steps.

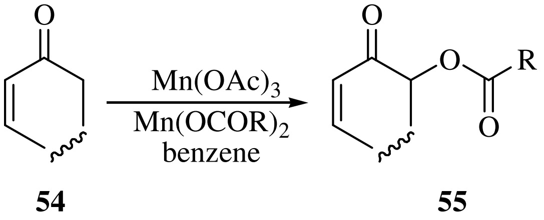
The conversion of cyclic β-diketones **58** to the β-alkoxy-α,β-unsaturated ketones **56** [72] and the oxidation of **56** using six equivalents of manganese (III) acetate [73] in combination with twelve equivalents of a carboxylic acid led to the α′-acyloxy-α,β-unsaturated ketones **57** in good yield. As in previous studies [56], the use of manganese (III) acetate as the sole oxidant was not successful, suggesting that an initial reaction between the manganese (III) acetate and the carboxylic acid led to an active “mixed” manganese (III) complex having both acetate and other carboxylate ligands. The interaction of the enol or enolate of **56** with this mixed manganese (III) complex presumably furnished the desired product **57**. Since the reduction and hydrolysis of α-acyloxy-β-alkoxy-α,β-unsaturated ketones provided access to γ-hydroxy-α,β-unsaturated ketones as exemplified in the case of 5,5-dimethyl-4-hydroxy-2-cyclohexenone **59** (Scheme 24), this process extended the utility of the manganese (III) oxidation procedure to the oxidation of α,β-unsaturated ketones at either the α′- or γ-positions.



Scheme 24

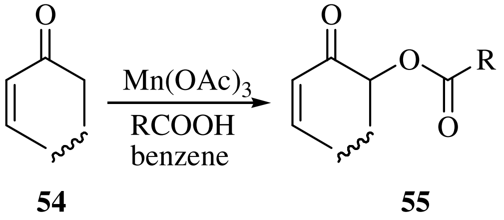
Demir *et.al.* [56] have demonstrated the synthesis of α-acyloxy enones **55** either from enones **54** using manganese (III) acetate *in combination with* either manganese (II) carboxylates or carboxylic acids.

Initial efforts have focused on the application of manganese (III) chloroacetate, propionate, pivalate, and benzoate that were prepared according to the procedure of Vaerman and Bertrand [74]. In each case, the oxidation of an enone **54** with these manganese (III) compounds furnished only unchanged starting material, although the corresponding manganese (III) acetate prepared using this same procedure [74] or other procedures [75, 76] was an effective oxidant for the α′-acetoxylation of enones. The use, however, of 6 equiv of manganese (III) acetate *in combination with* 6 equiv of manganese (II) carboxylate led to the desired α′-acyloxy enones **55** in good yields (Scheme 25).



Scheme 25

Oxidations conducted with 6 equiv of manganese (III) acetate in combination with 12 equiv of a carboxylic acid also proved to be particularly convenient procedure (Scheme 26)

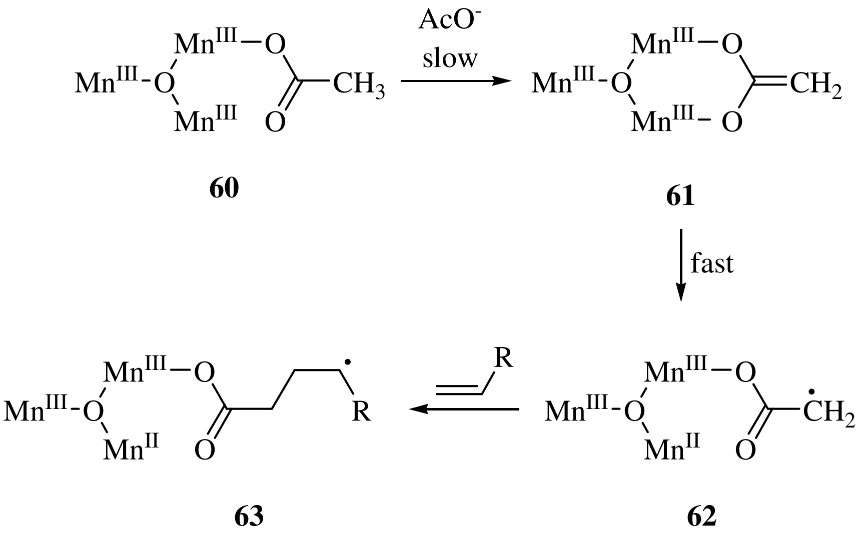


Scheme 26

1.11 Mechanistic Considerations

The mechanism of oxidation of monocarbonyl substrates with $Mn(OAc)_3.2H_2O$ has been extensively studied. Fristad and Peterson have shown that the rate-determining step in the oxidation of acetic acid by $Mn(OAc)_3.2H_2O$, which is actually an oxo-centered triangle of Mn(III) with bridging acetates [77], is the loss of a proton from a complexed acetate such as **60** to give **61** [78-82]. Rapid electron transfer to the oxocentered metal system gives radical **62**, which adds to the alkene to give **63**

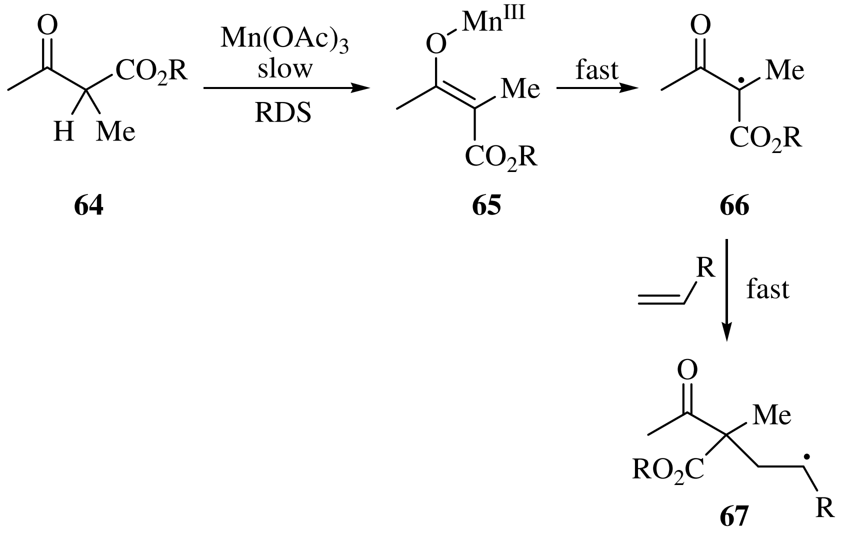
(Scheme 27). The rate of the reaction is independent of alkene concentration, since the alkene is not involved in the rate-determining step.



Scheme 27

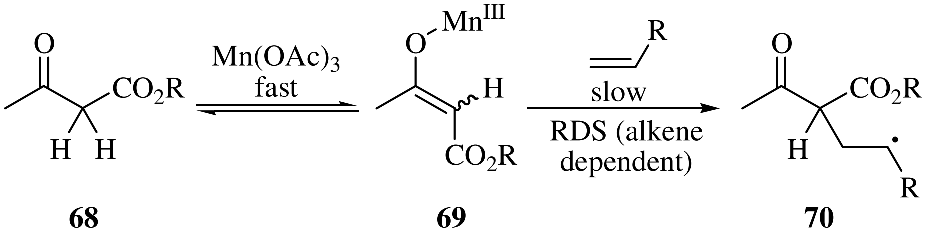
Snider have found that a similar mechanism is operative in the oxidation of α-alkyl β-keto esters **64** (Scheme 28) [83].

Enolization to give **65** is slow; electron transfer with loss of Mn(II) to give **66** is rapid which gives **67** with addition of alkene. The rate of the reaction is therefore independent of alkene concentration or the nature of the tether in cyclizations.



Scheme 28

On the other hand, Snider have found that the enolization of α-unsubstituted β-keto esters **68** is fast and reversible, and electron transfer to give the radical is very slow (Scheme 29) [83].



Scheme 29

The rate-determining step depends on alkene concentration and is presumably the reaction of the Mn(III) enolate **69** with the alkene to give radical **70** with loss of Mn(II). β-Keto ester radicals analogous to **66** do not appear to be intermediates in these reactions. If addition of the alkene to the Mn(III) enolate is the rate-determining step, the length of the tether should, and does, affect the rate of oxidative cyclization of unsaturated β-keto esters. 6-*exo*-cyclization is more rapid than 5-*exo*-cyclization [83]. The nature of the tether also affects the rate of oxidative cyclization of unsaturated β-keto acids [40].

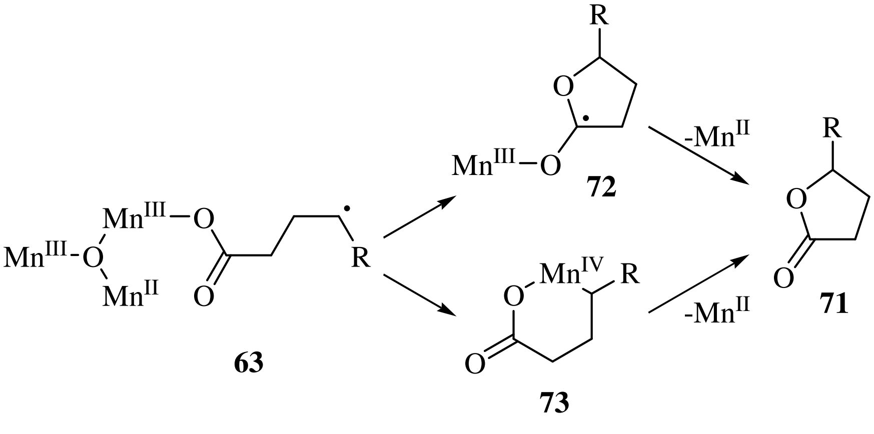
Why does the presence of the α-alkyl group change the mechanism of the reaction? A methyl group should slow down the formation of Mn(III) enolate **65**, since it is electron donating and decreases the acidity of the α-proton. On the other hand, the methyl group should facilitate the oxidation of **65** to **66** since it will stabilize the radical. Electrochemical data for the oxidation of enolates of β-dicarbonyl compounds to the radical in DMSO support this hypothesis. The nature of the reaction depends on two variables: the rate of formation of the Mn(III) enolate, which corresponds to the p*K*a, and the ease of oxidation of the enolate to give a free radical. For most compounds enolization is the rate-determining step. For very acidic compounds such as α-unsubstituted β-keto esters and β-diketones, enolization occurs readily and oxidation is slow.

Commercially available $Mn(OAc)_3.2H_2O$ has been used for the majority of oxidative cyclizations. Anhydrous $Mn(OAc)_3$ is slightly more reactive than the dihydrate. Reaction times with the anhydrous reagent are usually somewhat shorter but the yields of products are usually comparable. Both trifluoroacetic acid and potassium or sodium acetate have been used with $Mn(OAc)_3$. Use of trifluoroacetic acid as a cosolvent usually increases the rate of the reaction, but often decreases the yield of products. Acetate anion may accelerate enolization and act as a buffer.

Acetic acid is the usual solvent for $Mn(OAc)_3.2H_2O$ reactions. DMSO, ethanol, methanol, dioxane, and acetonitrile can also be used, although higher reaction temperatures are required and lower yields of products are sometimes obtained [54]. The use of ethanol can be advantageous in cyclizations to alkynes. Vinyl radicals formed by cyclization to alkynes are not readily oxidized by Mn(III) and will undergo undesired side reactions unless there is a good hydrogen donor available. Ethanol acts as a hydrogen donor, reducing the vinyl radical to an alkene and giving the α-hydroxyethyl radical, which is oxidized to acetaldehyde by Mn(III). Much higher yields of alkenes are obtained from cyclizations to alkynes in ethanol than in acetic acid [84].

$Mn(OAc)_3.2H_2O$ is not particularly expensive on a laboratory scale, but its use on an industrial scale may be problematic. Several groups have demonstrated that Mn(III) can be used in catalytic quantities and regenerated electrochemically *in situ* [85-89]. In some cases, good yields of products are obtained with only 0.2 equiv (10%) of Mn(III) or Mn(II). In other cases the electrochemically mediated reactions proceed in substantially lower yield or give different products. D'Annibale and Trogolo have reported that improved yields are obtained in some Mn(III) and Ce(IV) based oxidative cyclizations and additions if they are carried out with ultrasound irradiation [90-92].

Mn(III) will oxidize γ-carboxy radicals, e.g. **63**, to γ-lactones **71** regardless of whether the radical is secondary or tertiary [2, 9]. Thus, the addition of acetic acid and substituted acetic acids to alkenes to give γ-lactones is a general reaction for all classes of alkenes. Mn(III) does not oxidize isolated primary or secondary radicals, so the oxidation of **63** may involve addition of the radical to the carboxylate to give **72**, which is readily oxidized to **71**, or the formation of **73** followed by reductive elimination of Mn(II) to yield **71** (Scheme 30) [41].



Scheme 30

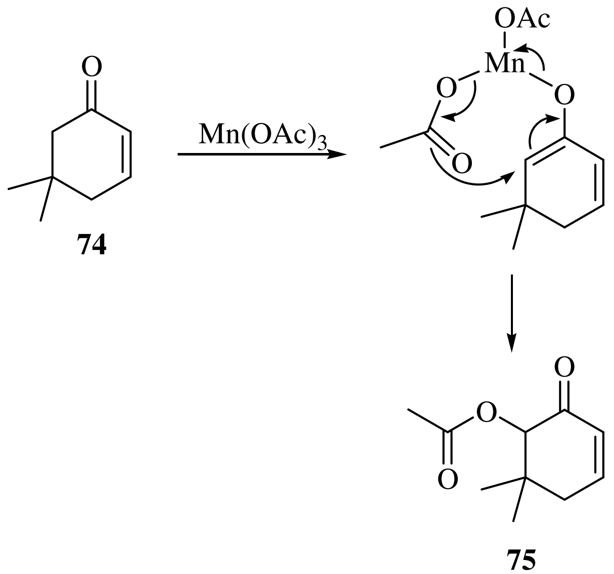
Addition of 1,3-dicarbonyl compounds to alkenes affords isolated radicals that do not contain a proximal manganese carboxylate, e.g., **46** and **53**. Mn(III) will oxidize tertiary radicals to cations that can lose a proton to give an alkene or react with solvent to give a tertiary acetate. Mn(III) will also oxidize allylic radicals to allylic acetates and cyclohexadienyl radicals, resulting from addition to aromatic rings, to the cation, which loses a proton to regenerate the aromatic system.

Mn(III) does not oxidize primary radicals such as **53** or secondary radicals such as **46**. If no cooxidant is used, hydrogen abstraction is the major pathway [41].

$Mn(OAc)_3$ is also involved in the termination step. It rapidly oxidizes tertiary radicals to cations that lose a proton to give an alkene or react with acetic acid to give acetate esters. $Mn(OAc)_3$ oxidizes allylic radicals to allylic acetates and oxidizes cyclohexadienyl radicals generated by additions to benzene rings to cations that lose a proton to regenerate the aromatic system. On the other hand, $Mn(OAc)_3$ oxidizes primary and secondary radicals slowly, so that hydrogen atom abstraction from solvent or starting material becomes the predominant process. Alkenes are formed efficiently from primary and secondary radicals by use of $Cu(OAc)_2$ as a cooxidant [41].

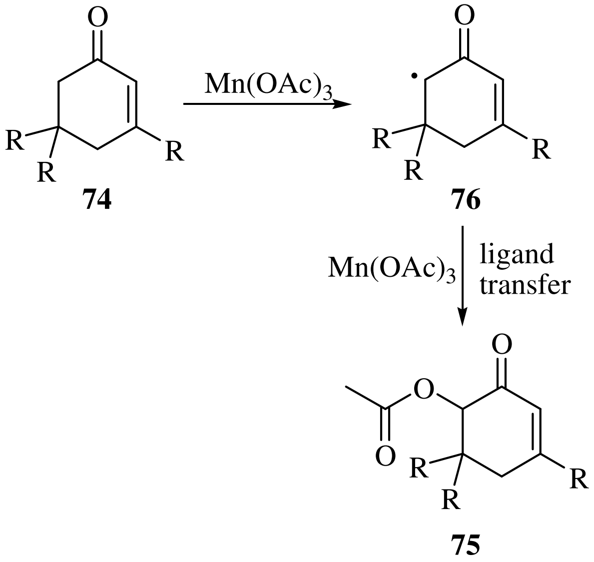
When 5,5-dimethylcyclohex-2-en-1-one **74** was treated with 4 mol equiv of manganese (III) acetate in glacial acetic acid, containing sodium acetate to raise the temperature of reflux, the only product was 6-acetoxy-5,5-dimethylcyclohex-2-en-1-one **75**. Clearly the ketone had not reacted at the double bond but α to the carbonyl to give the product α′-acetoxylation.

One can envisage several mechanisms for oxidation of the enones to the α′-acetoxyenones. For example, the formation of a metal enolate with acetate transfer (Scheme 31) analogous to the lead tetraacetate oxidation of enones is possible.



Scheme 31

However, since previous oxidations of carbonyl compounds with manganese (III) acetate have probably all involved the intermediacy of an α-keto radical resulting from the oxidation of an enol or enolate anion by Mn(III), it is possible that this α′-acetoxylation reaction also proceeds via α-keto radical **76** formation followed by ligand transfer oxidation to the product **75**. Oxidation of the α-keto radical to the carbocation by electron transfer is not favored due to the adjacent electron-withdrawing carbonyl group (Scheme 32).



Scheme 32

1.12 Aim of the Work

Selective α′-acetoxylation of α,β -unsaturated ketones provides key precursors for pharmaceutically important compounds and useful chiral ligands. Today, $Mn(OAc)_3$ mediated acetoxylation is one of the most useful methods for the synthesis of α′-acetoxy α,β -unsaturated ketones.

Although successful α′-acetoxylation of a great variety of substrates have been reported so far by us and others, there are some problems associated with the use of $Mn(OAc)_3$. These inconsistencies and the use of an undesirable amount of $Mn(OAc)_3$ reduced the value of the method. This indirectly indicates that the mechanism and the factors governing the outcome of this reaction are not so clear. Considering that there are not many simple methods for the direct acetoxylation of enones, optimization of $Mn(OAc)_3$ mediated α′-acetoxylation of enones and reaching its maximum potential has a great importance from a synthetic and economical point of view. Thus, we aimed to investigate and understand the nature of this reaction in order to increase its efficiency and reproducibility.

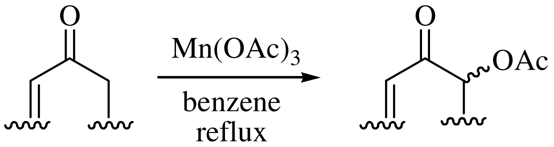
CHAPTER 2

RESULTS AND DISCUSSION

2.1 General Overview of $Mn(OAc)_3$ Mediated α′-Acetoxylation

α,β-Unsaturated ketones are among the most versatile building blocks in organic synthesis. Indeed, several natural products have been synthesized using enones as basic starting materials [93]. Selective oxidations yielding α′-hydroxy-α,β-unsaturated cyclic ketones possess a central position in synthetic methodology [94, 95]. Some analogues of those oxygenated compounds have interesting biological properties and are used in a number of medical preparations (e.g. monosaccharide carba-analogues as components for anti-viral medicines, hydroxycyclopentenones as anticancer drugs, etc.) [96]. The regioselective α′-oxidation of enones to α′-acetoxy enones constitutes a valuable procedure for manipulating a common functional group.

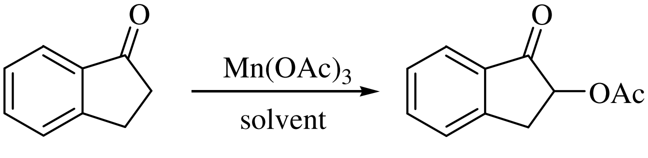
Selective α´-acetoxylation of α,β-unsaturated ketones **73** provides key precursors for pharmaceutically important compounds and useful chiral ligands. Although in 1976 Williams and Hunter have reported that the $Mn(OAc)_3$ oxidation of enones in AcOH produces α´-acetoxy enones, with low yields as compared to more commonly used lead(IV) acetate which hampered the utility of this reagent [62]. Watt and coworkers have greatly improved the yields by using excess dried $Mn(OAc)_3$ in refluxing benzene [97] and Demir *et.al.* have reviewed this subject providing valuable knowledge for future studies [57]. Today, $Mn(OAc)_3$ mediated acetoxylation is one of the most useful methods for the synthesis of α´-acetoxy α,β-unsaturated ketones **74** (Scheme 32).



73 **74**

Scheme 32

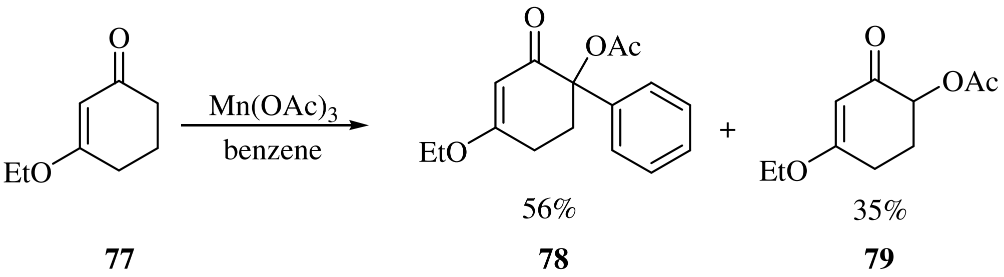
Although successful α´-acetoxylation of a great variety of substrates have been reported so far by us and others, there are some problems associated with the use of $Mn(OAc)_3$. A brief list of them is as follows: 1) excess $Mn(OAc)_3$ (4-6 equiv) is generally used for acceptable yields and reaction times; 2) many contradictory results can be seen when literature reports are closely inspected. These include, the amount of $Mn(OAc)_3$ which was employed to carry out the desired conversion, and irreproducible yields/reaction times were observed under the same set of conditions. A representative example to this is the α´-acetoxylation of 1-indanone **75** to 2'-acetoxy-1-indanone **76** that is a key precursor of the HIV protease inhibitor indinavir. Hiyama *et.al.* [98] reported a 53% yield as compared to the 82% previously reported by Demir *et.al.* [99] (Scheme 33).



75 **76**

Scheme 33

Possibly the most striking contradictory observation is the different chemoselectivity observed for the same substrate under seemingly identical reaction conditions. For example, $Mn(OAc)_3$ mediated oxidation of β-ethoxy cyclohexenone **77** was recently reported to be giving tandem α´-acetoxylation and α´-phenylation product **78** in a 56% yield together with a 35% acetoxylation product **79** (Scheme 34). This observation was shown to be general for a variety of β-alkoxy cyclohexenone and cyclopentenone derivatives [100]. The presence of the arylation product was explained on the basis of fast trapping of the α´-keto radical by the solvent benzene.



Scheme 34

These inconsistencies and the use of an undesirable amount of $Mn(OAc)_3$ lowered the value of the method. This indirectly indicates that the mechanism and the factors governing the outcome of this reaction are not so clear. Considering that there are not many simple methods for the direct acetoxylation of enones, optimization of $Mn(OAc)_3$ mediated α´-acetoxylation of enones and reaching its maximum potential have great importance from a synthetic and economical point of view.

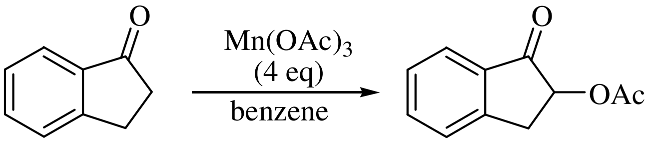
2.2 α′-Acetoxylation of Various Unsaturated Enones and Screening Studies

Our investigations have started with the synthesis of $Mn(OAc)_3.2H_2O$ from $Mn(OAc)_2.4H_2O$ and $KMnO_4$ according to well established methods [12, 101] in order to provide consistency for the source of $Mn(OAc)_3$ because Bush and

Finkbeiner [7] have shown that the reactivity of $Mn(OAc)_3$ may change with the way it is synthesized. According to this procedure, $Mn(OAc_2).4H_2O$ was added to glacial acetic acid. To this well-stirred mixture, $KMnO_4$ was added. Later, small amount of water was added to this solution and the cinnamon brown crystalline precipitate was collected on a glass filter and was washed with glacial acetic acid.

2.2.1 α′-Acetoxylation of 1-Indanone

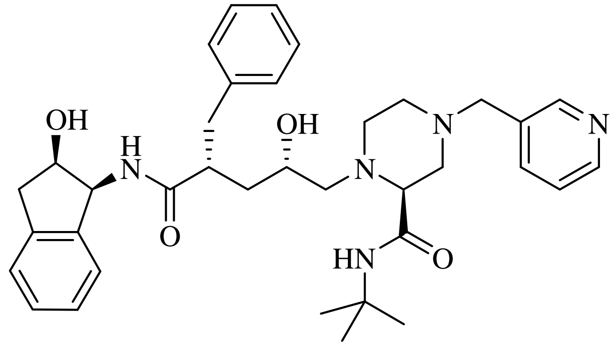
Next, 1-indanone **75** was chosen as the model substrate for our experiments and its reaction with 4 equiv. $Mn(OAc)_3$ to obtain 2'-acetoxy-1-indanone **76** was investigated (Scheme 35).



75 **76**

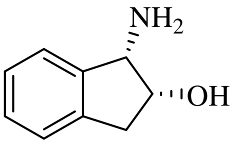
Scheme 35

2'-Acetoxy-1-indanone has great importance in pharmaceutical chemistry since it is the key precursor of Indinavir **80**. Indinavir is commonly known by its trade name, Crixivan, which is a protease inhibitor. Protease inhibitors block the part of HIV called protease. When protease is blocked, or inhibited, HIV makes copies of itself that can't infect new cells.

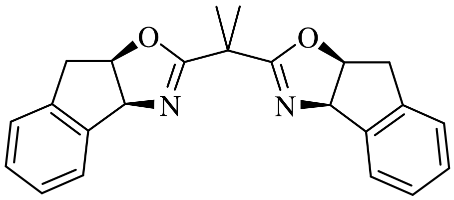


80

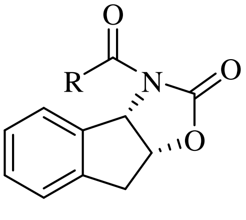
Enantiomerically pure 1-amino-2-indanol **81** is a key precursor of the chiral ligand **82** and the chiral auxiliary **83**. 1-Amino-1-indanol can be readily derived from optically active 2-hydroxy-1-indanone **84** through oxime formation and diastereoselective hydrogenation [102]. 2-Hydroxy-1-indanone **84** can be obtained from 2'-acetoxy-1-indanone **76** upon hydrolysis.



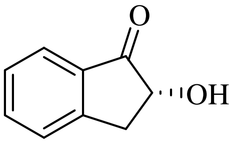
81



82



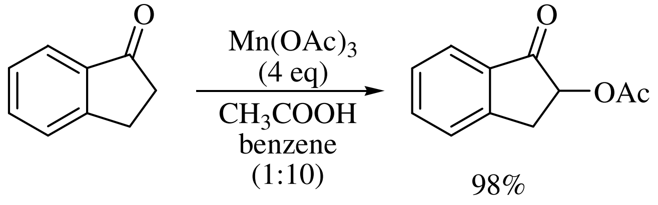
83



84

2.2.2 Determination of the Reactivity of $Mn(OAc)_3$

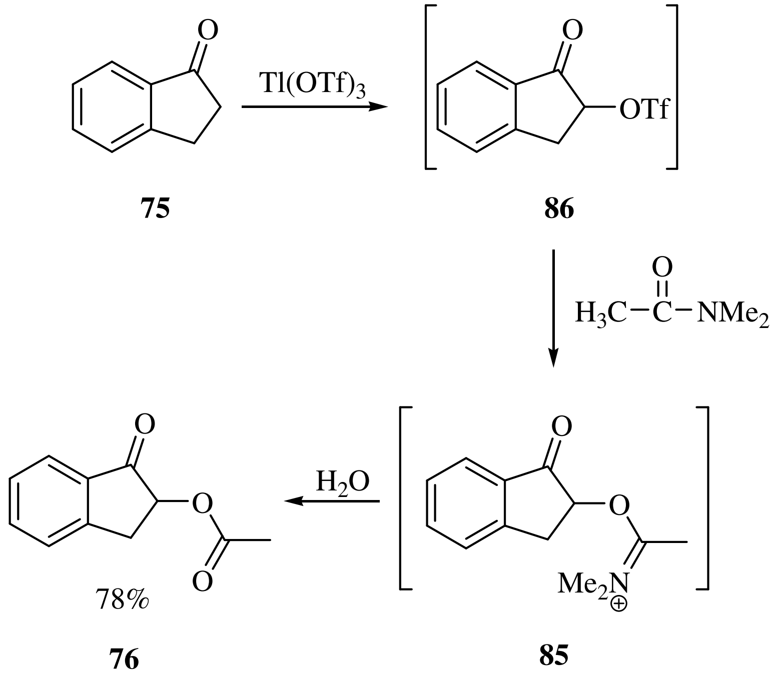
Our attention was first directed to the reactivity of $Mn(OAc)_3$ and conversion times. According to the optimized procedure by Watt [97], $Mn(OAc)_3$ was dried over P_2O_5 under high vacuum to remove water and was then reacted with 1-indanone **75** in refluxing benzene and was monitored by TLC and GC-MS. Although a smooth reaction was observed, conversion was slow, therefore $Mn(OAc)_3$ was further dried in a heating gun (refluxing xylene) under high vacuum to obtain a dark brown colored $Mn(OAc)_3$. Reaction with this extensively dried $Mn(OAc)_3$ provided only a trace amount of product. This was surprising because increasing the purity of $Mn(OAc)_3$ should cause an increase in the yield or a decrease in the reaction time but the opposite situation was observed. An interesting property of this dry $Mn(OAc)_3$ was the lack of AcOH odor that is typical for any $Mn(OAc)_3$ either from a commercial source or synthesized from $Mn(OAc)_2.4H_2O$ and $KMnO_4$. Considering that the absence of AcOH might be responsible for the slow conversions, the reaction was carried out in an AcOH:benzene (1:100) mixture. Reaction under this condition was quite successful with increased conversion rate. A careful monitoring revealed that increasing the AcOH content shortened the reaction time and full conversion was observed at 1:10 AcOH:benzene after 15 min. affording **76** in >99% yield (GC-MS) (Scheme 36). When the product was purified by flash column chromatography, 98% yield was obtained and the analytical data were in agreement with published values [4] (Figure 1 and 2 (Appendix A)). This is quite an improvement when compared to previous reports in terms of its yield, reaction time and reproducibility. The results are summarized in Table 3 and a comparison is made with previously reported results.



75 **76**

Scheme 36

Hiyama *et.al.* [98] have synthesized 2'-acetoxy-1-indanone **76** in the presence of $Mn(OAc)_3$ in 53% yield according to the procedure developed by Demir *et.al.* [103]. Demir *et.al.* have previously obtained 82% yield which is the highest yield for this compound found in literature [99]. $Mn(OAc)_3$ from a commercial source provided similar results as long as it was extensively dried. Lee *et.al.* [104] have studied the α′-acetoxylation of 1-indanone **75** in the presence of thallium (III) triflate in *N,N*-dimethylacetamide. Thallium (III) triflate is highly toxic and therefore be handled with extreme caution and all operations must be carried out in an efficient fume hood. This is a great disadvantage which suppresses the use of $Tl(OTf)_3$ in such reactions. This methodology was based on the hydrolysis of iminium salt intermediate **85** formed by the reaction of α-trifyloxy ketone **86** with the solvent, *N,N*-dimethylacetamide (Scheme 37).



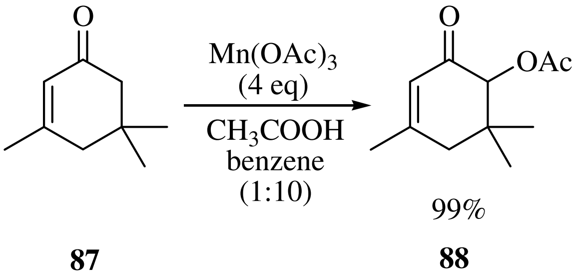
Scheme 37

In our study, many screening experiments were performed so as to observe the behaviour of $Mn(OAc)_3$ against structurally diverse enones, solvents and reagents and valuable results were obtained.

2.2.3 α′-Acetoxylation of Isophorone

After realizing the effect of AcOH, another study was done for the reaction of isophorone **87** to produce α′-acetoxy-isophorone **88** under the same set of reaction conditions as indicated above in order to prove our investigation.

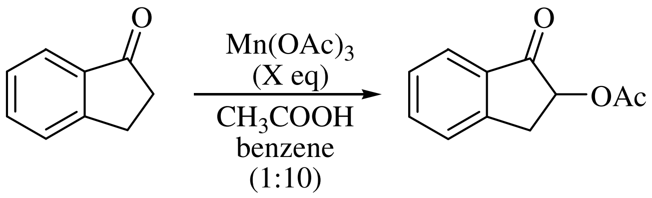
The reactions with $Mn(OAc)_3$ dried over P_2O_5 under high vacuum and with $Mn(OAc)_3$ further dried in a heating gun (refluxing xylene) under high vacuum have shown very little conversions without AcOH at the end of 7 hours. But the same reaction with 1:10 AcOH:benzene has shown 99% conversion after 7 hours indicating the success of our investigation (Scheme 38). When the product was purified by flash column chromatography, 99% yield was obtained and the analytical data were in agreement with published values [105] (Figure 3 (Appendix A)). The results are summarized in Table 3 and a comparison is made with previously reported results.



Scheme 38

2.2.4 Determination of the Required $Mn(OAc)_3$ Equivalency

When these reactions were closely inspected, it was observed that when the reactions reached completion, a white solid precipitated which was $Mn(OAc)_2$. During the oxidation, $Mn(OAc)_3$ was reduced to $Mn(OAc)_2$. In both experiments (for 1-indanone and isophorone), unreacted dark brown colored $Mn(OAc)_3$ was still present in the reaction media. This observation has informed us that 4 equiv. of $Mn(OAc)_3$ was probably in excess for those reactions. In order to determine the amount of $Mn(OAc)_3$ required, both reactions were repeated but this time 2 equiv. of $Mn(OAc)_3$ was used. It was seen that 2 equiv. of $Mn(OAc)_3$ was enough for full conversion. But still the reaction media contained dark brown colored $Mn(OAc)_3$ in addition to white $Mn(OAc)_2$. $Mn(OAc)_3$ was still in excess. This time, an NMR screening study was done in order to determine the minimum amount of manganese (III) acetate required for full conversion. For that purpose, two experiments were done with 1-indanone **75**; one containing 1 equiv. of manganese (III) acetate, other containing 2 equiv. (Scheme 39). Both reactions were monitored by NMR in 30 minutes intervals during 2.5 hours. These NMR monitoring results have shown that the reaction containing 2 equiv. of manganese (III) acetate has gone to completion before the one containing 1 equiv. of $Mn(OAc)_3$. Although the formation of 2'-acetoxy-1-indanone **76** was more rapid for the 2 equiv. manganese (III) acetate case, it was seen that excess $Mn(OAc)_3$ was still present in the reaction medium which causes complications in the work-up. For the 1 equiv. $Mn(OAc)_3$ case, the starting material **75** was finished at the end of two hours. When 0.25 equiv. of $Mn(OAc)_3$ was used in excess, full conversion was observed in 1 hour and all manganese (III) acetate was consumed providing a cleaner reaction than the 2 equiv. case.



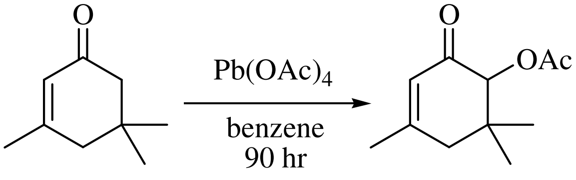
75 **76**

X = 1, 2 eq

Scheme 39

After several trials, we concluded that 1 equiv. of $Mn(OAc)_3$ was sufficient for these conversions but addition of a slight excess (0.25 equiv.) of $Mn(OAc)_3$ was useful to ensure complete conversion in minimum reaction times.

In the literature, only lead (IV) acetate was used for the α′-acetoxylation of isophorone **87**. Ellis [105] has indicated that when acetic acid was used as a solvent, acetate **88** could be isolated in only 38% yield [106]. Using benzene as a solvent in the presence of CaH_2 or BF_3 [107], only slightly better yields were observed. Benzene and $CaCO_3$ [108] gave yields of 74% but the best yields were obtained using benzene alone where the product was isolated by crystallization in 78% yield (Scheme 40) [105]. When compared to our method giving the desired product in 99% yield in 7 hours, this method has a low yield and long reaction time (90 hours).



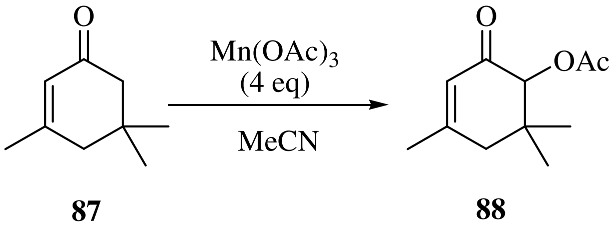
78%

87 **88**

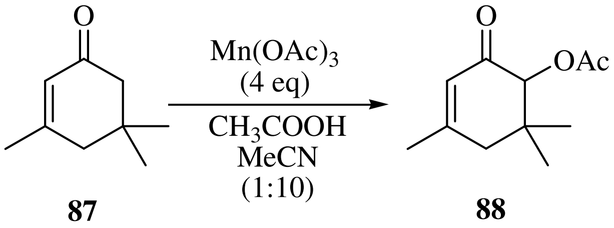
Scheme 40

2.2.5 Solvent Screening Studies

For solvent screening, the reaction of isophorone **87** in acetonitrile instead of benzene both in the absence and presence of AcOH was examined (Scheme 41 and 42).



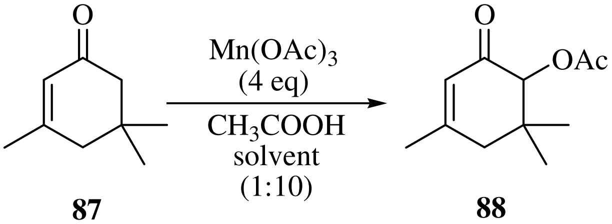
Scheme 41



Scheme 42

From previous experiments, it was known that in the presence of AcOH in benzene, the reaction needed 7 hours for complete conversion. During the set of experiments explained above, GC-MS analyses were done at the 2nd hour so as to see the effect of both acetonitrile and AcOH in the early stages of experiments. From the GC-MS spectra, in the absence of AcOH, no conversion was observed at the end of 2 hours (Figure 4 (Appendix A)), whereas in the presence of AcOH, formation of the acetoxylated product **88** can be seen at the end of 2 hours (Figure 5 (Appendix A)) which needs 7 hours more for complete conversion.

It was obvious that not only benzene but also acetonitrile needs AcOH for complete conversion in shorter reaction times. Taking this fact into account, screening of five different solvents (benzene, MeCN, cyclohexane, DMF, THF), using isophorone as the substrate in the same set of reaction conditions was performed (Scheme 43).



87 **88**

solvent: benzene, MeCN, cyclohexane, DMF, THF

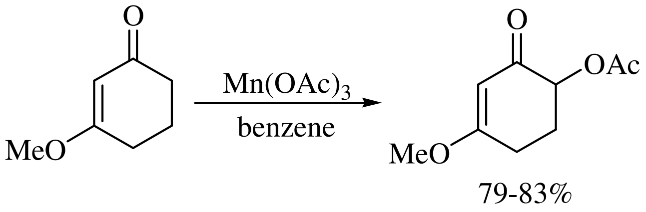
Scheme 43

In 1:10 AcOH:benzene mixture, at the end of 3 hours, the ratio of isophorone to acetoxylation product was 0.4:1 (Figure 6 (Appendix A)) whereas for 1:10 AcOH:MeCN solvent system, isophorone : 2'-acetoxy isophorone ratio was 1:0.5 (Figure 7 (Appendix A)). For 1:10 AcOH:cyclohexane system, the product formation is poorer which is 1:0.2 (Figure 8 (Appendix A)). In DMF and THF, reactions were very slow. In most of the literature studies, benzene was the most frequently used solvent after the report by Watt [97]. After determining the complete conversion times for all five solvents, we can say that in addition to benzene; cyclohexane and acetonitrile could also be used as the reaction solvent in 1:10 AcOH:solvent ratio and α´-acetoxylation was the only detectable product in GC-MS analyses. Although cyclohexane and MeCN have given only the expected α′-acetoxylation product, conversion rates were slower compared to 1:10 AcOH:benzene cases. Reactions in THF and DMF were too slow to be useful for α´-acetoxylation.

2.2.6 α′-Acetoxylation of β-Ethoxy Cyclohexenone

As was previously indicated, $Mn(OAc)_3$ mediated oxidation of β-ethoxy cyclohexenone **77** has given tandem α′-acetoxylation and α′-phenylation product **78** in a 56% yield together with a 35% acetoxylation product **79** (Scheme 34). This observation was shown to be general for a variety of β-alkoxy cyclohexenone and cyclopentenone derivatives [100].

In a previous study performed by Demir *et.al.*, acetoxylation of β-methoxy cyclohexenone **89** has given the desired α′-acetoxylated product **90** in a 79-83% yield and only a trace amount of unidentified arylated products were detected in crude ^{1}H-NMR spectrum (Scheme 44) [109].

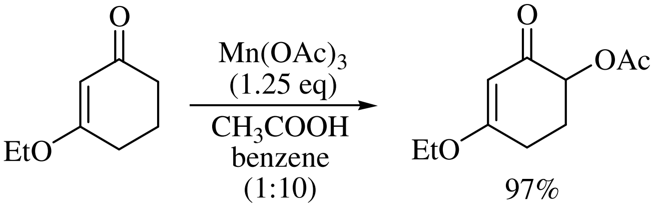


89 **90**

Scheme 44

This different chemoselectivity for very similar substrates under seemingly identical reaction conditions seems to be contradictory and limits the use of $Mn(OAc)_3$ in the oxidation of β-alkoxy cyclohexenone and cyclopentenone derivatives. For that purpose, we intended to try the method that we have developed in order to offer a reproducible α′-acetoxylation method for β-alkoxy cyclohexenone and cyclopentenone derivatives.

We have treated 3-ethoxy-2-cyclohexen-1-one **77** with 1.25 equiv. of $Mn(OAc)_3$ in the presence of 1:10 AcOH:benzene solvent system. A promising result was obtained giving the desired α′-acetoxy-β-ethoxy cyclohexenone **79** in 97% yield with only a trace amount of unidentified arylated product (Scheme 45). When the product was purified by flash column chromatography, 97% yield was obtained and the analytical data were in agreement with published values [9, 41] (Figure 9 and 10 (Appendix A)). The results are summarized in Table 3 and a comparison is made with previously reported results.

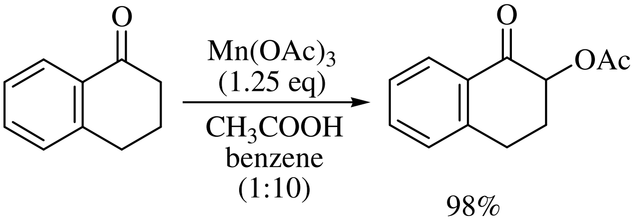


77 **79**

Scheme 45

2.2.7 α′-Acetoxylation of α-Tetralone

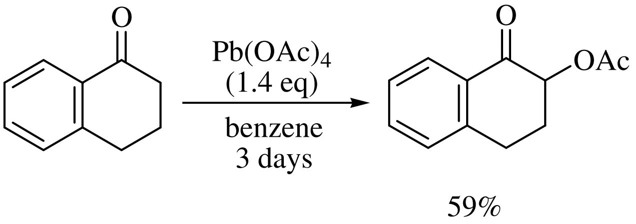
Next, α-tetralone **91** was treated with manganese (III) acetate under the same set of conditions. Reaction of α-tetralone **91** with 1.25 equiv. of manganese (III) acetate in the presence of 1:10 AcOH:benzene solvent system gave the desired α′-acetoxylated product **92** after 5 hours in 98% yield (Scheme 46) and the analytical data were in agreement with published values [110] (Figure 11 and 12 (Appendix A)). The results are summarized in Table 3 and a comparison is made with previously reported results.



91 **92**

Scheme 46

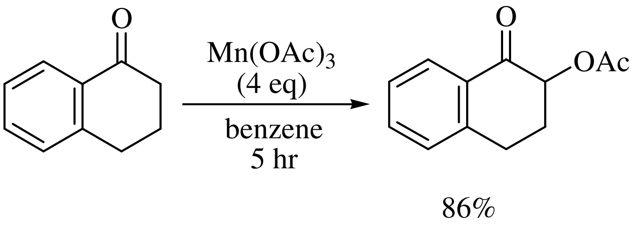
Naemura *et.al.* [110] have studied the synthesis of 2'-acetoxy-1-tetralone **92** starting from α-tetralone **91** in the presence of $Pb(OAc)_4$ in the synthesis of homochiral phenolic crown ethers having chiral subunits derived from 1,2-dihydroxytetralone (Scheme 47). As was previously the case for lead (IV) acetate mediated α′-acetoxylation, reaction time is too long with low yields.



91 **92**

Scheme 47

Later, Demir *et.al.* have used manganese (III) acetate for the same conversion in the enantioselective hydrolysis of α-acetoxy ketones and have decreased the reaction time with increasing yield (Scheme 48). Demir has mentioned depending on previous researches [57, 59, 60, 61, 111-113] that the source of manganese (III) acetate is very important for the high yields of the reactions. The anhydrous manganese (III) acetate used in that study was prepared from manganese (II) nitrate and acetic anhydride and dried over phosphorus pentoxide under high vacuum.

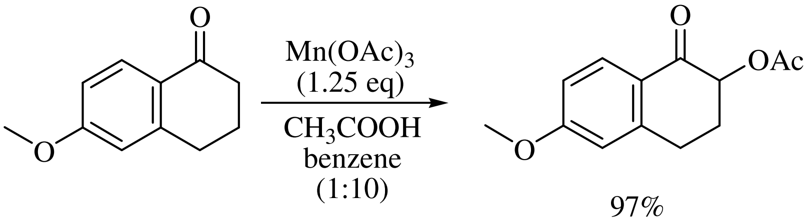


91 **92**

Scheme 48

2.2.8 α′-Acetoxylation of 6-Methoxy-1-Tetralone

6-Methoxy-1-tetralone **93** was the next molecule that was α′-acetoxylated in the presence of manganese (III) acetate. Treating 6-methoxy-1-tetralone **93** with 1.25 equiv. manganese (III) acetate in 1:10 AcOH:benzene solvent system afforded the desired α′-acetoxylated product 2'-acetoxy-6-methoxy-1-tetralone **94** in 97% yield in 5 hours (Scheme 49). The product was purified by flash column chromatography and the analytical data were in agreement with published values [103] (Figure 13 and 14 (Appendix A)). When compared to the highest yield given in the literature (82%) and reaction time [103], this is quite an improvement for this conversion. The results are summarized in Table 3 and a comparison is made with previously reported results.

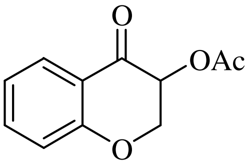


93 **94**

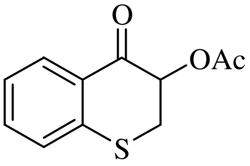
Scheme 49

2.2.9 α′-Acetoxylation of 4-Chromanone

Later, our attention was directed towards the synthesis of 2'-acetoxy-4-chromanone **95** and 2'-acetoxy-4-thiochromanone **96** because of their being the subunits of some potassium channel openers.



95

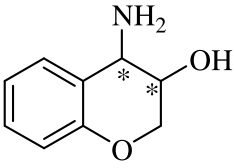


96

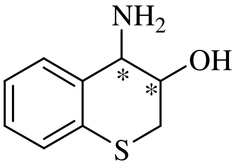
During the last 20 years, compounds have been discovered which can activate or block potassium channels [114]. In particular, K^+ channel activators (KCA) have been found to be smooth muscle relaxant with their main utility in hypertension and bronchodilation.

There are at least seven classes of KCA, of which the main four are the benzopyrans, thioformamides, cyanoguanidines and the organic nitrates. Best investigated subgroup is the benzopyrans.

Biologically active cis-amino chromanol **97** and cis-amino thiochromanol **98** are important benzopyran type synthons for the synthesis of anti HIV drugs specially HIV protease inhibitors and KCA's.



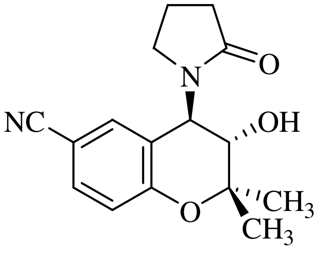
97



98

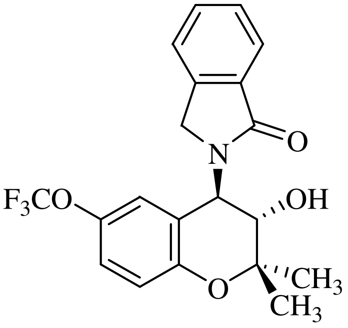
For example, in the synthesis of the HIV protease inhibitor Crixivan (Indinavir), as was discussed previously, an expedient way of producing cis-amino indanol and related amino alcohols was established using a Jacobsen epoxidation/Ritter-type reaction sequence [115]. These amino alcohols have been used successfully in a 'conformational toolbox' of oxazilidine ligands.

The first compound to be termed as a potassium channel activator (sometimes called potassium channel opener) is the benzopyran based structure cromakalim [(+)-3-hydroxy-2,2-dimethyl-trans-4-(2-oxopyrrolidin-1-yl)-chromane-6-carbonitrile] **99**, which is a powerful smooth muscle relaxant with potent antihypertensive and bronchodilator activity [116].

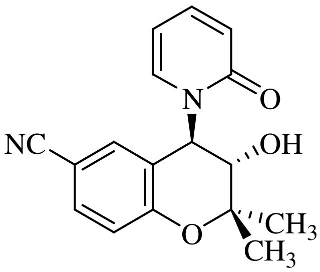


99

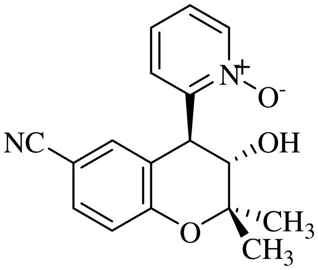
Since the discovery of cromakalim (racemic) in 1985 as a potent hypotensive agent, a large number of benzopyrans have been reported [117]. Among the most well-known of the lead compounds in this group are celikalim **100**, bimakalim **101**, and Ro 31-6930 **102.** All of these benzopyrans exert their hypotensive effect by relaxing smooth muscle via opening of cell membrane ATP-sensitive potassium channels. By virtue of this effect, potassium channel openers may have utility for treatment of hypertension, asthma, incontinence and impotence. In addition, potassium channel openers have been found to be useful for stimulation of hair growth.



100



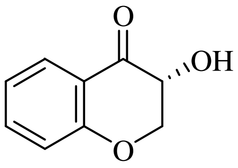
101



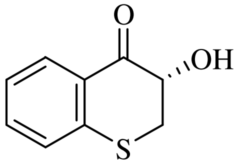
102

Potassium channels are ubiquitous amongst cells; different channels are not only being found amongst different cells, but also within the same cell. With increasingly sophisticated pharmological probes, new substances which selectively modulate the action of potassium channels are continually being found and the whole area is expanding.

Being the important building block of benzopyran type potassium channel activators, HIV protease inhibitors and also other biologically active cis amino alcohols, α-hydroxy ketones, 3-hydroxy-2,3-dihydro-4H-chromen-one **103** and 3-hydroxy-2,3-dihydro-4H-thiochromen-one **104** are of high current interest.

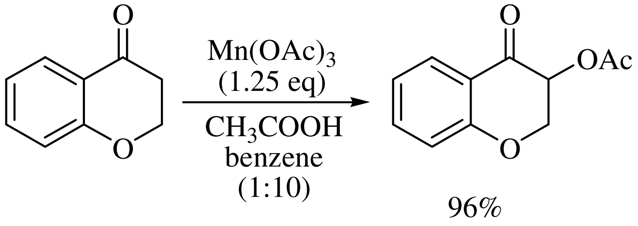


103



104

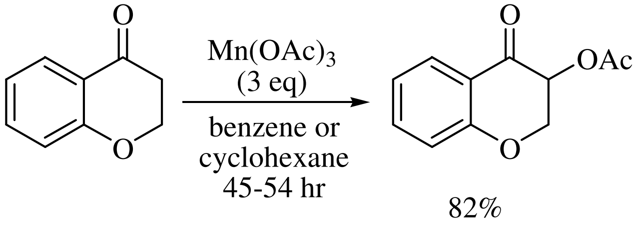
Reaction of 4-chromanone **105** with 1.25 equiv. of manganese (III) acetate in the presence of 1:10 AcOH:benzene solvent system gave the desired α′-acetoxylated product **95** in 96% yield after 5 hours (Scheme 50). The product was purified by flash column chromatography and the analytical data were in agreement with published values [118] (Figure 15 and 16 (Appendix A)). The results are summarized in Table 3 and a comparison is made with previously reported results.



105 **95**

Scheme 50

The best available result found in literature was the one performed by Demir *et.al.* [118] giving 82% yield in 45-54 hours (Scheme 51).

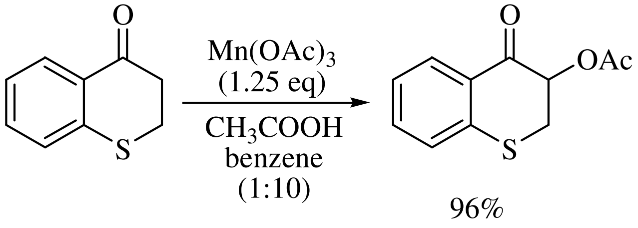


105 **95**

Scheme 51

2.2.10 α′-Acetoxylation of 4-Thiochromanone

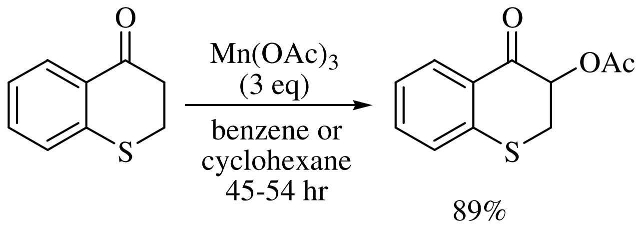
4-Thiochromanone **106** under the same set of conditions has given the desired α′-acetoxylated product **96** in 5 hours (Scheme 52). When the product was purified by flash column chromatography, 96% yield was obtained and the analytical data were in agreement with published values [118] (Figure 17 and 18 (Appendix A)). The results are summarized in Table 3 and a comparison is made with previously reported results.



106 **96**

Scheme 52

Similar to 4-chromanone; for 4-thiochromanone, Demir *et.al.* have synthesized 2'-acetoxy-4-thiochromane **96** in 89% yield in 45-56 hours in the presence of 3 equiv. Mn(OAc)$_3$ (Scheme 53) [118].

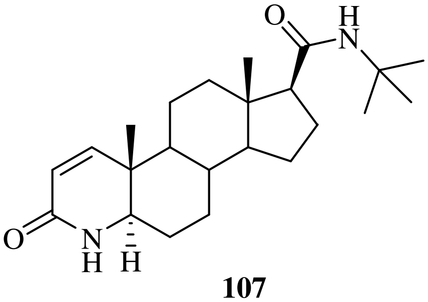


106 **96**

Scheme 53

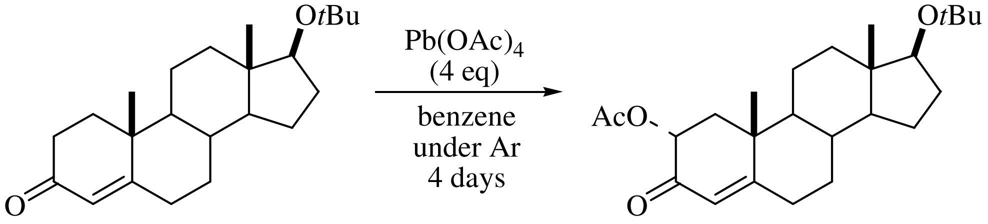
2.2.11 α′-Acetoxylation of 4-Cholesten-3-one

Investigations into the relationship of structural changes to biological activity in the steroid series, started over 50 years ago, and numerous reports have described syntheses and structure–activity studies on A- and B-ring modified steroids [119]. Dihydrotestosterone, produced by the reduction of testosterone *via* a process catalyzed by the enzyme 5α-reductase, is believed to be involved in the progression of benign prostatic hyperplasia and to be a causative factor in acne and male-pattern baldness [120]. In search for agents that could lower levels of dihydrotestosterone, a number of modified steroids were synthesized, some of them exhibiting high antiandrogenic activity. Work targeting the inhibition of 5α-reductase, which is believed to be involved in several androgen dependent diseases, gave rise to useful drugs such as Proscar **107** [121] (developed by Merck Sharp & Dohme) and Episteride **108** [122] (developed by Smith Kline Beecham), both modified steroids with changes localized on the A-ring and on segments attached at the C-17 position of the steroid nucleus.



107

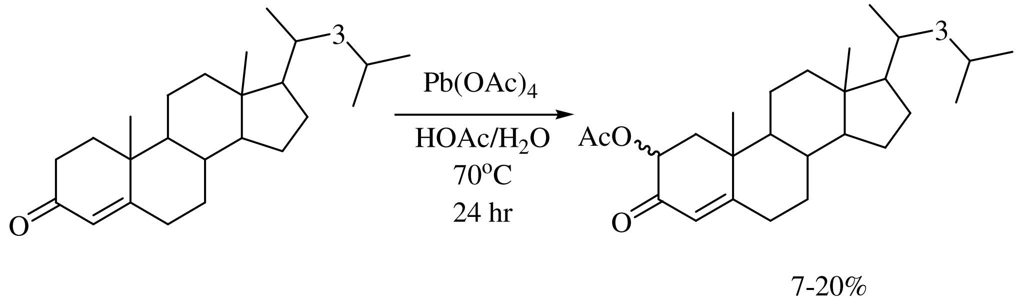
Arseniyadis *et.al.* [123] have studied the synthesis of modified steroids starting from steroidal unsaturated 1,2-diols. The preparation of the requisite steroidal diol was achieved straightforwardly from 17-O*t*Bu-protected testosterone **109**, via its corresponding C-2 acetoxy derivative **110** (Scheme 54).



109 **110**

Scheme 54

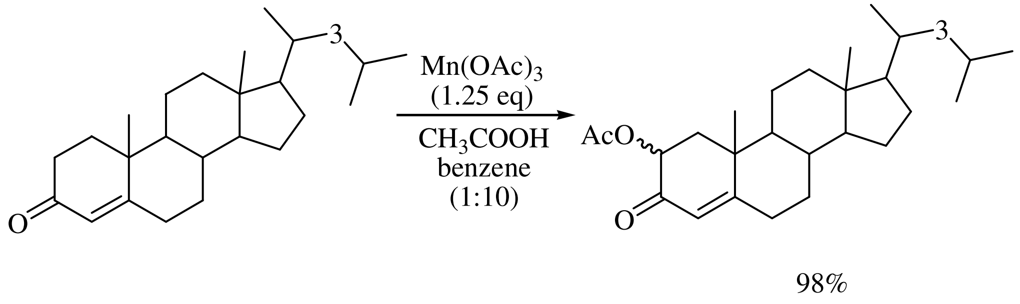
Knowing the importance of A- and B-ring modified steroids, we intended to perform α′-acetoxylation of a steroid derivative, 4-chloesten-3-one **111**. Literature survey has shown that there were a few studies for the acetoxylation of **111** into its corresponding α′-acetoxy derivative **112** in the presence of lead (IV) acetate, giving very low yields 7-20% in long reaction times [124-126] (Scheme 55).



111 **112**

Scheme 55

Our attempt to synthesize 2'-acetoxy-4-cholesten-3-one **112** has given a wonderful result when compared to the previous studies. The reaction has given 98% yield in 11 hours of reaction time with 1.25 equiv. of manganese (III) acetate (Scheme 56).



111 **112**

Scheme 56

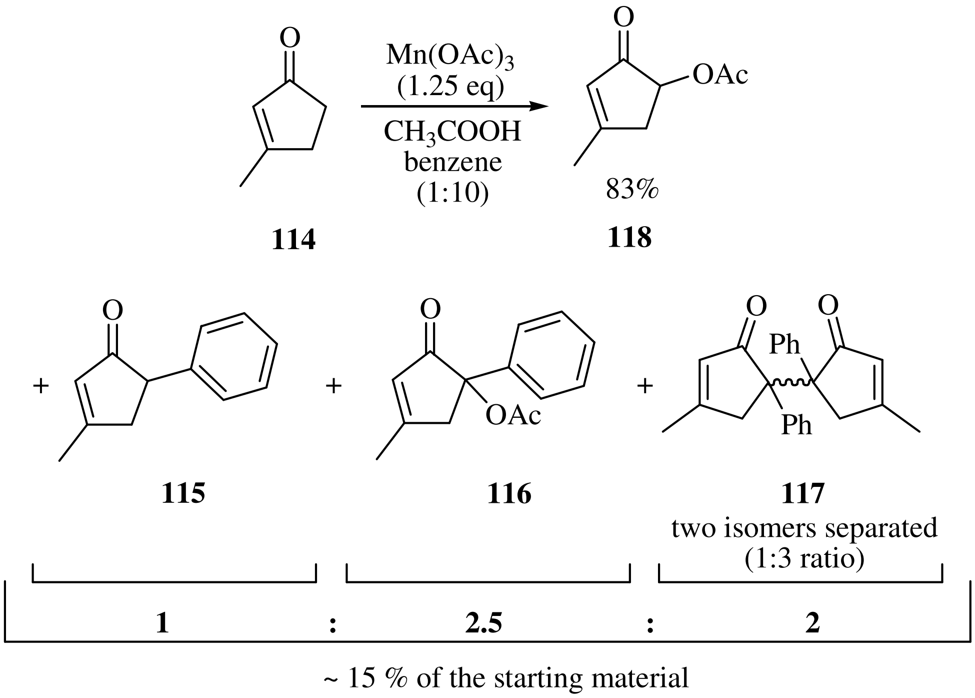
The product was purified by flash column chromatography and the analytical data were in agreement with published values [126, 127] where 1:6 mixture of easily separable isomers was obtained (Figure 19 and 20 (App A) for major isomer; Figure 21 and 22 (App A) for minor isomer). The results are summarized in Table 3 and a comparison is made with previously reported results.

2.2.12 α′-Acetoxylation of α,β-Unsaturated Cyclopentanone Derivatives

In the literature, there are numerous examples of regioselective oxidation of α,β-unsaturated cyclohexanone derivatives using lead(IV) acetate and manganese(III) acetate. However, only a few examples of lead(IV) acetate mediated selective oxidation of α,β-unsaturated cyclopentanone derivatives [128] are to be found.

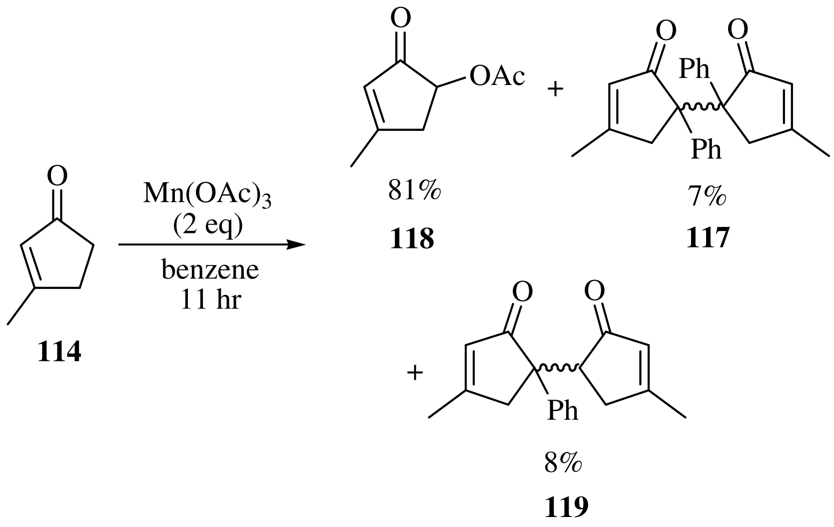
2.2.12.1 α′-Acetoxylation of 3-methyl-2-cyclopenten-1-one

Generally, no product other than acetoxylation was detected in the ^{1}H-NMR spectrum of crude products throughout our reactions and they were pure enough for further synthetic manipulations. An apparent exception was observed for the cyclopentenones, 2-cyclopenten-1-one **113** and 3-methyl-2-cyclopenten-1-one **114** in which a small amount of side products were detected in crude mixtures by NMR and GC-MS. These products were identified for **114** and found to be an α′-phenylation product, 3-methyl-5-phenyl-2-cyclopentenone, **115**, α′-phenylation and α′-acetoxylation product, 5-acetoxy-3-methyl-5-phenyl-2-cyclopentenone, **116** and a dimerization product, 4,4′-dimethyl-1,1′-diphenyl-bicyclopentyl-3,3′-diene-2,2′-dione, **117** with 83% of the targeted α′-acetoxylation product, 2′-acetoxy-3-methyl-2-cyclopenten-1-one, **118** in 2 hours. All the analytical data were in agreement with published values [129]. The results are summarized in Table 3 and a comparison is made with previously reported results. Products **115**, **116** and **117** (two isomers were separated providing a 1:3 ratio) were isolated in an approximate ratio of 1:2.5:2 accounting for ~15% of the starting material (Scheme 57) (Figure 23-30 (Appendix A)). These seem to be pointing out the intermediacy of **115**, which is acetoxylated at the benzylic position or dimerized in an alternative pathway. Thus, phenylation instead of acetoxylation is a minor alternative route, resulting in aromatic signals in NMR spectra of crude products of $Mn(OAc)_3$ mediated acetoxylation reactions.



Scheme 57

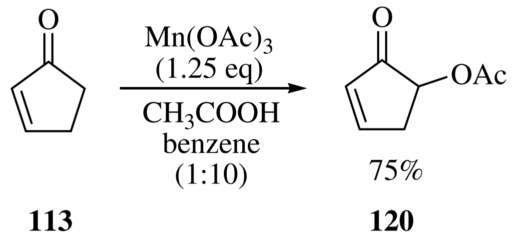
In a previous report, the formation of products **117** and **119** was reported in addition to the α′-acetoxylation product **118** (81%) after 11 hours, but not **115** and **116** (Scheme 58) [129]. Although these products do not have any importance from a synthetic point of view, they would be useful towards understanding the nature of the reaction which will be discussed later.



Scheme 58

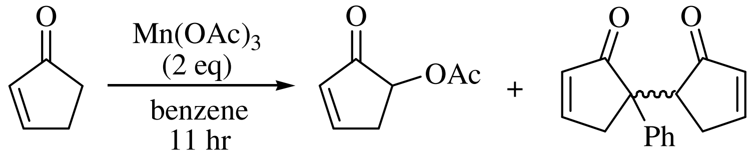
2.2.12.2 α′-Acetoxylation of 2-Cyclopenten-1-one

When 2-cycylopenten-1-one **113** was studied, as stated previously, a small amount of side products were detected in crude mixtures by NMR and GC-MS. The side products were not separated and characterized but the desired 5-acetoxy-2-cyclopenten-1-one **120** was obtained in 75% yield after purification by flash column chromatography in 2 hours (Scheme 59) and the analytical data were in agreement with published values [129] (Figure 31 (Appendix A)). The results are summarized in Table 3 and a comparison is made with previously reported results.



Scheme 59

In a previous report, 65% yield was obtained for α′-acetoxylation product **120** in addition to 6% **121** in 8 hours (Scheme 59).



65% 6%

113 **120** **121**

Scheme 59

Table 3. Yields and structures of α´-acetoxy α,β-unsaturated ketone[a]

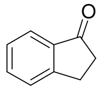
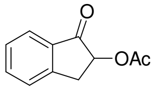
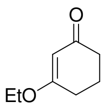
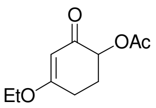
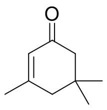
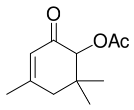
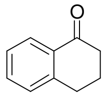
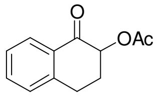
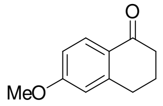
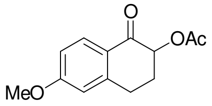
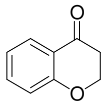
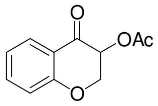
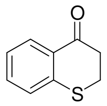
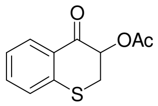
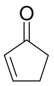
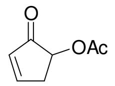
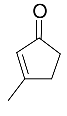
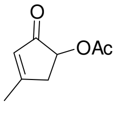
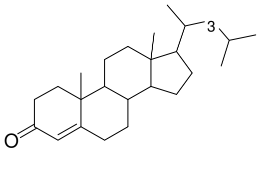
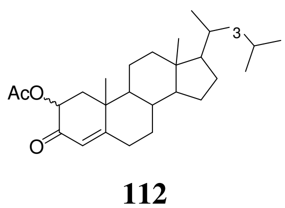
Entry	Enone	Acetoxy enone	Yield (%)[b]	Time	Yield (%)[c]
1	 **75**	 **76**	98	1 h	53, A[98] 72, A[99]
2	 **77**	 **79**	97	7 h	81,A[d,109] 35, A[100]
3	 **87**	 **88**	99	7 h	78, B[105]

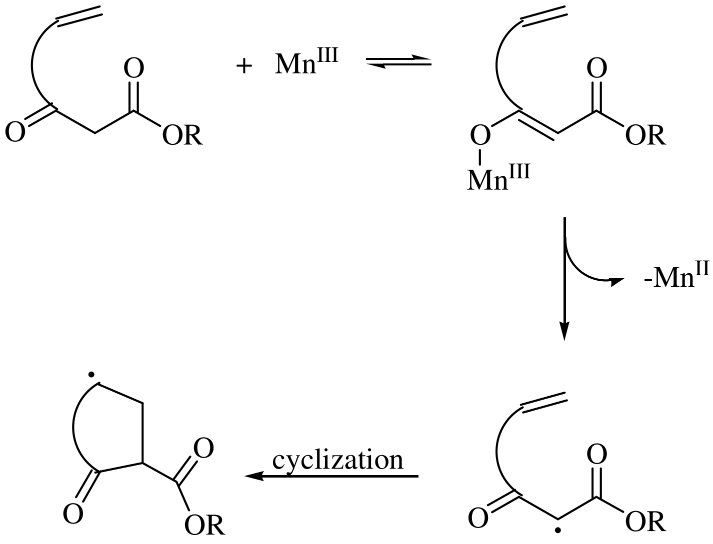
Table 3 Continued

4	 **91**	 **92**	98	5 h	59, B[110] 86, A[99]
5	 **93**	 **94**	97	5 h	82, A[103]
6	 **105**	 **95**	96	5 h	82[118]
7	 **106**	 **96**	96	5 h	89[118]
8	 **113**	 **120**	75	2 h	65, A[129]
9	 **114**	 **118**	83	2 h	81, A[126,127]
10[e]	 **111**	 **112**	98	11 h	20, B[14]

[a] Although 1.25 equiv. of $Mn(OAc)_3$ was used for full conversion, the addition of 0.25 equiv. of $Mn(OAc)_3$ towards the end of the reaction greatly shortens the reaction times. [b] isolated yields. [c] yields of previously reported acetoxylations mediated by Mn(III) acetate (Method A) or Lead(IV) acetate (Method B). [d] for methoxy derivative. [e] 1:6 mixture of easily separable isomers was obtained.

2.3 Yb(OTf)$_3$ Catalyzed α′-Acetoxylation Reactions

Yang *et.al.* have stated that lanthanide triflates catalyze Mn(III)-based oxidative radical cyclization reactions [130]. Previously, the oxidative free-radical cyclization reactions were proposed to proceed in at least three steps (Scheme 60) [83]. Mn(OAc)$_3$ both functions as a Lewis acid (LA) to promote enol formation and then as a single electron oxidant to generate the electrophilic radical, which subsequently adds to the C=C double bond. Yang *et.al.* [130] have conjectured that, when a stronger LA is used, the enol formation would be more favourable and the electrophilicity of the radical would be enhanced by chelation to the LA, thereby increasing the rates for radical cyclization reactions. Furthermore, recent studies reveal that LA may enhance the stereoselectivity of radical addition reactions [131-137]. Therefore, the effect of LA on the oxidative radical cyclization reactions was investigated.



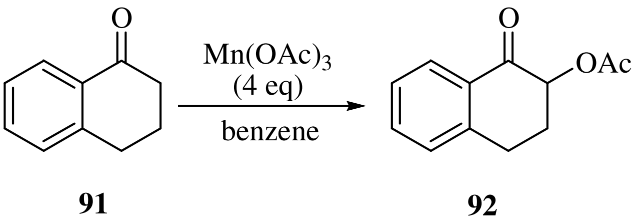
Scheme 60

Lanthanide triflates, Ln(OTf)$_3$, have been used as Lewis acid catalysts in protic solvents for a variety of reactions. Thus, in the same study, several lanthanide triflates were tested in the Mn(OAc)$_3$-mediated radical cyclization of chiral compounds. Without Ln(OTf)$_3$, cyclization reactions were very slow in AcOH at RT or in CF_3CH_2OH at 0°C. However, in the presence of ytterbium triflate, the reactions proceeded remarkably faster, providing higher yields. Among the lanthanide triflates tested, Yb(OTf)$_3$ and Er(OTf)$_3$ were found to be better than others. Most importantly, the use of catalytic amount of Ln(OTf)$_3$ did not result in a significant decrease in yields. According to Yang's discussion, these results clearly indicate that *lanthanide triflates catalyze the Mn(OAc)$_3$ mediated radical cyclization reactions by promoting enolization and increasing electrophilicity of the resulting radical.*

2.3.1 Yb(OTf)$_3$ Catalyzed α′-Acetoxylation of α-Tetralone

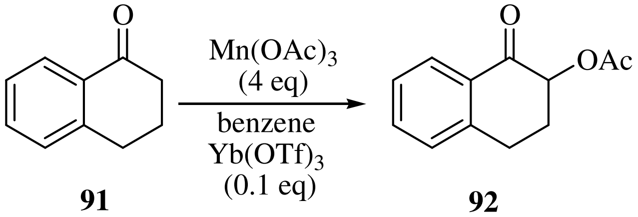
Keeping in mind that, Mn(OAc)$_3$ functions as a Lewis acid (LA) to promote enol formation and then as a single electron oxidant to generate the electrophilic radical and Yb(OTf)$_3$ catalyzes the Mn(OAc)$_3$ mediated radical cyclization reactions by promoting enolization and increasing electrophilicity of the resulting radical; we intended to see the behaviour of Yb(OTf)$_3$ on manganese (III) acetate mediated α′-acetoxylation reactions. The results would help us to clarify our minds about the mechanism of action.

In our foregoing screening studies, the effect of Yb(OTf)$_3$ (in benzene) was tested on α-tetralone **91** in a set of reactions (Scheme 61, 62 and 63).

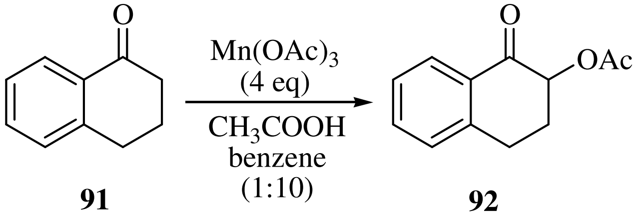


91 **92**

Scheme 61



Scheme 62

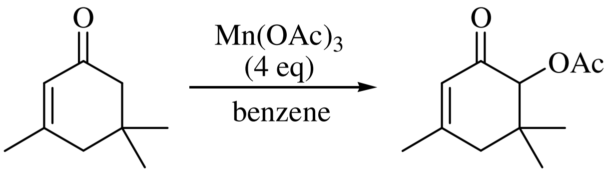


Scheme 63

At the end of 5 hours, it was observed by GC-MS analyses that the first (Figure 32 (Appendix A)) and the second reactions (Figure 33 (Appendix A)) have shown little conversions to 2'-acetoxy-1-tetralone **92** whereas the third one containing AcOH (Figure 34 (Appendix A)) has shown full conversion. From these results, it was obvious that reaction of α-tetralone needed AcOH for full conversion and $Yb(OTf)_3$ (in benzene) did not promote the reaction in the absence of acetic acid.

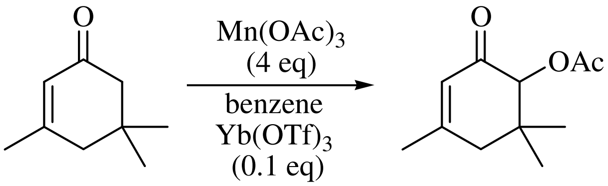
2.3.2 $Yb(OTf)_3$ Catalyzed α′-Acetoxylation of Isophorone

The same set of reactions was applied to isophorone **87** as a substrate (Scheme 64, 65 and 66). Similarly, at the end of 7 hours, GC-MS spectra indicated that the reaction with only isophorone and $Mn(OAc)_3$ (Figure 35 (Appendix A)) and the one with $Yb(OTf)_3$ (Figure 36 (Appendix A)) have shown little conversions and in the presence of $Yb(OTf)_3$, some other side products were observed in addition to 2'-acetoxy-isophorone **88**. The 1:10 AcOH:benzene solvent system reaction has shown full conversion (Figure 37 (Appendix A)). These results have revealed that $Yb(OTf)_3$ addition did not promote our α′-acetoxylation reactions in the absence of acetic acid.



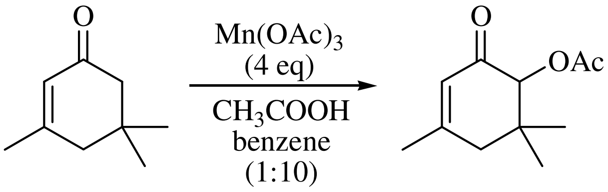
87 **88**

Scheme 64



87 **88**

Scheme 65



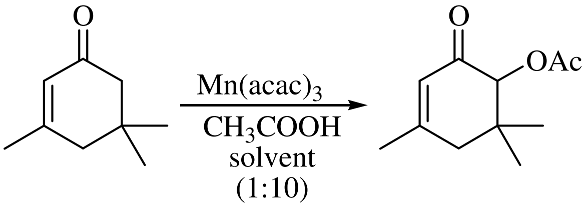
87 **88**

Scheme 66

2.4 Mn(acac)$_3$ Mediated α′-Acetoxylation Reactions

Mn(acac)$_3$ is another readily available Mn(III) reagent [41]. Mn(acac)$_3$ has been extensively used for oxidative coupling of phenols [55]. Mn(acac)$_3$ was suitable for oxidative radical cyclization reactions but it appeared to offer no advantages over Mn(OAc)$_3$ [54].

Knowing the fact that Mn(acac)$_3$ can be used in oxidative cyclization reactions instead of Mn(OAc)$_3$ has directed us to try the effect of Mn(acac)$_3$ in α′-acetoxylation reactions. For that purpose, for a series of experiments with isophorone **87**, Mn(acac)$_3$ was tried instead of Mn(OAc)$_3$. Several solvents (benzene, acetonitrile, cyclohexane and EtOH) were tested (Scheme 67).



87 **88**

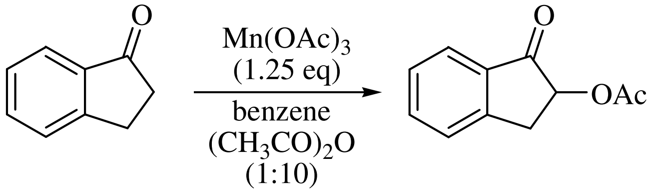
solvent: benzene, acetonitrile, cyclohexane, EtOH

Scheme 67

Throughout the experiments, it was observed from the GC-MS analyses that at the end of 3 hours, very little α′-acetoxylation product, 2'-acetoxy-isophorone **88**, was observed in all four solvents which makes the use of Mn(acac)$_3$ impractical for the α′-acetoxylation of isophorone.

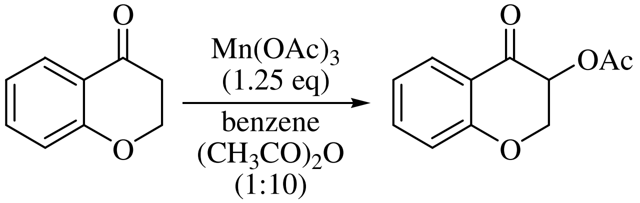
2.5 Determination of the Efficiency of Acetic Anhydride as a Co-solvent

As we have proven previously in this study, AcOH was a perfect co-solvent for the $Mn(OAc)_3$ mediated α´-acetoxylation of enones. Acetic anhydride could also have a similar effect in such reactions. For comparing the effectiveness of acetic anhydride instead of AcOH in such reactions, four different substrates (1-indanone **75**, 4-chromanone **105**, α-tetralone **91** and isophorone **87**) were tried (Scheme 68, 69, 70, 71 respectively). NMR and GC-MS results have revealed that acetic anhydride as a co-solvent instead of acetic acid showed a similar rate enhancement whereas the latter was more effective.



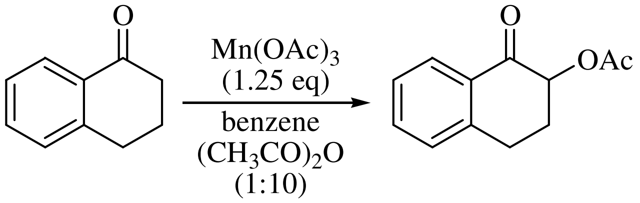
75 **76**

Scheme 68



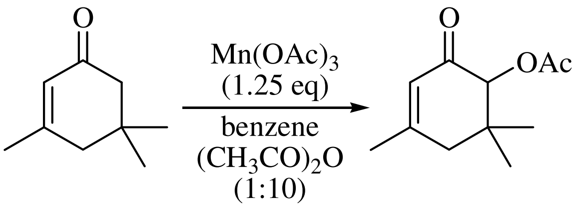
105 **95**

Scheme 69



91 **92**

Scheme 70



87 **88**

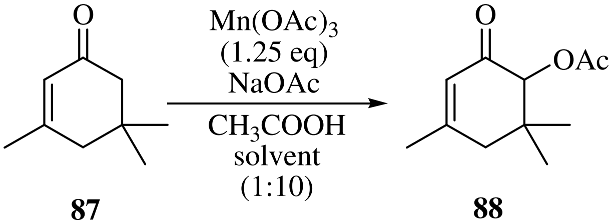
Scheme 71

2.6 Effects of NaOAc Addition to α′-Acetoxylation Reactions

Trying to produce valuable information for understanding the probable mechanism of manganese (III) acetate mediated α′-acetoxylation reactions, we intended to observe the results of enolization effect of sodium acetate. Heiba and Dessau have reported that the rate-determining step in α-keto radical formation from ketones involves reaction of Mn(III) with the enol or enolate [38]. The rate is independent of Mn(III) concentration, first order in ketone concentration and accelerated by acetate ion, which suggests that base-catalyzed enolization is the rate-determining step [138]. It has been stated in the literature that potassium or sodium acetate have been used with Mn(OAc)$_3$. Acetate anion may accelerate enolization and act as a buffer [41]. If, as Heiba and Dessau have reported, base-catalyzed enolization is the rate determining step [110], NaOAc addition should increase the reaction rates because of increasing enolization rate.

2.6.1 Solvent Screening Studies for Alkene Addition Reactions in the Presence of NaOAc

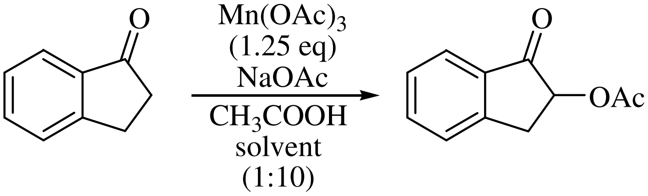
We have done a solvent screening study composed of the α′-acetoxylation reaction of isophorone **87** (Scheme 72) and 1-indanone **75** (Scheme 73) in benzene, acetonitrile and cyclohexane in the presence of NaOAc.



87 **88**

solvent: benzene, MeCN, cyclohexane

Scheme 72



75 **76**

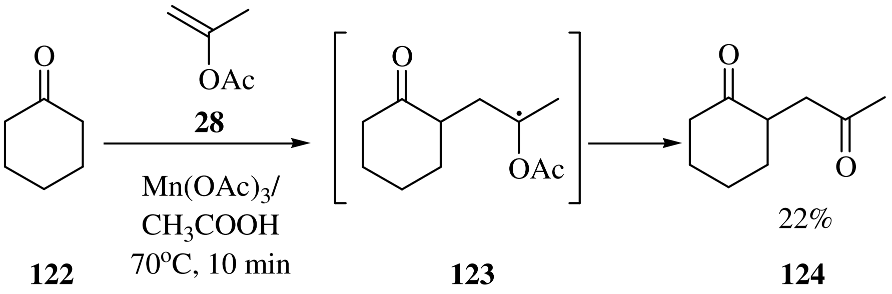
solvent: benzene, MeCN, cyclohexane

Scheme 73

Depending on the experimental results, we can say that we have not observed any beneficial improvement by the addition of NaOAc to the usual α'-acetoxylation reaction conditions. This observation conflicts with Heiba and Dessau's statement saying that the rate of the reaction was accelerated by acetate ion, which suggests that base-catalyzed enolization is the rate-determining step [138].

2.7 Addition of Unsaturated Systems to Ketones

Dessau and Heiba have stated that enol acetates as unsaturated systems can be used in reactions with aliphatic ketones, resulting in access to 1,4-diketones, key intermediates in cyclopentanone synthesis. Thus, the addition of cyclohexanone **122** to isopropenyl acetate **28** results initially in **123**, which stabilizes by β-elimination of an acetyl group forming 1,4-diketone **124** (Scheme 74) [45].



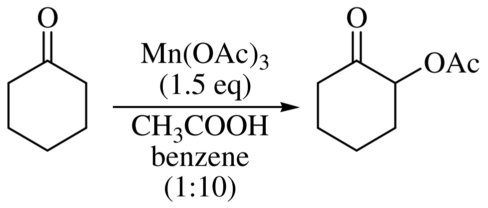
Scheme 74

Although yields are only moderate, reported due to polymerization of isopropenyl acetate, this route offers a single step preparation of 1,4-diketones from readily available reagents.

2.7.1 Oxidation of Cyclohexanone

2.7.1.1 Solvent Screening Studies for the Oxidation of Cyclohexanone

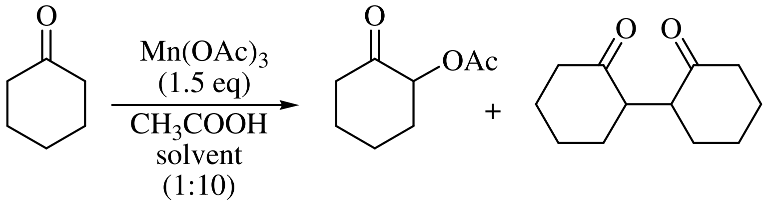
Keeping the above discussion in mind, we have planned to perform a screening study by reacting an unsaturated enol acetate, vinyl acetate **125** with both saturated and unsaturated ketones. First, we have started with cyclohexanone **122**. Before reacting with vinyl acetate, we intended to see the situation in the presence of only manganese (III) acetate. Oxidation of cyclohexanone afforded acetoxylation product, 2-acetoxycyclohexanone, **126** together with side products in an unoptimized reaction (GC-MS) (Scheme 75). The acetoxylated product **126** was purified by flash column chromatography and the analytical data of the product were in agreement with published values (Figure 38 (Appendix A)).



122 **126**

Scheme 75

When the GC-MS spectrum was closely inspected, the major side product was found to be the structure corresponding to the dimerization of cyclohexanone **127** (m/z 194). Although the amount of dimerization product was only 17% compared to acetoxylation product in the unoptimized reaction, we intended to see the behaviour of cyclohexanone in the acetoxylation reaction conditions but this time in different solvents. For that purpose, we carried out the same reaction in benzene, acetonitrile and cyclohexane and GC-MS analyses at the 4th hour have shown that the amount of cyclohexanone dimerization product greatly increased in cyclohexane and acetonitrile (Scheme 76). The change in the product distribution in different solvents most probably indicates that the route of the reaction shifts from one mechanism to another in different solvents.



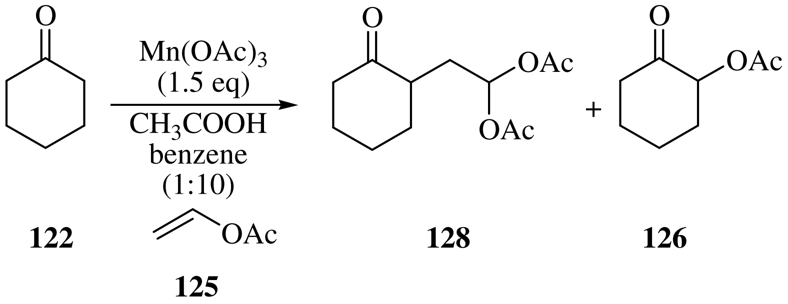
122 **126** **127**

solvent: benzene	**1**	:	**0.2**
acetonitrile	**0.8**	:	**1**
cyclohexane	**0.7**	:	**1**

Scheme 76

2.7.2 Addition of Vinyl Acetate to a Saturated Ketone (Cyclohexanone)

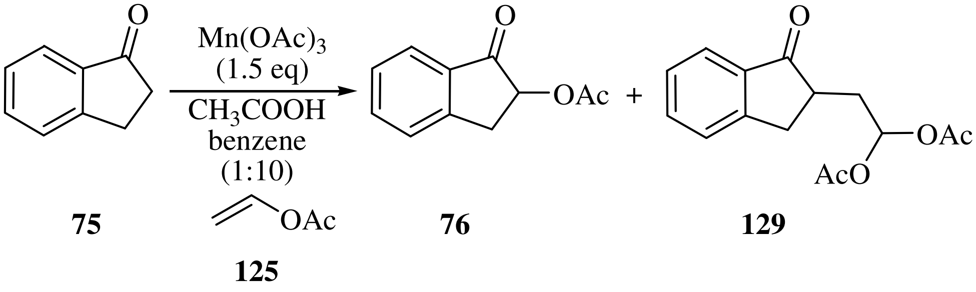
The same reaction in the presence of vinyl acetate **125** in 1:10 AcOH:benzene solvent system mainly afforded alkene addition product, 2-(2,2-diacetoxy-1-ethyl) cyclohexanone **128** along with little acetoxylation product **126** (Scheme 77). Analytical data of the alkene addition product were in accordance with its structure (Figure 39, 40 (Appendix A)).



Scheme 77

2.7.3 Addition of Vinyl Acetate to an Unsaturated Ketone (1-Indanone)

In the case of 1-indanone **75**, an unsaturated ketone, oxidation in the presence of vinyl acetate **125** afforded acetoxylation product **76** together with small amount (~15%) of alkene addition product, 2-(2,2-diacetoxy-1-ethyl) indanone **129** (Scheme 78). Analytical data of the alkene addition product were in accordance with its structure (Figure 41, 42 (Appendix A)).



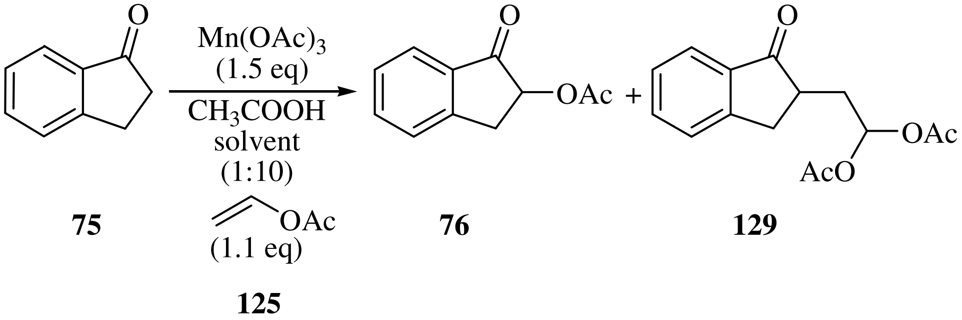
Scheme 78

From the above results it was seen that, in saturated systems (cyclohexanone), addition of vinyl acetate has afforded alkene addition as the major product and α′-acetoxylation as the minor one. But in unsaturated systems (1-indanone) the product distribution was just the opposite upon vinyl acetate addition; major product has come from α′-acetoxylation and alkene addition has given the minor product. This product distribution phenomenon will be discussed later.

We have wondered if the amount of the desired alkene addition product can be increased and α′-acetoxylation product can be decreased by decreasing the amount of acetic acid or omitting the addition of acetic acid at all. Normally, 1:10 acetic acid:benzene solvent system was being used. This time, 1:10 ratio, 1:100 ratio and no acetic acid cases were compared. Analytical data of the experimental results have shown that decreasing the amount of acetic acid decreases the formation of both α′-acetoxylated and alkene addition products. Adding no acetic acid greatly decreased the formation of both products. From the above observations, we can say that AcOH is needed for the formation of both α′-acetoxylation and alkene addition products.

2.7.3.1 Solvent Screening Study for the Addition of Vinyl Acetate to 1-Indanone

A solvent screening study was done for the vinyl acetate **125** addition to 1-indanone **75**. The reactivity and product distribution was compared for the reactions in benzene, acetonitrile and cyclohexane. The α′-acetoxylation:alkene addition product distribution was ~2:1 in benzene, ~1:2 in acetonitrile and ~1:1 in cyclohexane which was observed in crude NMR spectra (Scheme 79). These results have shown that when the reaction conditions are optimized, by changing the solvent system, either α′-acetoxylation or alkene addition product can be obtained depending on our needs. The change in the product distribution in different solvents most probably indicates that the route of the reaction shifts from one mechanism to another in different solvents.



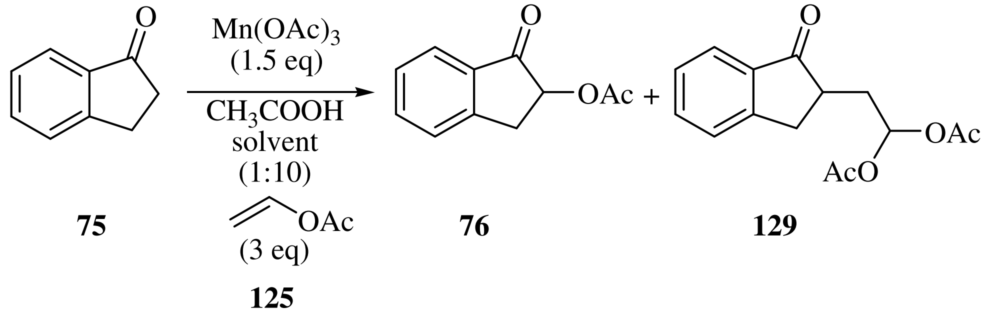
solvent: benzene	**2**	**:**	**1**
acetonitrile	**1**	**:**	**2**
cyclohexane	**1**	**:**	**1**

Scheme 79

2.8 Addition of Vinyl Acetate to 1-Indanone in the Presence of NaOAc

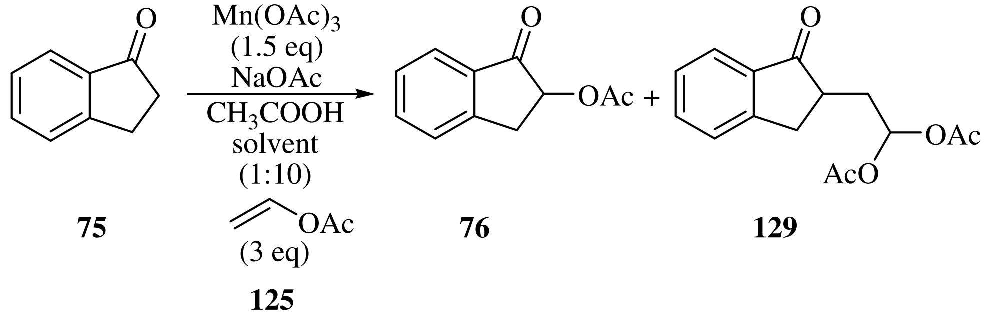
2.8.1 Solvent Screening Studies in the Presence of NaOAc

It was known from our previous solvent screening studies for addition of 1-indanone **75** to vinyl acetate **125** that the desired alkene addition product can be obtained in greater amounts than α′-acetoxylation product in acetonitrile and cyclohexane rather than in benzene. In another solvent screening study we intended to see whether addition of sodium acetate to the reaction mixture increases the formation of alkene addition product in acetonitrile and cyclohexane or not (Scheme 80 and 81); but this time amount of vinyl acetate was increased from 1.1 equiv. to 3 equiv.



solvent: acetonitrile, cyclohexane

Scheme 80



solvent: acetonitrile, cyclohexane

Scheme 81

When the reactions of 1-indanone **75** were followed by GC-MS and NMR, the following results were observed: In both acetonitrile and cyclohexane, the reactions which contain NaOAc have given lower alkene addition product yield and higher yield of α′-acetoxylated product when compared to the ones which do not contain NaOAc. From those results we can say that, addition of sodium acetate to the reactions of 1-indanone **75** and vinyl acetate **125** both in cyclohexane and acetonitrile decreases the formation of alkene addition product. The reaction of 1-indanone **75** with 3 equiv. of vinyl acetate **125** in cyclohexane in the absence of NaOAc has given similar results with the 1.1 equiv. of vinyl acetate case. The product distribution between α′-acetoxylation and alkene addition was again ~1:1 in cyclohexane. But in acetonitrile without NaOAc, increasing the amount of vinyl acetate from 1.1 equiv. to 3 equiv. greatly increased the amount of alkene addition product compared to the α′-acetoxylated one. Taking the above observations into account, we can say that formation of alkene addition product was maximum in acetonitrile (compared to benzene and cyclohexane) with 3 equiv. of vinyl acetate in the absence of sodium acetate which can further be optimized for better yields.

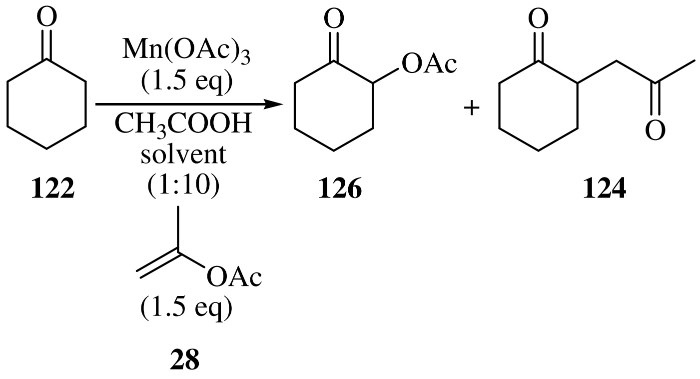
2.9 Addition of Other Unsaturated Systems to Ketones

2.9.1 Solvent Screening Studies

After obtaining valuable alkene addition products in the reactions of vinyl acetate **125** with both cyclohexanone **122** and 1-indanone **75**, we have planned to try other alkene addition reactions using different reagents. For that purpose we have selected cyclohexanone **122** as our candidate molecule and studied the alkene addition reactions with both isopropenyl acetate **28** and diphenyl ethylene **130**.

2.9.1.1 Addition of Isopropenyl Acetate to Cyclohexanone

The addition of isopropenyl acetate **28** to cyclohexanone **122** was performed in two different solvents –benzene and acetonitrile-. The crude GC-MS analyses have shown that two major peaks arise besides some trace amounts of side products in unoptimized reaction conditions (Scheme 82). The reaction which was performed in acetonitrile was much more efficient than the one in benzene when the side product amount was compared with the amount of the product. The ratio of α-acetoxylation product **126** to alkene addition product **124** was 0.5:1 in benzene and 0.1:1 in acetonitrile. So we can say that in order to obtain alkene addition product **124** in the presence of isopropenyl acetate **28**, acetonitrile was a better solvent compared to benzene. Better results can be obtained after optimizing the reaction conditions.

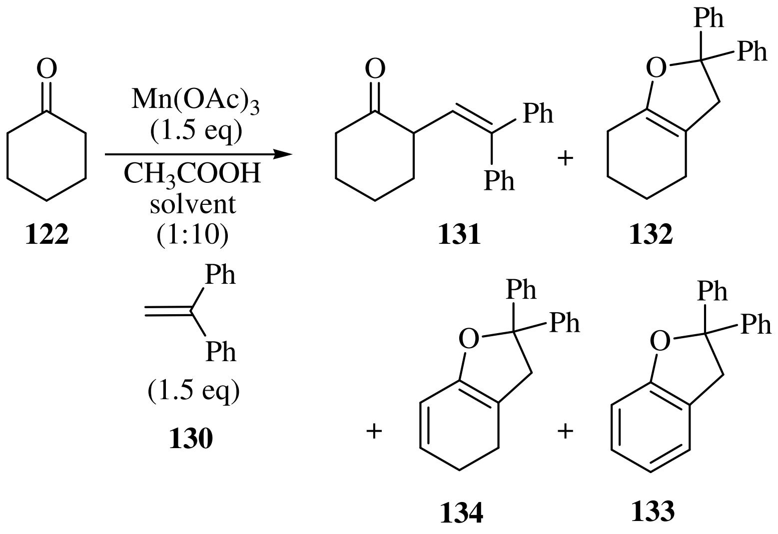


solvent: benzene	**0.5**	:	**1**
acetonitrile	**0.1**	:	**1**

Scheme 82

2.9.1.2 Addition of Diphenylethylene to Cyclohexanone

In our foregoing studies, we have tried another alkene addition reaction, but this time with diphenylethylene **130**. When the GC-MS spectrum was closely investigated, it was observed that the alkene addition product **131** was obtained. But in addition to alkene addition product, some other major peaks were observed in GC-MS spectrum. The mass data of the other peaks seen in GC have shown a furan formation reaction **132** followed by aromatization **133** passing through **134** (Scheme 83). In the GC-MS spectrum taken at the 2nd hour, the product distribution ratio was 1.8:1:1.3 for **132:134:133**. At the end of 3rd hour, it was observed that the intensity of the peak corresponding to **133** has shown a great increase whereas the intensities of the peaks corresponding to **132** and **134** have shown a drastic decrease. The molecular weights of **131** and **132** are the same, so from that knowledge we can say that alkene addition was successfully performed; later, that alkene addition product **131** experiences a cyclization reaction forming a furan ring followed by aromatization. Both reactions performed in benzene and acetonitrile have given similar results. After optimizing the reaction conditions, this alkene addition reaction can be used for specific needs.



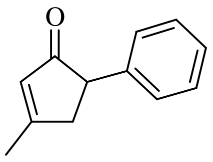
solvent: benzene, acetonitrile

Scheme 83

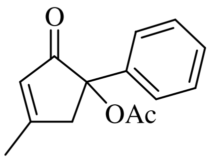
2.10 A Brief Summary of the Experimental Studies and Mechanism Discussion

In this study, we have done many screening studies so as to understand the behaviour of manganese (III) acetate towards different substrates in different solvent systems, with or without co-solvent, with additive reagents, and so on. A brief discussion of the results is done below.

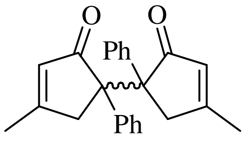
Although conditions were not optimized for any particular enone type, excellent results were obtained for a variety of enones. As can be seen in Table 3, these are the best available yields for the specified conversion except the fact that highly toxic reagent thallium(III) triflate (not shown in table) provides **76** in a 99% yield [104]. Considering many high yield (>90%) hydrolysis methods for α-acetoxy groups that were developed thus far, this optimized protocol can also be considered as one of the most useful ways to obtain α´-hydroxy α,β-unsaturated ketones [139]. Generally, no product other than acetoxylation was detected in the ^{1}H-NMR spectrum of crude products and they were pure enough for further synthetic manipulations. An apparent exception was observed for the cyclopentenones **113** and **114** in which a small amount of side products were detected in crude mixtures by NMR and GC-MS. These products were identified for **114** and found to be an α´-phenylation product **115**, α´-phenylation and α´-acetoxylation product **116** and a dimerization product **117**. Products **115**, **116** and **117** (two isomers were separated providing a 1:3 ratio) was isolated in an approximate ratio of 1:2.5:2 accounting for ~15% of the starting material. These seem to be pointing out the intermediacy of **115**, which is acetoxylated at the benzylic position or dimerized in an alternative pathway. Thus, phenylation instead of acetoxylation is a minor alternative route, resulting in aromatic signals in NMR spectra of crude products of $Mn(OAc)_3$ mediated acetoxylation reactions. In a previous report, the formation of products **117** and **119** was reported, but not **115** and **116** [129]. Although these products do not have any importance from a synthetic point of view, they would be useful towards understanding the nature of the reaction as discussed below.



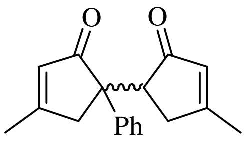
115



116

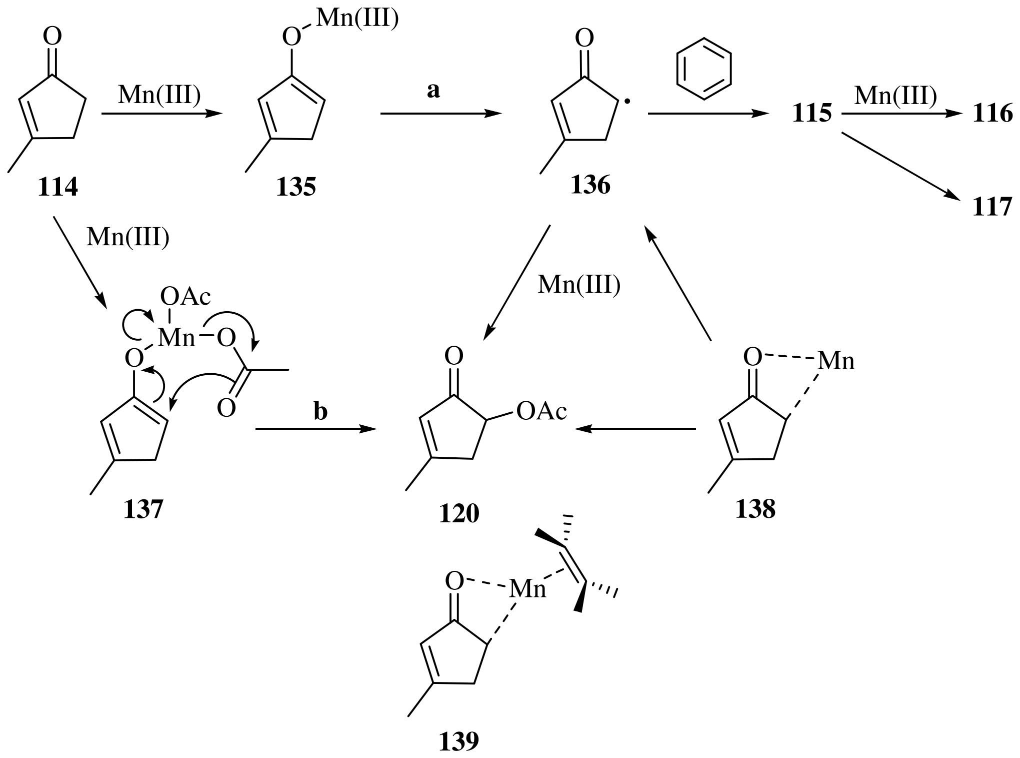


117



119

It is hard to justify the role of acetic acid, but it could be related to an increased solubility of $Mn(OAc)_3$ in the reaction mixture. Although the structure of $Mn(OAc)_3$ has been shown to be an oxo-centered triangle of Mn(III) with bridging acetates, the prevalent form in benzene and a benzene:acetic acid mixture can be quite different resulting in different conversion rates and isolated yields. For the mechanism of the reaction, both radical mechanism (route **a**) and ligand transfer via metal-enolate intermediate (route **b**, proposed based on $Pb(OAc)_4$ mediated acetoxylation of carbonyl compounds) have been proposed (Scheme 84) [62]. Since $Mn(OAc)_3$ is a single electron oxidant and a vast majority of the reactions mediated by it have been shown to be taking place via a radical mechanism, route **a** is widely accepted [9, 41, 140].



Scheme 84

Although discrimination between the mechanisms is not a trivial question at this stage, we wish to underline a few points. Stable Pb(II) is produced via reductive elimination in Pb(IV) mediated acetoxylation, whereas Mn(I) would be formed instead of a stable Mn(II) in a Mn(III) mediated reaction. Although this point differs Mn(III) from Pb(IV) and favor the radical mechanism, we obtained far beyond 50% conversion with 1 equiv. $Mn(OAc)_3$ in accordance with route **b** which should be at least 2 equiv. for a radical mechanism. Reaction rate depends on the $Mn(OAc)_3$ concentration under the specified reaction conditions. The use of NaOAc (in benzene, acetonitrile or cyclohexane) and $Yb(OTf)_3$ (in benzene) did not promote the reaction in the absence of acetic acid [141] Heiba and Dessau have reported that the rate of α-keto radical formation is independent of the Mn(III) concentration and enolization is the rate determining step [142] The dependence of reaction rate on the Mn(III) concentration could indicate that **135** is not an intermediate of this reaction, rather, carboxymethyl radicals generated by Mn(III) [9, 41, 140] might react with the enone to directly provide the **136** in a rate determining step. However, it was shown by ESR studies that radical initiators generate allylic radicals from enone systems unless the allylic position is not blocked by substituents [143]. Moreover computational calculations showed that allylic radicals are more stable compared to α´-keto radicals [144]. These clearly show that if an α´-keto radical is an intermediate, it should be formed via a kinetically favored enol oxidation, strongly supporting the intermediacy of enol-Mn(III) interaction **137**. In a preliminary experiment, oxidation of **75** in the presence of vinyl acetate **125** afforded acetoxylation together with small amount (~15%) of alkene addition product **129** (Scheme 78). Oxidation of cyclohexanone **122** afforded acetoxylation **126** together with side products in an unoptimized reaction (GC-MS). Same reaction in the presence of vinyl acetate **125** mainly afforded product **128** along with little acetoxylation **126** (Scheme 77). Different behavior of enones and saturated ketones towards the presence of alkenes can be solely explained by faster oxidation of α´-keto radicals derived from enones compared to ones derived from saturated ketones [145]. However this seems to be a rather weak explanation considering the variety of enones that provided similar (almost quantitative) yields without side products that could potentially be formed from a radical intermediate, a case only observed for cyclopentenones **113** and **114**. Although route **b** explains the results for enones, it fails not only for different behavior of enones and saturated ketones but also for cyclopentenones **113** and **114**. It is possible that different mechanisms are operative for these substrates. Thus detailed kinetic studies for a better revisioned mechanism are necessary. However, it is possible that both routes (**a** and **b**) are alternative parts of the real process and shares a common intermediate that determines the result of the reaction. A plausible scenario is that a homolysis labile organomanganese (or a radical weakly bound to manganese for which alkene and Mn(III) competes) intermediate **138** is formed from **137**, subsequently reductively eliminated to form **120** (requires 1 equiv. of $Mn(OAc)_3$) or homolytically cleaved to **136** depending on reaction conditions and substrate [146]. It is noteworthy to point out that **138** is a very simplistic picture of a possible intermediate showing a labile substrate-oxidant interaction and not indicative of any binding mode between them. It has been reported that alkenes coordinate to Mn(III) and change the rate of the reaction [83, 147]. This type of interaction like **139** could also be possible for the present reaction affecting the behavior of the possible intermediate **138** towards added alkenes in the reaction mixture. It should be remembered that the presence of Mn(IV) species in the starting oxidant or their formation during the reaction is another possibility to be questioned. Considering that there is no direct evidence currently available on the active species, it is hard to justify a more lengthy discussion necessarily based on speculation. However, detailed kinetic experiments including oxidation of saturated ketones and alkene additions can provide rational information about the intermediates, a subject already under investigation.

CHAPTER 3

EXPERIMENTAL

All reagents were of commercial quality and reagent quality solvents were used without further purification. NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ were reported in ppm relative to $CHCl_3$ (^1H: δ= 7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards. Column chromatography was conducted on silica gel 60 (mesh size 40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ= 254 nm). GC-MS: ThermoQuest Finnigan multi Mass (EI, 70 eV).

3.1 α′-Acetoxylation of Various Unsaturated Enones

3.1.1 α'-Acetoxy-1-Indanone 76

A solution of 1-indanone **75** (132.16 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 1 hour during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain colorless solid α'-acetoxy-1-indanone **76** (186.4 mg, 98% $C_{11}H_{10}O_3$).

^{1}H NMR ($CDCl_3$): δ=7.27-7.65 (m, 4H), 5.26-5.29 (m, 1H), 3.48-3.55 (m, 1H), 2.89-2.94 (m, 1H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=200.2, 170.2, 150.5, 135.9, 134.9, 128.3, 127.2, 124.7, 74.2, 33.7, 20.9.

3.1.2 α′-Acetoxy-Isophorone 88

A solution of isophorone **87** (138.21 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 7 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain yellowish solid α′-acetoxy-isophorone **88** (194.3 mg, 99% $C_{11}H_{16}O_3$).

^{1}H NMR ($CDCl_3$): δ=5.82 (s, 1H), 5.12 (s, 1H), 2.50 (s, 1H), 2.45 (s, 1H), 2.14 (s, 3H), 1.89 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H).

3.1.3 α′-Acetoxy-β-Ethoxy Cyclohexenone 79

A solution of 3-ethoxy-2-cyclohexen-1-one **77** (140.18 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 7 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain colorless oil α′-acetoxy-β-ethoxy cyclohexenone **79** (192.3 mg, 97% $C_{10}H_{14}O_4$).

^{1}H NMR ($CDCl_3$): δ=5.26 (s, 1H), 5.18 (dd, J_1=7.42, J_2=5.22 Hz, 1H), 3.84 (q, J=3.86 Hz, 2H), 2.50 (m, 1H), 2.26 (m, 1H), 2.08 (s, 3H), 1.99 (m, 1H), 1.30 (t, J=3.74 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=192.6, 176.5, 169.8, 101.3, 72.5, 64.9, 28.2, 26.9, 20.9, 14.1.

3.1.4 α′-Acetoxy-1-Tetralone 92

A solution of 1-tetralone **91** (146.19 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 5 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain colorless solid α′-acetoxy-1-tetralone (200.1 mg, 98% $C_{12}H_{12}O_3$).

^{1}H NMR ($CDCl_3$): δ=7.95 (d, *J*=7.8 Hz, 1H), 7.41 (t, *J*=7.41 Hz, 1H), 7.25 (t, *J*=7.63 Hz, 1H), 7.18 (t, *J*=7.8 Hz, 1H), 5.44 (dd, J_1=8.13, J_2=5.17 Hz, 1H), 3.20-2.96 (m, 2H), 2.35-2.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=192.4, 169.8, 142.9, 133.7, 133.7, 131.7, 128.5, 127.9, 126.9, 74.4, 29.2, 28.0, 20.8

3.1.5 2′-Acetoxy-6-Methoxy-1-Tetralone 94

A solution of 6-methoxy-1-tetralone **93** (176.21 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 5 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain yellow solid 2′-acetoxy-6-methoxy-1-tetralone **94** (227.2 mg, 97% $C_{13}H_{14}O_4$).

^{1}H NMR ($CDCl_3$): δ=7.92 (d, *J*=8.75 Hz, 1H), 6.76 (d, *J*=8.75 Hz, 1H), 6.60 (s, 1H), 5.40 (dd, J_1=13.1, J_2=5.1 Hz, 1H), 3.79 (s, 3H), 3.05 (m, 2H), 2.30 (m, 2H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=191.9, 170.4, 164.3, 146.0, 130.4, 125.3, 113.9, 112.8, 74.6, 55.8, 29.4, 28.5, 21.1.

3.1.6 2′-Acetoxy-4-Chromanone 95

A solution of 4-chromanone **105** (148.16 mg, 1 mmol) and Mn(OAc)$_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for5 hours during which the dark brown color of Mn(OAc)$_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over MgSO$_4$ and concentrated under vacuum to obtain colorless solid 2′-acetoxy-4-chromanone **95** (197.9 mg, 96% $C_{11}H_{10}O_4$).

^{1}H NMR (CDCl$_3$): δ=7.8 (d, *J*=7.8 Hz, 1H), 7.4 (t, *J*=8.4 Hz, 1H), 6.9 (t, *J*=7.5 Hz, 1H), 6.8 (d, *J*=8.4 Hz, 1H), 5.6 (dd, J_1=11.3, J_2= 5.5 Hz, 1H), 4.5 (dd, J_1=11.2, J_2= 5.5 Hz, 1H), 4.3 (dd, J_1=11.3, J_2= 11.2 Hz, 1H), 2.1 (s, 3H); ^{13}C NMR (CDCl$_3$): δ=187.8, 169.3, 161.6, 136.6, 128.0, 122.3, 120.3, 118.1, 69.7, 68.6, 20.8.

3.1.7 α′-Acetoxy-4-Thiochromanone 96

A solution of 4-thiochromanone **106** (164.22 mg, 1 mmol) and Mn(OAc)$_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 5 hours during which the dark brown color of Mn(OAc)$_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over MgSO$_4$ and concentrated under vacuum to obtain yellow solid α′-acetoxy-4-thiochromanone **96** (213.4 mg, 96% $C_{11}H_{10}O_3S$).

^{1}H NMR (CDCl$_3$): δ=8.0 (d, *J*=7.9 Hz, 1H), 7.4 (t, *J*=7.9 Hz, 1H), 7.2 (m, 2H), 5.7 (dd, J_1=13.5, J_2= 4.5 Hz, 1H), 3.5 (dd, J_1=13.2, J_2= 12.9 Hz, 1H), 3.1 (dd, J_1=12.6, J_2= 4.5 Hz, 1H); ^{13}C NMR (CDCl$_3$): δ=188.6, 169.0, 140.5, 133.5, 130.4, 129.9, 126.9, 125.1, 73.1, 30.1, 20.5.

3.1.8 2′-Acetoxy-4-Cholesten-3-One 112

A solution of 4-cholesten-3-one **111** (342.56 mg, 1 mmol) and Mn(OAc)$_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 11 hours during which the dark brown color of Mn(OAc)$_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over MgSO$_4$ and concentrated under vacuum to obtain 2′-acetoxy-4-cholesten-3-one **112** (392.6 mg, 98% $C_{26}H_{40}O_3$). Further purification was performed by flash column chromatography on silica gel (1:10 EtOAc:Hexane) and major and minor isomers were separated in 6:1 ratio.

Major isomer: White solid, mp 102-104°C (EtOAc-Hexane); ^{1}H-NMR (CDCl$_3$): δ=5.7 (s, 1H), 5.25 (dd, J_1=12.5, J_2=4.9 Hz, 1H), 2.47-2.37 (m, 1H), 2.23-2.14 (m, 2H), 2.07 (s, 3H), 2.0-1.7 (m, 4H), 1.6-1.15 (m, 10H), 1.12 (s, 3H), 1.1-0.9 (m, 9H), 0.83 (d, J=6.5 Hz, 3H), 0.79 (d, J=5.5 Hz, 6H), 0.63 (3H, s); ^{13}C NMR (CDCl$_3$): δ=194.0, 173.8, 170.6, 129.4, 120.8, 70.9, 56.4, 56.1, 51.0, 43.2, 41.4, 39.9, 39.8, 37.8, 36.4, 36.1, 35.0, 33.3, 28.6, 28.3, 24.5, 24.2, 23.2, 22.9, 22.6, 21.3, 18.9, 12.4. Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47; Found: C, 78.85; H, 10.66.

Minor isomer: White solid, mp 121-123 °C (EtOAc-Hexane); ^{1}H-NMR (CDCl$_3$): δ=5.67 (s, 1H), 5.38 (dd, J=15, 5.3 Hz, 1H), 0.85-2.35 [(1.24, CH$_3$ and 2.10, CH$_3$), m, 22H], 0.84 (d, J=6.4 Hz, 3H), 0.79 (d, J=6.5 Hz, 6H), 0.63 (s, 3H); ^{13}C NMR (CDCl$_3$) δ=194.1, 171.6, 170.7, 122.0, 71.7, 56.4, 56.1, 54.7, 42.7, 41.8, 41.0, 39.9, 39.8, 36.5, 36.1, 35.4, 32.9, 32.3, 28.5, 28.4, 24.4, 24.1, 23.2, 22.9, 21.3, 21.2, 19.0, 18.5, 12.3. Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47; Found: C, 78.75; H, 10.57.

3.2 α′-Acetoxylation of α,β-Unsaturated Cyclopentanone Derivatives

3.2.1 2′-Acetoxy-3-Methyl-2-Cyclopenten-1-One 118

A solution of 3-methyl-2-cyclopenten-1-one **114** (96.13 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 2 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain 2′-acetoxy-3-methyl-2-cyclopenten-1-one **118** (127.9 mg, 83% $C_8H_{10}O_3$). Further purification was performed by flash column chromatography on silica gel (1:7 EtOAc:Hexane) and in addition to **118** products **115**, **116** and **117** (two isomers were separated providing a 1:3 ratio) were isolated in an approximate ratio of 1:2.5:2 accounting for ~15% of the starting material.

3.2.1.1 2′-Acetoxy-3-Methyl-2-Cyclopenten-1-One 118

Colorless oil, (127.9 mg, 83% $C_8H_{10}O_3$); ^{1}H NMR ($CDCl_3$): δ=5.92 (s, 1H), 5.05 (dd, J_1=3.79, J_2= 3.10 Hz, 1H), 2.96 (m, 1H), 2.44 (m, 1H), 2.10 (s, 3H), 2.06 (s, 3H).

3.2.1.2 4,4′-Dimethyl-1,1′-Diphenyl-Bicyclopentyl-3,3′-Diene-2,2′-Dione 117

Major isomer. White solid, $C_{24}H_{22}O_2$; mp 165°C (decompose); ^{1}H NMR ($CDCl_3$): δ=7.57 (d, J=7.4 Hz, 4H), 7.13 (m, 6H), 5.47 (s, 2H,), 3.95 (d, J=19.6 Hz, 2H), 2.94 (d, J=19.6 Hz, 2H), 1.71 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=209.7, 177.8, 138.9, 130.6, 129.9, 128.1, 127.4, 60.7, 45.9, 19.1.

Minor isomer. White semi-solid, $C_{24}H_{22}O_2$; ^{1}H NMR ($CDCl_3$) δ=7.15 (m, 6H), 7.05 (m, 4H), 5.74 (s, 2H), 3.9 (d, J=18 Hz, 2H), 2.51 (d, J=18 Hz, 2H), 2.0 (s, 6H); ^{13}C NMR ($CDCl_3$) δ=209.3, 177.0, 139.7, 129.7, 129.1, 127.7, 127.6, 60.1, 46.0, 19.7.

3.2.1.3 5-Acetoxy-3-Methyl-5-Phenyl-2-Cyclopentenone 116

Colorless oil, $C_{14}H_{14}O_3$; ^1H NMR ($CDCl_3$) δ=7.25 (m, 5H), 5.99 (d, *J*=1 Hz, 1H), 3.24 (d, *J*=18.3 Hz, 1H), 3.05 (d, *J*=18.3 Hz, 1H), 2.16 (d, *J*=1 Hz, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=202.4, 174.2, 170.1, 138.2, 128.7, 128.54, 128.51, 124.9, 84.9, 47.2, 21.5, 19.9; MS (EI), m/z 230 ($M^{+\cdot}$, 7), 187 (33), 170 (15), 141 (10), 128 (9), 105 (100), 76 (29). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; Found: C, 73.15; H, 6.24.

3.2.1.4 3-Methyl-5-Phenyl-2-Cyclopentenone 115

White solid, $C_{12}H_{12}O$; ^1H NMR ($CDCl_3$): δ=7.16 (m, 5H), 5.94 (s, 1H), 3.53 (dd, J_1=4.57, J_2= 2.65 Hz, 1H), 3.04 (m, 1H), 2.62 (m, 1H), 2.15 (s, 3H).

3.2.2 2′-Acetoxy-2-Cyclopenten-1-One 120

A solution of 2-cyclopenten-1-one **113** (82.1 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 2 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum to obtain white solid 2′-acetoxy-2-cyclopenten-1-one **120** (105.1 mg, 75% $C_7H_8O_3$).

^1H NMR ($CDCl_3$): δ=7.59 (m, 1H), 6.18 (m, 1H), 5.01 (dd, J_1=3.82, J_2= 3.06 Hz, 1H), 3.09 (m, 1H), 2.53 (m, 1H), 2.06 (s, 3H).

3.3 Addition of Unsaturated Systems to Ketones

3.3.1 Oxidation of Cyclohexanone

A solution of cyclohexanone **122** (98.1 mg, 1 mmol) and $Mn(OAc)_3$ (335 mg, 1.25 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) for 4 hours during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. Further purification was performed by flash column chromatography on silica gel (1:7 EtOAc:Hexane).

3.3.1.1 2-Acetoxycyclohexanone 126

^{1}H NMR ($CDCl_3$): δ=5.10 (t, *J*=10 Hz, 1H), 2.10 (s, 3H), 2.7-1.7 (m, 8H).

3.3.2 Addition of Vinyl Acetate to a Saturated Ketone (Cyclohexanone)

A solution of cyclohexanone **122** (98.1 mg, 1 mmol), $Mn(OAc)_3$ (335 mg, 1.25 mmol) and vinyl acetate **125** (94.7 mg, 1.1 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. Further purification was performed by flash column chromatography on silica gel (1:7 EtOAc:Hexane).

3.3.2.1 2-(2,2-Diacetoxy-1-Ethyl)-Cyclohexanone 128

Colorless liquid, ^{1}H NMR ($CDCl_3$): δ=6.70 (dd, J_1=5.7, J_2=5.3 Hz, 1H), 2.38–2.16 (m, 6H), 2.0 (s, 3H), 1.98 (s, 3H), 1.81 (m, 1H,), 1.60 (m, 1H,), 1.47 (m, 1H,); 1.34

(m, 1H,); ^{13}C NMR ($CDCl_3$): δ=210.3, 168.8, 168.7, 89.7, 46.0, 42.1, 34.8, 33.3, 28.3, 25.5, 21.0. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49; Found: C, 59.65; H, 7.54.

3.3.3 Addition of Vinyl Acetate to an Unsaturated Ketone (1-Indanone)

A solution of 1-indanone **75** (132.16 mg, 1 mmol), $Mn(OAc)_3$ (335 mg, 1.25 mmol) and vinyl acetate **125** (94.7 mg, 1.1 mmol) in 11 mL benzene:AcOH (10:1) solvent system was stirred under reflux (Dean-Stark apparatus) during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC-MS and TLC. After all starting material was consumed; the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. Further purification was performed by flash column chromatography on silica gel (1:7 EtOAc:Hexane).

3.3.3.1 2-(2,2-Diacetoxy-1-Ethyl)-Indanone 129

Colorless viscous oil, ^{1}H NMR ($CDCl_3$) δ=7.6 (d, J=7.7 Hz, 1H), 7.52 (m, 1H), 7.6 (d, J=7.3 Hz, 1H), 7.3 (m, 1H), 6.88 (dd, J_1=4.6, J_2=6.6 Hz, 1H), 3.35 (dd, J_1=8.1, J_2=17.1 Hz, 1H,), 2.89 (dd, J_1=17.1, J_2=4.5 Hz, 1H), 2.66 (m, 1H), 2.48 (m, 1H), 2.03 (s, 3H), 1.97 (s, 3H), 1.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=206.1, 168.7, 168.6, 153.4, 136.6, 135.1, 127.8, 126.7, 124.4, 89.7, 43.2, 35.0, 33.4, 21.1. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; Found: C, 65.31; H, 5.97.

CHAPTER 4

CONCLUSION

In conclusion, we have presented an improved procedure based on the use of acetic acid as a co-solvent. From a synthetic point of view, excellent results were obtained for a variety of structurally diverse and synthetically important enones under optimized conditions. From an economical point of view, as low as 1.25 equiv. $Mn(OAc)_3$ can be used as compared to the previously used 4-6 equiv. Moreover, MeCN and cyclohexane can also be used instead of benzene and acetic anhydride instead of acetic acid even though the presented conditions seem to be the best choice. However, combinations of these possibilities may prove to be more useful for different substrates and applications. We have also shown in unoptimized reactions that saturated ketones can be substrates of the $Mn(OAc)_3$ mediated acetoxylation. Besides, these optimized conditions can be useful for the intramolecular addition of ketones to alkenes previously reported to be a low yield process that generally requires the use of an excess amount of carbonyl compound. As a result, this report will be helpful by providing not only reliable and reproducible results for the $Mn(OAc)_3$ mediated acetoxylation of enones, but also a better understanding of the reaction for other applications utilizing $Mn(OAc)_3$.

CHAPTER 5

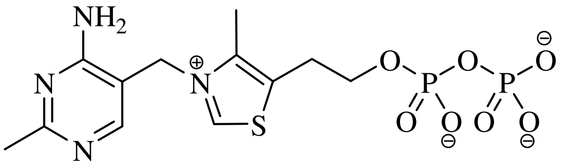
INTRODUCTION

5.1 Pyrroles as Natural Products

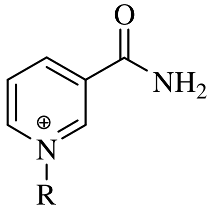
5.1.1 Monopyrroles as Natural Products

About one-half of all known compounds contain a heterocyclic ring, and many of these are aromatic heterocyclic rings. Heteroaromatics are found in many of the products of both primary and secondary metabolism as well as in many synthetic compounds of commercial interest such as drugs, pest control agents, colouring agents, flavourings. They comprise the basic building blocks for many new materials such as porphyrazines and semi-conducting polymers, and as ligands for homogeneous asymmetric catalysis. Thus they are of vital importance and still represent a very active area of current research.

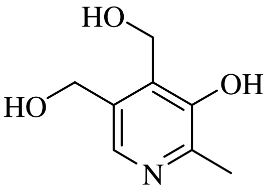
Heterocycles have played an important role in the evolution of life. Most coenzymes and vitamins contain heterocycles. The heterocyclic ring is often the central constituent necessary to fulfill the biological function of the coenzymes, thiamine pyrophosphate **140**, NAD^+ **141** and Vitamin B_6 **142**.



140

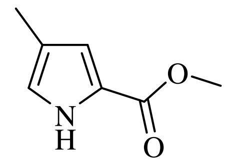


141



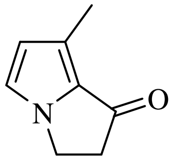
142

This observation has led to the idea that coenzymes were formed early in the history of life (they may have been present during the prebiotic period of evolution). In this context it is remarkable that the pyridine ring as a typical representative of the electron poor heterocycles is present in cofactors like NAD, NADH. In contrast to the electron poor heterocycles which are widely present in nature, the electron rich heterocycles like pyrroles, furans and thiophenes are found less often. Despite the fact that pyrrole belongs to the structurally simple five-membered heterocycles, relatively few natural products containing only one pyrrole ring are known [148-151]. Some examples to monopyrrolic natural products are given below (**143-148**).



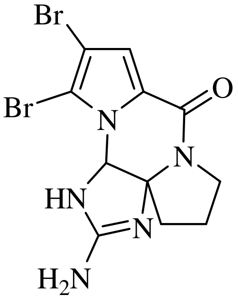
trail pheromone of
leaf-cutting ant
Acromyrmex

143



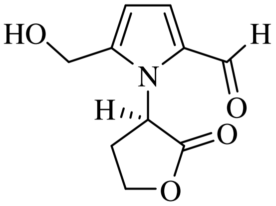
Male sex
pheromone from
butterfly family
Danainae

144



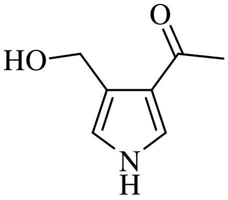
dibromophakellin
from marine sponge
Phakellia flabellata

145



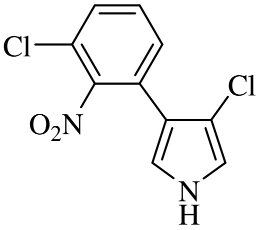
regulator of
trigonelline-induced
G2 arrest from
Pisum sativum

146



verrucarin E
from the fungus
Myrothecium verroceire

147



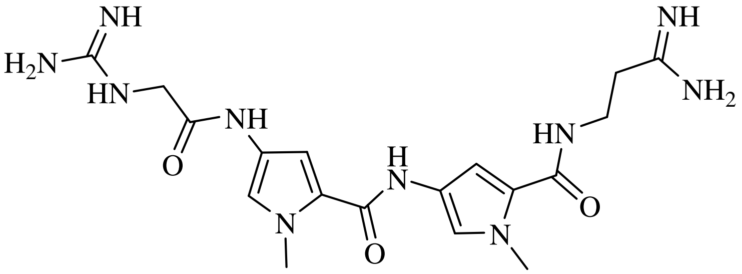
Pyrrolnitrin antibiotic
from *Pseudomonas*
pyrrocinia

148

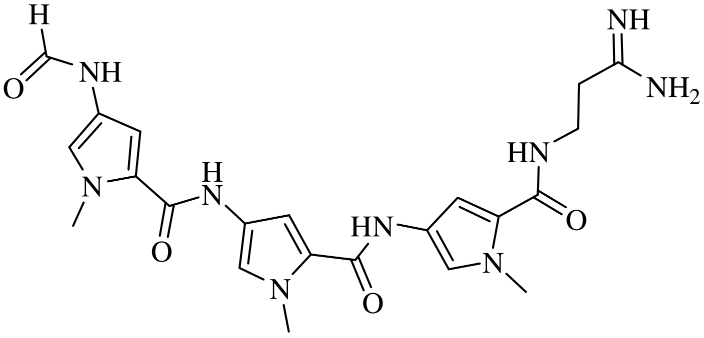
Their biological functions are as varied as their structures **143-148** [152-154]. Some natural pyrroles are pheromones **144** [155, 156], plant hormones **146** [157] or act as antibiotics **148** [158].

5.1.2 Polypyrroles as Natural Products

Two important examples of pyrrole derived natural products containing more than one pyrrole ring are Neotropsin **149** and Distamycin A **150** which bind to the minor groove of DNA [159]. They contain a series of pyrrole rings which are linked by amide bonds.



149

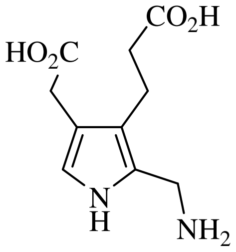


150

5.1.3 Pyrroles as Precursors of Biologically Active Compounds

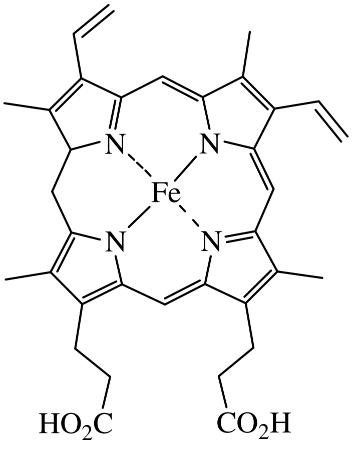
Pyrroles are important synthetic targets for their application as precursors to many useful classes of organic compounds such as porphyrins and alkaloids [160-162]. In particular, the biological importance of pyrroles and their derivatives is emphasized, because several natural pigments, such as heme, chlorophyll, or enzymes like the various cytochromes, include the pyrrole nuclei [163]. In addition, amino acids such as proline and hydroxyproline also contain the hydrogenated pyrrole ring, that is a pyrrolidine framework [164].

Porphobilinogen (PBG) **151**, the only aromatic pyrrole to play a function –a vitally important function- in fundamental metabolism is a dedicated intermediate in the biosynthesis of tetrapyrroles [165-167].

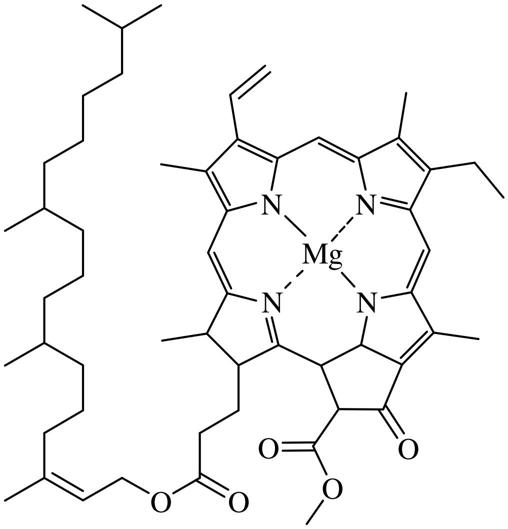


151

The tetrapyrrolic pigments, heme **152** and chlorophyll *a* **153** play an important role for central processes of life. They are universally distributed and have therefore been named the "pigments of life" [168, 169].

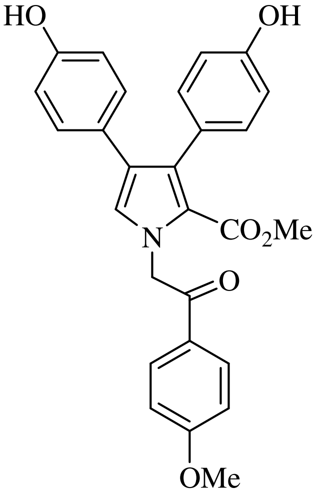


152

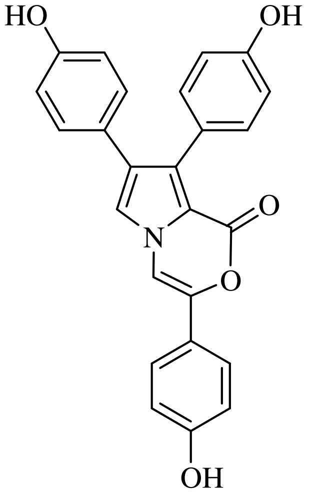


153

Regiospecific synthesis of polysubstituted pyrroles belong to an extremely attractive domain in heterocyclic chemistry as a result of their unusual bioactivities [170-174]. In particular, pyrrole skeletons with 2,3,4-substituents constitute the molecular framework of many biologically active compounds, e.g., porphobilinogen **151** [175], as well as the marine natural products lamellarin *O* **154** [176] and lukianol A **155** [177, 178]. Some of these marine compounds exhibit cytotoxic activities against tumor cells in vitro.

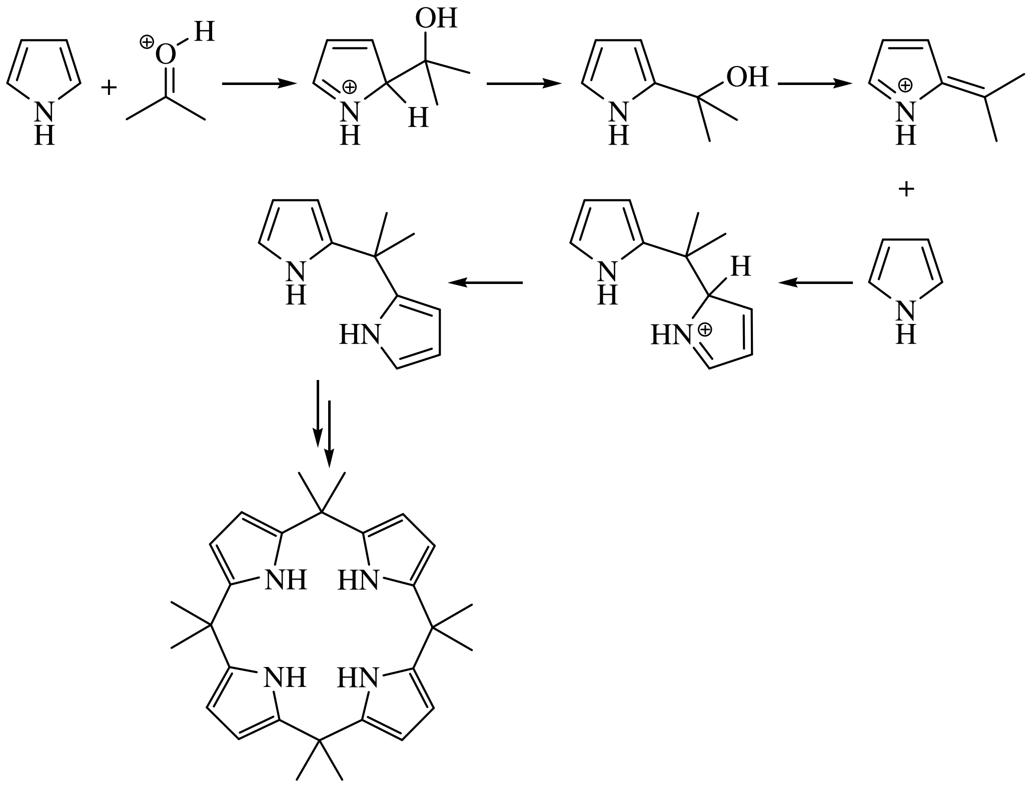


154

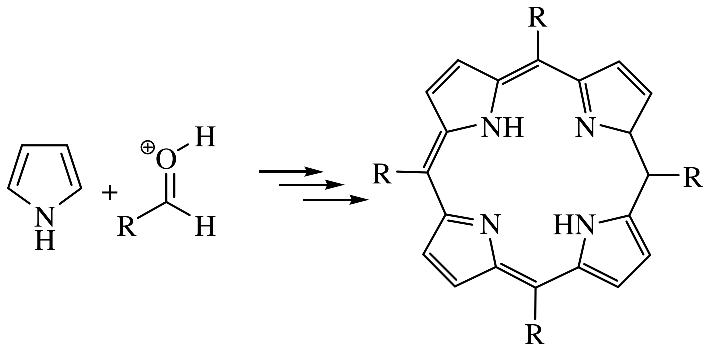


155

Condensation of pyrrole ring with a ketone or an aldehyde gives very valuable compounds, porphyrinogen **156** and porphyrin **157** respectively.

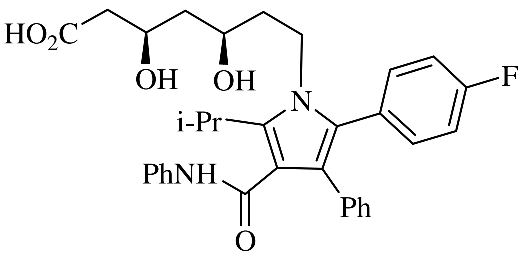


156



157

Anti-cholesterol drug, atorvastatin **158** is also a very important pharmaceutical compound that contains a pyrrole ring.



158

5.2 General Remarks on Pyrrole Synthesis

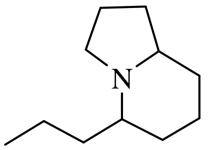
The valuable and diverse biological properties of pyrroles make the development of efficient methods for the preparation of these compounds having a defined substitution pattern a focus of considerable synthetic effort [179-187].

Pyrroles represent an important class of heterocyclic compounds [188-193], and numerous synthetic routes exist for their preparation. Many procedures, however, provide limited access to pyrroles in terms of substituents and substitution patterns [194].

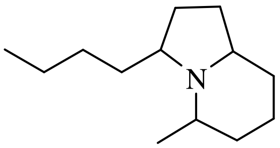
A wide variety of chemistry has been used for the preparation of pyrroles [195-197] but most of the available methods lead to pyrroles which are substituted at various positions with functional groups and thus require further synthetic operations to afford simple alkyl or aryl substituted pyrroles. In particular, synthetic routes to 2,4-diaryl substituted pyrroles are limited [198-203].

Although there are quite a number of methods available for the synthesis of pyrroles [204-214], most of them involve multistep synthetic operations which lower the overall yield. Recently, a few one-step procedures [215, 216, 164] have been reported; however these are not very satisfactory with regard to reaction conditions (long reaction period), yield, generality and scope of substitution at the ring. Most of the syntheses involve a condensation reaction of some sort. Thus, there is a need for a simple, efficient and more general method for the synthesis of this useful heterocyclic nucleus [217].

Many efficient syntheses of pyrroles have been reported but developing new synthetic methods still remains an attractive goal [194, 217-222]. Special attention is devoted to the asymmetric synthesis of heterocyclic compounds due to the enantiospecificity shown by most biological systems in their responses to drugs and to the regulatory pressure [223] on the pharmaceutical industry to market chiral drugs as single enantiomers [224]. Chiral pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of many biologically active compounds. A short, enantiogenic syntheses [225] of (-)-indolizidine 167B **159**, (+)-monomorine **160** and indolizidine alkaloids [226] based on the reaction of pyrrole derivatives of amino acids has been reported. There are limited reports on the preparation of the enantiomers of pyrrole derivatives having **1-N** directly linked to the stereogenic center [227-228].



159



160

Since the first pyrrole syntheses [229-231] at the end of the last century many efforts were made to develop new methodologies for the formation of alkyl-aryl-substituted and side chain functionalized [232-235] pyrroles.

5.3 Properties of Pyrrole Ring

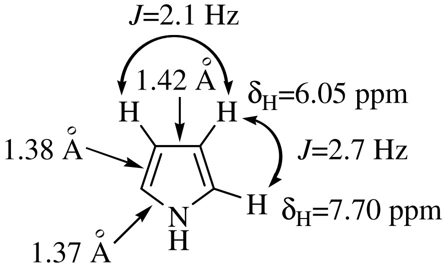
5.3.1 General Properties of 5-Membered Rings

Pyrroles are **aromatic** by virtue of their planarity and the uninterrupted cycle of p-orbitals containing six electrons: four from the two double bonds and two from a lone pair of the heteroatom (*i.e.* obeys Hückel's 4n + 2 rule). However, the extent of aromaticity (as determined by resonance energies, see below) for these compounds is different from that of benzene (which undergoes electrophilic substitution reactions) and this is the determining factor in their chemistry (*vide infra*).

Resonance Energies:
Pyrrole 100 KJmol-1
Benzene 151 KJmol-1

5.3.2 Physical and Spectroscopic Properties

Pyrrole is expected to be **aromatic** since it complies with Hückel's rule. The bond lengths and ^{1}H-NMR shifts are consistent with this expectation.



5.4 Synthesis of Pyrroles

5.4.1 General Comments

There are a (seemingly overwhelming) number of methods (each of which generally has it own name) for the construction of heteroaromatic ring systems, but the heteroaromatics are typically synthesized by the pertinent use of a small family of well known reaction types:

1. **Aldol** Reactions
2. **Michael** Additions
3. **Enamine** Reactions
4. **Condensation** Reactions

5.4.2 Type I and Type II Syntheses

As far as disconnection strategies go, almost every angle has been explored, and it was concluded that the majority of the most efficient syntheses can be classified as either "Type I" or Type II":

Type I C4 fragment + X (for a five membered ring)

Type II C2 fragment + C2X (for a five membered ring)

In these cases, X is a heteroatom and usually a nucleophile, hence the C-fragments must be electrophilic.

5.4.3 Classical Methods for the Synthesis of Pyrroles

There are three classical methods:

1. **Paal-Knorr** Synthesis (Type I)

Involves the reaction of 1,4-dicarbonyl compounds with ammonia or primary amines.

2. **Knorr** Synthesis (Type II)

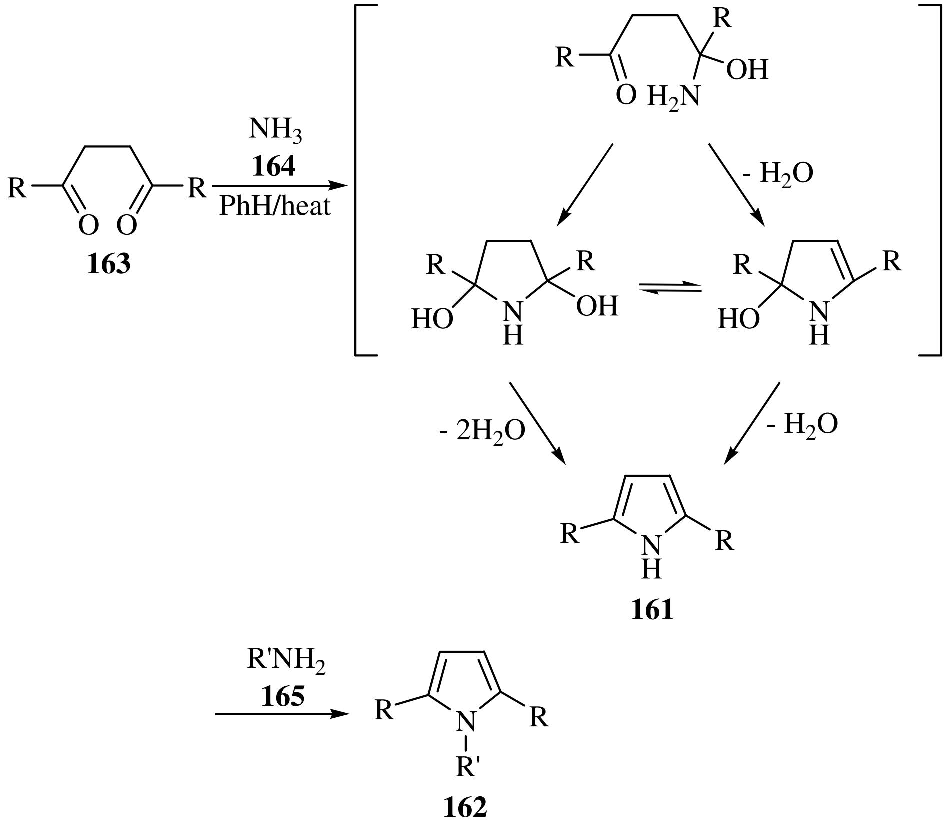
Condensation between α-aminoketones and β-ketoesters. Gives pyrroles after hydrolysis and decarboxylation.

3. **Hantzsch** Synthesis (Type II)

Involves reaction between enaminoester and an α-chloroketone. Gives pyrroles after hydrolysis and decarboxylation.

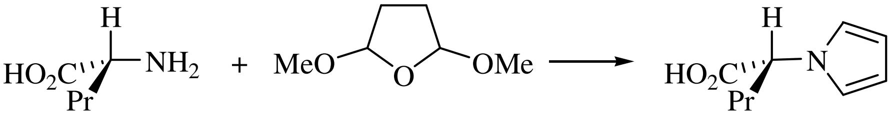
5.4.3.1 Paal-Knorr Synthesis (Type I)

Formation of pyrroles **161** and **162** via cyclization of 1,4-dicarbonyl compounds **163** with ammonia **164** or primary amines **165** (Scheme 85) [236, 237]:



Scheme 85

Paal-Knorr synthesis can also be performed by starting from primary amines **166** and the masked equivalents of 1,4-dicarconyl compounds [225, 226] such as tetrahydro-2,5-dimethoxyfuran **167** to obtain the corresponding pyrrole derivatives **168** (Scheme 86).



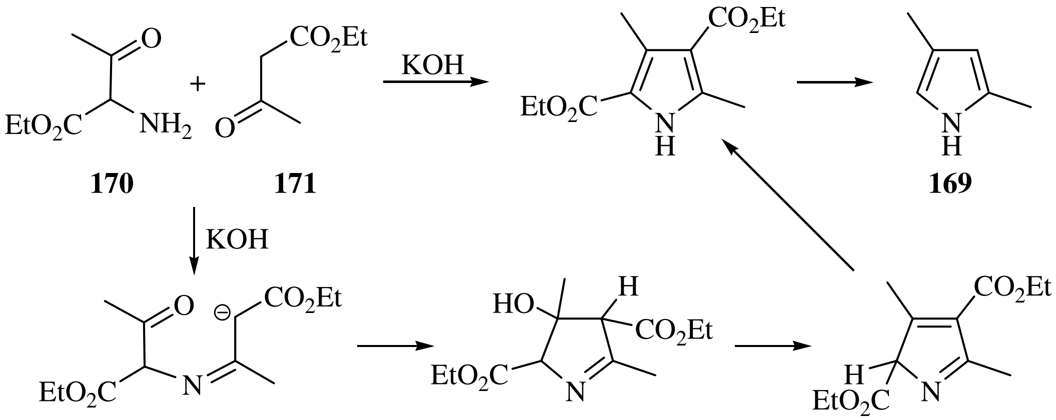
166 **167** **168**

Scheme 86

But with amino acids, often partial racemization occurs during the condensation reaction for the formation of pyrrole ring and racemization limits the usage of this method in asymmetric synthesis.

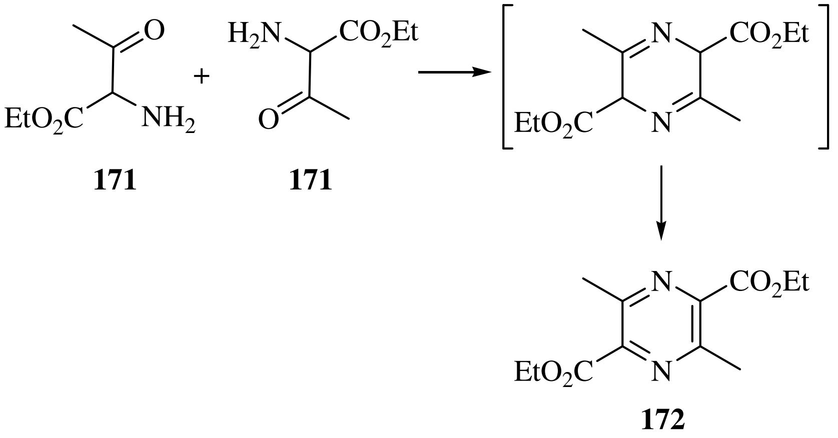
5.4.3.2 Knorr Synthesis (Type II)

Formation of pyrrole derivatives **169** occurs by condensation of α-amino ketones **170** as such or generated *in situ* from isonitrosoketones with β-ketoesters **171** containing active α-methylene groups (Scheme 87) [229, 238, 239]:



Scheme 87

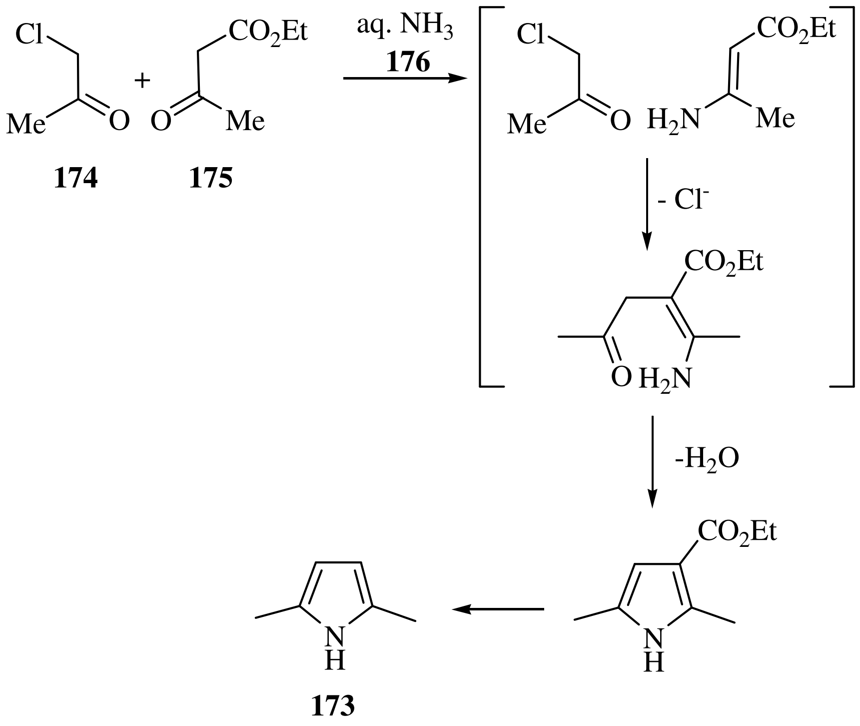
The Knorr synthesis works well only if the methylene group of the β-ketoesters **171** is further activated to enable the desired condensation leading to pyrrole to compete effectively with the self-condensation leading to pyrazine **172** (Scheme 88).



Scheme 88

5.4.3.3 Hantzsch Synthesis (Type II)

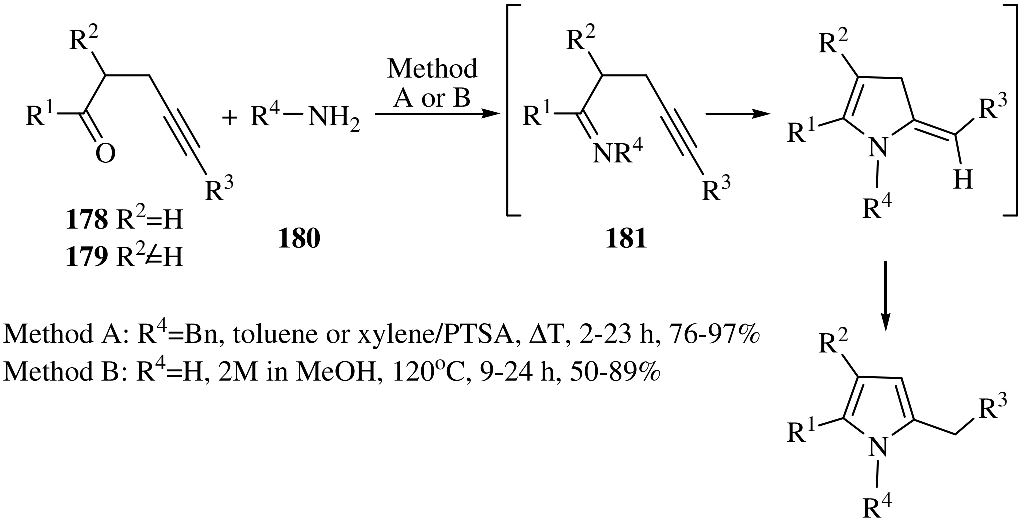
Formation of pyrrole derivatives **173** from α-chloromethyl ketones **174**, β-keto esters **175** and ammonia or amines **176** (Scheme 89) [232]:



Scheme 89

5.4.4 Synthesis of Alkyl and Aryl Substituted Pyrroles

Arcadi *et.al.* [240] have synthesized functionalized pyrroles **177** in good to high yields by the reaction of **178** and **179** with benzylamine or ammonia **180** (Scheme 90). The reaction mechanism probably involves the formation of an imine **181** that undergoes a *5-exo-dig* cyclization followed by isomerization to give pyrroles.



178 R^2=H
179 R^2≠H

180

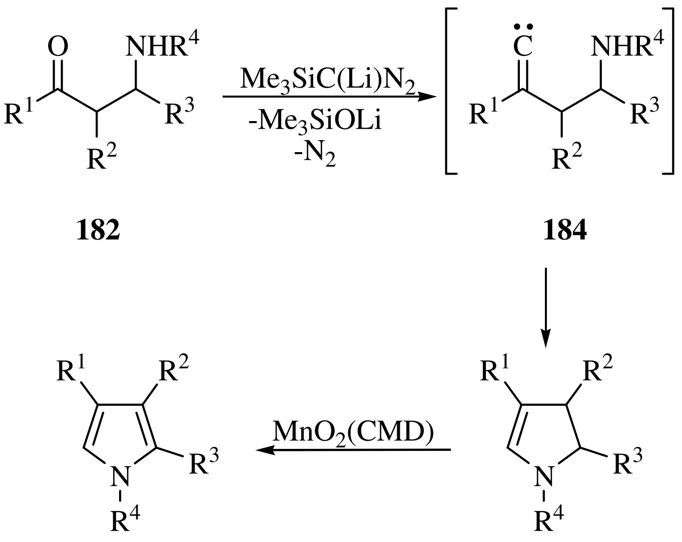
181

177

Method A: R^4=Bn, toluene or xylene/PTSA, ΔT, 2-23 h, 76-97%
Method B: R^4=H, 2M in MeOH, 120°C, 9-24 h, 50-89%

Scheme 90

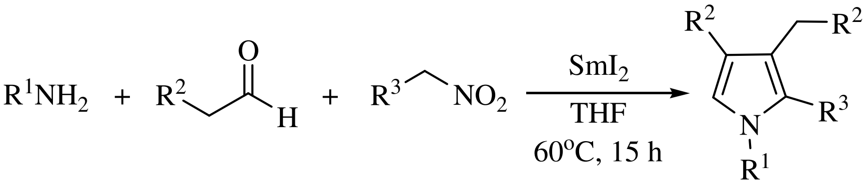
In a previous study, it was revealed that the reaction of lithium trimethylsilyldiazomethane (TMSC(Li)N_2) with carbonyl compounds smoothly proceeds to generate alkylidene carbenes by Shioiri *et al.* [241]. First, the reaction of TMSC(Li)N_2 with *N*-substituted β-amino ketones **182** was investigated –where TMSC(Li)N_2 was used as an alkylidene carbene generator- and it was found that TMSC(Li)N_2 smoothly reacted with **182** in THF to give the 2-pyrrolines **183**, the intramolecular N-H insertion product, via the alkylidene carbene intermediates **184**. The 2-pyrrolines **183** thus obtained were easily converted to the pyrroles **185** by treatment with MnO_2 (CMD, chemical manganese dioxide) [242], as shown in Scheme 91 [243]. The pyrroles obtained by this method were achiral.



182 **184** **185** **183**

Scheme 91

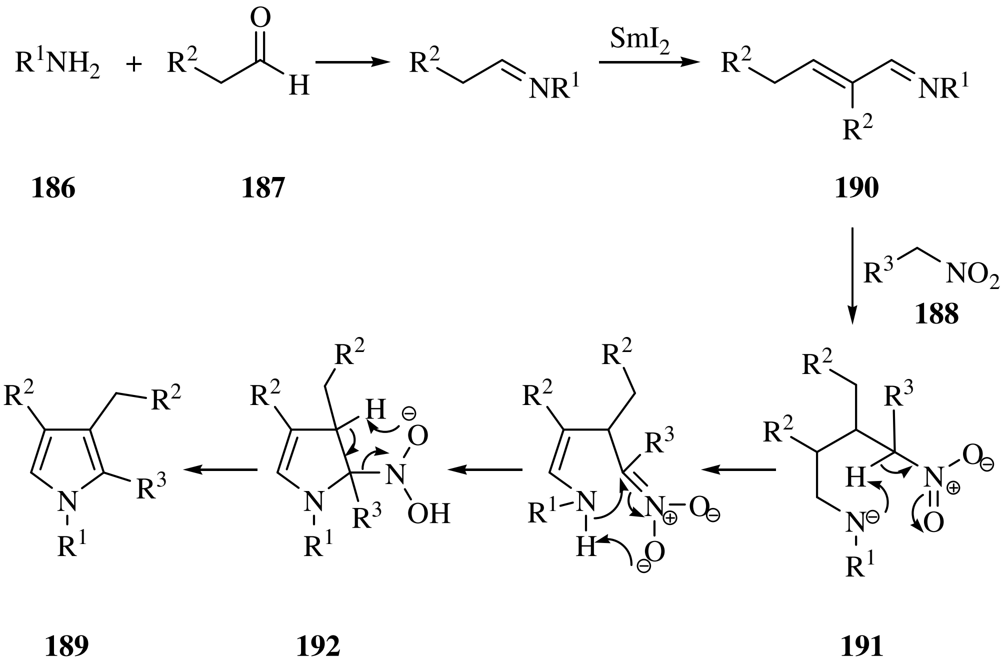
A three-component pyrrole synthesis which was performed by Shiraishi *et al.* is illustrated in Scheme 92 [215]. The samarium(II) iodide catalyzed condensation of alkylamines **186**, aldehydes **187** and nitroalkanes **188** gave 1,2,3,4-tetrasubstituted pyrroles **189** in moderate to good yields.



186 **187** **188** **189**

Scheme 92

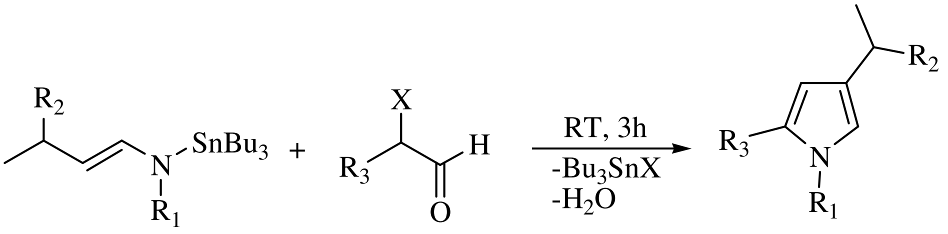
On the basis of these results, a plausible reaction path for the present coupling reaction is shown in Scheme 93.



Scheme 93

It was previously shown by the same group that the aldol-type condensation of the imine derived from amine **186** and aldehyde **187** in the presence of a samarium catalyst provides an α,β-unsaturated imine **190**. Therefore, the most important step in the present three-component coupling reaction was considered to be the formation of α,β-unsaturated imine **190**, resulting from the condensation of imine which is catalyzed by SmI_2. The thus-generated **190** couples with nitroalkane **188** to give an intermediate **191**. Proton transfer and successive intramolecular cyclization of **191** to **192** followed by elimination of H_2O and HNO from the intermediate **192** lead to pyrrole **189**.

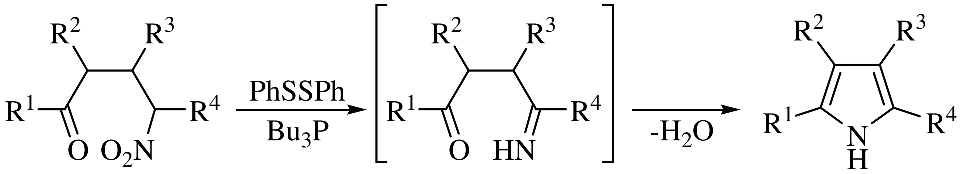
Yasuda *et al.* [244] have reported the synthesis of 2,4-disubstituted N-alkyl pyrroles **193** by the effective coupling of organotin(IV) enamines **194** and α-haloaldehydes **195**, in which [3+2] cyclization-dehydration took place (Scheme 94). Although the [3+2] cyclization process is a very common method for pyrrole synthesis, the generation of water in the dehydration step is often a serious problem and the obtained pyrroles are not chiral.



194 **195** **193**

Scheme 94

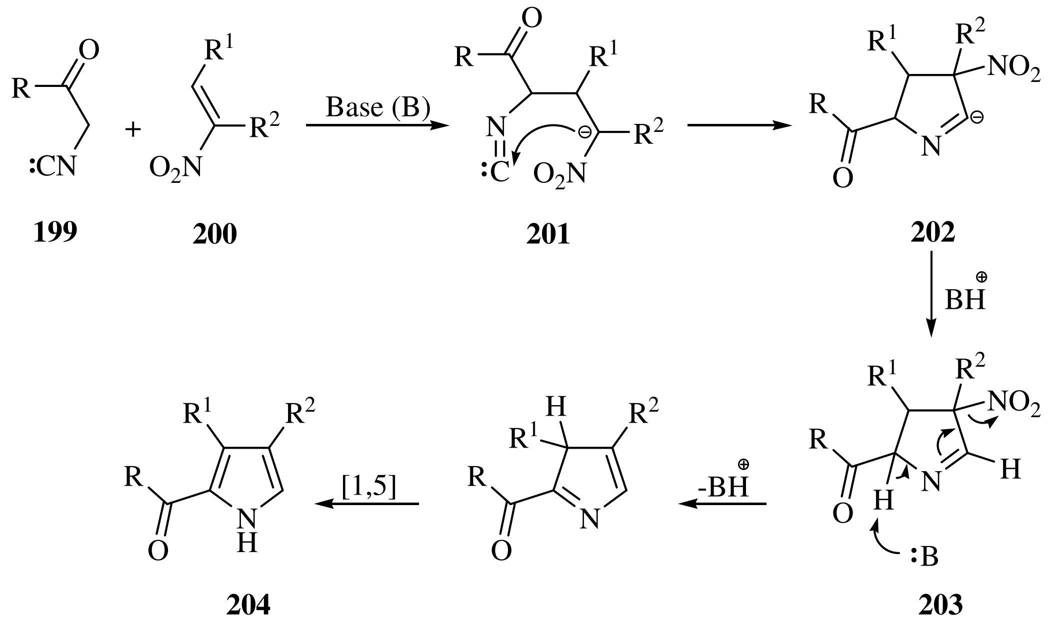
Nitro compounds, and especially nitro-olefins, have previously served for the preparation of pyrroles [245]. Zard *et.al.* [246] have shown that tributylphosphine-diphenyl disulfide deoxygenating system for oximes and nitroalkanes, that the easily accessible 1,4-nitro ketones **196** were smoothly reduced by this reagent combination to an intermediate imino-ketone **197**, which underwent spontaneous cyclization and dehydration to produce the corresponding pyrroles **198** in good yields, as depicted in Scheme 95.



196 **197** **198**

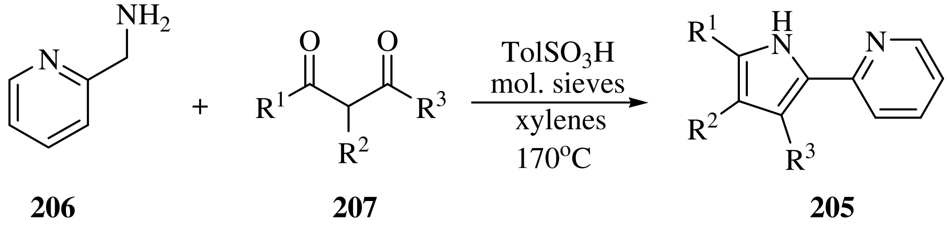
Scheme 95

A more interesting approach to pyrrole building blocks for porphyrin synthesis consisted of taking advantage of the strong ability of a nitro group to activate an olefin towards Michael additions as well as of its propensity to act as a leaving group in situations where $E1_{CB}$ type eliminations are favorable. These considerations become clear on inspection of the reaction manifold displayed in Scheme 96, where the nucleophile in the Michael addition is an activated isocyano derivative **199** which reacts with the nitro-olefin **200**. The first step leads to an adduct **201** which can cyclize to **202** through internal attack of the nitronate on the isocyano group. Similar cyclizations constitute the basis of a powerful methodology for the construction of heterocyclic rings. The cyclic intermediate **203** resulting from proton exchange can now eliminate a nitronate ion through a vinylogous $E1_{CB}$ mechanism to give pyrrole **204**, after aromatization through a [1,5] sigmatropic shift of the hydrogen [246].



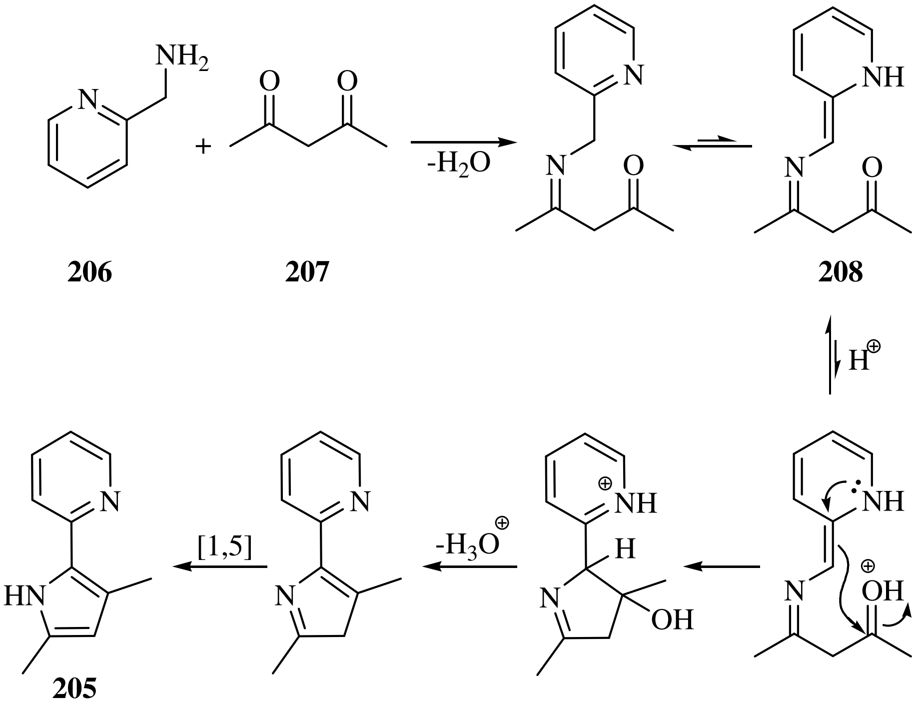
Scheme 96

2-(2-Pyridyl)pyrroles are a potentially useful class of compounds. They have been shown to be antioxidants and P38 kinase inhibitors. Klappa *et. al.* [247] have studied the synthesis of 3,5-disubstituted and 3,4,5-trisubstituted-2-(2-pyridyl)pyrroles **205** from 2-(aminomethyl)pyridine **206** and 1,3-diones **207** (Scheme 97). The reaction appears to proceed through the intermediacy of a β-iminoketone, which usually forms readily under ambient conditions.



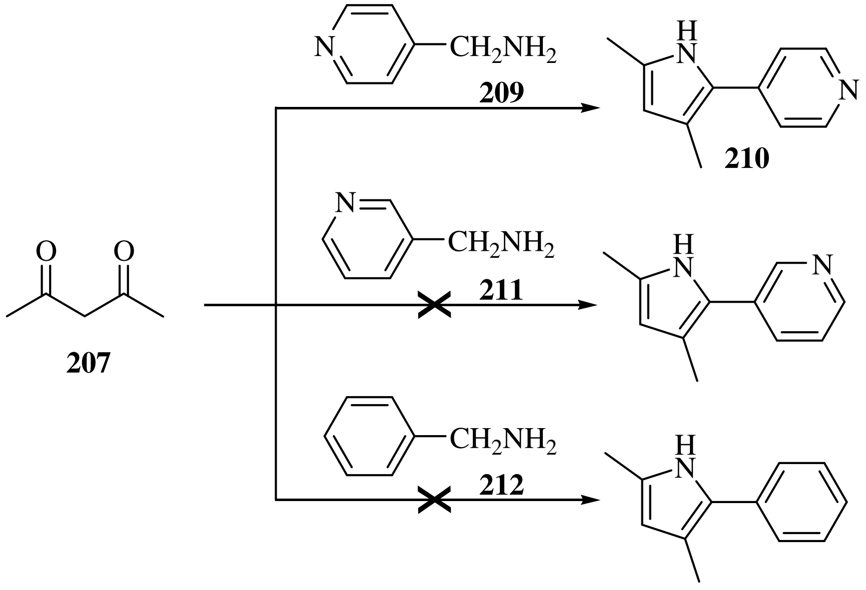
Scheme 97

The cyclization is thought to occur by nucleophilic attack on the ketone carbonyl by the carbon atom α to the pyridine (Scheme 98). It is proposed that the nucleophilicity of the (2-pyridyl)methyl carbon arises from the enamine tautomer **208**. After [1,5] sigmatropic shift, the corresponding pyrrole **205** is obtained.



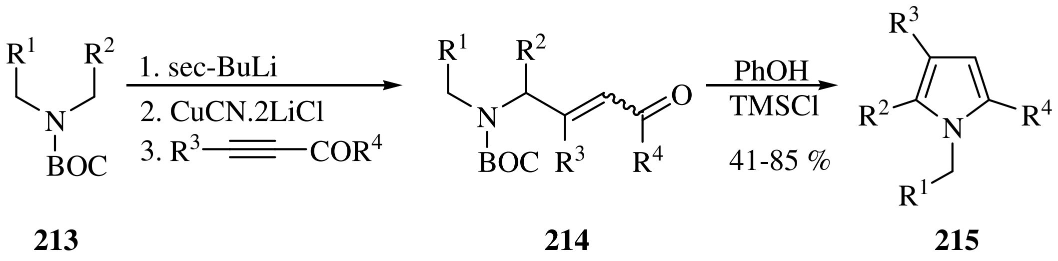
Scheme 98

This hypothesis is bolstered by the fact that 4-(aminomethyl)pyridine **209**, which can also tautomerize to an enamine structure, participates in this reaction to give **210**, whereas 3-(aminomethyl)pyridine **211** and benzylamine **212**, which are unable to form enamines, do not participate in the reaction under the same conditions (Scheme 99).



Scheme 99

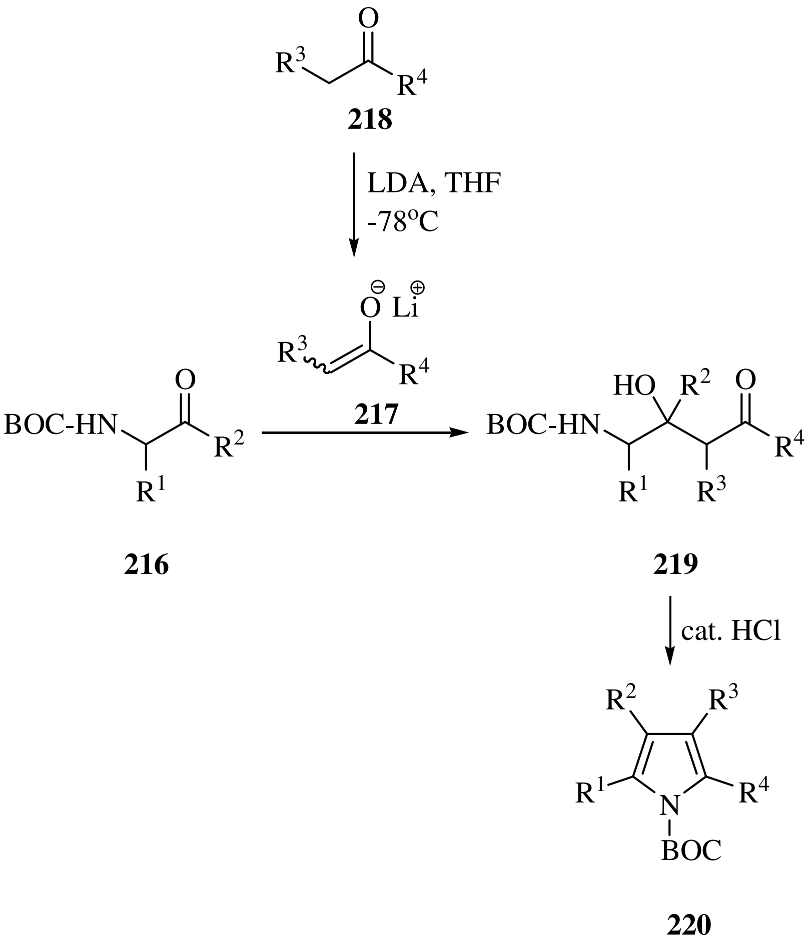
Dieter *et.al.* [194] have developed a flexible two step synthesis of substituted pyrroles involving initial Beak deprotonation of tert-butoxycarbonyl (BOC) amines **213** followed by addition of CuX-2LiCl (X = Cl, CN) to afford α-aminoalkylcuprates. Such cuprates undergo conjugate addition reactions to α,β-alkynyl ketones affording α,β-enones **214**, which upon treatment with PhOH/TMSCl undergo carbamate deprotection and intramolecular cyclization to afford the pyrroles **215** (Scheme 100).



Scheme 100

However, the possibility of obtaining regioisomers when R^1 and R^2 are unsymmetrical, the need to synthesize alkynyl ketones, and the inability to synthesize 2,5-diaryl pyrroles were thought to be limitations of this synthetic route [194].

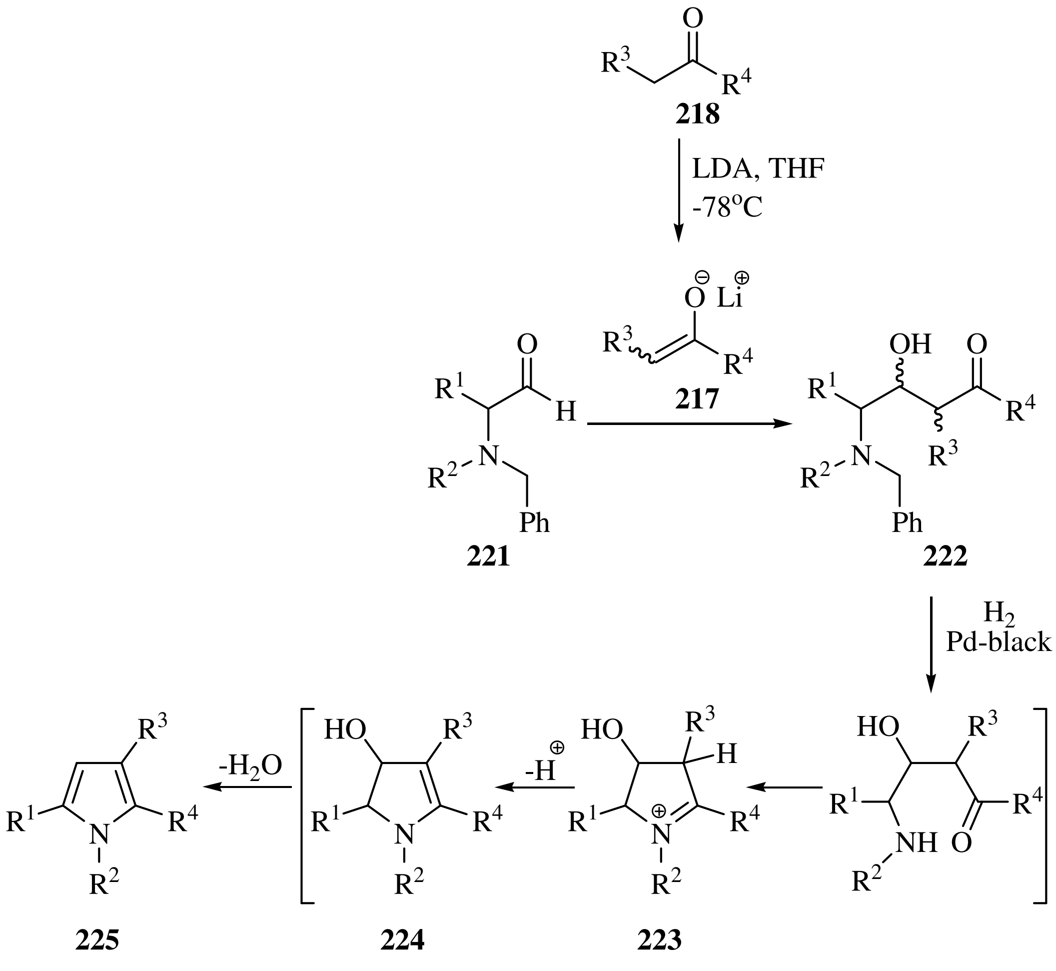
Cushman *et. al.* [248] have reported the elegant synthesis of pyrroles by a method which utilizes aldol products formed by the reaction between (*N*-BOC)-α-amino aldehydes and ketones. The potential elaboration of a new pyrrole synthesis in which BOC-R-amino aldehydes (**216**, R^2= H) or ketones (**216**, R^2=CH_3) are reacted with the lithium enolates **217** derived from ketones **218** to afford, after protonation, aldol intermediates **219**, which then cyclize to the desired pyrroles **220** under mild acidic conditions (Scheme 101) has been studied. Although conceptually related to the familiar Knorr pyrrole synthesis, in which α-oximino ketones are reduced to α-amino ketones and then reacted with β-diketones or β-keto esters to afford substituted pyrroles, the present method would offer the advantage of employment of BOC-α-amino aldehydes or ketones **216** that are readily available from a wide variety of amino acids.



Scheme 101

Some noteworthy features of this synthetic route are the ready availability of the starting materials, mild conditions and the number of substituents at R^1, R^2 and R^3 that can be accessed. However, the yields were rather modest (5-40 %) and in all cases pyrroles with alkyl substituents on the nitrogen could not be accessed by this route. A possible explanation for the low yields could be a rapid polymerization of the resulting pyrroles under the acidic conditions employed [248].

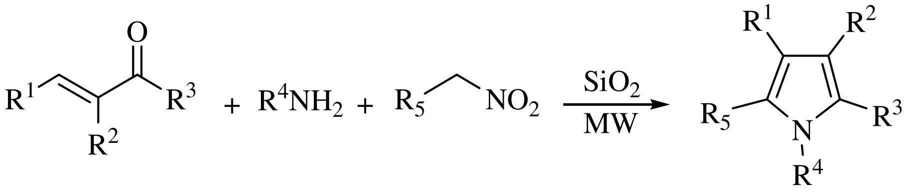
Lagu *et.al.* [249] have proposed a solution for the low yields in Cushman's synthesis which was discussed above. They have stated that if one could replace the *tert*-butoxycarbonyl group on the nitrogen with another protecting group that can be removed under relatively neutral conditions, the yields of pyrroles could be improved and allow for a number of substituents to be introduced on the pyrrole nitrogen. A benzyl group was considered as a potential replacement for the *tert*-butoxycarbonyl group on the nitrogen of the α-amino aldehydes to be used in the aldol reactions. Benzyl-protected aldehydes or ketones **221** react with lithium enolates **217** derived from ketones **218** to afford **222**. It was speculated that deprotection of the benzyl groups could lead to the formation of an iminium ion **223** which could undergo a deprotection to provide an enamine **224**. The enamine can then undergo dehydration to yield pyrrole **225** (Scheme 102).



Scheme 102

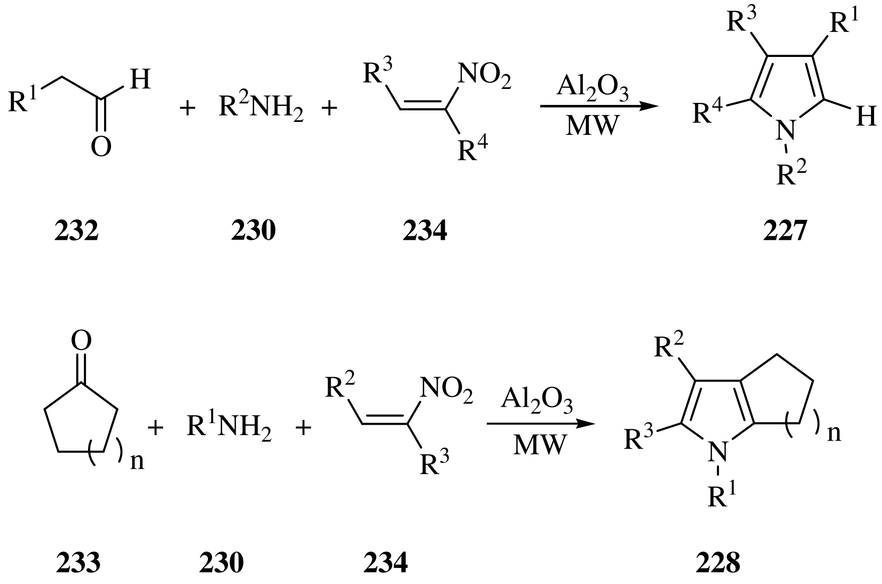
It is evident that various substituents, including the sterically demanding *tert*-butyl group, are tolerated at the 2-, 3- and 5-positions of the pyrroles. The synthetic methodology is flexible enough to yield a variety of substituent combinations and 1,2-di-, 1,2,3-tri-, 1,2,5-tri and 1,2,3,5-tetra-substituted pyrroles can be synthesized. The methodology described by Lagu *et.al.* allows for the introduction of a number of alkyl and aryl substituents on the nitrogen of pyrroles that cannot be readily synthesized using known procedures. Pyrrole without a substituent on the nitrogen could not be synthesized by this methodology.

Ranu *et.al.* [217] have studied the synthesis of alkyl-substituted pyrroles by three-component coupling of carbonyl compound, amine and nitro-alkane/alkene on a solid surface of silica gel/alumina under microwave radiation. Efficient syntheses of highly substituted alkylpyrroles **226** and **227** and fused pyrroles **228** by a three-component coupling of α,β-unsaturated aldehyde/ketone **229**, amine **230** and nitroalkane **231** (Scheme 103) and aldehyde/ketone **232** (in case of fused pyrrole formation, cyclic ketones **233**), amine **230** and α,β-unsaturated nitroalkane **234** (Scheme 104) on the surface of silica gel and alumina without any solvent under microwave irradiation were performed.



229 **230** **231** **226**

Scheme 103



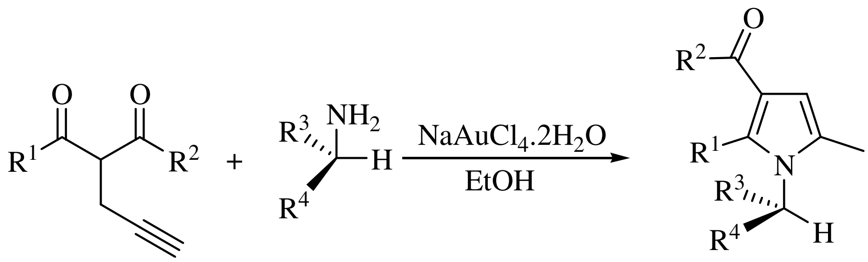
Scheme 104

In general, the reactions were very fast and clean. The yields were reasonably good (60-86 %) for a three-component coupling reaction. None of these operations involved any strong acid, base and solvent [217].

Conversion of homochiral amines and α-amino esters to their chiral 1,2,3,5-susbtituted pyrrole derivatives via gold-catalyzed amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds **235** have been reported by Arcadi *et. al.* [240]. The reaction of primary amines, β-amino alcohols and α-amino esters **236** with **235** afforded the chiral pyrrole derivatives **237** (Scheme 105).

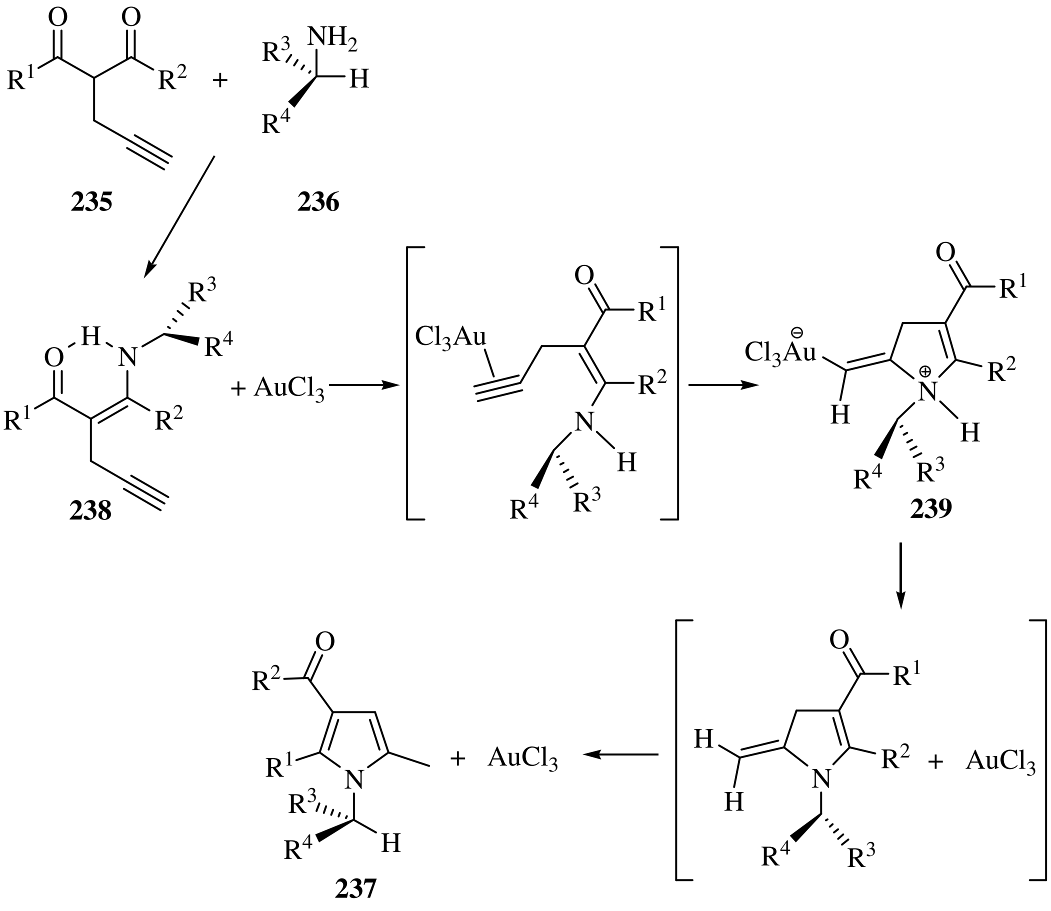
The reaction of primary amines **236** with 2-propynyl-1,3-dicarbonyls **235** led to enaminone derivatives **238**, which undergo regioselective cycloamination to pyrroles **237** under the catalytic action of $NaAuCl_4.2H_2O$ (Scheme 106). The formation of **237** has been suggested to proceed by the *anti*-addition of nitrogen and gold moieties in a 5-exo-*dig* manner to the acetylenic bond to give the vinylaurate species **239**.

Subsequent protonolysis of the Csp^2-Au bond and isomerization reactions afford the pyrroles **237**.



235 **236** **237**

Scheme 105



Scheme 106

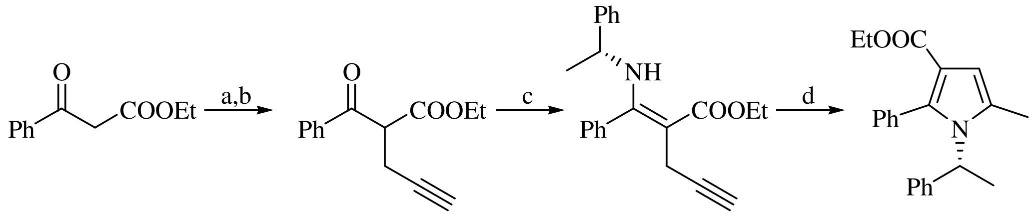
As a result of this study, a new, simple and efficient synthetic methodology for the preparation of 1,2,5-trisubstituted-4-acylpyrroles in homochiral form was developed. In this synthetic procedure, readily available compounds were used and the reactions proceeded under mild conditions [240].

Demir *et.al.* [250] have described an efficient one-pot two component synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives through acid-catalyzed cyclization of 2-propynyl-1,3-dicarbonyl compounds **235**. In the first part of the study, they have synthesized the desired pyrrole derivatives **242** by conversion of 2-propynyl-1,3-dicarbonyl compounds **235** to their enaminones **241** followed by metal mediated cyclization. For that purpose, enaminone **241** was synthesized through simple condensation reaction of 2-propynyl-1,3-dicarbonyl compound **235** with (R)-phenylethylamine in the presence of catalytical amount of *p*-TsOH. Then the enaminone was reacted with catalytical amount of $Cu(OAc)_2$ in 1,2-dichloroethane and the corresponding pyrrole derivative **242** was obtained (Scheme 107).

The attack of nitrogen on the carbon atom leads to *5-exo-dig* type cyclization which leads to pyrrole derivative and this was the only product, the rest of the materials were the unreacted starting materials. No *6-endo-dig* type cyclization product was observed.

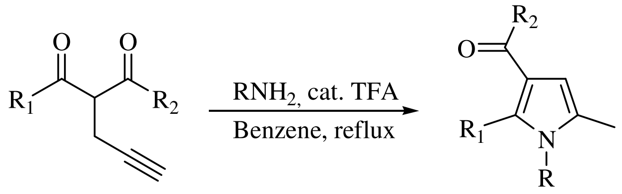
The idea of combining the enaminone formation with cyclization step prompted the same group to carry out the conversion with one single step starting from 2-propynyl-1,3-dicarbonyl compounds **235**. During the screening reactions to find out acceptable conditions for the formation of enaminones and their cyclizations, they have found that catalytical amount of TFA was able to convert enaminones to pyrroles **243** (Scheme 107). Since activation of triple bond is the main requirement for the attack of nitrogen, catalytical amount of TFA was used as a proton source for both activation of triple bond and catalysis of enaminone formation.

This study has shown that the condensation reaction of 2-propynyl-1,3-dicarbonyl compounds **235** with amines catalyzed by TFA represents a new general one-pot entry into functionalized pyrroles. The formation of the pyrroles was suggested to proceed through the sequential amination of carbonyl compounds followed by regioselective *5-exo-dig* cyclization of the enaminone intermediate and aromatization reaction. The reaction requires a catalyst. TFA is the most efficient and selective catalyst and its application is general, but Cu (OAc)$_2$ was also efficient catalyst when enaminones were used. When the optical purity of the products was compared with the corresponding racemic compounds using chiral HPLC column, it was observed that the formation of pyrroles work without racemization [250].



240 **235** **241** **242**

a) NaH, THF; b) Propargylbromide; c) (R)-Phenylethanamine; *p*-TsOH, benzene, reflux; d) Cu(OAc)$_2$, 1,2-Dichloroethane



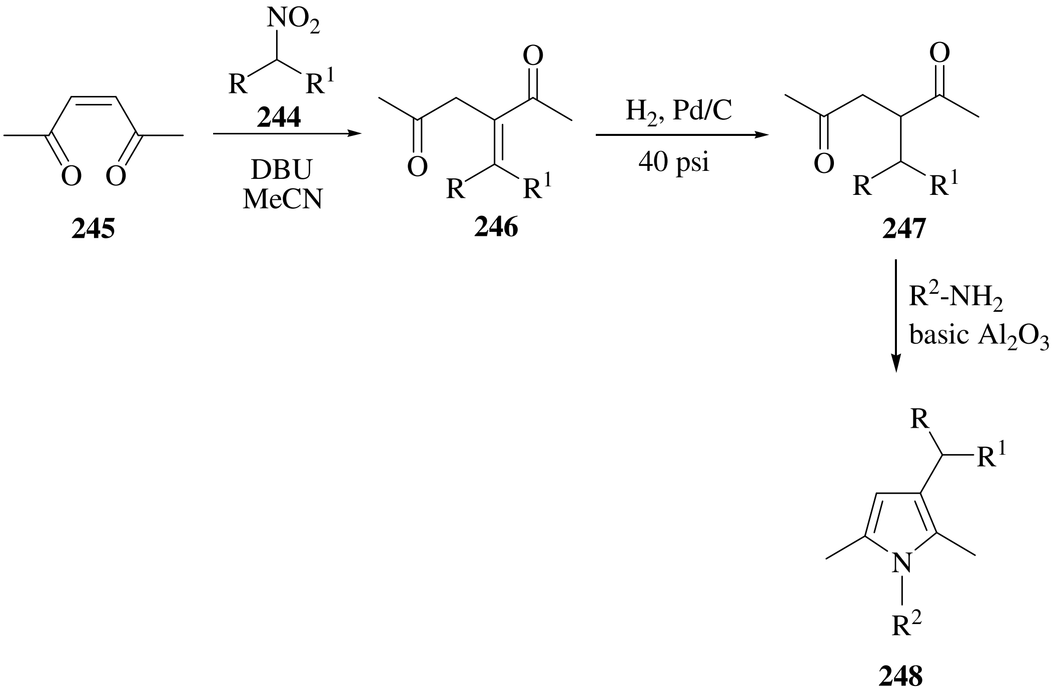
235 **243**

Scheme 107

Alternatively, Ballini *et.al.* [251] devised a new strategy to synthesize tri-alkylated pyrroles from 2,5-dialkylfurans and nitroalkanes.

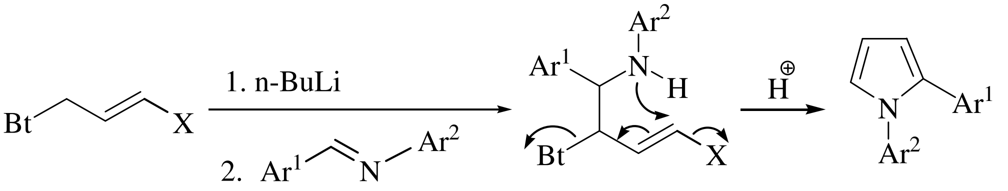
In recent years, aliphatic nitro compounds were emerging as versatile starting materials and intermediates in organic synthesis. This is primarily due to the fact that they are easily available, they undergo a variety of carbon-carbon bond forming processes, and the nitro group can be converted into several other functional groups.

During previous researchs to explore the potential of nitroalkanes in the Michael reaction, Ballini *et.al.* [251] have found that the nitro group may, simultaneously, behave both as an electron withdrawing and as a leaving group. This discovery suggested a new strategy to synthesize tri-alkylated pyrroles from 2,5-dialkylfurans and nitroalkanes. Conjugate addition of the nitronate, derived from the nitro compound **244**, to *cis*-3-hexen-2,5-dione **245** (a masked equivalent of 2,5-dimethylfuran) in acetonitrile with DBU (1 eq.) as base, followed by chemoselective hydrogenation (10% Pd/C as catalyst) of the C-C double bond of the enones **246**, obtained by elimination of nitrous acid from the Michael adduct, completes the conversion to the alkylated γ-diketones **247** (70-88%). The next step is the Paal-Knorr reaction, generally carried out under acid-catalyzed conditions and/or under thermal conditions which has given pyrrole **248** (Scheme 108).



Scheme 108

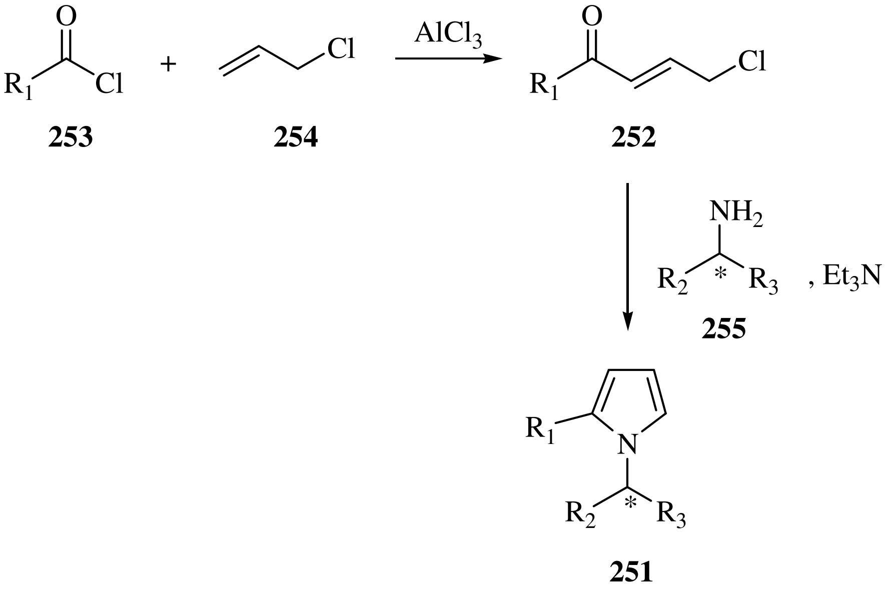
Katrizky *et.al.* [252] have developed a facile synthesis of 1,2-diaryl(heteroaryl) pyrroles in a two-step procedure from *N*-allylbenzotriazoles via intramolecular acid-catalyzed oxidative cyclization. The strong electron-withdrawing ability and nucleofugicity of the benzotriazolyl group have been used successfully for the preparation of a number of 1,2-diarylpyrroles. It was shown that *N*-allylbenzotriazoles **249** of the general formula $BtCH_2CH{=}CHX$, where X is a second leaving group, easily undergo lithiation at the allylic carbon. The reaction of the anion obtained with a diarylimine and subsequent acid-catalyzed cyclization with the elimination of both benzotriazolyl and X groups affords 1,2-diarylpyrroles **250** in moderate yields (Scheme 109). The nature of the leaving group X (OEt or morpholino) does not affect the yield of the final product significantly.



249 **250**

Scheme 109

As was previously reported, the most widely used method for pyrrole synthesis is Paal-Knorr synthesis in which 1,4-dicarbonyl compounds and their masked equivalents such as tetrahydro-2,5-dimethoxyfuran are cyclized with ammonia or primary amines to form pyrrole rings. But with amino acids, often partial racemization occurs during the condensation reaction for the formation of pyrrole ring which is an undesirable situation for asymmetric pyrrole synthesis. Therefore, the development of a flexible and selective method to obtain such compounds is desirable. Demir *et al.* [253] have developed a convenient method for the construction of substituted pyrrole rings **251** from amines, amino alcohols and amino acids with chloroenones **252** prepared from acid chlorides **253** and allyl chlorides **254** in the presence of $AlCl_3$. Ring construction process was performed by the reaction of a specific chloroenone and amino acid ester salts, amines or amino alcohols **255** in the presence of Et_3N (Scheme 110). This study has solved the racemization problem observed in not only Paal-Knorr synthesis but also other synthetic routes in which racemization occurs because in this method, the cyclization works without racemization.



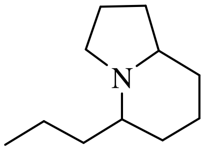
Scheme 110

In the first part of study, 2-methylpyrrole derivatives of amines, amino alcohols and amino acids were synthesized. In the continuing work, Demir *et al.* [227] have enlarged the study to the synthesis of 2-isopropyl-, -cyclohexyl-, and -phenyl-substituted pyrrole derivatives.

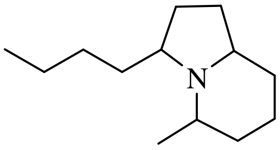
5.5 Pyrroles as Precursors of Indolizidine Alkaloids

Nearly three hundred alkaloids belonging to about two dozen different structural classes have been partly or fully characterized from the skin secretions of amphibians. One of the largest of these classes is the indolizidine alkaloids which occur in dendrobatid frogs from Central and South America as well as in some unrelated frogs and toads from locations as far apart as Australia and Madagascar. The most thoroughly explored amphibian indolizidines are the pumiliotoxins and allopumiliotoxins, but the more recently discovered 5-alkylindolizidines and 3,5- and 5,8-disubstituted indolizidines are now attracting increasing attention. Because of their extremely low natural abundance, there is still uncertainity about the relative and absolute stereostructure of many of these alkaloids and this accounts for at least part of their popularity as synthetic targets. They are also simple enough to use as models for illustrating new synthetic methodologies.

A stereoselective approach for the synthesis of biologically active indolizidine alkaloids based on the reduction of bicyclic pyrroles has been reported by Jefford *et al.* [225]. Indolizidine alkaloids offer attractive targets for synthesis because of their exotic provenance, scarcity and marked biological activity. Two typical examples are indolizidine 167B **159**, a vanishingly minor constituent of the skin of a dendrobatid frog, caught on Isla de Colon, Panama, and (+)-monomorine **160**, a trail pheromone of the Pharaoh's ant, a pest in heated buildings.



159

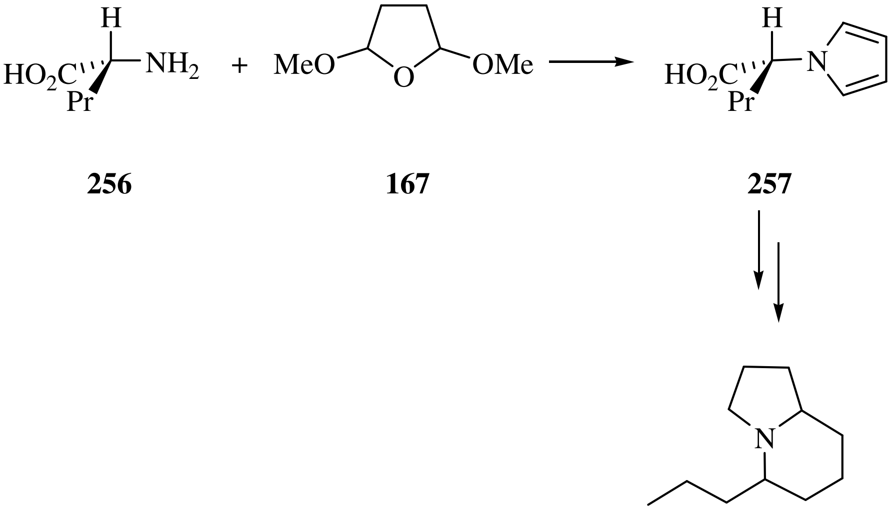


160

Although frogs of the genus *Dendrobates* were never used as a source of arrow poisons, unlike the Colombian genus *Phyllobates*, several of the constituents contained in their skins and closely related to 167B, are noncompetitive blockers of neuromascular transmission. Consequently, the practical preparation of these rare and potent substances is of some importance. Unfortunately, most methods are multistep procedures giving the product in poor yields.

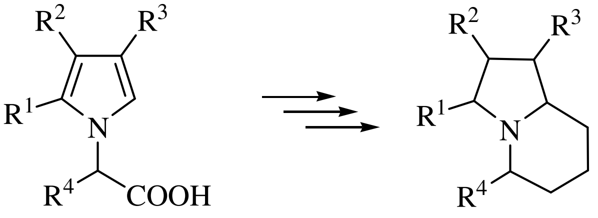
(-)-Indolizidine 167B was detected by Daly *et.al.* in the skin secretions of neotropical frogs of the genera *Dendrobates* and the family Dendrobatidae [254-256] The skin secretions of these frogs contain a wide variety of toxic alkaloids that appear to serve as defensive agents. Recent work by Daly *et.al.* has shown that the "dendrodaid alkaloids" result from a dietary uptake system which allows accumulation of these poison alkaloids in the skin of the frogs [257, 258].

By Jefford *et al.* [225], substantial improvements were made by exploiting the chemistry of pyrrole and appropriate substituents to obtain the requisite stereochemical control. They have developed a three-part method for synthesizing enantiomerically pure indolizidine alkaloids which starts with the condensation of chiral α-amino acid, exemplified by D-norvaline **256**, and tetrahydro-2,5-dimethoxyfuran **167** to give the corresponding 1-pyrrolyl derivative **257** as shown in Scheme 111. Subsequent homologation and cyclization followed by catalytic hydrogenation then affords indolizidine 167B **159**. (+)-Monomorine **160** was synthesized by the same route.



Scheme 111

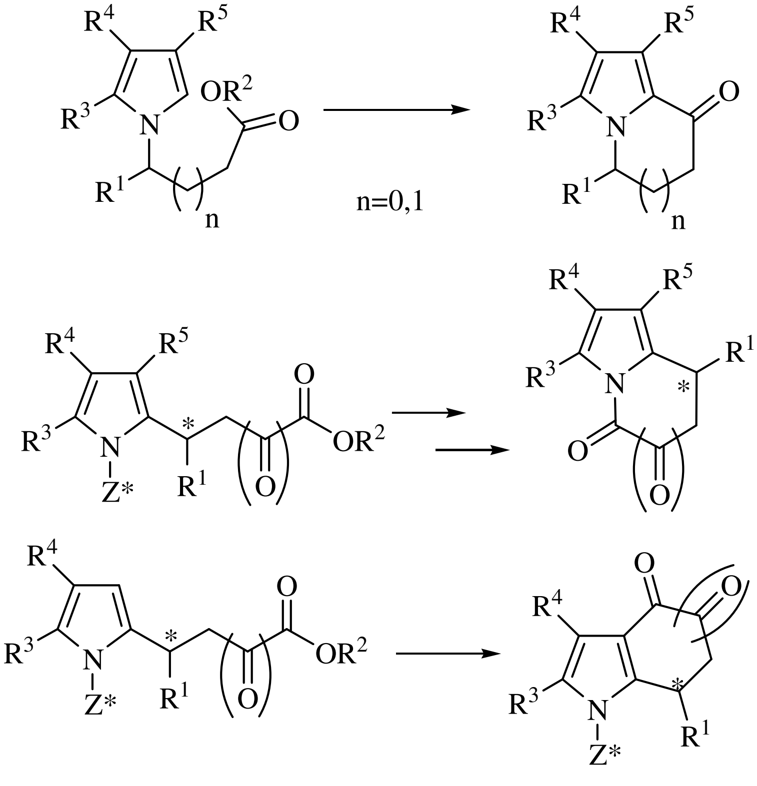
Substituted pyrrole derivatives **258** also provide access to substituted indolizidine alkaloids **259** as shown in Scheme 112.



258 **259**

Scheme 112

Synthesis of 5,5- and 5,6-ring systems can also be performed starting from suitable pyrrole derivatives as outlined in Scheme 113.



Scheme 113

5.6 Aim of the Work

Pyrrole derivatives represent a class of compounds that are of great importance in heterocyclic chemistry primarily due to the fact that many pyrroles are subunits of natural products, pharmaceutical agents and polymers. The valuable and diverse biological properties of pyrroles lead to the development of efficient methods for the preparation of these compounds, which have a defined substitution pattern, the focus of considerable synthetic effort.

Although there are quite a number of methods available for the synthesis of pyrroles, most of them involve multistep synthetic operations which lower the overall yield. Most of the methods given in literature consist of the preparation of alky- or aryl-substituted pyrrole derivatives but with unsubstituted nitrogen atom in the pyrrole ring. There are limited reports on the preparation of the enantiomers of pyrrole derivatives having **1-N** directly linked to the stereogenic center. Thus we aimed to develop a new synthetic method for the efficient preparation of 1,2,4-trisubstituted pyrroles from haloenones and amines, amino alcohols and esters of amino acids where cyclization works without racemization.

CHAPTER 6

RESULTS AND DISCUSSION

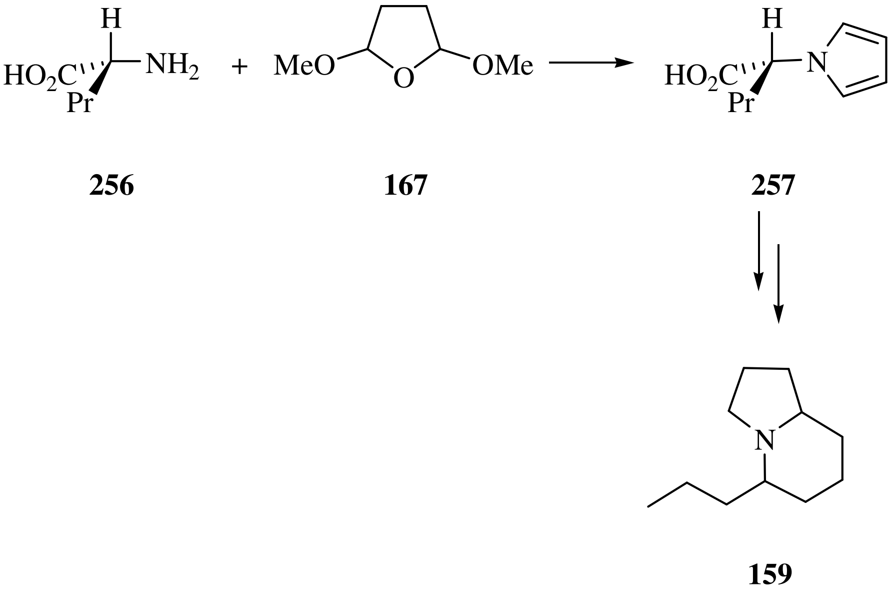
6.1 General Overview of Pyrrole Chemistry

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry primarily due to the fact that many pyrroles are subunits of natural products, pharmaceutical agents and polymers [259]. The valuable and diverse biological properties of pyrroles make the development of efficient methods for the preparation of these compounds, having a defined substitution pattern, a focus of considerable synthetic effort.

Compounds containing a pyrrole ring can be found in many naturally occurring compounds and they have found applications in medicine and agriculture [260]. Chiral pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of many different biologically active compounds. Several useful variants of classical methods can be found in the literature. A stereoselective approach to the synthesis of indolizidine alkaloids based on the reaction of pyrrole derivatives of amino acids has been reported [225]. C-2 substituted pyrrole derivatives also provide access to substituted indolizidine alkaloids.

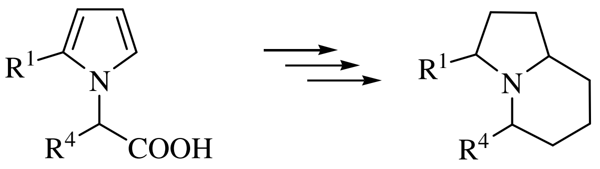
The Paal–Knorr synthesis, starting from primary amines and 1,4-dicarbonyl compounds [236, 237] and their masked equivalents such as tetrahydro-2,5-dimethoxyfuran, is often used for the construction of pyrrole rings [225, 226]. During the condensation reaction for the formation of the pyrrole ring with amino acids, partial racemization often occurs.

However, by Jefford *et al*. [225], substantial improvements were made by exploiting the chemistry of pyrrole and appropriate substituents to obtain the requisite stereochemical control. They developed a three-part method for synthesizing enantiomerically pure indolizidine alkaloids which starts with the condensation of chiral α-amino acid, exemplified by D-norvaline **256**, and tetrahydro-2,5-dimethoxyfuran **167** to give the corresponding 1-pyrrolyl derivative **257** as shown in Scheme 115. Subsequent homologation and cyclization followed by catalytic hydrogenation then affords indolizidine 167B **159**.



Scheme 115

Polysubstituted pyrrole derivatives **258** also provide access to substituted indolizidine alkaloids **259** as outlined in Scheme 116.



Scheme 116

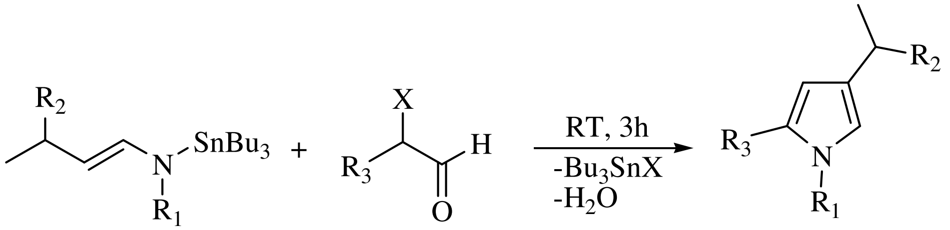
6.2 Pyrrole Synthesis

Although there are quite a number of methods available for the synthesis of pyrroles [204-214], most of them involve multistep synthetic operations which lower the overall yield. Recently, a few one-step procedures [164, 215, 216] have been reported; however these are not very satisfactory with regard to reaction conditions (long reaction period), yield, generality and scope of substitution at the ring [217].

As described in Chapter 5, the most popular procedures have so far been based on the Paal-Knorr reaction and related variants involving the reaction of α-amino ketones with β-diketones. The most important problem with this method is the partial racemization of amino acids during the condensation reaction.

As shown in the following examples, the methods in literature describe the formation of pyrrole ring starting from one or two components to afford substituted derivatives.

Effective coupling of organotin(IV) enamines **194** with α-haloaldehydes **195** via [3+2] cyclization-dehydration has given 2,4-disubstituted N-alkyl pyrroles **193** as was described by Yasuda *et al.* (Scheme 117) [244].

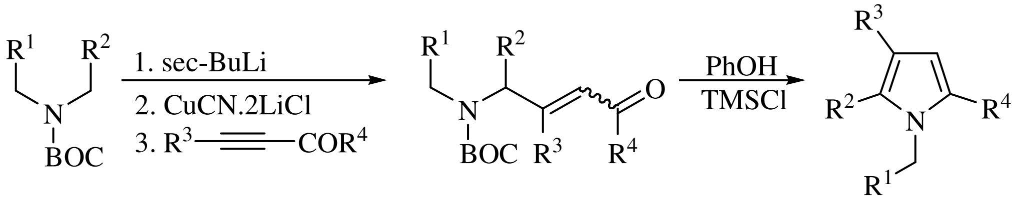


194 **195** **193**

Scheme 117

The serious problem which arises during this reaction is the generation of water in dehydration step and the obtained pyrroles are not chiral.

A two step synthesis of substituted pyrroles involving initial Beak deprotonation of tert-butoxycarbonyl (BOC) amines **213** followed by addition of CuX-2LiCl (X = Cl, CN) to afford α-aminoalkylcuprates was reported by Dieter *et.al.* [194]. Such cuprates undergo conjugate addition reactions to α,β-alkynyl ketones affording α,β-enones **214**, which upon treatment with PhOH/TMSCl undergo carbamate deprotection and intramolecular cyclization to afford the pyrroles **215**.



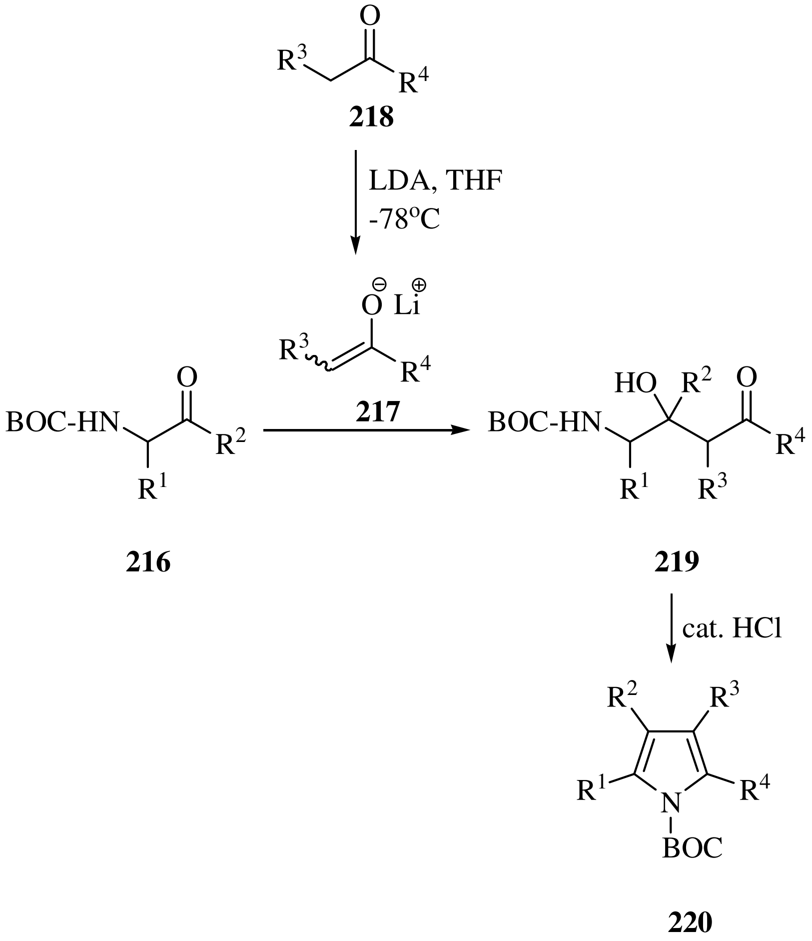
41-85 %

213 **214** **215**

Scheme 118

The main limitations of this reaction are the possibility of obtaining regioisomers when R^1 and R^2 are unsymmetrical, the need to synthesize alkynyl ketones and the inability to synthesize 2,5-diaryl pyrroles.

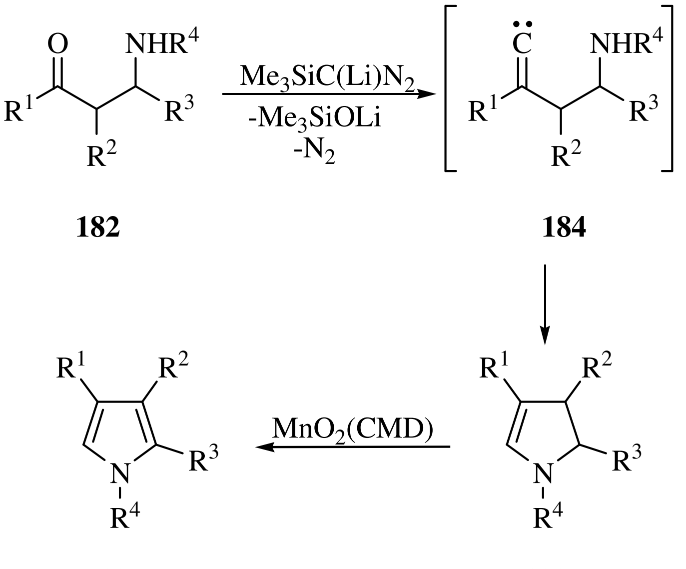
The aldol reaction between (*N*-BOC)-α-amino aldehydes and ketones has given pyrroles which was reported by Cushman *et. al.* [184]. In this reaction, BOC-R-amino aldehydes (**216**, R^2= H) or ketones (**216**, R^2=CH_3) were reacted with the lithium enolates **217** derived from ketones **218** to afford, after protonation, aldol intermediates **219**, which then cyclize to the desired pyrroles **220** under mild acidic conditions (Scheme 119).



Scheme 119

The main disadvantages of this type of reactions are obtaining the products in low yields (5-40 %) and in all cases pyrroles with alkyl substituents on the nitrogen could not be accessed. Since pyrrole formation is carried out under acidic conditions, a possible explanation for the low yields could be a rapid polymerization of the resulting pyrroles under the acidic conditions employed [184].

Shioiri *et al.* [241], have reported that the reaction of lithium trimethylsilyldiazomethane (TMSC(Li)N_2) with carbonyl compounds smoothly proceeds to generate alkylidene carbenes. The reaction of TMSC(Li)N_2 with *N*-substituted β-amino ketones **182** was investigated –where TMSC(Li)N_2 was used as an alkylidene carbene generator- and it was found that TMSC(Li)N_2 smoothly reacted with **182** in THF to give the 2-pyrrolines **183**, the intramolecular N-H insertion product, via the alkylidene carbene intermediates **184**. The 2-pyrrolines **3** thus obtained were easily converted to the pyrroles **185** by treatment with MnO_2 (CMD, chemical manganese dioxide) [242], as shown in Scheme 120 [243].



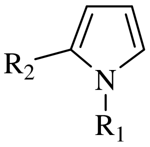
Scheme 120

The main disadvantage of this method was obtaining achiral pyrroles in all cases.

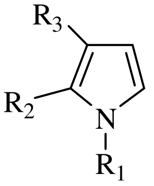
6.3 Synthesis of Chiral Pyrrole Derivatives from Chloroenones

Special attention is devoted to the asymmetric synthesis of heterocyclic compounds due to the enantiospecificity shown by most biological systems in their responses to drugs and to the regulatory pressure [223] on the pharmaceutical industry to market chiral drugs as single enantiomers [224]. Chiral pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of many biologically active compounds. A short, enantiogenic syntheses [225] of (-)-indolizidine 167B, (+)-monomorine and indolizidine alkaloids [226] based on the reaction of pyrrole derivatives of amino acids has been reported. There are limited reports on the preparation of the enantiomers of pyrrole derivatives having **1-N** directly linked to the stereogenic center [227, 228]. Most of the methods given in literature consist of the preparation of alky- or aryl-substituted pyrrole derivatives but with unsubstituted nitrogen atom in the pyrrole ring.

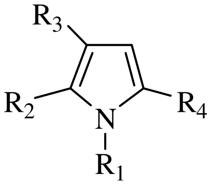
In the light of foregoing introductory comments, it is not surprising that a vast amount of work has and is being devoted to the development of practical methods for the synthesis of pyrrole building blocks containing appropriate substitution patterns and the development of a flexible and selective method to obtain pyrroles with a variety of substituents is desirable. As Demir *et.al.* have described in previous papers, we have designed a convenient route to 1,2- (**260**), 1,2,3- (**261**), 1,2,3,5- (**262**) substituted pyrrole rings from amines, amino alcohols and amino acids with simple accessible haloenones [227, 252, 261-263]. As part of our continued interest in the chemistry of homochiral pyrrole derivatives, we have extended this chemistry to the synthesis of 1,2,4-trisubstituted pyrrole derivatives (**263**).



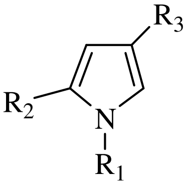
260



261



262



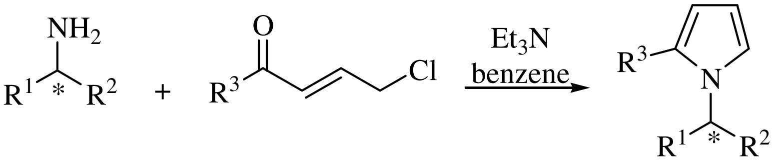
263

Pyrrole-amino acid N-conjugates are effective $^1O_2$ quenchers. Their quenching ability toward $^1O_2$ favorably compares with that of natural antioxidants such as vitamins E and C [264, 265] Recently, it was shown that 1,2,4-trisubstituted pyrroles are a new class of synthetic hystone deacetylase inhibitors [266, 267].

The conversion of the amine function of different compounds into pyrrole ring shows more difficulties than the simple construction of the pyrrole ring from one or two components. Especially the conversion of amine group of amino acids into pyrrole ring shows difficulties in different aspects such as keeping the optical purity, chemo- and regioselectivity of the reaction.

With this respect, our aim is to develop a new attractive way to obtain chiral substituted pyrrole derivatives of amino alcohols, amino acids and amino acid esters.

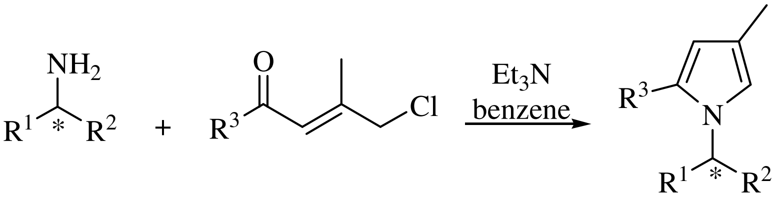
It is suggested that different substituted chloroenones **252** could be convenient key compounds for the construction of the pyrrole rings **251** from amine group of amino acids and amino alcohols **255** (Scheme 121).



255 **252** **251**

Scheme 121

In this work, it is aimed to develop methods for the synthesis of 1,2,4-trisubstituted pyrrole derivatives **264** starting from amines, amino acid esters and amino alcohols **265** and simple chloroenones **266** as shown in Scheme 122.



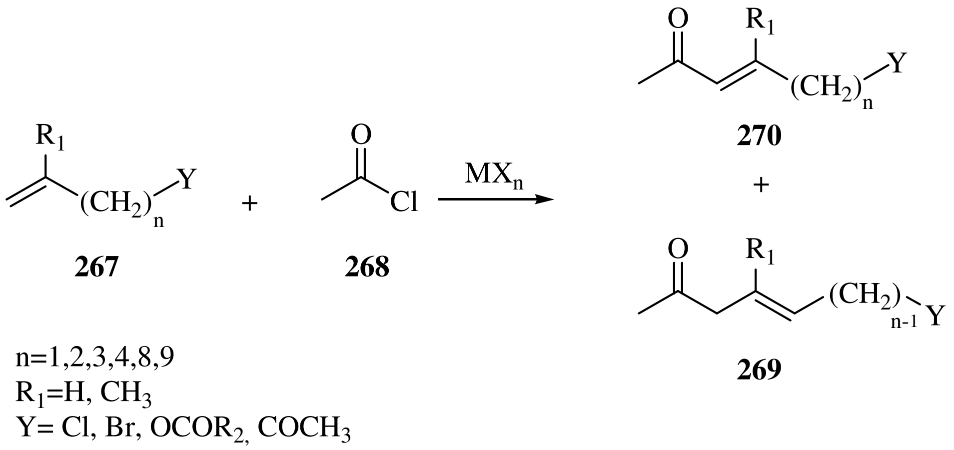
265 **266** **264**

Scheme 122

6.3.1 The Synthesis of Chloroenones

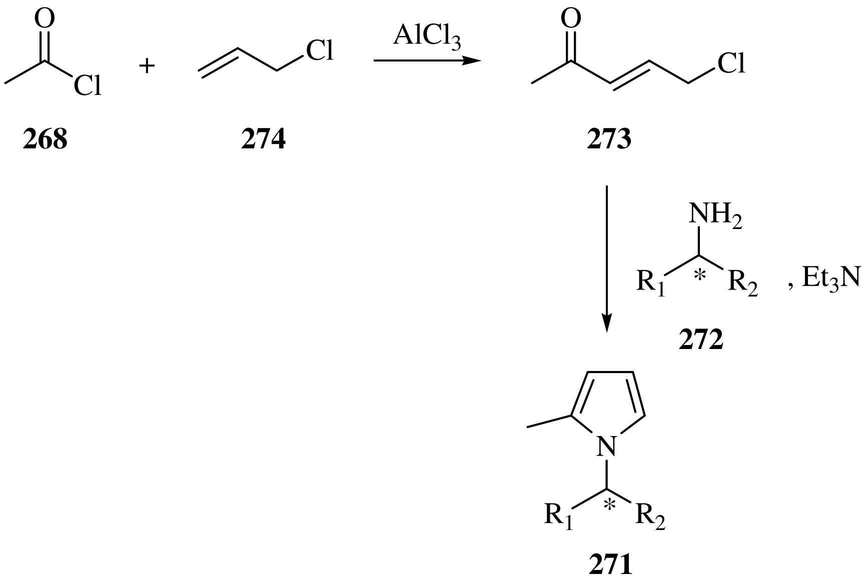
Chloroenones were chosen as starting materials for the pyrrole ring construction in our studies. The reaction of suitable chloroenone with chiral amino alcohol, amino acid or amino acid ester in the presence of triethylamine should afford 1,2,4-trisubstituted pyrrole derivatives.

Barbry *et.al.* [268] have studied the acylation of unsaturated halides. Acylation of unsaturated halide **267** has been conducted in dichloromethane with acetyl chloride **268** and various Lewis acids: Silver tetrafluoroborate has led selectively to the β,γ-unsaturated ketone **269** (Scheme 123). In the presence of ferric, stannic or aluminum chloride, the reaction has afforded a mixture of α,β-unsaturated ketones **270** and β,γ-unsaturated ketones **269**, with a dichloro compound. The best yields of **269** and **270** with lower amounts of dichloro compound are obtained with aluminum chloride.



Scheme 123

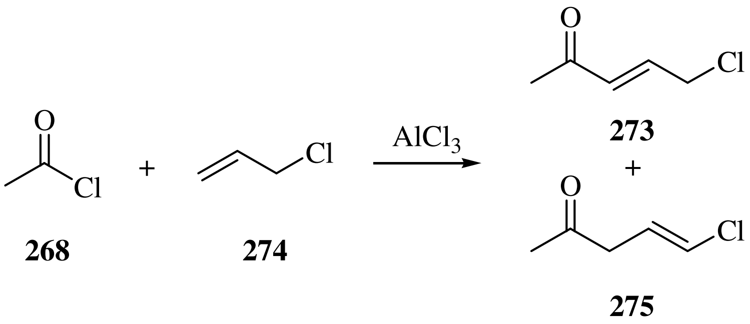
As was described by Demir *et.al.* previously, we have designed a convenient new route to 2-methyl-substituted pyrrole rings **271** from amines, amino alcohols and amino acids **272** with 5-chloropent-3-en-2-one **273** where the chloroenone **273** was prepared from acetyl chloride **268** and allyl chloride **274** in the presence of $AlCl_3$ similar to the above method (Scheme 124).



Scheme 124

The chloroenone contains four carbon units. The reaction of amino group with carbonyl function and the carbon atom on which the chloride is bound should afford pyrrole ring after the elimination of water and hydrochloric acid. Since the reaction takes place under mild conditions and in a way so that no bonds directly linked to the stereocenter are broken or formed, the reaction should proceed without racemization.

For the synthesis of the simplest chloroenone, 5-chloropent-3-en-2-one **273**, acetyl chloride **268** was added very slowly to $AlCl_3$ suspension in CH_2Cl_2 at 0^oC. To this stirred mixture, 3-chloropropene (allyl chloride) **274** dissolved in CH_2Cl_2 was added dropwise at this temperature. When addition was completed, the reaction mixture was stirred for 30 minutes at 0^oC. According to the ^{1}H-NMR data, the reaction yielded 5-chloropent-3-en-2-one **273** as a major product (76% yield). In addition to this, the isomer **275** was also obtained in 18% yield (Scheme 125).



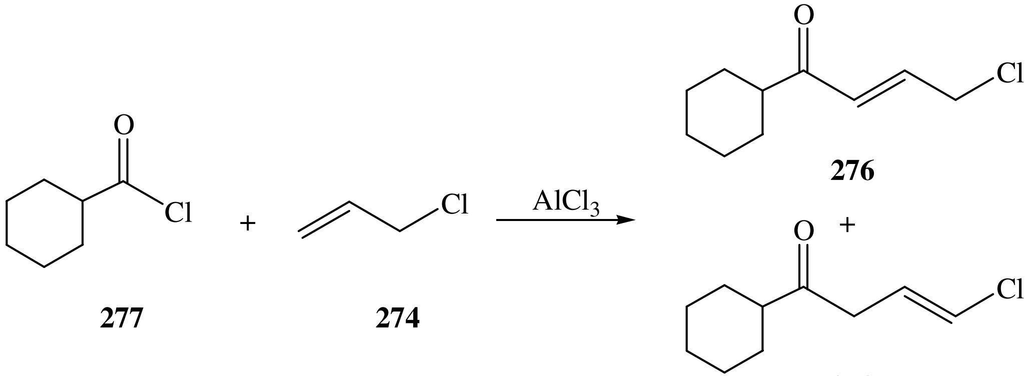
Scheme 125

The yield of the reaction depends on the reaction temperature and the reaction time. At low temperatures (-5°C – 0°C) and short reaction time (30 minutes), amount of **273** has increased. Increasing the reaction temperature caused decomposition and polymerization of the product.

The crude product was tried to be purified by vacuum distillation. Since the products are temperature sensitive, decomposition was observed during distillation and the desired product **273** was obtained in very low yield (17%).

As it will be described in the formation of the pyrrole rings, both **273** and **275** give the same reaction with amino acids, amino alcohols and amino acid esters to yield pyrrole derivatives so the crude product was used without purification.

A similar reaction was applied for the synthesis of 4-chloro-1-cyclohexylbut-2-en-1-one **276** (Scheme 126). The reaction of cyclohexanecarbonyl chloride **277** with allyl chloride **274** in the presence of $AlCl_3$ at -5°C yielded two products in which **276** is the major product (71%) and **278** is the minor product (15-18%) according to ^{1}H-NMR spectrum.



277

274

276

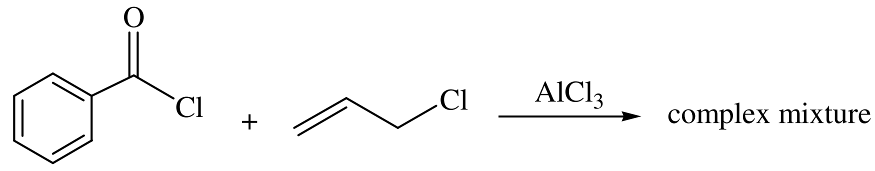
278

Scheme 126

The control of reaction temperature is important for this reaction. Above -5°C, the reaction gives many unidentified products in addition to **276** and **278**.

The purification of the product was tried to be done by vacuum distillation but even under reduced pressures, the temperature was high enough to decompose the product so the crude product was again used without purification.

The synthesis of 4-chloro-1-phenylbut-2-en-1-one which was planned to be used as starting material for the synthesis of 2-phenyl substituted pyrrole derivatives, was tried to be performed by the reaction of benzoylchloride **279** with allyl chloride **274** in the presence of aluminum chloride. Different reaction conditions (temperature: from -10°C to 10°C; reaction time: from 30 min to 2.5 hr) were applied. The reaction yielded a complex mixture of unidentified products and polymerized materials (Scheme 127). The solution for this problem will be explained in Section 6.3.2.

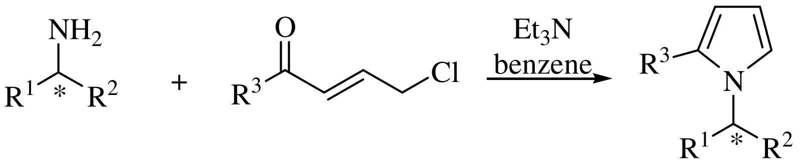


279 **274**

Scheme 127

6.3.2 Synthesis of 1,2-Disubstituted Chiral Pyrrole Derivatives

Later on, we have extended this chemistry to the conversion of homochiral amines, β-amino alcohols and α-amino acids to their chiral 2-methyl-, -isopropyl- and -cyclohexyl-substituted pyrrole derivatives (Scheme 128) [227].



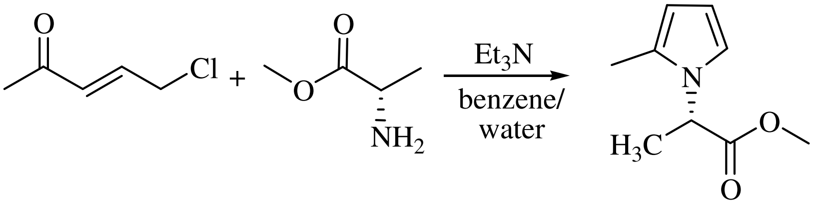
265 **266** **264**

$R^3 = CH_3$
$(CH_3)_2CH$
C_6H_{11}

Scheme 128

According to Scheme 129, L-alanine methyl ester (S)-**280** was refluxed with methyl substituted chloro enone **273** in benzene and water for 5 hours and during this time the reaction was monitored by TLC. Purification of the crude product has afforded the desired pyrrole derivative (S)-**281** in 80% yield as a colorless oil. The same reaction was also carried out with the isopropyl and cyclohexyl derivatives of the enone. The reaction has afforded the corresponding pyrrole derivatives in 76% and

72% respectively. The reaction has also worked with alanine under similar conditions to obtain the free acid pyrrole derivative in 52% yield.



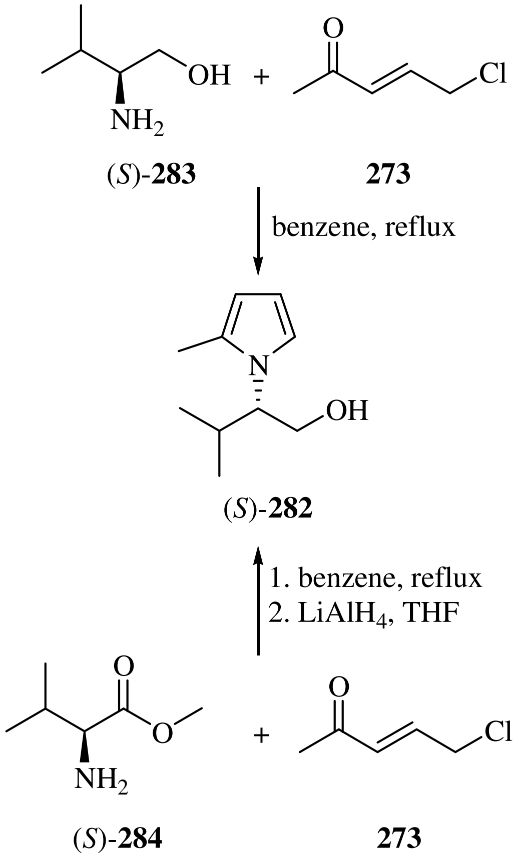
273 (S)-**280** (S)-**281**

Scheme 129

Under the same reaction conditions, valine, valine methyl ester, aspartic acid methyl ester, tyrosine ethyl ester and phenylglycine were converted to their 2-methyl-, isopropyl- and cyclohexyl-pyrrole derivatives in 44–82% yields.

As the results of our previous studies have shown, the esters of amino acids give higher yields than their free acids. Comparable yields are obtained with different R^3-groups and this shows that varying the substituents on the chloroenone does not have a large influence on the yield of the products.

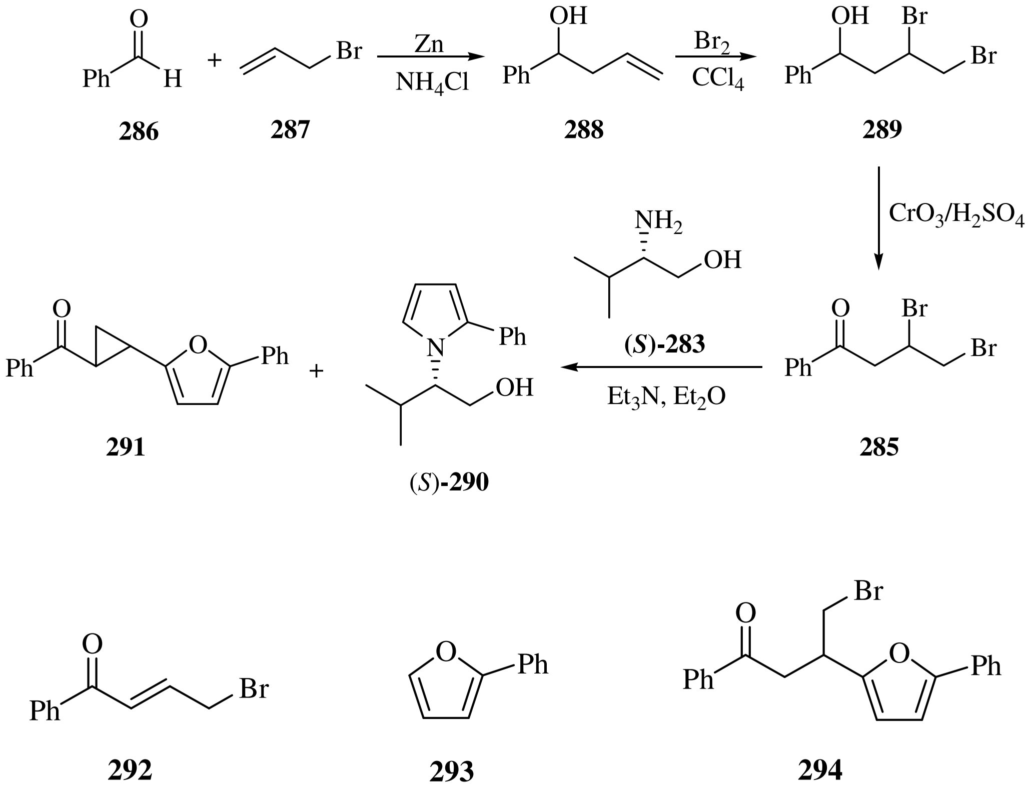
Formation of the optically pure pyrrole derivative of L-valinol (*S*)-**282**, starting from methyl substituted chloroenone **273** with optically pure L- valinol (*S*)-**283** and L-valine methyl ester (*S*)-**284**, have shown that no racemization occurred during the formation of (*S*)-**282** (Scheme 130).



Scheme 130

The pyrrole derivative of amino acid esters and amino alcohols showed excellent separation properties by chiral HPLC column [269]**.** Comparison of the optical purity of the products with that of racemic mixtures by chiral HPLC column gave the same result, which is that, no racemization occurs by the formation of the pyrrole ring from amino acids and their esters.

In the case of 2-phenyl-substituted pyrrole derivatives, problems occurred during the synthesis of the corresponding chloroenone. The reaction of allyl chloride **274** with benzoyl chloride **279** in the presence of $AlCl_3$ afforded the chloroenone in very low yield (4–6%, ^{1}H NMR). For the synthesis of 2-phenyl derivatives of pyrrole, the use of the dibromo compound **285** was suggested. As shown in Scheme 131, the reaction of benzaldehyde **286** with allyl bromide **287** afforded the alcohol **288** in 75% yield according to a literature procedure [270]**.** The bromination of alcohol **288** and subsequent CrO_3-mediated oxidation of dibromo alcohol **289** afforded the desired dibromo compound **285** in 80% yield. As illustrated in Scheme 131, the reaction of dibromo compound **285** with L-valinol, **(***S*)-**283**, afforded two different products after separation of the crude product by column chromatography. The major product was identified as the desired 2-phenylpyrrole derivative (*S*)-**290** (85%). The minor product was obtained in 10% yield and identified as a cyclopropane derivative **291** using ^1H and ^{13}C NMR spectroscopy. The cyclopropane ring is assigned as *trans*. For the formation of **291**, we have proposed the following mechanism: The enone **292** can be formed from **285** with Et_3N. It is possible that this compound yields furan derivative **293**, which can then form **294** with **292** *via* the Michael addition reaction. The intramolecular cyclization reaction of **294** in the presence of Et_3N can form **291**. This reaction, which is outlined in Scheme 131, takes 4–6 hours. With interruption of the reaction after 2 hours, it is possible to isolate the products **293** and **294** from the reaction mixture. Both products are identified spectroscopically. The formation of the pyrrole ring from **285** should work *via* the formation of enone **292** in the presence of Et_3N. Using a similar reaction, norephedrine was also converted into 2-phenylpyrrole derivative in good yield. In all reactions, **291** was formed as a minor product. No product formation was observed with **285** with the use of amino acids and their esters. The reactions afforded an undefined mixture of products.

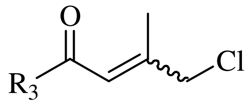


Scheme 131

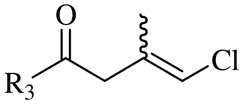
6.3.3 Synthesis of 1,2,4-Trisubstituted Chiral Pyrrole Derivatives

After synthesizing 1,2-disubstituted chiral pyrrole derivatives, we have intended to extend the scope of the reaction to 1,2,4-trisubstituted chiral pyrroles.

Haloenones are valuable intermediates for the construction of nitrogen heterocycles. Chloroenones **295-298** provide a four carbon unit with a carbonyl and halide functionality to form pyrrole rings with primary amines. Chloroenones, **295-298**, were synthesized starting from the corresponding acyl chlorides and 3-chloro-2-methylprop-1-ene (methallyl chloride) in the presence of $AlCl_3$ [268, 271, 272]. According to the ^1H NMR spectrum of the crude products, the reaction furnished the chloroenones **295-298** as the major products. The crude mixtures were used for pyrrole ring formation without further purification.

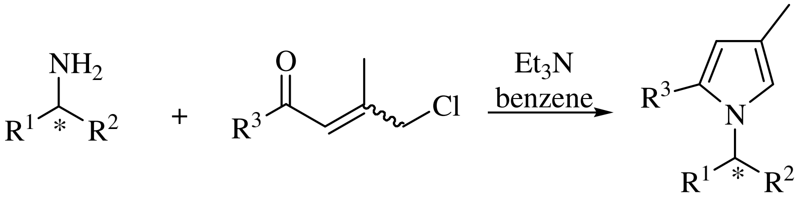


295 R_3 = Me
296 R_3 = *i*-Pr
297 R_3 = cyclohexyl
298 R_3 = Ph



301 R_3 = Me
302 R_3 = *i*-Pr
303 R_3 = cyclohexyl
304 R_3 = Ph

Amines, amino acid esters and amino alcohols **299** were refluxed with chloroenones **295-298** in benzene in the presence of triethylamine in order to obtain 1,2,4-trisubstituted chiral pyrrole derivatives **300** as shown in Scheme 132.



299 **295-298** **300**

Scheme 132

Purification of the crude products furnished the desired pyrrole derivatives **300** in high yields. According to the yields of the reactions, both isomers of chloroenones, **295-298** and **301-304**, should form the pyrrole ring. We propose therefore that enones **295-298** are vitally required starting materials for the formation of the pyrrole ring and that chloroenones **301-304** isomerize to **295-298** during the ring formation reaction [227].

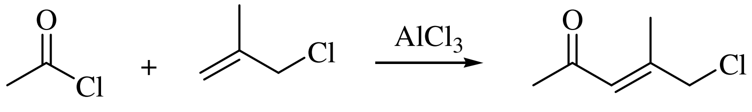
Using the same reaction conditions, different chiral amine compounds are converted to their substituted pyrrole derivatives in 83-96% yields as summarized in Table 4.

The products are viscous oil and their spectroscopic data are in full agreement with their structure.

6.3.3.1 Formation of Chiral Pyrrole Derivatives Using Methyl Substituted Chloroenone

6.3.3.1.1 Synthesis of Methyl Substituted Chloroenone

In the first part of the study, methyl substituted chloroenone **295** was synthesized from acetyl chloride **268** and 3-chloro-2-methylprop-1-ene (methallyl chloride) **305** according to the procedure that was previously developed by Demir *et.al.* (Scheme 133) [252].

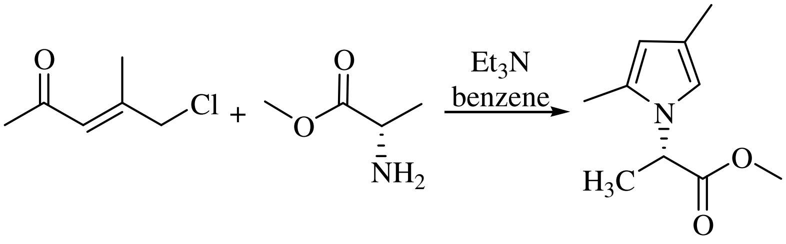


268 **305** **295**

Scheme 133

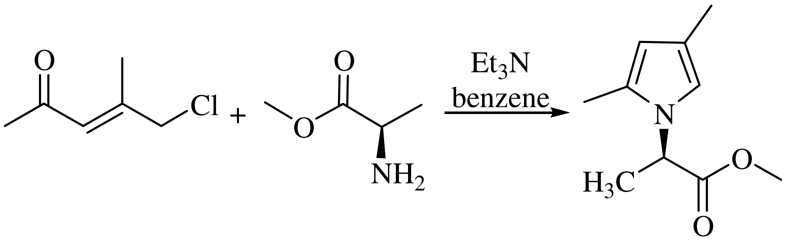
6.3.3.1.1.1 Synthesis of 1,2,4-Trisustituted Pyrrole Derivatives Using Methyl Substituted Chloroenone

The synthesized chloroenone **295** was then reacted with L-Alanine methyl ester (S)**-306** (Scheme 134) and D-Alanine methyl ester (R)**-306** (Scheme 135) and the corresponding chiral pyrrole derivatives (S)-**307** and (R)-**307** were obtained respectively. Analytical data of the products were in accordance with their structure (Figure 43-46 (Appendix A)).



295 (S)-**306** (S)-**307**

Scheme 134

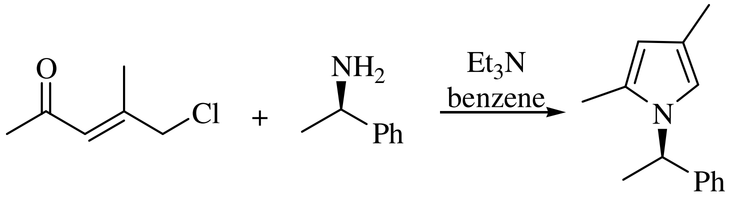


295 (R)-**306** (R)-**307**

Scheme 135

The optical purity of both products were compared with the racemic mixture by chiral HPLC column and the optical rotation values were measured by polarimeter; and it was observed that no racemization has occurred during the formation of the pyrrole ring as expected.

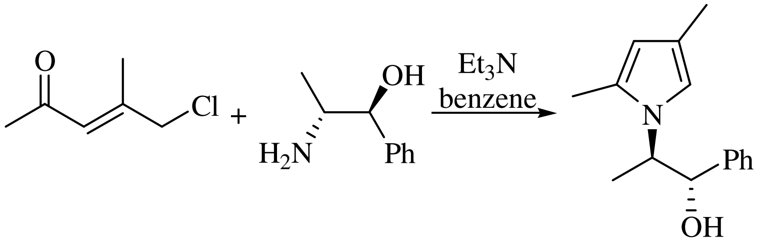
Next, methyl substituted chloroenone **295** was reacted with (R)-(+)-1-phenylethyl amine (R)**-308** under the same set of conditions and the expected pyrrole derivative (R)-**309** was obtained in high yield (Scheme 136). Analytical data of the product were in accordance with its structure (Figure 47 and 48 (Appendix A)).



295 (R)-**308** (R)-**309**

Scheme 136

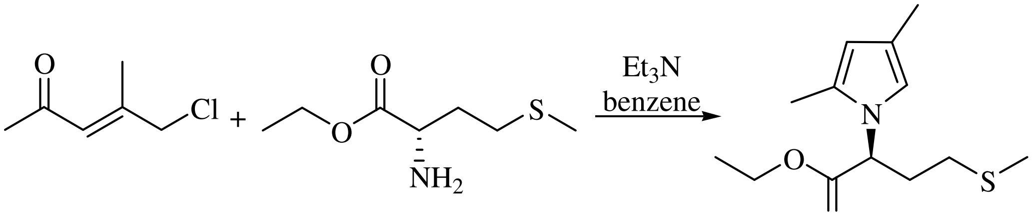
Later, (1S,2R)-(+)-norephedrine, (S,R)-**310** which is an amino alcohol having two stereogenic center was used as amine containing compound and the reaction of this compound with **295** has given the corresponding pyrrole derivative (S,R)-**311** (Scheme 137). Analytical data of the product were in accordance with its structure (Figure 49 and 50 (Appendix A)).



295 (S,R)-**310** (S,R)-**311**

Scheme 137

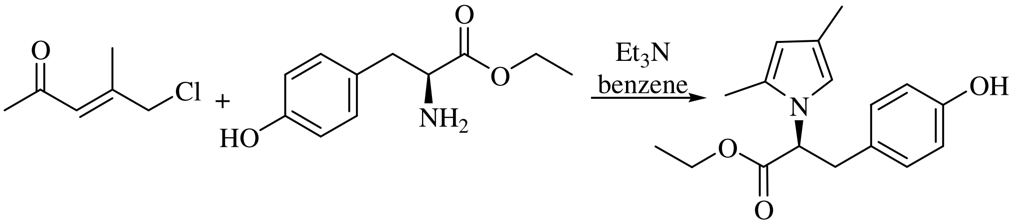
L-Methionine ethyl ester (S)-**312** was the next candidate amine containing compound to be used in 1,2,4-trisubstituted chiral pyrrole derivative synthesis. The reason for choosing this amino acid ester was obtaining a pyrrole derivative which can be converted into pyrrolidine alkaloid and to compounds having sulfur heterocycles fused to pyrrole ring by known methods given in literature which will be discussed later. The outcome of the pyrrole formation was chiral pyrrole derivative (S)-**313** as expected (Scheme 138). Analytical data of the product were in accordance with its structure (Figure 51 and 52 (Appendix A)).



295 (S)-**312** (S)-**313**

Scheme 138

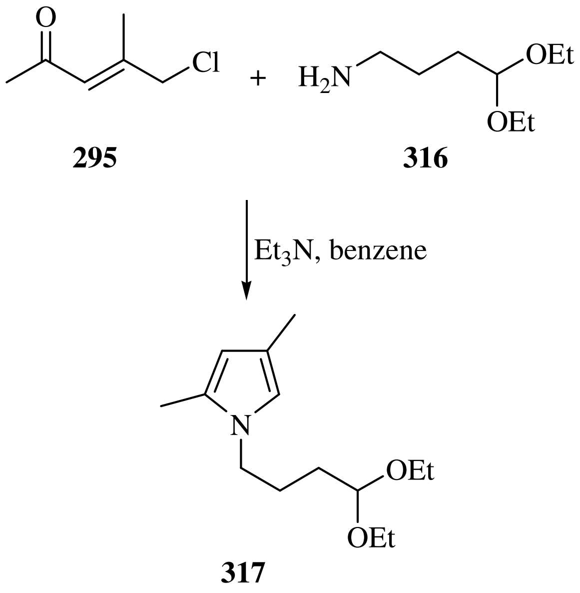
The methyl substituted chloroenone **295** was reacted with L-tyrosine ethyl ester (S)-**314** which is a crowded compound having various functional groups and the corresponding chiral pyrrole derivative (S)-**315** was obtained (Scheme 139). Analytical data of the product were in accordance with its structure (Figure 53 and 54 (Appendix A)).



295 (S)-**314** (S)-**315**

Scheme 139

Pyrrole derivatives containing 4-aminobutyraldehyde diethyl acetal substituent directly linked to nitrogen atom can be converted into indolizine alkaloids which will be discussed later. In order to obtain such a pyrrole derivative, 4-aminobutyraldehyde diethyl acetal **316** was reacted with **295** and the expected pyrrole derivative **317** was obtained (Scheme 140). Analytical data of the product were in accordance with its structure (Figure 55 (Appendix A)).

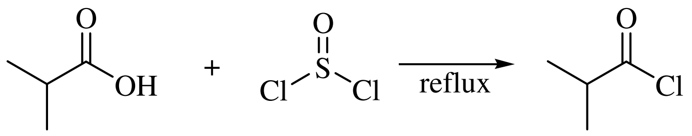


Scheme 140

6.3.3.2 Formation of Chiral Pyrrole Derivatives Using Isobutyryl Substituted Chloroenone

6.3.3.2.1 Synthesis of Isobutyryl Substituted Chloroenone

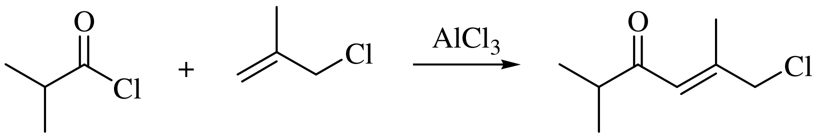
Next, a more crowded group instead of methyl was investigated and isobutyryl group was chosen as the substituent on the pyrrole ring. First, isobutyryl chloride **318** was synthesized from isobutyric acid **319** in the presence of thionyl chloride **320** (Scheme 141).



319 **320** **318**

Scheme 141

Isobutyryl substituted chloroenone **296** was synthesized from isobutyryl chloride **318** and methallyl chloride **305** in the presence of $AlCl_3$ (Scheme 142).

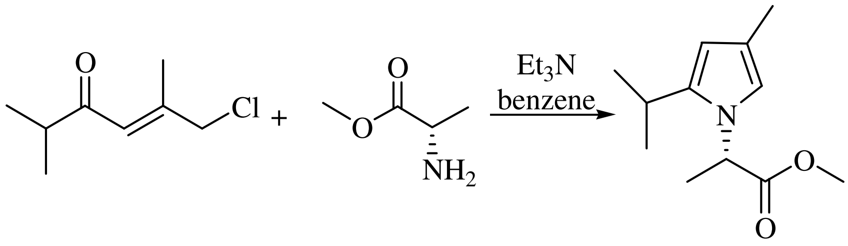


318 **305** **296**

Scheme 142

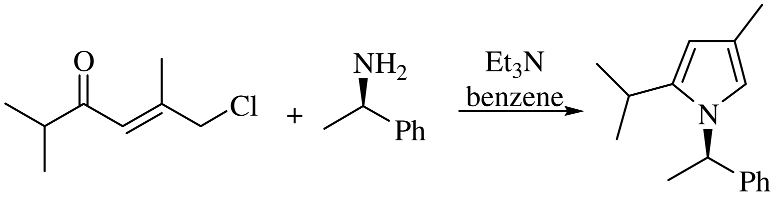
6.3.3.2.1.1 Synthesis of 1,2,4-Trisustituted Pyrrole Derivatives Using Isobutyryl Substituted Chloroenone

Isobutyryl substituted chloroenone **296** was reacted with L-alanine methyl ester (S)**-306** (Scheme 143), (R)-(+)-1-phenylethyl amine (R)**-308** (Scheme 144), (1S,2R)-(+)-norephedrine (S,R)**-310** (Scheme 145) and L-methionine ethyl ester (S)**-312** (Scheme 146) and the corresponding chiral pyrrole derivatives (S)-**321**, (R)-**322**, (S,R)-**323** and (S)-**324** were obtained respectively. Analytical data of the products were in accordance with their structure (Figure 56-63 (Appendix A)).



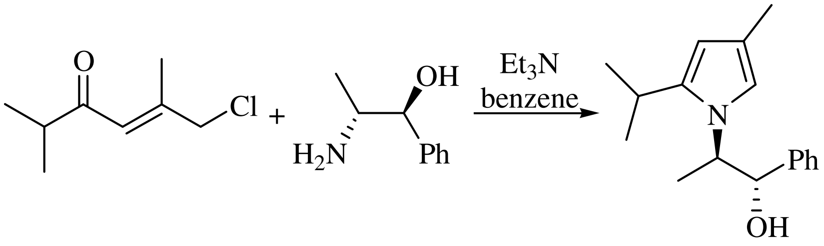
296 (S)-**306** (S)-**321**

Scheme 143



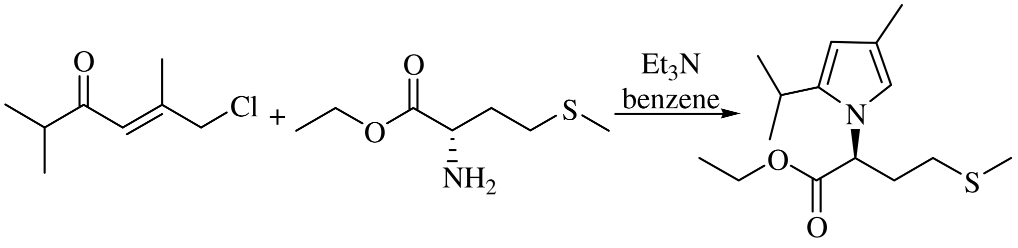
296 (R)-**308** (R)-**322**

Scheme 144



296 (S,R)-**310** (S,R)-**323**

Scheme 145



296 (S)-**312** (S)-**324**

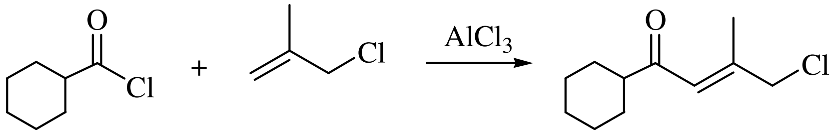
Scheme 146

6.3.3.3 Formation of Chiral Pyrrole Derivatives Using Cyclohexyl Substituted Chloroenone

6.3.3.3.1 Synthesis of Cyclohexyl Substituted Chloroenone

After performing 1,2,4-trisubstituted pyrrole formation reactions using methyl and a substituted alkyl –isobutyryl- group, a cyclic group –cyclohexyl- was tried.

Cyclohexylcarbonyl chloride **277** was reacted with methallyl chloride **305** in the presence of $AlCl_3$ in order to obtain the corresponding cyclohexyl substituted chloroenone **297** (Scheme 147).

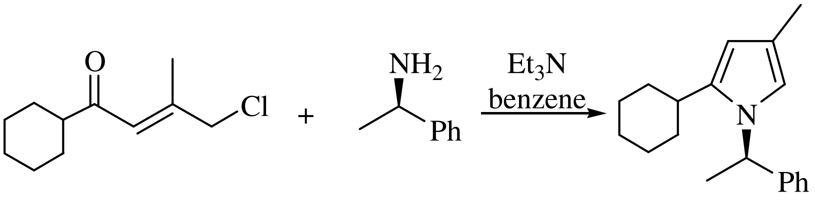


277 **305** **297**

Scheme 147

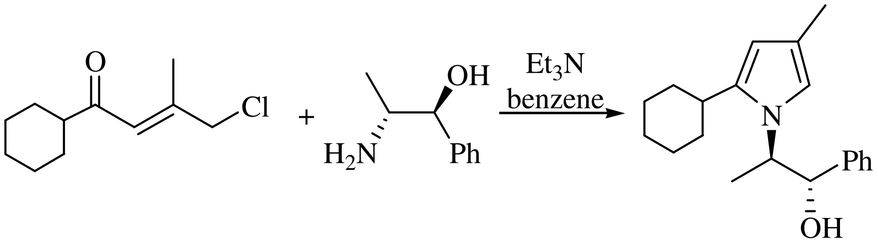
6.3.3.3.1.1 Synthesis of 1,2,4-Trisustituted Pyrrole Derivatives Using Cyclohexyl Substituted Chloroenone

Cyclohexyl substituted chloroenone **297** was then reacted with (R)-(+)-1-phenyl ethyl amine (R)**-308** (Scheme 148) and (1S,2R)-(+)-norephedrine (S,R)**-310** (Scheme 149) and the corresponding chiral pyrrole derivatives (R)-**325** and (S,R)-**326** were obtained respectively. Analytical data of the product were in accordance with its structure (Figure 64-67 (Appendix A)).



297 (R)**-308** (R)-**325**

Scheme 148



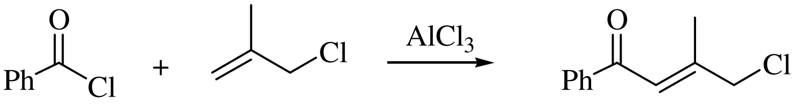
297 (S,R)**-310** (S,R)-**326**

Scheme 149

6.3.3.4 Formation of Chiral Pyrrole Derivatives Using Phenyl Substituted Chloroenone

6.3.3.4.1 Synthesis of Phenyl Substituted Chloroenone

As was indicated before, in the case of 2-phenyl-substituted pyrrole derivatives, problems occurred during the synthesis of the corresponding chloroenone in our previous 1,2-disubstituted chiral pyrrole derivatives studies. The reaction of allyl chloride with benzoyl chloride in the presence of $AlCl_3$ afforded the chloroenone in very low yield (4–6%, ^1H NMR). Because of the difficulty in synthesizing phenyl substituted chloroenone, another pathway was followed in producing 2-phenyl-substituted pyrrole derivatives. We intended to see whether synthesizing phenyl substituted chloroenone starting with methallyl chloride instead of allyl chloride would give such low yields or not. For that purpose, we have applied the same procedure that was used for the synthesis of methyl, isobutyryl and cyclohexyl substituted chloroenones starting from methallyl chloride and corresponding acyl chloride for the synthesis of phenyl substituted chloroenone. In this case, benzoyl chloride **279** was reacted with methallyl chloride **305** in the presence of $AlCl_3$ and the corresponding phenyl substituted chloroenone **298** was obtained in high yield (75-80%) (Scheme 150).

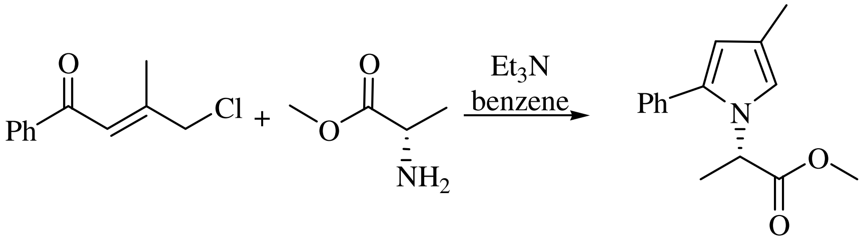


279 **305** **298**

Scheme 150

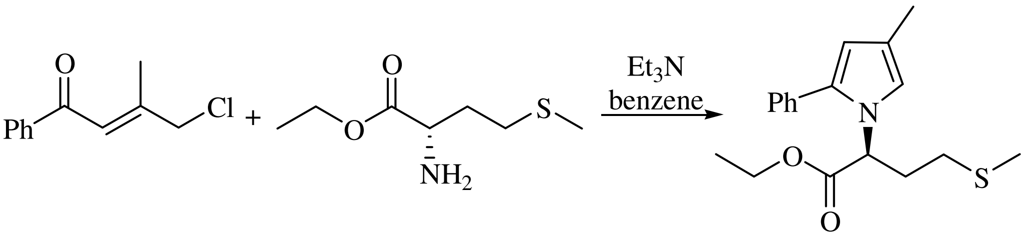
6.3.3.4.1.1 Synthesis of 1,2,4-Trisustituted Pyrrole Derivatives Using Phenyl Substituted Chloroenone

After obtaining phenyl substituted chloroenone **298**, it was reacted with L-alanine methyl ester (S)**-306** (Scheme 151) and L-methionine ethyl ester (S)**-312** (Scheme 152) and the corresponding chiral pyrrole derivatives (S)-**327** and (S)-**328** were obtained respectively. Analytical data of the product were in accordance with its structure (Figure 68-71 (Appendix A)).



298 (S)**-306** (S)-**327**

Scheme 151



298 (S)**-312** (S)-**328**

Scheme 152

6.4 Comparison of the Results

As shown in Table 4, comparable yields are obtained with different R^1-, R^2- and R^3-groups and this shows that varying the substituents on nitrogen and chloroenone does not have a large influence on the yields of the products.

The pyrrole derivatives of amino acid esters and amino alcohols showed excellent separation properties by chiral HPLC column. Therefore, pyrroles (*S*)-, (*R*)- and *rac*-**281**, synthesized starting from the corresponding (*S*)-, (*R*)- and *rac*-alanine methylester **306**, were analyzed by HPLC using chiral column and the results have shown that by the formation of a pyrrole ring from amino acid esters, no racemization occurs [273].

Table 4. The synthesis of 1,2,4-trisubstituted pyrroles

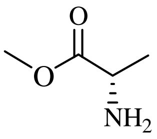
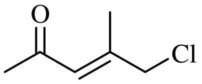
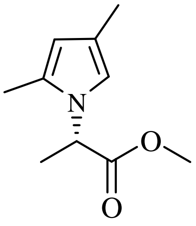
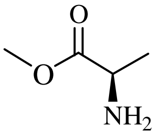
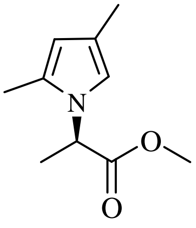
Amine Compound	Chloroenone	Pyrrole	Yield (%)
 (*S*)-**306**	 **295**	 (*S*)-**307**	83
 (*R*)-**306**	**295**	 (*R*)-**307**	86

Table 4 Continued

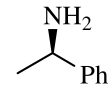
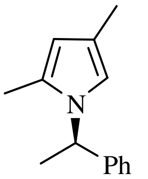
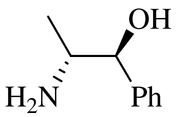
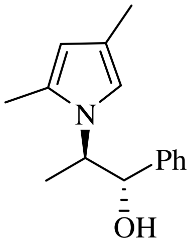
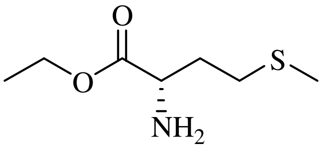
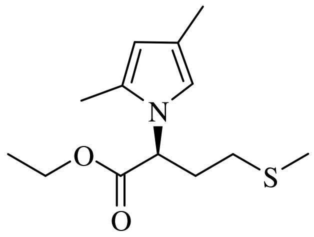
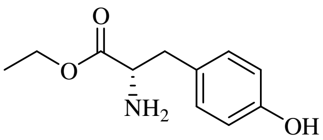
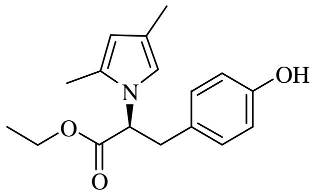
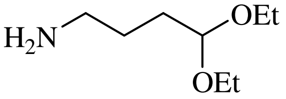
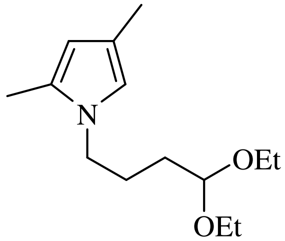
 (*R*)-**308**	**295**	 (*R*)-**309**	93
 (*S*,*R*)-**310**	**295**	 (*S*,*R*)-**311**	89
 (*S*)-**312**	**295**	 (*S*)-**313**	86
 (*S*)-**314**	**295**	 (*S*)-**315**	89
 **316**	**295**	 **317**	78

Table 4 Continued

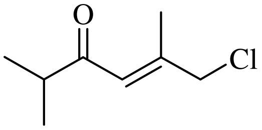
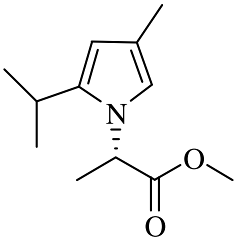
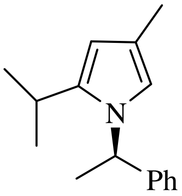
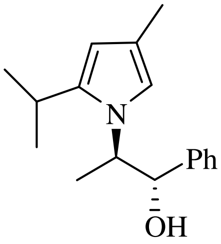
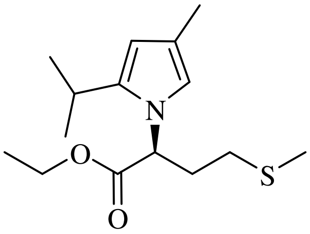
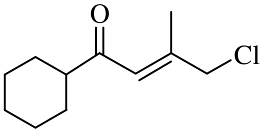
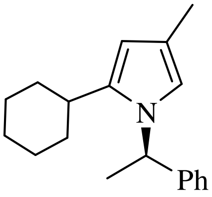
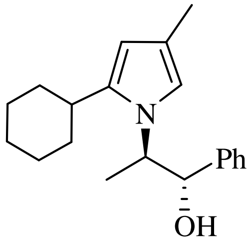
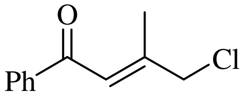
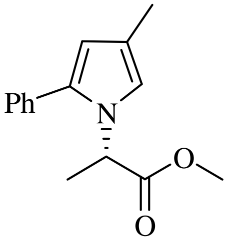
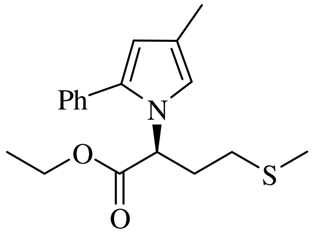
(*S*)-**306**	 **296**	 (*S*)-**321**	87
(*R*)-**308**	**296**	 (R)-**322**	95
(*S*,*R*)-**310**	**296**	 (*S*,*R*)-**323**	96
(*S*)-**312**	**296**	 (*S*)-**324**	91
(*R*)-**308**	 **297**	 (*R*)-**325**	90

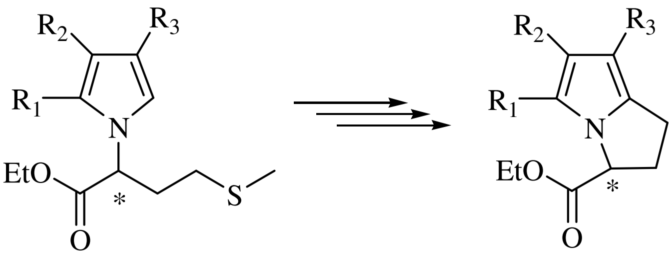
Table 4 Continued

(*S*,*R*)-**310**	**297**	 (*S*,*R*)-**326**	87
(*S*)-**306**	 **298**	 (*S*)-**327**	87
(*S*)-**312**	**298**	 (*S*)-**328**	86

6.5 Possible Conversion of Pyrroles to Izidine Alkaloids

Chiral pyrrole derivatives containing methionine and 4-aminobutyraldehyde diethyl acetal substituents directly linked to nitrogen atom are very valuable compounds.

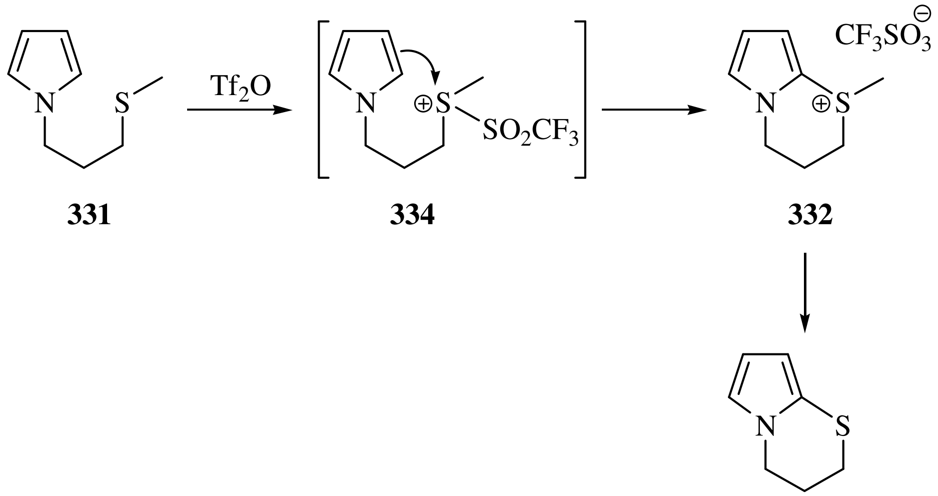
Substituted chiral pyrrole derivatives containing methionine substituent on the nitrogen atom of the heterocycle **329** can be converted into pyrrolidine alkaloids **330** (Scheme 153)**.**



329 **330**

Scheme 153

Nenajdenko *et al.* [274] elaborated a novel method for the preparation of sulfur heterocycles based on the electrophilic cyclization of hetaryl(aryl) substituted aliphatic sulfides **331** promoted by triflic anhydride. They have proposed that intramolecular cyclization of sulfides promoted by triflic anhydride can lead to cyclic sulfonium salts **332**, and after their demethylation to sulfur heterocycles **333**. The proposed method includes intermediate formation of sulfonylsulfonium salts **334** followed by electrophilic attack on the aromatic ring (Scheme 154). The reaction of diethylamine with six-membered sulfonium salts **332** has given the corresponding heterocyclic sulfides **333**.

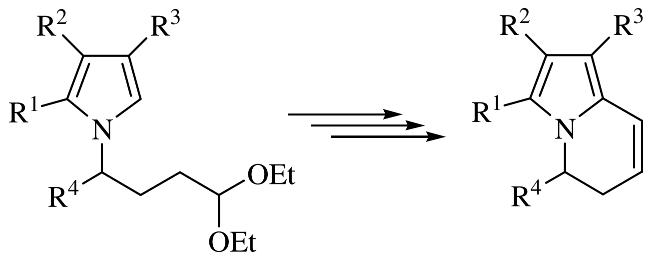


331 **334** **332**

333

Scheme 154

Pyrrole derivatives containing 4-aminobutyraldehyde diethyl acetal substituent directly linked to nitrogen atom **335** can be converted into indolizine alkaloids **336** (Scheme 155).



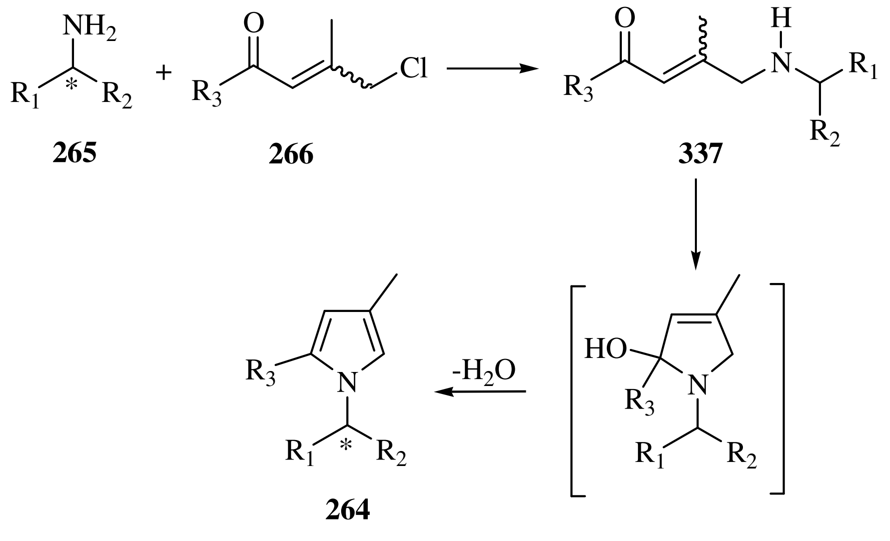
335 **336**

Scheme 155

Taking these reactions into account, the similar pyrrole derivatives that we have synthesized can be used for similar reactions.

6.6 Proposed Mechanism

The suggested mechanism for the formation of pyrroles **264** is outlined in Scheme 156. It seems reasonable to suggest that the amine **265** reacts initially with the chloroenone **266** to form **337** and the cyclization onto the ketone occurs as the ring closure step, followed by elimination of water to give the product **264**.


NH2
R1
*
R2
265
+
O
R3
Cl
266
O
H
N
R3
R1
R2
337
HO
R3
N
R1
R2
-H2O
R3
N
R1
*
R2
264

Scheme 156

CHAPTER 7

EXPERIMENTAL

All reagents were of commercial quality and reagent quality solvents were used without further purification. IR spectra were determined on a Philips model PU9700 spectrometer. NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ were reported in ppm relative to $CHCl_3$ (^{1}H: δ= 7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards. Column chromatography was conducted on silica gel 60 (mesh size 40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ= 254 nm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column. GC-MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). Optical rotations were measured with a Krüss P3002RS automatic polarimeter.

7.1 Synthesis of Chloroenones

7.1.1 4-(Chloromethyl)pent-3-en-2-one (Methyl-substituted chloroenone) 295

Aluminum chloride (7.34 g, 55 mmol) was dissolved in 110 mL dichloromethane at RT. The temperature was adjusted to 0°C and stirring was continued for 15 minutes. To the cold suspension, acetyl chloride 268 (3.93 g, 50 mmol) in 20 mL CH_2Cl_2 was added dropwise through a dropping funnel at 0°C over 20 minutes, followed by the addition of methallyl chloride 305 (4.53 g, 50 mmol) in 20 mL CH_2Cl_2 at 0°C over 5 minutes. Stirring was continued for 40 minutes at 0°C. The cold reaction mixture was poured into ice-water mixture slowly. After separating the layers, organic phase was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was used without any further purification.

7.1.2 6-Chloro-2,5-dimethylhex-4-en-3-one (Isopropyl-substituted chloroenone) 296

Aluminum chloride (7.34 g, 55 mmol) was dissolved in 110 mL dichloromethane at RT. The temperature was adjusted to 0^oC and stirring was continued for 15 minutes. To the cold suspension, isobutyryl chloride **318** (7.33 g, 50 mmol) in 20 mL CH_2Cl_2 was added dropwise through a dropping funnel at 0^oC over 20 minutes, followed by the addition of methallyl chloride **305** (4.53 g, 50 mmol) in 20 mL CH_2Cl_2 at 0^oC over 5 minutes. Stirring was continued for 40 minutes at 0^oC. The cold reaction mixture was poured into ice-water mixture slowly. After separating the layers, organic phase was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was used without any further purification.

7.1.3 4-Chloro-1-cyclohexyl-3-methylbut-2-en-1-one (Cyclohexyl-substituted chloroenone) 297

Aluminum chloride (7.34 g, 55 mmol) was dissolved in 110 mL dichloromethane at RT. The temperature was adjusted to 0^oC and stirring was continued for 15 minutes. To the cold suspension, cyclohexylcarbonyl chloride **277** (7.33 g, 50 mmol) in 20 mL CH_2Cl_2 was added dropwise through a dropping funnel at 0^oC over 20 minutes, followed by the addition of methallyl chloride **305** (4.53 g, 50 mmol) in 20 mL CH_2Cl_2 at 0^oC over 5 minutes. Stirring was continued for 40 minutes at 0^oC. The cold reaction mixture was poured into ice-water mixture slowly. After separating the layers, organic phase was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was used without any further purification.

7.1.4 4-Chloro-3-methyl-1-phenylbut-2-en-1-one (Phenyl-substituted chloroenone) 298

Aluminum chloride (7.34 g, 55 mmol) was dissolved in 110 mL dichloromethane at RT. The temperature was adjusted to 0^{o}C and stirring was continued for 15 minutes. To the cold suspension, benzoyl chloride **279** (7.03 g, 50 mmol) in 20 mL CH_2Cl_2 was added dropwise through a dropping funnel at 0^{o}C over 20 minutes, followed by the addition of methallyl chloride **305** (4.53 g, 50 mmol) in 20 mL CH_2Cl_2 at 0^{o}C over 5 minutes. Stirring was continued for 40 minutes at 0^{o}C. The cold reaction mixture was poured into ice-water mixture slowly. After separating the layers, organic phase was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was used without any further purification.

7.2 Synthesis of 1,2,4-Trisubstituted Chiral Pyrrole Derivatives

7.2.1 (*S*)-2-(2,4-Dimethyl-pyrrol-1-yl)-propionic acid methyl ester (*S*)-307

To a stirred solution of *L*-alanine methyl ester (*S*)**-306** (0.7 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (0.75 g, 83%). $[\alpha]_D^{25}$ = 3.75 (c=0.8 , CH_2Cl_2); IR(neat): 2890, 1780, 1470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.39 (s, 1H), 5.66 (s, 1H), 4.62 (q , *J*=7.3 Hz, 1H), 3.64 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H), 1.58 (d, *J*=7.3 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=172.0, 128.5, 118.2, 115.2, 108.8, 53.3, 52.5, 18.0, 11.93, 11.90. Anal. calcd. for $C_{10}H_{15}NO_2$ (181.23): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.54; H, 8.52.

7.2.2 (*R*)-2-(2,4-Dimethyl-pyrrol-1-yl)-propionic acid methyl ester (*R*)-307

To a stirred solution of *L*-alanine methyl ester (*R*)-**306** (0.7 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (0.78 g, 86%). $[\alpha]_D^{25}$ = -3.77 (c=0.8, CH_2Cl_2).

7.2.3 (*R*)-2,4-Dimethyl-1-(1-phenyl-ethyl)-1*H*-pyrrole (*R*)-309

To a stirred solution of (*R*)-(+)-phenyl ethyl amine (*R*)-**308** (0.61 g, 5 mmol) in benzene (10 mL), was added to triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (0.93 g, 93%). $[\alpha]_D^{25}$= -4.2 (c=1.1, $CHCl_3$); IR(neat): 2840, 1540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.39 (s, 1H) , 5.60 (s, 1H), 4.58 (q , *J* = 7.2 Hz, 1H), 3.64 (s, 3H) , 2.08 (s, 3H), 1.96 (s,3H), 1.58 (d, *J*=7.3 Hz, 3H); ^{13}C NMR

(400 MHz, $CDCl_3$): δ=171.6, 128.1, 118.1, 114.8, 109.0, 53.2, 52.3, 18.0, 12.0, 11.9. Anal. calcd. for $C_{14}H_{17}N$(199.2): C, 84.37; H, 8.60; N, 7.03. Found C, 84.12; H, 8.46.

7.2.4 (*S*,*R*)-2-(2,4-Dimethyl-pyrrole-1-yl)-1-phenyl-propan-1-ol (*S*,*R*)-311

To a stirred solution of (1*S*,2*R*)-(+)-norephedrine (*S,R*)-**310** (0.76 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.02 g, 89%). $[\alpha]_D^{25}$ = -3.8 (c= 0.6, $CHCl_3$); IR(neat): 3600, 1560, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.11 (m, 5H), 6.35 (s, 1H), 5.45 (s, 1H), 4.56 (d, *J*=5.1 Hz, 1H), 3.99 (m, 1H), 2.32 (br s, 1H),1.91 (s,3H), 1.83 (s, 3H), 1.27 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=141.6, 128.2 (2C), 128.0, 127.7, 127.6, 125.8, 117.5, 114.5, 108.3, 56.7, 15.0, 12.1, 12.0. Anal. calcd. for $C_{15}H_{19}NO$ (229.3): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.77; H, 8.58.

7.2.5 (*S*)-2-(2,4-Dimethyl-pyrrol-1-yl)-4-methylsulfanyl-butyric acid ethyl ester (*S*)-313

To a stirred solution of *L*-methionine ethyl ester (*S*)-**312** (1.07 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.10 g, 86%). $[\alpha]_D^{25}$= -3.4 (c=1.3, $CHCl_3$); IR(neat): 2890, 1776, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.27 (s, 1H), 5.56 (s, 1H), 4.66 (m, 1H), 4.10 (m, 2H), 2.35 (m, 1H), 2.22-2.11 (m, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H), 1.17 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=170.5, 128.8, 118.5, 114.8, 108.9, 61.2, 56.0, 31.2, 30.2, 15.2, 14.1, 12.1, 12.0. Anal. calcd. for $C_{13}H_{21}NO_2S$ (255.3): C, 61.14; H, 8.29; N, 5.48. Found: C, 61.32; H, 8.48.

7.2.6 (*S*)-2-(2,4-Dimethyl-pyrrol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (*S*)-315

To a stirred solution of *L*-tyrosine ethyl ester (*S*)-**314** (1.27 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.28 g, 89%). $[\alpha]_D^{25}$= -4.4 (c=1, $CHCl_3$); IR(neat): 3735, 1740, 1680, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.69 (d, *J*=8.4 Hz, 2H), 6.51 (d, *J*=8.5 Hz, 2H), 6.46 (s, 1H), 5.49 (s, 1H), 4.0 (m, 1H), 3.99 (m, 2H), 3.15 (dd, J_1=13.8, J_2=6.5 Hz, 1H), 2.96 (dd, J_1=13.8 J_2=8.6 Hz, 1H), 1.93 (s, 3H), 1.80 (s, 3H), 1.06 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=170.5, 154.8, 129.9, 128.6, 127.7, 118.0, 115.2, 114.7, 108.2, 61.2, 59.6, 44.8, 38.0, 21.0, 13.6, 11.7, 11.4. Anal. calcd. for $C_{17}H_{21}NO_3$(287.3): C, 71.06; H, 7.37; N, 4.87. Found: C, 71.33; H, 7.55.

7.2.7 1-(4,4-diethoxybutyl)-2,4-dimethyl-1H-pyrrole 317

To a stirred solution of 4-aminobutyraldehydediethyl acetal **316** (0.81 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-(chloromethyl)pent-3-en-2-one **295** (0.66 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (0.93 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.19 (s, 1H), 5.54 (s, 1H), 4.32 (t , *J*=5.53 Hz, 1H), 3.64 (t, *J*=7.27 Hz, 2H), 3.52 (m, 2H), 3.37 (m, 2H), 2.08 (s, 1H), 1.94 (s, 1H), 1.64 (m, 2H), 1.51 (m, 2H), 1.11 (m, 6H); Anal. calcd. for $C_{14}H_{25}NO_2$ (239.35): C, 70.25; H, 10.53; N, 5.85. Found: C, 70.82; H, 10.11.

7.2.8 (*S*)-2-(2-Isopropyl-4-methyl-pyrrol-1-yl)-propionic acid methyl ester (*S*)-321

To a stirred solution of *L*-alanine methyl ester (*S*)-**306** (0.7 g, 5 mmol) in benzene (10mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 6-chloro-2,5-dimethylhex-4-en-3-one **296** (0.80 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (0.91 g, 87%). $[\alpha]_D^{25}$= +3.6 (c=1.2, $CHCl_3$); IR(neat): 2885, 1776, 1470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.34 (s, 1H), 5.64 (s, 1H), 4.68 (q *J*=7.2 Hz, 1H), 3.64 (s, 3H), 2.73 (m, 1H), 1.96 (s, 3H), 1.58 (d, *J*=7.2 Hz, 3H), 1.15 (dd, J_1=6.7, J_2=5.0 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=171.3, 138.9, 117.6, 114.3, 104.6, 52.1, 51.8, 24.8, 23.1, 22.4, 18.2, 11.6. Anal. calcd. for $C_{12}H_{19}NO_2$(209.2): C, 68.87; H, 9.15; N, 6.69. Found: C, 68.61; H, 9.31.

7.2.9 (*R*)-2-Isopropyl-4-methyl-1-(1-phenylethyl)-1*H*-pyrrole (*R*)-322

To a stirred solution of (*R*)-(+)-1-phenyl ethyl amine (*R*)-**308** (0.61 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 6-chloro-2,5-dimethylhex-4-en-3-one **296** (0.80 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.08 g, 95%). $[\alpha]_D^{25}$= +31.6 (c=3.3, $CHCl_3$); IR(neat): 2850, 1550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (m, 3H), 6.89 (d, *J*=7.6 Hz, 2H), 6.35 (s, 1H), 5.68 (s, 1H), 5.20 (q, *J*=7.1 Hz, 1H), 2.67 (q, *J*=6.8 Hz, 1H), 2.01 (s, 3H), 1.69 (d, *J*=7.1 Hz, 3H), 1.14 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=144.3, 140.0, 128.5 (2C), 126.9, 125.7 (2C), 117.3, 114.6, 105.0, 53.8, 25.4, 24.1, 23.1, 22.6, 12.2. Anal. calcd. for $C_{16}H_{21}N$(227.3): C, 84.53; H, 9.31; N, 6.16. Found: C, 84.78; H, 9.57.

7.2.10 (*S*,*R*)-2-(2-Isopropyl-4-methyl-pyrrol-1-yl)-1-phenyl-propan-1-ol (*S*,*R*)-323

To a stirred solution of (1*S*,2*R*)-(+)-norephedrine (*S,R*)-**310** (0.76 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 6-chloro-2,5-dimethylhex-4-en-3-one **296** (0.80 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.24 g, 96%). $[\alpha]_D^{25}$= -5.1 (c=1.3, $CHCl_3$); IR(neat): 3580, 2860, 1550, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.19 (m, 5H), 6.50 (s, 1H), 5.59 (s, 1H), 4.73 (d, *J*=5.2 Hz, 1H), 4.17 (m, 1H), 2.50 (m, 1H), 2.07 (br s, 1H), 2.03 (s, 3H), 1.39 (d, *J*=6.9 Hz, 3H), 1.08 (d, *J*=6.7 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=141.5, 139.6, 128.2, 128.0, 127.5, 125.7 (2C), 117.6, 114.4, 104.4, 77.4, 56.1, 25.3, 24.5, 22.2, 15.3, 12.1. Anal. calcd. for $C_{17}H_{23}NO$(257.3): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.52; H, 9.24.

7.2.11 (*S*)-2-(2-Isopropyl-4-methyl-pyrrol-1-yl)-4-methylsulfanyl-butyric acid ethyl ester (*S*)-324

To a stirred solution of *L*-methionine ethyl ester (*S*)-**312** (1.07 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 6-chloro-2,5-dimethylhex-4-en-3-one **296** (0.80 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.29 g, 91%). $[\alpha]_D^{25}$= -15.6 (c=3, $CHCl_3$); IR(neat): 2890, 1776, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=6.29 (s, 1H), 5.63 (s, 1H), 4.76 (m, 1H), 4.14 (m, 2H), 2.85 (m, 1H), 2.37 (m, 1H), 2.20 (m, 6H), 2.02 (s, 3H), 2.00 (s, 3H), 1.21 (t, *J*=8.2 Hz, 3H), 1.12 (d, *J*=6.8 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=170.7, 140.3, 118.5, 114.7, 105.0, 61.3, 55.6, 31.8, 30.3, 25.2, 23.6, 23.1, 15.3, 14.1, 12.1.

Anal. calcd. for $C_{15}H_{25}NO_2S$(283.4): C, 63.56; H, 8.89; N, 4.94. Found: C, 63.38; H, 8.67.

7.2.12 (*R*)-2-Cyclohexyl-4-methyl-1-(1-phenyl-ethyl)-1*H*-pyrrole (*R*)-325

To a stirred solution of (*R*)-(+)-1-phenyl ethyl amine (*R*)-**308** (0.61 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-chloro-1-cyclohexyl-3-methylbut-2-en-1-one **297** (1.00 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.20 g, 90%). $[\alpha]_D^{25}$= -2.8 (c=0.9, $CHCl_3$); IR(neat): 2860, 1540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (m, 3H), 7.0 (d, *J*=7.0 Hz, 2H), 6.43 (s, 1H), 5.77 (s, 1H), 5.27 (q, *J*=7.1 Hz,1H), 2.36 (m, 1H), 2.09 (s, 3H), 1.88 (m, 1H), 1.75 (d, *J*=7.0 Hz, 3H), 1.65–1.51 (m, 3H), 1.41–1.11 (m , 6H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ=144.4, 139.6, 129.1, 128.6, 128.4, 127.1, 125.8, 117.5, 114.6, 105.3, 53.8, 35.8, 34.9, 33.8, 27.0, 26.9, 26.3, 22.6, 12.3. Anal. calcd. for $C_{19}H_{25}N$(267.4): C, 85.34; H, 9.42; N, 5.24. Found: C, 85.11; H, 9.71.

7.2.13 (*S*,*R*)-2-(2-Cyclohexyl-4-methyl-pyrrol-1-yl)-1-phenyl-propan-1-ol (*S*,*R*)-326

To a stirred solution of (1*S*,2*R*)-(+)-norephedrine (*S,R*)-**310** (0.76 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-chloro-1-cyclohexyl-3-methylbut-2-en-1-one **297** (1.00 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.29 g, 87%). $[\alpha]_D^{25}$= +2.5 (c=0.5, $CHCl_3$); IR(neat): 3600, 1560, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.21 (m, 5H), 6.41 (s, 1H), 5.47 (s, 1H), 4.67 (d, *J*=5.5 Hz, 1H), 4.13 (m, 1H), 2.31 (br s, 1H), 1.97 (s, 3H), 1.34 (d, *J*=6.9 Hz, 3H), 1.78–1.51 (m, 5H), 1.42–1.11 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=176.5, 141.7, 138.8, 128.4, 127.9, 126.3, 125.6, 114.1, 104.8, 56.1, 50.7, 35.6, 32.7, 29.7, 29.5, 26.8, 26.2, 25.7, 15.4, 12.2. Anal. calcd. for $C_{20}H_{27}NO$(297.4): C, 80.76; H, 9.15; N, 4.71. Found: C, 80.51; H, 9.33.

7.1.14 (*S*)-2-(4-Methyl-2-phenyl-pyrrol-1-yl)-propionic acid methyl ester (*S*)-327

To a stirred solution of *L*-alanine methyl ester (*S*)-**306** (0.7 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-chloro-3-methyl-1-phenylbut-2-en-1-one **298** (0.97 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.06 g, 87%). $[\alpha]_D^{25}$= +4.2 (c=0.5, $CHCl_3$); IR(neat): 2890, 1770, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.85 (m, 1H), 7.24 (m, 4H), 6.53 (s, 1H), 5.90 (s, 1H), 4.79 (q, *J*=7.2 Hz, 1H), 3.63 (s, 3H), 2.05 (s,3H), 1.53 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=171.8, 134.7, 133.2, 129.1, 128.6, 128.4, 128.3, 127.1, 119.4, 110.5, 53.4, 52.3, 18.9, 17.5, 12.0. Anal. calcd. for $C_{15}H_{17}NO_2$(243.3): C, 74.05; H, 7.04; N, 5.76. Found: C, 74.36; H, 7.22.

7.1.15 (*S*)-2-(4-Methyl-2-phenyl-pyrrol-1-yl)-4-methylsulfanyl-butyric acid ethyl ester (*S*)-328

To a stirred solution of *L*-methionine ethyl ester (*S*)-**312** (1.07 g, 5 mmol) in benzene (10 mL), was added triethylamine (2.53 g, 25 mmol) at room temperature. To this mixture, 4-chloro-3-methyl-1-phenylbut-2-en-1-one **298** (0.97 g, 5 mmol) was gradually added and the reaction mixture was refluxed for 4-6 hours. The reaction was monitored by TLC. After cooling to room temperature, distilled water (10 mL) was added to dissolve the salt of triethylamine and the mixture was extracted with dichloromethane (3 x 25 mL). Combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed by flash column chromatography on neutral aluminum oxide (1:10 EtOAc:Hexane).

Yellow oil, (1.36 g, 86%). $[\alpha]_D^{25}$= -9.6 (c=1.3, $CHCl_3$); IR(neat): 2885, 1780, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.85 (m, 1H), 7.29 (m, 4H), 6.53 (s, 1H), 5.90 (s, 1H), 4.79 (q, *J*=5.1 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 2.17 (m, 4H), 2.05 (s, 3H), 1.87 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=170.0, 132.6, 135.0, 128.8, 128.1, 127.9, 127.8, 126.6, 122.5, 119.5, 116.4, 60.9, 56.4, 32.1, 29.5, 14.8, 13.7, 11.6. Anal. calcd. for $C_{18}H_{23}NO_2S$(317.4): C, 68.10; H, 7.30; N, 4.41. Found: C, 68.36; H, 4.66.

CHAPTER 8

CONCLUSION

In conclusion, we have developed a new synthetic method for the efficient preparation of 1,2,4-substituted pyrroles, which is not known in literature, from haloenones and amines, amino alcohols and esters of amino acids. The cyclization works without racemization. Furthermore, this methodology can be extended to the synthesis of poly functionalized pyrroles and alkaloids.

The notable advantages of this procedure are: a) reasonably good yields; b) fast reaction; c) mild reaction conditions; d) choice of appropriate substituents on the pyrrole ring and nitrogen; e) general applicability. Thus it provides a better and more practical alternative to the existing methodologies for the synthesis of pyrroles.

Since the reaction takes place under mild conditions and in a way so that no bonds directly linked to the stereocenter are broken or formed, the reaction proceeds without racemization.

REFERENCES

1. Minisci, F. A. *Acc. Chem. Res.* **1975**, *8,* 165.
2. de Klein *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J.; de Jodge, R. H. I.; Plenum: New York, 1986.
3. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds;* Pergamon: Oxford, 1986.
4. Ramaih, M. *Tetrahedron* **1987**, *43*, 3541.
5. Curran, D. P. In *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon: Oxford, 1992, Ch. 4.1, 4.2, and references therein.
6. a) Walling, Ch.; Hauser, E. S. *Org. React.* **1966**, *13*, 103; b) Stacey, F. W.; Harris, J. F. Org. React. 1966, 13, 170.
7. Bush, J. B.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903.
8. Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Am. Chem.Soc.* **1968**, *90,* 5905.
9. Melikyan, G. G. *Synthesis.* **1993**, 833.
10. de Klein W. J., Thesis, Leiden **1967**.
11. Christensen, O. T. *J. Prakt. Chem.* **1883**, *28*, 1.
12. Christensen, O. T. *Z. Anorg. Allgem. Chem.* **1901**, *27*, 323.
13. Spath, E. *Monatsh.Chem.***1912**, *33*, 242.
14. Chretien, A.; Varga, G. *Bull. Soc. Chim. France* **1936**, *3*, 2385.
15. de Korte, R. W., Thesis, Leiden **1964**.
16. Hessel, L. W., Thesis, Leiden **1968**.
17. Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 2450.
18. Sem, M. *Z. Elektrochem*. **1915**, *21*, 426.
19. Copaux, H. *C. R. Acad. Sci.* **1903**, *136*, 373.
20. Butter, S. A. U.S. Patent No.3, **1969**, 647, 835.
21. Vaerman, J. M.; Bertrand, J. N. M. German Patent No.2, **1972**, 124, 876.
22. Hessel, L. W.; Romers, C. *Recl Trav. Chim*. **1969**, *88*, 545.
23. Andrulis, P. J.; Dewar, M. J. S.; Dietz, R.; Hunt, R. L. *J. Am. Chem. Soc.* **1966**, *88*, 5473.
24. Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Org. Chem.* **1974**, *39*, 3456.
25. Klein, W. J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 48; U.S. Patent No. 4,014,910 **1977.**
26. Heiba, E. I.; Dessau. R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977.
27. Klein, W. J. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 22.

28. McQuillin, F. J.; Wood, M. *J. Chem. Soc. Chem. Commun.* **1976**, 65.
29. Nikishin, G. I.; Vinogradov, M. G.; Fedorova, T. M. *J. Chem. Soc. Chem. Commun.* **1973**, *18*, 693.
30. Klein, W. J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 151.
31. Miles, M. G. British Patent No. 1,303,831 **1970**.
32. Mane, R. B.; Krishna Rao, G. S. *J. Chem. Soc. Perkin Trans I,* **1975**, 1235.
33. Vinogradov, M. G.; Verenchikov, S. P.; Nikishin, G. I. *Izv. Akad. Nauk SSSR Ser. Khim.* **1972**, 982.
34. Vinogradov, M. G.; Il'ina, G. P.; Ignatenko, A. V.; Nikishin, G. I. *Zh. Org. Khim.* **1972**, *8*, 539.
35. Nikishin, G. I.; Vinogradov, M. G.; Verenchikov, S. P. *Izv. Akad. Nauk SSSR Ser.* Khimi **1969**,1835.
36. Nikishin, G. I.; Vinogradov, M. G.; Verenchikov, S. P.; Kostyukov, I. N.; Kereselidze, R. V. *Zh. Org. Khim.* **1972**, *8*, 539.
37. Heiba, E. I.; Dessau, R. M. U.S. Patent No. 4,011,239; German Patent No. 1,936,261
38. Heiba, E. I.; Dessau, R. M. J. Am. Chem. Soc. **1971**, *93*, 524.
39. Vinogradov, M. G.; Verenchikov, S. P.; Fedorova, T. M.; Nikishin, G. I. *Zh. Org. Khim.* **1975**, *11*, 947.
40. Corey, E. J.; Kang, M. C. J. *Am. Chem. Soc.* **1984**, 106, 5384.
41. Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.
42. Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.
43. Ernst, A. B.; Fristad, W. E. *Tetrahedron Lett.* **1985**, *26*, 3721.
44. Heiba, E. I.; Dessau, R. M. J. Am. Chem. Soc. **1972**, 94, 2888.
45. Dessau, R. M.; Heiba, E. I. *J. Org. Chem.* **1974**, *39*, 3457.
46. Chatzopoulos, M.; Montheard, J. P. *C. R. Acad. Sci.* **1977**, *284*, 133.
47. Demir, A. S.; Reis, O.; Ozgul-Karaaslan, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, *30*, 3042.
48. Beadle, J. R.; Korzeniowsky, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. J. Org. Chem. 1984, 49, 1596.
49. Demir, A. S.; Reis, O .; Emrullahoglu, M. *Tetrahedron* **2002**, *58*, 8055.
50. Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. J. Org. Chem. 1997, 62, 6733.
51. Demir, A.S.; Reis, O.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578.
52. Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.
53. Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427.
54. Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217.
55. Dewar, M. J. S.; Nakaya, T. *J. Am. Chem. Soc*. **1968**, *90*, 7134.
56. Demir, A. S.; Jeganathan, A.; Watt, D. S. *J. Org. Chem.* **1989**, *54*, 4020.
57. Demir, A. S.; Sayrac, T.; Watt, D. S. *Synthesis* **1990**, 1119.
58. Demir, A. S.; Camkerten, N.; Akgun, H.; Tanyeli, C.; Mahasneh, A. S.; Watt, D. S. *Synth. Commun*. **1990**, *20*, 2279.

59. Demir, A. S.; Akgun, H.; Tanyeli, C.; Sayrac, S.; Watt, D. S. *Synthesis* **1991**, 719.
60. Demir, A. S.; Jeganathan, A. *Synthesis* **1992**, 235.
61. Demir, A. S.; Saatcioglu, A. *Synth. Commun.* **1993**, *23*, 571.
62. Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976**, *54*, 3830.
63. Koreeda, M.; Chem, Y.P.L. *Tetrahedron Lett.* **1981**, *22*, 15.
64. de Groot, A. E.; Jansen, B. J. M. *Rec. Trav. Chim. Pays-Bas* **1976**, *95*, 81.
65. Chen, Y. L.; Mariano, P. S.; Huesmann, P. L. *J. Org. Chem.* **1981**, *46*, 4643.
66. Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
67. Boschelli, D.; Smith III, A. B. *Tetrahedron Lett.* **1981**, *22*, 4385.
68. Orchin, M.; Butz, l. W. *J. Am. Chem. Soc.* **1943**, *65*, 2296.
69. Vandewalle, M.; Compernolle, F. *Bull. Soc. Chim. Belg.* **1966**, *75*, 349.
70. Demir, A. S.; Enders, D. Z. *Naturforsch.* **1989**, *44b*, 10.
71. Klunder, H. C. *U.S. Patent* 4159 99 (1979); *C. A.* **1979**, *91*, 140 424.
72. Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968.
73. Hassel, L.W.; Romers, C. *Recl. Trav. Chim. Pays.Bas* **1969**, *88*, 545.
74. Vaerman, J. M.; Bertrand, J. N. M. Ger. Pat. 2,124,876, **1972**, *Chem. Abstr*. **1972**, *77*, 100812z.
75. Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. J. Am. Chem. Soc. **1969**, 91, 138.
76. Arndt, D. *Manganase Compounds as Oxidizing Agents in Organic Chemistry;* Open Court Publishing Co.: La Salle, IL, 1981; Chapter 1.
77. Hessel, L. W.; Romers, C. *Rec. Trav. Chim.* **1969**, *88*, 545.
78. Fristad, W. E.; Peterson. J. R. *J. Org. Chem.* **1985**, 50*,*10.
79. Fristad, W. E.; Hershberger, S. S. *J. Org. Chem.* **1985**, *50*,1026.
80. Fristad, W. E.; Peterson. J. R.; Ernst, A. B. *J. Org. Chem.* **1985**, *50*, 3143.
81. Fristad, W. E.; Peterson. J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, 42, 3429.
82. Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, 28, 1493.
83. Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.
84. Snider, B. B.; Merritt, J. E.; Domboski, M. A.; Buckman, B. O. J. *Org. Chem.* **1991**, *56*, 5544.
85. Snider, B. B.; McCarthy, B. A. In *Benign by Design, Alternative Synthetic Design for Pollution Prevention*; Anastas, P.T., Ferris, C.A., Eds; ACS Symposium Series 577; American Chemical Society: Washington, DC, **1994**; pp 84-97.
86. Bergamini, F; Citterio, A.; Gatti, N.; Nicolini, M.; Santi, R.; Sebastiano, R.J. *Chem.* Res. S **1993**, 364.
87. Warsinsky, R.;Steckhan, E. *J.Chem.Soc.,Perkin Trans.*1 **1994**, 2027.
88. Colemen, J.P.; Hallcher, R.C.; McKacknis, D.E.; Rogers, T.E.; Wagenknecht , J.H. *Tetrahedron* **1991**, *47*, 809.

89. Nedelec, J.Y.; Nohair, K. *Synlett*. **1991**, 659.
90. Allegretti, M.;D'Annibale,A.;Trogolo,C. *Tetrahedron* **1993**, *49,* 10705.
91. D'Annibale, A.;Trogolo, C. *Tetrahedron Lett.* **1994**, *35*,2083.
92. Bosman, C.; D'Annibale, A.; Resta, S.;Trogolo, C. *Tetrahedron* **1994**, *50*, 13847.
93. Schapiro, V.; Cavalli, G.; Scoane, G. A.; Faccio, R.; Mombru, A. W. *Tetrahedron Asymmetry* **2002**, *13*, 2453.
94. Oppolzer, W.; Mahalanabis, K. K. Tetrahedron Lett. 1975, 3411.
95. Polonsky, J. *Forts. Chem. Org. Naturst.* **1986**, *47*, 221.
96. Paju, A.; Kanger, T.; Pehk, T.; müürisepp, A. M.; Lopp, M. Tetrahedron: Asymmetry 2002, 13, 2439.
97. Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett*. **1984**, *25*, 5839.
98. Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron: Asymmetry* **1998**, *9*, 907.
99. Demir, A. S.; Hamamci, H.; Tanyeli, C.; Akhmedov, I. M.; Doganel, F. *Tetrahedron: Asymmetry* **1998**, *9*, 1673.
100. Tanyeli, C.; Ozdemirhan, D.; Sezen, B. *Tetrahedron* **2002**, *58*, 9983.
101. Brauer, G.; *Handbuch der Praparativen Anorganischen Chemie*, Stuttgart, 1962.
102. Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Synlett* **1998** 51.
103. Demir, A. S.; Camkerten, N.; Akgun, H.; Tanyeli, C.; Mahasneh, A. S.; Watt, D. S. *Synth. Commun*. **1990**, *20*, 2279.
104. Lee, J. C.; Jin, Y. S.; Choi, *J. Chem. Commun.* **2001**, 956.
105. Ellis, J. W. *J. Org. Chem*. **1958**, 1154.
106. Fort, A.W. *J. Org. Chem.* **1961**, *26*, 332
107. Henbest, H. B.; Jones, D.N.; Slater, G.P. *J. Chem. Chem.* **1961**, 4472.
108. Hartshorn, M. P.; Wallis, A. F. A. *J. Chem. Chem*. **1964**, 5254.
109. Demir, A. S.; Sesenoglu, O. *Org. Lett*. **2002**, *4*, 2021.
110. Naemura, K.; Wakebe, T.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry*, **1997**, *8*, 2585.
111. Demir, A. S.; Tanyeli, C.; Akgün, H.; Çalışkan, Z.; Özgül, E. *Bull. Chem. Soc. Fr*. **1995**, *132*, 423.
112. Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün, H.; *Turkish J. Chemistry* **1996**, *20*, 244.
113. Tanyeli, C.; Calışkan, Z.; Demir, A. S. *Synth. Commun*. **1997**, *27*(19), 3471.
114. Mannhold R., Cruciani G., Weber H., Lemoine H., Derix A., *J. Med. Chem;* **1999,** *42*, 981.
115. Davies, I. W.; Taylor, M.; Marcoux, J. F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P. J. *Tetrahedron Lett*. **2000**, *41*, 8021.
116. Roxburgh C. J., *Synthesis Review;* **1995,** 307.
117. Gadwood, R. C.; Kamdar, B. V.; Loretta, A.; Cipkus, D. *J. Med. Chem.***1993**, *36*, 1480.
118. Demir, A. S.; Aybey, A.; Sesenoglu, Ö.; Polat, F. Tetrahedron:

Asymmetry 2003, 14, 1489.

119. A-Homosteroids: Goldberg, M. W.; Kirchensteiner, H. Helv. Chim. Acta **1943**, 26, 288; Velgova, H.; Cerny, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1973**, *38*, 2751; B-Homostereoids: Ringold H. J. *J. Am. Chem.. Soc.* **1960**, *82*, 961; Kohut, L.; Fajkos, J.; Sorm, F. *Collect. Czech. Chem.. Commun*. **1967**, *32*, 1210; Kohut, L. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2227; D-Homostereoids: Goldberg, M. W.; Monnier, R. *Helv. Chim. Acta* **1940**, *23*, 376; A-nor-B-homosteroids: Suginome, H.; Yabe, T.; Osawa, E. J. *Chem. Soc. Perkin Trans. 1* **1982**, 931.
120. 5α-Reductase is the NADPH-dependent enzyme which irreversibly converts testosterone to the more potent androgen dihydrotestosterone. Anderson, K. M.; Liano, S. *Nature* **1968**, *219*, 277; Imperato-McGinley, J.; Guerro, L.; Gautier, T.; Peterson, R. E. *Science* **1974**, *186*, 1213; Bardin, C. W.; Catterall, J. F. *Science* **1981**, *211*, 1285.
121. Rasmusson, G. H.; Reynolds, G. F; Steinberg, N. G.; Walson, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.;Cheung, A. H.; Brooks, J. R.; Berman, C. J. *Med. Chem*. **1986**, *29*, 2298.
122. Audet, P. R.; Baine, N. H.; Benincose, L. J.; Holt, D. A.; Wier, P. J.; Rappaport, E. B.; Metcalf, B. W.; Levy, M. A. *Drugs Fut* **1994**, *19*, 646.
123. Ferreira, M. R. R.; Hernando, J. I. M.; Lena, J. I. C.; Moral, J. Q.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1527.
124. Fieser, L. F.; Romero, M. A. *J. Am. Chem. Soc*. **1953**, *75*, 4716.
125. Seebeck, E.; Reichstein, T. *Helv. Chim. Acta* **1944**, *27*, 948.
126. Mihailovic, M. L.; Forsek, J.; Lorenc, L.; Maksiomovic, Z.; Fuhrer, H.; Kalvado, J. *Helv. Chim. Acta* **1969**, *52*, 459.
127. improved Pb(OAc)$_4$ mediated acetoxylation of steroidal substrates has been reported; for recent examples see: Ferreira, M. R. C.; Hernando, J. I. M.; Lena, J. I. C.; Moral, J. Q.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1527; Hernando, J. I. M.; Ferreira, M. R. C.; Lena, J. I. C.; Toupet, L.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron: Asymmetry*, **1999**, *10*, 3977.
128. Russell, G. A.; Blankespoor, R. L.; Trahanovsky, K. D.; Chung, C. S.; Wkittle, P. R.; Mattox, J.; Myers, C. L.; Penny R.; Ku T.; Kosugi, Y.; Givens, R. S. *J. Am. Chem.. Soc*. **1975**, *97*, 1906.
129. Tanyeli, C.; Tosun, A.; Turkut, E.; Sezen, B. *Tetrahedron* **2003**, *59*, 1055.
131. Curran, D. P.; Morgan, T. M.; Schwartz, C. F.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.
132. Guindon, Y.; Lavallee, J. F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701.
133. Guindon, Y.; Guerin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem.. Soc.* **1996**, *118*, 12528.
134. Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc*. **1994**, *116*, 6455.
135. Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063.
136. Sibi, M. P.; Ji. J.; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 190.

137. Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274.
138. Cole, B. M.; Han, L.; Snider, B. B. J. Org. Chem. 1996, 61, 7832.
139. Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1553.
140. Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.
141. Yang, D.; Ye, X. Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579.
142. Reported reaction solvents varies from AcOH to AcOH:ketones mixtures, for examples see: (a) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524. (b) Cole, B. M.; Han, L.; Snider, B. B.; *J. Org. Chem*, **1996**, *61*, 7832 and references cited therein.
143. Hudson, A.; Bona, M. A. D.; Waterman, D.; Alberti, A.; Benaglia, M.; Macciantelli, D. *J. Chem. Soc. Perkin Trans 2* **1997**, 2487.
144. Akdağ, A.; Tarhan, O.; Türker, L. *J. Mol. Struct. (Theochem)* **2001**, *571*, 201.
145. Snider stated that oxidation of α´- keto radical derived from enones is a very fast process relative to oxidation of radicals derived from saturated ketones. Attempted alkene addition to an enone in the presence of 1-octene provided only acetoxylation and oligomer: Snider, B. B.; Kiselgof, E. Y. *Tetrahedron* **1996**, *52*, 6073.
146. The potential of $Mn(OAc)_3$ to mediate reactions that is possibly based on reductive elimination of arylmanganese intermediates was recently shown: Demir A. S.; Reis, Ö.; Emrullahoglu, M. *J. Org. Chem. In press.*
147. Nishino, H.; Nguyen, V.; Yoshinaga, S.; Kurosawa, K. *J. Org. Chem.* **1996**, *61*, 8264 and references cited therein.
148. Gossauer, A. Pyrrole als Naturprodukte In Die Chemie der Pyrrole; Springer: Berlin, 1974, 189-208.
149. Goto, T. In *Natural Products Chemistry*; Nakanishi, K.; Goto, T.; Ito, S.; Natori, S., Nozoe, S.; Eds. ;Academic: New York, **1975**, 470
150. Jackson, A.H. Pyrroles In *Comprehensive Organic Chemistry*; Sammes, P.G.; Ed.; Pergamon Press, Vol. IV: Oxford, **1979**, 311-312.
151. Sundberg, R.J. Pyrroles and their benzo derivatives: (iii) Synthesis and applications In *Comprehensive Heterocyclic Chemistry Vol. 4*; Bird, C.W., Cheeseman, G.W.H.; Eds. ;Pergamon Press: Oxford, **1984**, 372-376.
152. Tumlinson, J. H.; Silverstein, R. M.; Moser, J. C.; Brownlee, R. G.; Ruth, J. M. *Nature (London)* **1971**, *234*, 348
153. Sharma, G. M.; Burkholder, P. R. *J.Chem.Soc., Chem. Commun.* **1971**, 151
154. Härri, E.; Loeffler, W.; Stigg, H. P.; Stähelin, H.; Stoll, Ch.; Tamm, Ch.; Wiesinger, D. *Helv.Chim.Acta* **1962**, *45*, 839
155. Edgar, J. A.; Culvenor, C. C. J.; Smith, L. W. *Experientia* **1971**, *27*, 761
156. Meinwald, J.; Ottenheym, H. C. J. *Tetrahedron* **1971**, *27*, 3307
157. Lynn, D. G.; Jaffe, K.; Cornwall, M.; Tramontano, W. *J.Am.Chem.Soc.* **1987**, *109*, 5858-5859.
158. Imanaka, H.; Kousaka, M.; Tamura, G.; Arima, K. *J.Antibiot.(Tokyo) Ser.A* **1965**, *18*, 207.
159. Zimmer, Ch. *Prog.Nucleic Acid Res.Mol.Biol.* **1975**, *15*, 285-318

160. Baltazzi, B.; Krimen, L. I. *Chem. Rev*. **1963***,* *63*, 511

161. Jones, R.A.; Bean, G.P.*The Chemistry of Pyrroles*, Academic Press, New York, 1977.

162. Chadwick, D. J. *Comprehensive Hetrocyclic Chemistry*, vol 4, Pergamon Press, 1984, 155.

163. Friedman, M. *J.Org. Chem.* **1965**, *30*, 859

164. Shiraishi, H.; Nishitani, T.; Nishihara, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **1999**, *55,* 13957

165. Leeper, R. J. *Nat. Prod. Rep.* **1985**, *2*, 19

166. Leeper, F. J: *Nat. Prod. Rep.* **1985**, *2*, 561

167. Leeper, F. J. *Nat. Prod. Rep.* **1989**, *6*, 171-203

168. Battersby, A. R.; Fookes, C. J. R.; Matcham, G. W. J.; McDonald, E. *Nature (London)* **1980**, *285*, 17

169. Battersby, A. R. *Nat. Prod. Rep.* **1987**, *4*, 77

170. Patterson, J.M. *Synthesis* **1976**, 281.

171. Jones, R.A.; Chapman, B.J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 2, 1-38

172. Black, D. St. C. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford**, 1996**; Vol. 2, 39-118

173. Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford, **1996**; Vol. 2, 119-206.

174. Gribble, G. W. . In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford, **1996**; Vol. 2, 207-257

175. Battersby, A. R.; McDonald, E. In *Porphyrins and Metalloporphyrins;* Smith, K. M., Ed.; Elsevier: Amsterdam, **1975**; 61-122

176. Urban, S.; Butler, M.S.; Capon, R.J. *Aust. J. Chem.* **1994**, *47*, 1919

177. Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuer, P. J. *Helv. Chim. Acta* **1992,** *75*, 1721

178. Liu, J-H.; Yang, Q-C.; Mak, T. C. W.; Wong, H. N. C. *J.Org. Chem.* **2000**, *65*, 3587

179. a) Paine, J. B., III; Brough, J. R.; Buller, K.K.; Erikson, E.E. *J. Org. Chem.* **1987**, *52,* 3986; b) Simmons, H. E.; Vest, R.D.; Vladuchick, S. A.; Webster, O.W. *J. Org. Chem*. **1980,** *45,* 5113

180. Vedejs, E.; Grissom, J.W. *J. Org. Chem.* **1988**, *53*, 1876

181. Eberlin, M.N.; Kascheres, C. *J. Org. Chem* **1988**, *53,* 2084

182. Katritzky, A. R.; Zhu, L.; Lang, H.; Denisko, O.; Wang, Z. *Tetrahedron* **1995***, 51,* 13271

183. Barluenga, J.; Tomas, M.; Kouznetsov, V.; SuarezSobrino, A.; Rubio, E. *J. Org. Chem.***1996**, *61*, 2185

184. Nagafuji, P.; Cushman, M. . *J. Org. Chem.***1996**, *61*, 4999

185. Katritzky, A. R.; Cheng, D.; Musgrave, R.P. *Heterocycles* **1997**, *44*, 67

186. Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505

187. Katritzky, A. R.; Huang, T-B.; Voronkov, M. V.; Wang, M.; Kolb, H. . *J. Org. Chem.* **2000**, *65,* 8819

188. Laitron, J.A. H.; Huffman, J. W.; Martin, B.R.; Compton, D.R.

*Tetrahedron Lett.*1995, 36, 1401.

189. De Leon, C,Y.; Ganem, B. *Tetrahedron* **1997,** *53,* 7731
190. Jacobi, P.A.; Coutts, L.D.; Guo, J.S.; Hauck S.I.; Leung, S.H. *J. Org. Chem.* **2000**, *65,* 205
191. Gupton, J.T.; Krumpe, K.E.; Burnham, B.C.; Dwornik, K.A.; Petrich, S.A.; Du, K.X.; Bruce, M.A.; Vu, P.; Vargas, M.; Keertikar, K.M.; Hosein, K.N.; Jones, C. R.; Sikorski, J.A. *Tetrahedron* **1998**, *54,* 5075
192. Sessler, J.L.; Weghorn, S.J. *Expanded, Contracted & Isomeric Porphyrins;* Elsevier Science Ltd: Oxford, **1997**
193. Thoresen, L. H.; Kim, H.; Welch, M.B.; Burghart, A.; Burgess, K. *Synlett* **1998**, 1276
194. Dieter, R. K.; Yu, H.; *Org. Lett.* **2000**, *2*, 2283.
195. Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky. A.; Rees, C.W.; Scriven, E.F.V., Eds.; Pergamon: Oxford, **1996**; Vol. 2 , 119-206
196. Gilchrist, T.L. *J.Chem. Soc., Perkin Trans. 1* **1999**, 2849
197. Gilchrist, T.L. *J .Chem. Soc., Perkin Trans. 1* **1998,** 615
198. Campi, E. M.; Fallon, G.D.; Jackson, W.R.; Nilsson, Y. *Aust. J. Chem.* **1992,** *45,* 1167
199. Buchwald, S.L.; Wannamaker, M.W.; Watson, B.T. *J. Am. Chem. Soc.* **1989,** *111*, 776
200. Nitta, M.; Kobayashi, T. *Chem. Lett.* **1983**, 1715
201. Padwa, A.; Gruber, R.; Pashayan, D. *J. Org. Chem* **1968**, *33*, 454
202. Deady, L. W. *Tetrahedron* **1967,** *23,* 3505
203. Fan, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43,* 1863
204. Fischer, H. *Organic Synthesis,* Wiley: New York, **1943,** Coll. Vol. II, 202
205. Cooney, J.V.; McEven, W.E. *J. Org. Chem.* **1981**, *46,* 2570
206. Berree, F.; Marchand, E.; Morel, G. *Tetrahedron Lett.* **1992,** *33*, 6155
207. Furstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem***.1995**, *60,* 6637
208. Roskamp, E.J.; Dragovich, P. S.; Hartung, Jr, J.B.; Pederson, S.F. *J. Org. Chem.* **1989***, 54,* 4736
209. Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, *64,* 4204
210. Tsutsui, H.; Narasaki, K. *Chem.Lett.* **1999,**45
211. Fejes, I.; Toke, L.; Blasko, G.; Nyerges, M.; Pak, C.S.; *Tetrahedron* **2000,** *56*, 8545
212. Grigg, R,; Savie, V. *Chem. Comm.* **2000,** 873
213. Burley, I.; Bilic, B.; Hewson, A.T.; Newton, J.R.A. *Tetrahedron Lett.* **2000,** *41,* 8969
214. Liu, J.-H.; Yang, Q.-C.; Mak, T.C.W.; Wong, H.N.C. *J. Org. Chem.* **2000***,* *65,* 327
215. Shiraishi, H.; Nishitani, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998,** *63,* 6234
216. Danks, T.N.; *Tetrahedron Lett.***1999,** *40,* 3957
217. Ranu, B.C.; Hajra, A. *Tetrahedron* **2001**, *57,* 4767

218. Kel'in, A. V.; Sromek, A.W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001,** *123,* 2074
219. Farcas, S.; Namy, J.-L. *Tetrahedron* **2001**, *57,* 4881
220. Attanasi, O.; Fillipone, P.; Perrulli, F. R.; Santensanio, S. *Tetrahedron* **2001**, *57*, 1387.
221. Aeltterman, W.; De Kimpe, N.; Tyvorskii, V.; Kulinkovich, O. *J. Org. Chem* **2001,** *66*, 53
222. Gabriele,B.; Salerno, G.; Fazio, A.; Bossio, M.R. *Tetrahedron Lett.* **2001,** *42,* 1339
223. Laganiere, S. In *The Impact of Stereochemistry on Drug Development and Use*; Abdoul-Enein, H.Y.; Winer, I.W., Eds.; John Wiley & Sons: New York, **1997**; 545
224. McCague, R.; Casy, G. In *Progress in Medicinal Chemistry*; Ellis, G.P.; Luscombe, D.K.; Eds.; Elsevier Science Publishers, BV: Amsterdam, **1997;** Vol. 34, 203
225. Jefford, C. W., Tang, Q., Zaslona, A., *J. Am. Chem. Soc.*, **1991**, 113, 3513.
226. Jefford, C.W.; *Curr. Org. Chem.***2000**, *4,* 205
227. Demir, A. S.; Akhmedov, I. M.; Sesenoglu, O.; Alpturk, O.; Apaydin, S.; Gercek, Z.;Ibrahimzade, N. *J. Chem. Soc. Perkin Trans. 1* **2001**,1162.
228. Grigg, R.; Yoganathan, G. *Tetrahedron Asymmetry* **1996,** *7*, 273
229. Knorr, L. *Ber.* **1884**, *17*, 1635
230. Engel, N.; Steglich, W. *Angew. Chem.* **1978**, *90*, 719.
231. Ahlbrect, H.; von Daacke, A. *Synthesis* **1984**, 610.
232. Hantzsch, A. *Chem. Ber.* **1890,** *23,* 1474
233. Feist, F. Chem. Ber. **1902***, 35,* 1537
234. Chelucci, G.; Marchetti, M. *Heterocyclic Chem.* **1988**, *25*, 1135.
235. Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193.
236. Paal, C. *Ber.* **1885**, *18***,** 367.
237. Knorr, L. *Ber.* **1885**, *18*, 299.
238. Knorr, L. *Ann.* **1886**, *236*, 290.
239. Knorr, L.; Lange, H. *Ber.* **1902**, 35.
240. Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron Asymmetry* **2001**, *12*, 2715.
241. Shioiri, T.; Aoyama, T. *J. Synth. Org. Chem. Japan*, **1996**, *54*, 918.
242. Shioiri, T.; Aoyama, T.; Hamada, Y. *Wakojunyakujiho* **1997**, *56*, 12
243. Yagi, T.; Aoyama, T.; Shioiri, T. *Synlett*, **1997**, 1063.
244. Yasuda, M.; Morimoto, J.; Shibata, I.; Baba, A.; *Tetrahedron Letters*, **1997**, 38, 3265.
245. Gairaud, C. B.; Lappin, G. R. *J. Org. Chem.* **1953**, *18*, 3.
246. Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron*, **1990**, *46*, 7587.
247. Klappa DEVAMINI BUL, YAZ
248. Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996,** *61,* 4999.
249. Lagu, B.; Pan, M.; Wachter, M. P. *Tetrahedron Lett.* **2001**, *42*, 6027.

250. Demir, A. S.; Aybey, A.; Kayalar, M. *Arkivoc.* **2005**, *15*, 105.
251. Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. *Synlett* **2000**, 391.
252. Katrizky, A. R. *J. Org. Chem.* **2000**, *65*, 8074
253. Demir, A. S., Akhmedov, I. M., Tanyeli, C., Gercek, Z., Gadzhili, R. A. *Tetrahedron: Asymmetry*, **1997**, 8, 753.
254. Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549.
255. Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205-340.
256. Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023-1095.
257. Daly, J. W.; Spanade, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1.
258. Daly, J. W.; Secunda, S. I.; Garraffo, H. M.; Spande, T. F.; Wisnieski, A.; Cover Jr., J. F. *Toxicon* **1994**, *32*, 657-663.
259. Caldarelli, M.; Habermann, J.; Ley, S.V.; *J. Chem. Soc., Perkin Trans.1*, **1999**, 107.
260. Haubmann, C.; Hubner, H.; Gmenier, P.; Bioorg. Med. Chem. Lett., 1999, 9, 3143.
261. Demir, A. S.; Akhmedov, I. M.; Sesenoglu, O. *Tetrahedron* **2002**, *58*, 9793.
262. Aydogan, F.; Demir, A. S. *Tetrahedron* **2005**, *61*,3019.
263. Aydogan, F.; Demir, A. S. *Tetrahedron: Asymmetry* **2004**, *15*, 259.
264. Gaullier, J-M.; Bazin, M.; Valla, A.; Girand, M.; Santus, R. *J. Photochem. Photobiology B: Biology* **1995**, *30*, 195.
265. Gaullier, J-M.; Valla, A.; Bazin, M.; Girand, M.; Dubertret, L.; Santus, R. J. Photochem. Photobiology B: Biology 1997, 39, 24.
266. Mai, A.; Massa, M.; Cerbara, I.; Valente, S.; Ragno, R.; Bottoni, P.; Scatena, R.; Loidl, P.; Brosch, G. *J. Med. Chem.* **2004**, *47*, 1098.
267. Mai, A.; Massa, S.; Ragno, R.; Cerbara, I.; Jesacher, F.; Loidl, P.; Brosch, G. J. Med. Chem. 2003, 46, 512.
268. Barbry, D.; Faven, C.; Ajana, A. *Synth. Commun.* **1993**, *23*, 2647.
269. Optical purity is determined by chiral HPLC analysis (Chiral pack AD column, UV detection at 220 nm, 90 : 10 isohexane : propan-2-ol, flow rate 0.75 ml/min
270. Coqueret, X.; Bourelle, F.; Chuche, W. J. *Tetrahedron Lett.* **1983**, *34*, 5382.
271. Ibragimov, I. I.; Mamedov, E. I.; Ismailov, A. T.; Aliev, A. G.; Mekhtieva, Sh. Z.; Dzhafarov, V. G.; Belyaeva, V. I. *Zhurnal Organicheskoi Khimii* **1990** , *26(8)*, 1648.
272. Ibragimov, E. I.; Ismailov, A. T.; Mekhtieva, Sh. Z.; Mamedov, N. N.; Belyaeva, V. I. Zhurnal Organicheskoi Khimii 1990 , 26(11), 2294.
273. Chiralcel OD, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.8 ml/min. tR (R) = 8.6 min; tR (S) = 10.2 min.
274. Shevchenko, N. E.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2003**, *8*, 1191.

APPENDIX A

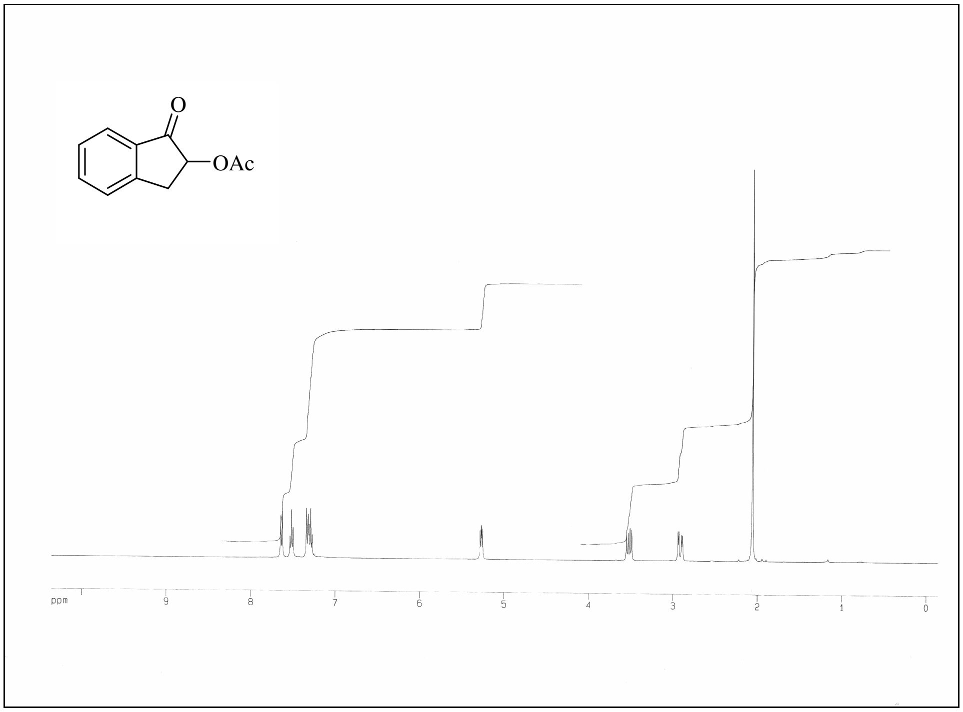


Figure 1. ^{1}H NMR Spectrum of **76**

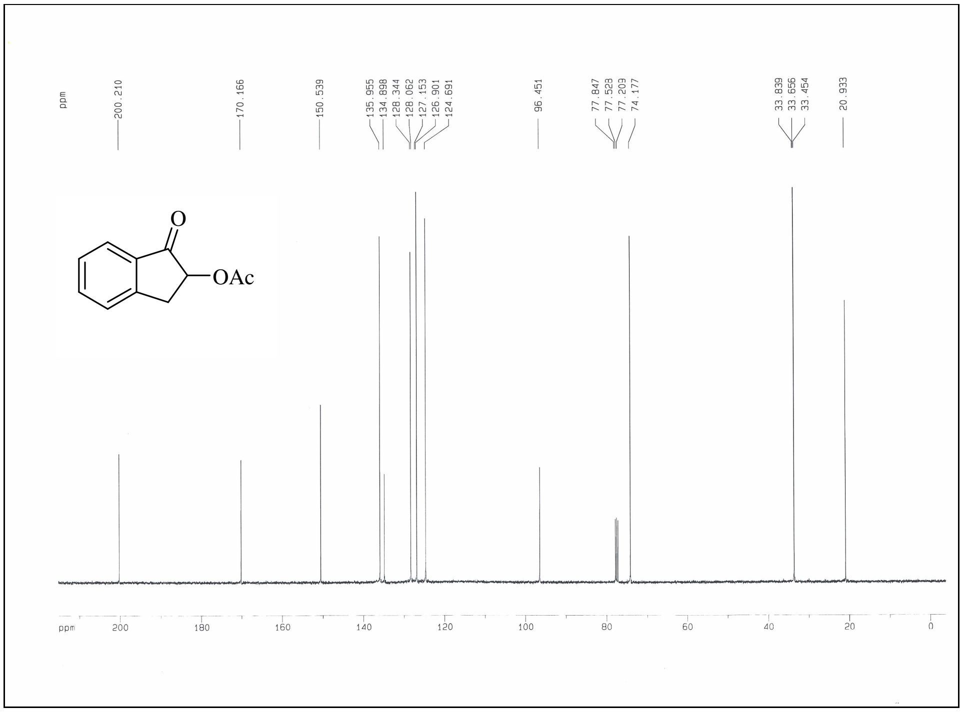


Figure 2. ^{13}C NMR Spectrum of **76**

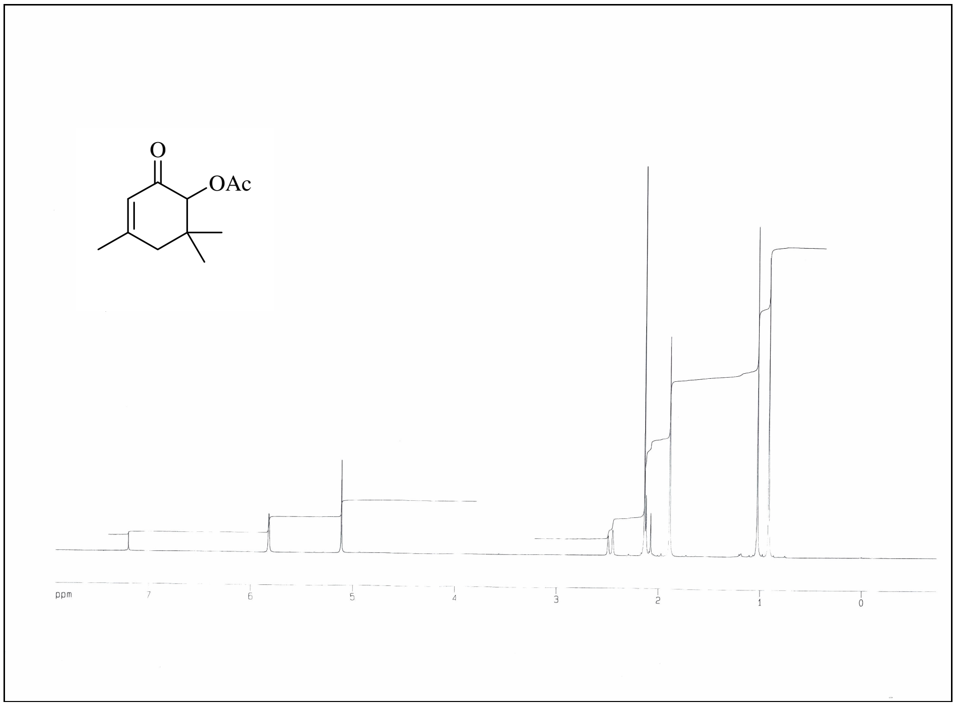


Figure 3. ^{1}H NMR Spectrum of **88**

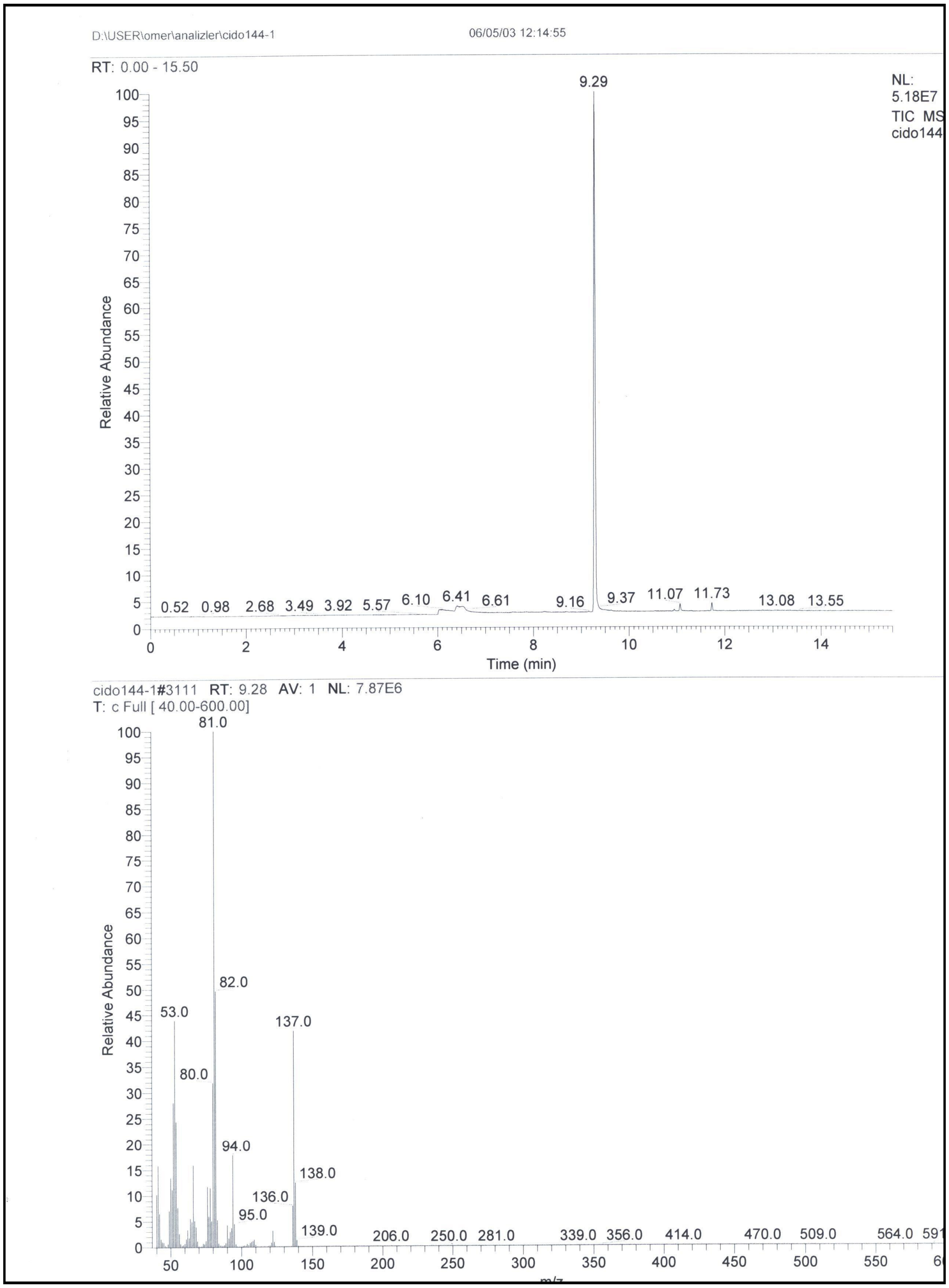


Figure 4. GC-MS Spectrum of **88** (in acetonitrile 2nd hour)

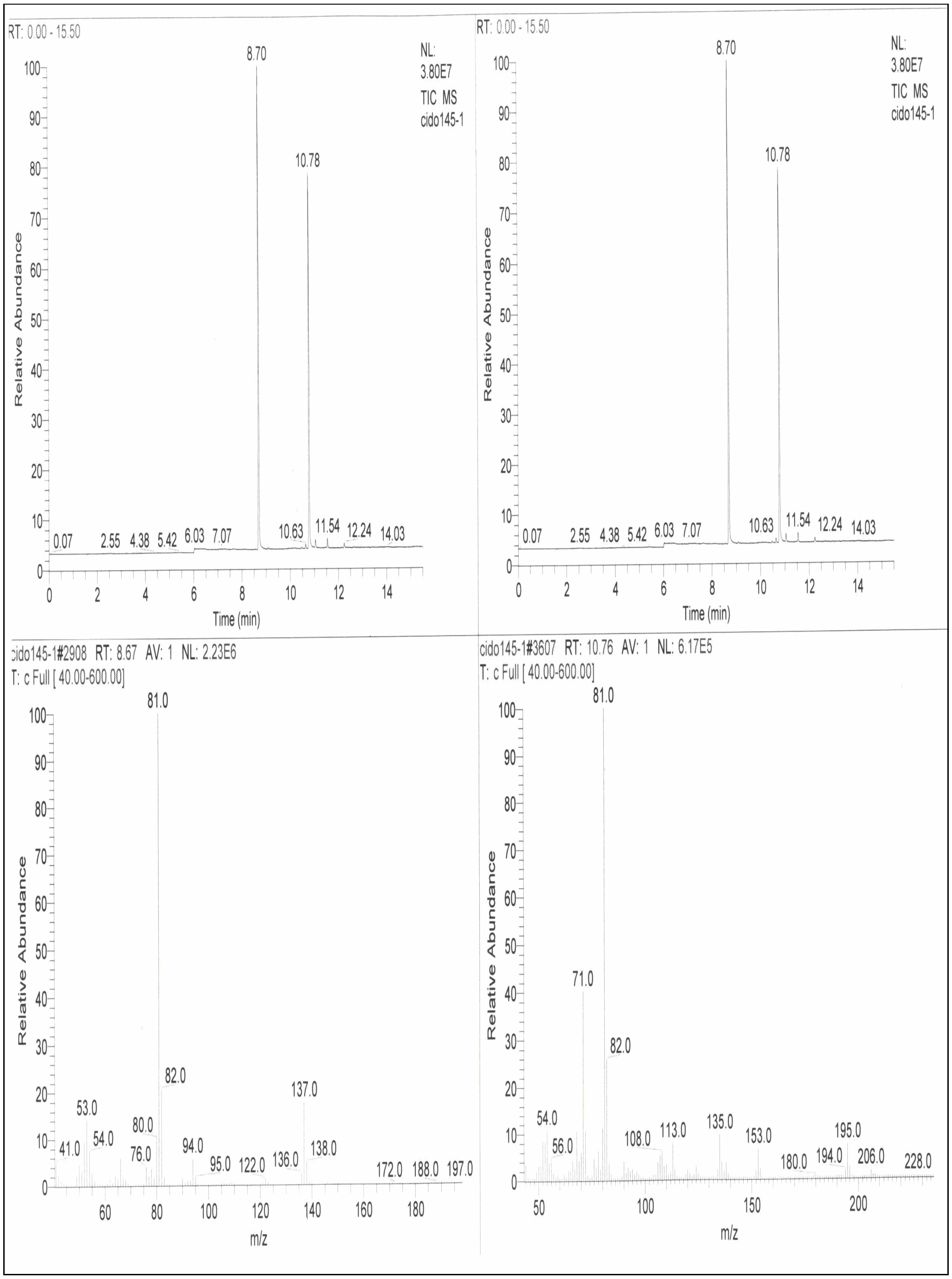


Figure 5. GC-MS Spectrum of **88** (in acetonitrile 9th hour)

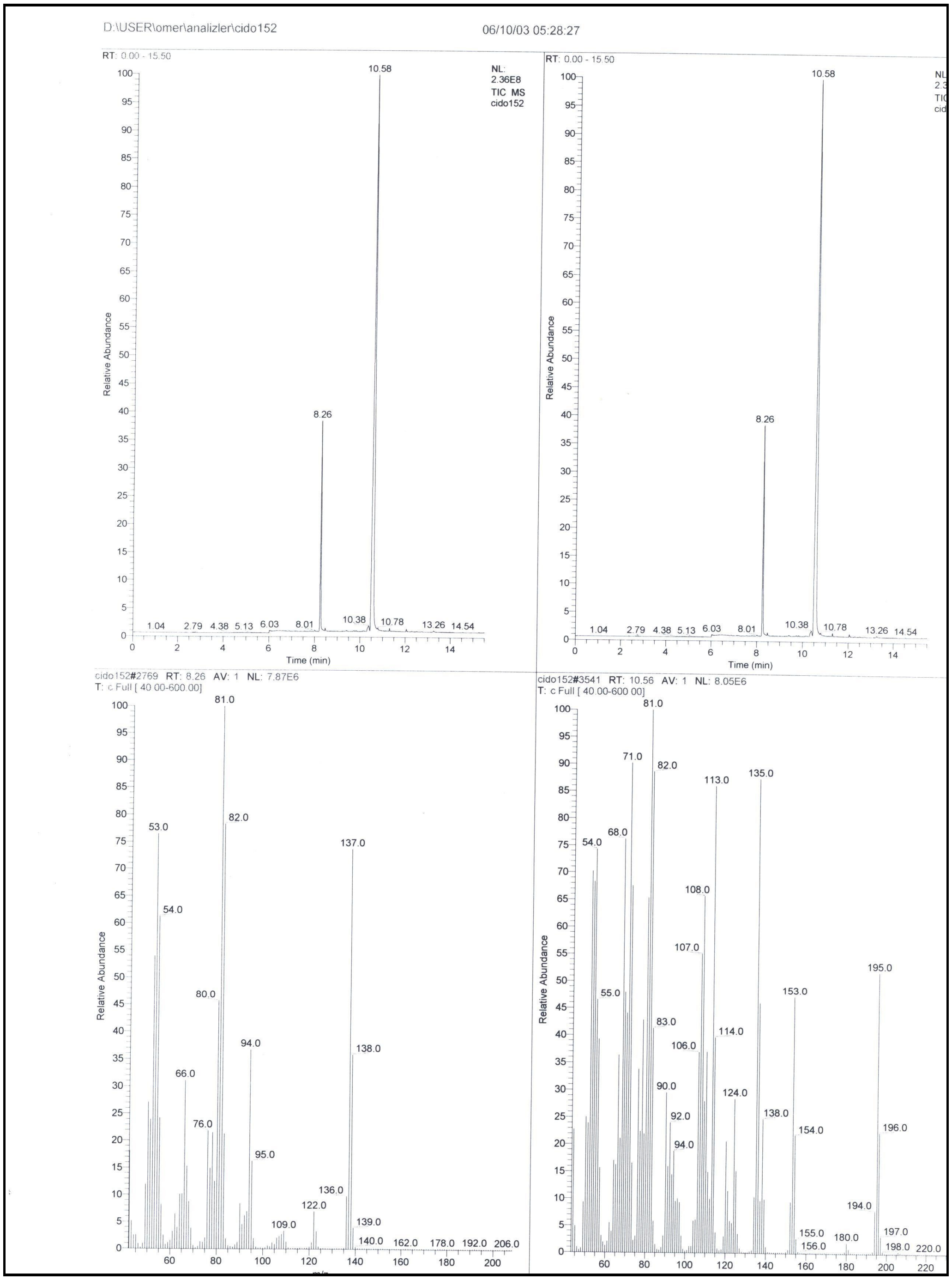


Figure 6. GC-MS Spectrum of **88** (in benzene 3rd hour)

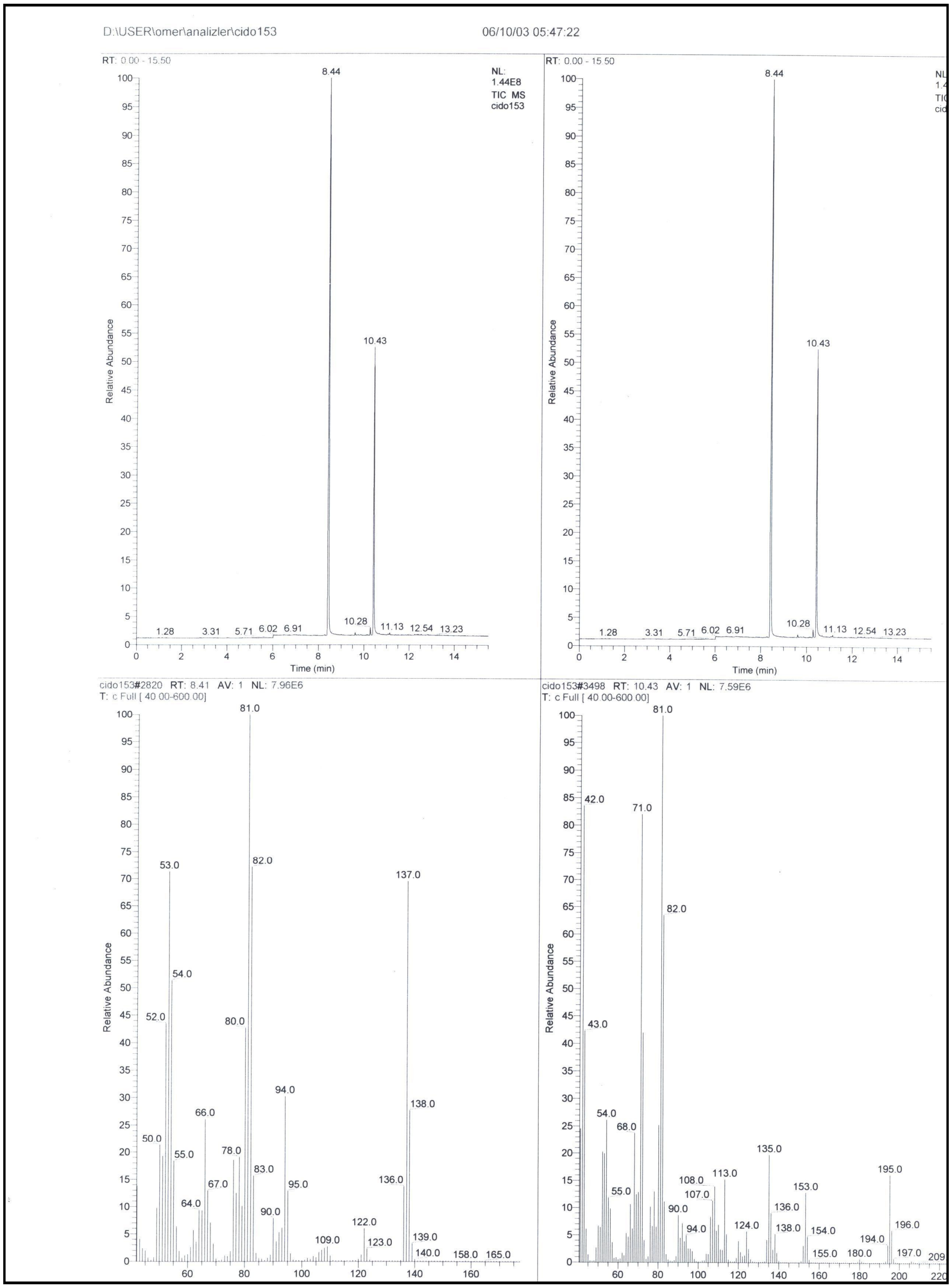


Figure 7. GC-MS Spectrum of **88** (in acetonitrile 3rd hour)

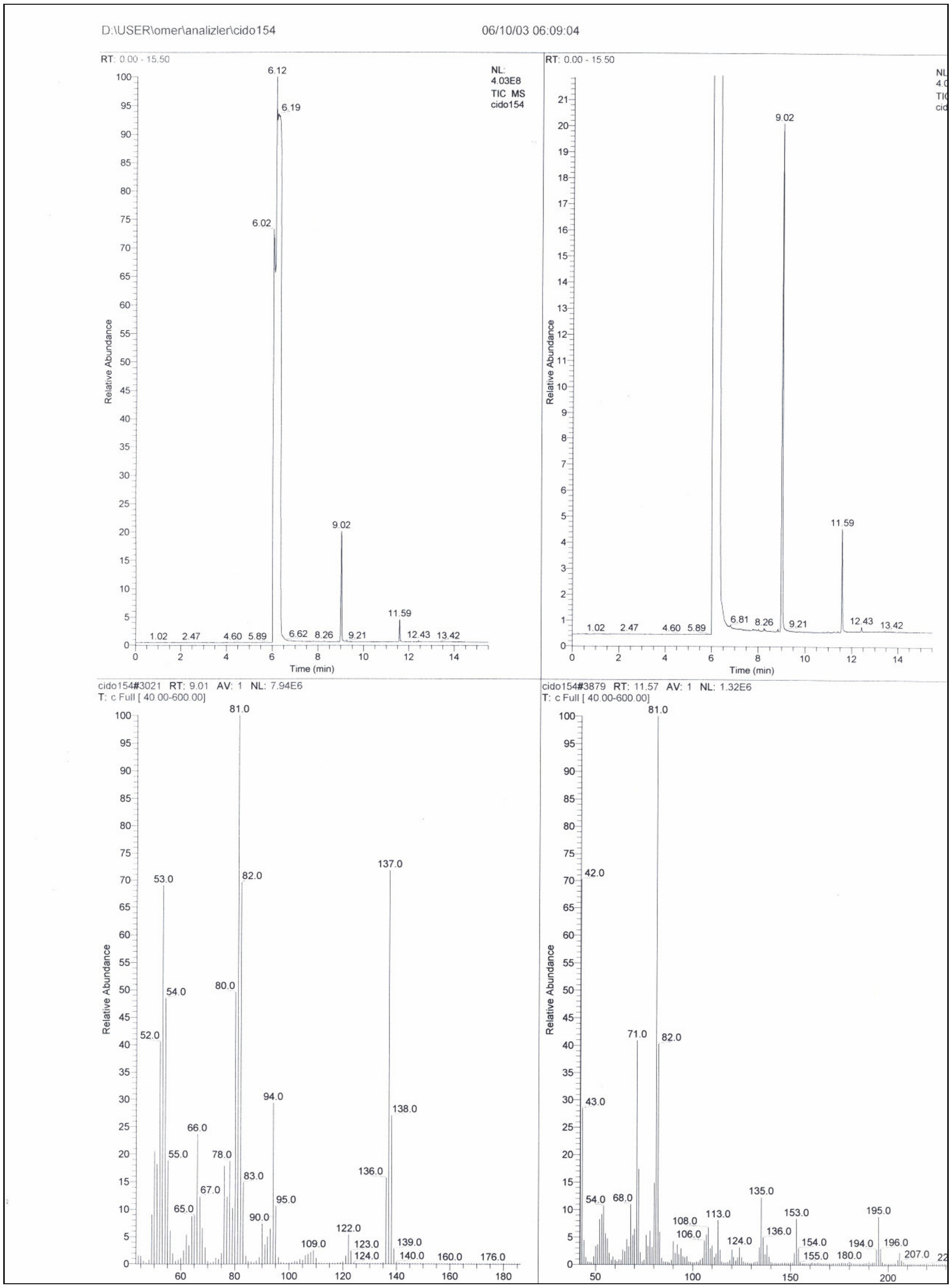


Figure 8. GC-MS Spectrum of **88** (in cyclohexane 3rd hour)

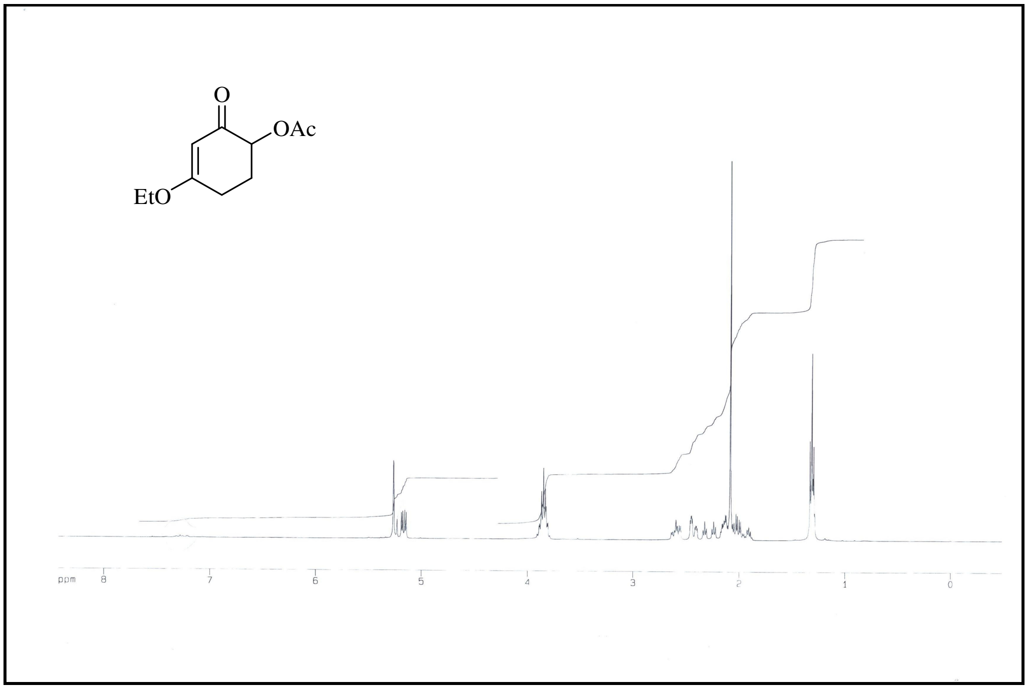


Figure 9. ^{1}H NMR Spectrum of **79**

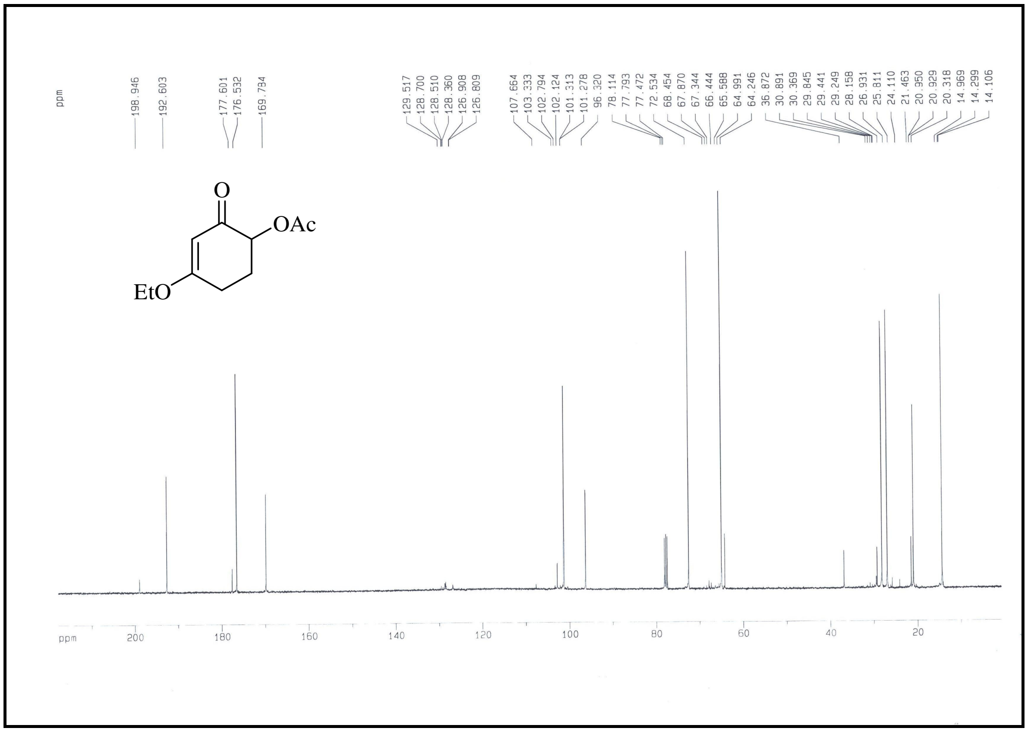


Figure 10. ^{13}C NMR Spectrum of **79**

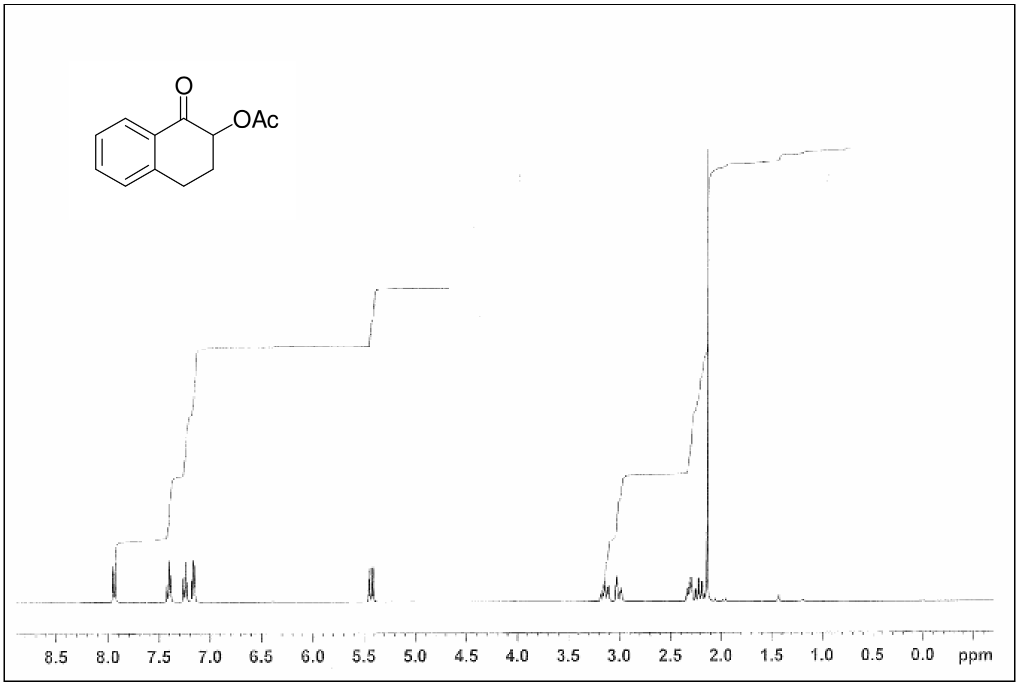


Figure 11. ^{1}H NMR Spectrum of **92**

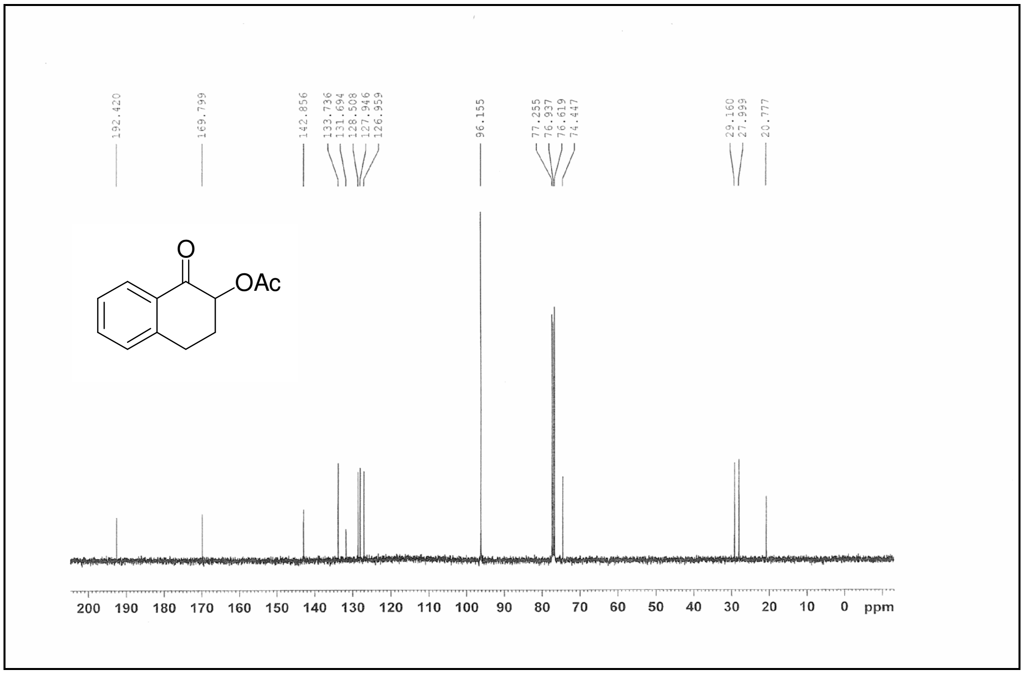


Figure 12. ^{13}C NMR Spectrum of **92**

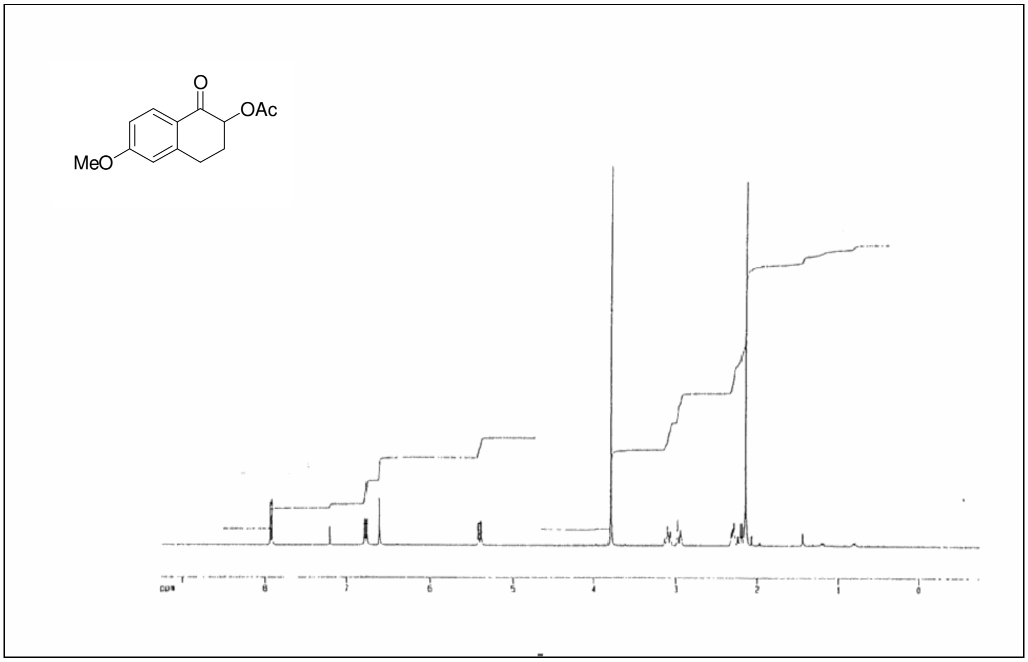


Figure 13. ^{1}H NMR Spectrum of **94**

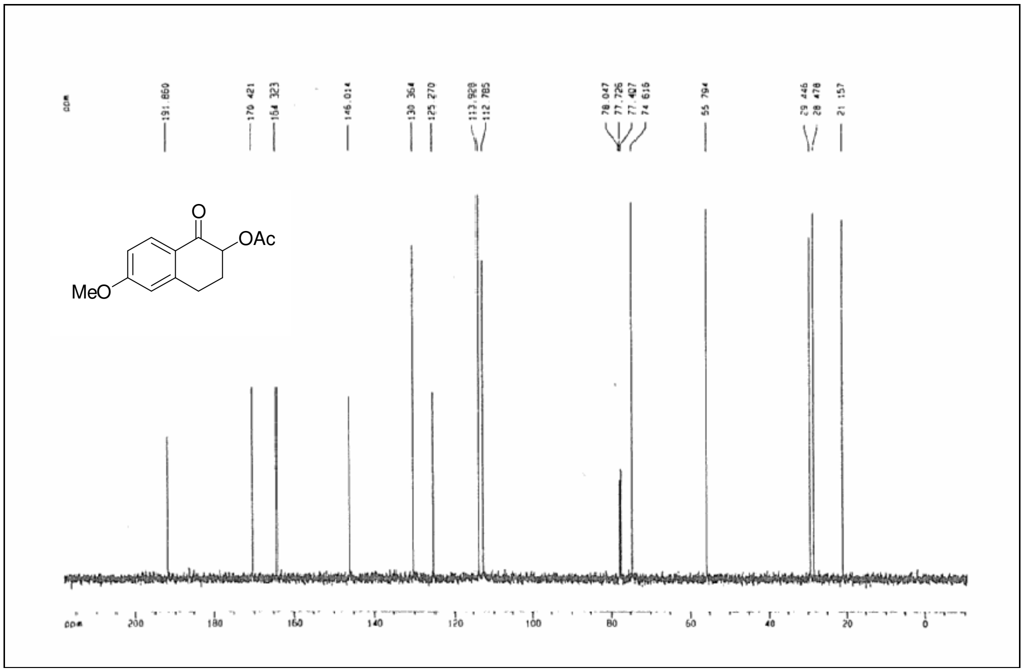


Figure 14. ^{13}C NMR Spectrum of **94**

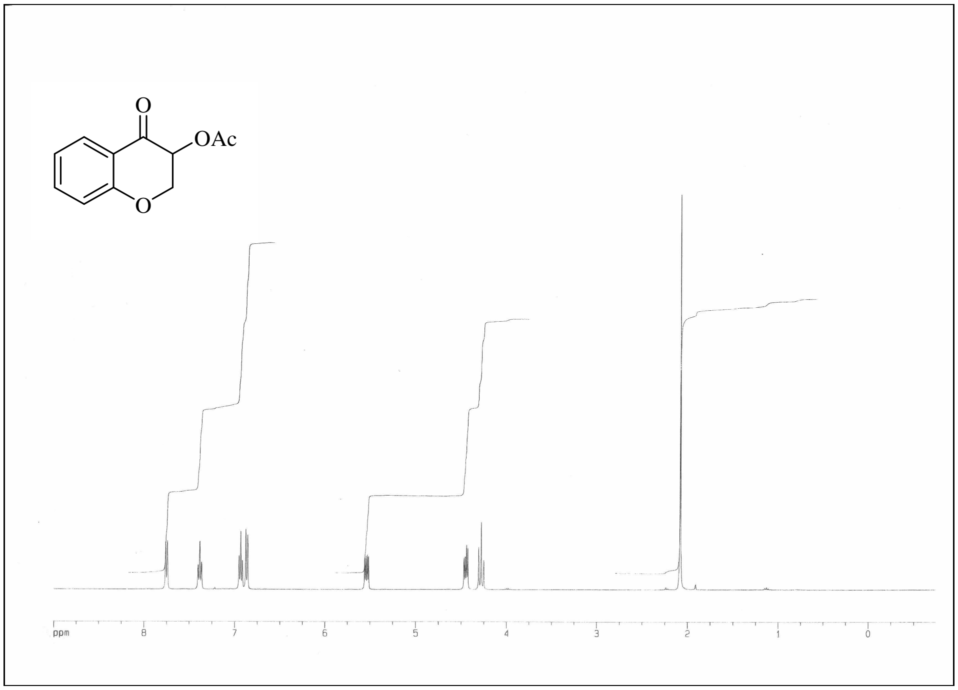


Figure 15. ^{1}H NMR Spectrum of **95**

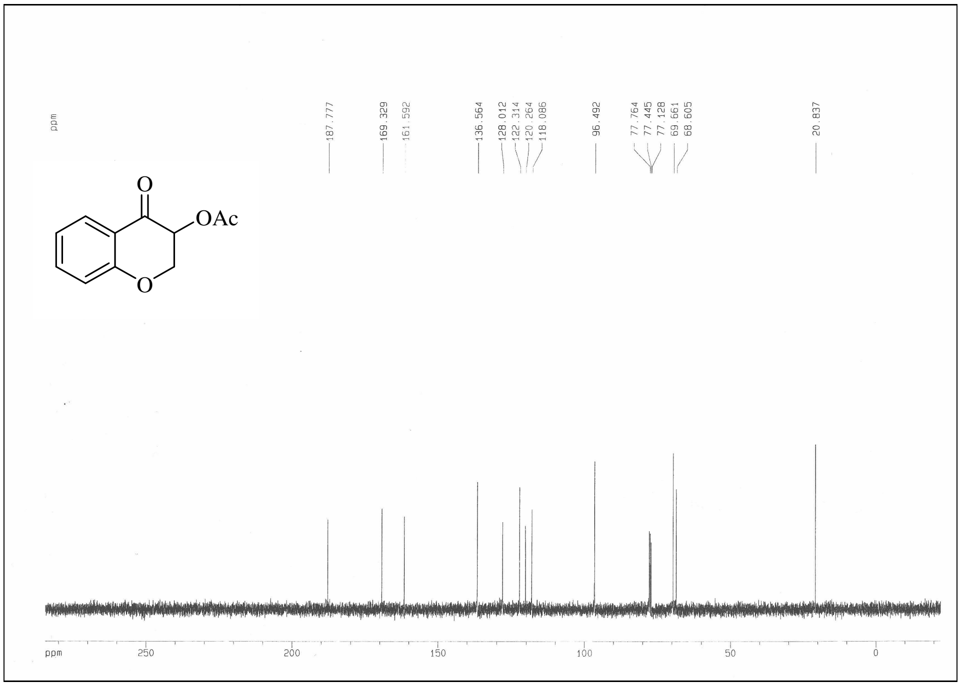


Figure 16. ^{13}C NMR Spectrum of **95**

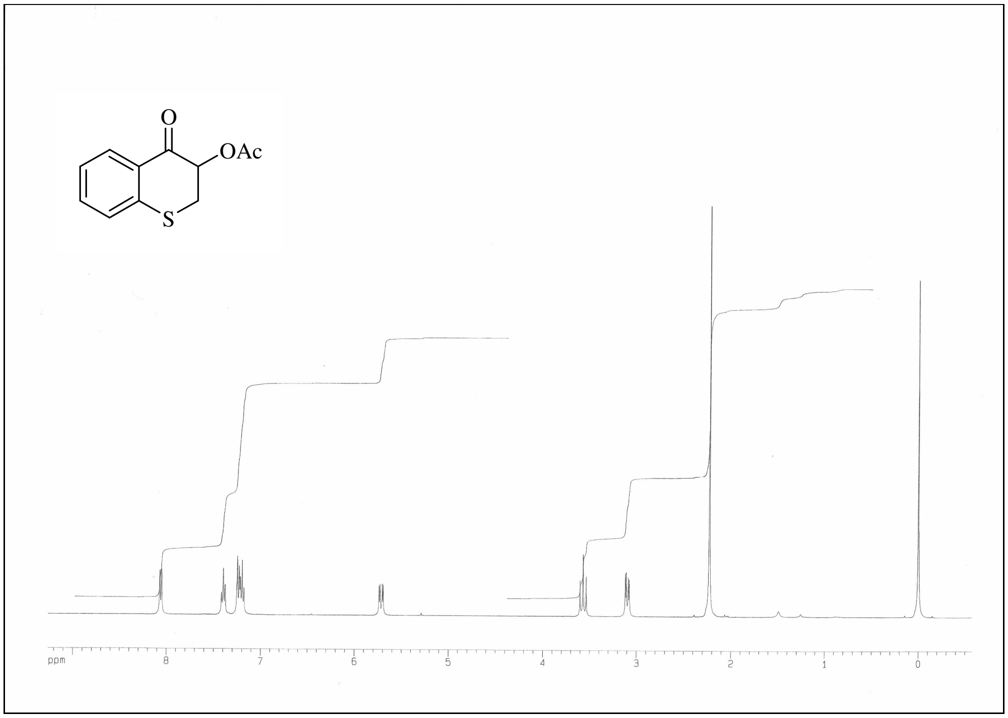


Figure 17. ^{1}H NMR Spectrum of **96**

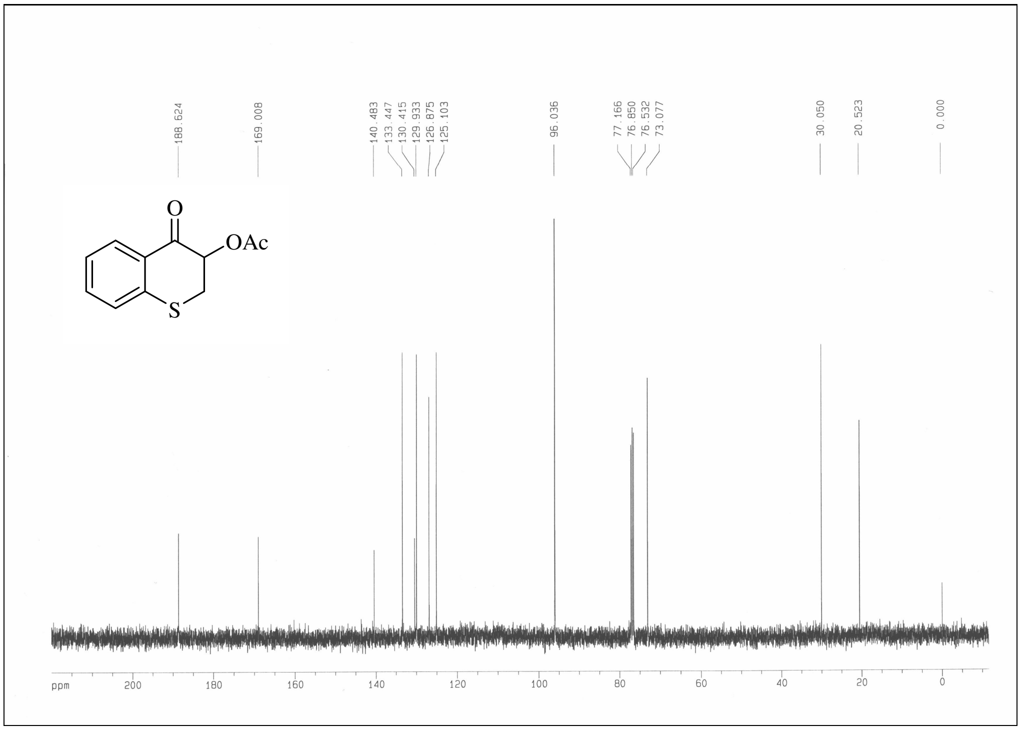


Figure 18. ^{13}C NMR Spectrum of **96**

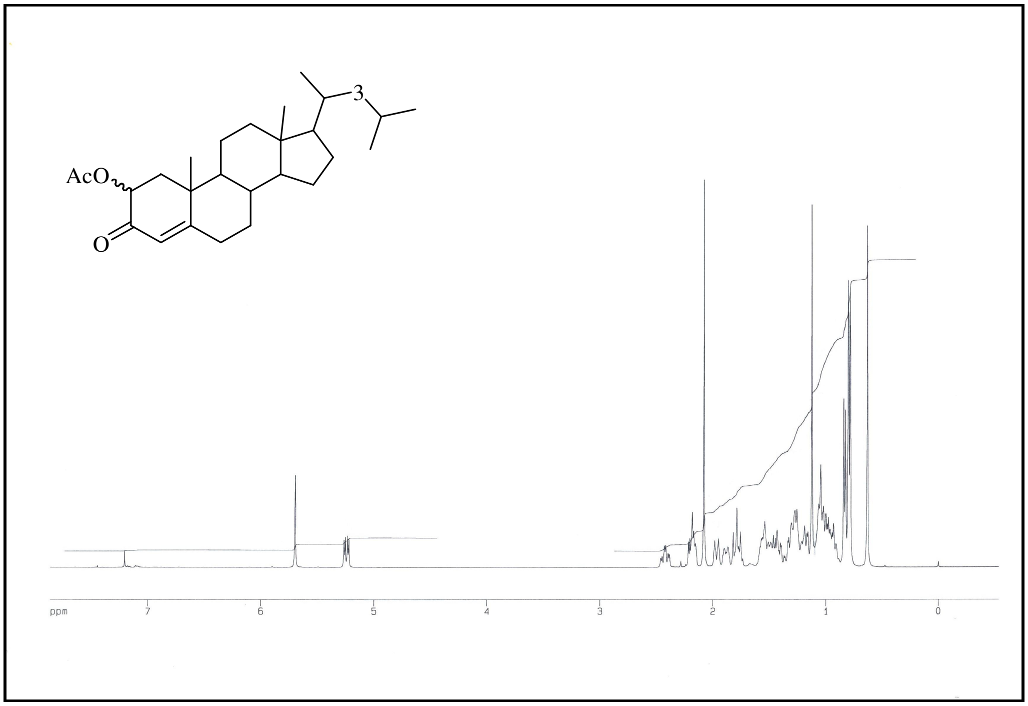


Figure 19. ^{1}H NMR Spectrum of **112** (major isomer)

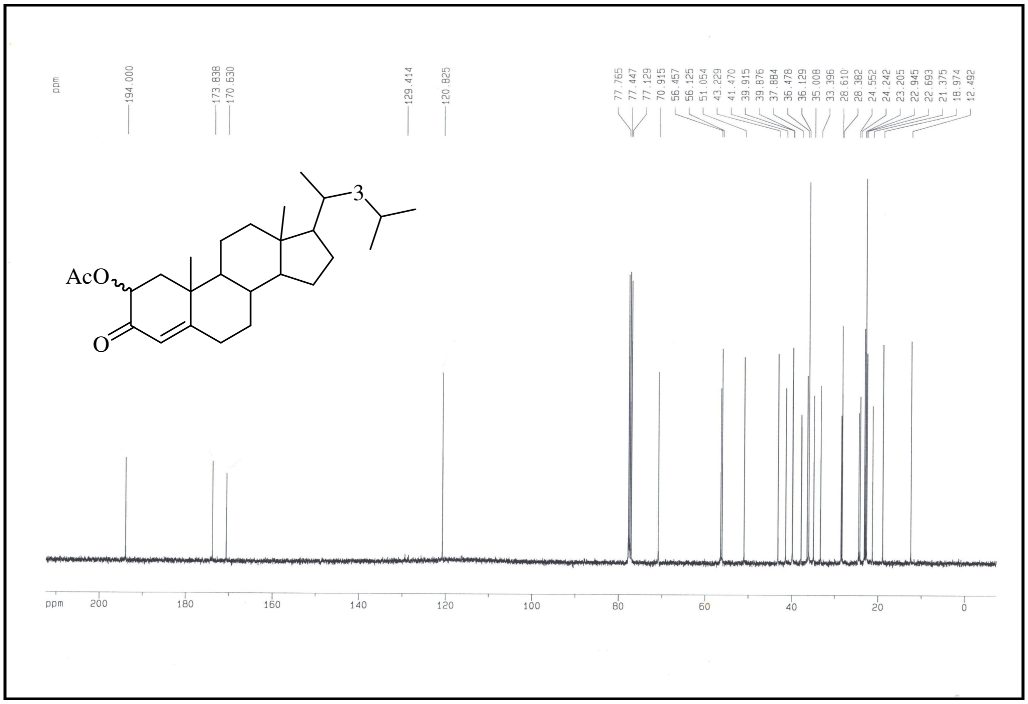


Figure 20. ^{13}C NMR Spectrum of **112** (major isomer)

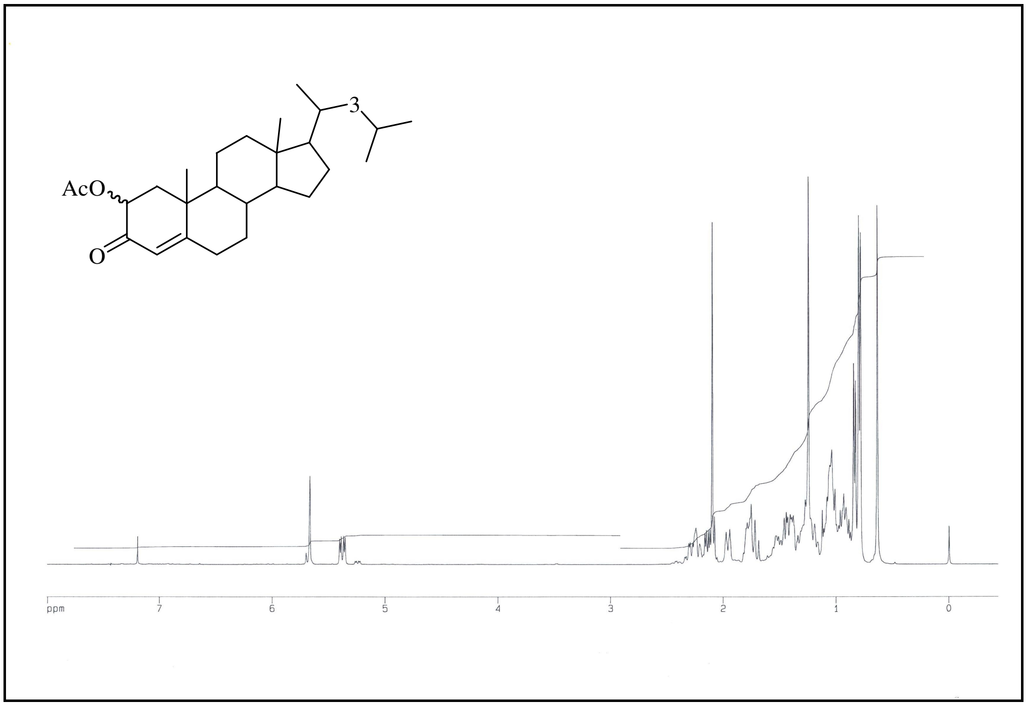


Figure 21. ^{1}H NMR Spectrum of **112** (minor isomer)

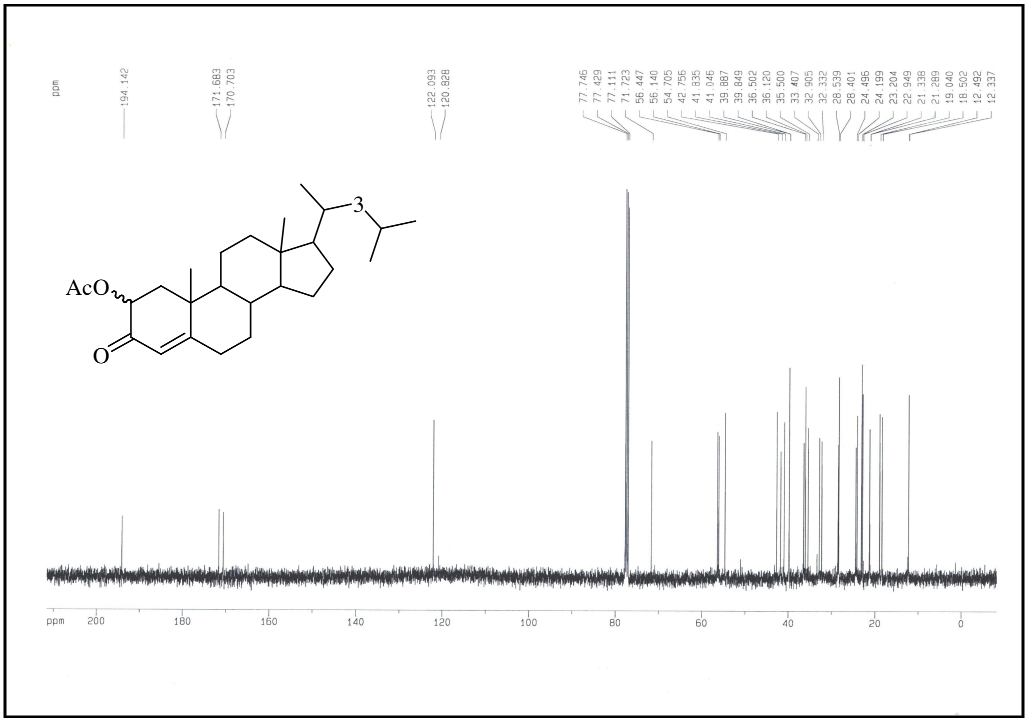


Figure 22. ^{13}C NMR Spectrum of **112** (minor isomer)

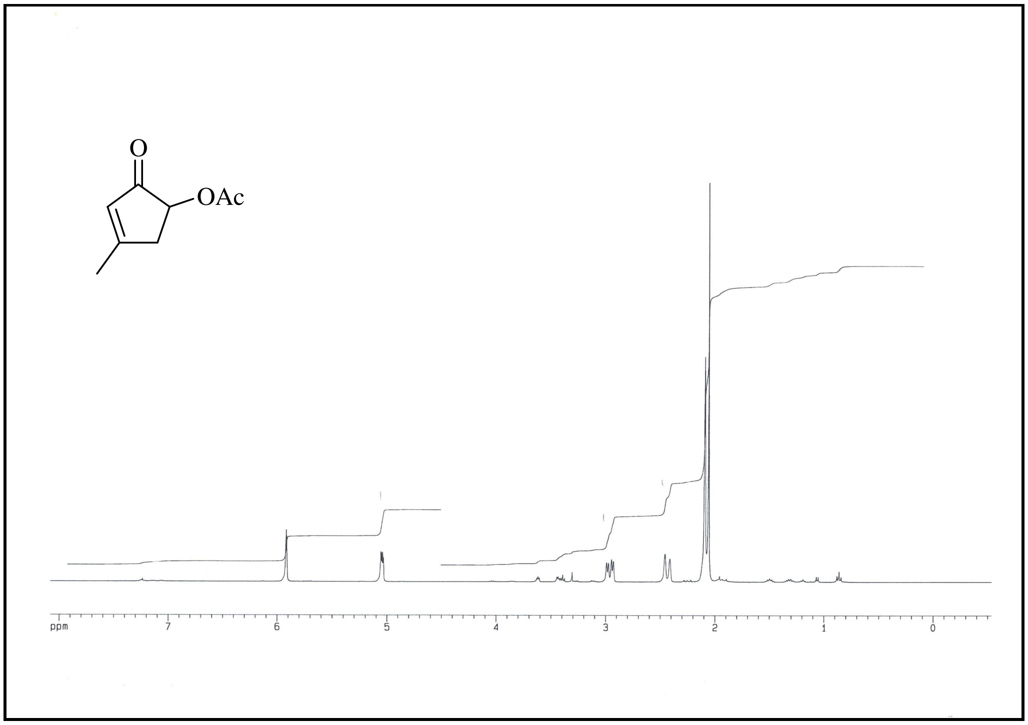


Figure 23. ^{1}H NMR Spectrum of **118**

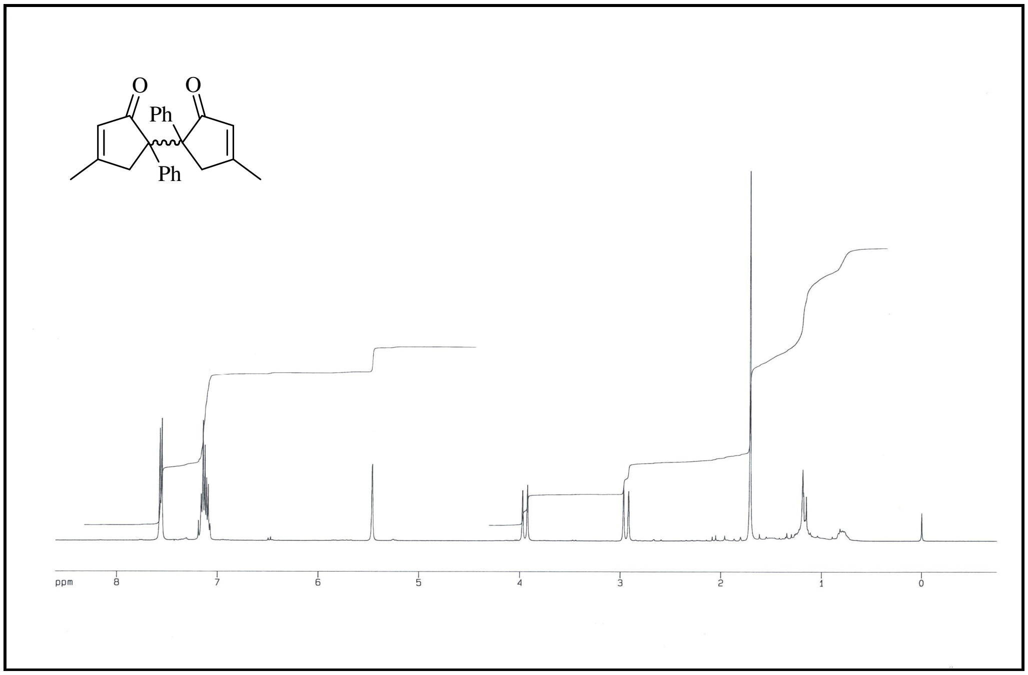


Figure 24. ^{1}H NMR Spectrum of **117** (major isomer)

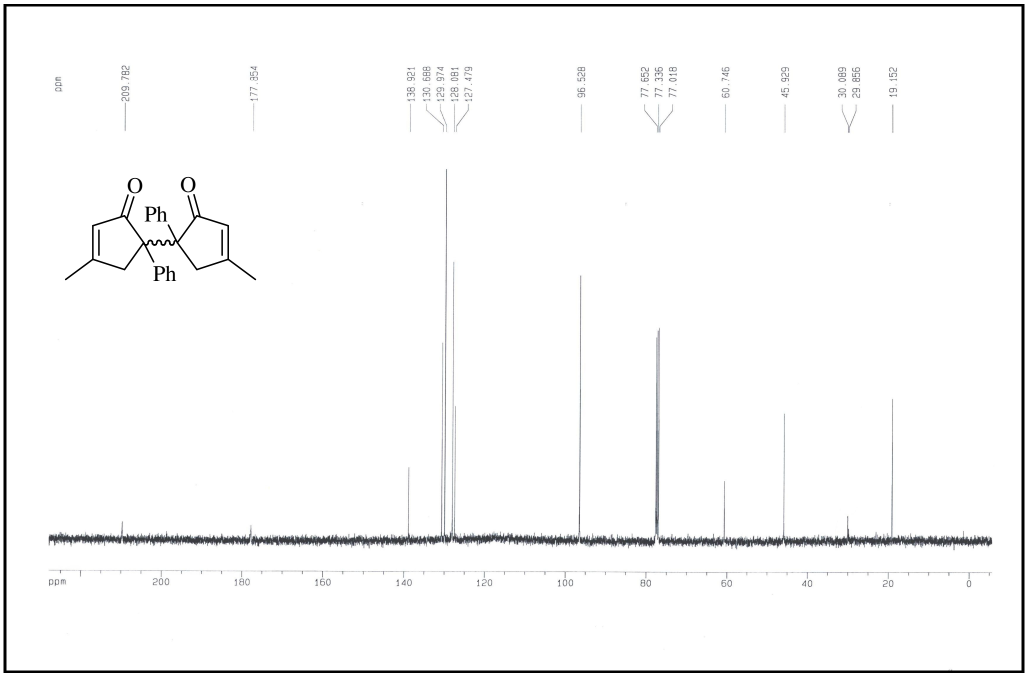


Figure 25. ^{13}C NMR Spectrum of **117** (major isomer)

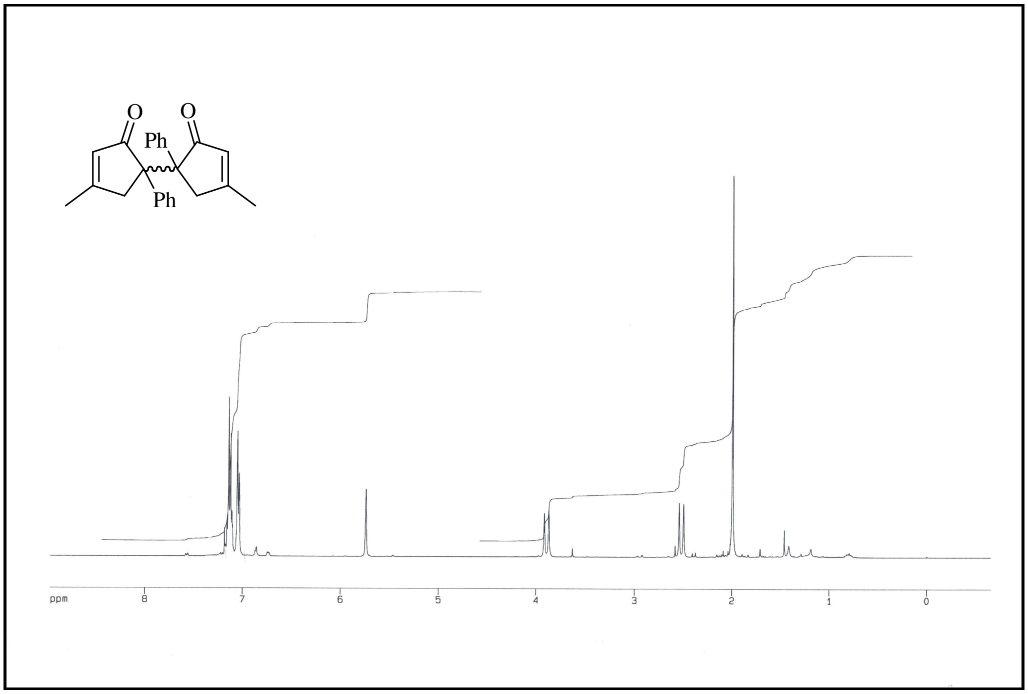


Figure 26. ^{1}H NMR Spectrum of **117** (minor isomer)

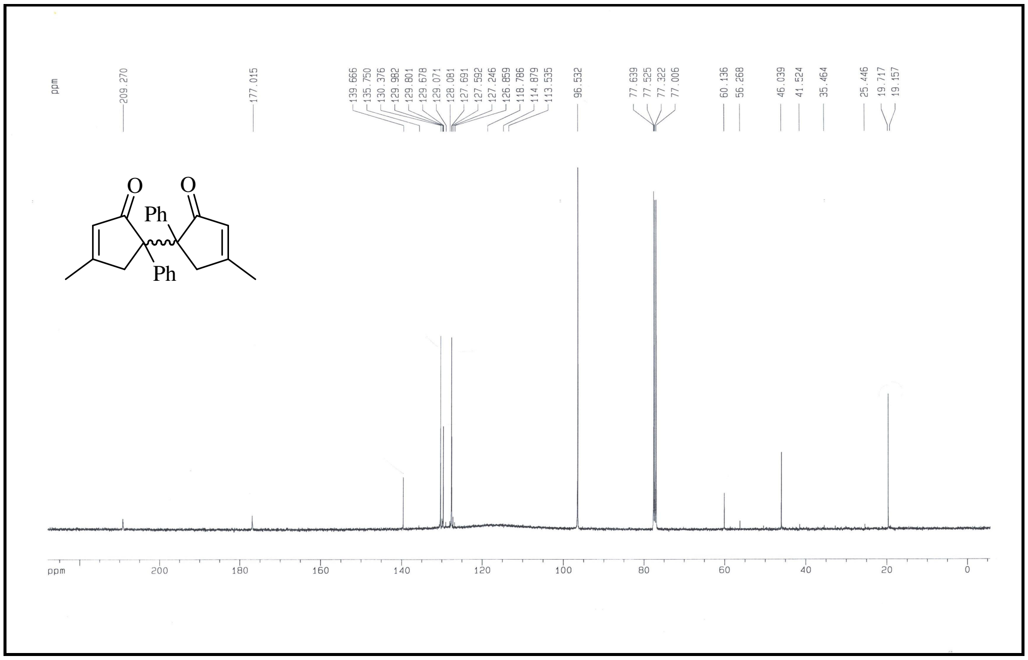


Figure 27. ^{13}C NMR Spectrum of **117** (minor isomer)

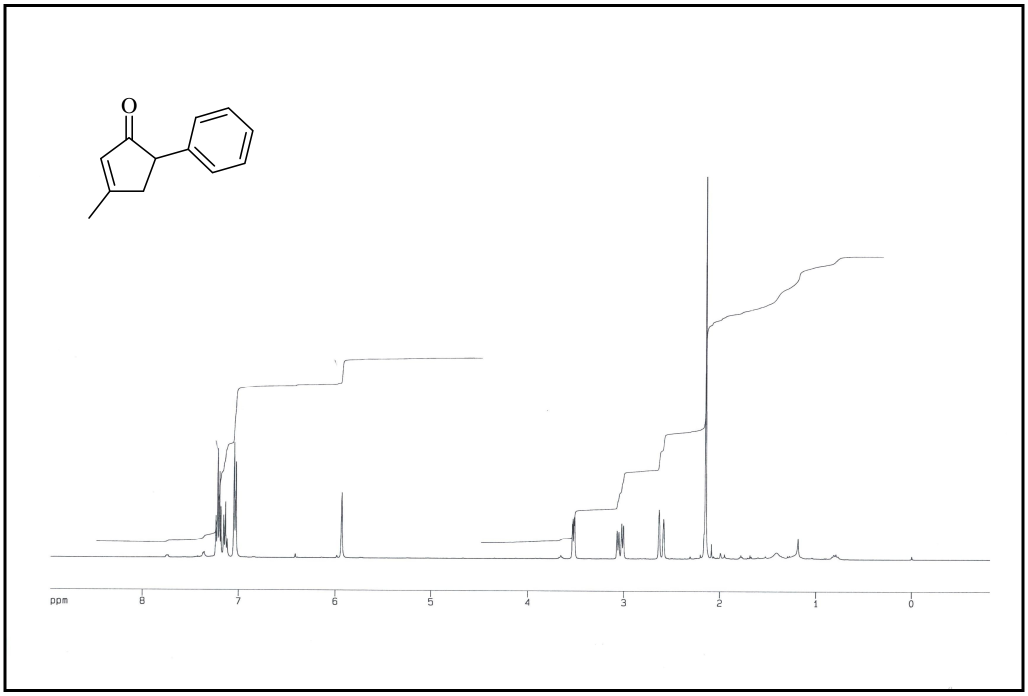


Figure 28. ^{1}H NMR Spectrum of **115**

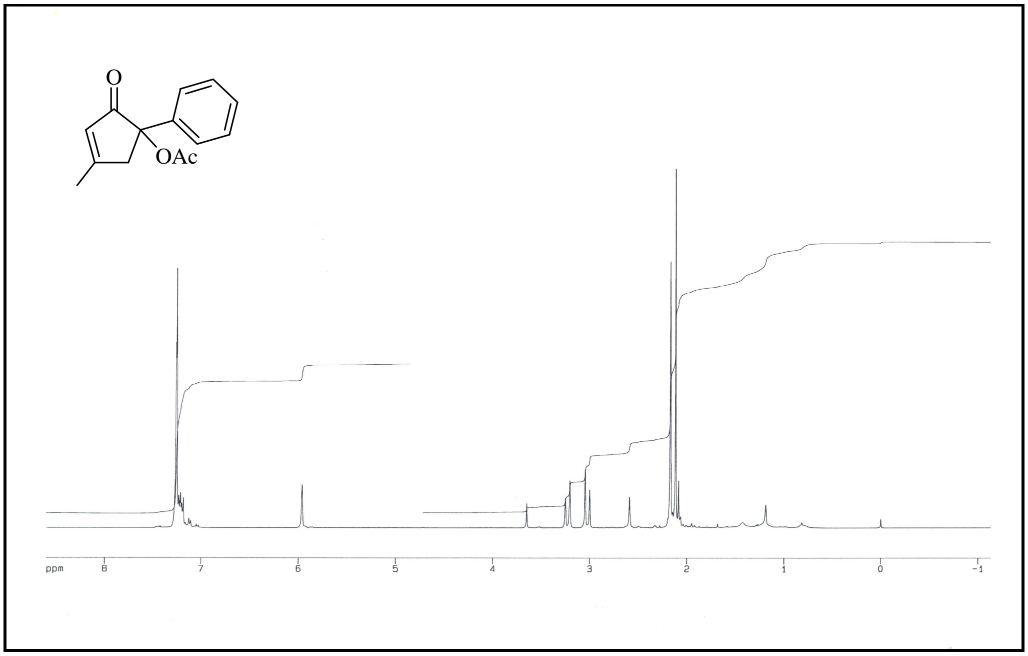


Figure 29. ^{1}H NMR Spectrum of **116**

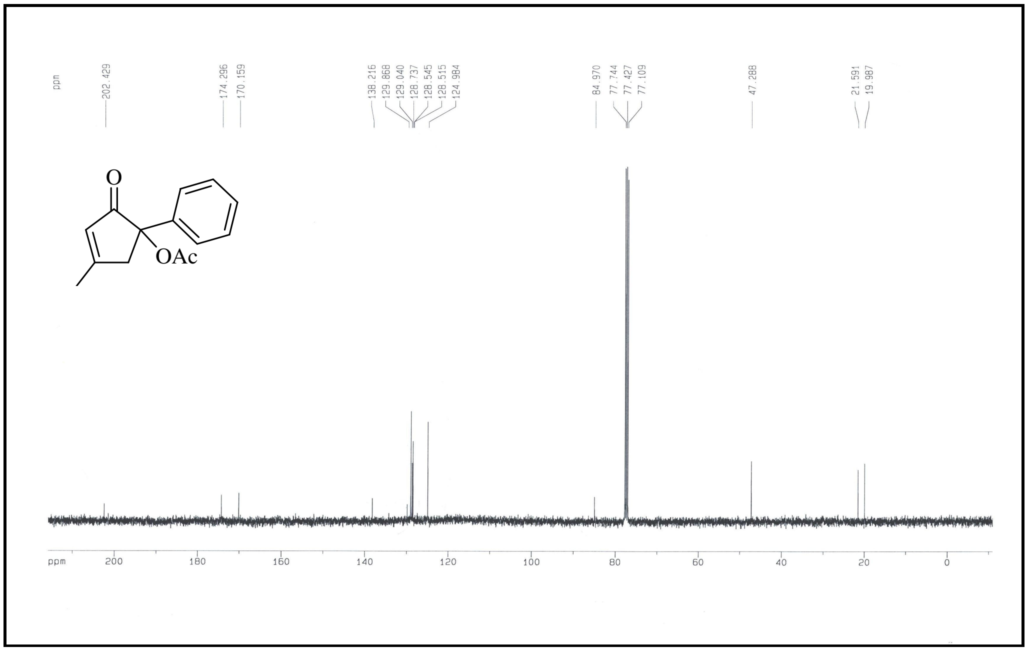


Figure 30. ^{13}C NMR Spectrum of **116**

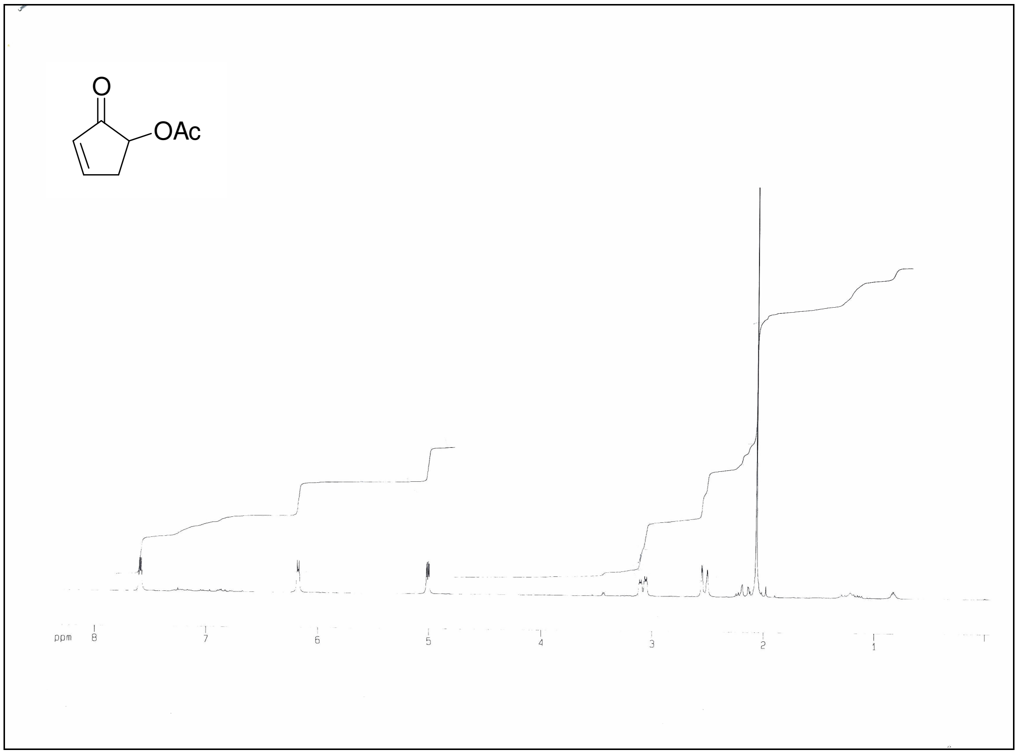


Figure 31. ^{1}H NMR Spectrum of **120**

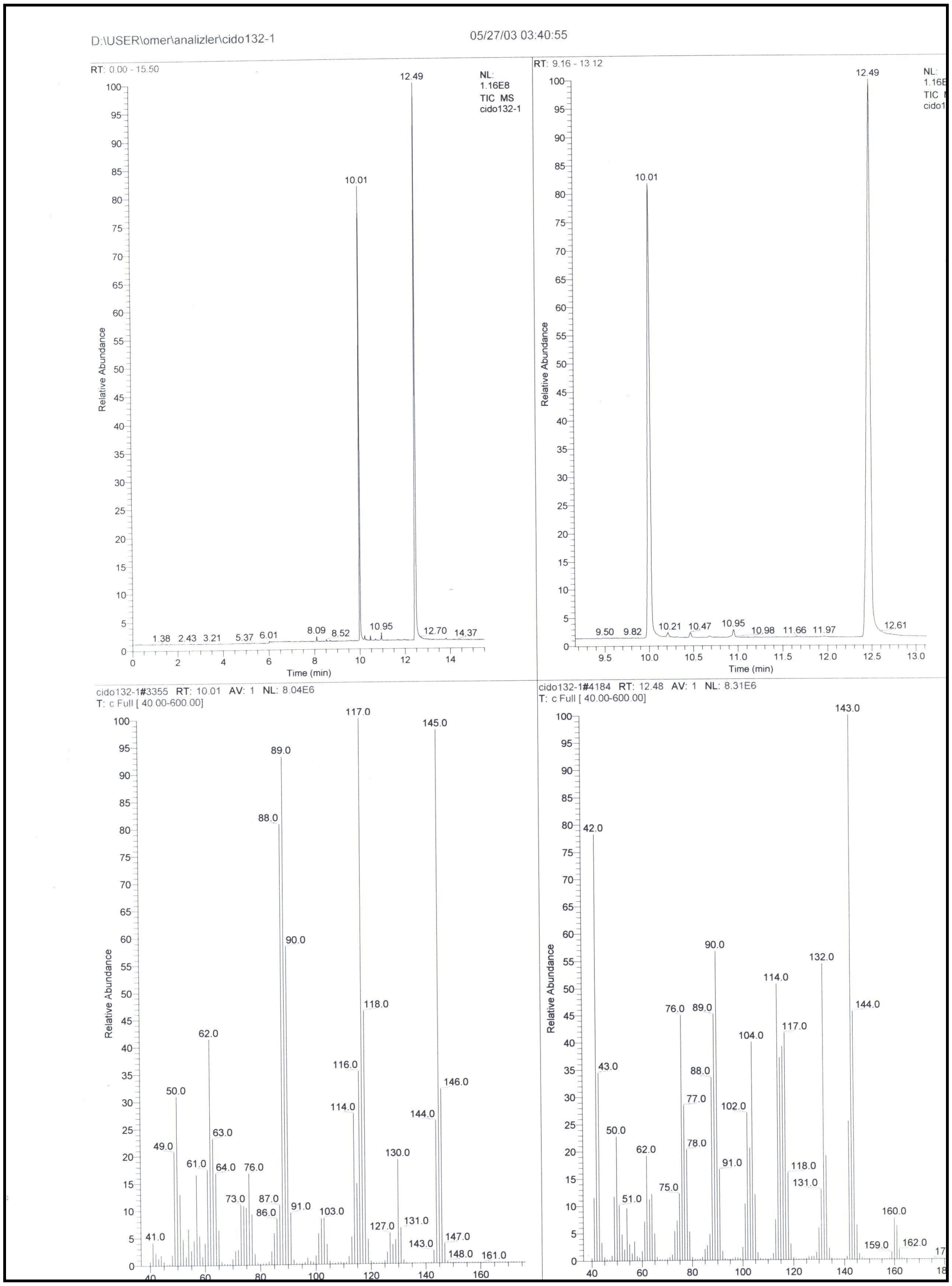


Figure 32. GC-MS Spectrum of **92** (without AcOH)

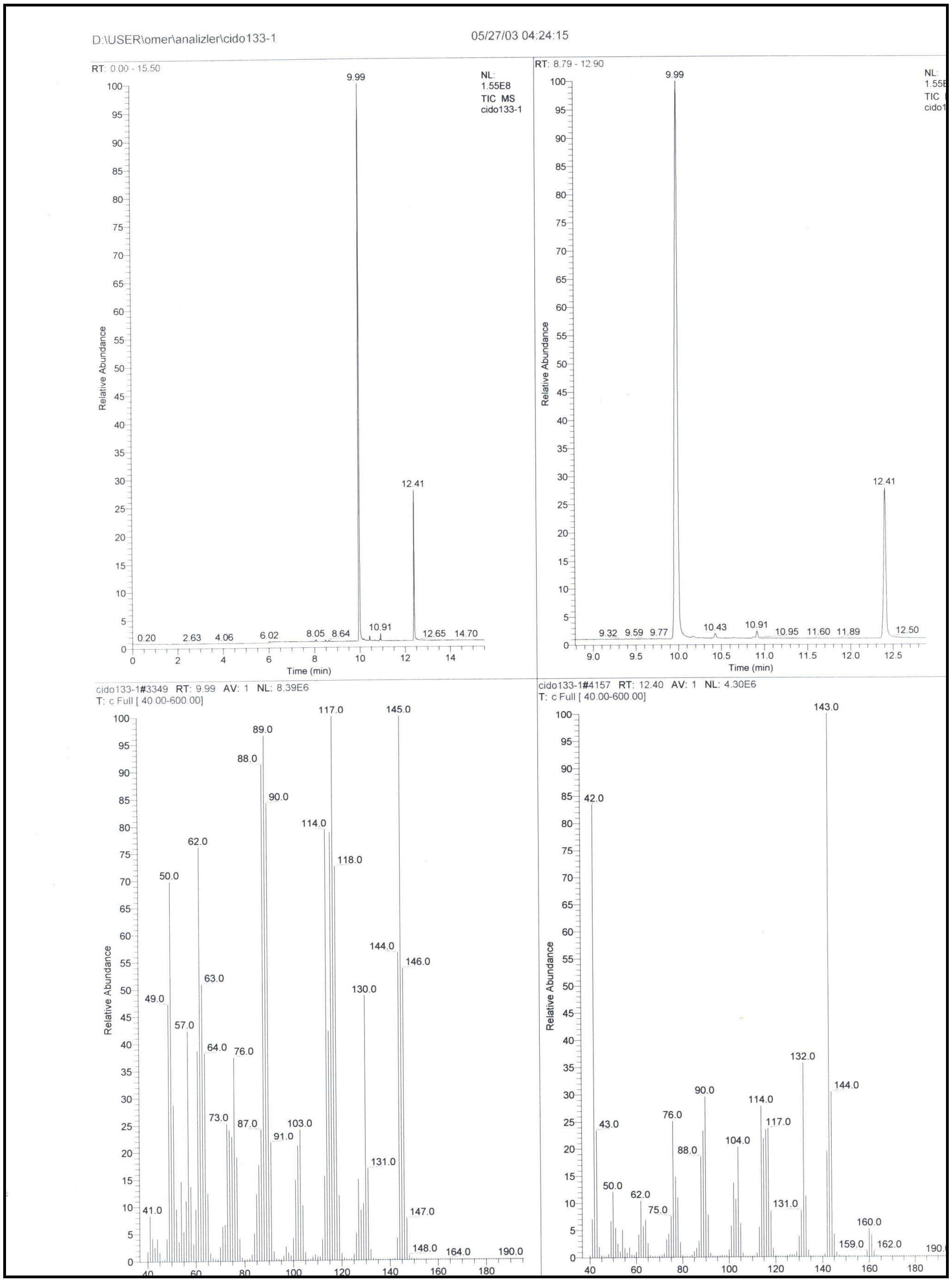


Figure 33. GC-MS Spectrum of **92** (with Yb(OTf)$_3$)

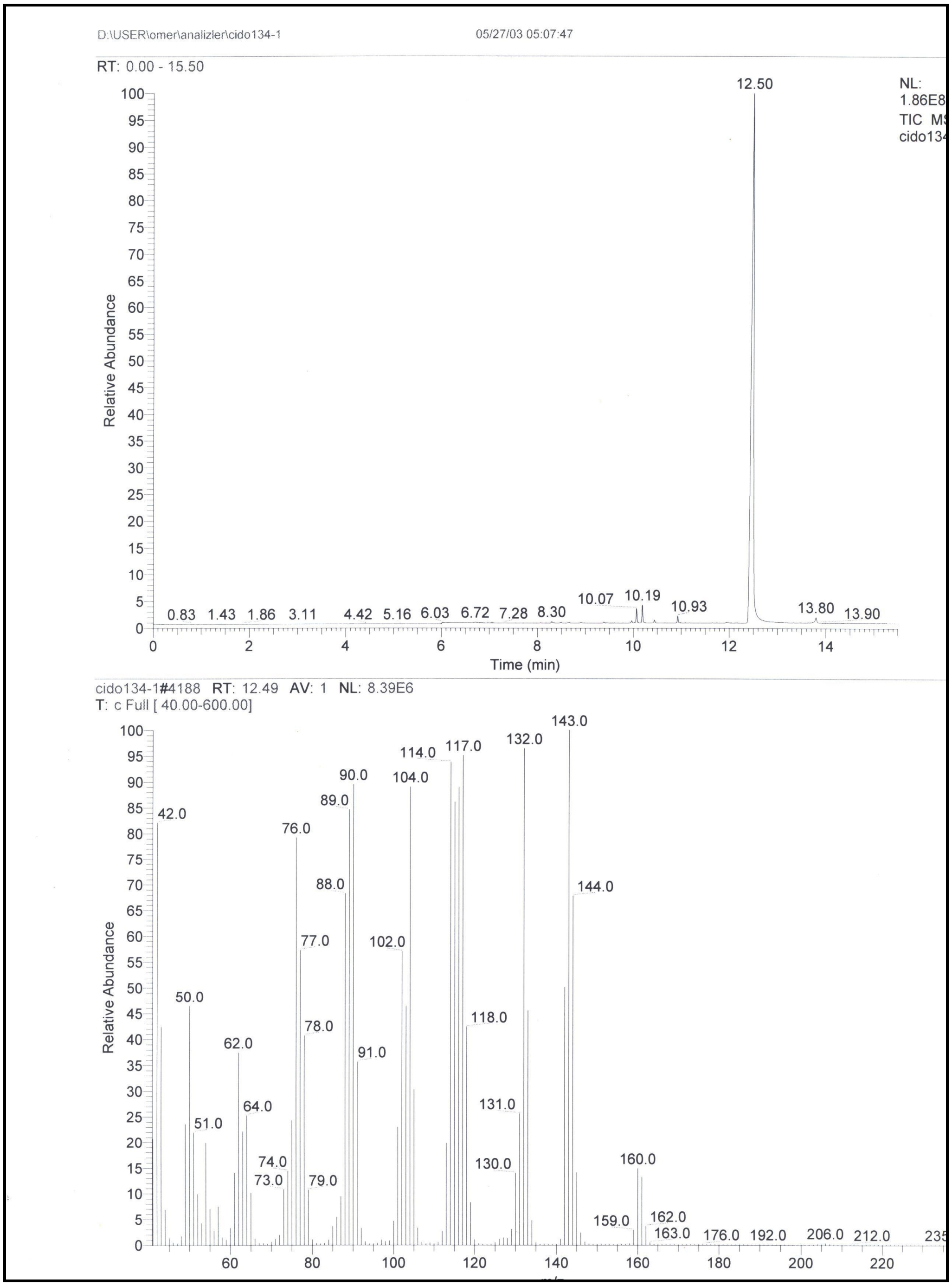


Figure 34. GC-MS Spectrum of **92** (with AcOH)

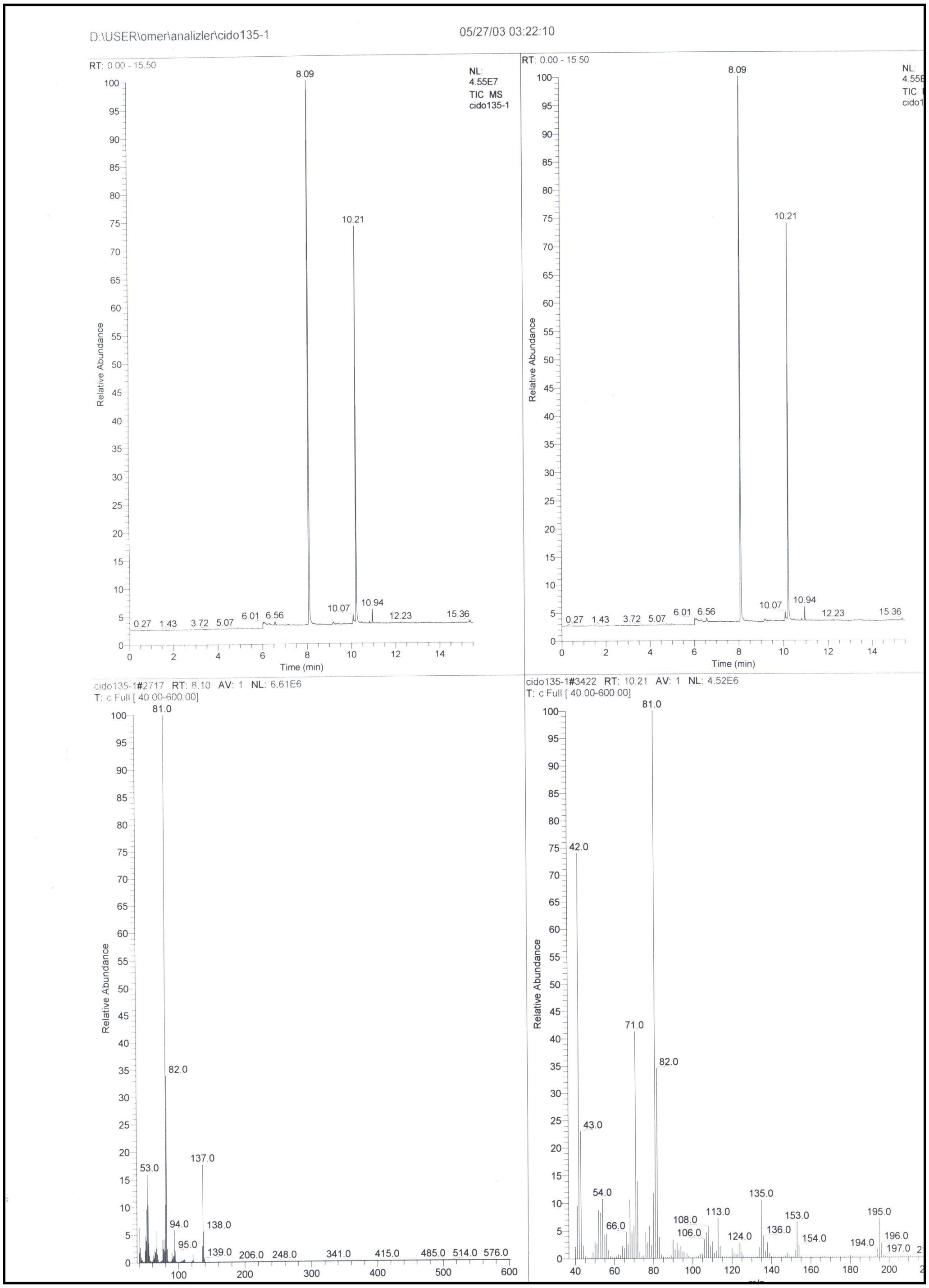


Figure 35. GC-MS Spectrum of **87** (without AcOH)

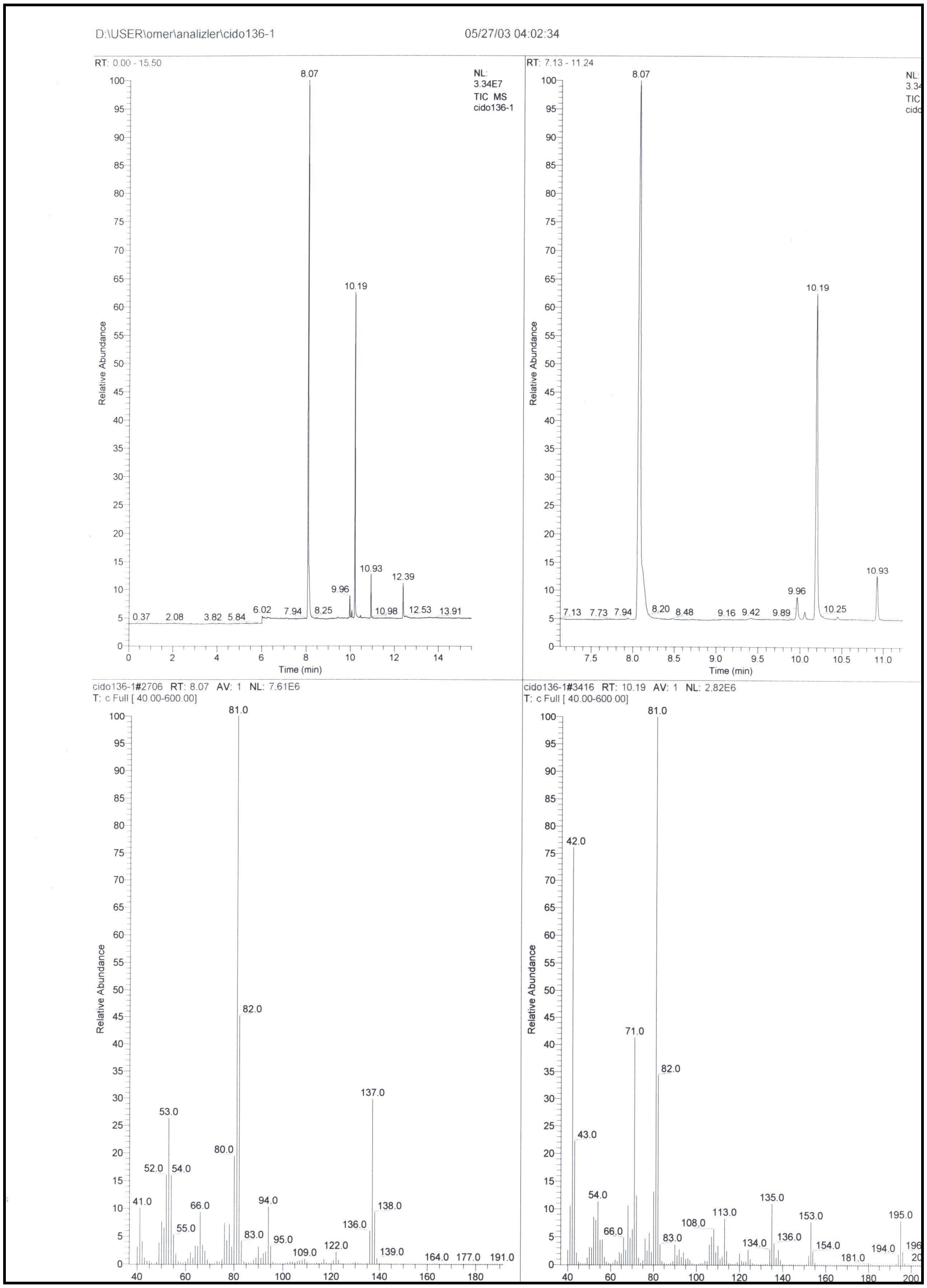


Figure 36. GC-MS Spectrum of **87** (with Yb(OTf)$_3$)

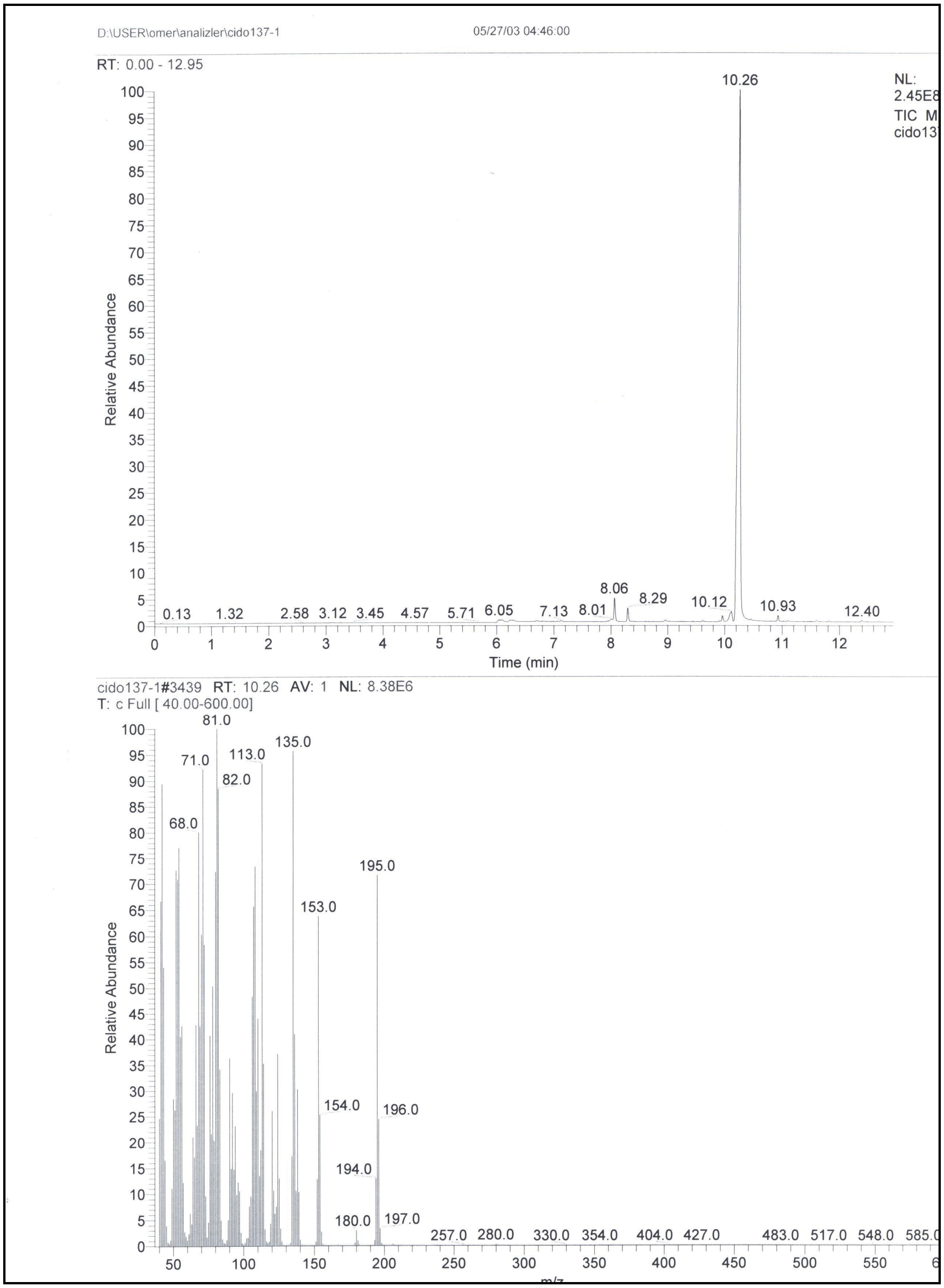


Figure 37. GC-MS Spectrum of **87** (with AcOH)

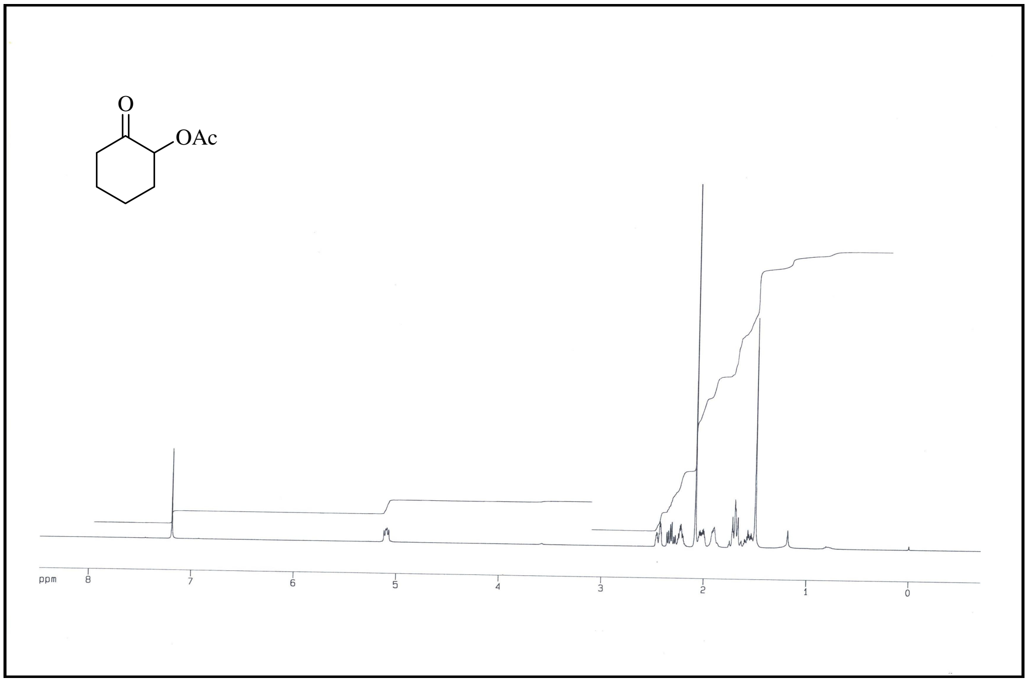


Figure 38. ^{1}H NMR Spectrum of **126**

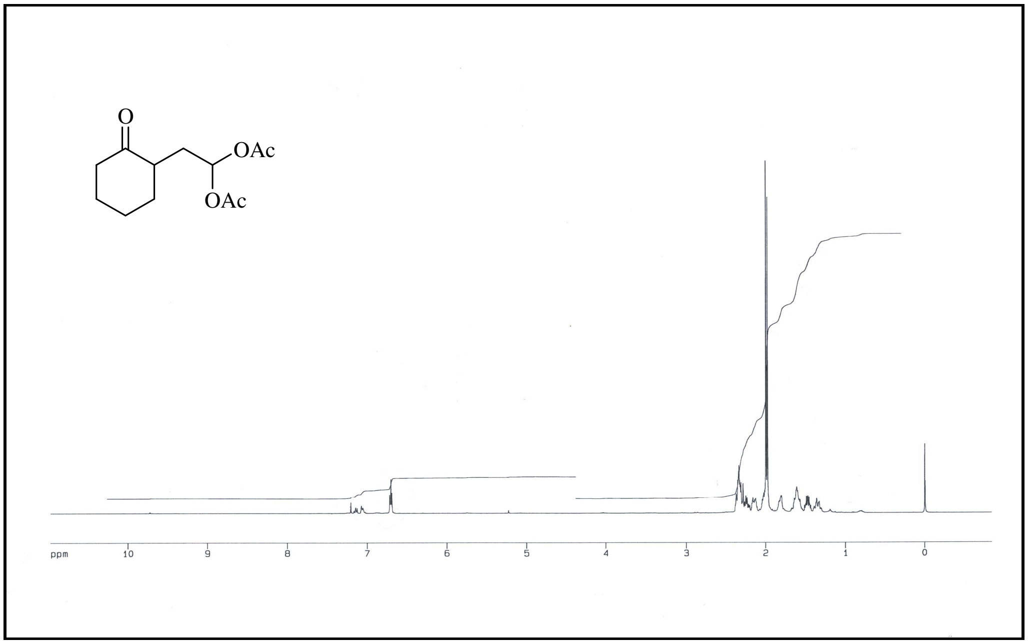


Figure 39. ^{1}H NMR Spectrum of **128**

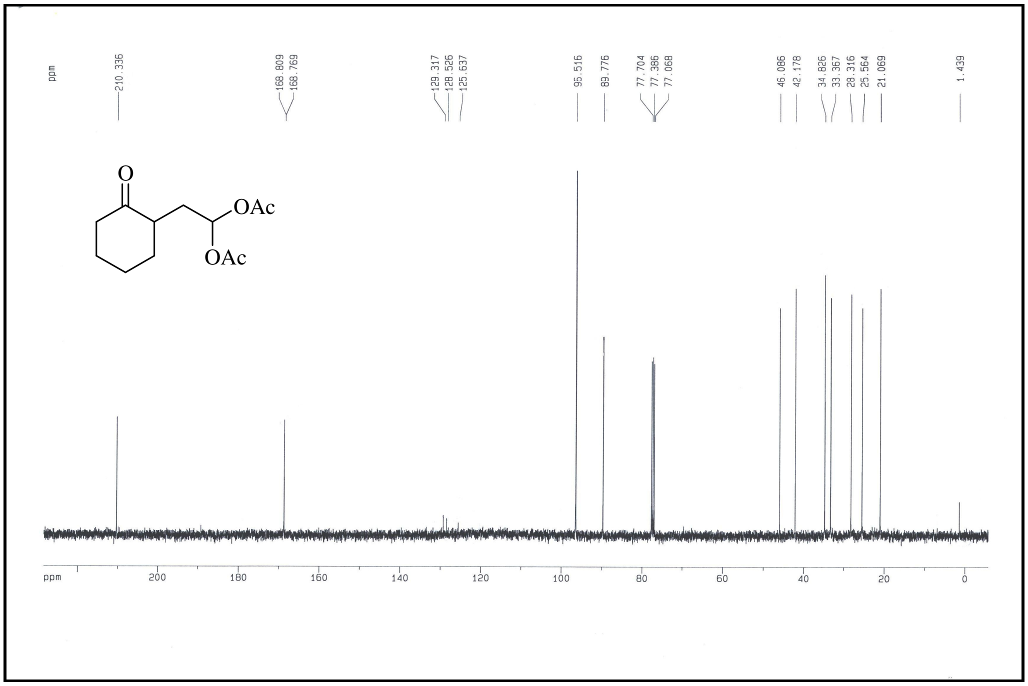


Figure 40. ^{13}C NMR Spectrum of **128**

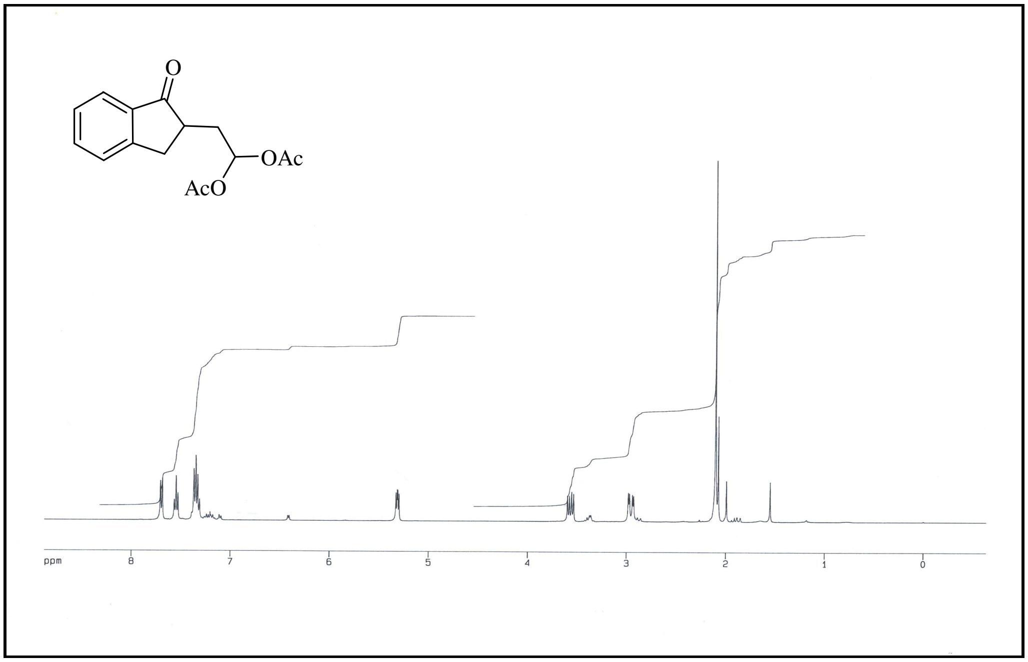


Figure 41. ^{1}H NMR Spectrum of **129**

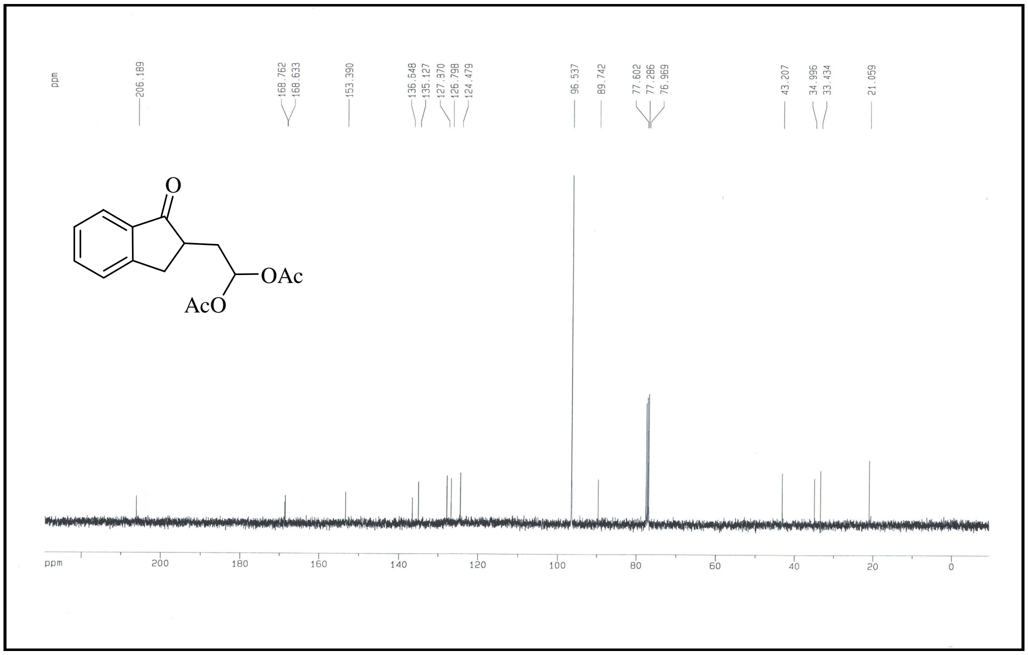


Figure 42. ^{13}C NMR Spectrum of **129**

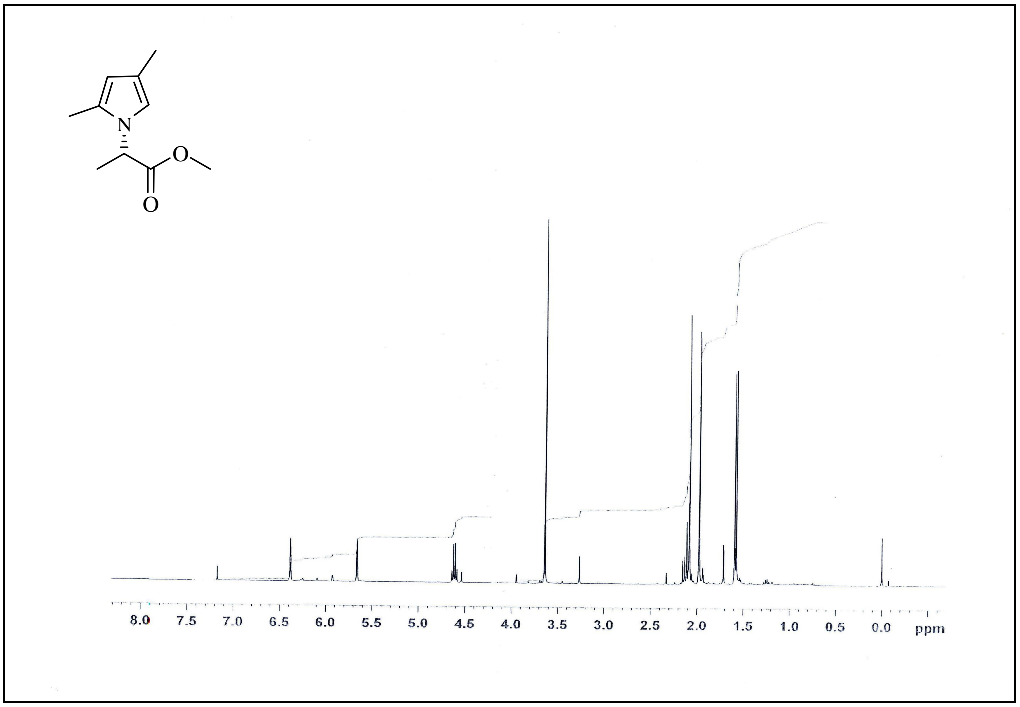


Figure 43. ^{1}H NMR Spectrum of (S)-**307**

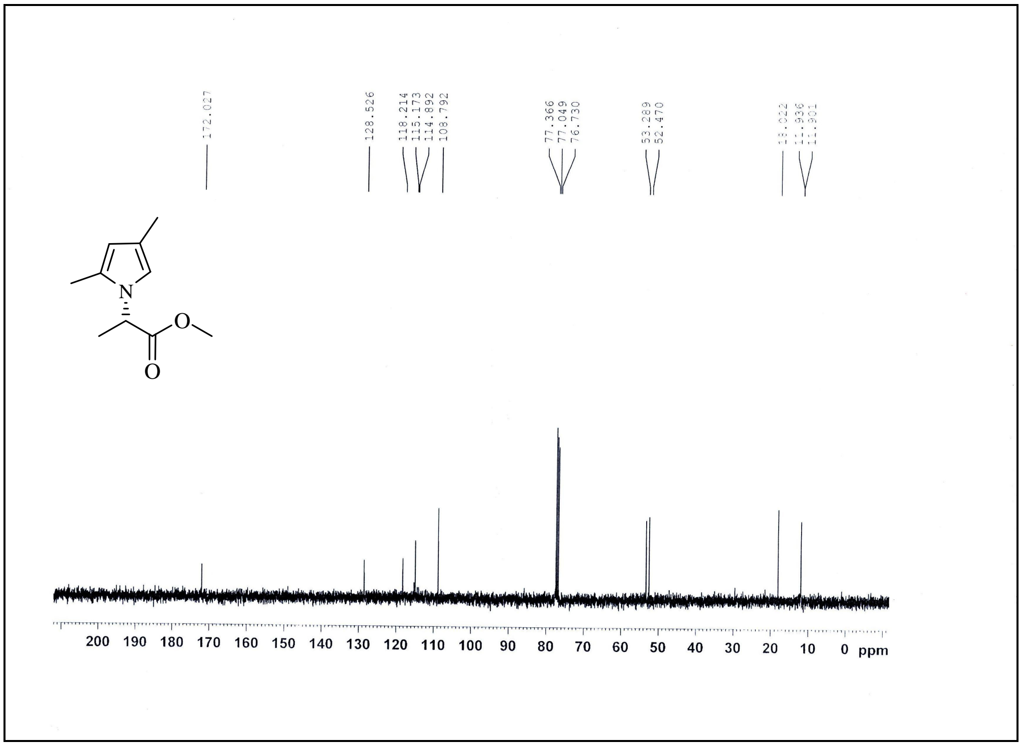


Figure 44. ^{13}C NMR Spectrum of (S)-**307**

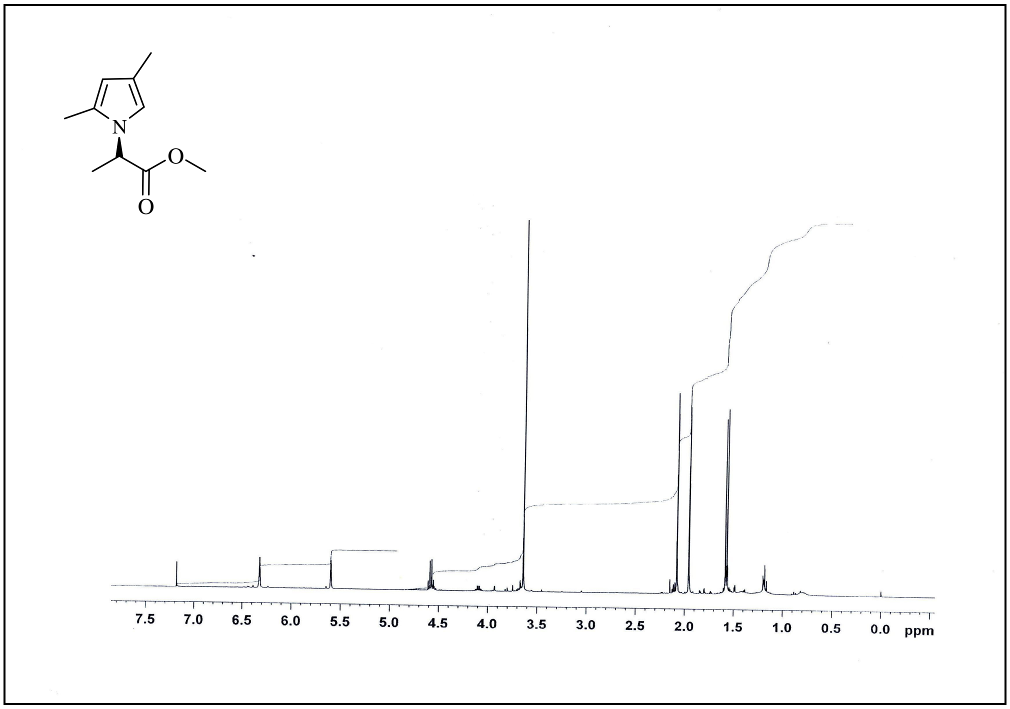


Figure 45. ^{1}H NMR Spectrum of (R)-**307**

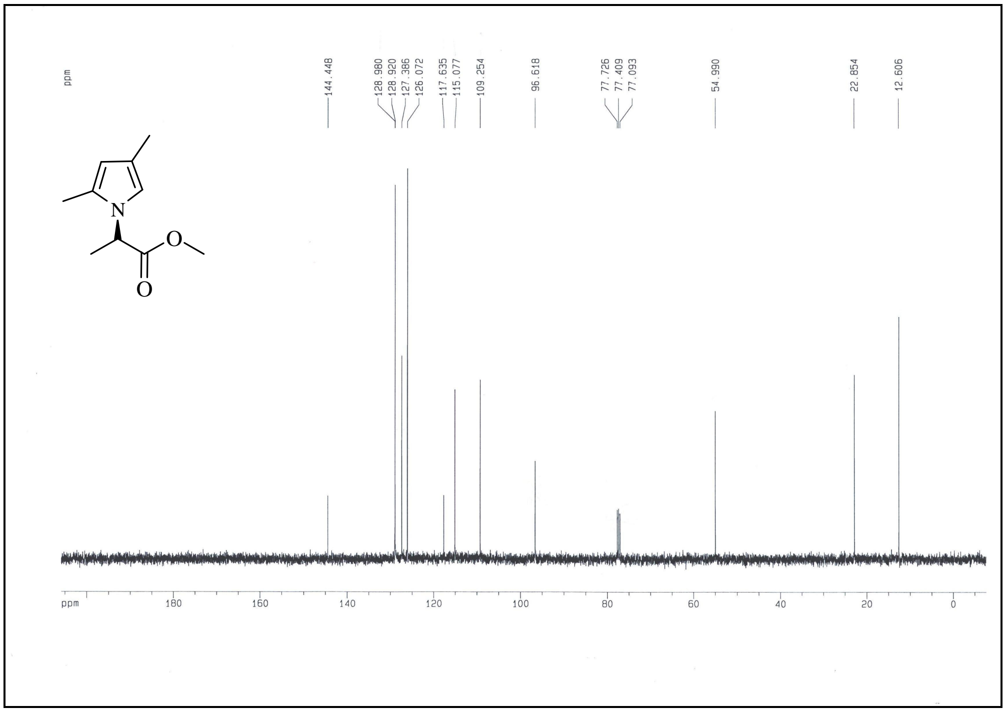


Figure 46. ^{13}C NMR Spectrum of (R)-**307**

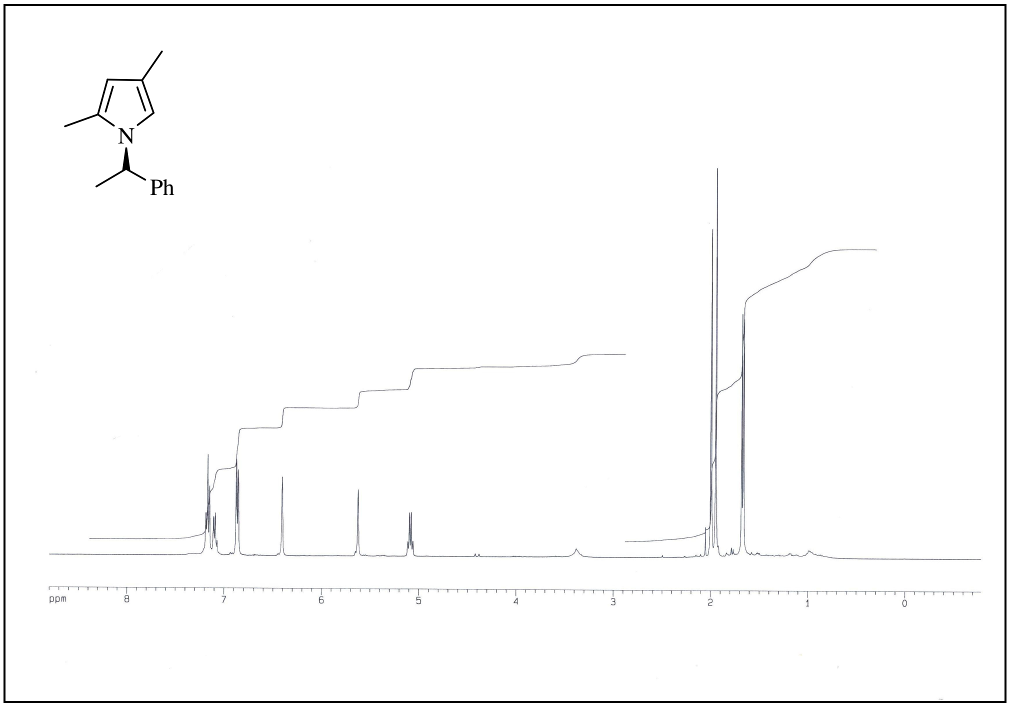


Figure 47. ^{1}H NMR Spectrum of (R)-**309**

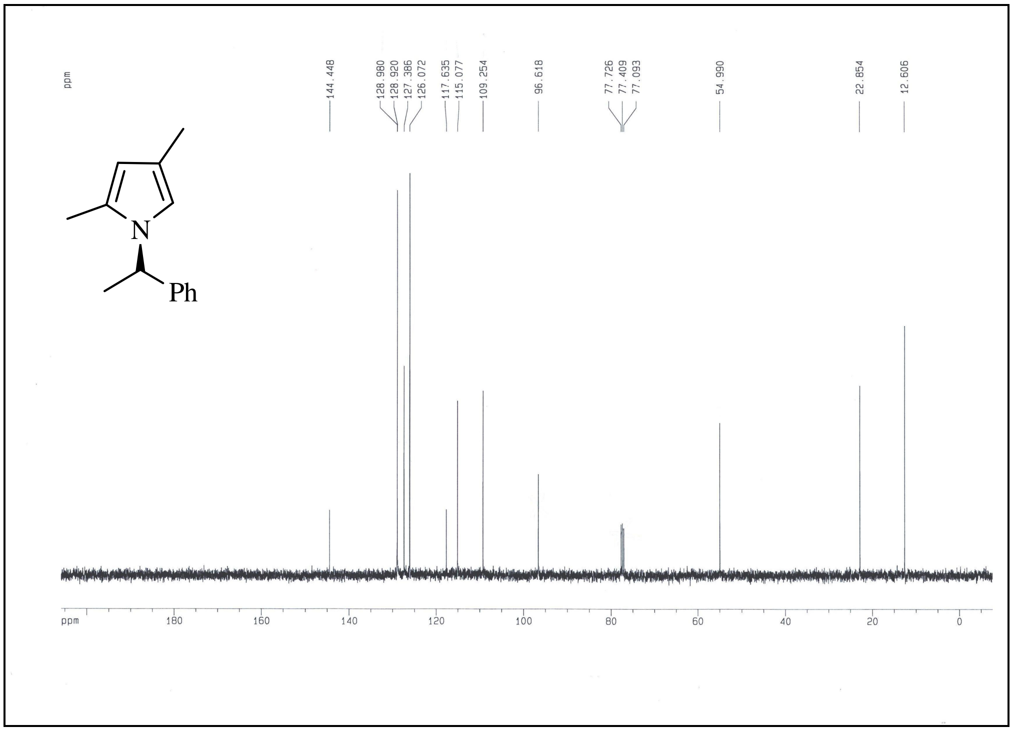


Figure 48. ^{13}C NMR Spectrum of (R)-**309**

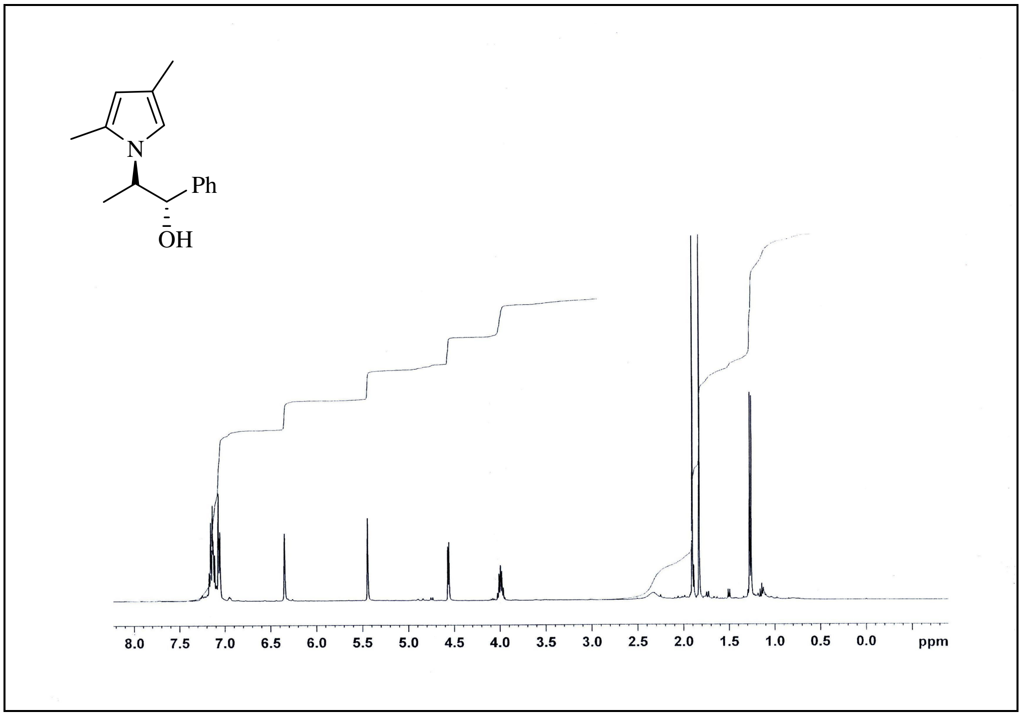


Figure 49. ^{1}H NMR Spectrum of (S,R)-**311**

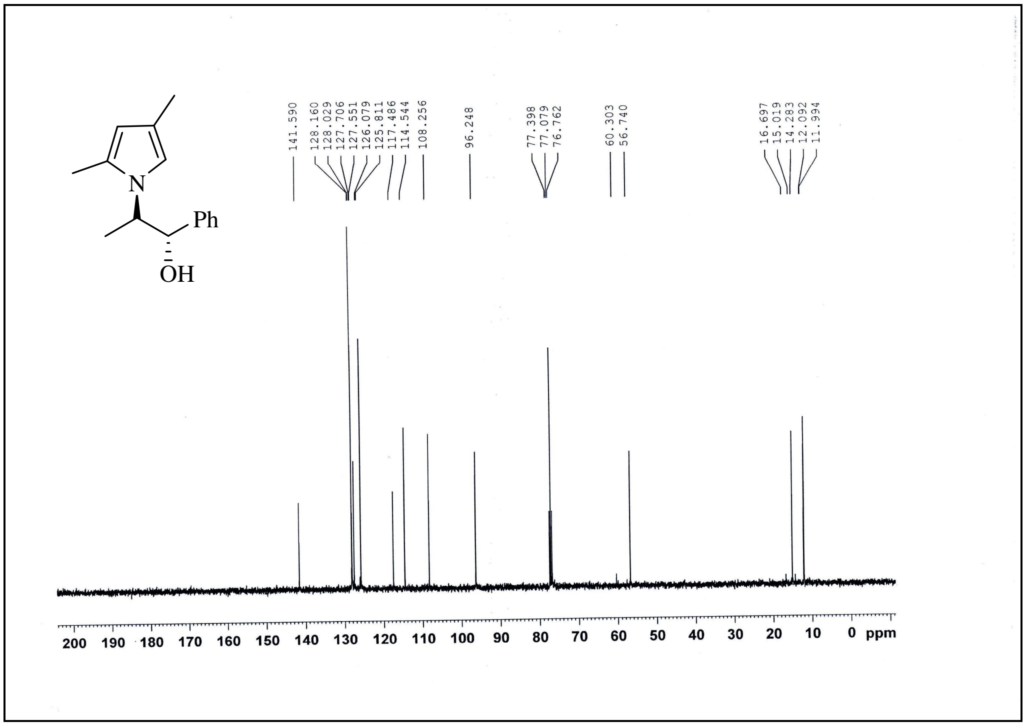


Figure 50. ^{13}C NMR Spectrum of (S,R)-**311**

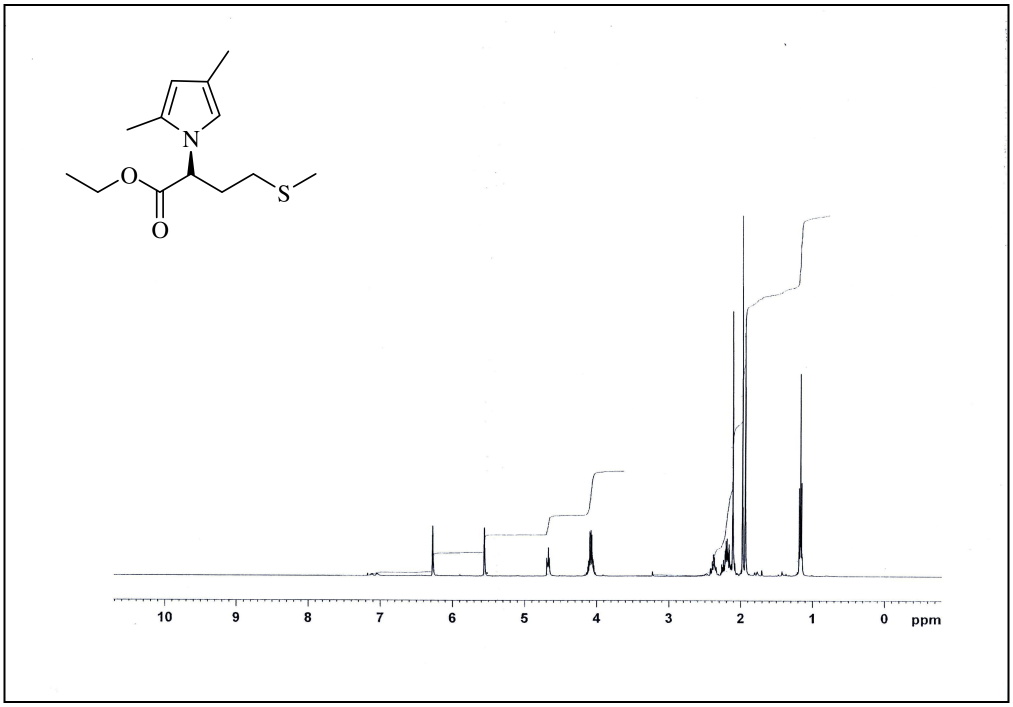


Figure 51. ^{1}H NMR Spectrum of (S)-**313**

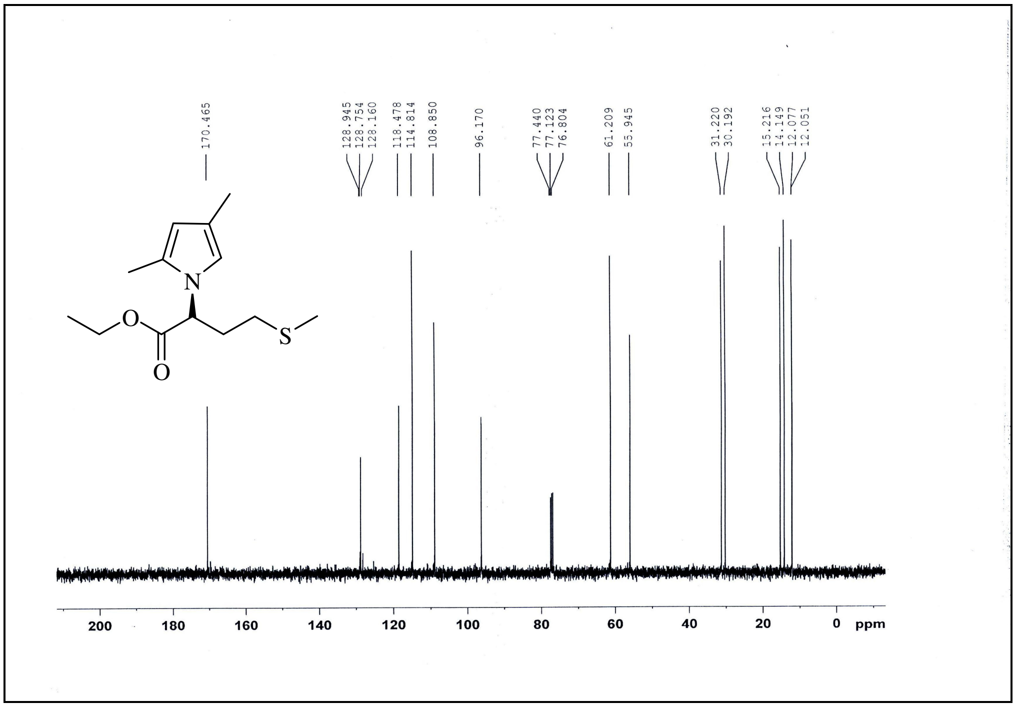


Figure 52. ^{13}C NMR Spectrum of (S,R)-**313**

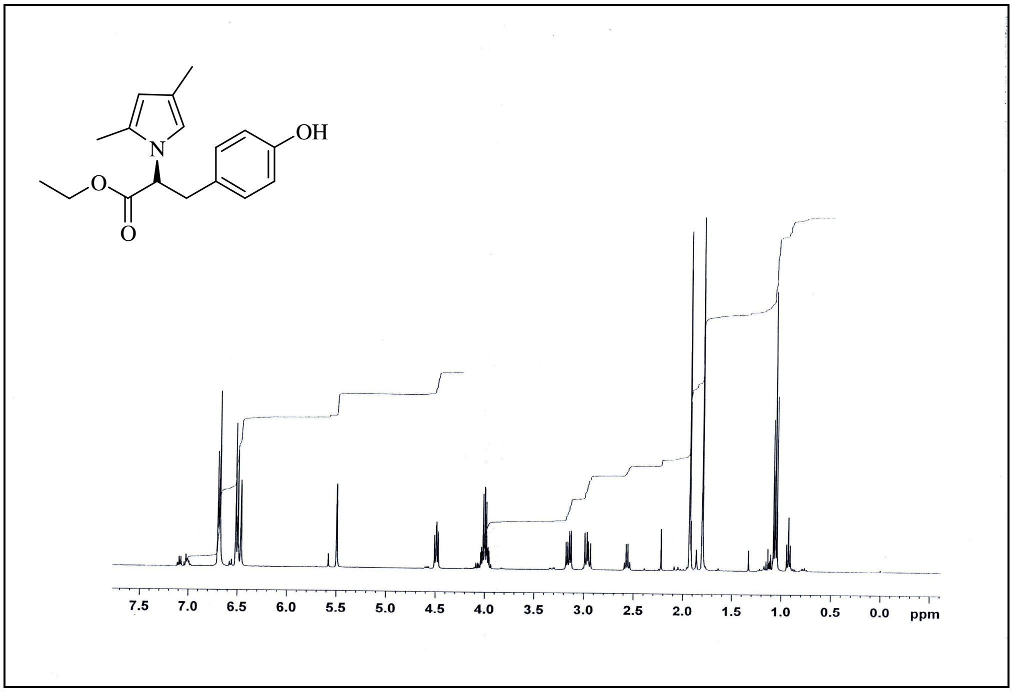


Figure 53. ^{1}H NMR Spectrum of (S)-**315**

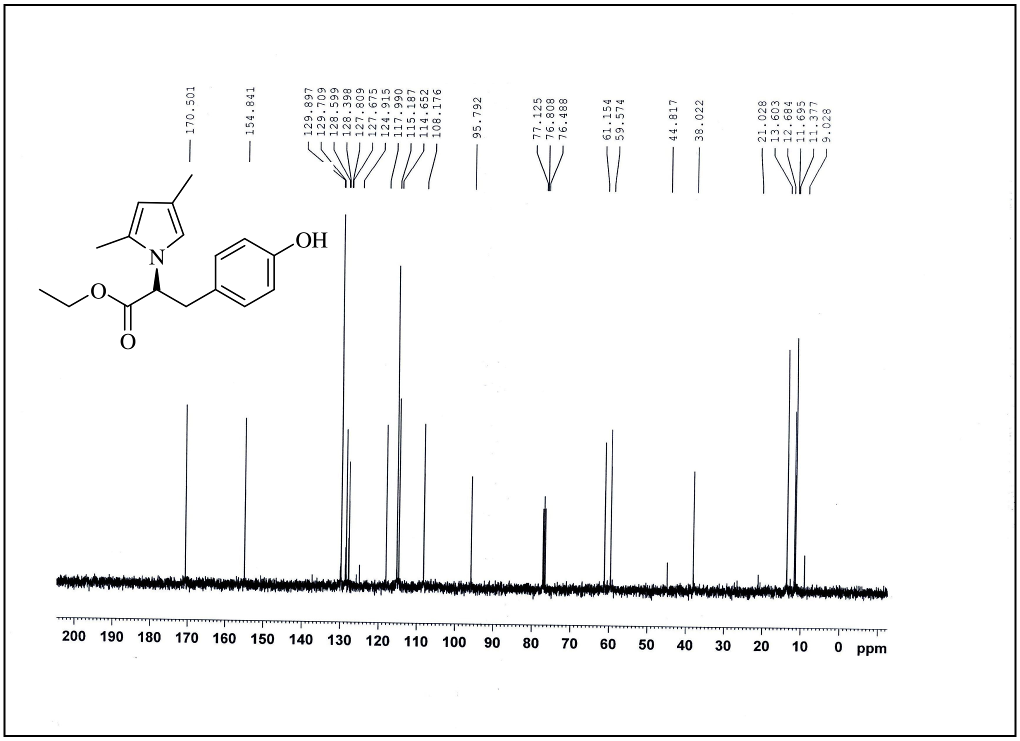


Figure 54. ^{13}C NMR Spectrum of (S,R)-**315**

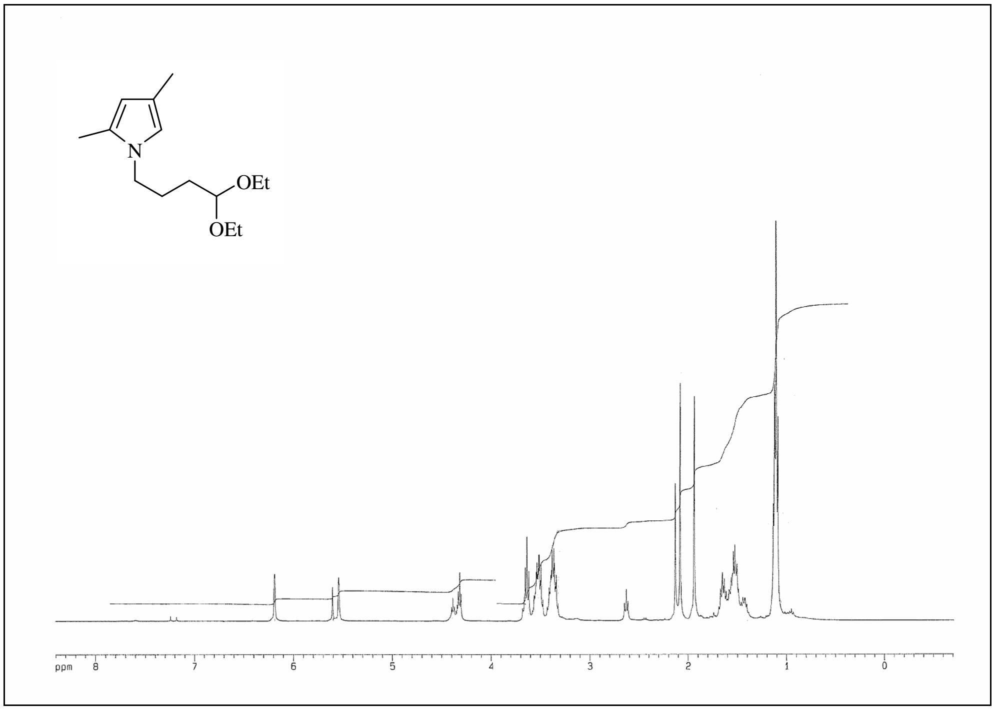


Figure 55. ^{1}H NMR Spectrum of **317**

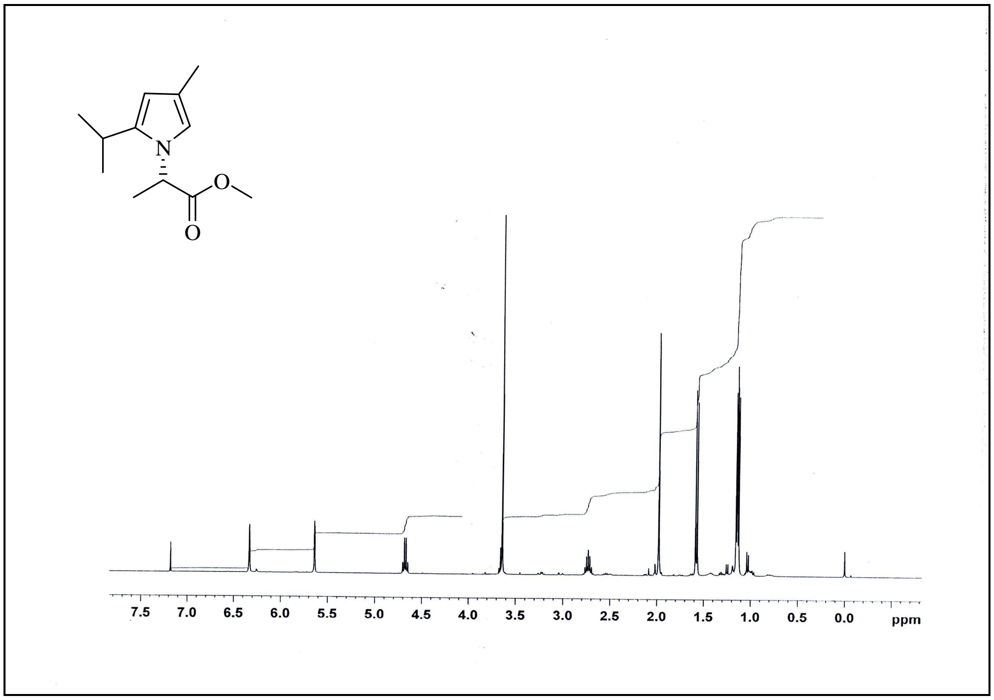


Figure 56. ^{1}H NMR Spectrum of (S)-**321**

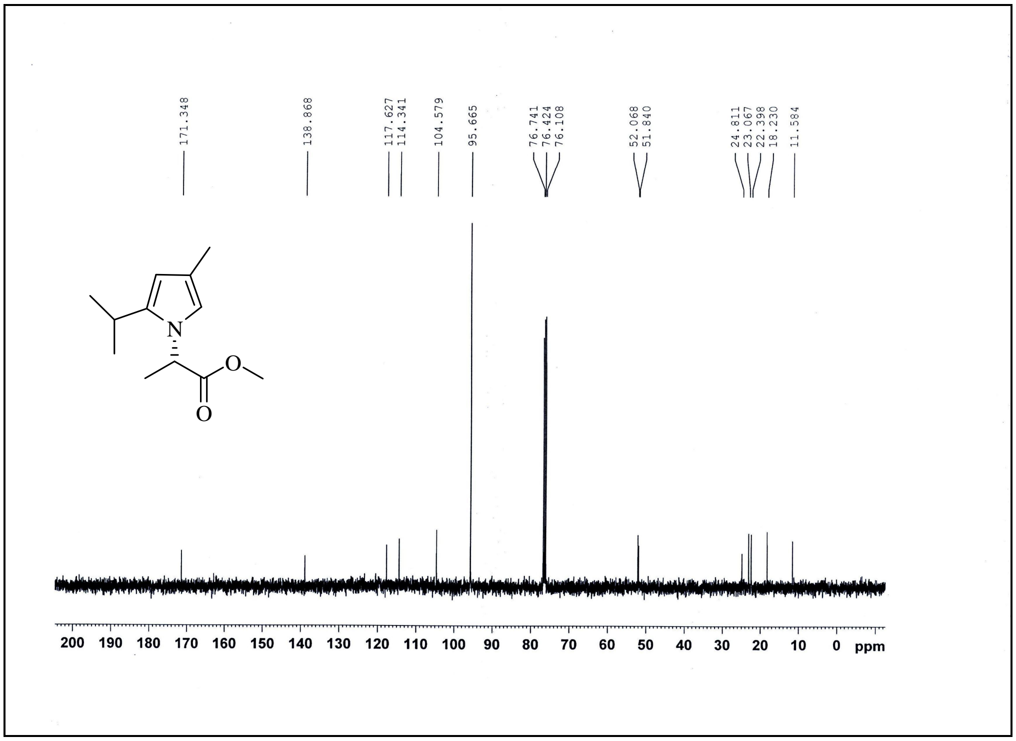


Figure 57. ^{13}C NMR Spectrum of (S)-**321**

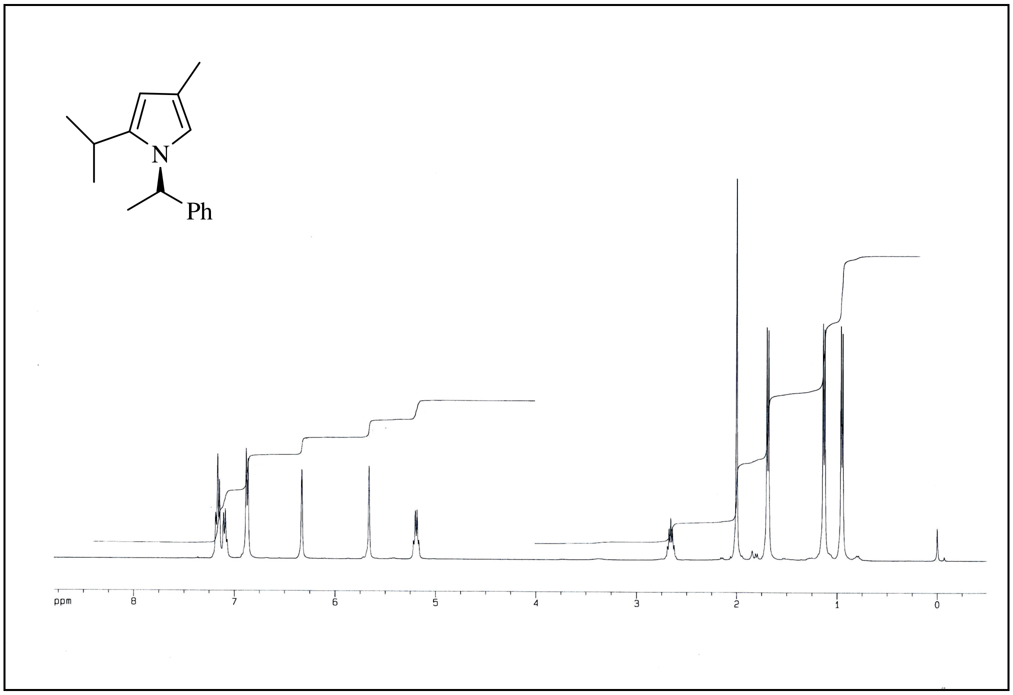


Figure 58. ^{1}H NMR Spectrum of (R)-**322**

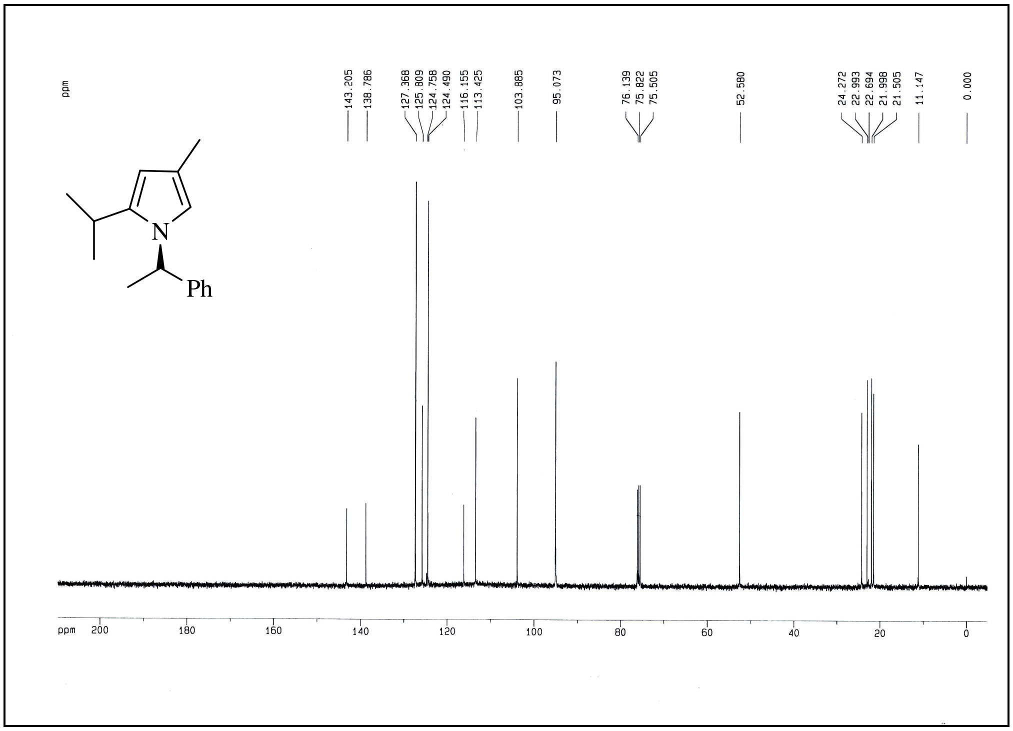


Figure 59. ^{13}C NMR Spectrum of (R)-**322**

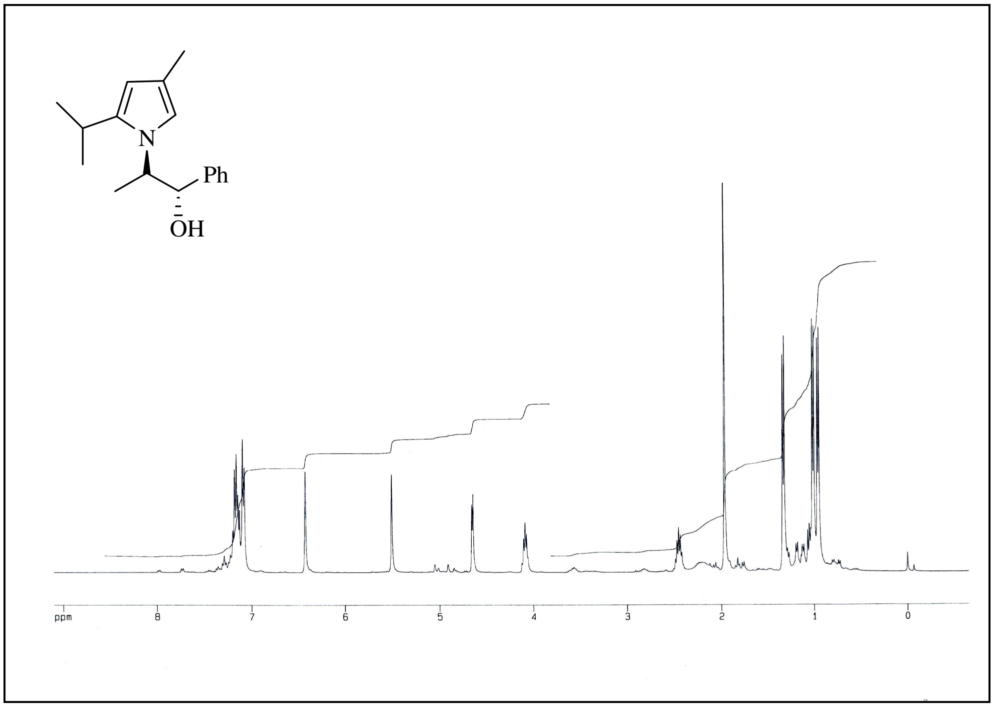


Figure 60. ^{1}H NMR Spectrum of (S,R)-**323**

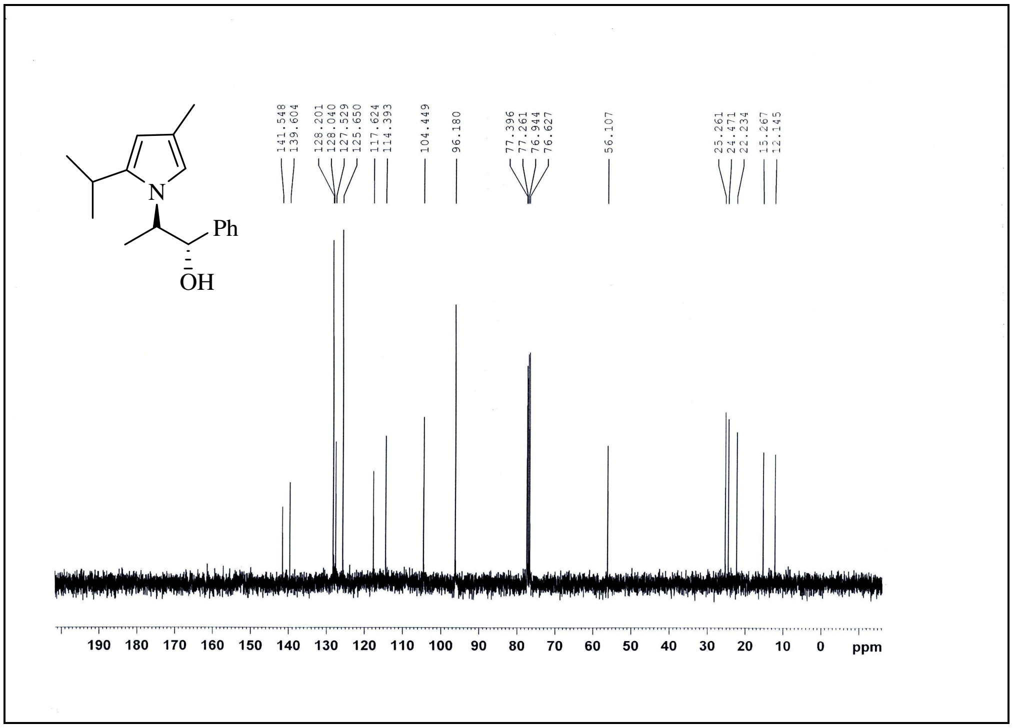


Figure 61. ^{13}C NMR Spectrum of (S,R)-**323**

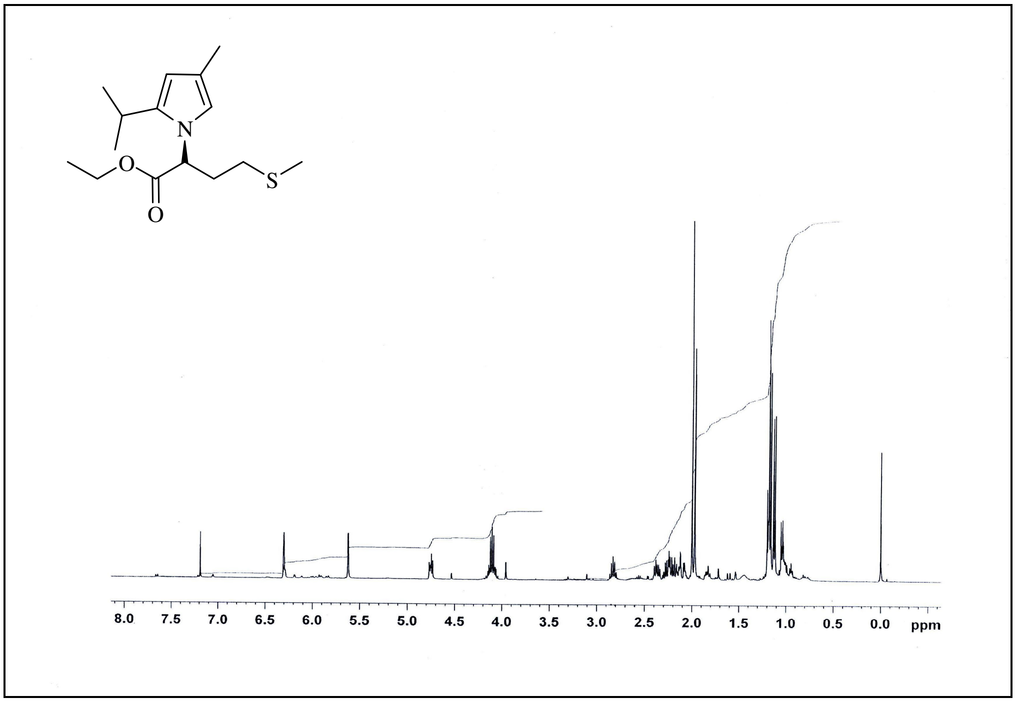


Figure 62. ^{1}H NMR Spectrum of (S)-**324**

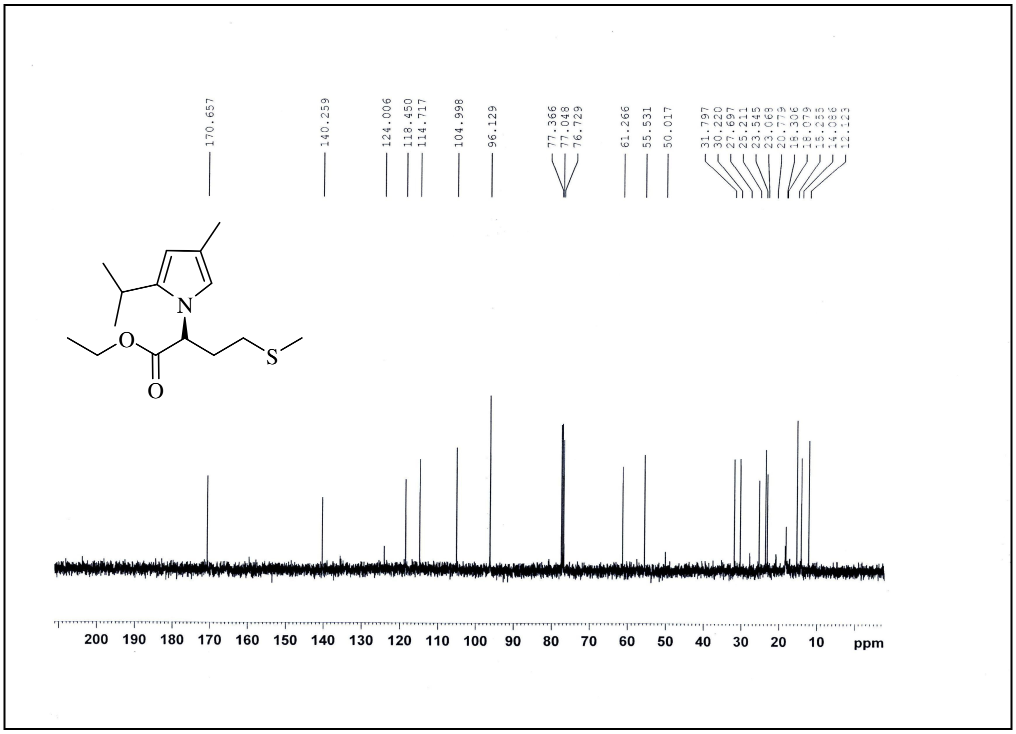


Figure 63. ^{13}C NMR Spectrum of (S)-**324**

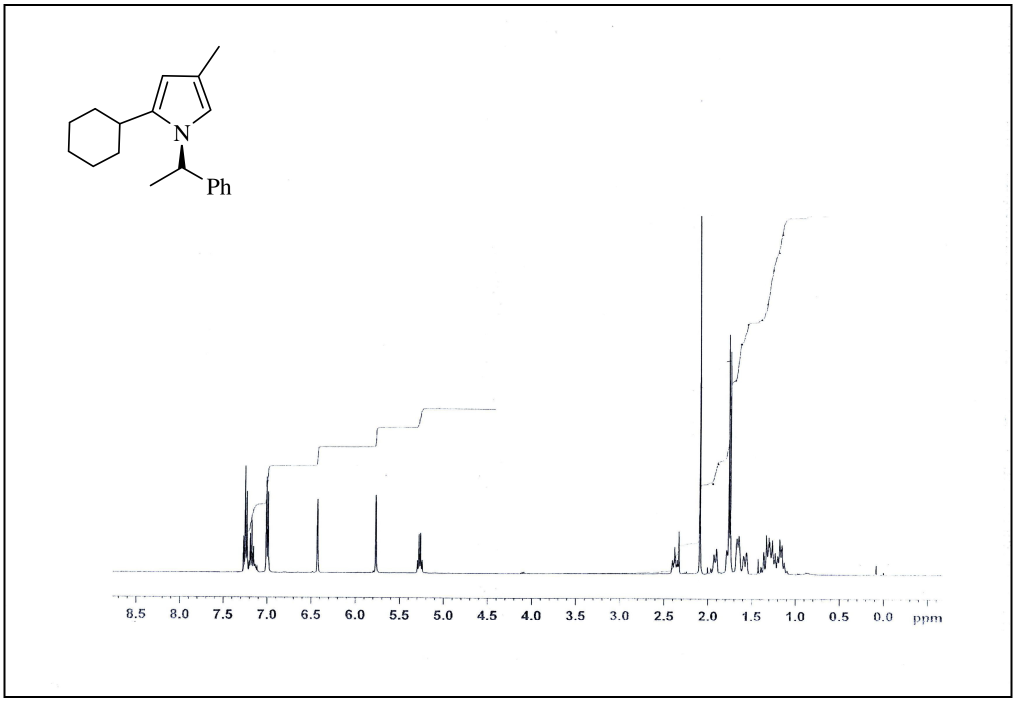


Figure 64. ^{1}H NMR Spectrum of (R)-**325**

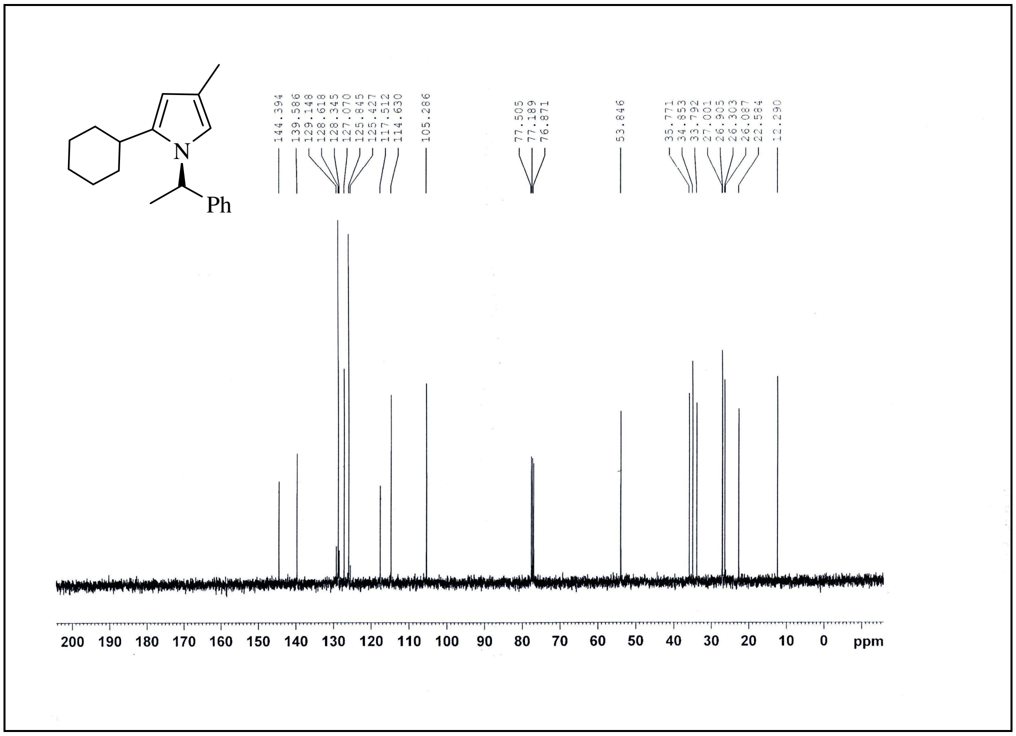


Figure 65. ^{13}C NMR Spectrum of (R)-**325**

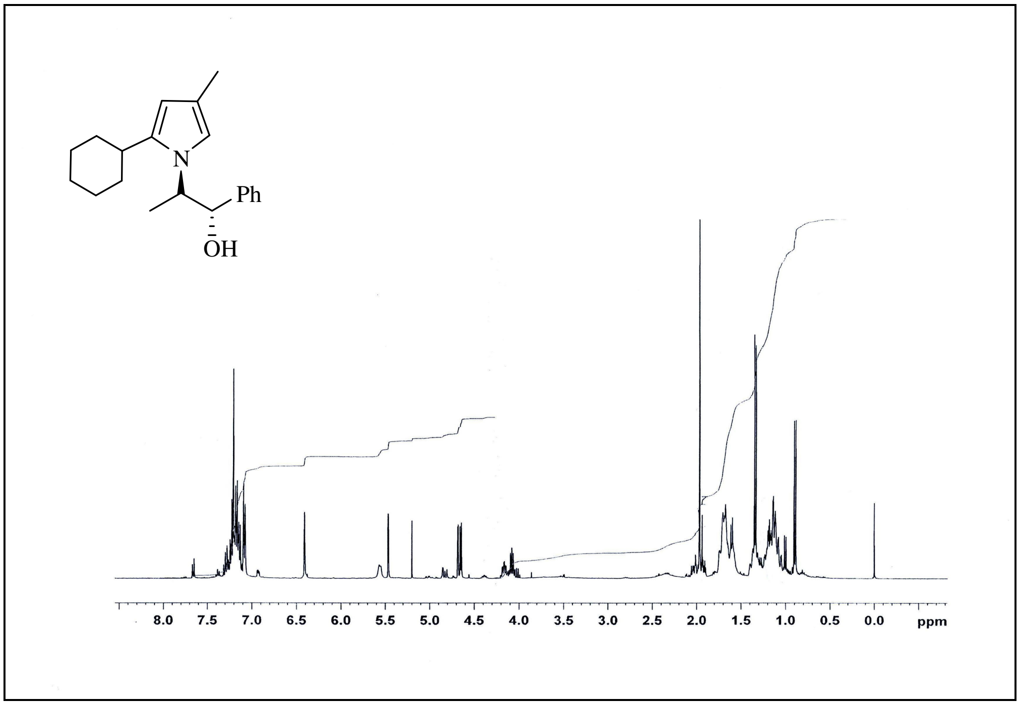


Figure 66. ¹H NMR Spectrum of (S,R)-**326**

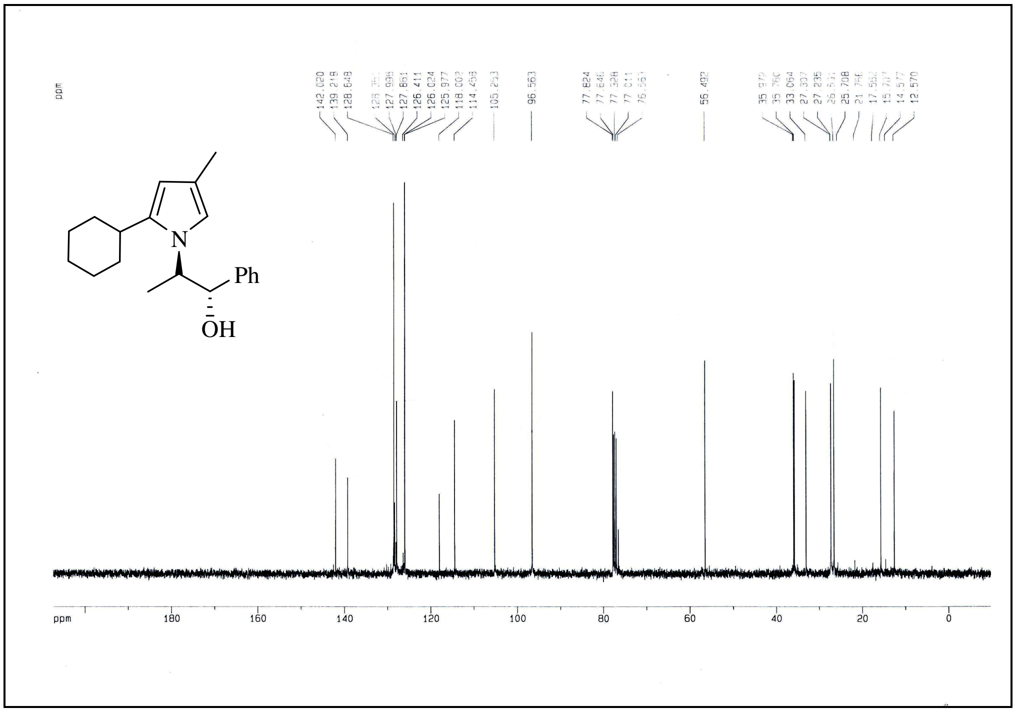


Figure 67. ¹³C NMR Spectrum of (S,R)-**326**

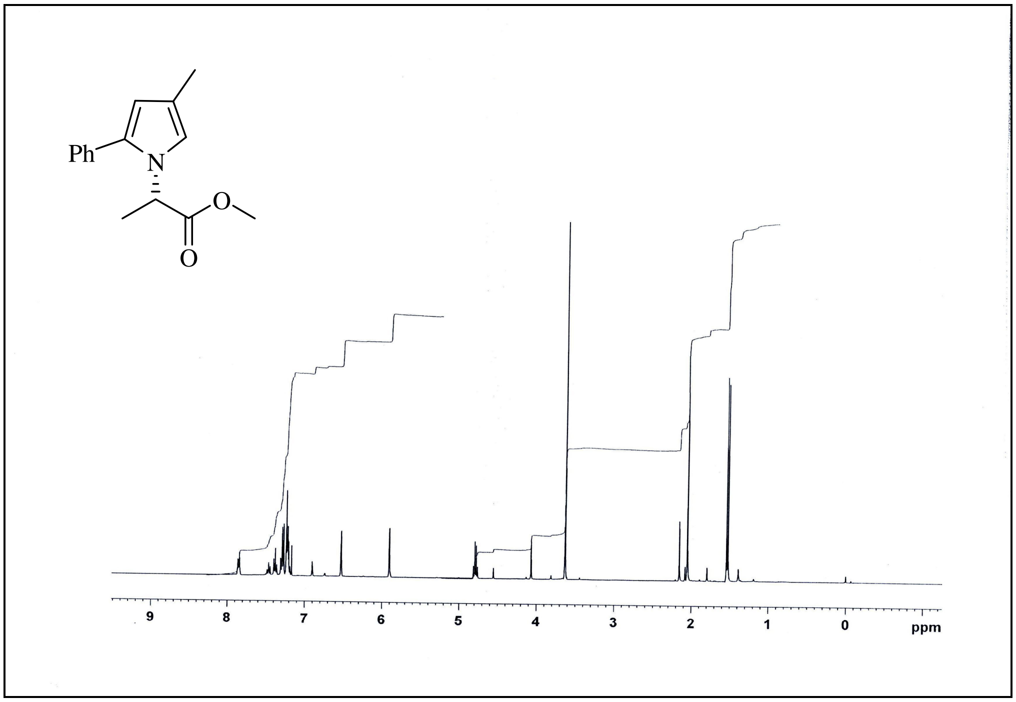


Figure 68. ^{1}H NMR Spectrum of (S)-**327**

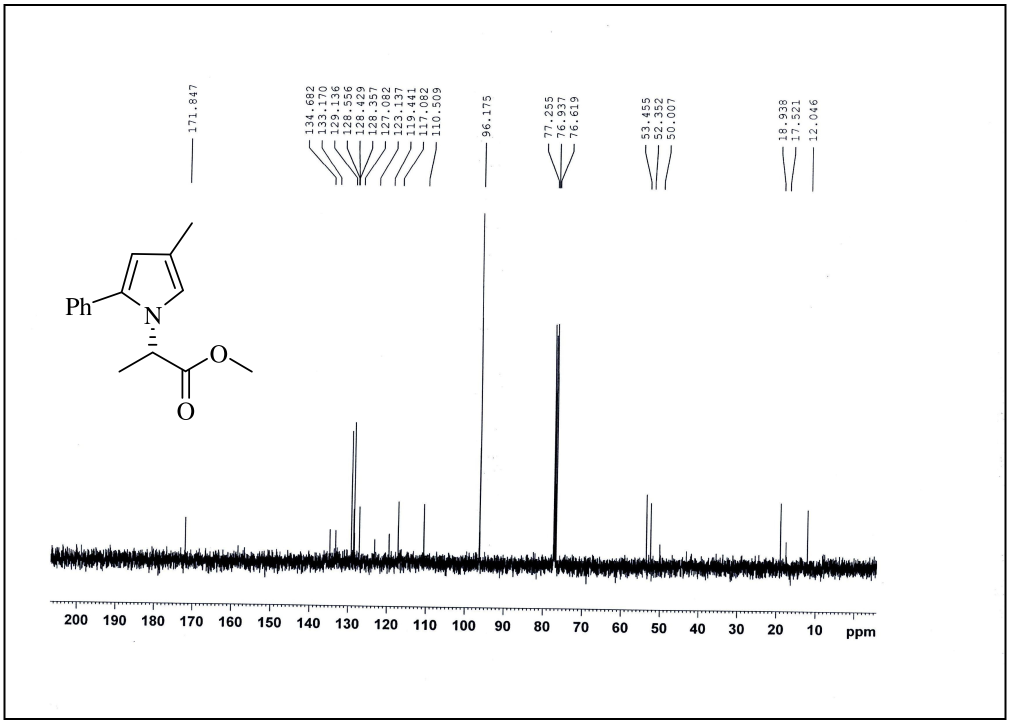


Figure 69. ^{13}C NMR Spectrum of (S)-**327**

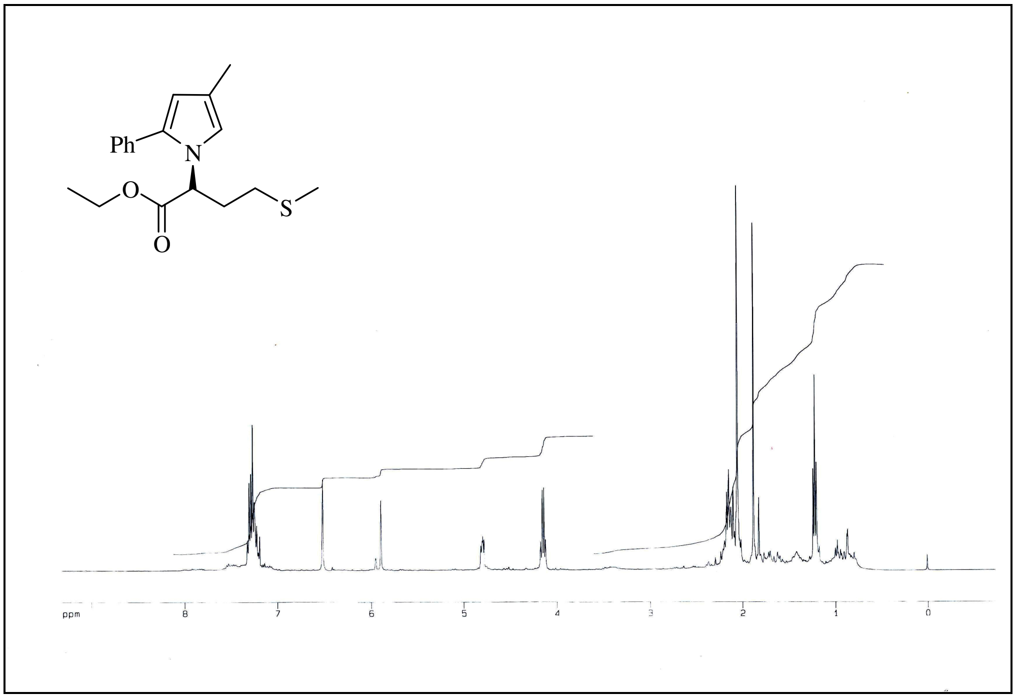


Figure 70. ^{1}H NMR Spectrum of (S)-**328**

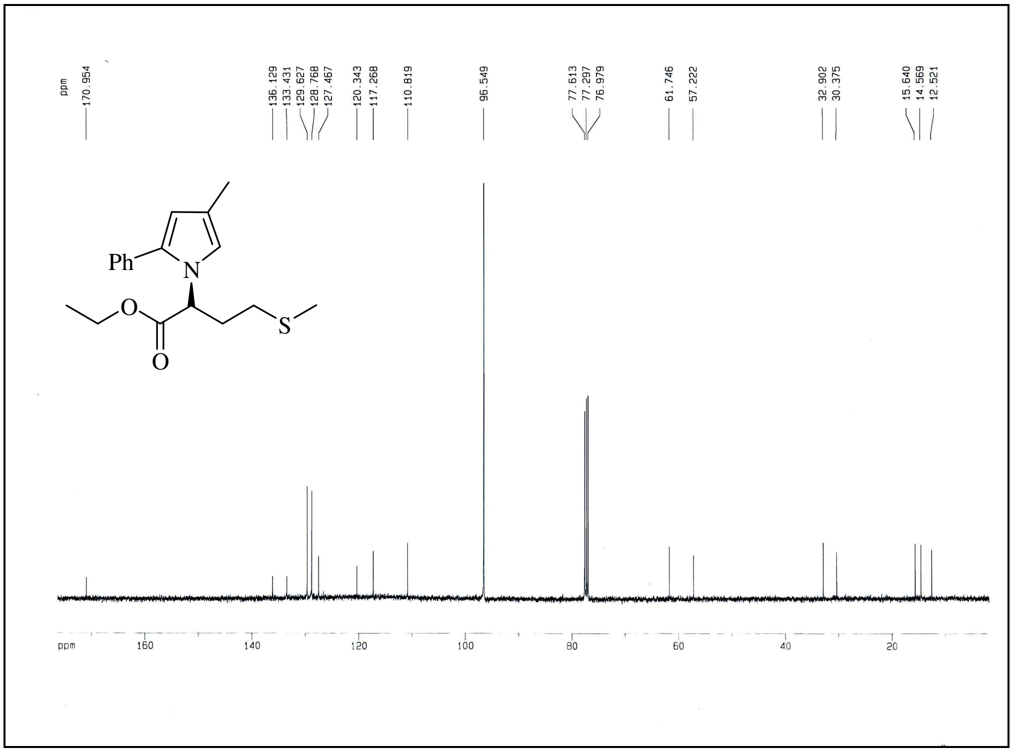


Figure 71. ^{13}C NMR Spectrum of (S)-**328**

CURRICULUM VITAE

PERSONAL INFORMATION

Surname, Name: İğdir, Ayşe Çiğdem
Nationality: Turkish (TC)
Date and Place of Birth: 27 February 1975 , Ankara
Marital Status: Single
email: cigdem.igdir@eczacibasi.com.tr
cigdir@gmail.com

EDUCATION

Degree	**Institution**	**Year of Graduation**
PhD	METU Chemistry	2006
MS	METU Chemistry	2000
BS	METU Chemistry	1997

FOREIGN LANGUAGES

English

PUBLICATIONS

1. "Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate-Phosphate Rearrangement: A Highly Practical Method for Cross Benzoin Reaction", Demir, A.S., Reis, Ö., **Igdir, A.C.**, Esiringü, I., Eymur, S.; **J. Org. Chem.**, 70 (25), **2005**, 10584.

2. "Amination/annulation of chlorobutenones with chiral amine compounds: synthesis of 1,2,4-trisubstituted pyrroles", Demir, A.S., **Igdir, A.C.**; Gunay, B.; **Tetrahedron: *Asymmetry***, 16, **2005**, 3170.

3. "Fungi mediated conversion of benzil to benzoin and hydrobenzoin", Demir, A.S., Hamamci, H., Ayhan, P., Duygu, A.N., **Igdir, A.C.**, Capanoglu, D.; **Tetrahedron: *Asymmetry***, 15, **2004**, 2579.

4. "Enzyme catalyzed hydroxymethylation of aromatic aldehydes with formaldehyde. Synthesis of hydroxyacetophenones and (*S*)-benzoins", Demir, A.S., Ayhan, P., **Igdir, A.C.**, Duygu, A.N.; **Tetrahedron**, 60, **2004**, 6509.

5. "Reinvestigation of the synthetic and mechanistic aspects of Mn(III) acetate mediated oxidation of enones", Demir, A.S., Reis, Ö., **Igdir, A.C.**; **Tetrahedron**, 60, **2004**, 3427.

6. “Novel Coupling of Thiols into Disulfides, via S-Nitrosothiol Intermediates Using Trichloronitromethane”, Demir, A.S., **Igdir, A.C.**, Mahasneh, A.S.; **<u>Tetrahedron</u>**, 77, **1999**, 12399.

7. “Butenolide Annelation Using Manganese(III) Oxidation. A synthesis of Chromolaenin (Laevigatin)”, Demir, A.S., Gercek, Z., Duygu, N., **Igdir, A.C.**, Reis, Ö.; **<u>Can. J. Chem.</u>**, 77, **1999**, 1336.