SYNTHESIS OF CHIRAL LACTONES VIA THE BAEYER VILLIGER OXIDATION OF CYCLIC AROMATIC ACETOXY KETONES

NOVEL ANNULATION REACTIONS OF 2-PROPYNYL-1,3-DICARBONYL COMPOUNDS TO FORM PYRROLES

ADDITION OF ACYL PHOSPHONATES TO DIETHYL CYANOPHOSPHONATE (DEPC)

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ABSTRACT

SYNTHESIS OF CHIRAL LACTONES VIA THE BAEYER VILLIGER OXIDATION OF CYCLIC AROMATIC ACETOXY KETONES

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Chiral Baeyer-Villiger (BV) oxidation of cyclic ketones allows rapid access to asymmetric lactones as valuable intermediates in organic chemistry and frequently encountered precursors in enantioselective synthesis. In the first part, BV oxidation of functionalized ketones, especially cyclic α-hydroxy and acetoxy ketones is described which could be a straightforward route to the α-hydroxy lactones and α-hydroxyalkanoic acid derivatives. The α-acetoxylation of indanone, tetralone and chromanone derivatives by using $Mn(OAc)_3$ followed by the enzyme catalyzed kinetic resolution of acetoxy ketones gives both of the enantiomers of α-acetoxy ketones in good chemical and optical yields. The Bayer-Villiger oxidation of α-acetoxy ketones with *m*-CPBA, CF_3SO_3H, and CH_2Cl_2, at rt gives the corresponding

lactones without racemization. The phenyl moiety migrates selectively in order to form lactones. The mild hydrolysis of lactones affords phenolic α-hydroxycarboxylic acid derivatives.

Because of the high importance of pyrrole derivatives which exist in the structure of many natural products possessing biological activity beside their valuable feature of being versatile building blocks in organic synthesis and important starting materials for various synthetic transformations, a convenient method for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives starting from 1,3,-dicarbonyl compounds throuh acid catalyzed cyclization reaction is presented in the second part of the thesis. Alkylation of 1,3-dicarbonyl compound with propargyl bromide followed by one step cyclization with the introduction of primary amines in the presence of catalytic amount of trifluoroacetic acid (TFA) affords the corresponding pyrrole derivatives in high yields.

The third part of the thesis describes the cyano-phosphorylation of various alkyl and aryl phosphonates in the presence of diethyl cyanophosphonate (DEPC) as the phosphorylating agent under the promotion of the KCN catalyst. Reaction of acyl phosphonates with DEPC forms the phosphonocyanohydrin-*O*-phosphates which are the important starting materials of quaternary α-hydroxy carboxylic acid and phosphonate containing β-aminoalcohol derivatives.

Keywords: Baeyer Villiger oxidation, phenolic α-hydroxycarboxylic acid, asymmetric lactone, 1,2,3,5-tetrasubstituted pyrroles, cyclization, dicarbonyl compounds, cyanophosphorylation, acyl phosphonate, diethyl cyanophosphonate.

ÖZ

SİKLİK AROMATİK ASETOKSİ KETONLARIN BAEYER VİLLİGER YÜKSELTGENMESİYLE KİRAL LAKTONLARIN SENTEZİ

2-PROPİNİL-1,3-DİKARBONİL BİLEŞİKLERİNİN PİROL OLUŞTURMAK İÇİN HALKALAŞMA TEPKİMELERİ

AÇİL FOSFONATLARIN DİETİL SİYANOFOSFONATA EKLENMESİ

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Siklik ketonların kiral Baeyer-Villiger yüksetgenmeleri, organik kimyada önemli ara ürün ve enantiyoseçici sentezlerde sıkça karşılaşılan başlangıç maddeleri olan asimetrik laktonlara hızlı bir geçiş sağlar. İlk kısımda, α-hidroksi lakton ve α-hidroksi alkanoik asit türevlerine direk geçiş sağlayabilecek bir yöntem olan fonksiyonel ketonların özellikle de α-hidroksi ve asetoksi ketonların BV yükseltgenmeleri tanımlanmıştır. İndanon, tetralon ve kromanon türevlerinin $Mn(OAc)_3$ kullanılarak α-asetoksillenmesi ve sonrasında bu asetoksi ketonların enzim katalizörlüğünde kinetik ayrışımı her bir enantiomerin iyi bir kimyasal ve optik verimle eldesini sağlar. Kiral asetoksi ketonların oda sıcaklığında m-CPBA, CF_3SO_3H ve dichloromethane ile Baeyer-Villiger yükseltgenmeleri, istenen

laktonları rasemikleşme olmadan verir. Lakton oluşumu sırasında, fenil grubu seçici bir şekilde göç eder. Laktonların yumuşak koşullarda hidrolizi fenolik α-hidroksikarboksilik asit türevlerini verir.

Organik kimyada önemli yapı taşları ve sentetik dönüşümlerde önemli başlangıç maddeleri olmalarının yanı sıra birçok biyolojik aktiviteye sahip doğal ürünün yapısında bulunan pirol türevlerinin önemi sebebiyle, tezin ikinci kısımında 1,3-dikarbonil bileşiklerinden başlayarak asitle katalize edilmiş halkalaşma tepkimesiyle 1,2,3,5-tetrasübstitüe pirol türevleri sentezleme konusunda uygulanabilir bir yöntem sunulmuştur. 1,3-dikarbonil bileşiklerinin propargil bromür ile alkillenmesi daha sonra da primer amin ve katalitik miktarda trifloroasetik asit (TFA) eklenmesiyle tek basamakta gerçekleşen dönüşüm, yüksek verimlerle pirol türevlerini verir.

Tezin üçüncü kısmı, çeşitli alkil ve aril açil fosfonatların dietil siyanofosfonat (DEPC) varlığında ve KCN katalizörlüğünde siyano-fosforilasyon reaksiyonlarını tanımlar. Açil fosfonatların DEPC ile reaksiyonları, kuaterner α-hidroksi karboksilik asitlerin ve fosfonat içeren β-aminoalkol türevlerinin önemli başlangıç maddeleri olan polifonksiyonel siyanohidrin türevlerini verir.

Anahtar kelimeler: Baeyer Villiger yükseltgenmesi, fenolik α-hidroksikarboksilik asit, asimetrik lakton, 1,2,3,5-tetrasübstitüe piroller, halkalaşma, dikarbonil bileşikleri, siyanofosforilasyon, açil fosfonat, dietil siyanofosfonat.

To My Father,

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CHAPTER 1

INTRODUCTION

1.1. Synthesis of chiral lactones via the Baeyer-Villiger oxidation of cyclic aromatic acetoxy ketones

1.1.1. Baeyer Villiger oxidation and applications in organic chemistry

The Baeyer-Villiger oxidation of ketones is an important and interesting reaction because of its large number of applications.[1] In 1899, Adolf Baeyer and Victor Villiger reported the oxidation of menthone **1** to the corresponding lactone **2** (Figure 1.1) using a mixture of sodium persulfate and concentrated sulfuric acid (Caro's acid).[2]

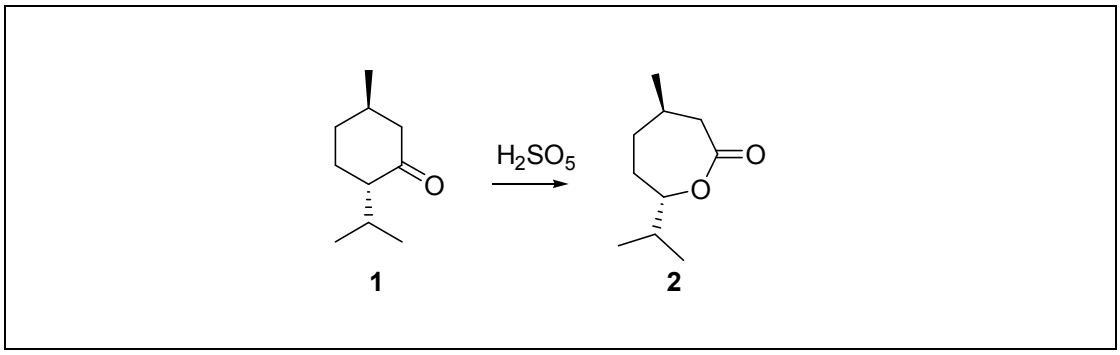


Figure 1.1. Oxidation of menthone with Caro's acid.

The persulfuric acid was subsequently replaced by an organic peracid, and the Baeyer-Villiger (BV) reaction became one of the most well-known and widely applied reactions in organic synthesis. Its success is largely due to its versatility:
(i) A variety of carbonyl compounds can be oxidized; that is, ketones are converted into esters, cyclic ketones into lactones, benzaldehydes into phenols, or carboxylic acids and α-diketones into anhydrides. (ii) A large number of functional groups are tolerated. (iii) The regiochemistry is highly predictable with the migratory aptitude being tertiary alkyl > cyclohexyl > secondary akyl > benzyl > phenyl > primary alkyl > methyl.[3] (iv) The reaction is generally stereoselective; that is, the migrating group retains its configuration. (v) A wide range of oxidants may be used with their activity decreasing in the order: CF_3CO_3H > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > p-nitroperbenzoic acid > m-CPBA, HCO_3H > $C_6H_5CO_3H$ >CH_3CO_3H >> H_2O_2 > t-BuOOH. Among these oxidizing agents, m-chloroperbenzoic acid (m-CPBA) is the most commonly used because it provides a simple and efficient alternative to the existing procedures for this reaction, notwithstanding the fact that it requires sometimes prolonged reaction time.[4] To enhance its reactivity, the combined use of the reagent with an appropriate promoter such as sulfonic acids, Nafion-H, CF_3COOH, hydrotalcite, and $SnCl_4$ has become an increasingly important tool. More recent reagent systems include the magnesium salt of monoperoxyphthalic acid (MMPP), sodium perborate, hydrogen peroxide in the presence of boron trifluoride or diselenides. Catalytic Baeyer-Villiger oxidations are also feasible with methyltrioxorhenium and hydrogen peroxide.

The generally accepted mechanism for the BV oxidation is a simple two-step reaction that involves the so-called Criegee intermediate or adduct. In the first step, a peroxide attacks the polarized C=O bond. The second step follows a concerted pathway[5] (Figure 1.2).

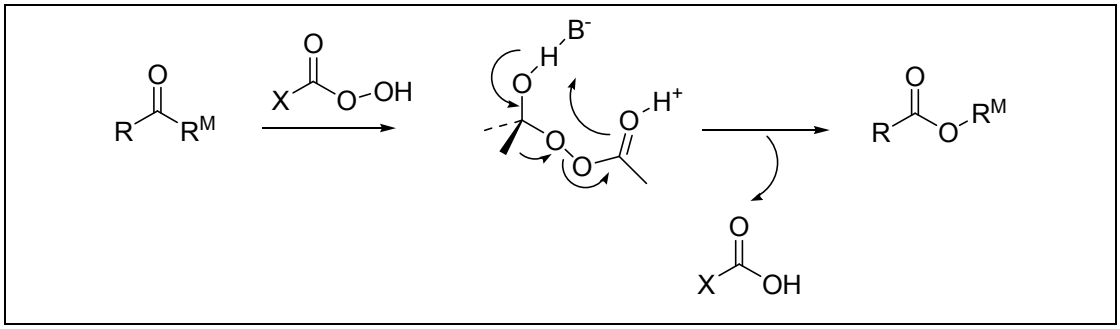
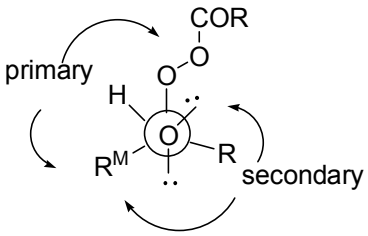


Figure 1.2. Mechanism for BV reaction as proposed by Criegee.

The salient features of the mechanism are:

1) Retention of the stereochemistry by the migrating group.
2) Migration is concerted by the departure of the leaving group. The concerted step is the rate determining.
3) Migrating groups with greater electron donating power have correspondingly greater migratory aptitude because of the increased ability to stabilize a positive charge in the transition state. This renders stereoselectivity to the oxidation of unsymmetrical ketones.
4) Migration is favored when the migrating (R^M) group is antiperiplanar to the O-O bond of the leaving group; this is konown as the primary stereoelectronic effect. The antiperiplanar alignment of the lone pair of electrons on oxygen with the migrating group is termed as the secondary steroelectronic effect;



5) Electron-withdrawing groups on the peroxy acid and peroxide enhance the rate of rearrangement.

It should be noted that in many reactions the two steps have activation energies that are in the same order of magnitude. Hence, catalysts may need to facilitate both steps of the reaction. A more detailed mechanism (Figure 1.3) shows the possible mechanisms by which catalysts may improve BV reactions.

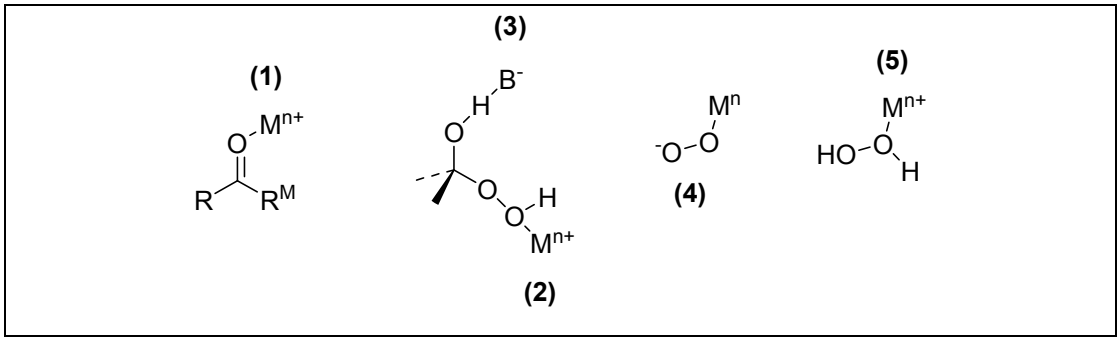


Figure 1.3. Electrophilic and nucleophilic activation of the BV reaction.

Here, one can distinguish (1) electrophilic activation of the substrate, (2) electrophilic activation of the intermediate, (3) nucleophilic activation of the intermediate, (4) nucleophilic activation of (hydrogen) peroxide and (5) electrophilic activation of (hydrogen) peroxide.

1.1.1.1. Electrophilic activation of the substrate

The action of acids (H^+ or metal cations) is in part to activate the carbonyl functionality toward nucleophilic attack of peroxide or peracid via increasing the polarization of the C=O double bond (Figure 1.3, intermediate 1)

One example of transition metal-catalyzed electrophilic activation of substrates is the platinum-CF_3 system, described below, which was developed in the group of Strukul[6] (Figure 1.4).

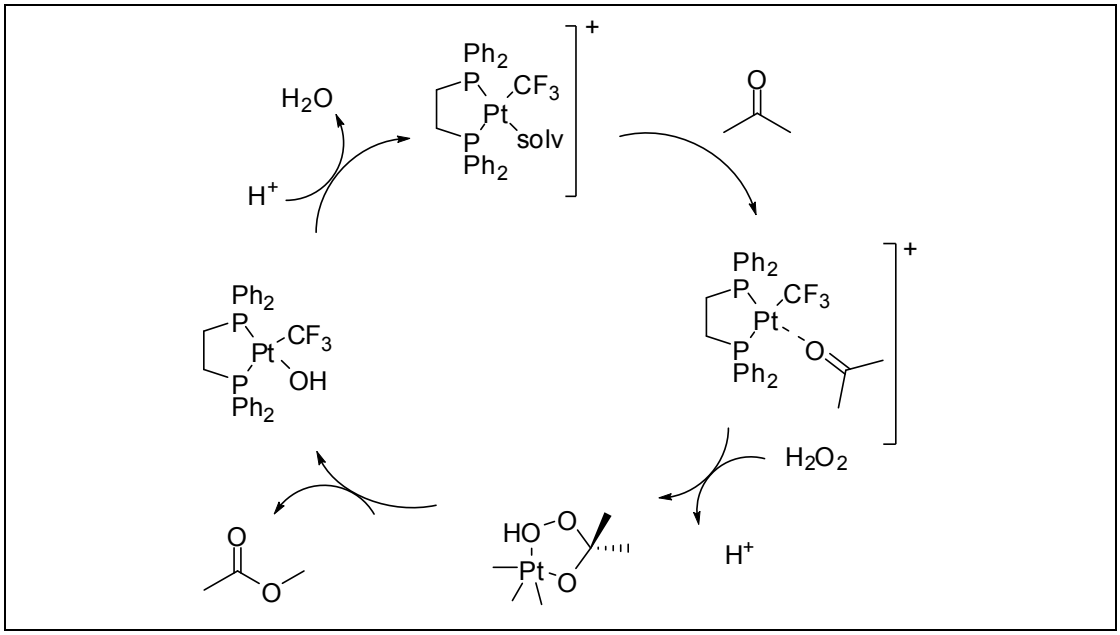


Figure 1.4. BV oxidation with $(dppe)Pt(CF_3)]^+$.

Activation of the ketone via coordination to Lewis acids seems to be the most general way to activate substrates for BV oxidation. In this case, the ketone coordinates to an electron poor platinum center and becomes susceptible to attack of free hydrogen peroxide.

1.1.1.2. Electrophilic activation of the intermediate

In BV reactions with peracids as oxidants, strong acids, such as CF_3CO_2H, may also catalyze the rearrangement step via protonation of the carbonyl functionality of the leaving group (Figure 1.5). As this reaarrangement step is usually rate limiting, the catalyst has a large effect here.

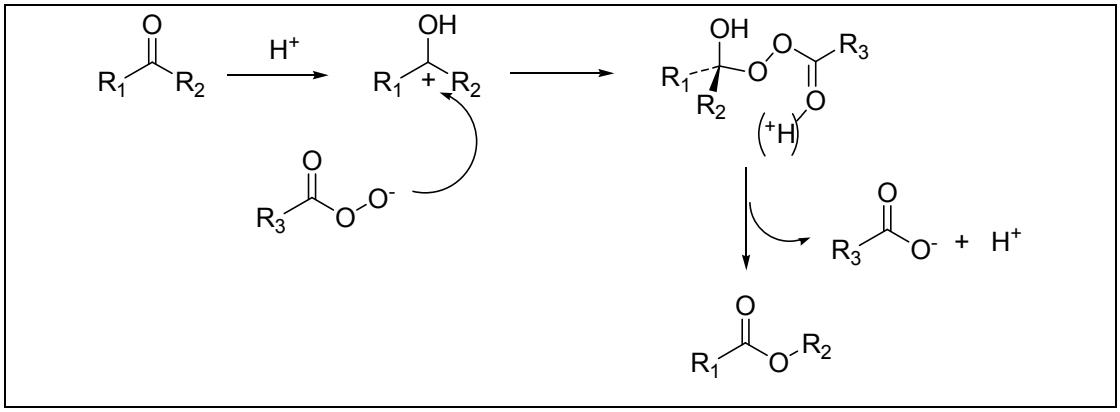


Figure 1.5. Acid-catalyzed BV oxidation with peracids as the oxidant

Activation of the intermediate hydroperoxy adduct is similar to activation of the acylhydroperoxy intermediate. A Lewis acid may also facilitate the migration step, via coordination or protonation of the hydroxide (alkoxide), which is otherwise a very poor leaving group. In most if not all cases, Lewis acid catalysts facilitate both steps of the reaction.

1.1.1.3. Nucleophilic activation of the intermediate

On the basis of the mechanism depicted in Figure 1.5, it is difficult to imagine base catalysis to activate the intermediate. Base catalysis was observed when bicarbonate was added to a solution of m-CPBA and a bicyclic ketone in dichloromethane.[7]

The reaction rate nearly doubled, which was described to an accelerated rearrangement step of an anionic Criegee adduct as compared to the neutral adduct (Figure 1.6).

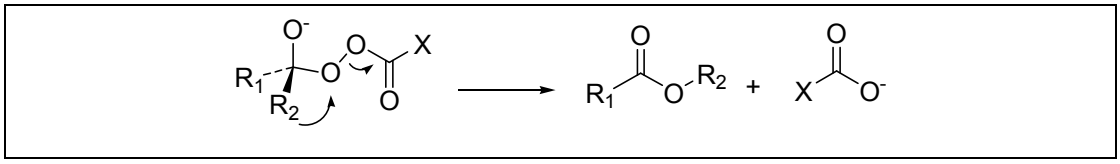


Figure 1.6. Rearrangement of anionic Criegee adduct

Renz and Meunier noted in their review that in the reaction mentioned above, bicarbonate also removed the coproduct, m-CBA, from the reaction mixture via deprotonation and precipitation.[8] In this way, the m-CBA could not compete with m-CPBA for the substrate, resulting in an increase in rate.

Although BV reactions are sometimes carried out under neutral to basic conditions to avoid acid-catayzed side reactions, base cataysis is not commonly observed in BV reactions with hydrogen peroxide.

1.1.1.4. Nucleophilic activation of the peroxide

Very few transition metals can catalyze BV reactions with hydrogen peroxide. The early transition metals (Ti, V, Mo, and W) may form peroxo complexes with hydrogen peroxide, but these are generally electrophilic in nature. Therefore, these complexes are active in, for example, epoxidation via electrophilic attack an preferably electron-rich olefins. A nucleophilic attack on the partially positively charged carbon of the C=O functionality is unlikely to occur with these complexes. Such a reaction seems to be the domain of the late transition metal peroxo complexes such as (ligand)$Pt(O)_2$ or (ligand)$Pd(O)_2$, which are partially nucleophilic in nature.

MTO is an extremely active catalyst for the epoxidation of olefins with aqueous hydrogen peroxide.[9] The active bisperoxo intermediate gives an electrophilic attack on the double bond of the alkene. Therefore, a proposed nucleophilic attack of the same bisperoxo complex on the C=O double bond of, e.g., cyclobutanone (Figure

1.7), would seem unlikely. However, with the evidence available until now, it appears that MTO can exhibit electrophilic properties in epoxidation and nucleophilic properties in BV oxidation.

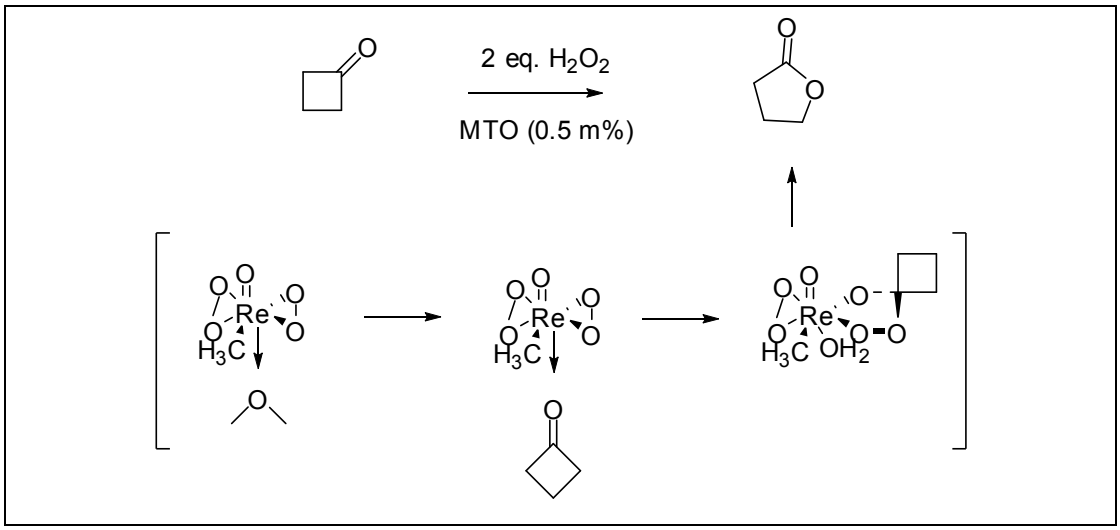


Figure 1.7. MTO-catalyzed oxidation of cyclobutanone

1.1.1.5. Electrophilic activation of the peroxide

In a recent study, Brinck et al. showed that in the BF_3-catalyzed reaction of acetone and hydrogen peroxide, the Lewis acid facilitated the reaction via coordination to hydrogen peroxide, making the latter more acidic and increasing hydrogen bonding to the carbonyl functionality[10] (Figure 1.8).

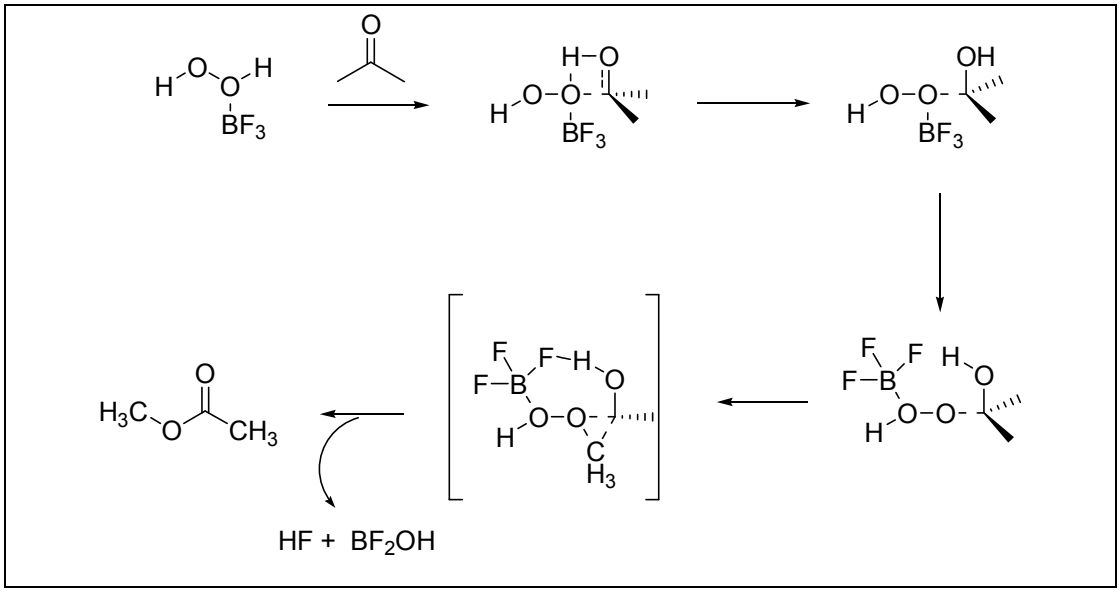


Figure 1.8. BF_3-catalyzed oxidation of acetone with hydrogen peroxide

As was pointed out above, many early transition metals can coordinate to hydrogen peroxide, making it more electrophilic and more eager to attack electron rich subtrates such as olefins. Such electrophilic activation, however, would decrease the tendency to attack already electron-poor ketones in a BV reaction.

1.1.2. Baeyer Villiger oxidation of cyclic ketones

The transformation of cyclic ketones into lactones by the Baeyer–Villiger reaction has been widely employed for the synthesis of many natural and other valuable products. As a result, much research has been devoted to developing a variety of methods and conditions for the reaction. From an industrial point of view, oxidation of cyclohexanone to ε-caprolactone is one of the more interesting BV reactions. The product lactone is polymerized and used in foams, biodegradable plastics, etc. The reaction is often carried out with oxygen in combination with a sacrificial aldehyde such as acetaldehyde or benzaldehyde[11] (Figure 1.9). Alternatively, oxidation is carried out with a carboxylic acid, which is converted in situ to its corresponding peracid by the action of hydrogen peroxide plus an acid catalyst.

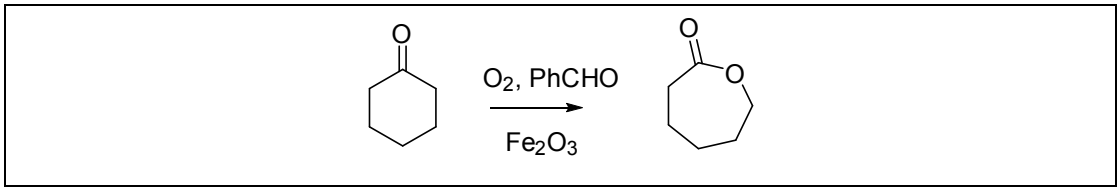


Figure 1.9. Oxidation of cyclohexanone to ε-caprolactone.

Successfull oxidation of a 4-chromanone derivative **3** was achieved with a β-methoxy substituent present in the substrate (Figure 1.10).[12]

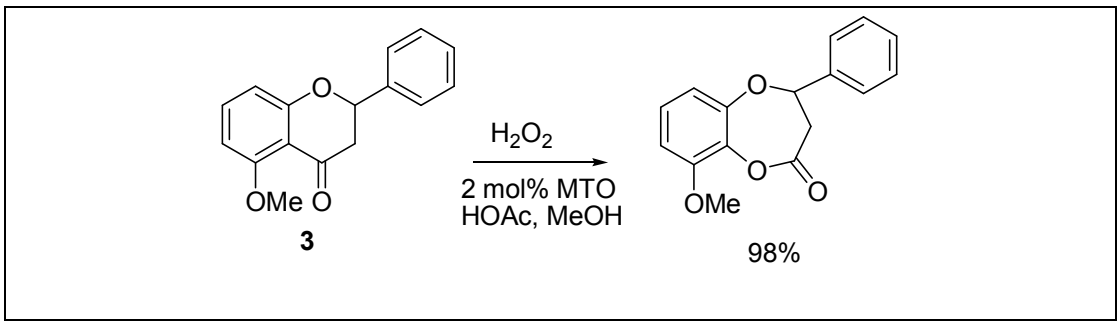


Figure 1.10. MTO-catalyzed oxidation chromanone derivative.

Recently, bismuth triflate has also shown to be a very efficient catalyst for the BV oxidation of cyclic ketones using m-CPBA(Figure 1.11).[13]

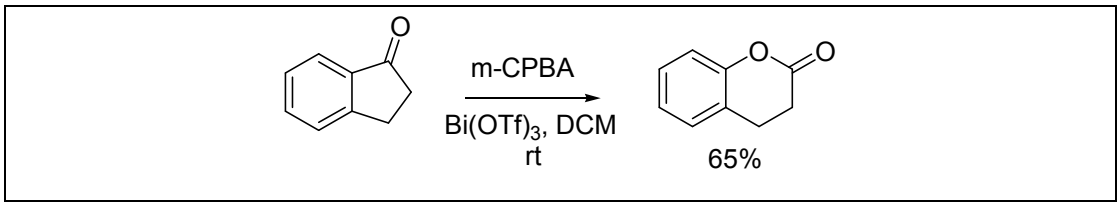


Figure 1.11. $Bi(OTf)_3$-catalyzed oxidation indanone derivative.

Additionally, the catalyst could be recovered easily from the reaction mixture and reused without significant loss of catalytic activity. Further studies are currently underway to perform such reactions under heterogeneous conditions.

Several achievements have been disclosed in the use of rare earth metal trifluoromethanesulfonates such as $Re(OTf)_3$ and also trifluoromethanesufonic acid (TfOH) for BV oxidation with m-CPBA (Figure 1.12).[14]

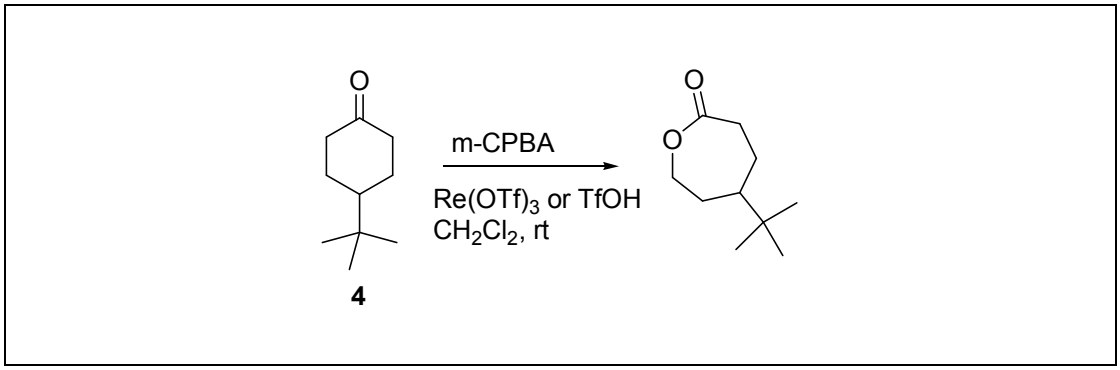


Figure 1.12. Catalytic acitivity of rare earth metal triflate and TfOH in the BV oxidation of **4**

In the oxidation of 4-*t*-butylcyclohexanone **4**, the most satisfactory result was obtained for the reaction using TfOH as the catalyst. Apparently, the role of $Sc(OTf)_3$ and TfOH in these Baeyer-Villiger oxidations can be attributed to their respective strong coordinating and protonation ability.

Sodium perborate has also been used successfully in the BV oxidation of aryl and diaryl ketones.[15] More recently the sodium perborate/formic acid system has found a wider application in the formation of simple monocyclic lactones. It is also cheap, safe and readily alternative to the commonly used peracetic acid for the Baeyer-Villiger oxidation step of the Corey aldehyde synthesis.[16] Chloroketo acid **5** is smoothly converted by sodium perborate tetrahydrate in formic acid to the chloroketolactone **6** in 66% isolated yield (Figure 1.13).

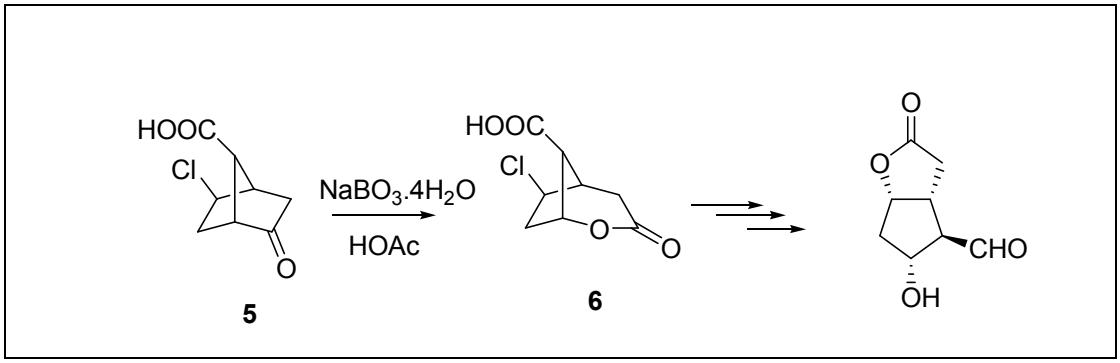


Figure 1.13. Synthetic pathway for the Corey aldehyde

1.1.3. Further Interesting Aspects

During one century of Baeyer-Villeger oxidation, the reaction has been used in the preparation of many different organic molecules. Many examples are collected in the recent review of Krow. Polycyclic substrates showed often an abnormal selectivity for the migration step in the BV rearrangement which was influenced by many different factors. Noyori has postulated stereoelectronic conditions for the transition state based on remote substituent influences.[17] Metal-catalyzed Baeyer-Villiger oxidations have been recently reviewed by Strukul.[18] It should be noted that the BV reaction is easily performed by enzymes such as flavin-dependent peroxygenases. Many cyclic ketones are oxidized by the cyclohexanone oxygenase isolated from the bacteria Acinetobacter, or by modified yeast as well as by microorganisms (Figure 1.14).[19]

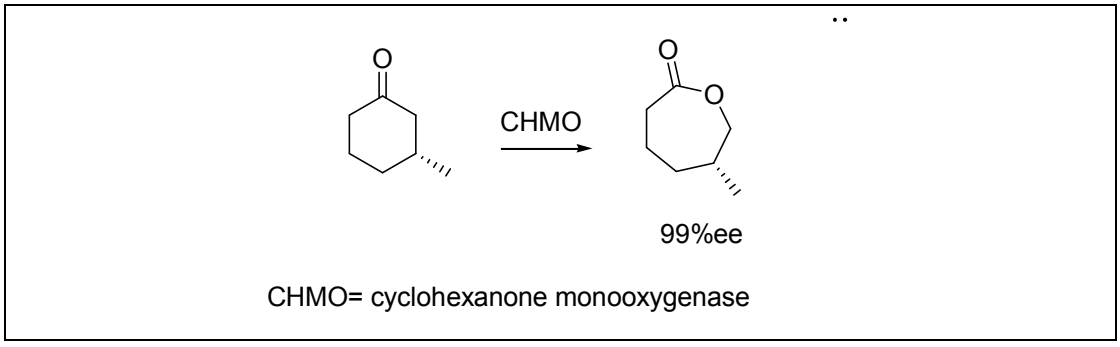


Figure 1.14. Monooxygenase mediated BV oxidation

1.1.4. $Mn(OAc)_3$ mediated oxidation of enones

Procedures for the selective oxidation of common functional groups occupy a central position in the synthesis of complex natural products. In 1976, Williams and Hunter reported that the $Mn(OAc)_3$ oxidation of enones led to modest yields of α-acetoxyenones.[20] $Mn(OAc)_3$ mediated α-oxidation of enones was applied to several enones with a variety of functional groups. These interesting and useful intermediates were used for several transformations in synthetic organic chemistry. Many target specific compounds were synthesized using this oxidation. Especially protected 1,2- and 1,3-diketones with and without functional groups were acetoxylated in good to excellent yield without affecting the protecting groups.

The $Mn(OAc)_3$ oxidation was also applied to the cyclic and noncyclic aromatic ketones, in which the acetoxylation products were obtained in good to excellent yields. The oxidation worked with high selectivity, in which only α-oxidation products were obtained in high yields. These interesting products were not readily available by using other oxidation methods and can be used for several interesting conversions to obtain important and useful materials.[21] By the reinvestigation of the synthetic and mechanistic aspects of $Mn(OAc)_3$ mediated oxidation of enones, the successful α-acetoxylation of a great variety of substrates was reported, in which there were 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 eq.) is generally used for acceptable yields and reaction times; (2) many contradictory results can be seen when the literature reports are closely inspected.[22]

These inconsistencies along with the use of an undesirable amount of $Mn(OAc)_3$ reduced the value of the method. 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 great importance from a synthetic and economic point of view. Demir and coworkers reported their investigation of their understanding of the nature of this reaction, along with increasing its efficiency and reproducibility. They presented an

improved procedure that was based on the use of acetic acid as a co-solvent. According to this procedure, AcOH shortened the reaction time and increased the yields. The role of acetic acid could be related to an increased solubility of $Mn(OAc)_3$ in the reaction mixture. From a synthetic point of view, excellent results were obtained for a variety of structurally diverse and synthetically important enones under optimized conditions.

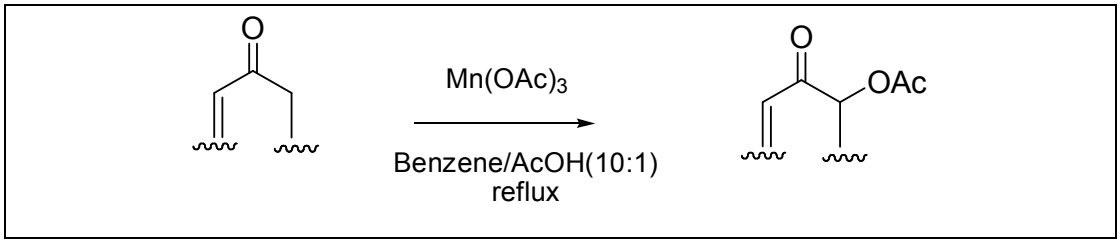


Figure 1.15. Simple methods for the direct acetoxylation of enones

The mechanism for the oxidation of enones to α-acetoxyenones was not fully described. Several mechanisms were suggested for this oxidation. One might expect the formation of a metal enolate followed by acetate transfer (Figure 1.16), analogous to the lead(IV) acetate oxidation.[20,23] However, since the oxidation of carbonyl compounds with $Mn(OAc)_3$ was reported to involve an α-oxo radical resulting from the oxidation of an enol or enolate anion by $Mn(OAc)_3$, it is possible that this reaction also proceeds *via* the formation of an α-oxo radical followed by ligand transfer, (Figure 1.17) in order to yield the product.

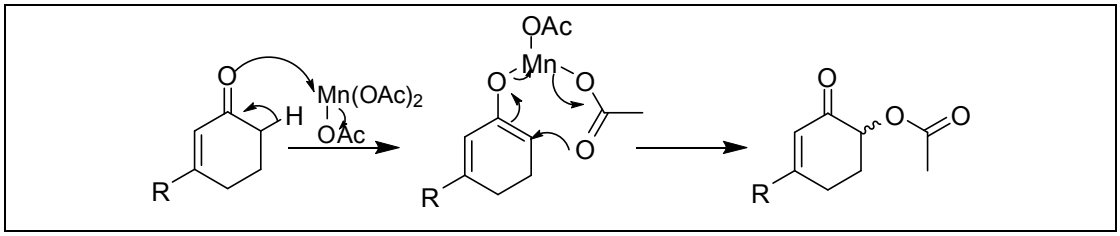


Figure 1.16. First suggested mechanisms about α-acetoxylation with manganese (III) acetate

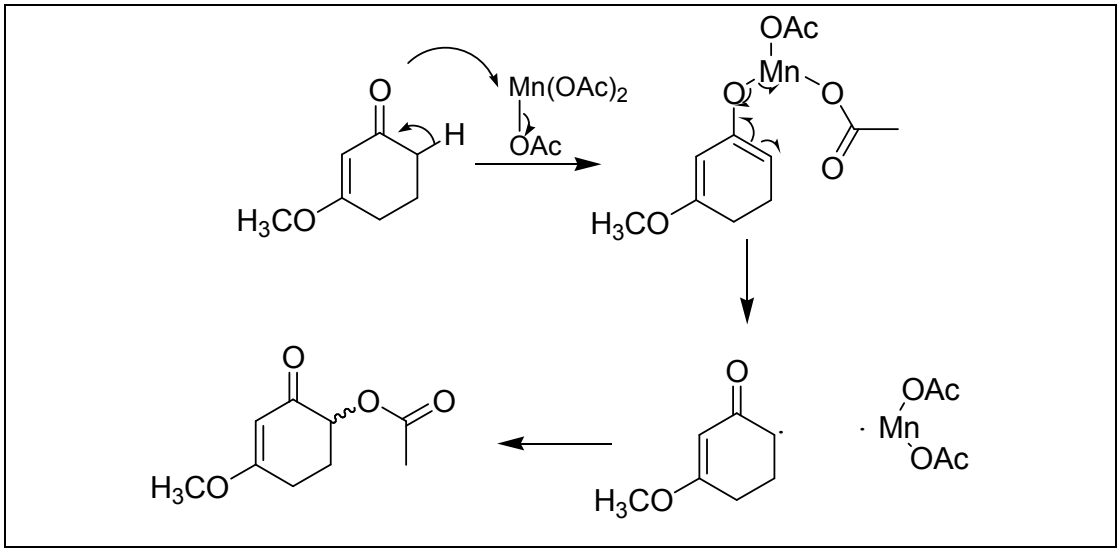


Figure 1.17. Second suggested mechanisms about α-acetoxylation with manganese (III) acetate

The α-acetoxyenones as starting materials opened an entry for the synthesis of their enantiomers by using enzymatic kinetic resolution, which are not readily available using other methods (Figure 1.18). A chemoenzymatic synthesis of pharmacological interesting compounds in optically pure form, such as 2-hydroxypropiophenones, 2-hydroxyindanone, and 2-hydroxytetralone from an appropriate enone, was described. $Mn(OAc)_3$ mediated acetoxylation followed by enzyme-mediated hydrolysis afforded the products in high enantiomeric excess.

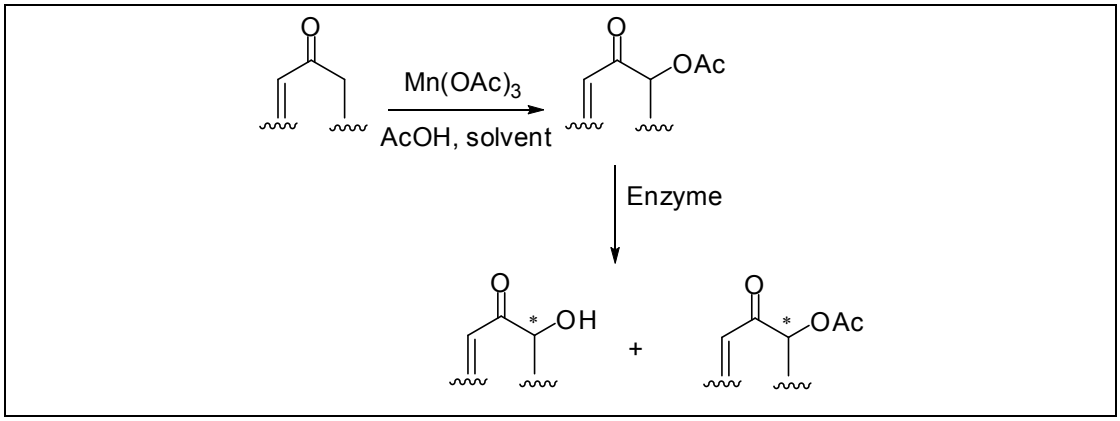


Figure 1.18. $Mn(OAc)_3$ mediated acetoxylation followed by enzymatic kinetic resolution

1.2. Novel annulation reactions of 2-propynyl-1,3-dicarbonyl compounds to form pyrroles

1.2.1. Pyrroles, strategies for pyrrole synthesis, properties

Pyrrole derivatives are very important compounds as they occur in a large number of natural products and display a variety of physiological activities[24] in particular, 1,2,3,5-tetrasubstituted pyrrole derivatives[25] are biologically active and have been proven to show antibacterial[26], antiviral, anti-inflammatory and antioxidant activities and to inhibit cytokine-mediated diseases.[27] Additionally, they have been found to show potent inhibiting platelet aggregation and anti-hypertensive activities.[28] Moreover, they are important starting materials for various synthetic transformations. Finally, they are widely used in materials science. These properties of pyrrole derivatives let them be crucial in the synthesis of many drugs particularly anticancer drugs.

Although many efficient synthesis of pyrroles have been reported, developing new synthetic methods remains an attractive goal. One-pot multicomponent processes have recently gained a considerable and steadily increasing academic, economic, and ecological interest because they address very fundamental principles of synthetic efficiency and reaction design.[29]

In many recent studies on the construction of the pyrrole ring, attack of nitrogen to the activated triple bond is the original idea for the pyrrole ring closure.[30] This is valid for the construction of other heterocyclic five-membered rings in many recent studies. This attack may lead to either 5-exo-dig or 5-endo-dig type cyclization according to the number of carbon atoms between nitrogen and triple bond. If there exist 3 carbon atom between nitrogen and triple bond 5-endo-dig type cyclization takes place. In the case of 4 carbon atom ring closure is 5-exo-dig one (Figure 1.19).

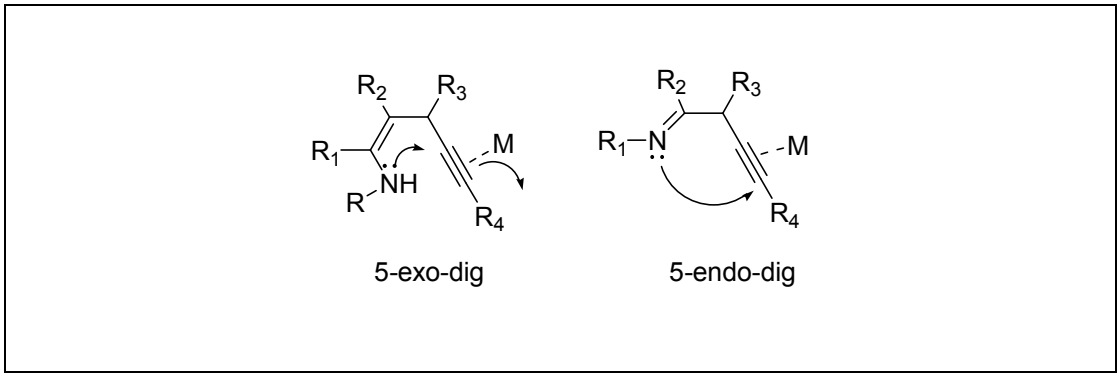


Figure 1.19. Construction of the pyrrole ring

1,3-Dicarbonyl compounds are versatile intermediates for the synthesis of pyrrole derivatives.[31] Pioneering work on the synthesis of pyrroles from 1,3-dicarbonyl compounds was carried out by Hantzsch in 1890. Many studies have been published on the synthesis of pyrroles using the principle of Hantzsch' method starting from 1,3-dicarbonyl compounds.[32]

1.2.1.1. General Synthesis of Pyrrole Derivatives

There are three generally important approaches to pyrroles from nonheterocyclic precursors. These are; Paal-Knorr, Hantzsch and Knorr synthesis of pyrroles. In addition to these famous methods, metal mediated cyclization reactions have become popular recently.

1.2.1.1.1 Paal-Knorr Pyrrole Synthesis

Pyrroles are formed by the condensation reaction of ammonia or a primary amine with 1, 4 dicarbonyl compound. Nucleophilic addition of the amine to the two carbonyl carbon atoms and the loss of the two moles of water affords the pyrrole (Figure 1.20). This method provides a convenient method for the synthesis of pyrroles having alkyl or aryl substituents in both 2- and 5- positions.

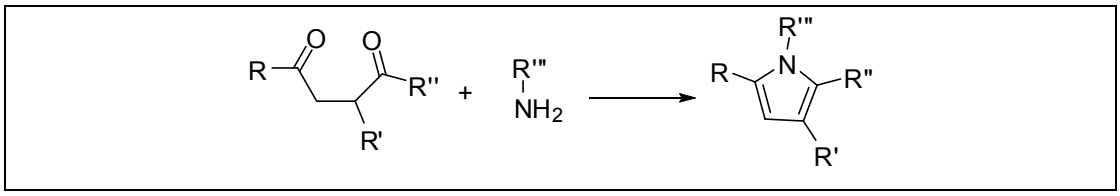


Figure 1.20. Paal-Knorr pyrrole synthesis

The key strategy for the synthesis of desired pyrrole derivative is the construction of modified 1,4-dicarbonyl compound with desired substituents. It is the striking property of Paal-Knorr synthesis to lead many pyrrole synthesis methods for the construction of 1,4-dicarbonyl skeleton.

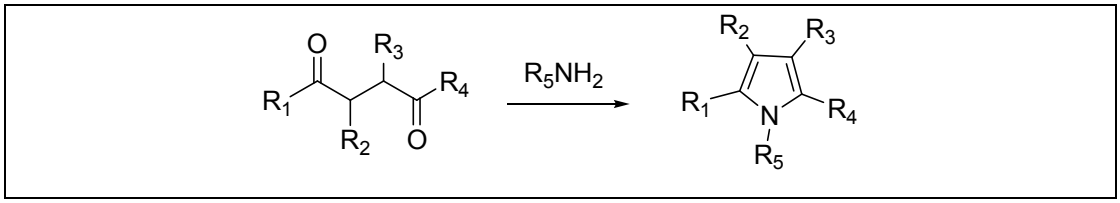


Figure 1.21. Key strategy of Paal-Knorr pyrrole synthesis

Different Paal-Knorr pyrrole synthesis methods differ only in the way that the 1,4-dicarbonyl skeleton is formed. For instance, Müller et al.[33] developped a novel one pot pyrrole synthesis method using the Paal-Knorr strategy. According to this method 1,2,3,5-tetrasubstituted pyrroles can be synthesized in good yields in a one-pot, three-step, four-component process by a coupling-isomerization-Stetter reaction-Paal-Knorr sequence of an electron-poor (hetero)aryl halide, a terminal propargyl alcohol, an aldehyde, and a primary amine (Figure 1.22).

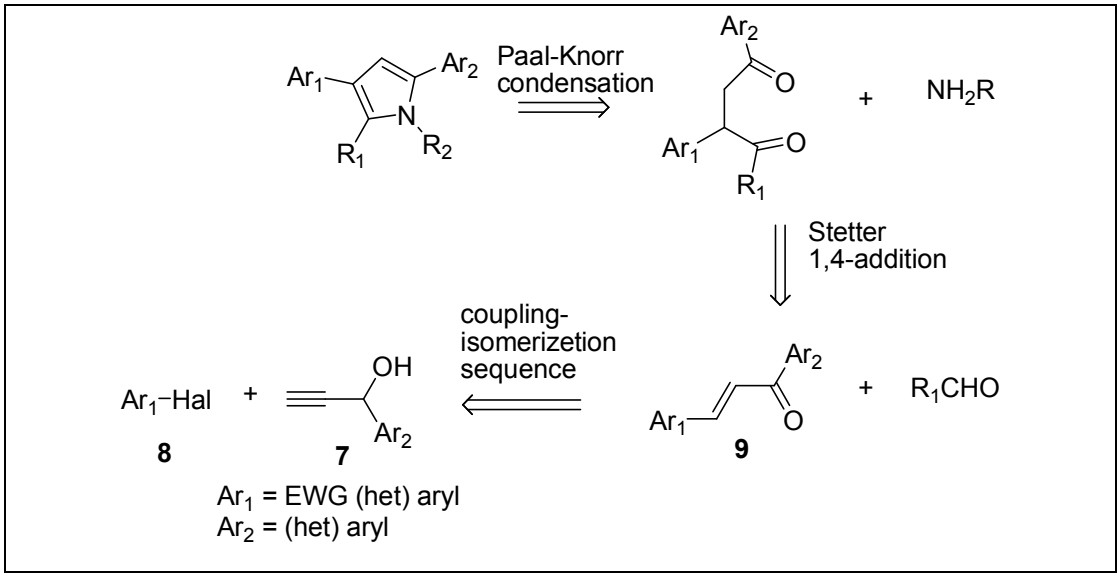


Figure 1.22. One pot pyrrole synthesis using Paal-Knorr strategy

Amarath has shown that meso- and dl-3,4-diethyl-2,5-hexanediones cyclize at unequal rates, and that the stereochemical configuration of the unchanged dione is preserved during the reaction.[34] A mechanism includes the cyclization of hemiacetal which is followed by different dehydration steps:

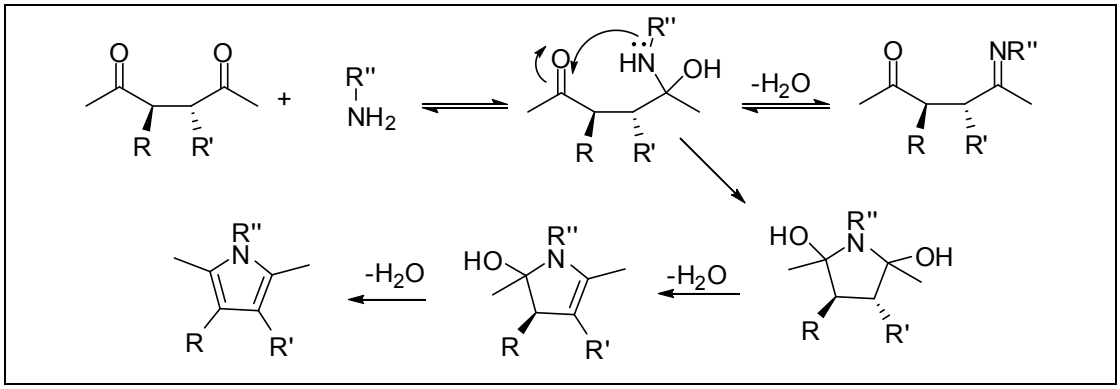


Figure 1.23. Application of Paal-Knorr mechanism on meso-3,4-diethyl-2,5-hexanediones

1.2.1.1.2. Hantzsch Pyrrole Synthesis

Substituted 2-alkylpyrrole-3-carboxylic esters **12** are conveniently prepared from the reaction of α-haloketone **10** or aldehyde with a α-ketoester **11** and ammonia or primary amines by a procedure generally referred as the Hantzsch synthesis (Figure 1.24).

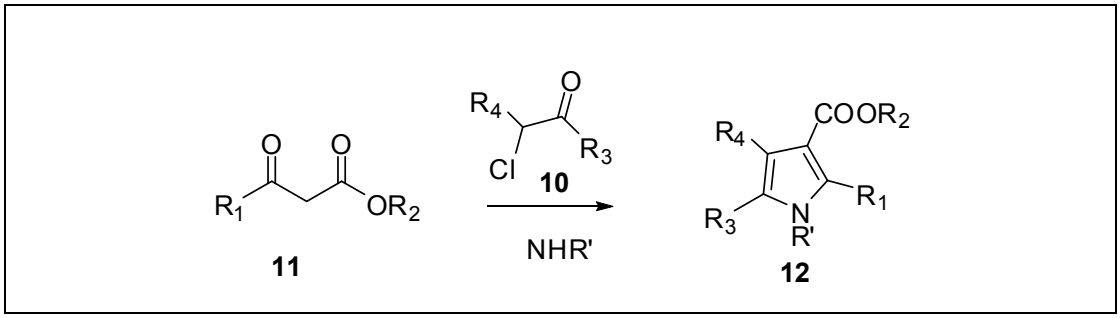


Figure 1.24. Hantzsch pyrrole synthesis

Since nucleophilic attack by ammonia on a α-chloroketone may occur either at the α-carbon atom, with the displacement of the halide ion, or on carbonyl group, there is the possibility that two isomeric pyrroles may be formed. The first reaction pathway leading to the initial formation of a α-amino ketone followed by the Knorr condensation is not observed. The first step of Hantzsch pyrrole synthesis is not the formation of the α-aminoketone or the attack of the carbanion on the α-haloketone, but the formation of an aminocrotonic ester **13** (α-amino acrylic ester) (Figure 1.25).

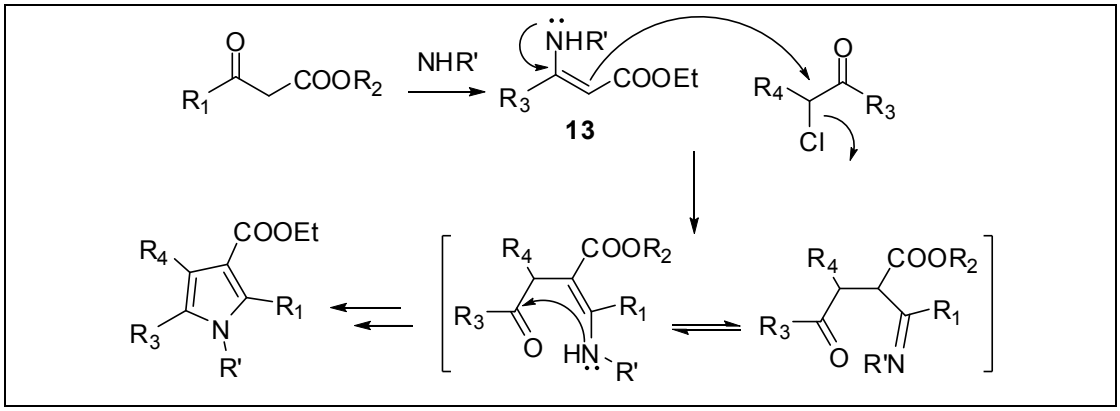


Figure 1.25. Mechanism of Hantzsch pyrrole synthesis

There are a number of important syntheses of pyrroles that are operated in the manner of the Hantzsch synthesis, despite having mechanisms of very different connectivity between the starting materials and the pyrrolic product. For example the reaction between 3-aminocrotonates with oxindole-3-ylidine derivatives in rexluxing toluene resulted in 2-pyrrolo-3'-yloxindoles in high yields. The 3-aminocrotonates behave as 1,3 dinucleophiles when utilized in ring closure reactions such as the Hantzsch pyrrole synthesis (Figure 1.26).

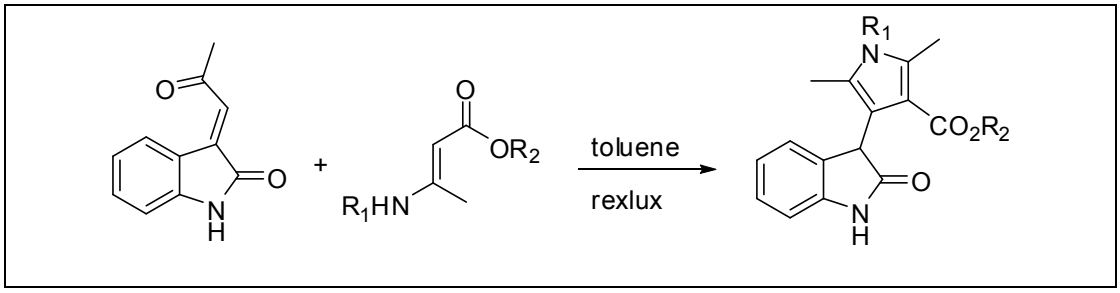


Figure 1.26. Application of Hantzsch pyrrole synthesis

1.2.1.1.3. Knorr Pyrrole Synthesis

The Knorr pyrrole synthesis is a widely used chemical reaction that synthesizes substituted pyrroles **16**. The method involves the reaction of an α-amino ketone **14** and a compound containing a methylene group α- to a carbonyl group **15**. (Figure 1.27). This method utilizes two components, the first one of which is the α-aminocarbonyl component **14** supplying the nitrogen and the carbon atoms at the second and third position of the pyrrole ring. The second component **15** supplies carbon atoms at the fourth and fifth position and must have a methylene group α- to carbonyl.

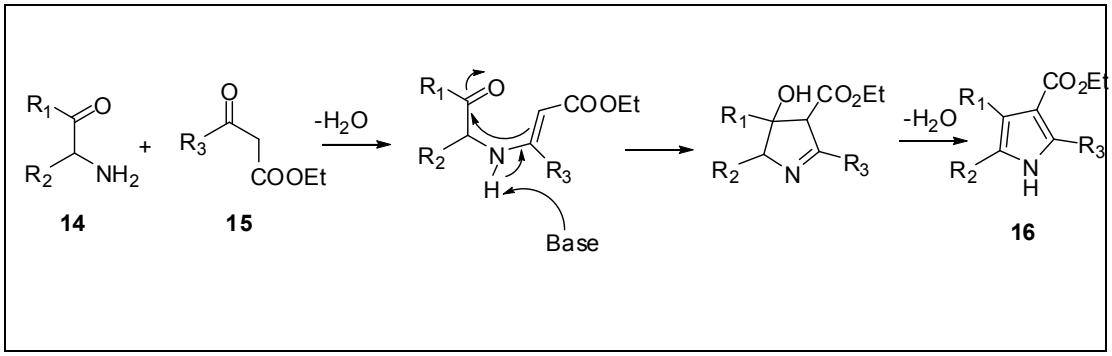


Figure 1.27. Mechanism of Knorr pyrrole synthesis

The reaction is proceeded at room temperature. Because α-amino-ketones self-condense very easily, they must be prepared *in situ*. Therefore, the utility of the reaction is limited by the tendency of α-aminoketones towards self condensation.[34] If the methylene ketone is not sufficiently reactive, the amino ketone will condense to form a pyrazine **17** instead of pyrrole **16** (Figure 1.28).[35] This condensation proceeds so readily that α-amino ketones are, in general, not capable of independent existence and must be isolated as hydrochlorides.

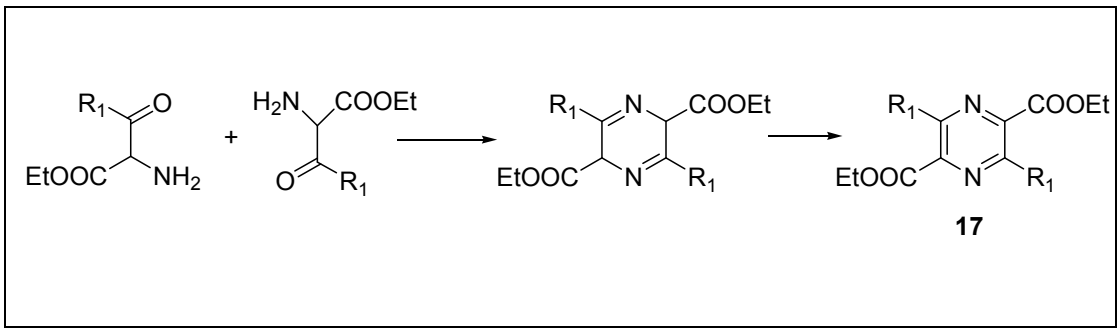


Figure 1.28. Limitation of the Knorr pyrrole synthesis

The Knorr synthesis works well only if the methylene group of the second component is further activated (for example as in the case of acetoacetic ester **18**) to enable the condensation leading to pyrrole to compete effectively with self

condensation of the α-aminocarbonyl component **19**. An alternative way of avoiding the difficulty in handling α-aminocarbonyl compounds is to prepare them in the presence of the second component, with which they are to react. Zinc-acetic acid or sodium dithionite can be used to reduce oximino groups to amino while leaving ketone and ester groups untouched (Figure 1.29).

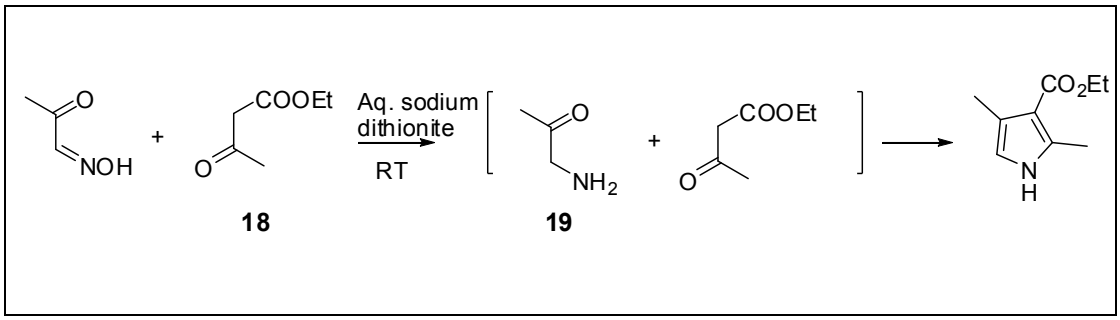


Figure 1.29. Alternative way of Knorr pyrrole synthesis

As mentioned before, Knorr synthesis is the most frequently applied method for the synthesis of pyrrole moiety. An example to the recent study in which Knorr synthesis is used for the construction of pyrrole ring was performed by Carey et al.[36] on the synthesis of SB-342219 which is a selective -opioid receptor antagonist and as such has undergone preclinical evaluation for the potential treatment of neuropathic pain. The synthetic pathway for this synthesis requires formation of pyrrole moiety in compound **21** starting from ketone **20** (Figure 1.30).

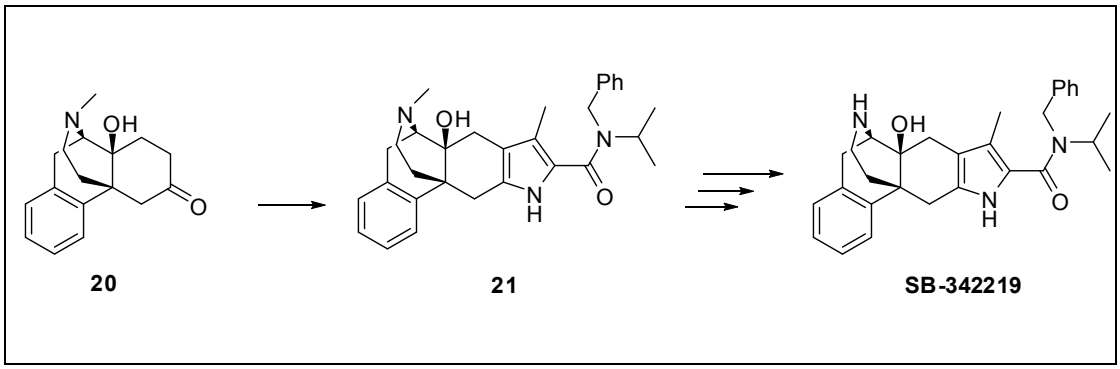


Figure 1.30. Application of the Knorr pyrrole synthesis

1.2.1.1.4. Metal-Mediated Ring Closure

Attack of nitrogen to the activated triple bond has become common strategy of synthesis of many heterocyclic derivatives, in particular pyrroles. However this attack often requires high activation energy. To overcome this drawback, triple bond must somehow be activated. For this purpose Lewis acids are used frequently.

A representative study for the 5-endo-dig type ring closure of pyrrole moiety has been performed by Hiroya et al. for the synthesis of indoles **22** starting from 2-ethynylaniline derivatives **23** with the use of Cu (II) salts in catalytic amount. General reaction is illustrated in Figure 1.31.

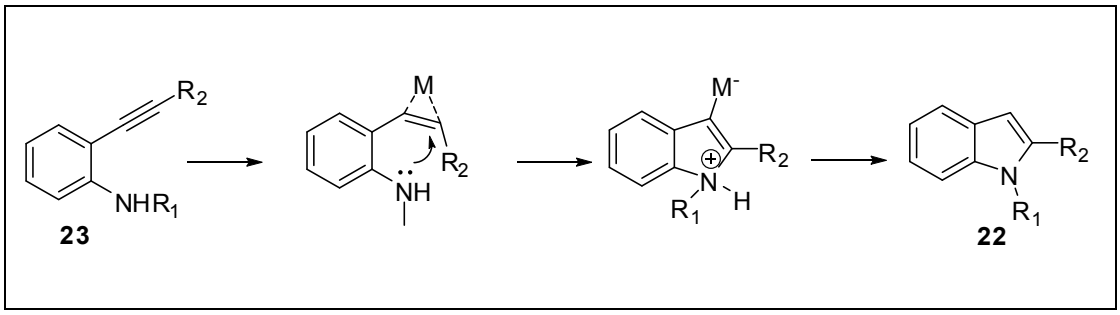


Figure 1.31. 5-endo-dig type ring closure reaction

The suggested mechanism for the Cu (II) salts catalyzed cyclization is summarized in Figure 1.32.

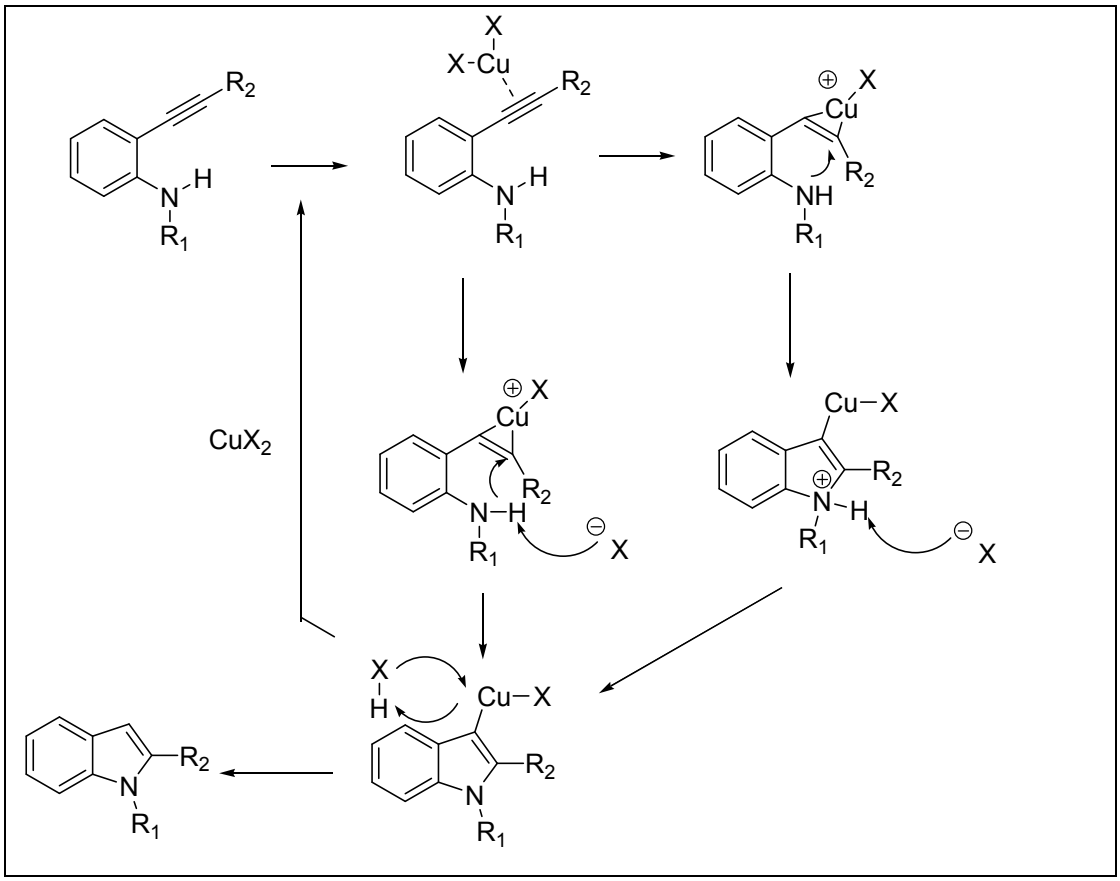


Figure 1.32. Cu (II) salt catalyzed pyrrole formation mechanism

In the case of 4 carbon atoms between "N" and triple bond, 5-exo-dig cyclization takes place. Gabriele et al. carried out a study with the Pd catalyzed cycloisomerization reaction to form pyrrole ring (Figure 1.33).

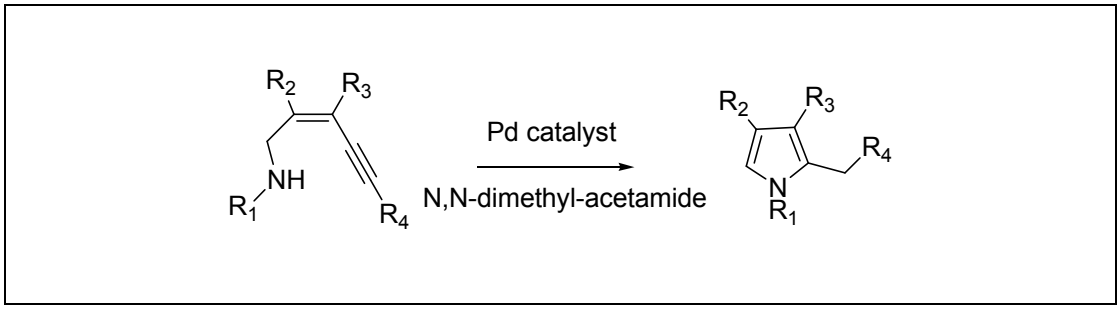


Figure 1.33. 5-exo-dig type ring closure reaction

Although Pd and Cu is frequently used for activation of triple bond for cyclization, Ru and Pt, Au, Ag metals have been used as well for both exo and endo type cyclizations.

A very recent publication from Dovey et al. is another example to this strategy.[42] In this study activation of triple bond was carried out by means of using $AgNO_3$ and the synthesis was achieved in one pot. The general mechanism is illustrated in Figure 1.34.

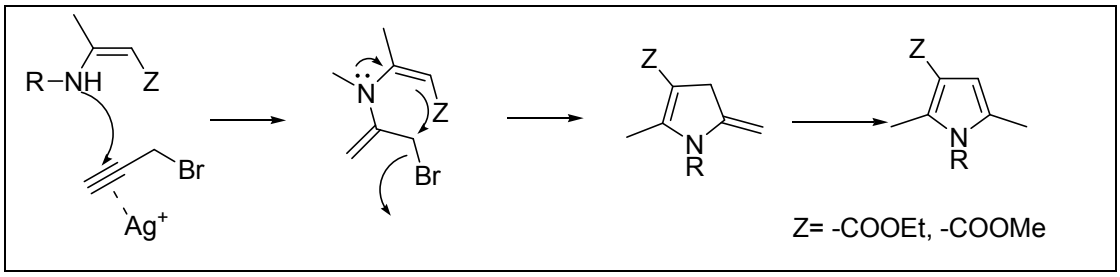


Figure 1.34. Activation of the triple bond by the $Ag(NO)_3$

1.2.2. Synthesis of pyrroles from 1,3-dicarbonyl compounds

1,2,5-trisubstituted-3-acylpyrrole derivatives were found to show potent inhibiting activity of platelet aggregation and were worthy of clinical testing as antihypertensive agents. During the structure activity relationship studies on these pharmaceutically relevant compounds, Arcadi et al.[39] developed a new methodology of the target 1,2,5-trisubstituted-3-acylpyrrole derivatives **24** through gold catalyzed amination/annulation reactions for the preparation of these compounds in homochiral form (Figure 1.35).

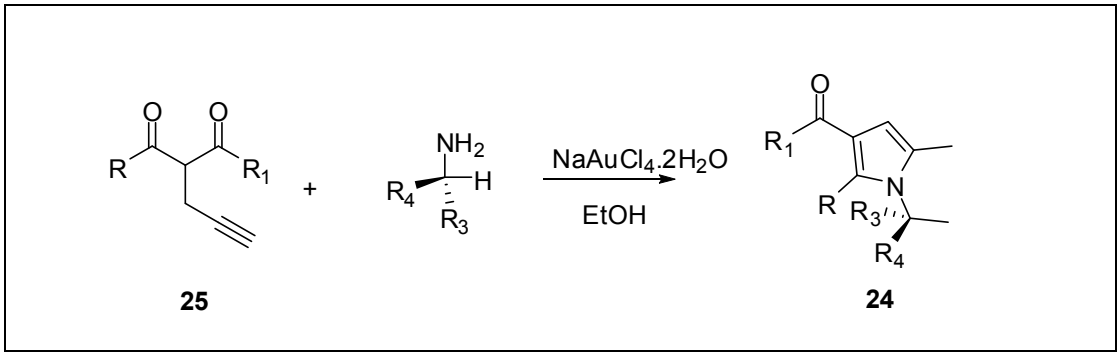


Figure 1.35. Gold catalyzed amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds

The reaction of primary amines with 2-propynyl-1,3-dicarbonyls **25** led to enaminone derivatives **26**, which undergo regioselective cycloamination to pyrroles under the catalytic action of $NaAuCl_4 \cdot 2H_2O$ (Figure 1.36). The above formation of pyrrole derivatives 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 **27**. Then the protonolysis of the Csp^2-Au bond and the isomerization afford the pyrrole derivatives **28** (Figure 1.36).

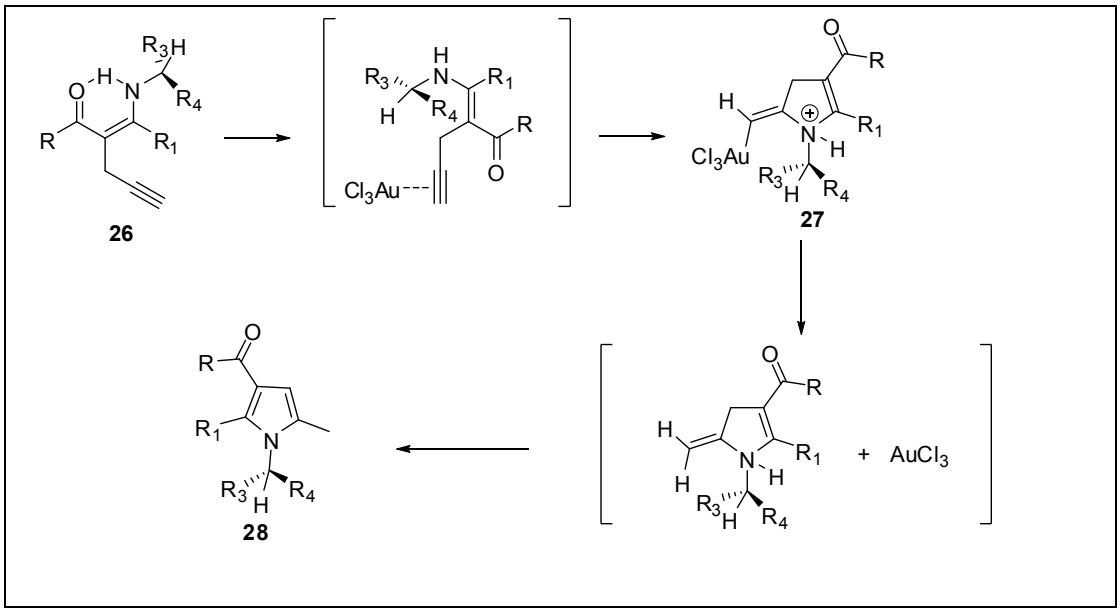


Figure 1.36. Mechanism for the gold-catalyzed pyrrole formation reaction

In addition to the method developed by Arcadi et al., Ferraz et al. described the synthesis of N-substituted pyrrole and tetrahydroindole derivatives from alkenyl 1,3-dicarbonyl compounds **29** via the formation of iodo-1,3-enamino esters **30** followed by dehydroiodination (Figure 1.37).[40]

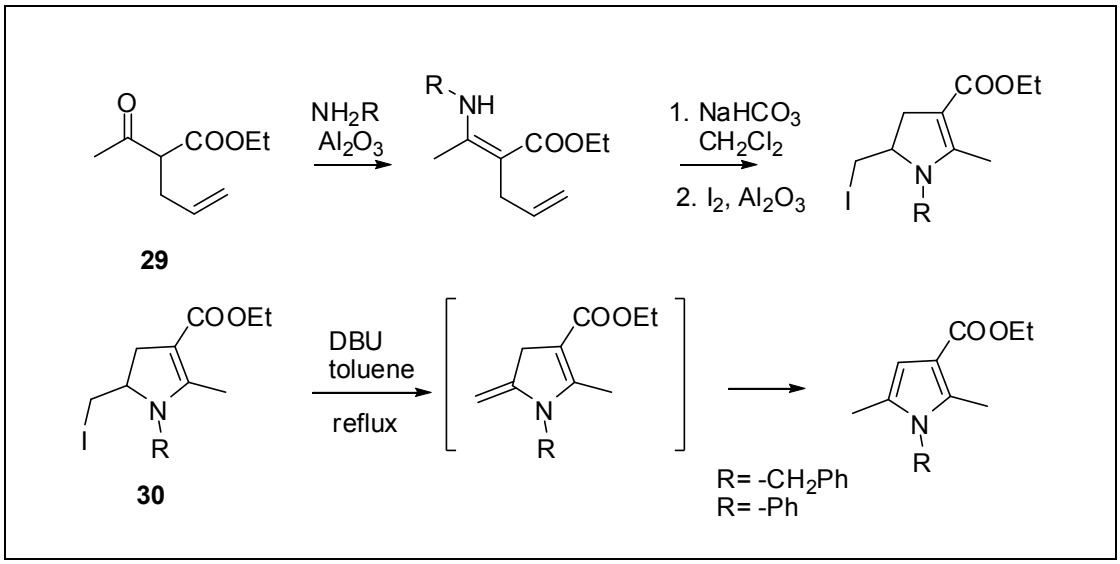


Figure 1.37. Synthesis of pyrroles from alkenyl 1,3-dicarbonyl compounds

Another study on the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives was performed by Demir et al. starting from 2-(2-bromoallyl)-1,3-dicarbonyl compounds **31**.[41] In this study, 1,3-dicarbonyl compounds were α-alkylated with 2,3-dibromoprop-1-ene followed with enamine formation. Then the isolated enamines **32** were led to the cyclization reaction to form pyrrole derivatives **33** (Figure 1.38).

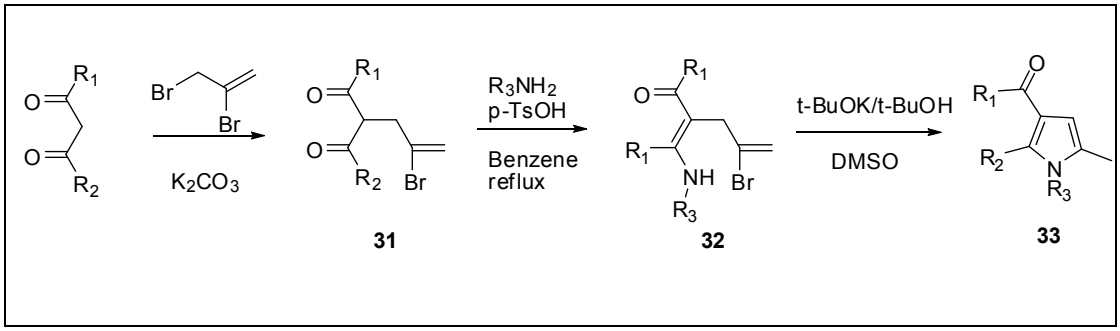


Figure 1.38. Synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives from -(2-bromoallyl)-1,3-dicarbonyl compounds

For the formation of pyrrole ring from enamines, two separate cyclization mechanism were suggested. Accoding to first mechanism the enamine could form either the allene **34** or alkyne intermediate after HBr elimination. The formation of allene is more likely than the formation of alkyne because of higher acidity of the allylic proton. Then the reaction of N-deprotonated enamine with allene can give the carbanion intermediate which furnishes the desired product after protonation (Figure 1.39).

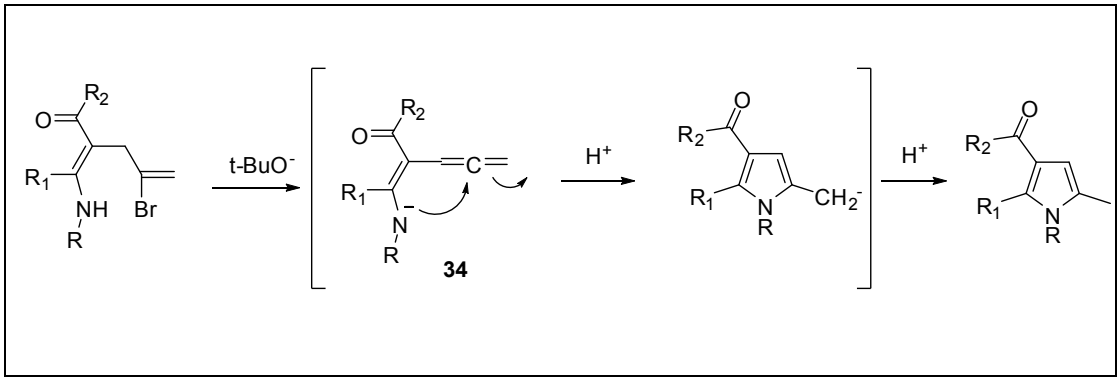


Figure 1.39. Pyrrole formation mechanism through the allene intermediate

By the other possible mechanism the deprotonated enamine can react can react with the vinylic carbon to form a 5-methylene pyrrole derivative via a nucleophilic vinylic substitution reaction. This compound then isomerizes to the pyrrole derivatives (Figure 1.40).

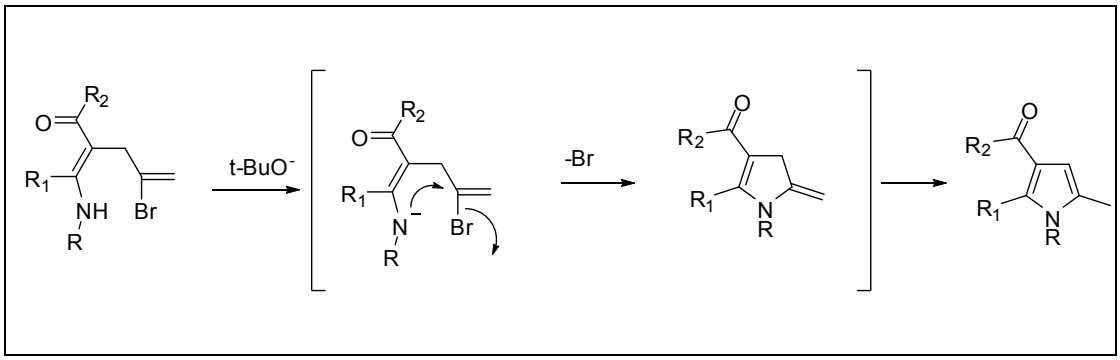


Figure 1.40. Pyrrole formation mechanism through the nucleophilic vinylic substitution reaction

Although many studies including the synthesis of 1,2- , 1,2,3- , and 1,2,3,5 substituted pyrrole rings exist in te literature, highly flexible and efficient synthesis of different substituted pyrroles in high yields with minimum number of steps through catalytic reaction are highly desired.

1.3. Addition of acyl phosphonates to diethlycyanophosphonate (DEPC)

1.3.1. Acyl phosphonates, their applications in organic chemistry

Phosphonate esters have found a wide range of applications in the areas of industrial, aggricultural, an medicinal chemistry owing to their physical properties as well as their utility as synthetic intermediates. Phosphonates are interesting complements to phosphates in terms of biological activity. Within this class of compounds there exist an important subdivision, the α-ketophosphonates or acyl phosphonates. Acyl phosphonates are very useful compounds. They were used as precursors to biologically active α-aminophosphonic acids and hydroxyphosphonic acids for years. The reactivity of acyl phosphonates is particularly interesting. Inspection of the literature reveals a reactivity pattern that can be defined as hybrid of wide range of carbonyl compounds of varying oxidation states. Their reactivity is enhanced by the electron-withdrawing phosphonate moiety making them as excellent electrophiles and they are generally compared to ketones in this respect.[43] Some of their properties sometimes directly compared with trihaloketones.[44] Their reactions with Grignard reagents provide the corresponding ketones upon hydrolysis that can classify them as reminiscent of secondary amides. On the other side they are very good acylating reagents and can easily be hydrolysed under the proper reaction conditions or reacts with secondary amines to afford secondary amides that put them into the same row with activated carboxylic acids.[45] Although these properties make acylphosphonates an interesting platform for a variety of transformations, they can be thought as an underutilized class of reagents.

The presence of phosphonate moiety provides a perfect binding site for protons and especially for metals. This Lewis acid activation site has already been utilized in enantioselective Michael addition, Diels-Alder and Mukaiyama-Aldol reactions.[46]

Hovewer there is still much space for further applications in this area. This potential extra coordination ability could be very interesting in acyl anion chemistry which hasnot any precedent yet.

Acyl phosphonates are easily available compounds. The Michael Arbuzov reaction is a general method for the preparation of acyl phosphonates from acylchlorides **35** and trialkylphosphites **36**.[47] Reaction is initiated with the S_N2 reaction of the nucleophilic phosphite with the electrophilic acyl halide to give unstable phosphonium intermediate **37**. The displaced halide anion reacts via another S_N2 reaction with the phosphonium intermediate to give the desired acylphosphonate **38**. (Figure 1.41). It is generally carried out by mixing neat reactants at or below room temperature. In cases one of the reactants is solid, it can be carried out in organic solutions. Gaseous alkyl chloride is the only side product.

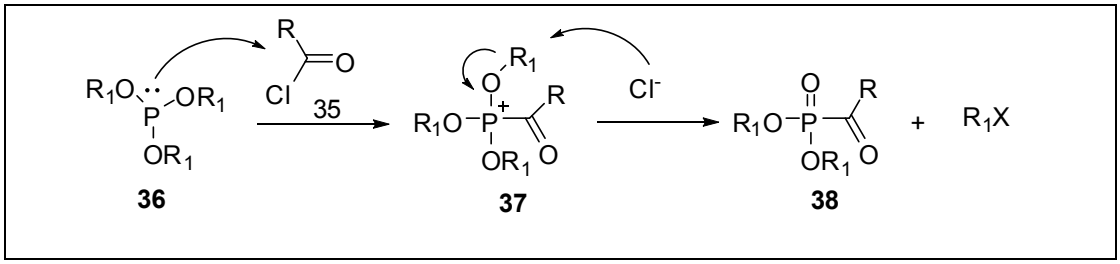


Figure 1.41. Arbuzov synthesis of acyl phosphonates

Acylphosphonates are easily accessible in multigram quantities and very high yields from simple starting materials. Their synthesis does not require any special condition or apparatus..

Besides they can be used as they obtained without altering the efficiency of the reaction carried out. Their synthesis from carboxylic acids is highly intriguing since nature provides vast amount of compounds in this oxidation states. This also establishes a connection between acid oxidation state and acyl anion equivalents which generally obtained from aldehydes. At last phosphonate moiety in acylphosphonates provides a useful platform for fine tuning of their reactivity.

1.3.2. Addition reactions to acyl phosphonates

Phosphonate group in the α-ketophosphonates has electron withdrawing properties and enhances the electrophilicity of carbonyl group. By addition of suitable carbon nucleophiles to carbonyl group, quarternery α-hydroxy phosphonates are obtained. Hard nucleophiles like organolithium compunds cause cleavage of P-C bond.

Wiemer et al. reported allylic addition to α-ketophosphonates **39** by means of allylic bromide **40** in the presence of indium metal (Figure 1.42).[48] The reaction is carried out in THF in the presence of acetic acid. The target compounds are obtained in excellent yields in these conditions. The scope of the reaction is quite wide. The method works with both aliphatic and aromatic phosphonates. Also, the reaction proceeds with crowded allyl bromides with high level of yields.

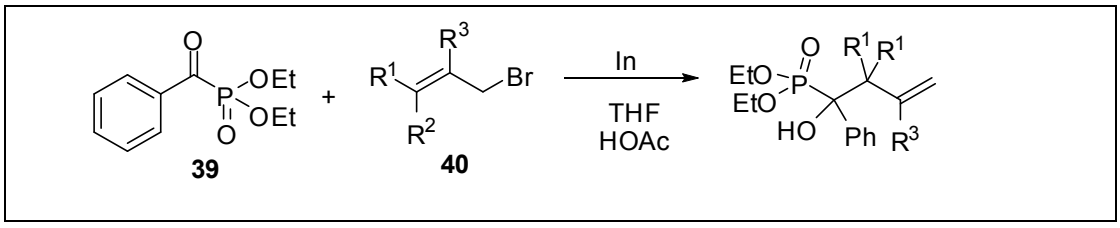


Figure 1.42. Allylation of acyl phosphonates

Another method to get quarternery α-hydroxy phosphonates is the aldol condensation of α-ketophosphonates **41** with acetone **42** catalyzed by L-proline (Figure 1.43).[49] L-proline and proline based organocatalysts have attracted great attention since 2001.[50] In aldol reaction catalyzed by organocatalyst, while donors can be ketone or aldehydes, acceptors are mainly aldehydes. In their work, Samanta et al. take α-ketophosphonates as acceptor and aceton as donor. Highest yields and enantioselectivities are obtained in neat conditions. Both aliphatic and aromatic α-ketophosphonates undergo the reaction with moderate to high yields and with high enetioselectivities. 2-Butanone and methoxyacetone participate in this reaction

when L-prolinamide is used as the catalyst. The reaction is regioselective: one regioisomer is formed.

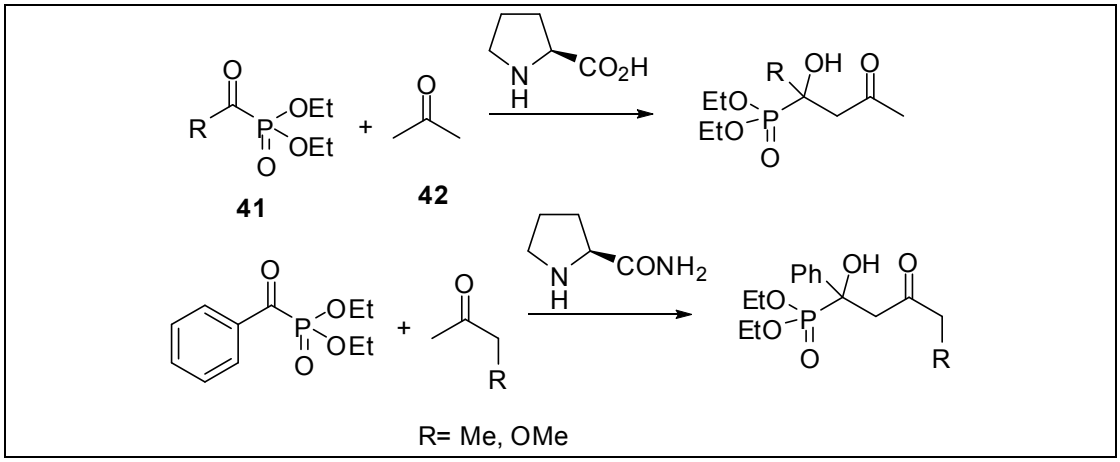


Figure 1.43. Aldol condensation of acyl phosphonates

Also, Demir et al. described a new method for synthesizing α-hydroxyphosphonates.[51] The reaction of acyl phosphonates with trimethylsilyl cyanide gives the trimethylsilyloxycyanophosphonates **43** (Figure 1.44). The reaction proceeds quantatively without any catalyst in various solvents. The protected product can be hydrolyzed to α-hydroxyphosphonates **44** with 1 N HCl.

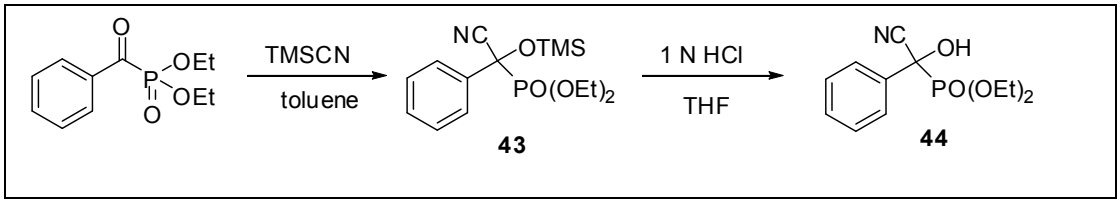


Figure 1.44. TMSCN addition to acyl phosphonates

Using the same strategy, addition reactions of nucleophilic CF_3TMS to acyl phosphonates were also investigated by Demir et al. Various acyl phosphonates reacted readily with CF_3TMS in the presence of K_2CO_3 in DMF to give 1-alkyl-2,2,2-trifluoro-1-trimethylsilyloxyethyl phosphonate (Figure 1.45).

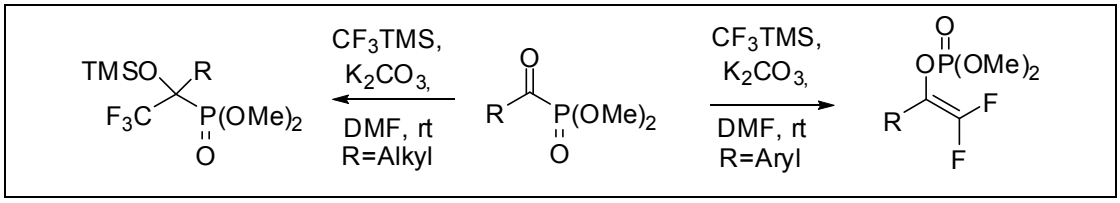


Figure 1.45. Addition of CF_3TMS to acyl phosphonates

Another convenient, one-pot procedure for preparing various polyfunctionalized tertiary carbinol with two new carbon-carbon bonds starting from readily available acyl phosphonates and ethyl cyanoformate has been developed by Demir et al. under very mild conditions in good to excellent yields (74-95%). Phase-transfer cocatalysts and cyanide ions have been used successfully in the formation of cyanohydrine (Figure 1.46).

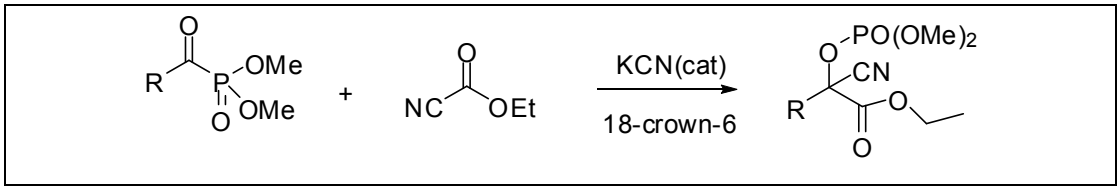


Figure 1.46. Addition of ethyl cyanoformate to acyl phosphonates

In addition, olefination of acyl phosphonates with ethyl diazoacetate in the presence of triphenylphosphine and catalytic amount of cobalt(II) porphyrin complex Co(TPP) has been already reported by Demir at al. (Figure 1.47). By using this one pot methodology, densely functionalized vinyl phosphonates were obtained in high yields.

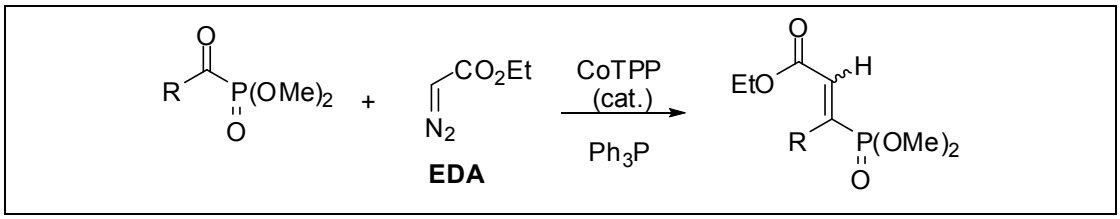


Figure 1.47. Addition of ethyl diazoacetate to acyl phosphonates

3.3 Diethylcyanophosphonate (DEPC) addition to carbonyl compounds

Owing to the fact that optically active α-hydroxynitriles (cyanohydrins) are versatile building blocks for the synthesis of biologically active compounds,[52] the search for simple processes for the enantioselective hydrocyanation of carbonyl compounds has occupied organic chemists for a number of years. Enzymatic methods aside,[52b]until recently most of the chiral catalysts designed and developed by chemists for these endeavors have been monofunctional catalysts, such as standard Lewis acids or organocatalysts.

The catalytic asymmetric cyanation reaction of carbonyl compounds is one of the most powerful tools available for supplying useful chiral building blocks.[53] Although various methods have been developed over the last two decades, $(CH_3)_3SiCN$ (TMSCN) and/or HCN are the most often used cyanide sources to afford cyanohydrins and their TMS ethers. The intrinsic instability of cyanohydrins and their TMS ethers, however, is sometimes problematic for further transformations. Therefore, the development of a one-pot cyanatin-o-protection reaction with a stable protecting group is desirable. To adress this issue, Deng,[54]

Najera and Saa,[55] North and Belokon,[56] and Moberg[57] recently develepod a catalytic asymmetric cyano-ethoxycarbonylation reaction of aldehydes ad ketones using ethyl cyanoformate as the cyanide source.

Cyanohydrin phosphates have been widely utilized as versatile intermediates for the synthesis of agriculturel chemicals, nitriles, carbon anion synthons, α-hydroxycarboxylic acids, and methylene groups. Matsunaga and Shibasaki et al. presented a preliminary report of a catalytic asymmetric cyano-phosphorylation reaction of aldehydes using YLi_3tris(binaphthoxide) complex[58-60] YLB in the presence of diethyl cyanophosphonate (DEPC) **45** to obtain stable cayanohydrin phosphate derivatives (Figure 1.48).

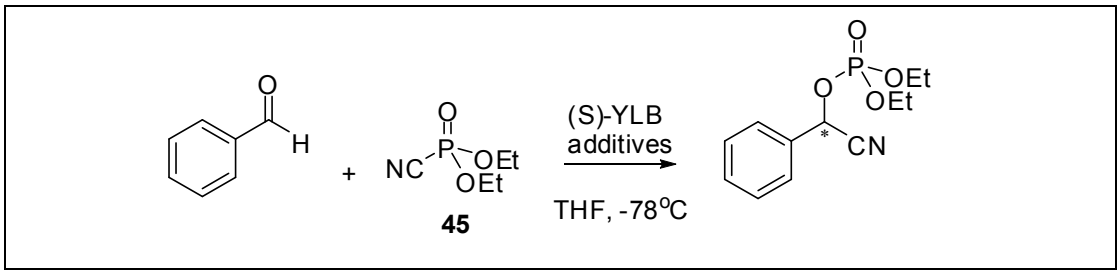


Figure 1.48. Catalytic asymmetric cyanophosphorylatin reaction

The postulated catalytic cycle of the reaction is shown in Figure 1.49. The catalytic cycle occurs in three steps: a reversible interaction between aldehyde **46** and catalyst species cat-1 (step A); cyanide addition to the aldehyde activated by the catalyst, affording the cyanohydrincatalyst complex cat-3 **47** (step B); and trapping of the cyanohydrin intermediate to form product **48** and regenerate cat-1. The rate determining step is probably step C, because DEPC **45** was added slowly to the reaction mixture. Both product **48** and cyanide source **45** have a P=O moiety, thus **48** and **45** might adversely interact with the active species. Trials to reduce catalyst loading failed in the present reaction.

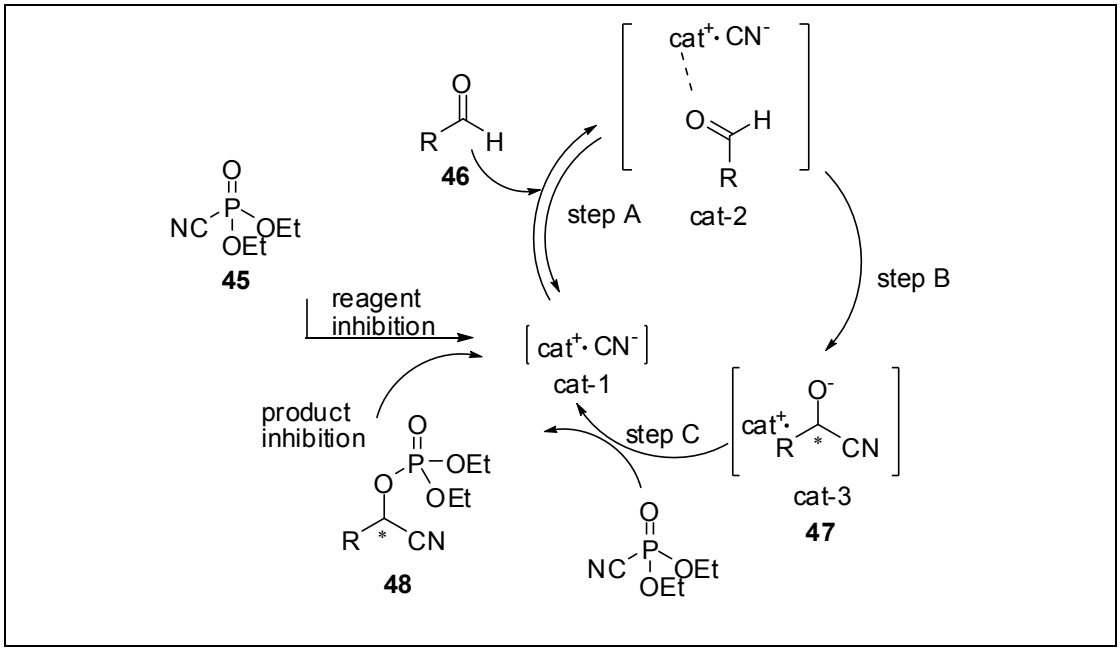


Figure 1.49. Supposed catalytic cycle

Najera et al. have reported the first enantioselective cyanophosphorylation of aldehydes catalyzed by the monometallic bifunctional system. They also described herein a number of useful applications of the resulting enantiomerically enriched cyanohydrin O-phosphates as valuable, previously unknown chiral building blocks in standard modern organic synthesis.[61,62] In the search for the best catalytic system for the cyanophosphorylation of aldehydes, the reaction of p-chlorobenzaldehyde **49** with commercially available diethyl cyanophosphonate **45** in the presence of a series of Lewis acids under a variety of reaction conditions was examined, as shown in Figure 1.50.

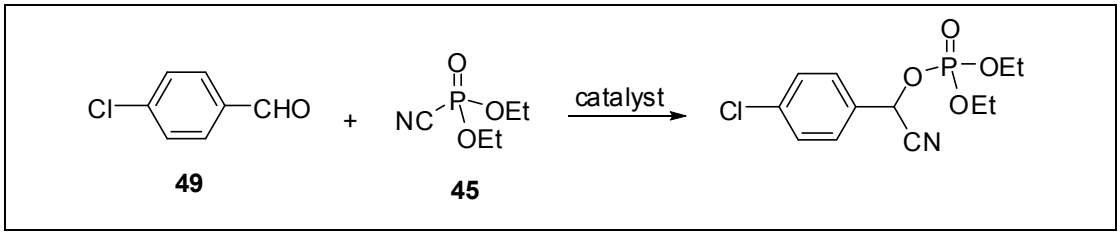


Figure 1.50. Cyanophosphorylation of p-chlorobenzaldehyde **49** catalyzed by Lewis acid complexes

In the second generation catalytic asymmetric synthesis of Tamiflu, which is the antiinfluenza drug for protecting humans against a potential future pandemic of otherwise lethal flu, more practical route has been described by the Shibasaki et al (Figure 1.51).[63]

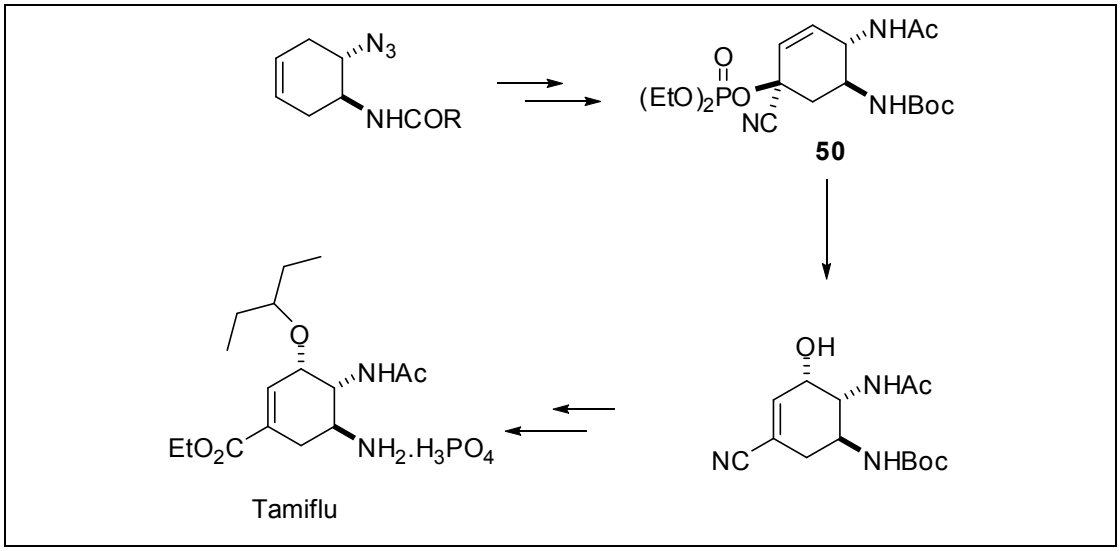


Figure 1.51. Synthesis of tamiflu

The intermediate **50** was synthesized from its enone **51** via cyanophosphorylation.

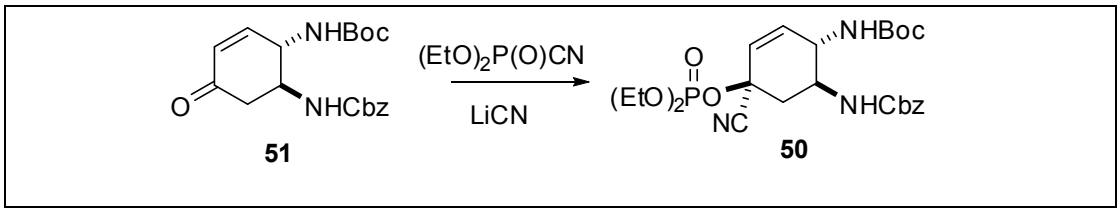


Figure 1.52. Cyanophosphorlation of enone 51

Cyanophosphorylation of enone **51** proceeded stereoselectively with use of DEPC in the presence of a catalytic amount of LiCN affording cyanophosphate **50** (Figure 1.52).

1.6 Aim of the work

The aim of the first part of this research is to develop simple and selective method for the synthesis of chiral lactones **52** and their phenolic α-hydroxycarboxylic acid derivatives **53** which are interesting intermediates for the synthesis of amino acids and other interesting compounds. The aim of this work is shown retrosynthetically in Figure 1.53.

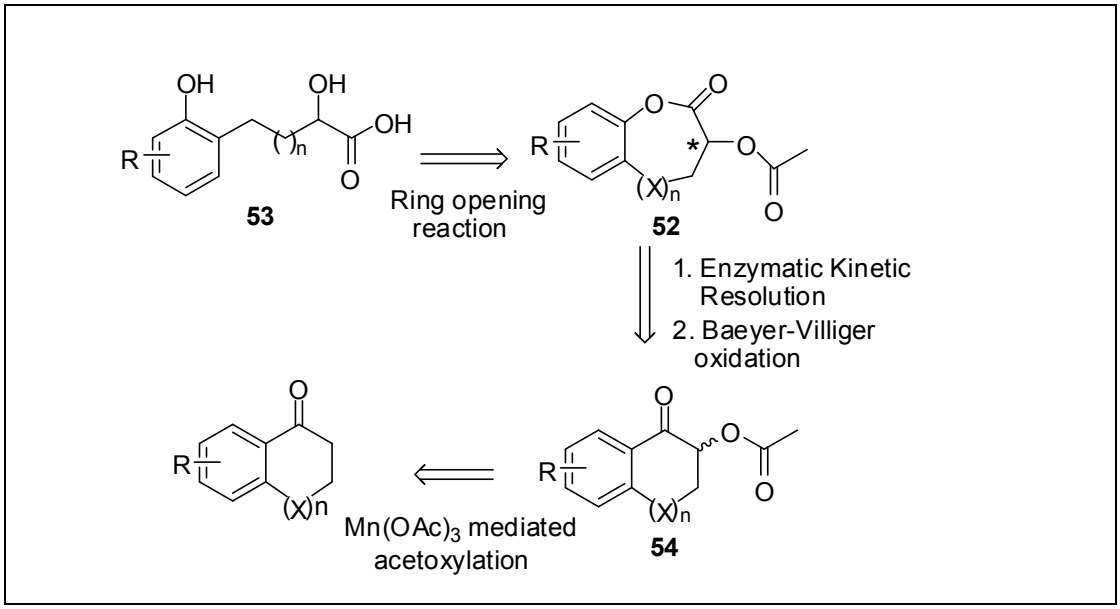


Figure 1.53. Retrosynthetic scheme for the synthesis of phenolic α-hydroxycarboxylic acids

There is no convenient method for the BV oxidation of aromatic ketones with electron rich substituents at the α-position. Our first approach to enantiopure lactones **52** was to synthesize the racemic form of the corresponding acetate derivatives **54** and then BV oxidation of corresponding acetates should give the desired lactones in racemic form. In relation to our previous studies concerning the enantioselective synthesis of acetoxy-chromanone[64], it was also aimed to syntesize the chiral tetralone, indanone and chromanone derivatives in high optical purity by

enzymatic kinetic resolution. Then we aimed to apply the BV oxidation to those enantiomerically pure acetates in order to obtain chiral lactones without any racemization.

In the second part of the study, we aimed to develop an efficient method for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives through acid catalyzed cyclization reaction. Synthesis of pyrrole derivatives was aimed by conversion of 2-propynyl-1,3-dicarbonyl compounds to their enaminones followed by acid mediated cyclization (Figure 1.54).

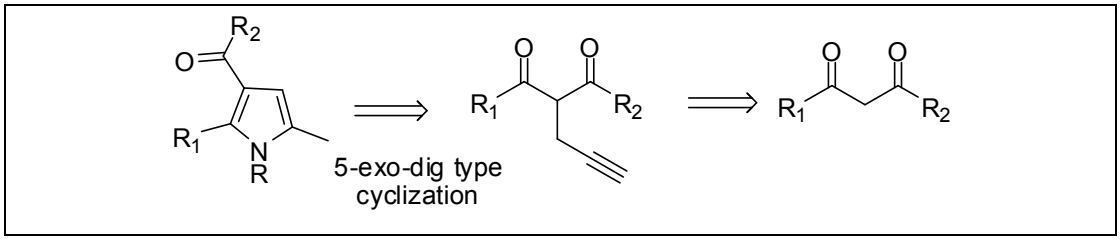


Figure 1.54. Retrosynthetic scheme for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives

Finally, the main concern of the third part of the thesis was to develop a method for cyanophosphorylation of various acyl phosphonates with diethyl cyanophosphonate (DEPC) by using the idea of creating acyl anions from acyl phosphonates in the catalytic amount of KCN. Addition of the acyl anion to the electrophilic DEPC should give the desired polyfunctionalized cyanohydrins **55** which are the important starting materials of quaternary α-hydroxy carboxylic acid and phosphonate containing β-aminoalcohol derivatives (Figure 1.55).

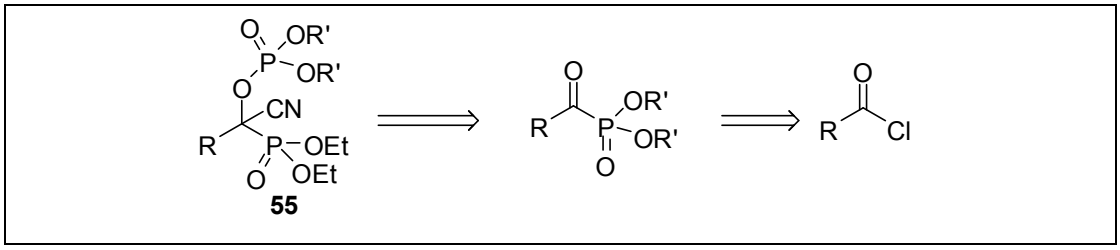


Figure 1.55. Synthesis of polyfunctionalized cyanohydrins **55**

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of chiral lactones via the Baeyer-Villiger oxidation of cyclic aromatic acetoxy ketones

2.1.1 Perspective of the work

The Baeyer-Villiger (BV) oxidation of ketones represents a powerful methodology in synthesis for cleaving carbon-carbon bonds in an oxygen-insertion process. BV oxidation has been widely employed for the transformation of carbonyl compounds to the corresponding esters or lactones using peracids or hydrogen peroxide.[65,66] The chiral BV oxidation of cyclic ketones allows for rapid access to chiral lactones, which are valuable intermediates in organic chemistry. The biocatalytic equivalent to the above peracids is represented by monooxygenases, which are a sub-class of the oxygenase enzyme family in green processes.[67]

There are several methods for the BV oxidation of simple cycloalkanes, but to our best knowledge, much less attention has been paid to the synthetic applications of the BV oxidation of functionalized ketones, especially cyclic α-hydroxy ketones, which could be a straightforward route to the α-hydroxy lactones and α-hydroxyalkanoic acid derivatives. In this study, we report an effective chemoenzymatic synthetic approach to α-acetoxy ketones, their BV product lactones, and hydroxyalkanoic acid derivatives by the $Mn(OAc)_3$ mediated acetoxylation of cyclic aromatic ketones and BV oxidation followed by hydrolysis

under mild conditions as shown in Figure 2.1. These BV products and hydroxy alkanoic acid derivatives are either a precursor of some important biologically active compounds or they demonstrate biological activity.[68]

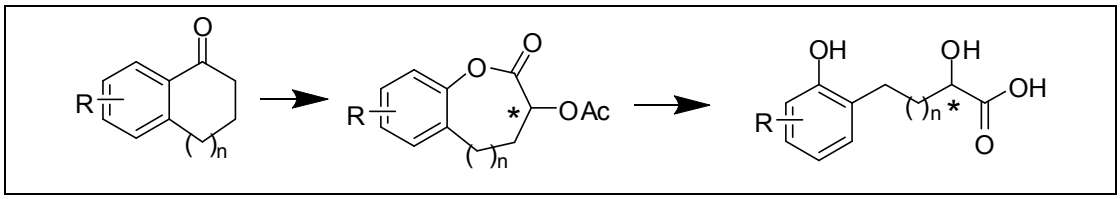


Figure 2.1. General reaction scheme for the synthesis of phenolic α-hydroxy carboxylic acids

2.1.2 Synthesis of acetoxy ketones

Demir et al. have published several papers on the $Mn(OAc)_3$-mediated direct acetoxylation and acyloxylation (carried out via metathesis of acetic acid with various carboxylic acids) of enones and aromatic ketones followed by the enzyme- and fungus-mediated resolution of acyloxy enones to obtain enantiomerically pure α-hydroxy ketones.[69]

As an initial reaction (Figure 2.2), the oxidation of commercially available tetralone **56a** with $Mn(OAc)_3$ in benzene was performed to obtain the desired 2-acetoxytetralone **54a** in 89% yield after purification of the crude product by column chromatography.

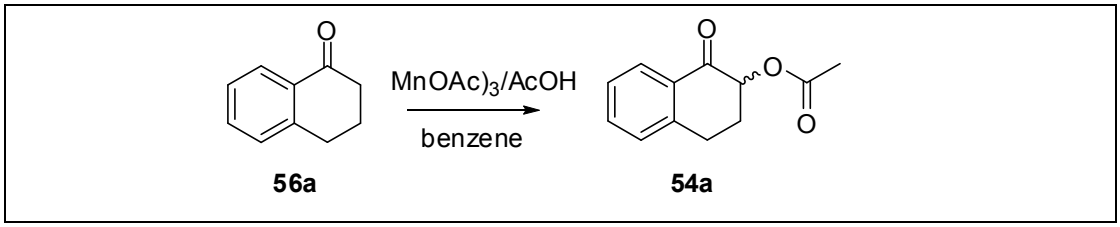


Figure 2.2. $Mn(OAc)_3$ mediated acetoxylation of tetralone

Using similar procedures starting from the commercially available ketones, α-acetoxytetralone, indanone, and chromanone derivatives **54a-g** were synthesized in good to high yields as shown in Table 2.1. The direct synthesis of acetoxy enones under mild conditions from **56a-g** using $Mn(OAc)_3$ is an attractive alternative to the other (multistep) procedures for α-oxidation.

Table 2.1. $Mn(OAc)_3$ mediated acetoxylation of aromatic ketones

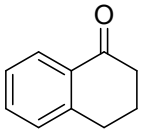
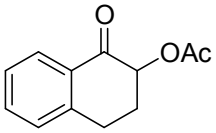
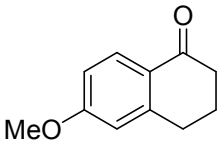
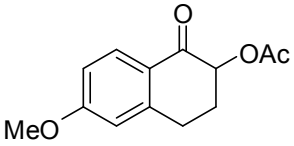
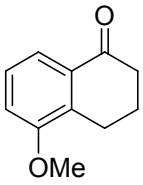
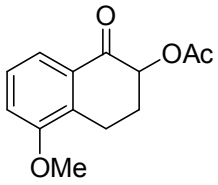
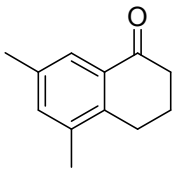
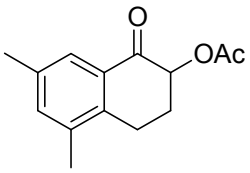
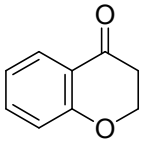
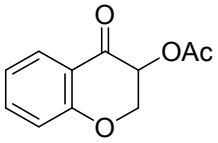
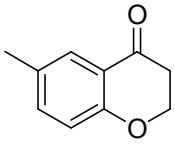
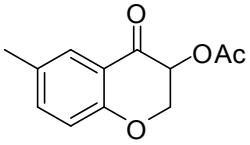
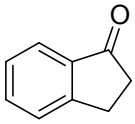
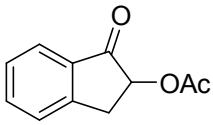
Aromatic Ketones 56	**Acetoxy ketones 54**	**Yield(%)**
 **a**	 **a**	89
 **b**	 **b**	85
 **c**	 **c**	80
 **d**	 **d**	96
 **e**	 **e**	75

Table 2.1. cont'd

Aromatic Ketones 56	Acetoxy Ketones 54	Yield(%)
 **f**	 **f**	83
 **g**	 **g**	81

The products were identified by NMR spectroscopy. From the ^{1}H-NMR spectrum of compounds **54a-g** we observed a singlet around 2.20 ppm from the $-CH_3$ group protons and dd around 5.50 ppm for the α-proton. From the ^{13}C-NMR spectrum of the products we observed a singlet at 20.6 ppm for the CH_3 carbon and a singlet around 169.6 ppm for the $-OCOCH_3$ ester carbon.

2.1.3 Baeyer-Villiger oxidation of α-acetoxy ketones

Baeyer-Villiger oxidation, which involves the transformation of ketones to esters and lactones, is one of the more important reactions in organic chemistry.[70] Although more than a century has gone by its discovery, the BV reaction is far from being at the end of its development.

A large number of catalysts have been shown to be active in the oxidation of cycloalkanones to lactones using several oxidants but none of them describe the BV oxidation of aromatic ketones with electron rich substituents at the α-position. In most cases, *m*-chloroperbenzoic acid (m-CPBA) is used as an oxidizing agent.

In an initial reaction, the oxidation of **54a** was carried out with *m*-CPBA in $CHCl_3$, in which the reaction was monitored by TLC and no product formation was observed (48h). To enhance the reactivity of m-chloroperbenzoic acid, the reagent is combined with an appropriate promoter, such as sulfonic acids, Nafion-H, CF_3COOH, hydrotalcite, $SnCl_4$, $Re(OTf)_3$, as well as trifluoromethanesulfonic acid.[71] As shown in Table 2.2, m-CPBA was used with various reagents for the BV oxidation of the acetoxylated products, in which the reactions were monitored by TLC: Method A[72]: m-CPBA, $KHCO_3$, CH_2Cl_2, reflux (36-96h); Method B[73]: $NaBO_3.4H_2O$, HCOOH, 0^oC (3-24h), Method C[74]**:** m-CPBA, PTSA, CH_2Cl_2, rt, (10-24h), Method D[75]**:** m-CPBA, $Bi(OTf)_3$, CH_2Cl_2, 0^oC, (48-96h), Method E[76]**:** m-CPBA, $CHCl_3$, (48h) and Method F[77]: m-CPBA, CF_3SO_3H, CH_2Cl_2, rt (15-45 min.).

Depending on the reagents and conditions, most of the reactions furnished the desired products **52a-g** in moderate to high yields with the same regioselectivity (Figure 2.3).

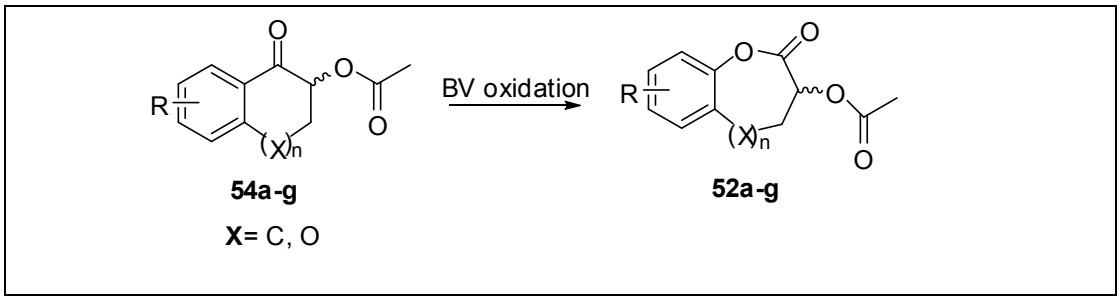


Figure 2.3. Baeyer-Villiger oxidation of racemic acetoxy ketones

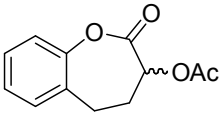
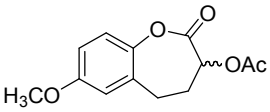
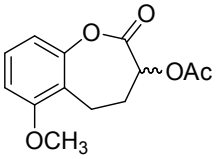
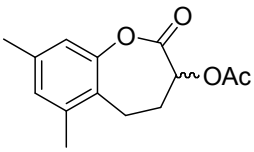
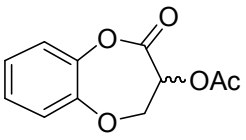
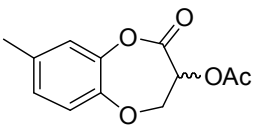
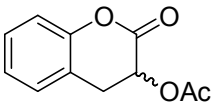
All the compounds were solid except **52d**. The substituents attached to the phenyl ring affected the yield slightly as shown in table 2.3. However, the yields of the reactions with chromanone derivatives were lower than that of the tetralone and indanone derivatives.

According to the spectroscopic data, the phenyl group migrated in order to form the BV products and no other isomer was detected (GC, NMR, and GC-MS). The ^{1}H-NMR spectrum of the resulting compounds showed the formation of the lactones by a shift to higher field for the proton at α-position.

The ^{13}C-NMR spectrums also showed the formation of the products by the disappearance of ketone carbon near 190 ppm and instead appearance of ester carbon near 170 ppm.

As shown in Table 2.2, Methods **A** and **F** work with all the compounds and method **F**: **(**m-CPBA, CF_3SO_3H (10mol%), CH_2Cl_2, rt) gave the best yields (68-95%) in a short reaction time (15-45 min.) compared to the other conditions. No product formation was observed by using method E.

Table 2.2. The BV oxidation of α-acetoxy ketones

Acetoxy ketones	Products	Method A	Method B	Method C	Method D	Method E	Method F
54	**52**	Yield (%)	Yield (%)	Yield (%)	Yield (%)	Yield (%)	Yield (%)
a	 **a**	60	-	20	-	-	90
b	 **b**	85	-	30	-	-	95
c	 **c**	65	-	40	-	-	90
d	 **d**	80	-	-	-	-	95
e	 **e**	35	40	25	65	-	68
f	 **f**	40	45	30	60	-	70
g	 **g**	55	-	-	-	-	70[15]

2.1.4. Enzymatic kinetic resolution of α-acetoxy ketones

The enantiomerically pure α-acetoxy ketones and their respective BV products are interesting and important synthetic precursors for various compounds. Therefore, we first attempted to perform the BV oxidation reaction with biocatalysts. BV oxidations can also be performed using enzymes (Baeyer–Villigerases). These biocatalysts enable one to reach very high enantioselectivity, and several examples demonstrating the possible preparative scale use of whole cell microorganisms, starting from either racemic or prochiral substrates, have been described .[78] The BV oxidation of **54b, 54d, and 54e** were carried out with cyclohexanone monooxygenase Acinetobacter sp. (EC 1.14.13.22) (CHMO,NADPH, DMSO/buffer (pH= 8-9). Mainly unchanged starting material was isolated together with a trace amount of the hydrolysis product. After unsuccessful biocatalytical BV reactions, it was needed to synthesize chiral α-acetoxy ketones firstly, in order to achive the synthesis of their corresponding chiral lactone derivatives after BV oxidation reactions.

In order to obtain enantiomerically pure α-acetoxy ketones from their racemic forms, we attempted the traditional well proven enzyme catalyzed kinetic resolution of the α-acetoxy ketones. Demir et al. published some results for the enzyme catalyzed kinetic resolution of acetoxy ketones.[69] In light of these preliminary results, acetoxy ketones were screened with enzymes for kinetic resolution.

Ester hydrolysis was investigated using commercially available enzymes: Amano PS, CCL(Lipase from candida cylindracea), PPL (Porcine pancreatic lipase), HPL (Lipase from hog pancreas), WGL (Lipase from wheat germ), MML (Lipase from mucor miehei), PRL (Lipase from penicillium roqueforti), RAL (Lipase from Rhizopus arrhizus), RNL (Lipase from rhizopus niveus), PFL (Lipase from Pseudomonas fluorescens), QLM (Lipase from Alcaligenes sp), AL (Lipase from aspergillus).

In a typical experiment, for enzymatic hydrolysis, the racemic acetates, **54a-g**, were dissolved in an appropriate organic solvent, and then phosphate buffer (pH 7.0) (1:10) was added and the mixture was stirred at room temperature in the presence of an enzyme. The reaction was monitored by TLC, HPLC, and LC-MS with a chiral column using racemic acetate, and alcohol (synthesized from acetate with K_2CO_3/MeOH)[79] as references. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to afford acetate **54**, and alcohol **57** (Figure 2.4).

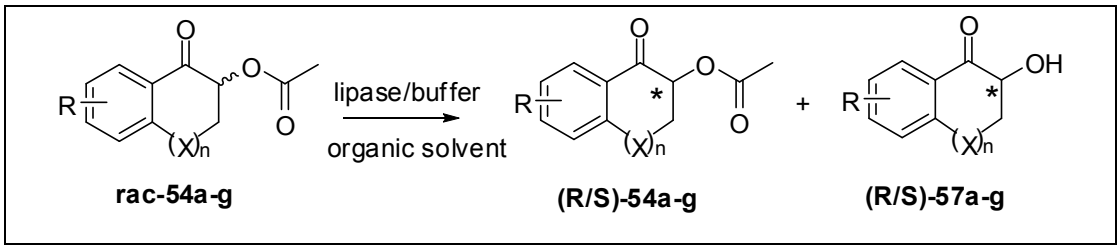


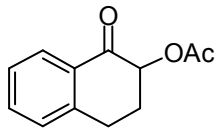
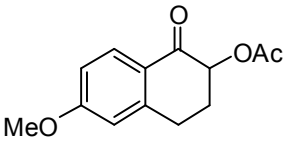
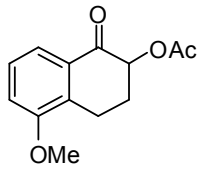
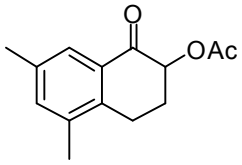
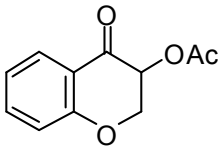
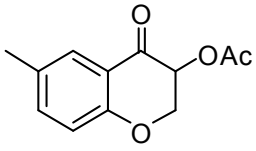
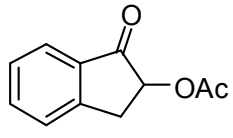
Figure 2.4. Enzymatic kinetic resolution of racemic acetoxy ketones

All the enzymes achieved hydrolysis for all the substrates. Among them, Amano PS and WGL furnished the best results. All of the other enzymes give moderate ee (reaction time 48-120h, ee: 25-52% for acetate 17-43% for alcohol; solvents: DMSO, toluene, dioxane, THF, acetonitrile, and xylene). In case of **54d** Amano PS and WGL showed reverse selectivity.

After screening all the enzymes with all the substrates, the optimum conditions giving the highest enantiomeric excess values were determined for each substrate and we could obtain the enantiomerically pure α-acetoxy and hydroxy ketones as the substrates for the chiral BV oxidation.

The best reaction conditions giving the highest ee values (58-97%) are summarized in Table 2.3.

Table 2.3. Enzymatic kinetic resolution conditions for racemic acetoxy ketones

α-Acetoxyketones rac-54a-g	**Conditions**	**Acetate Ee (%),yield**	**Alcohol Ee (%), yield**
	Amano PS-buffer/ acetonitrile	(-)-*S*-54a (89), 45	(+)-57a (81), 36
	Amano PS-buffer/ toluene	(-)-54b (90), 35	(+)-57b (71), 39
	Amano PS-buffer/ Toluene	(-)-54c (84), 40	(+)-57c (66), 41
	Lipase from wheat germ buffer/DMSO	(+)-54d (85), 48	(-)-57d (81), 41
	Amano PS buffer/toluene	(-)-54d (60), 45	(+)-57d (41), 34
	Amano PS buffer/toluene	(-)-*S*-54e (97), 36	(+)-*R*-57e (88), 38
	Amano PS buffer/toluene	(-)-54f (58), 45	(+)-57f (61), 41
	AmanoPS buffer/acetonitrile	(+)-*S*-54g (86), 48	(-)-*S*-57g (81), 38

2.1.5. Baeyer-Villiger oxidation of chiral α-acetoxy ketones

The BV oxidation of the chiral acetoxy ketones was carried out under the conditions as described for racemic acetoxy ketones. The carefully monitoring of the ee value of the BV product **52a** by HPLC equipped with chiral column showed that no racemization occurred during the oxidation. This procedure was applied to all of the acetoxy ketones and chiral BV products were obtained in 69-94% yields (Figure 2.3). The results are summarized in Table 2.4.

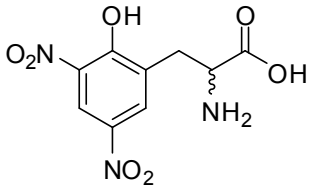
Table 2.4 Enzymatic-kinetic resolution and BV oxidation of α-acetoxy ketones

α-Acetoxy ketone ***Rac*-54**	**Acetate 54 ee (%),Yield(%)**	**BV Product 52 ee (%),Yield(%)**
a	(-)-(*S*)-**54a** 89, 45	**52a** 87, 89
b	(-)-**54b** 90, 35	**52b** 87, 93
c	(-)-**54c** 84, 40	**52c** 83, 90
d	(+)-**54d** 85, 48	**52d** 85, 94
	(-)-**54d** 60, 45	58, 91
e	(-)-(*S*)-**54e** 97, 36	**52e** 97, 69
f	(-)-**54f** 58, 45	**52f** 56, 71
g	(+)-(*S*)-**54g** 86, 4	**52g** 85, 73

Under similar BV conditions as described by the acetate, the oxidation of chiral alcohol **57a** gave a mixture of the products, in which difficulties were produced by the separation and identification of the products. This reaction is still under investigation. These difficulties can be overcome when the alcohols are converted to their acetate immediately after separation by flash column chromatography.

2.1.6. Represantative ring opening reactions

Phenolic α-hydroxy carboxylic acids are important building blocks of phenolic aminoacids and most of them are biologically active and known as phenolic antioxidant compounds. For example 3,5-dinitro-o-tyrosine (a phenolic aminoacid), known as AMPA receptor, is involved in the pathophysiology of a number of neurological diseases such as epilepsy, dementia of the Alzheimer type, and Parkinsonism (Figure 2.5).



AMPA receptor

Figure 2.5. Phenolic aminoacid 3,5-dinitro-o-tyrosine

There are also some naturally occuring phenolic α-hydroxy carboxylic acids like Crocus satiuus or saffran **58** and it is known as traditional chinese medicine. Another naturally occuring phenolic α-hydroxy carboxylic acid **59** has physiological activity of plant hormone and useful as a synthetic intermediate for enalapril and its derivatives (Figure 2.6).

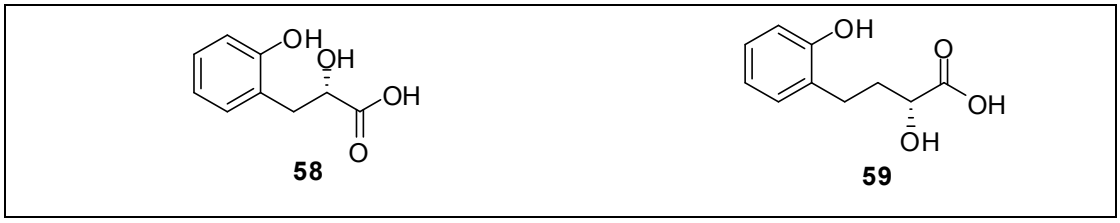


Figure 2.6. Naturally occuring phenolic α-hydroxy carboxylic acids

The BV product lactones are starting materials for those interesting α-hydroxycarboxylic acids with phenolic groups.

As a representative examples, **52e** and **52g** were converted to the α-hydroxy esters **53a, 53b** with K_2CO_3 in methanol. The reaction works under mild conditions at RT to form the products in 84-88 % yield as shown in Figure 2.7.

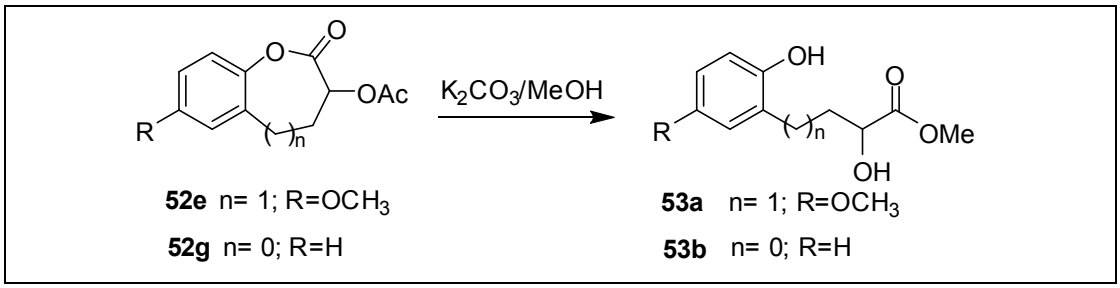


Figure 2.7. Ring opening reactions of lactones

2.2. Novel annulation reactions of 2-propynyl-1,3-dicarbonyl compounds to form pyrroles

2.2.1. Perspective of the work

The strategy for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives is to find out new and easily synthesized acyclic precursors and then to develop practical and flexible cyclization method. For this purpose 2-propynyl-1,3-dicarbonyl compounds **60**, which are available via alkylation of 1,3-dicarbonyl compounds **61** with propargyl halide **62**, are chosen as an acyclic precursor (Figure 2.8).

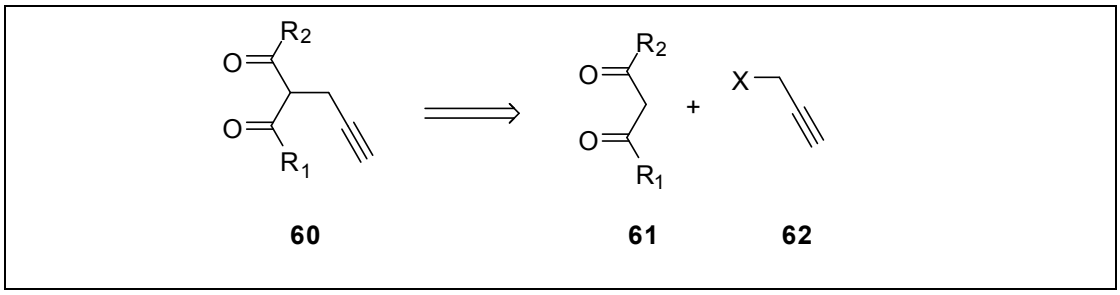


Figure 2.8. Synthesis of acyclic precursor

The formation of enaminone **63** from 1,3-dicarbonyl compounds followed by cyclization should give desired pyrrole ring **64**.

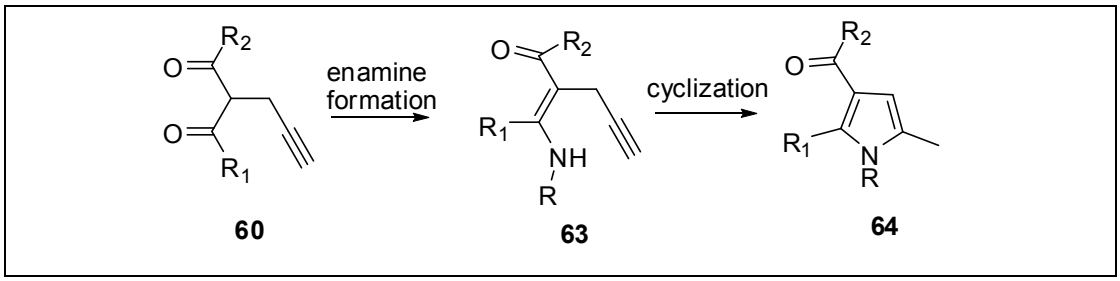


Figure 2.9. Synthesis of 1,2,3,5-tetrasubstituted pyrroles from an acyclic precursor

The most important part is to find out an appropriate 5-exo-dig type cyclization method for construction of pyrrole ring. In order to carry out such a cyclization, the triple bond must be activated since attack of nitrogen to triple bond is a high activation energy requiring process. As discussed in the introduction part, this process can be achieved by means of using acidic species such as Lewis acids as shown in Figure 2.10.

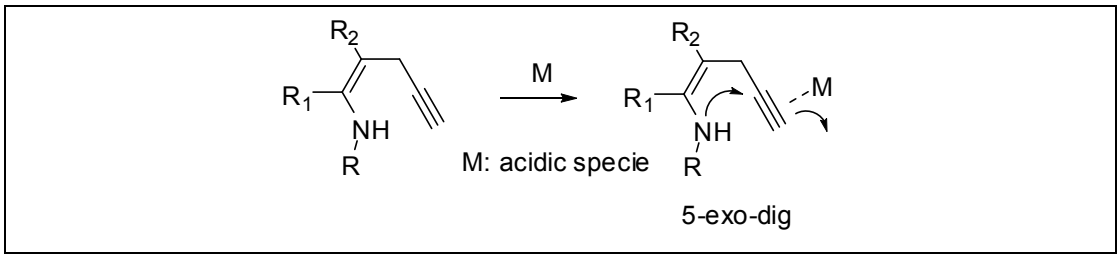


Figure 2.10. Activation of the triple bond by a Lewis acid

Among the Lewis acids used for this kind of reaction, Cu containing ones operates properly according to recent studies.[80,81,82]

Although this synthetic pathway seems reasonable for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives, the idea of combining these two separate steps into one single step by using acid itself arises so that number of the steps can be reduced and the use of metal can be prevented. The enaminone formation requires addition of catalytic amount of acid to increase the partial positive character of carbon atom at which nitrogen will attack. Similarly, cyclization step requires acidic specie (frequently Lewis acids) to lower the activation barrier of attack of nitrogen to triple bond. In the light of these information, the new synthetic route becomes as in Figure 2.11.

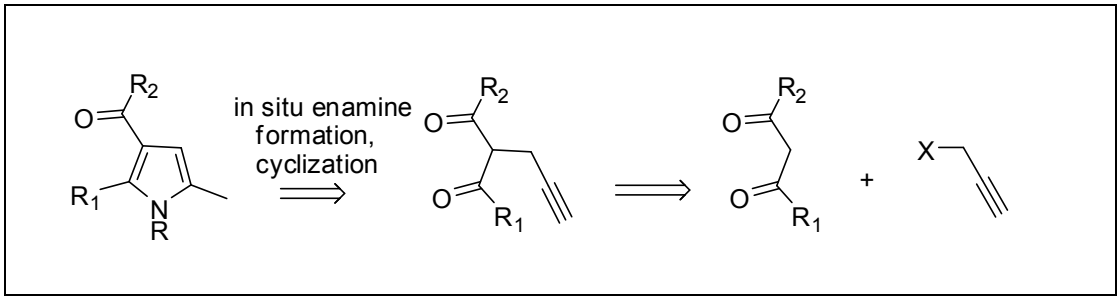


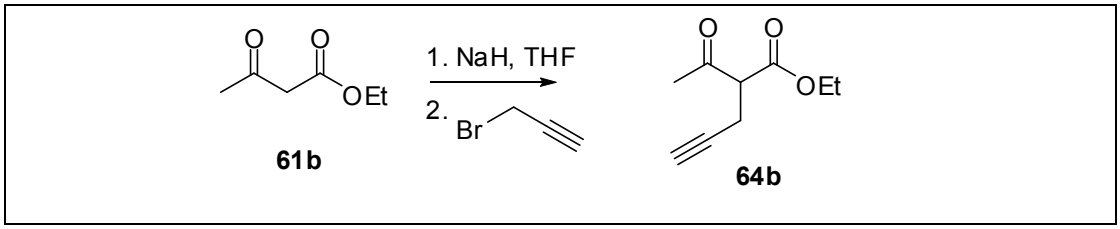
Figure 2.11. New synthetic route for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives

According to this new strategy 1,2,3,5-tetrasubstituted pyrrole derivatives can be synthesized in two steps without the use of metal which can be considered as green chemistry.

2.2.2. Alkylation of 1,3-dicarbonyl compounds

In order to construct the acyclic precursor which will enable us to synthesize desired 1,2,3,5-tetrasubstituted pyrrole derivative, 1,3-dicarbonyl compounds must be alkylated with propargyl bromide. The α-hydrogens in 1,3-dicarbonyl compounds being acidic is a key advantage for making substitution at this carbon atom. Taking one of the protons attached to that carbon with a proper base and making a substitution reaction with the addition of propargyl bromide is the strategy for the alkylation of 1,3-dicarbonyl compounds studied in this project.

For the alkylation of 1,3-dicarbonyl compounds **61a-d**, NaH/THF at room temperature and then addition of propargyl bromide gave the corresponding alkylated compounds with moderate yields (Figure 2.12).

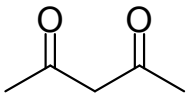
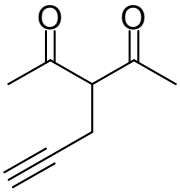
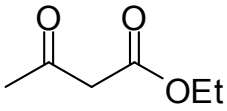
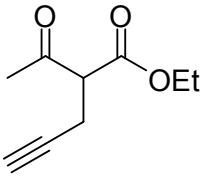
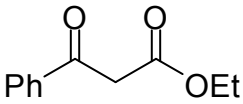
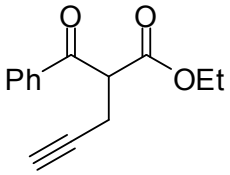
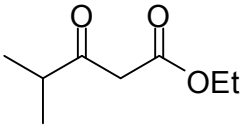
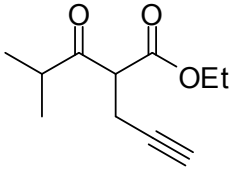


61b **64b**

Figure 2.12. General reaction scheme for the alkylation of ethyl acetoacetate

Results of the alkylation reactions were summarized in Table 2.5. The yields' being moderate is due to the steric interference of the substituents on the dicarbonyl compounds as well as effect of dialkylation. Owing to the high acidity of the protons attached to the α-carbon between two carbonyls, second proton is abstracted from the monoalkylated product leading to the dialkylation of 1,3-dicarbonyl compound. Although this problem could not be sort out completely, it was minimized by means of addition of propargyl bromide in small portions. By doing so, 1,3- dicarbonyl compounds were alkylated with moderate yields (62-75 % yield).

Table 2.5. Alkylation of 1,3-dicarbonyl compounds

1,3-dicarbonyl compound 61a-d	Alkylated 1,3-dicarbonyl compounds 64a-d	Yield %
 **a**	 **a**	75
 **b**	 **b**	66
 **c**	 **c**	62
 **d**	 **d**	64

Characterization of the alkylated compounds was carried out by considering the ^{1}H-NMR spectra. The common peaks of all alkylated dicarbonyl compounds are triplets belonging to the H_2 proton around 3.5-4.0 ppm and doublets belonging to the H_1 protons around 2.5-3.0 ppm as illustrated in Figure 2.13.

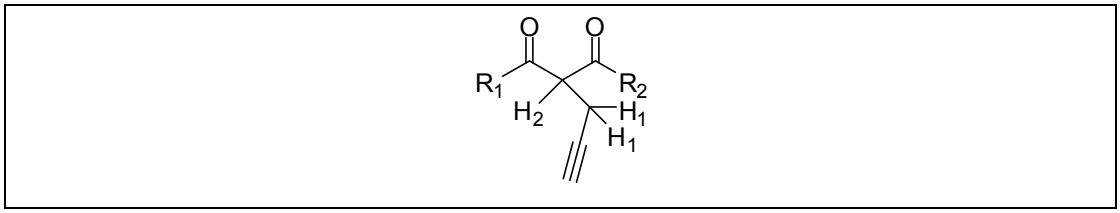


Figure 2.13. Common protons of alkylated dicarbonyl compounds

2.2.3. Annulation reactions with 2-propynyl-1,3-dicarbonyl compounds

Cyclization of the acyclic precursor can be achieved either by using Lewis acid which can be considered as metal-mediated cyclization or by using acid that can be named as acid catalyzed cyclization. It must be kept in mind that for the metal mediated cyclization, acyclic precursor (enaminone system) must be isolated while for acid catalyzed cyclization there is no need for the isolation of the acyclic precursor.

The recent study performed by Hiroya et al.[84] for the synthesis of indoles starting from 2-ethynylaniline derivatives with the use of Cu (II) salts in catalytic amount prompted us to carry out the cyclization step with $Cu(OAc)_2$.

In the first part of the study, the desired pyrrole derivatives were synthesized by conversion of 2-propynyl-1,3-dicarbonyl compounds **64a-d** to their enaminones **65a-d** followed by metal-mediated cyclization. For this purpose the enaminone **65a** was synthesized through simple condensation reaction of 1.3-dicarbonyl compound **61c** with (R)-phenylethylamine ((R)-**67a**) in the presence of catalytic amount of p-TsOH. Then the enaminone was reacted with catalytical amount of $Cu(OAc)_2$ in

1,2-dichloroethane and pyrrole derivative (R)-**66a** was obtained in 70% yield after purification (Figure 2.14.

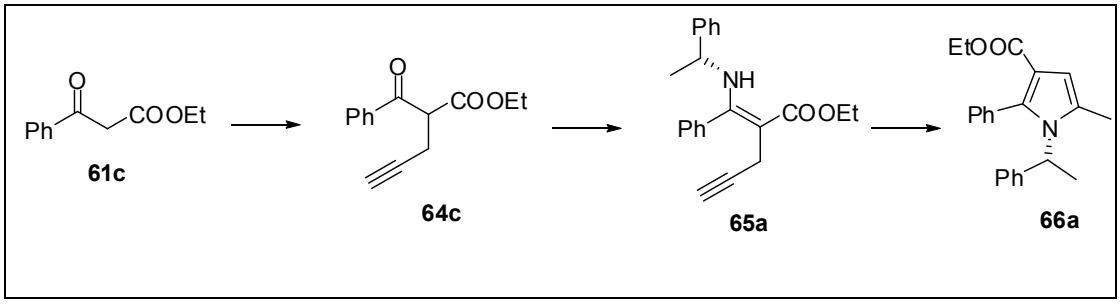


Figure 2.14. Synthesis of **66a**

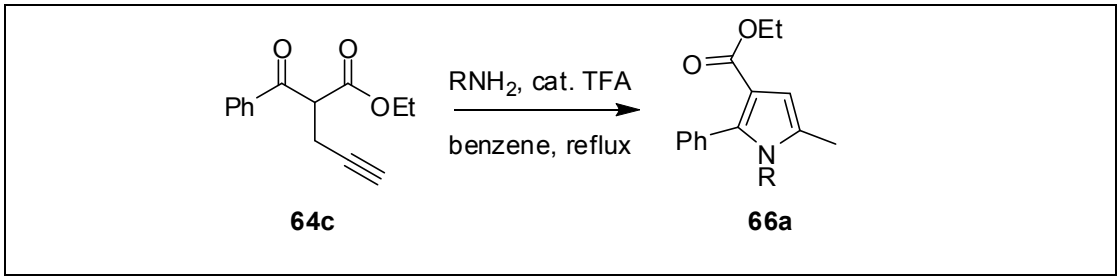
The p-TsOH catalyzed reaction also furnished the pyrrole 66a in 7% yield.

The idea of combining the enaminone formation with cyclization step prompted us to carry out the conversion with one single step starting from 2-propynyl-1,3-dicarbonyl compounds. After this result we carried out the pyrrole formation reaction by using different amount of p-TsOH in different reaction conditions but non of them furnished the pyrrole **66a** in acceptable yields. We had little success in optimizing these yields. This reaction, although facile, does not generate high enough yields (~14%) to be synthetically useful.

During the screening reactions to find acceptable conditions for the formation of enaminones and their cyclizations, we found that catalytical amount of TFA is able to convert enaminone to pyrrole. Since activation of triple bond is the main requirement for the attack of nitrogen, catalytic amount of TFA was used as proton source for both activation of triple bond and catalysis of enaminone formation.

The test reaction of 1 mmol **64c** was dissolved in benzene. 1.2 mmol amine together with (0.01 equivalent) TFA was added to the stirring mixture and refluxed for 15 hours by using Dean-Stark trap. The formation of product was monitored by TLC

using 1:10 ethyl acetate:hexane solvent system.The pyrrole derivative **66a** was isolated in 76% yield after purification (Figure 2.15).



64c **66a**

Figure 2.15. TFA catalyzed cyclization reaction of **64a**

Using the same procedure various 2-propynyl-1,3-dicarbonyl compounds were refluxed with amines **67a-c** for 12-15 h and pyrrole derivatives **66a-m** were synthesized in high yields (65-97%). The results of TFA catalyzed cyclization of 2-propynyl-1,3-dicarbonyl compounds are summarized in Table 2.6. In case of (S)-66l and (S)-66m, the optical purity of the products was compared with the corresponding racemic compounds (rac-**66l** and rac-**66m**) using chiral HPLC column and it showed that the formation of a pyrroles (S)-**66l** and (S)-**66m** works without racemization.

Table 2.6. Acid catalyzed synthesis of pyrrole derivatives

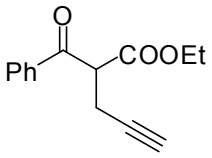
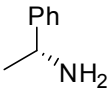
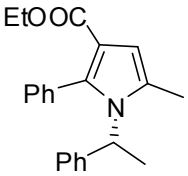
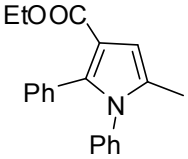
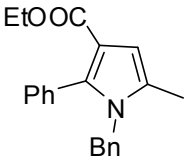
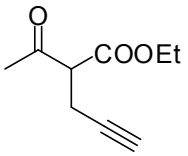
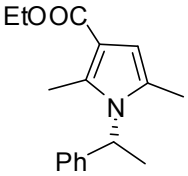
1,3-dicarbonyl compound	Amine	Pyrrole	Yield
64	**67**	**66**	
 **c**	 **a**	 **a**	**76**
c	$PhNH_2$ **b**	 **b**	**92**
c	$BnNH_2$ **c**	 **c**	**94**
 **b**	**a**	 **d**	**94**

Table 2.6. cont'd

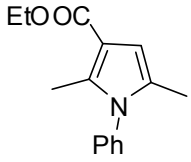
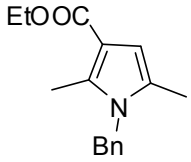
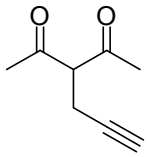
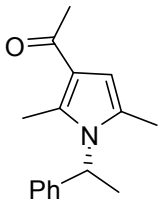
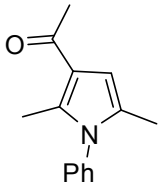
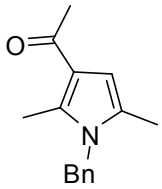
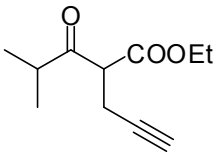
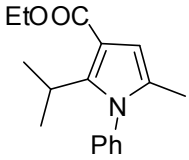
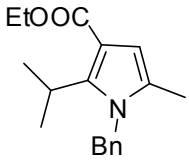
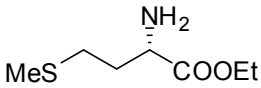
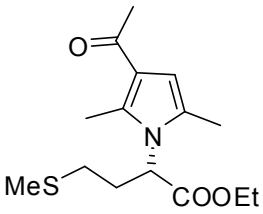
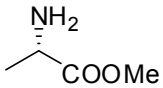
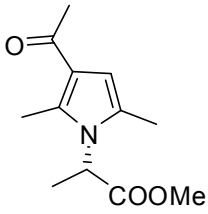
b	**b**	 **e**	**96**
b	**c**	 **f**	**92**
 **a**	**a**	 **g**	**93**
a	**b**	 **h**	**65**
a	**c**	 **i**	**97**

Table 2.6. cont'd

 **d**	**b**	 **j**	**75**
d	**c**	 **k**	**95**
c	 **d**	 **l**	**95**
c	 **e**	 **m**	**88**

All the compounds were synthesized and this part of the thesis was published in cooperation with Metin Kayalar (Demir A. S.; Aybey A.; Kayalar M. *ARKIVOC*, **2005**, 15, 105-116).

Characterization of the pyrrole derivatives were done from the ^{1}H and ^{13}C-NMR spectra. For ^{1}H-NMR spectra there are two kind of characteristic protons. These are illustrated in Figure 2.16. H_1 proton of the different pyrrole derivatives resonate between 6.17-6.60 ppm as singlet. Moreover, H_2 protons resonate around 2 ppm as singlet.

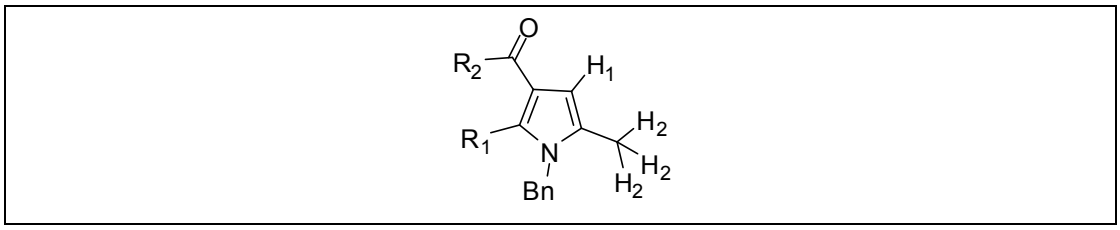


Figure 2.16. Characterstic protons of pyrrole derivatives

When the ^{13}C NMR spectra of different pyrrole derivatives are interpreted, C1, C2, C3, C4 belonging pyrrole ring and C5 belonging methyl group are common in all pyrrole derivatives and resonate around similar values. C1 usually resonates around 127 ppm, C2 around 105-110 ppm, C3 around 134-139 ppm, C4 around 128-132 ppm and C5 around 12 ppm (Figure 2.17).

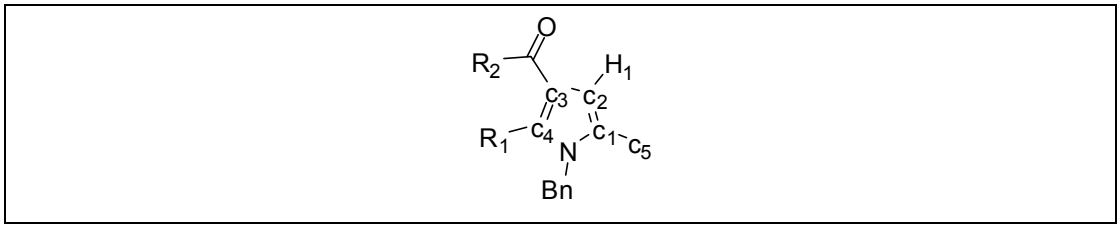


Figure 2.17. Characterstic carbons of pyrrole derivatives

The mechanism in operation is assumed to involve the TFA catalyzed formation of enaminone, then attack of nitrogen to triple bond affecting hydroamination and affording cyclic intermediate **68** (Figure 2.18). This initial step is followed by

rearrangement to afford pyrrole **66**. The attack of nitrogen on the triple bond often requires high activation energy. To overcome this drawback, triple bond is activated by the TFA. This mechanism is consistent with the generally accepted mechanism of nucleophilic addition to metal-activated carbon–carbon multiple bonds.

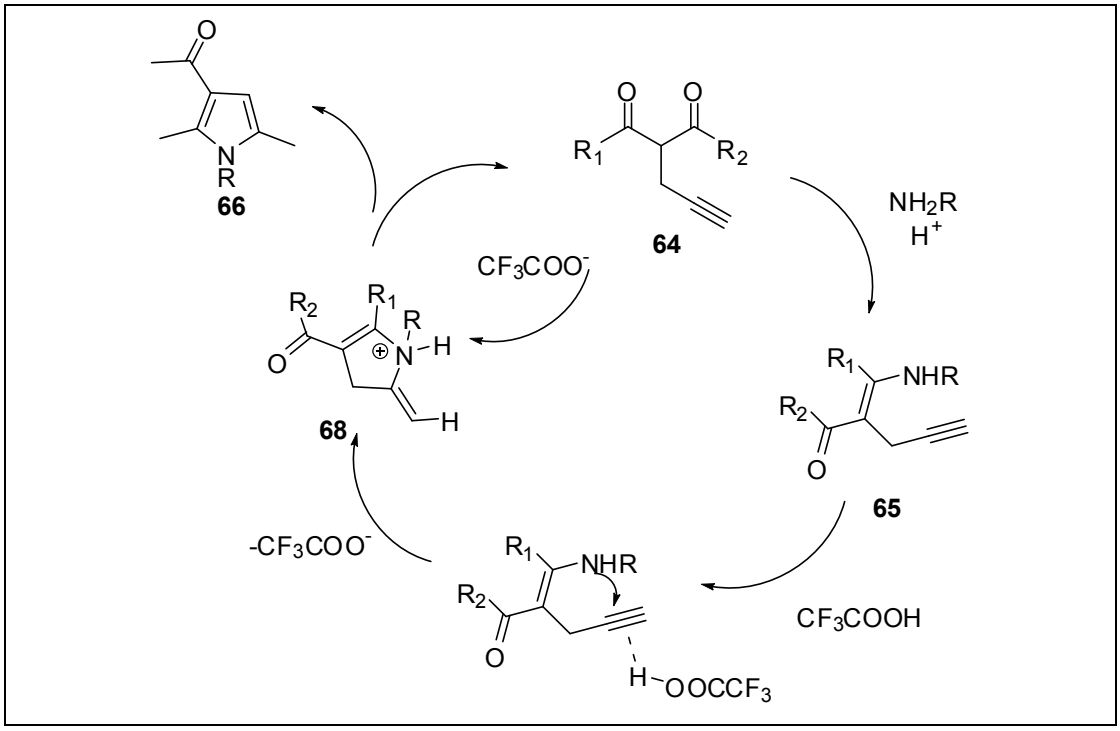


Figure 2.18. TFA assisted pyrrole formation mechanism

2.3. Addition of acyl phosphonates to diethyl cyanophosphonate (DEPC)

2.3.1 Perspective of the work

Phosphorus, like silicon, has the ability to migrate both from carbon to oxygen and oxygen to carbon under appropriate conditions.[85] However this ability of phosphorus has not grown in to a well disciplined area as one could expect. In our previous reports we have envisioned that acylphosphonates are potent acyl anion precursors that generate acyl anion equivalents that are nucleophilic enough to participate in reactions with electrophiles. (Figure 2.19)

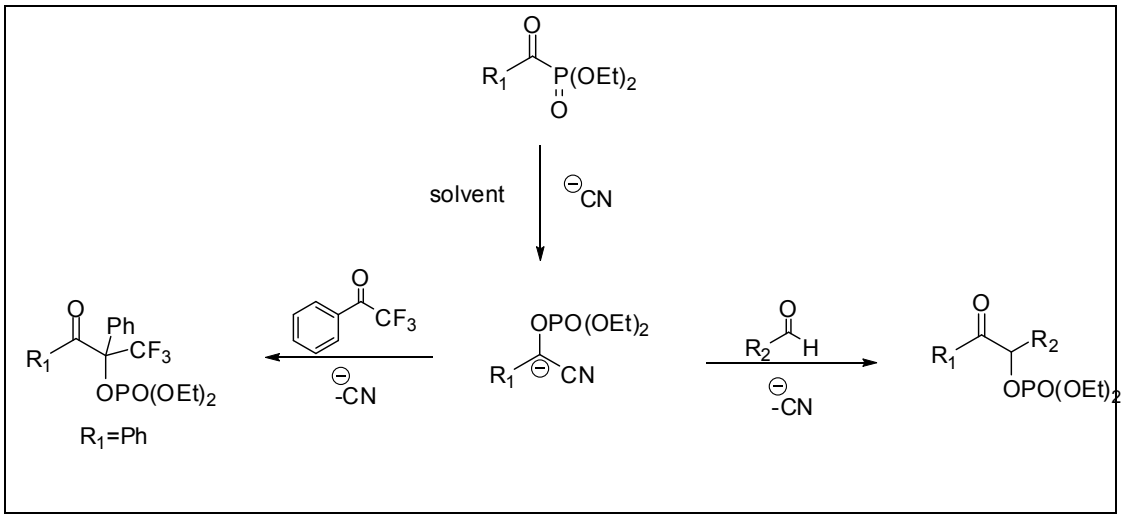


Figure 2.19. Generation and reactions of acyl anion equivalent

We previosly reported that the typical nucleophilic catalysis of benzoin and Stetter reactions might promote acyl phosphonates to generate an appropriate concentration of the corresponding acyl anion equivalents that are sufficiently nuclephilic in order to participate in the reactions with electrophiles. At this point it is important to note that Kurihara et al.[86] reported the use of derivatives of cyanophosphates **68** (Figure 2.20) as acyl anion precursors. The cyanophosphates used in their study were prepared by reaction of aldehydes **69** with diethyl cyanophosphonate (DEPC) **45**

and LiCN. Deprotonation of **68** to **70** and subsequent reaction with various electrophiles including alkylhalides, acylhalides and aldehydes provided alkylated **71**, acylated **72** and benzoin (or acyloins) **73** type products respectively. Although this is a new type of acyl anion precursor, it has no apparent advantage over the corresponding O-silylcyanohydrins or dithianes. Besides aliphatic derivatives of **68** were failed to give any product and only starting materials were recovered.

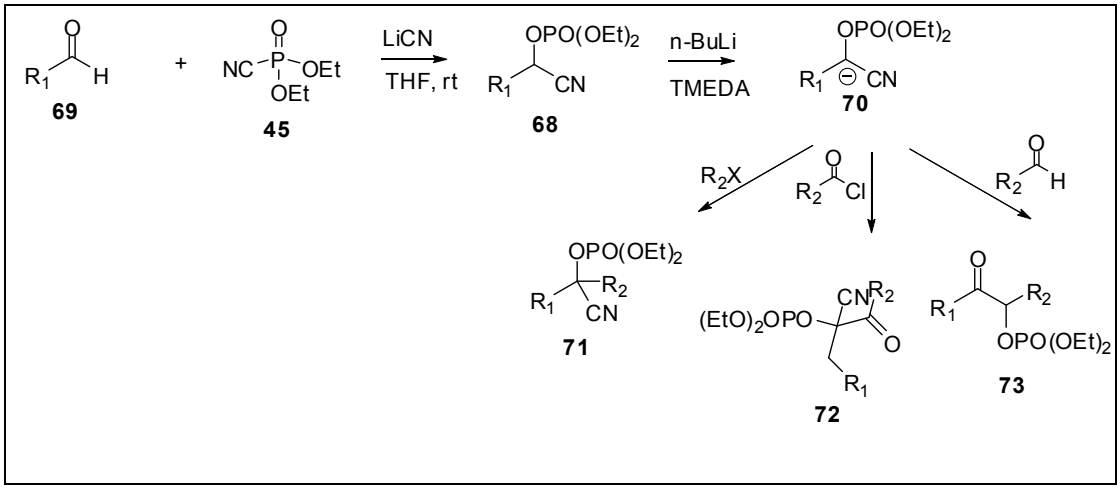


Figure 2.20. Generation of acyl anion equivalent from cyanophoshates

Under the light of these reports and also our initial proposals, cyanide ion promoted addition of acyl phosphonates to cyanoformate esters were described by our group. By using ethyl cyanoformate **74** as a cyanide source and electrophile, a new cyanide ion promoted cyanation/phosphonate-phosphate rearrangement/C-acylation sequence was developed that results in the efficient formation of polyfunctionalized cyanohydrin derivatives (Figure 2.21).

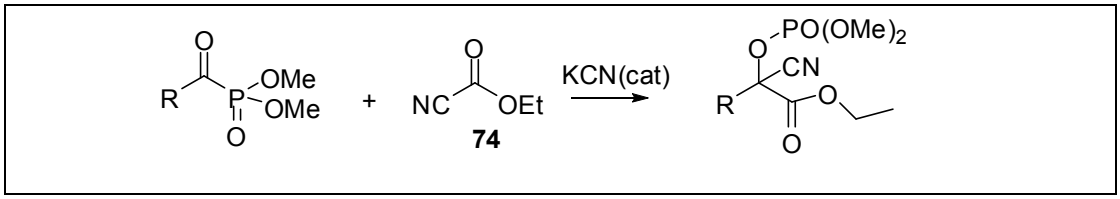


Figure 2.21. Addition of acyl phosphonates to ethylcyanoformate

As mentioned before, cyanohydrin phosphates and their trimethylsilyl ether derivatives are versatile intermediates in organic synthesis.[87,88] Many methods have been devised for the synthesis of these target compounds in a racemic and enantioselective manner. The typical method for their synthesis is the addition of a cyanide source, in various forms, to the corresponding carbonyl compounds.[89] The source of cyanide determines the type of protecting group on the hydroxyl functionality, which is, most of the time, crucial for the sake of subsequent transformations.

Since the instability of cyanohydrins and and their trimethylsilyl ethers is sometimes problematic for further transformations, development of a one-pot cyanation-O-protection reaction with a stable protecting group has become desirable.[90] In 1983, one-pot reaction of carbonyl compounds with diethyl cyanophosphonate (DEPC) in the catalytic amount of lithium diisopropylamide has been reported by Shioiri et al.[91] Then several catalytic asymmetric cyano-phosphorylation methods have been developed for aldehydes and prochiral ketones. Recently Najera and Saa et al. reported a catalytic asymmetric cyano-phosphorylation reaction using a chiral aluminum catalyst[92] with DEPC which is revealed as an excellent phosphorylating agent in asymmetric processes. There are several methods for the transformation of aldehydes and ketones into racemic cyanohydrin-O-phosphates by the reaction with DEPC[93], however there is no convenient method for the cyano-phosphorylation of acyl phosphonates in the literature. Therefore, in the third part of the study, we report cyano-phosphorylation

of various alkyl and aryl phosphonates by reaction with stoichiometric amounts of DEPC and substochiometric amounts of KCN as shown in Figure 2.22.

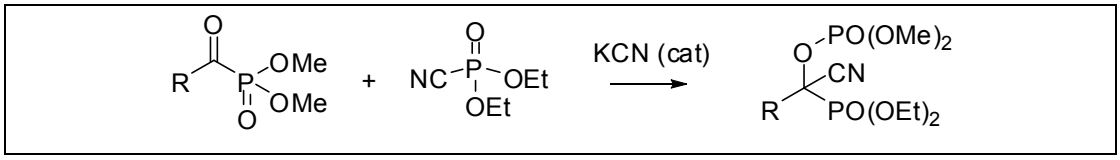


Figure 2.22. General reaction scheme for the addition of acyl phosphonates to DEPC

2.3.2 Synthesis of acyl phosphonates

Acyl phosphonates have found a wide range of applications in the areas of industrial, aggricultural and medicinal chemistry owing to their physical properties as well as their utility as synthetic intermediates. The Michael Arbuzov reaction is a general method for the preparation of α-ketophosphonates from acyl chlorides and trialkyl phosphites. (Figure 2.23).

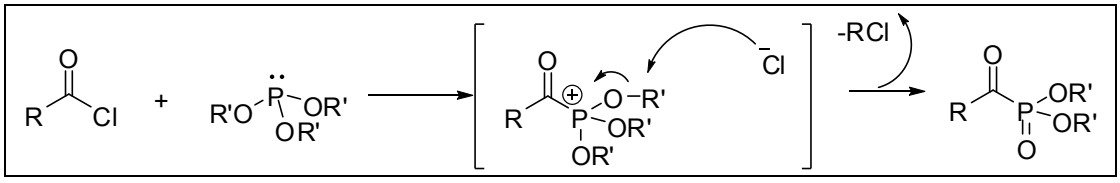


Figure 2.23. Synthesis of acyl phosphonates from Arbuzov reaction

Oxidation of α-hydroxyphosphonates is another method for the preparation acyl phosphonates. A new method for the preparation of acyl phoshonates by oxidation of α-hydroxyphosphonates on the solid surface is described. It was found that alumina (neutral)-supported CrO_3 under solvet free conditions capable of producing

high yields of acyl phosphonates from α-hydroxyphosphonates under mild reaction conditions (Figure 2.24).

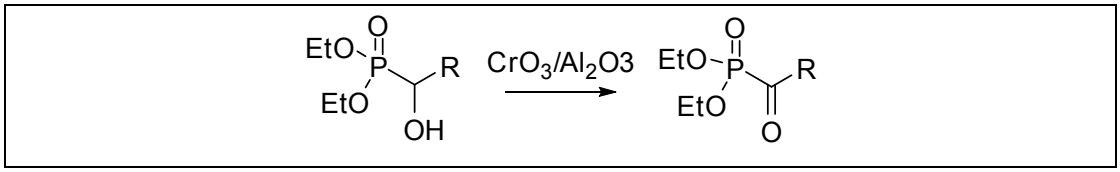


Figure 2.24. Synthesis of acyl phosphonates from α-hydroxyphosphonates

Several aromatic and aliphatic acylphosphonates **78a-h** (Figure 2.25) were synthesized and routinely used in our studies. These compounds were synthesized via classical Arbuzov route according to literature procedures.

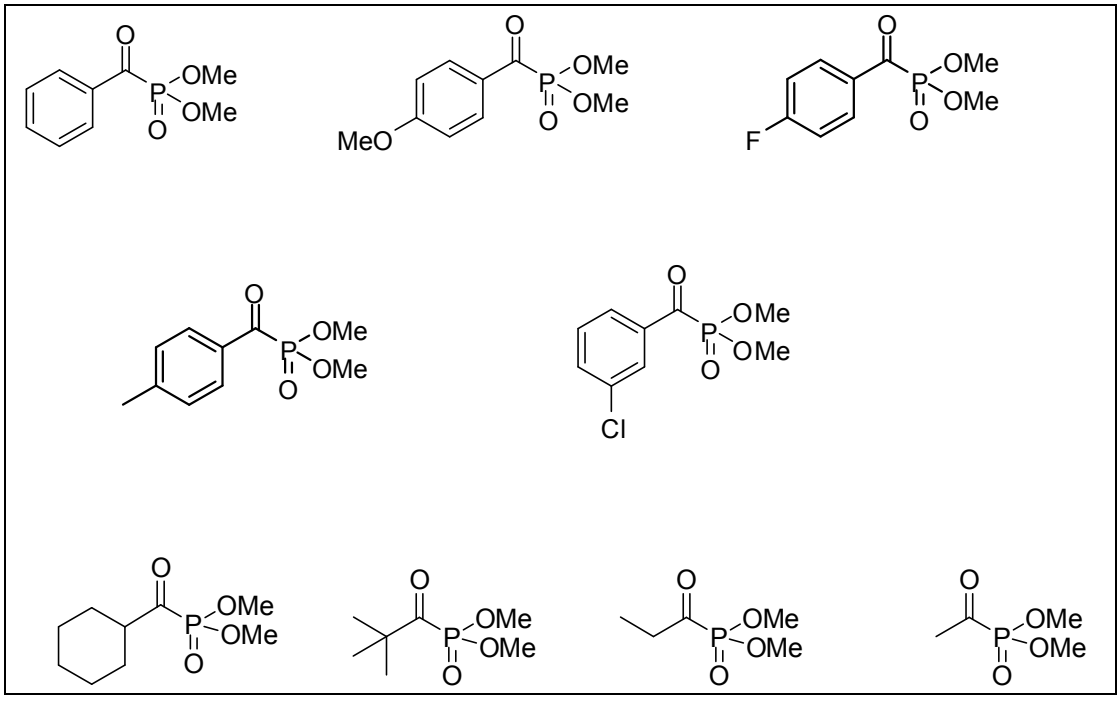


Figure 2.25. Acylphosphonates synthesized and used in this study

2.3.3 Addition reactions of acyl phosphonates to diethyl cyanophosphonate (DEPC)

For the investigation of the reaction of the DEPC with acyl phosphonates, we planned to gain direct and uncatalyzed access to phosphonocyanohydrin-O-phosphates by using DEPC as a cyanide source and an electrophile. Moreover, we hoped that DEPC could supply a catalytic amount of cyanide ion by decomposition in order to provide cyanohydrine phosphate, which can subsequently start the reaction. The formation of cyanohydrine phosphate, via phosphonate-phosphate rearrangement, and followed by C-phosphonylation should in turn form phosphonocyanohydrin-O-phosphates.

In the first reaction, which is shown in figure 2.26, benzoylphosphonate **78e** was reacted with DEPC at ambient temperature in ether and monitored by TLC, in which no product formation was observed. However, in the presence of catalytic quantities of KCN, benzoylphosphonate reacted slowly with DEPC in Et_2O to afford the desired product **79e** in a very low yield. The reaction was repeated with various solvents, and at various temperatures. As shown in Table 2.7, the best result was obtained with THF. Under the given conditions, the competing proton abstraction product, the cyanohydrin *O*-phosphate, was also formed which was separable from the desired product by chromatography. Desired phosphonocyanohydrin-*O*-phosphate **79e** was obtained in 90% yield after purification by column chromatography.

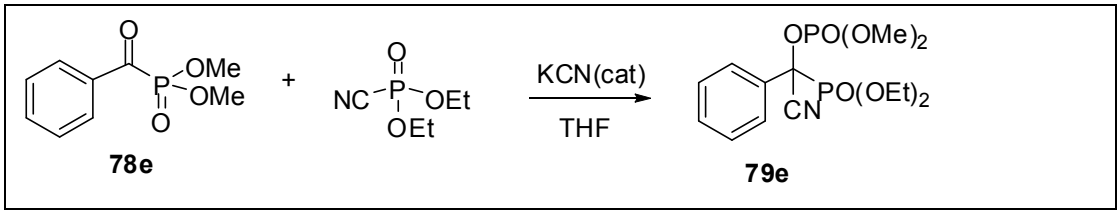


Figure 2.26. Addition of benzoyl phosphonate to DEPC

The reaction scope was studied using a variety of benzoyl and alkyl phosphonates and corresponding cyanohydrins were synthesized in good to high yields (Table 2.7).

Table 2.7. Addition of acyl phosphonates to diethyl cyanophosphonate (DEPC)

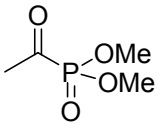
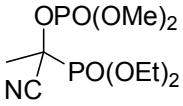
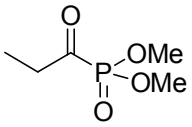
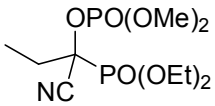
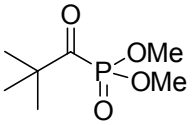
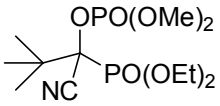
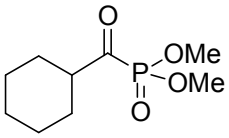
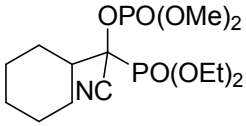
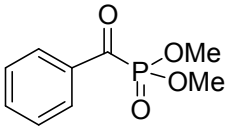
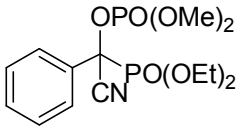
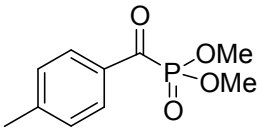
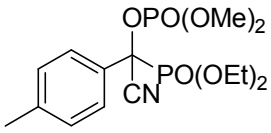
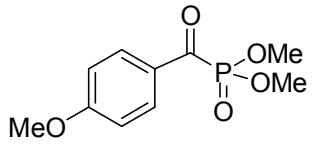
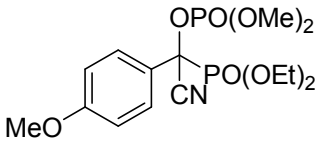
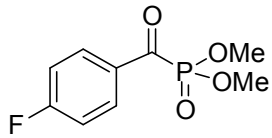
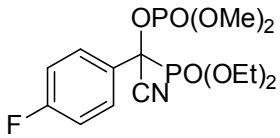
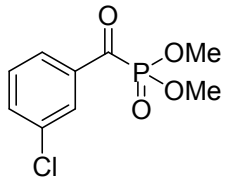
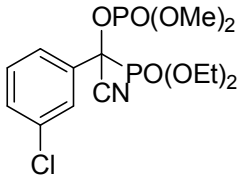
Acyl phosphonates(78a-i)	**Products(79a-i)**	**Yield**
 **a**	 **a**	75
 **b**	 **b**	73
 **c**	 **c**	81
 **d**	 **d**	85
 **e**	 **e**	90
 **f**	 **f**	86

Table 2.7. cont'd

Acyl phosphonates(78a-i)	Products(79a-i)	Yield
 **g**	 **g**	82
 **h**	 **h**	80
 **i**	 **i**	75

Benzoyl phosphonates with electron-withdrawing and electron-donating groups attached to the phenyl ring affected the yield slightly as shown in Table 2.7

By using DEPC as a cyanide source and electrophile, a new cyanide ion promoted cyanation/phosphate-phosphonate rearrangement/C-phosphorylation sequence was developed that results in the efficient formation of phosphonocyanohydrin-*O*-phosphates which are the important starting materials of quaternary α-hydroxy carboxylic acid and phosphonate containing β-aminoalcohol derivatives.

In this transformation, the addition of cyanide ion to acyl phosphonates forms the intermediate alkoxide **80** which rearranges to the carbanion **81** that in turn reacts

with the DEPC in order to provide the product. The proposed catalytic cycle is outlined in Figure 2.27.

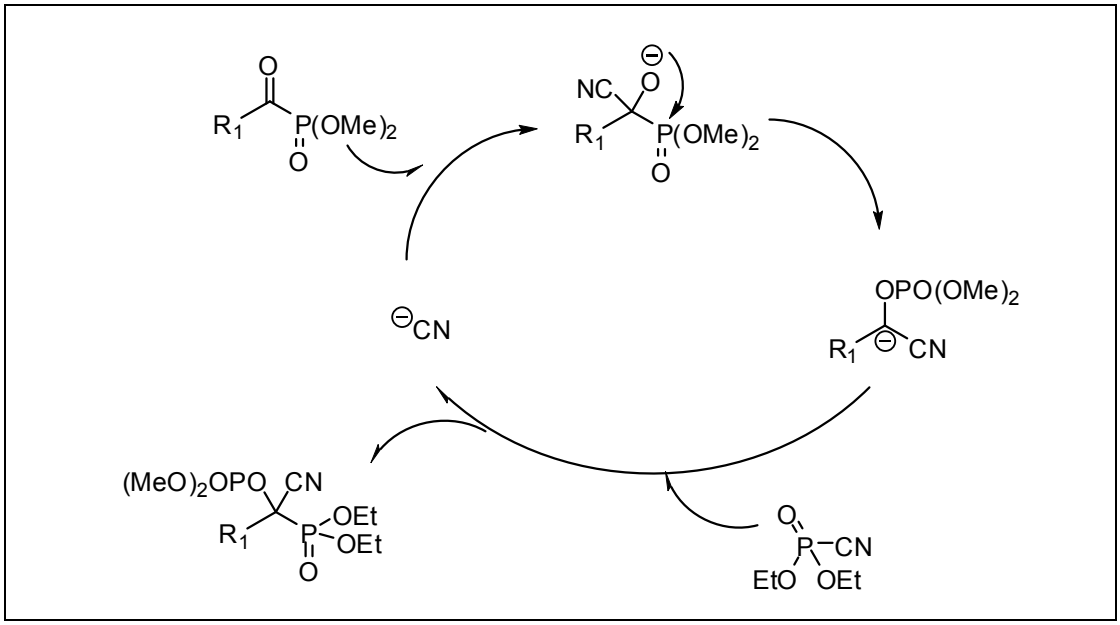


Figure 2.27. Proposed catalytic cycle of the reaction

In conclusion, we developed a convenient, one-pot procedure for preparing various polyfunctionalized cyanohydrins with the formation of new carbon-phosphorus bond starting from readily available acyl phosphonates and diethyl cyanophosphonate under mild conditions in good to high yields (73-90%). The general applicability of the reaction with a range of acyl phosphonate and DEPC has been demonstrated.

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

In this study all compounds were identified by using Nuclear Magnetic Resonance Spectometer (NMR) (Bruker DPX 400 MHz) by using tetramethylsilane (TMS) as an internal Standard and deutereo chloroform as solvent. Chemical shifts were reported in ppm relative to $CHCl_3$ (^1H: d = 7.26) and $CDCl_3$ (^{13}C: d = 77.0) as an internal standard; coupling constnats are reported in Hz.

Flash column chromatography was done for purifying the products by using Merck Silica Gel 60 (partical size 40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm). MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). Melting points were measured on a capillary tube apparatus and are uncorrected.

Optical rotations were measured with a Bellingham-Stanley P20 polarimeter. Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC-LC-MS equipped with an appropriate optically active column.

3.2 Synthesis of chiral acetoxy lactones via the Baeyer-Villiger oxidation of cyclic aromatic acetoxy ketones

3.2.1 General procedure for α-acetoxylation of enones.

A solution of 3 mmol of $KMnO_4$ in 100 mL benzene–acetic acid (10:1) was stirred under reflux (Dean–Stark apparatus) until the purple color of $KMnO_4$ turned brown (15-30 min.). To this solution, 1 mmol of enone was added and reflux was continued. The reaction was monitored by TLC. After all the starting material was consumed, the reaction mixture was diluted with ether and neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc–hexane as an eluent.

(±)-1,2,3,4-tetrahydro-5-methoxy-1-oxonaphthalen-2-yl acetate 54c

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **54c** (80%) as a yellow solid. M.p. 94-95^{o}C. IR (KBr): 3049, 2953, 1750, 1673, 1590, 1240, 1104, 940. HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1), t_R : 29.4, 41.7. ^{1}H-NMR (400MHz, $CDCl_3$): 7.6 (d, J=7.9, 1H); 7.27 (t, J=8.0, 1H); 7.0 (d, J=8.0, 1H); 5.48 (dd, J=13.7, 5.0, 1H); 3.87 (s, 3H); 3.24 (m, 1H); 2.84 (m, 1H); 2.07-2.30 (m, 2H); 2.21 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 192.4, 169.6, 156.6, 132.7, 131.8, 127.4, 119.4, 114.4, 74.2, 55.5, 28.3, 21.8, 20.7.

(±)-1,2,3,4-tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate 54d

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **54d** (96%) as a yellow solid. M.p. 101-103^{o}C. IR($CHCl_3$): 3447, 1693, 1608, 763. HPLC (Chiralcel OBH column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1), t_R : 27.6, 41.9**.** ^{1}H-NMR (400MHz, $CDCl_3$): 7.6 (s, 1H); 7.1 (s, 1H); 5.4 (dd, J=13.7, 5.0, 1H); 2.80-3.0 (m, 2H); 2.34 (m, 1H); 2.27 (s, 3H); 2.21 (s, 3H); 2.15

(s, 3H); 2.12 (m, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 192.9, 169.9, 138.2, 136.3, 136.2, 135.9, 131.7, 125.8, 74.2, 28.4, 25.0, 20.9, 19.3.

(±)-3,4-dihydro-6-methyl-4-oxo-2*H*-chromen-3-yl acetate 54f

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **54f** (83%) as a yellow oil. IR (neat): 3443, 1693, 1609, 1060, 762. HPLC (Chiralpak IA column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1), t_r : 15.9, 18.9. ^{1}H-NMR (400MHz, $CDCl_3$): 7.65 (s, 1H); 7.29 (d, J=8.4, 1H); 6.86 (d, J=8.4, 1H); 5.6 (dd, J=11.3, 5.4, 1H); 4.5 (dd, J=11.0, 5.5, 1H); 4.35 (dd, J=11.3, 11.0, 1H); 2.33 (s, 3H); 2.20 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 187.7, 169.3, 159.7, 137.6, 131.6, 127.4, 119.9, 117.8, 69.7, 68.6, 20.8, 20.6.

3.2.2. General procedures for the Baeyer Villiger oxidation of α-acetoxy ketones

Method A: A solution of α-acetoxy ketones **54a-g** (50mg, 0.28 mmol) and $KHCO_3$ (35mg, 0.35 mmol) in 10 mL CH_2Cl_2 were stirred and commercial grade m-CPBA (80% activity, 61 mg, 0.35 mmol) was added to this mixture. The reaction mixture was stirred under reflux.

Method B: A solution of α-acetoxy ketone **54e** (50 mg, 0.24 mmol) in formic acid (0.5 mL, 98%) was stirred and cooled in an ice bath. Sodium perborate tetrahydrate (55 mg, 0.36 mmol, 90%) was added subsequently in small portions over a period of 6h. Stirring was continued for another 2 hours. The precipitate was filtered off and washed with ethyl acetate. The filtrate was diluted with water. Sodium metabisulphite was slowly added in order to quench remaining peroxides. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $CaSO_4$ and concentrated in vacuum to dryness.

Method C: Baeyer-Villiger oxidation of **54c** (50 mg) with MCPBA (217 mg) and p-toluenesulfonic acid (27 mg) in dichloromethane (5 mL) for 5 h gave a crude product.

Method D: To a mixture of an appropriate ketone **54e** and **54f** (0.2 mmol) and $Bi(OTf)_3$ (5 mol%) in 10 mL of anhydrous dichloromethane at 0ºC was added commercial grade m-CPBA (80% activity, 69 mg, 0.4 mmol) and the reaction mixture was stirred at room temperature. After the completion of the reaction, the catalyst was separated by simple filtration and unreacted m-CPBA was decomposed by addition of an aq. $Na_2S_2O_3$ solution. The product was extracted using ethylacetate, and all the organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated to yield crude product.

Method E: To a solution of α-acetoxy ketones **54a-g** (0.2 mmol) in 5 mL dry $CHCl_3$ was added commercial grade m-CPBA (80% activity, 69 mg, 0.4 mmol) and the reaction mixture was stirred under reflux.

Method F: To a mixture of the starting material (0.2 mmol) and TfOH (3 mg, 0.02 mmol) in 10 mL of anhydrous CH_2Cl_2 at 0 °C was added commercial grade m-CPBA (80% activity, 69 mg, 0.4 mmol) and the mixture was stirred at room temperature. After completion of the reaction, the excess of the reagent was decomposed by addition of an aq $Na_2S_2O_3$ solution. Conventional workup and purification by silica gel column chromatography gave the desired esters or lactones.

(±)-2,3,4,5-tetrahydro-2-oxobenzooxepin-3-yl acetate 52a

The crude mixture was purified by column chromatography (hexane/AcOEt 5:1) to give **52a** (90%) as a colorless solid. M.p. 67-68^{o}C. IR (KBr): 3461, 2953, 1782, 1738, 1450, 1384, 1169, 766. HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1), t_R : 26.6, 34.6. ^{1}H-NMR (400MHz, $CDCl_3$): 7.16-7.33 (m, 4H); 5.08 (dd, J=10.4, 8.7, 1H); 3.05 (dt, J=13.6, 7.9, 1H); 2.71 (dt, J=14.0, 7.9, 1H); 2.28-2.48 (m, 2H); 2.10 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 169.8, 168.1, 150.5, 129.5, 129.0, 128.9, 126.4, 119.7, 69.1, 32.3, 25.7, 20.5

(±)-2,3,4,5-tetrahydro-7-methoxy-2-oxobenzooxepin-3-yl acetate 52b

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **52b** (95%) as a semisolid. IR (KBr): 3445, 2949, 1769, 1738, 1494, 1380, 1163, 835. HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1), t_R : 54.7, 58.2. ^{1}H-NMR (400MHz, $CDCl_3$): 7.04 (d, J=8.8, 1H); 6.71 (dd, J=8.8, 2.9, 1H); 6.63 (d, J=2.9, 1H); 4.99 (dd, J=10.5, 8.7, 1H); 3.73 (s, 3H); 2.96 (m, 1H); 2.57 (m, 1H); 2.19-2.37 (m, 2H); 2.05 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 169.6, 168.3, 157.8, 144.4, 130.7, 120.9, 115.3, 112.8, 69.2, 55.7, 32.3, 26.4, 20.8.

(±)-2,3,4,5-tetrahydro-6-methoxy-2-oxobenzooxepin-3-yl acetate 52c

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **52c** (90%) as a yellow solid. M. p. 122-123^{o}C. IR (KBr): 3450, 2948, 1772, 1736, 1485, 1379, 1157, 784. HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1), t_r : 34.1, 37.2. ^{1}H-NMR (400MHz, $CDCl_3$): 7.20 (t, J=8.3, 1H); 6.81 (d, J=8.1, 1H); 6.74 (d, J=8.3, 1H); 5.03 (t, J=8.7, 1H); 3.85 (s, 3H); 3.26 (dd, J=13.9, 6.5, 1H); 2.60 (dt, J=13.6, 7.5, 1H); 2.21-2.43 (m, 2H); 2.1 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 169.3, 167.6, 156.9, 151.5, 128.3, 117.9, 112.2, 108.2, 69.3, 55.8, 31.6, 20.4, 17.4.

(±)-2,3,4,5-tetrahydro-6,8-dimethyl-2-oxobenzooxepin-3-yl acetate 52d

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **52d** (95%) as an oily compound. IR (neat): 3441, 2940, 1768, 1743, 1448, 1376, 1076, 838. HPLC (Chiralcel OD column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1), t_r : 8.9, 9.8. ^{1}H-NMR (400MHz, $CDCl_3$): 6.77 (s, 2H); 4.91 (t, J=9.1 Hz, 1H); 2.65-2.84 (m, 2H); 2.24 (s, 3H); 2.23 (s, 3H); 2.12-2.31 (m, 2H); 2.04 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 169.6, 168.2, 151.1, 138.2, 136.3, 129.1, 125.0, 118.3, 69.5, 30.1, 21.4, 21.3, 20.7, 19.6.

(±)-3,4-dihydro-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate 52e

The crude mixture was purified by column chromatography (hexane/AcOEt 3:1) to give **52e** (68%) as a colorless solid. M. p. 125-126°C. IR (KBr): 3433, 2956, 1772, 1735, 1491, 1252, 1091, 832. HPLC (Chiralcel OBH column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1), t_r : 47.0, 52.4. ^{1}H-NMR (400MHz, $CDCl_3$): 7.1 (m, 4H); 5.4 (t, J=8.5, 1H); 4.5 (d, J=8.0, 2H); 2.1 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 167.5, 164.2, 145.7, 143.4, 126.5, 125.2, 121.5, 119.4, 72.9, 66.7, 19.4.

(±)-3,4-dihydro-8-methyl-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate 52f

The crude mixture was purified by column chromatography (hexane/AcOEt 3:1) to give **52f** (70%) as a yellow solid. M. p. 107-108°C. IR (KBr): 3447, 2944, 1792, 1751, 1403, 1274, 1091, 832. HPLC (Chiralpak IA column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1), t_r : 15.5, 22.2. ^{1}H-NMR (400MHz, $CDCl_3$): 6.96 (d, J=7.8, 2H); 6.88 (d, J=8.0, 1H); 5.36 (t, J=8.7, 1H); 4.40 (d, J=8.6, 2H); 2.28 (s, 3H); 2.06 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): 168.6, 165.5, 144.4, 144.0, 136.4, 127.0, 122.0, 120.8, 73.9, 67.8, 20.8, 20.0.

3.2.3. General procedure for the lipase-catalyzed asymmetric hydrolysis of α-acetoxy ketones

Lipase was dissolved in potassium phosphate buffer (pH 7, 25 ml) and added to a solution of the pure substrate (200 mg) in organic solvent (5 ml) and the reaction mixture was stirred at rt. The reaction was monitored by TLC and HPLC and when 50% conversion was reached, the reaction was terminated by filtration.

(-)-(S)-1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl acetate 54a

HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1): t_R 26.1. $[\alpha]_D$=-63.3 (c 0.57, CH_2Cl_2)

(-)-1,2,3,4-tetrahydro-6-methoxy-1-oxonaphthalen-2-yl acetate 54b

HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1): t_R 45.6. $[\alpha]_D$=-200 (c 0.074, CH_2Cl_2)

(-)-1,2,3,4-tetrahydro-5-methoxy-1-oxonaphthalen-2-yl acetate 54c

HPLC (Chiralcel OBH column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1): t_R 29.4. $[\alpha]_D$=-61 (c 0.32, $CHCl_3$)

(+)-1,2,3,4-tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate 54d

HPLC (Chiralcel OBH column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1): t_R 41.9. $[\alpha]_D$=8.9 (c 0.36, CH_2Cl_2)

(-)-1,2,3,4-tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate 54d

HPLC (Chiralcel OBH column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1): t_R 27.6. $[\alpha]_D$=-49.1 (c 0.81, CH_2Cl_2)

(-)-(S)-3,4-dihydro-4-oxo-2*H*-chromen-3-yl acetate 54e

HPLC (Chiralcel OD column, flow rate of 0.8 ml/min, hexane/i-propanol 9:1): t_R 12.1. $[\alpha]_D$=-63 (c 0.5, $CHCl_3$)

(-)-3,4-dihydro-6-methyl-4-oxo-2*H*-chromen-3-yl acetate 54f

HPLC (Chiralpak IA column, flow rate of 0.5 ml/min, hexane/i-propanol 9:1): t_R 18.3. $[\alpha]_D$=-19.5 (c 0.6, CH_2Cl_2)

(+)-(S)-2,3-dihydro-1-oxo-1*H*-inden-2-yl acetate 54g

HPLC (Chiralcel OD column, flow rate of 0.8 ml/min, hexane/i-propanol 95:5): t_R 23.3. $[\alpha]_D$=16.2 (c 0.81, CH_2Cl_2)

3.2.4. General procedure for the hydrolysis of lactones

To 50 mg of starting compound in 10 mL MeOH, anhydrous K_2CO_3 (1:2 equivalent) was added. The mixture was stirred for 2 h at room temperature.

Methyl 2-hydroxy-3-(2-hydroxyphenyl)propanoate 53a

Oily; ^{1}H-NMR δ 2.84 (m, 1H), 3.06 (d, J=13.9 Hz, 1H), 3.50 (s, 3H), 4.23 (d, J=5.7 Hz, 1H), 6.75 (m, 2H), 7.15 (m, 2H); ^{13}C-NMR ($CDCl_3$+CCl_4) δ 180.7, 160.4, 131.6, 128.3, 125.3, 120.6, 113.5, 72.8, 35.4, 23.5

Methyl 2-hydroxy-4-(2-hydroxy-5-methoxyphenyl)butanoate 53b

Oily; ^{1}H-NMR δ 1.67-1.87 (m, 2H), 2.5 (m, 2H), 3.20 (s, 3H), 3.37 (s, 3H), 3.87 dd, J=4.1 Hz, J= 7.7 Hz, 1H), 6.60 (m, 2H), 6.69 (d, J=2.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$+CCl_4) δ 181.5, 151.7, 150.2, 130.3, 129.5, 117.2, 111.6, 71.9, 56.3, 50.8, 34.7, 25.7

3.3. Novel annulation reactions of 2-propynyl-1,3-dicarbonyl compounds to form pyrroles

3.3.1. General procedure for alkylation of 1,3-dicarbonyl compounds

5.0 mmol of 1,3-dicarbonyl compound was dissolved in 10 ml THF and stirred. Under Ar atmosphere NaH (120 mg, 5.0 mmol,) was added carefully and stirred for 2-3 hours. After that, propargyl bromide (655 mg, 5.0 mmol) was added in 4 or 5 portions during 4 hours. The formation of products was monitored by TLC using 1:7 ethyl acetate:hexane solvent system.

After completion of the reaction, unreacted NaH was neutralized with water, reaction mixture was acidified with 2-3 drops of concentrated HCl, extracted with ethylacetate three times (3x30ml), dried over MgSO4, and concentrated under reduced pressure. Further purification was achieved by flash column chromatography (1:7 ethyl acetate:hexane) to afford the alkylated 1,3-dicarbonyl compounds.

Ethyl 2-(isobutyryl)pent-4-ynoate (64d)

Ethyl 4-methyl-3-oxopentanoate (980 mg 5.0 mmol) was alkylated according to the general procedure and the product is obtained as an oil (628 mg, 64 %) after purification by column chromatography. Alkylated form exists in both keto and enol form according to the ^{1}H-NMR spectrum. Yellow oil, IR(neat):3050-2850, 2110, 1740, 1710 cm- 1.^{1}H-NMR (400 MHz, $CDCl_3$): 1.03-1,07 (m, 6H), 1.18 (t, J=7 Hz, 3H), 1.94 (t, J=2.7 Hz, 1H), 2.59-2.62 (m, 1H), 2.80-2.83 (m, 1H), 3.41 (d, J=7.2 Hz, 1H), 3.83 (t, J=3.2 Hz, 1H), 4.10 (q, J=3.2 Hz, 2H). Anal. Calcd for $C_{11}H_{16}O_3$(196.24): C 67.32, H 8.22; found: C 67.55, H, 8.45.

3.3.2. $Cu(OAc)_2$ Catalyzed Cyclization Reaction: Ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate, 66a

(*Z*)-Ethyl 2(((*R*)-1-phenylethylamino)(phenyl)methylene)pent-4-ynoate 65a.

Ethyl 2-(benzoyl)pent-4-ynoate (300 mg,1.3 mmol) was condensed with (*R*)-phenylethylamine (158 µL, 1.56 mmol) in the presence of catalytic amount of *p*-TsOH in benzene (10) by using Dean-Stark trap to remove water from the medium. The formation of products was monitored by TLC (by using 1:10 ethyl acetate:hexane solvent system). After completion of the reaction, the reaction mixture was extracted with ethyl acetate three times (3x10), dried ($MgSO_4$), and concentrated under reduced pressure. Then purification performed via flash column chromatography (1:10 ethyl acetate:hexane solvent system) to isolate (*Z*)-Ethyl 2(((*R*)-1-phenylethylamino)(phenyl)methylene)pent-4-ynoate **65a** as a yellow oil (347 mg, 80 %). IR(neat): 3035-2917, 2069, 1649, 1591, 1562cm-1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.35 (t, J=7.2 Hz, 3H), 1.38 (d, J=6.9 Hz, 3H), 1.93-1.95 (br, 1H), 2.55 (dd, J=2.7 Hz, J=18.2 Hz, B part of A-B system, 1H), 2.62 (dd, J=2.7 Hz, J=18.2 Hz, A part of A-B system, 1H), 4.02 (q, J=19 Hz, 2H), 4.15-4.20 (m, 2H), 6.66 (d, J=7.6 Hz, 1H), 6.91 (d, J=7.0 Hz, 1H), 7.06-7.21 (m, 4H), 7.24-7.31 (m, 2H), 7.34-7.40 (m, 1H), 9.53 (d, J=9.0 Hz, 1H). Anal. Calcd for $C_{22}H_{23}NO_2$(333.42): C 79.25, H 6.95, N, 4.20; found: C 79.11, H, 6.41, N, 4.43.

(*R*)-Ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (66a).

(*Z*)-Ethyl 2((*R*)-1-phenylethylamino)(phenyl)methylene)pent-4-ynoate **65a** (150 mg, 0.45 mmol) was dissolved in 1,2-dichloroethane and $Cu(OAc)_2$ (16 mg**,** 0.09 mmol) was added. Then the resulting mixture was refluxed for 6 hours. The formation of products was monitored by TLC (by using 1:7 ethyl acetate:hexane solvent system). After completion of the reaction, the reaction mixture was extracted with diethyl ether three times (3x5), dried ($MgSO_4$), and concentrated under reduced pressure. Then purification was performed via flash column chromatography (1:10 ethyl acetate:hexane) to afford (*R*)-Ethyl 5-methyl-2-phenyl-

1-(1-phenylethyl)-1*H*-pyrrole 3-carboxylate as a yellow oil (114 mg, 76 % yield). $[\alpha]_D^{20}$: +185.1 (*c* 0.47, $CHCl_3$). IR(neat): 3040-2975, 1680, 1533 cm-1. ^{1}H-NMR (400 MHz, CDCl3): δ (ppm) 1.09 (t, J=7.0 Hz, 3H), 1.77 (d, J=7.1 Hz, 3H), 1.88 (s, 3H), 4.06 (q, J=7.1 Hz, 2H), 5.29 (q, J=7.0 Hz, 1H), 6.38 (s, 1H), 7.0 (d, J=7.5 Hz, 2H), 7.2-7.43 (m, 8H). ^{13}C-NMR ($CDCl_3$): δ (ppm) 14.1, 14.2, 19.1, 53.2, 58.9, 110.5, 112.6, 125.9, 127.1, 127.9, 128.2, 128.3, 128.5, 128.7, 128.8, 129.1, 130.1, 130.8, 133.1, 139.1, 141.2, 164.4. Anal. Calcd for $C_{22}H_{23}NO_2$(333.4): C 79.25, H 6.95, N, 4.20; found: C 79.35, H, 6.87, N, 4.05.

3.3.3. General Procedure for the Acid Catalyzed Cyclization Reaction

Alkylated 1,3-dicarbonyl compound (1 mmol) was dissolved in benzene (10 mL). Corresponding amine (1.2 mmol) together with TFA (77.5 μL, 0.01 mmol) was added to the stirring mixture and refluxed 12-15 hours by using Dean-Stark trap. The formation of products was monitored by TLC (by using 1:10 ethyl acetate:hexane solvent system).

After completion of the reaction, the reaction mixture extracted with ethyl acetate three times (3x10), dried ($MgSO_4$), and concentrated under reduced pressure. When further purification needed, flash column chromatography was performed (1:10 ethyl acetate:hexane) to afford the pyrrole derivatives.

Ethyl 1-benzyl-5-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate 66c.

Yellow solid (302 mg, 94%), mp 88-90^{o}C. IR(KBr): 3035-2985, 1685, 1536, 1420 cm-1. ^{1}H-NMR (400 MHz,$CDCl_3$): δ= 1.14 (t, J=7.1 Hz, 3H), 2.04 (s, 3H), 4.01 (q, J=7.1 Hz, 2H), 4.83 (s, 2H), 6.40 (s, 1H), 6.75 (d, J=7.3 Hz, 2H), 7.11-7.23 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.4, 14.2, 47.6, 59.0, 109.2, 112.9, 125.6, 127.2, 127.7, 128.1, 128.7, 128.8, 130.7, 132.3, 137.8, 138.5, 164.5, Anal. Calcd for $C_{21}H_{21}NO_2$ (319.4): C, 78.97; H, 6.63; N, 4.39. Found: C, 78.81; H, 6.77; N, 4.58.

Ethyl 2-isopropyl-5-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate 66j

Orange solid (204 mg, 75%), mp 89°C. IR(KBr): 3025-2965, 1690, 1540, 1420 cm-1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ =1.14 (d, J=7.1 Hz, 6H), 1.26 (t, J=7.1 Hz, 3H), 1.80 (s, 3H), 2.87-3.00 (m, 1H), 4.17 (q, J=7.2 Hz, 2H), 6.26 (s, 1H), 7.3 (d, J=7.3 Hz, 2H), 7.33- 7.41 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.6, 14.6, 20.7, 26.8, 59.0, 108.9, 110.7, 127.7, 128.5, 128.6, 128.7, 129.1, 138.7, 145.5, 164.7. Anal. Calcd for $C_{17}H_{21}NO_2$ (271.35): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.41; H, 7.79; N, 4.38.

Ethyl 1-benzyl-2-isopropyl-5-methyl-1*H*-pyrrole-3-carboxylate 66k.

Yellow oil (271 mg, 95%). IR(neat): 3030-2945, 1688, 1543, 1430 cm-1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, J=7.2 Hz, 6H), 1.27 (t, J=7.1 Hz, 3H), 2.0 (s, 3H), 3.34-3.39 (m, 1H), 4.16 (q, J=7.1 Hz, 2H), 5.1 (s, 2H), 6.26 (s, 1H), 6.8 (d, J=7.5 Hz, 2H), 7.13-7.23 (m, 3H). ^{13}C-NMR (100 MHz, CDCl3): δ =12.2, 14.6, 20.7, 25.9, 43.8, 47.5, 59.0, 109.4, 110.6, 125.4, 127.3, 127.6, 128.1, 128.5, 128.7, 137.7, 144.6, 164.9. Anal. Calcd for $C_{18}H_{23}NO_2$ (285.38): C, 75.76; H, 8.12; N, 4.91. Found: C, 75.58; H, 8.28; N, 4.68.

(*S*)-Ethyl 2-(3-acetyl-2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(methylthio)butanoate 66l.

Yellow oil (283 mg, 95%). $[\alpha]_D^{20}$: -21.5 (*c* 0.65 *),* $CHCl_3$). IR(neat): 3010, 2358, 1733, 1646, 1589 cm-1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.16-1.20 (m, 3H), 2.00 (s, 3H), 2.13 (s, 3H), 2.27 (s, 3H), 2.41-2.54 (m, 4H), 4.13 (q, J=7.1 Hz, 2H), 4.95 (t, J=7.1 Hz 1H), 6.11 (s, 1H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.1, 13.0, 14.1, 21.6, 27.4, 28.6, 29.5, 54.0, 60.7, 108.2, 120.5, 127.6, 135.6, 168.7, 193.2. Anal. Calcd for $C_{15}H_{23}NO_3S$(297.41): C, 60.58; H, 7.79; N, 4.71. Found: C, 60.37; H, 7.68; N, 4.53.

(*S*)-Methyl 2-(3-acetyl-2,5-dimethyl-1*H*-pyrrol-1-yl)propanoate 66m.

Yellow oil (262 mg, 88%). [α]D 20: -41.2 (*c* 0.42, $CHCl_3$). IR(neat): 3007, 2360, 1744, 1648, 1520 cm-1. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, J=7.3 Hz, 3H), 2.10 (s, 3H), 2.28 (s, 3H),2.43 (s, 3H), 3.68(s, 3H),4.83 (q, J=7.3 Hz, 1H), 6.15 (s, 1H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.1, 12.8, 17.1, 28.5, 52.3, 52.8, 109.3, 120.5, 127.3, 134.7, 170.9, 194.9. Anal. Calcd for $C_{12}H_{17}NO_3$(297.41): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.33; H, 7.78; N, 6.11.

3.4. Addition of acyl phosphonates to diethyl cyanophosphonate (DEPC)

3.4.1 General procedure for the addition of acyl phosphonates to DEPC

To a solution of 0.5 mmol of acyl phosphonate in 2 mL of dry THF, 0.5 mmol of (1 equiv.) diethyl cyanophosphonate was added under argon at room temperature. After cooling to -20°C, KCN (2 mg) was added in one portion. The reaction was stirred at room temperature and monitored by TLC (completed within 12-24 hr). After completion of the reaction, THF was removed under reduced pressure and crude product was purified with flash column chromatography using ethyl acetate as eluent.

1-(Ethoxyphosphono)-1-cyanoethyl-dimethyl phosphate 79a:

Yield 75 %, yellow oil, IR (KBr): 2990, 2256, 1435, 1270, 1028, 845, 590. ^{1}H-NMR (400MHz, $CDCl_3$): 1.33 (m, 6H); 1.97 (d, J= 14.7 Hz, 3H); 3.89 (d, J= 6.5 Hz, 3H); 3.92 (d, J= 6.5 Hz, 3H); 4.07-4.21 (m, 4H). ^{13}C NMR (100MHz, $CDCl_3$): 114.9 (d, J= 6.2 Hz), 69.6 (dd, J= 178, 9.4 Hz), 64.8 (d, J= 6.0 Hz), 64.6 (d, J= 6.0 Hz), 55.7 (d, J= 6.3 Hz), 55.1 (d, J= 6.5 Hz), 22.1, 16.0 (d, J= 6.7 Hz). ^{31}P-NMR ($CDCl_3$) -5.4, -5.1, 13.0, 13.2.

1-(Ethoxyphosphono)-1-cyanopropyl-dimethyl phosphate 79b:

Yield 73%, yellow oil, IR (KBr): 2985, 2240, 1470, 1375, 1281, 1027, 835, 559. ^{1}H-NMR (400MHz, $CDCl_3$): 1.16 (t, J= 7.6 Hz, 3H)); 1.33 (m, 6H); 2.27 (m, 2H); 3.89 (d, J= 2.9 Hz, 3H); 3.91 (d, J= 2.9 Hz, 3H); 4.16 (m, 4H). ^{13}C-NMR (100MHz, $CDCl_3$): 114.2 (d, J= 4.5 Hz), 73.9 (dd, J= 189, 14.5 Hz), 64.8 (d, J= 6.1 Hz), 64.6 (d, J= 6.1 Hz), 55.5 (d, J= 7.0 Hz), 54.9 (d, J= 7.2 Hz), 29.6, 16.0 (d, J= 6.8 Hz), 8.4. ^{31}P-NMR: -5.1, -4.9, 13.2, 13.4.

1-(Ethoxyphosphono)-1-cyano-2,2-dimethylpropyl-dimethyl phosphate 79c:

Yield 81%, yellow oil, IR (KBr): 2983, 2245, 1479, 1372, 1275, 1031, 837, 589. ^{1}H-NMR (400MHz, $CDCl_3$): 1.21 (s, 9H); 1.33 (t, J= 7.0 Hz, 6H); 3.88 (d, J= 10.9 Hz, 3H); 3.92 (d, J= 10.9 Hz, 3H); 4.13-4.21 (m, 4H). ^{13}C-NMR (100MHz, $CDCl_3$): 114.0 (d, J= 6.2 Hz), 79.7 (dd, J= 170.0, 13.0 Hz), 64.7 (d, J= 5.8 Hz), 55.2 (d, J= 8.7 Hz), 55.1 (d, J= 7.0 Hz), 40.6, 25.8 (d, J= 4.3 Hz), 16.0 (d, J= 5.7 Hz). ^{31}P-NMR: -5.8, -5.7, 12.5, 12.6.

(Ethoxyphosphono)(cyano)(cyclohexyl)methyl-dimethyl phosphate 79d:

Yield 85%, yellow oil, IR (KBr): 2987, 2254, 1449, 1270, 1046, 808, 764. ^{1}H-NMR (400MHz, $CDCl_3$): 1.17-1.35 (m, 12H); 1.62-2.18 (m, 5H); 3.88 (d, J= 3.8 Hz, 3H); 3.91 (d, J= 3.9 Hz, 3H); 4.12-4.20 (m, 4H). ^{13}C-NMR(100MHz, $CDCl_3$): 113.9 (d, J= 5.9 Hz), 75.7 (dd, J= 220, 11.8 Hz), 64.7 (d, J= 5.3 Hz), 63.4 (d, J=5.5 Hz), 55.4 (d, J= 7.3 Hz), 54.9 (d, J= 7.3 Hz), 44.8, 27.3 (dd, J= 16.7, 3.6 Hz), 25.9, 25.6, 16.0 (m). ^{31}P-NMR: -5.3, -5.1, 12.8, 12.9

(Ethoxyphosphono)(cyano)(phenyl)methyl-dimethyl phosphate 79e:

Yield 90%, colorless oil, IR (KBr): 2986, 2256, 1443, 1273, 1028, 847, 808. ^{1}H-NMR (400MHz, $CDCl_3$): 1.19 (t, J= 7.0 Hz, 3H); 1.24 (t, J= 7.2 Hz, 3H); 3.60 (d, J= 10.8 Hz, 3H); 3.87 (d, J= 10.8 Hz, 3H); 3.94-4.10 (m, 4H); 7.40 (m, 3H); 7.70 (m, 2H). ^{13}C-NMR (100MHz, $CDCl_3$): 130.0 (d, J= 4.0 Hz), 129.1, 128.0, 127.4, 126.3 (d, J= 4.5 Hz), 113.0 (d, J= 4.0 Hz), 74.0 (dd, J= 172.5, 11.0 Hz), 63.6 (d, J= 5.8 Hz), 63.4 (d, J= 5.9 Hz), 54.7 (d, J= 7.0 Hz), 54.5 (d, J= 6.9 Hz), 14.8 (m). ^{31}P-NMR: -4.9, -4.6, 11.5, 11.8

(Ethoxyphosphono)(cyano)(p-tolyl)methyl-dimethyl phosphate 79f:

Yield 86%, colorless oil, IR (KBr): 2986, 2260, 1446, 1274, 1020, 859, 763. ^{1}H-NMR (400MHz, $CDCl_3$): 1.20 (m, 6H); 2.33 (s, 3H); 3.59 (d, J= 10.8 Hz, 3H); 3.87 (d, J= 10.8 Hz, 3H); 3.93-4.10 (m, 4H); 7.18 (d, J= 8.1Hz, 2H); 7.57 (dd, J= 8.2, 1.8 Hz, 2H). ^{13}C-NMR (100MHz, $CDCl_3$): 140.3, 130.0, 129.7, 127.9, 127.5, 127.3, 114.3, 74.6 (dd, J= 173.0, 10.7 Hz), 64.6 (d, J= 5.2 Hz), 64.5 (d, J= 5.6 Hz), 55.8 (d, J= 7.3 Hz), 55.5 (d, J= 6.9 Hz), 21.2, 15.8 (m). ^{31}P-NMR: -4.9, -4.6, 11.6, 11.

(Ethoxyphosphono)(cyano)(4-methoxyphenyl)methyl-dimethyl phosphate 79g:

Yield 82%, colorless oil, IR (KBr): 2978, 2247, 1435, 1270, 1018, 850, 785. ^{1}H-NMR (400MHz, $CDCl_3$): 1.24 (m, 6H); 3.58 (d, J= 10.8 Hz, 3H); 3.76 (s, 3H); 3.88 (d, J= 10.6 Hz, 3H); 3.92-4.09 (m, 4H); 6.88 (d, J= 8.6Hz, 2H); 7.60 (d, J= 8.5 Hz, 2H). ^{13}C-NMR (100MHz, $CDCl_3$): 161.1, 133.1, 132.0, 129.3 (d, J= 4.5 Hz), 114.3, 113.9, 73.8 (dd, J= 187.0, 11.7 Hz), 64.6 (d, J= 6.1 Hz), 64.4 (d, J= 5.9 Hz), 55.8 (d, J= 7.6 Hz), 55.5 (d, J= 7.3 Hz), 55.1, 16.0 (d, J= 6.4 Hz). ^{31}P-NMR: -5.5, -5.2, 11.1, 11.4.

(Ethoxyphosphono)(cyano)(4-fluorophenyl)methyl-dimethyl phosphate 79h:

Yield 80%, colorless oil, IR (KBr): 2990, 2260, 1465, 1284, 1048, 875. ^{1}H-NMR (400MHz, $CDCl_3$): 1.23 (m, 6H); 3.63 (d, J= 10.7 Hz, 3H); 3.90 (d, J= 10.8 Hz, 3H); 3.96-4.11 (m, 4H); 7.08 (t, J= 8.5 Hz, 2H); 7.70 (m, 2H). ^{13}C-NMR (100MHz, $CDCl_3$): 163.7 (d, J=250 Hz), 129.7 (d, J= 4.5 Hz), 129.6 (d, J= 4.6 Hz), 115.8, 115.6, 114.0, 109.3, 74.4 (dd, J= 173.7, 10.7 Hz), 64.8 (d, J= 6.0 Hz), 64.6 (d, J= 5.9 Hz), 55.9 (d, J= 6.8 Hz), 55.5 (d, J= 6.3 Hz), 15.8 (d, J= 5.1 Hz). ^{31}P-NMR: -5.3, -5.0, 10.8, 11.1.

(Ethoxyphosphono)(3-chlorophenyl)(cyano)methyl-dimethyl phosphate 79i:

Yield 75%, pale-yellow oil, IR (KBr): 2985, 2257, 1446, 1280, 1050, 855. ^{1}H-NMR (400MHz, $CDCl_3$): 1.22 (m, 6H); 3.67 (d, J= 10.8 Hz, 3H); 3.88 (d, J= 10.8 Hz, 3H); 4.02 (m, 4H); 7.34 (m, 2H); 7.58 (dd, J= 7.0, 2.2 Hz, 1H), 7.64 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 134.7, 133.0 (d, J= 4.2 Hz), 130.4, 129.8, 127.3 (d, J= 4.6 Hz), 125.4 (d, J= 4.8 Hz), 113.8, 74.4 (dd, J= 171.7, 10.6 Hz), 64.8 (d, J= 5.9 Hz), 64.7 (d, J= 6.0 Hz), 56.1 (d, J= 7.1 Hz), 55.7 (d, J= 7.1 Hz), 15.8 (m). ^{31}P-NMR: -4.7, -4.5, 11.0, 11.3.

CHAPTER 4

CONCLUSION

Phenolic α-hydroxy carboxylic acids are important building blocks of phenolic aminoacids and most of them are biologically active and known as phenolic antioxidant compounds. Because this type of hydroxycarboxylic acid compounds and their derivatives have very often been shown to be biologically active, their synthesis gained much importance in recent years.

A new and efficient route has been developed for the synthesis of chiral lactones and their phenolic α-hydroxycarboxylic acid derivatives which are interesting intermediates for the synthesis of amino acids and other interesting compounds. The α-acetoxylation of aromatic ketones by using $Mn(OAc)_3$ followed by the enzyme catalyzed kinetic resolution of acetoxy ketones furnished both of the enantiomers of α-acetoxy ketones in good chemical and optical yields. The Bayer-Villiger oxidation of chiral α-acetoxy ketones with m-CPBA, triflic acid (CF_3SO_3H), and CH_2Cl_2, at rt gave the corresponding lactones without racemization (Figure 4.1). The acetoxy ketone moiety migrates selectively in order to form lactones. In a representative example, lactones were converted to phenolic α-hydroxy esters **5a,b** in 84-88% yields.

The results show that the $Mn(OAc)_3$-mediated acetoxylation of aromatic ketones followed by BV oxidation selectively furnishes lactones in good to high yields.

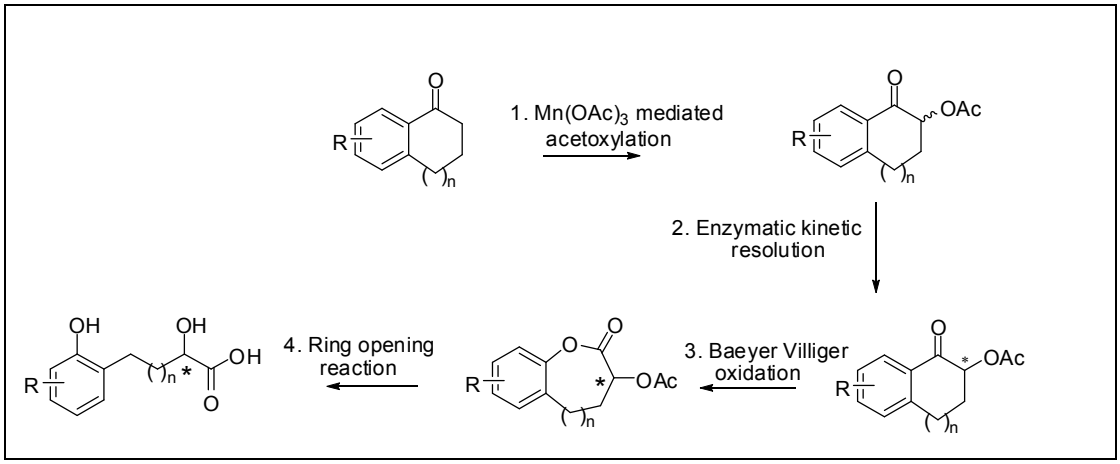


Figure 4.1. General reaction scheme for the synthesis of phenolic α-hydroxy carboxylic acids

1,2,3,5-tetrasubstituted pyrrole derivatives are biologically active and have been proven to display antibacterial, antiviral, anti-inflammatory and antioxidant activities to inhibit cytokine-mediated diseases. Therefore, synthesis of pyrroles in high yields with minimum number of steps through catalytic reaction are highly desired.

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 (Figure 4.2). The reaction requires a catalyst. TFA is the most efficient and selective catalysts and its application is general, but $Cu(OAc)_2$ is also efficient catalysts when enaminones are used. In summary, the condensation reaction of 2-propynyl-1,3-dicarbonyl compounds with amines catalyzed by TFA represents a new general one-pot entry into fuctionalized pyrroles.

According to this new strategy 1,2,3,5-tetrasubstituted pyrrole derivatives could be synthesized in two steps without the use of metal which can be considered as green chemistry.

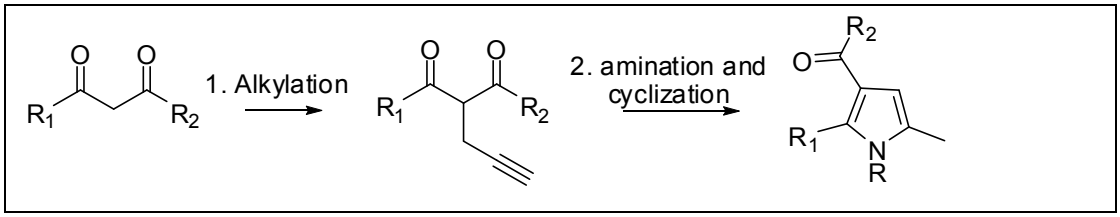


Figure 4.2. General reaction scheme for the synthesis of 1,2,3,5-tetrasubstituted pyrroles

The synthesis of cyanohydrins has gained much attention due to the importance of cyanohydrins as a synthetic building block for a variety of pharmaceutically desirable compounds.

Cyanide ion catalyzed addition of acyl phosphonates to diethyl cyanophosphonate furnished in high yield phosphonocyanohydrin-*O*-phosphates. The reaction works via phosphonate-phosphate rearrangement and is then followed by the addition of cyanohydrin phosphate anion to diethylcyanophosphonate.

In conclusion, we developed a convenient, one-pot procedure for preparing various phosphonocyanohydrin-*O*-phosphates with the formation of a new carbon-phosphorus bond starting from readily available acyl phosphonates and diethyl cyanophosphonate under mild conditions in good to high yields (83-98%) (Figure 4.3).

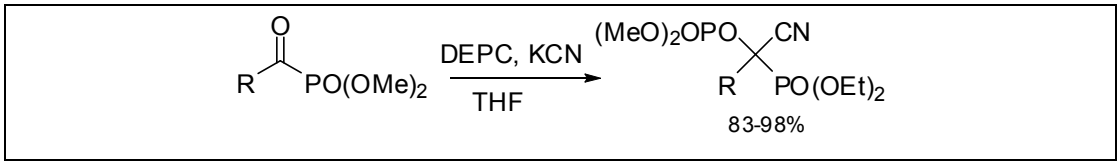


Figure 4.3. General reaction scheme for the synthesis of phosphonocyanohydrin-*O*-phosphates

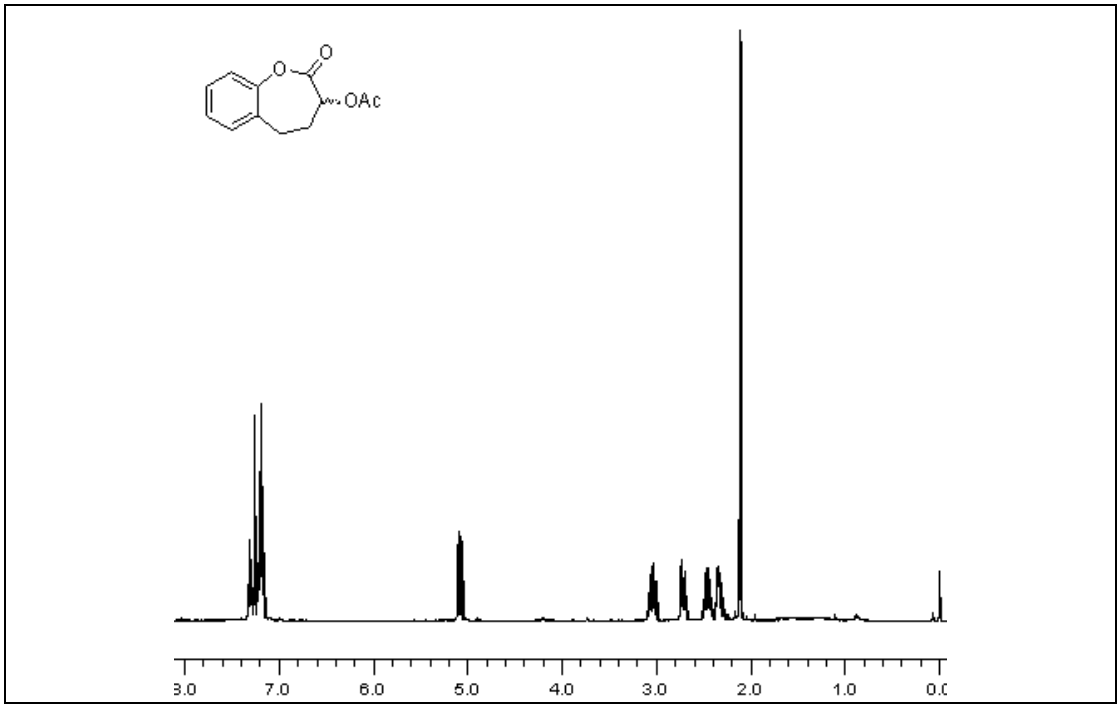


Figure 4.4. H^1 NMR spectrum of (±)-2,3,4,5-tetrahydro-2-oxobenzooxepin-3-yl acetate **52a**

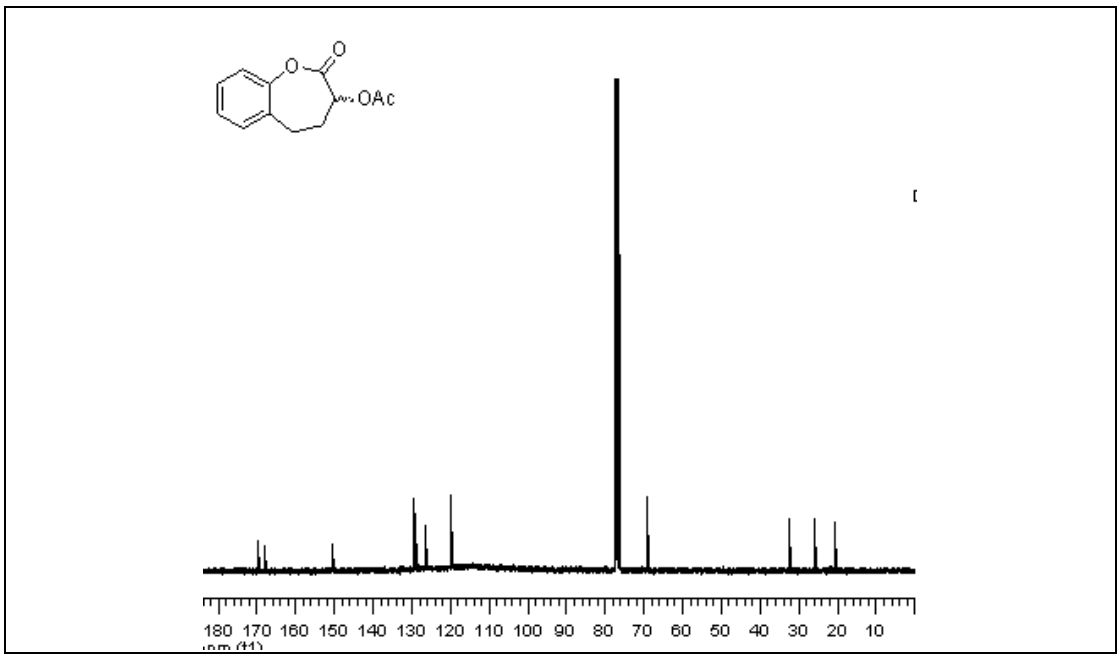


Figure 4.5. ^{13}C NMR spectrum of (±)-2,3,4,5-tetrahydro-2-oxobenzooxepin-3-yl acetate **52a**

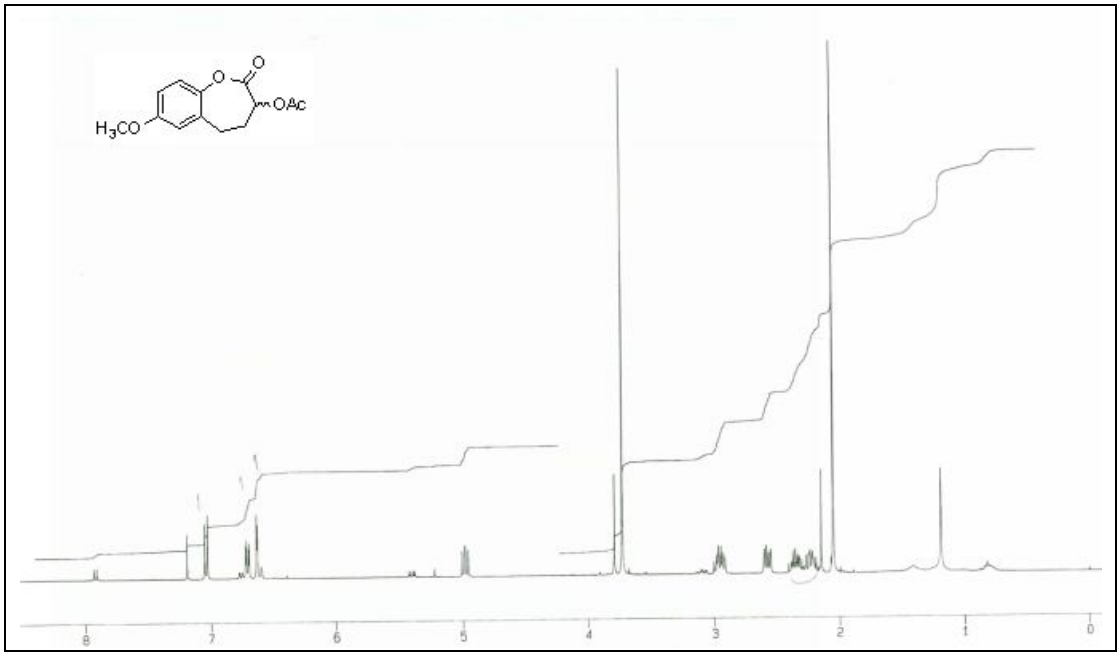


Figure 4.6. H^1 NMR spectrum of (±)-2,3,4,5-tetrahydro-7-methoxy-2-oxobenzooxepin-3-yl acetate **52b**

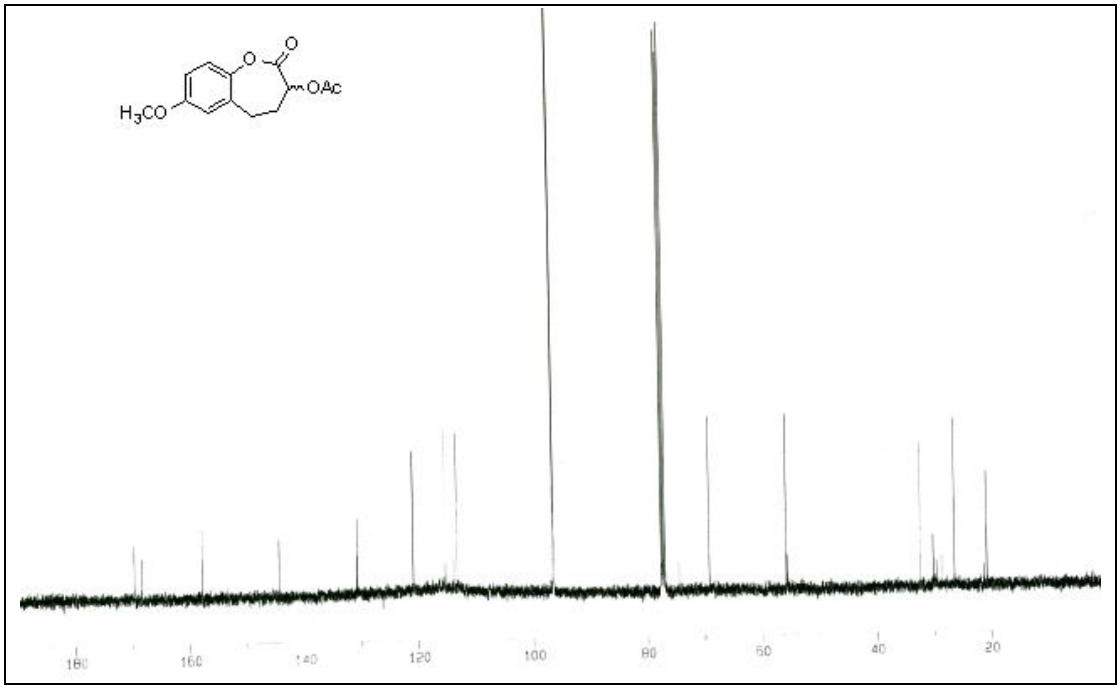


Figure 4.7. ^{13}C NMR spectrum of (±)-2,3,4,5-tetrahydro-7-methoxy-2-oxobenzooxepin-3-yl acetate **52b**

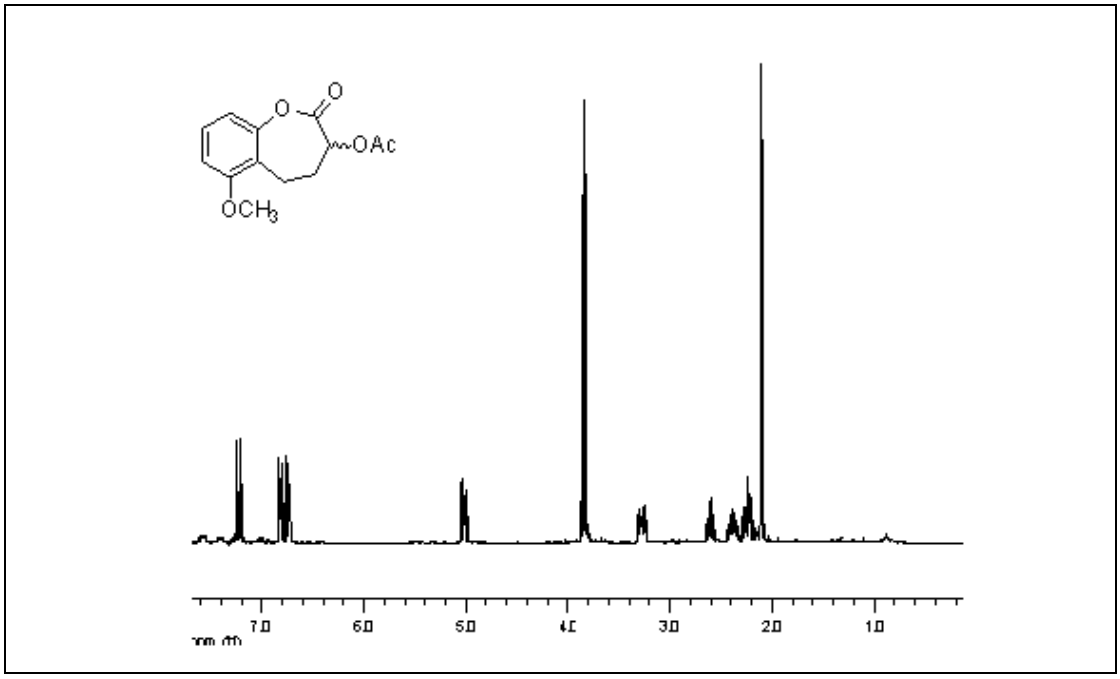


Figure 4.8. H^1 NMR spectrum of (±)-2,3,4,5-tetrahydro-6-methoxy-2-oxobenzooxepin-3-yl acetate **52c**

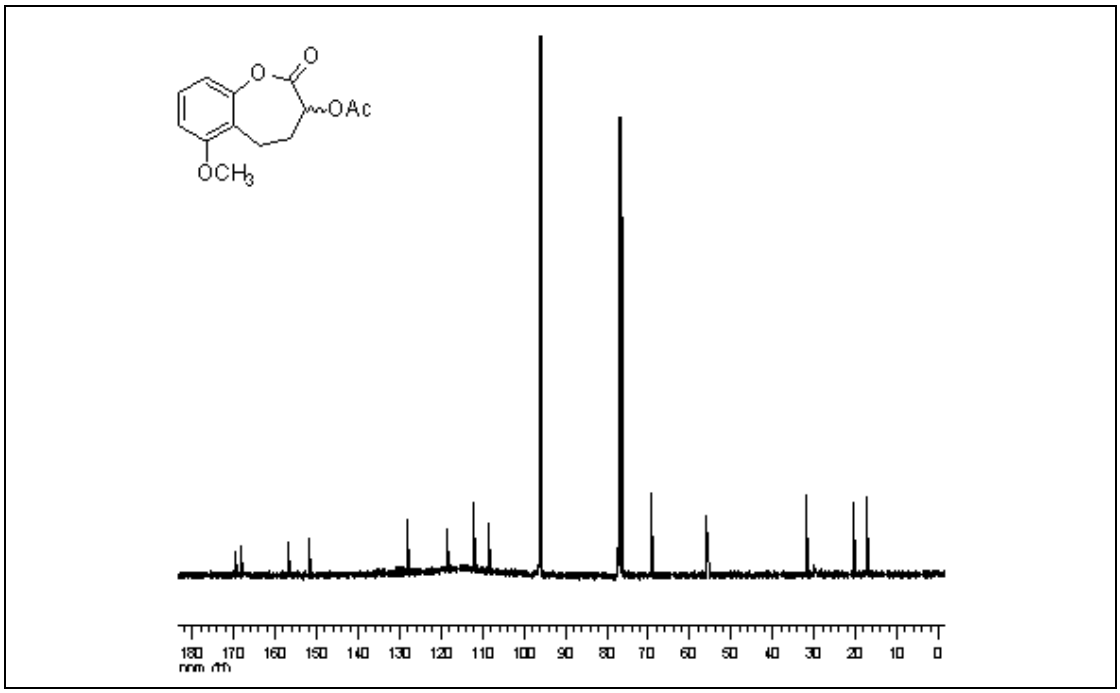


Figure 4.9. ^{13}C NMR spectrum of (±)-2,3,4,5-tetrahydro-6-methoxy-2-oxobenzooxepin-3-yl acetate **52c**

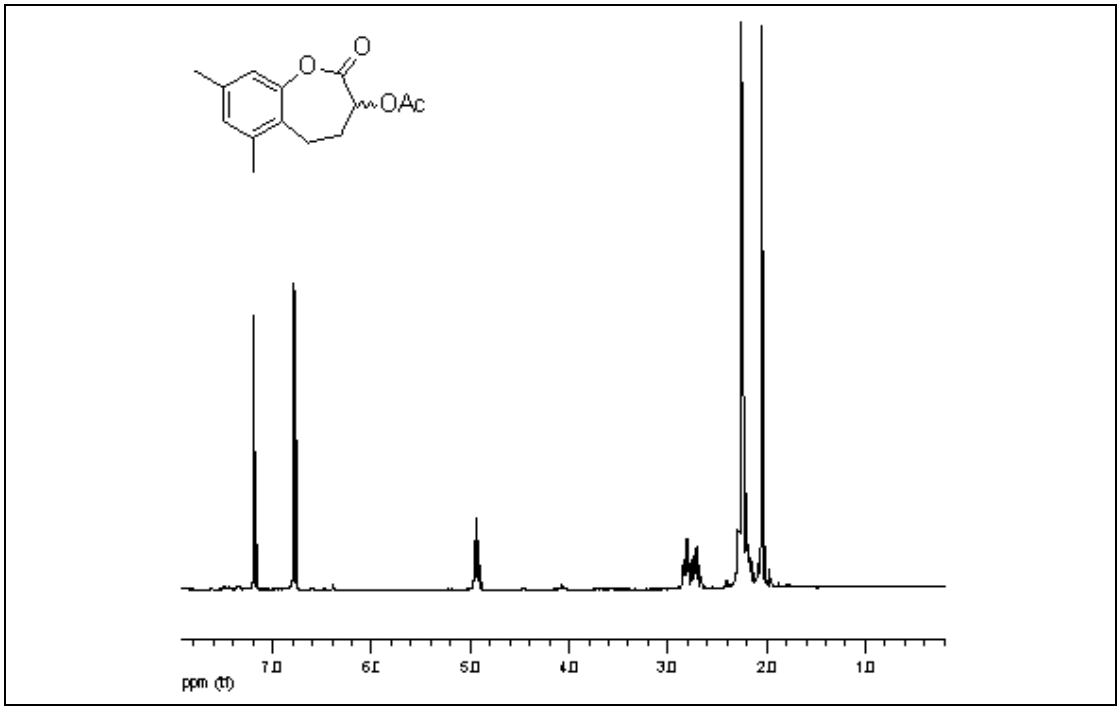


Figure 4.10. H^1 NMR spectrum of (±)-2,3,4,5-tetrahydro-6,8-dimethyl-2-oxobenzooxepin-3-yl acetate **52d**

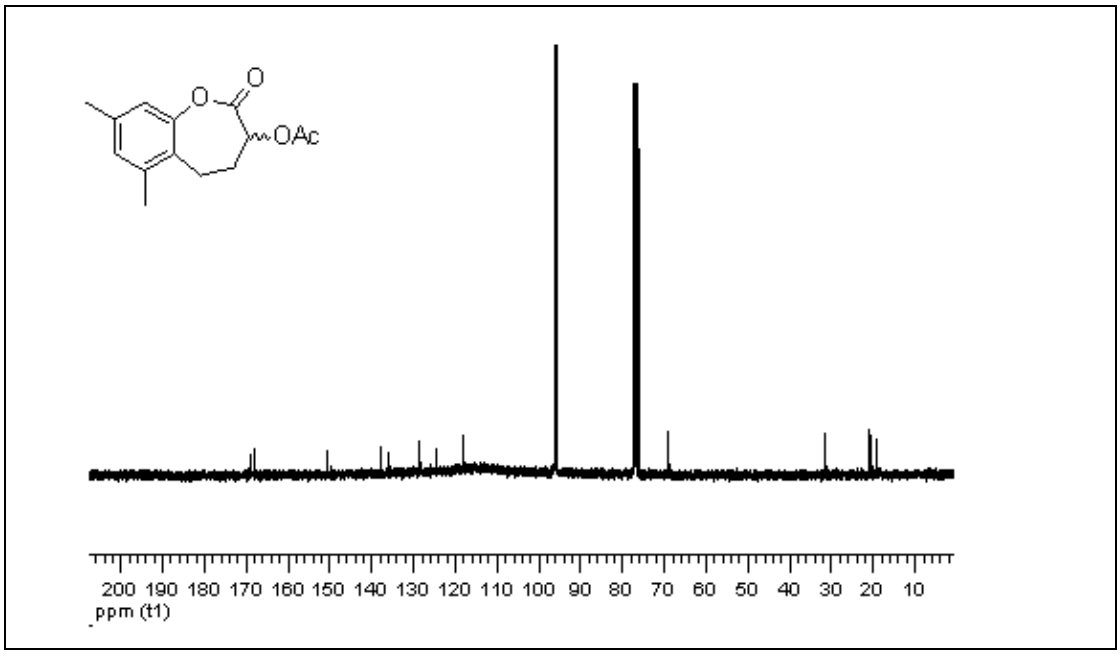


Figure 4.11. ^{13}C NMR spectrum of (±)-2,3,4,5-tetrahydro-6,8-dimethyl-2-oxobenzooxepin-3-yl acetate **52d**

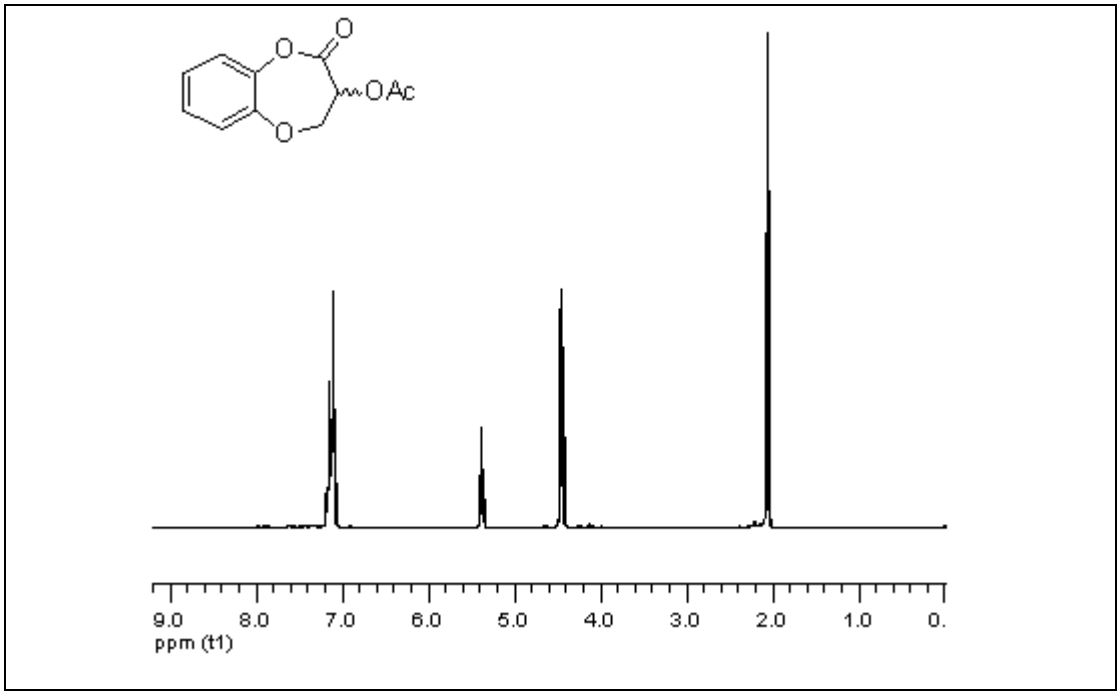


Figure 4.12. H^1 NMR spectrum of (±)-3,4-dihydro-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate **52e**

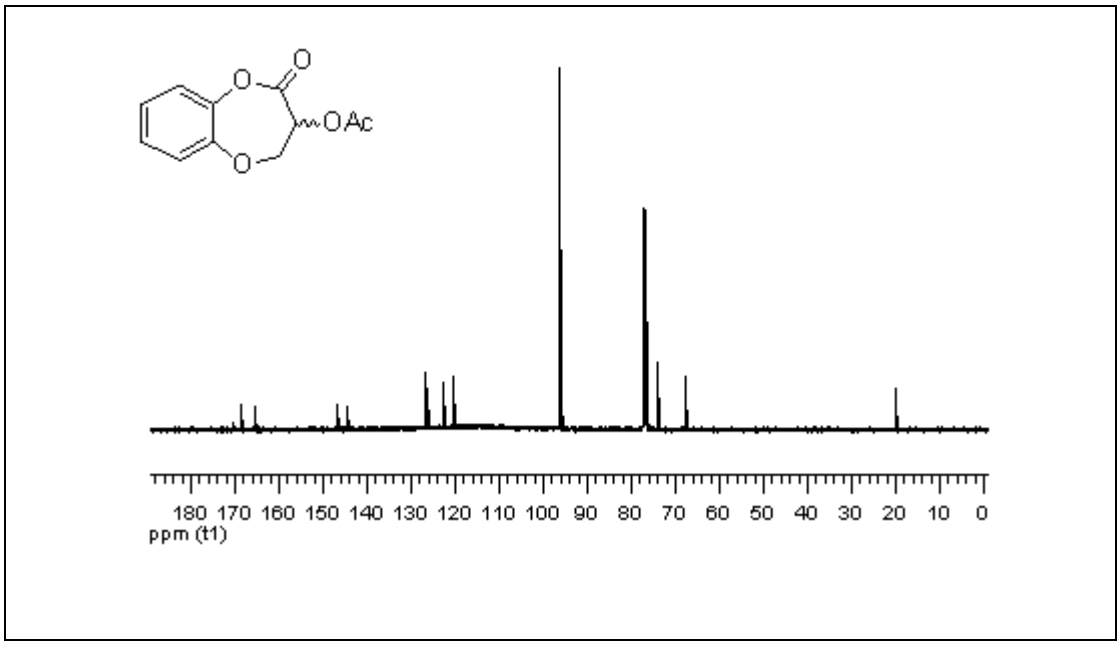


Figure 4.13. ^{13}C NMR spectrum of (±)-3,4-dihydro-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate **52e**

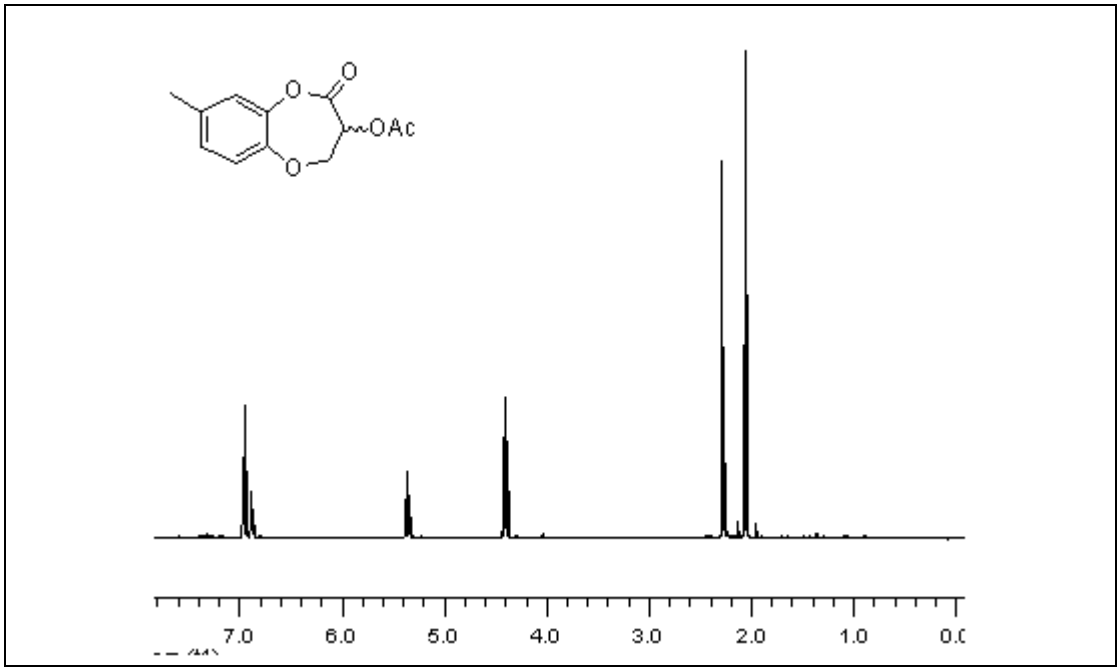


Figure 4.14. H^1 NMR spectrum of (±)-3,4-dihydro-8-methyl-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate **52f**

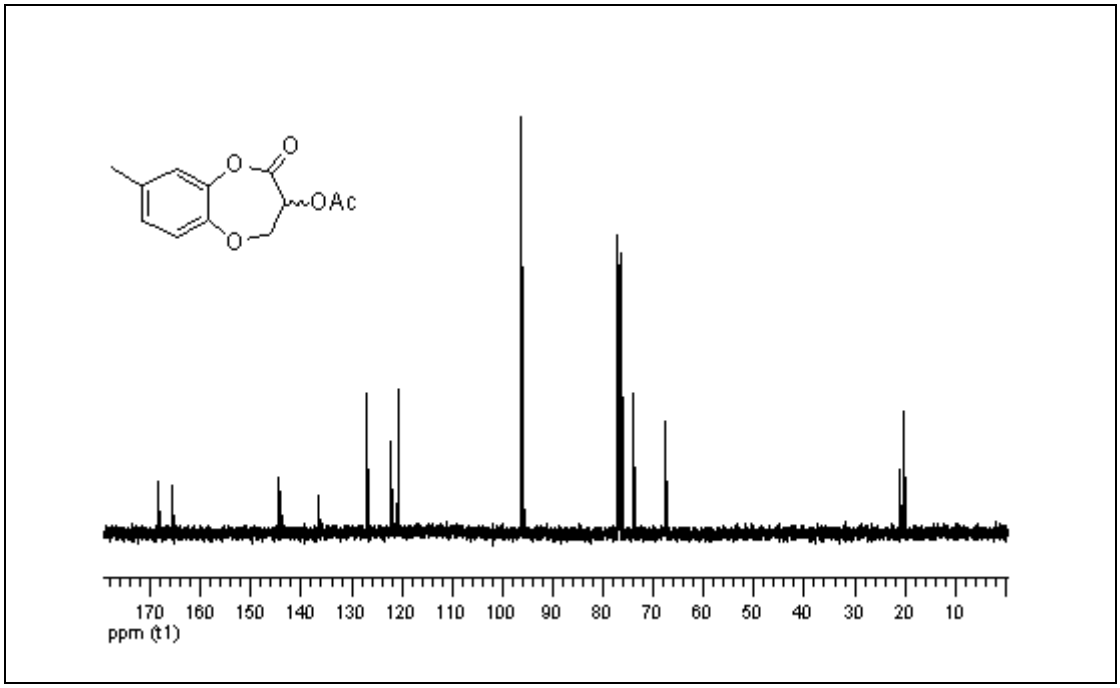


Figure 4.15. ^{13}C NMR spectrum of (±)-3,4-dihydro-8-methyl-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate **52f**

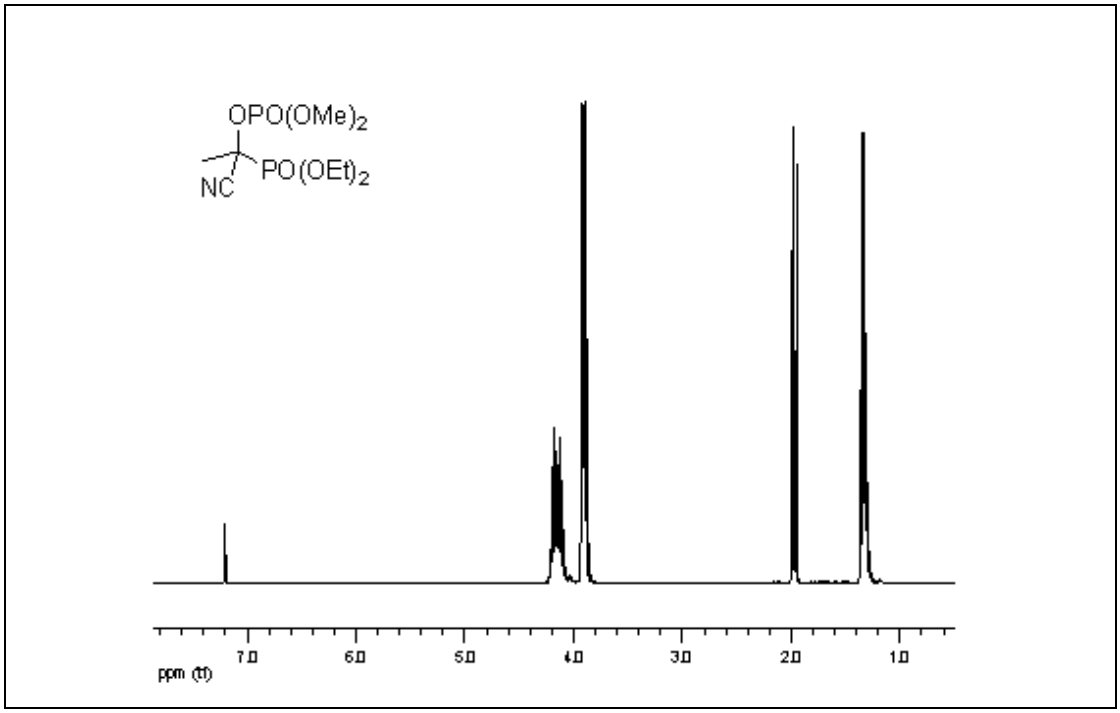


Figure 4.16. H^1 NMR spectrum of 1-(Ethoxyphosphono)-1-cyanoethyl-dimethyl phosphate **79a**

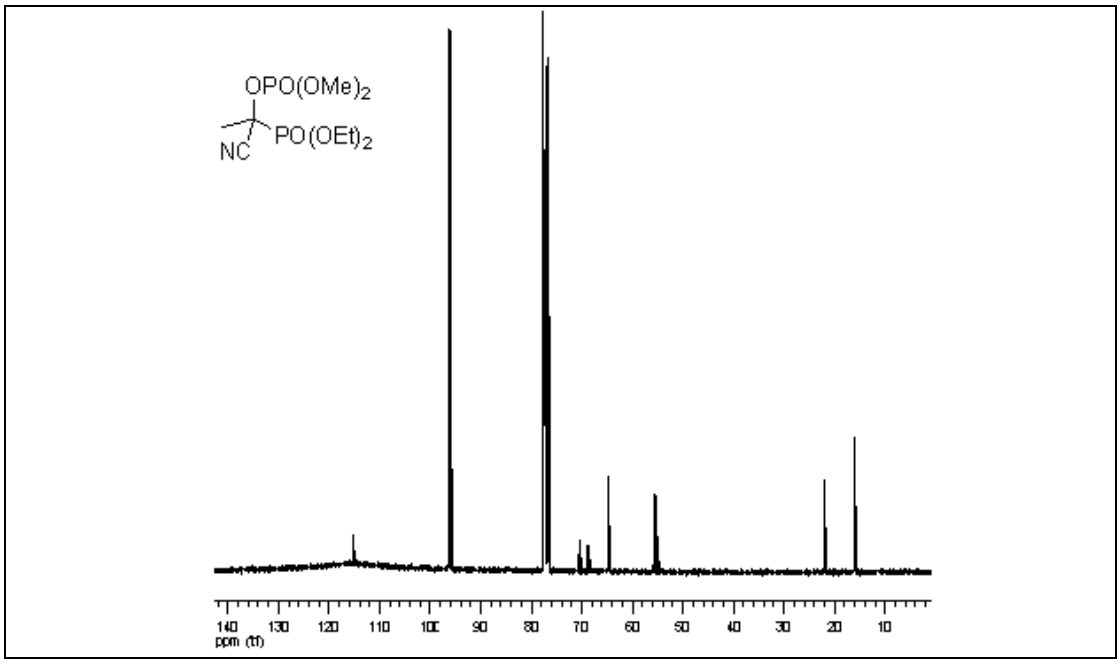


Figure 4.17. ^{13}C NMR spectrum of 1-(Ethoxyphosphono)-1-cyanoethyl-dimethyl phosphate **79a**

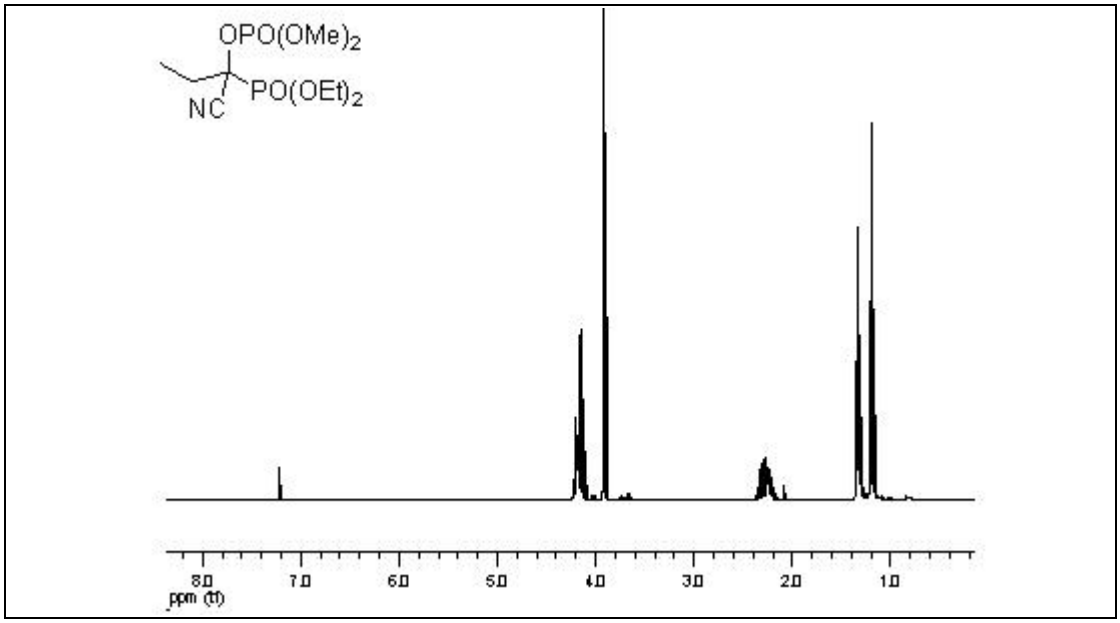


Figure 4.18. H^1 NMR spectrum of 1-(Ethoxyphosphono)-1-cyanopropyl-dimethyl phosphate **79b**

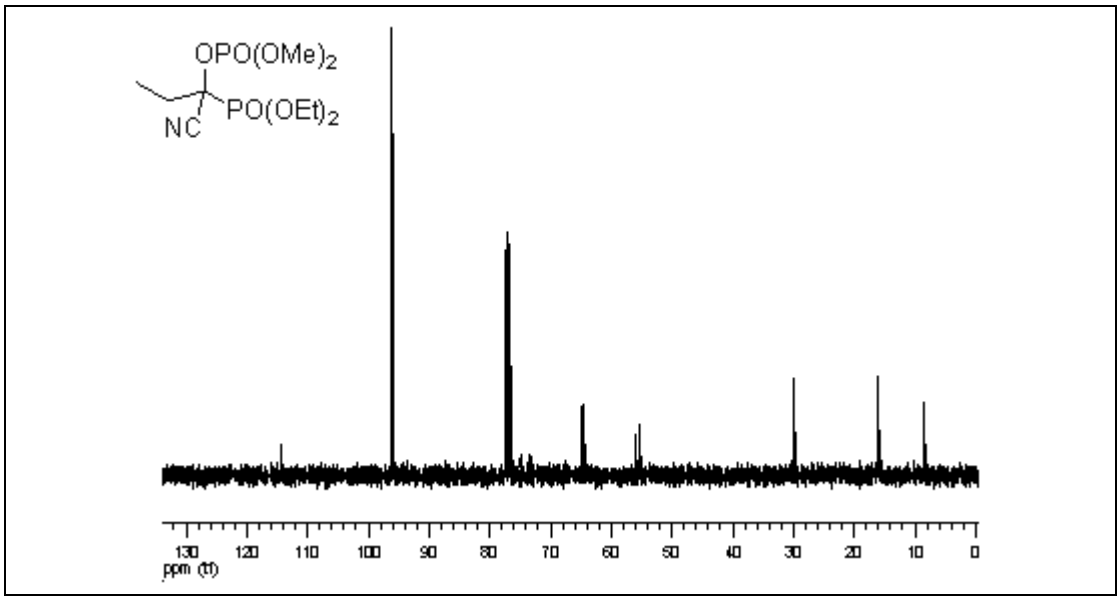


Figure 4.19. ^{13}C NMR spectrum of 1-(Ethoxyphosphono)-1-cyanopropyl-dimethyl phosphate **79b**

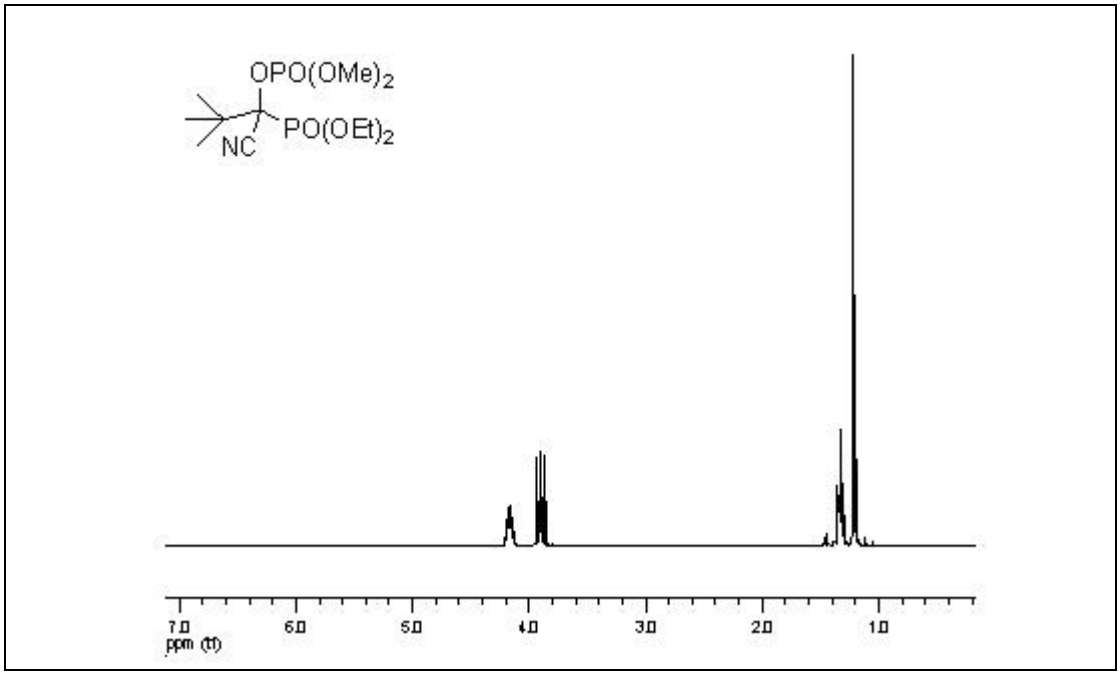


Figure 4.20. H^1 NMR spectrum of 1-(Ethoxyphosphono)-1-cyano-2,2-dimethylpropyl-dimethyl phosphate **79c**

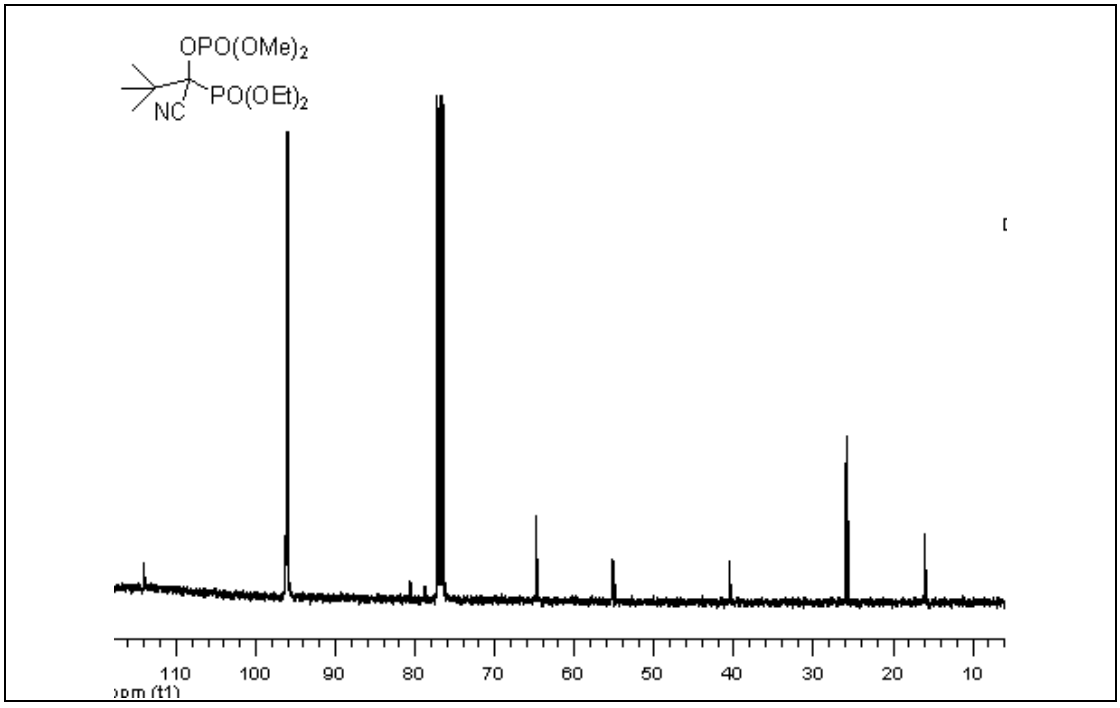


Figure 4.21. ^{13}C NMR spectrum of 1-(Ethoxyphosphono)-1-cyano-2,2-dimethylpropyl-dimethyl phosphate **79c**

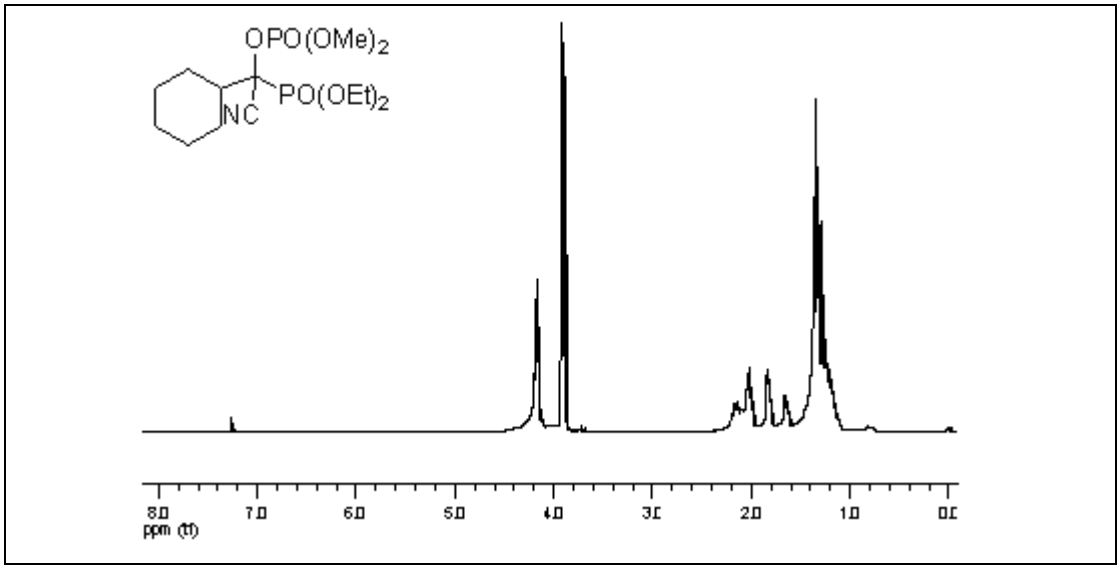


Figure 4.22. H^1 NMR spectrum of (Ethoxyphosphono)(cyano)(cyclohexyl)methyl-dimethyl phosphate **79d**

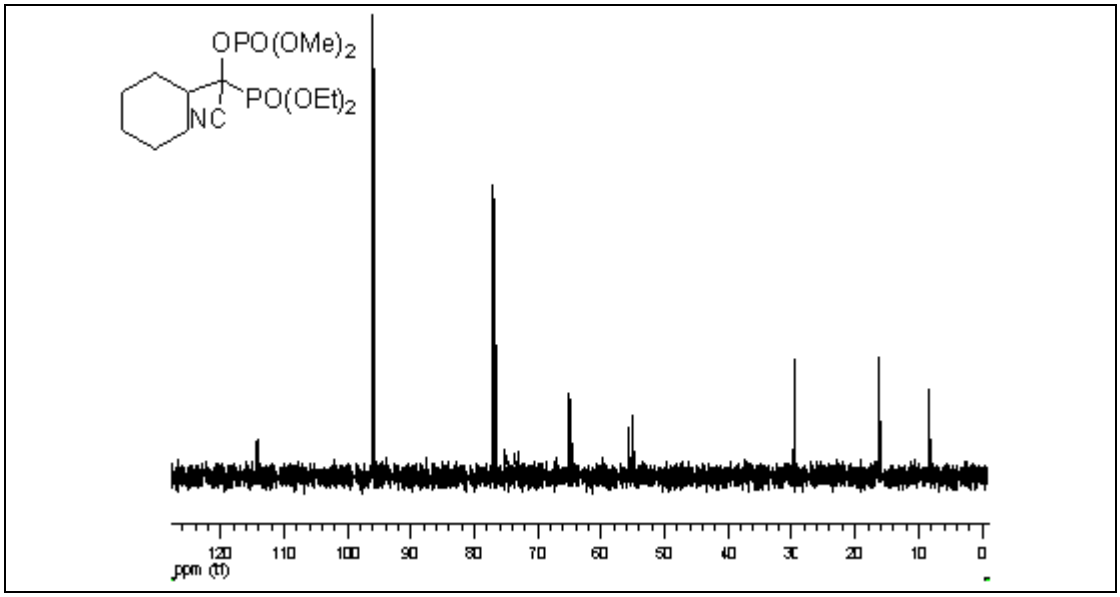


Figure 4.23. ^{13}C NMR spectrum of (Ethoxyphosphono)(cyano)(cyclohexyl)methyl-dimethyl phosphate **79d**

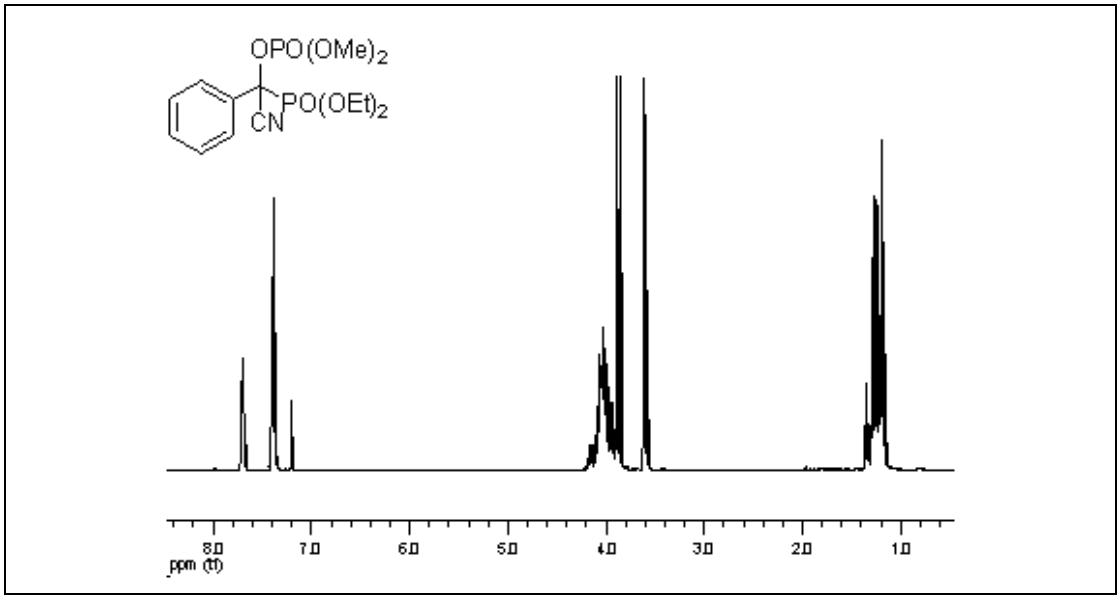


Figure 4.24. H^1 NMR spectrum of (Ethoxyphosphono)(cyano)(phenyl)methyl-dimethyl phosphate **79e**

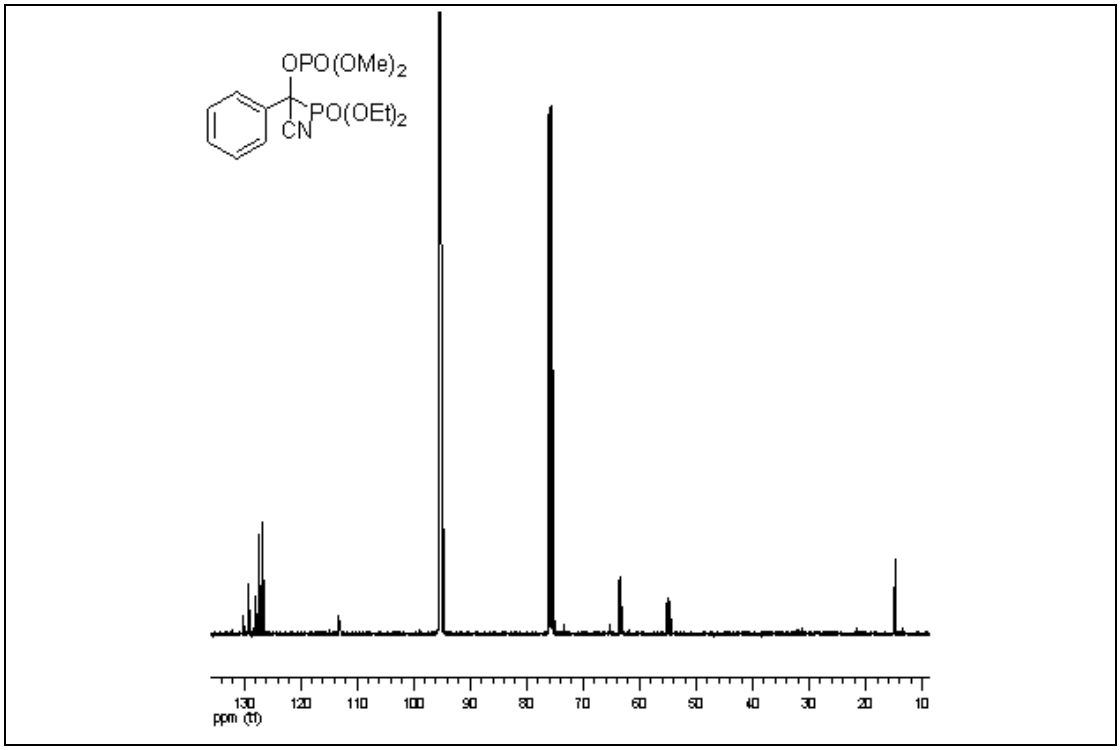


Figure 4.25. ^{13}C NMR spectrum of (Ethoxyphosphono)(cyano)(phenyl)methyl-dimethyl phosphate **79e**

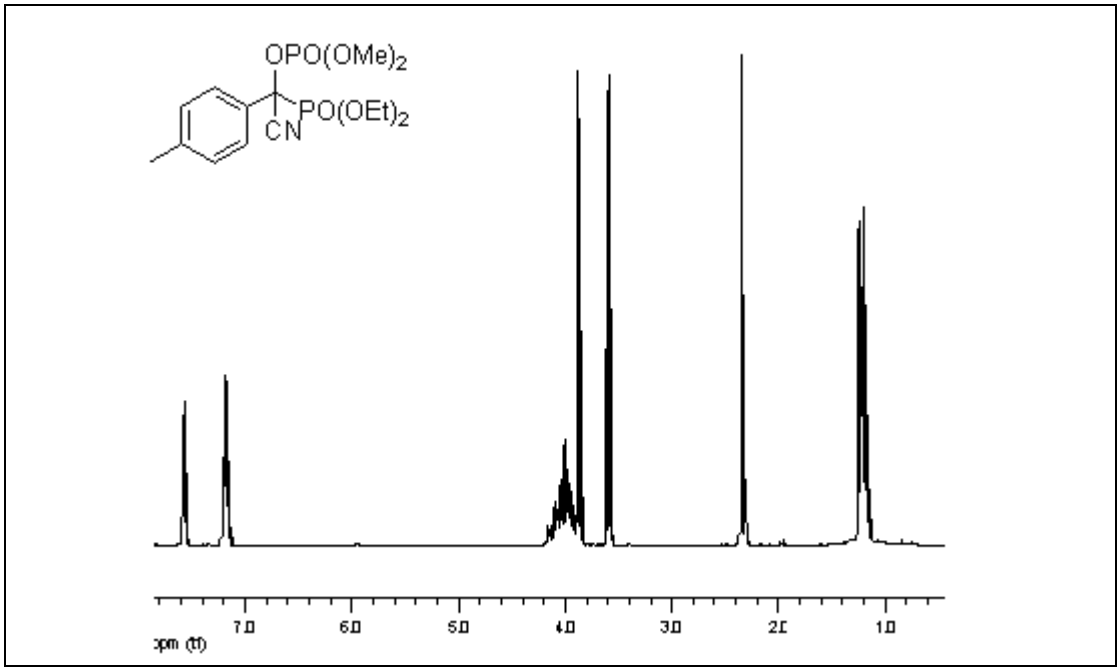


Figure 4.26. H^1 NMR spectrum of (Ethoxyphosphono)(cyano)(p-tolyl)methyl-dimethyl phosphate **79f**

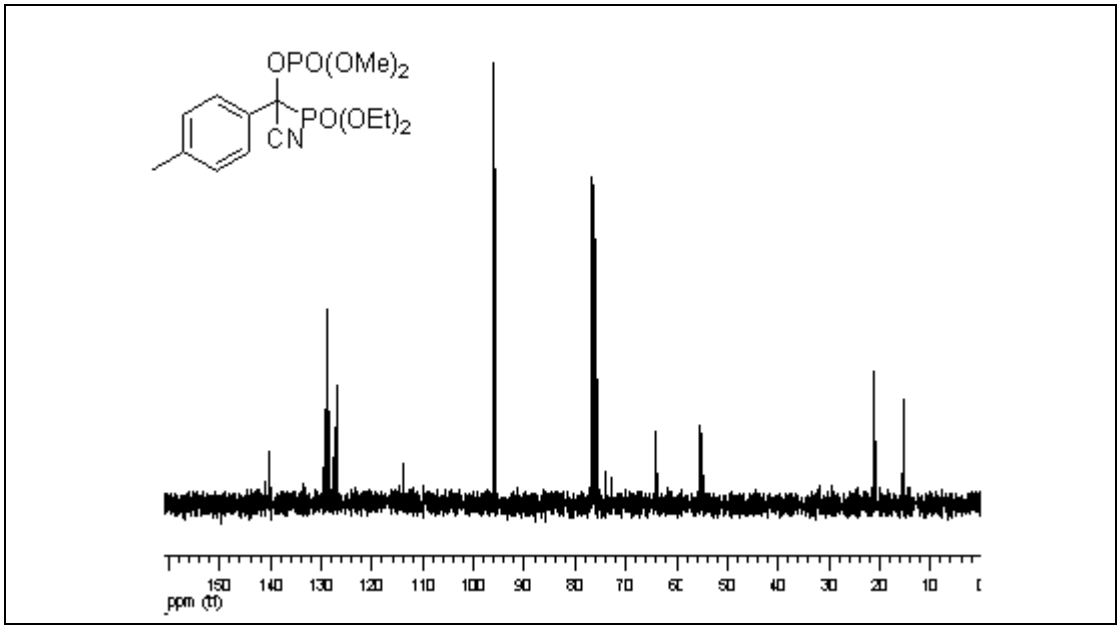


Figure 4.27. ^{13}C NMR spectrum of (Ethoxyphosphono)(cyano)(p-tolyl)methyl-dimethyl phosphate **79f**

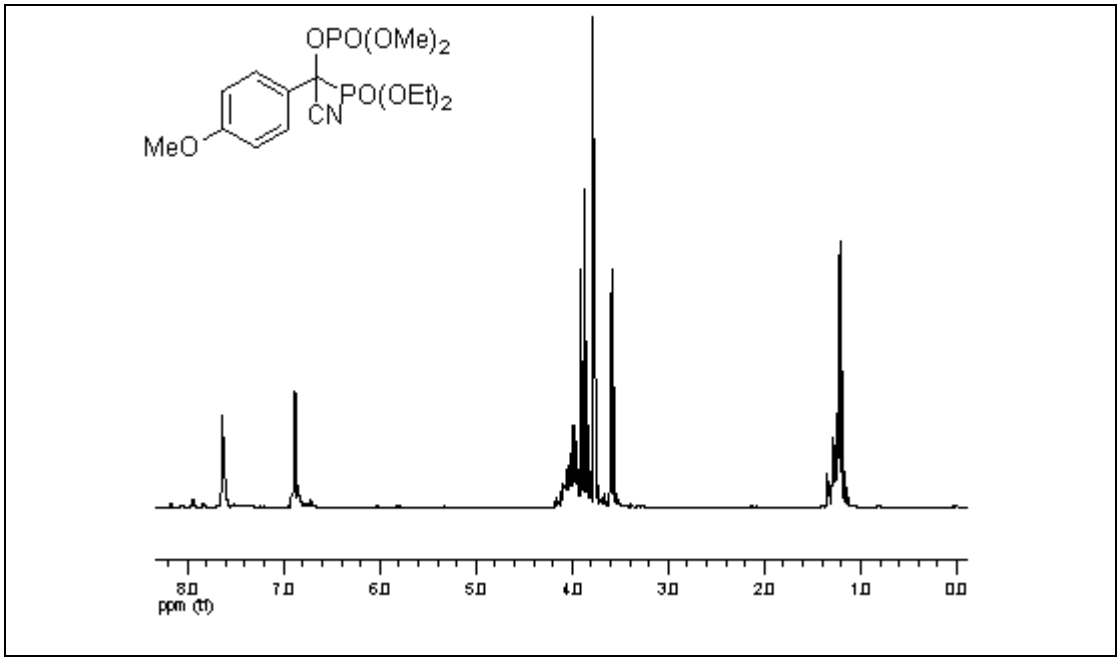


Figure 4.28. H^1 NMR spectrum of (Ethoxyphosphono)(cyano)(4-methoxyphenyl)methyl-dimethyl phosphate **79g**

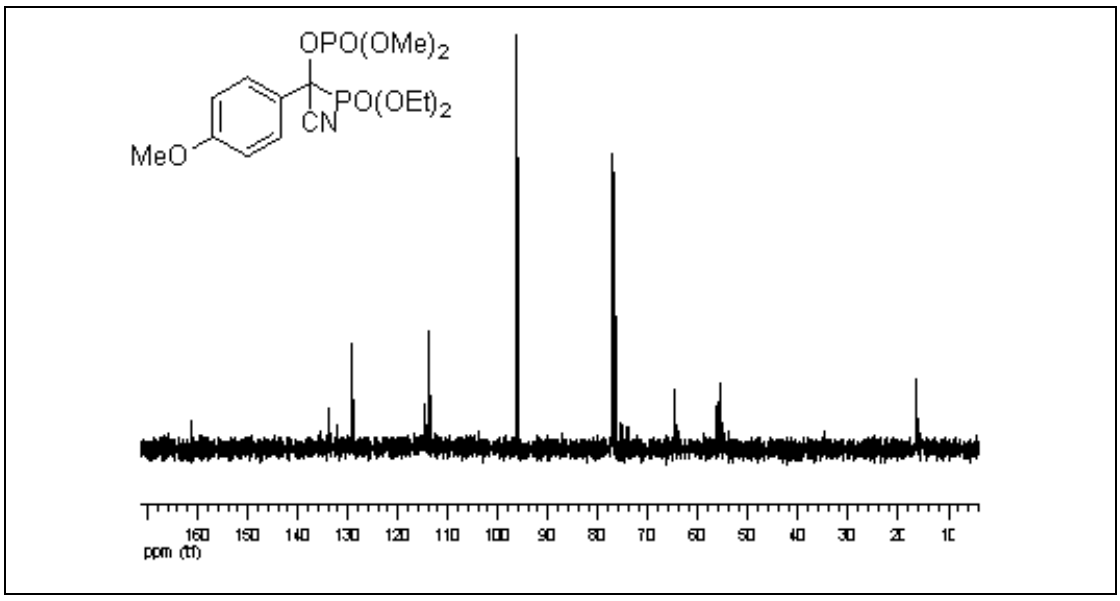


Figure 4.29. ^{13}C NMR spectrum of (Ethoxyphosphono)(cyano)(4-methoxyphenyl)methyl-dimethyl phosphate **79g**

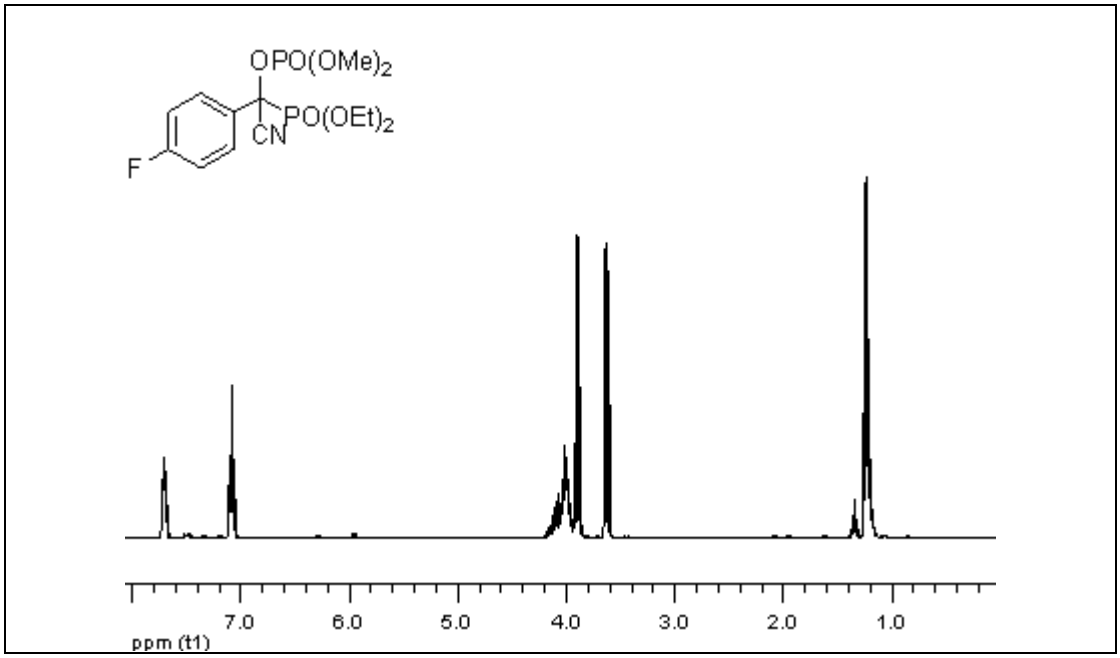


Figure 4.30. H^1 NMR spectrum of (Ethoxyphosphono)(cyano)(4-fluorophenyl)methyl-dimethyl phosphate **79h**

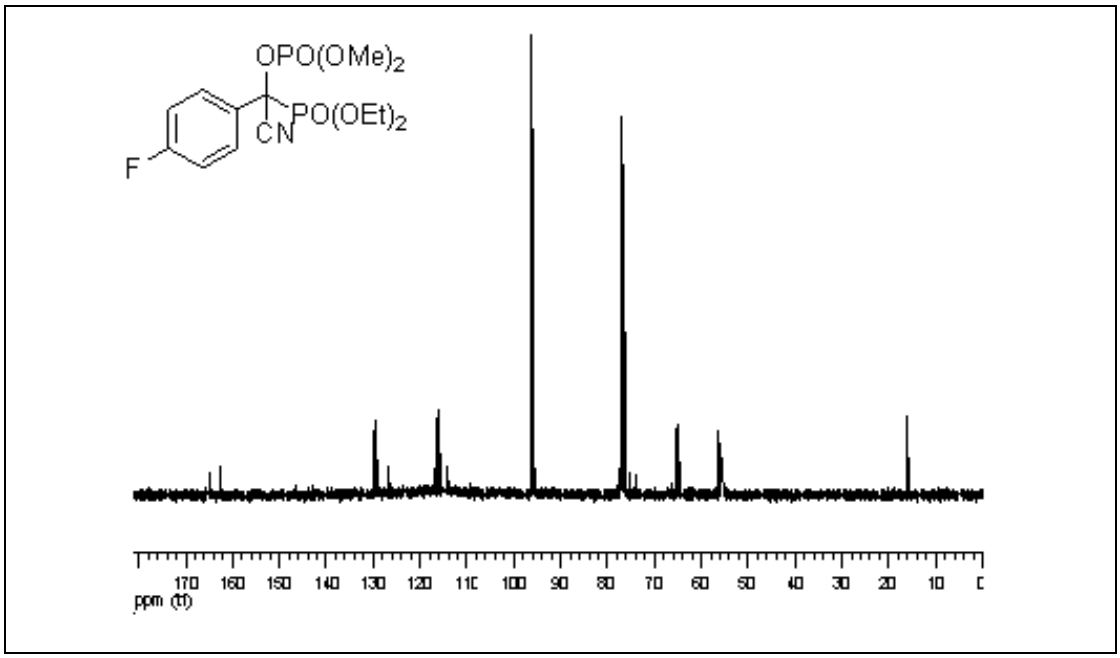


Figure 4.31. ^{13}C NMR spectrum of (Ethoxyphosphono)(cyano)(4-fluorophenyl)methyl-dimethyl phosphate **79h**

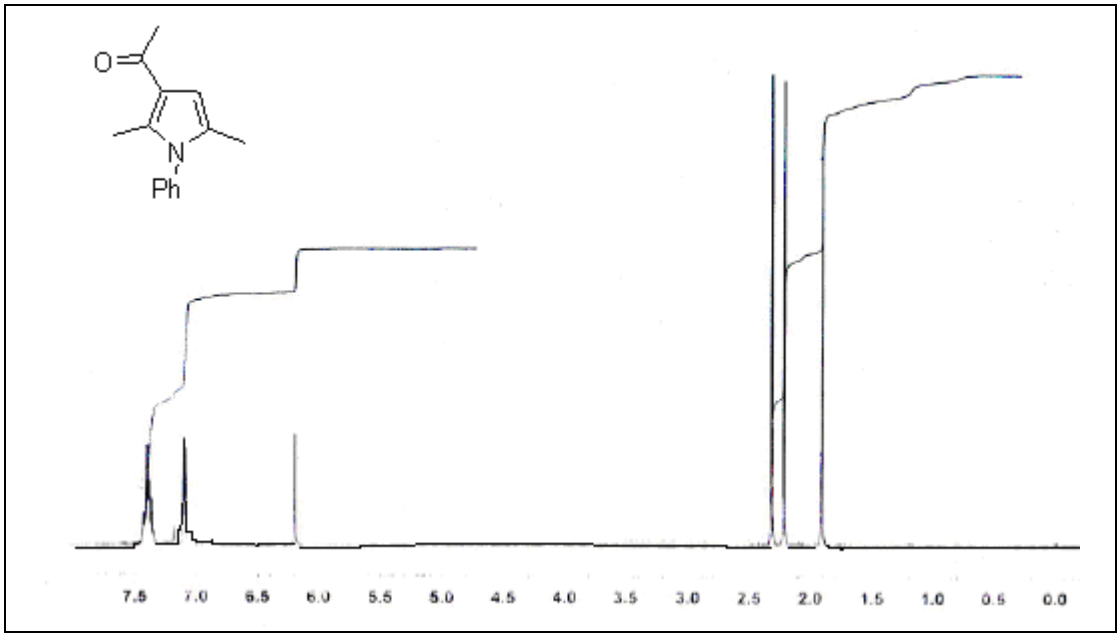


Figure 4.32. ^{1}H-NMR spectrum of 3-Acetyl-2,5-dimethyl-1-phenyl-1H-pyrrole **66h**

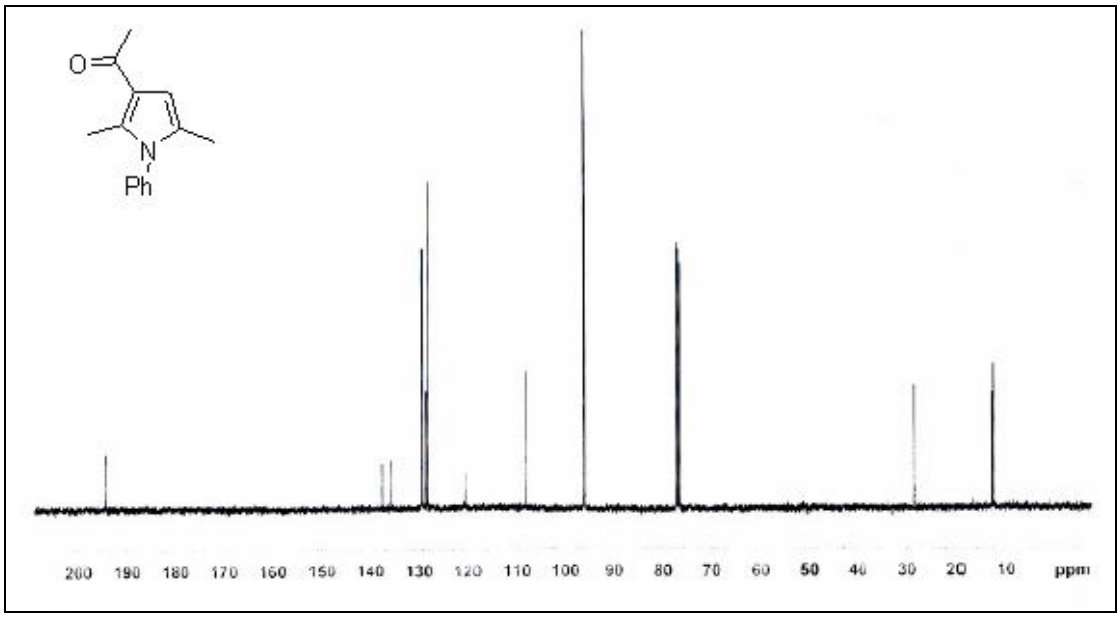


Figure 4.33. ^{13}C-NMR spectrum of 3-Acetyl-2,5-dimethyl-1-phenyl-1H-pyrrole **66h**

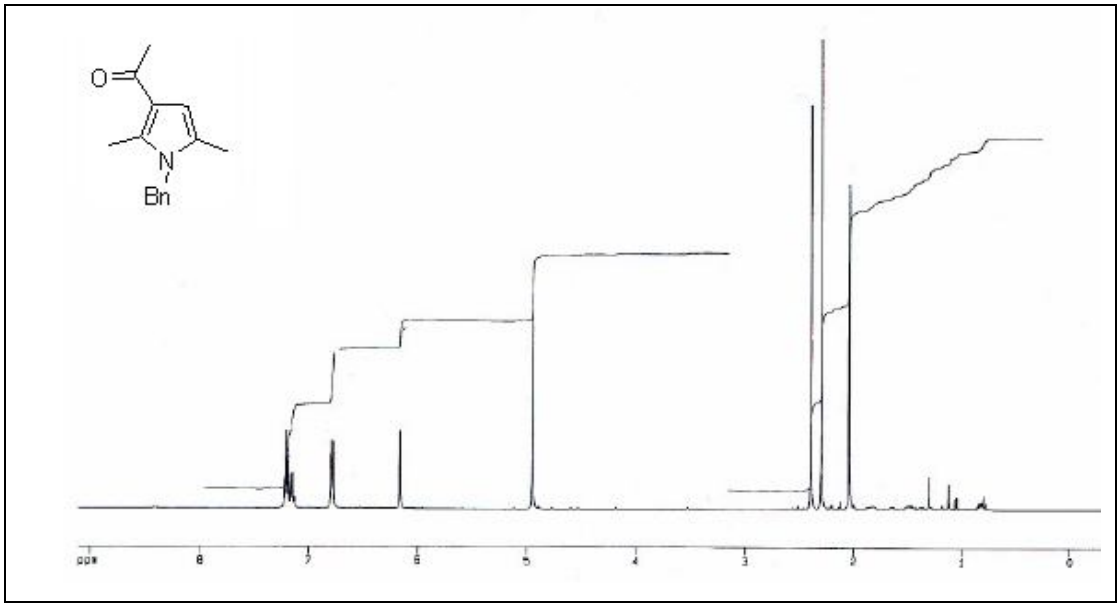


Figure 4.34. ^{1}H-NMR spectrum of 3-Acetyl-1-benzyl-2,5-dimethyl-1H-pyrrole **66i**

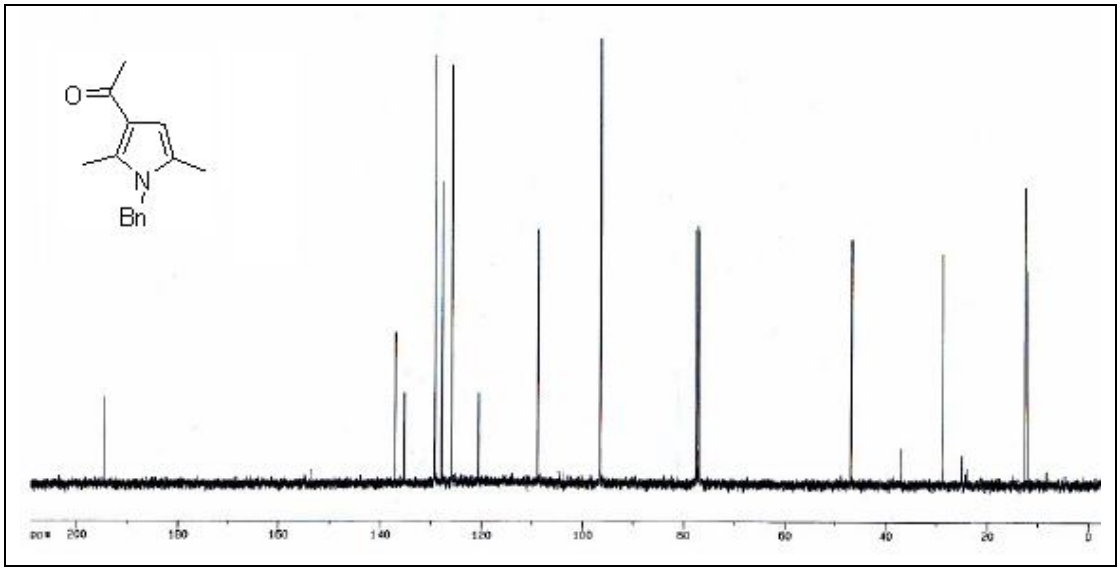


Figure 4.35. ^{13}C-NMR spectrum of 3-Acetyl-1-benzyl-2,5-dimethyl-1H-pyrrole **66i**

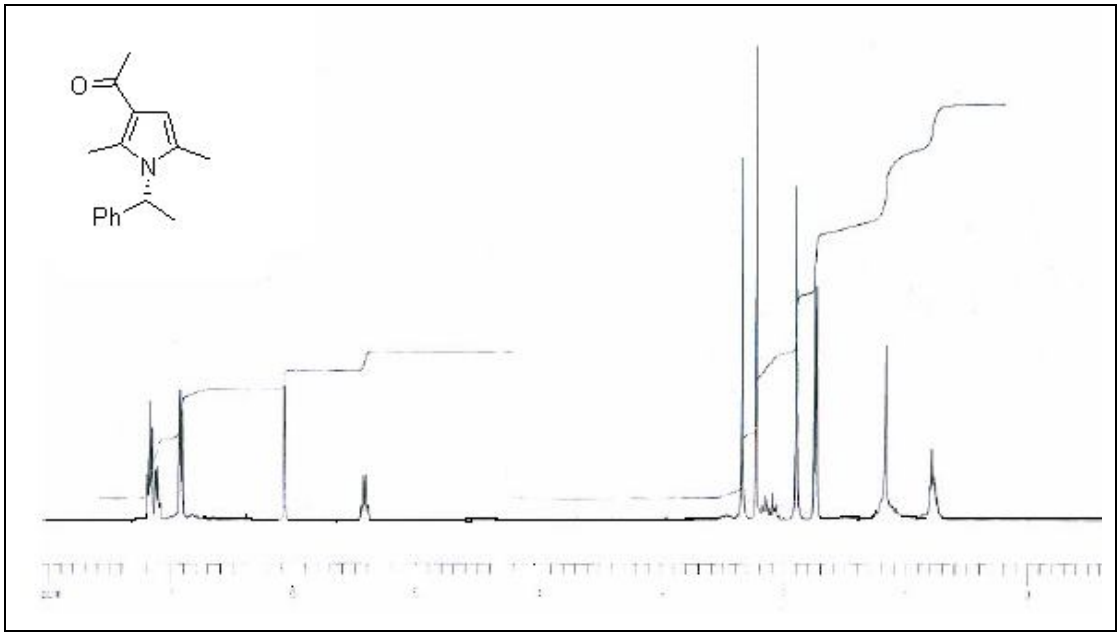


Figure 4.36. ^{1}H-NMR spectrum of (*R*)-3-Acetyl-2,5-Dimethyl-1(1-H-phenyl ethyl)-1H-pyrrole **66j**

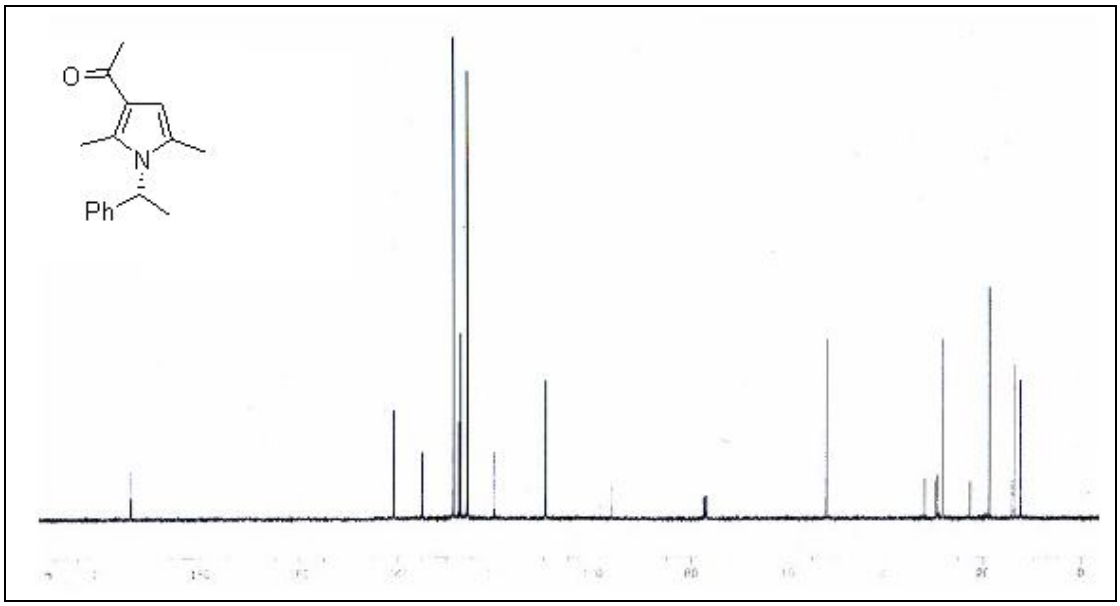


Figure 4.37. ^{13}C-NMR spectrum of (*R*)-3-Acetyl-2,5-Dimethyl-1(1-H-phenyl ethyl)-1H-pyrrole **66j**

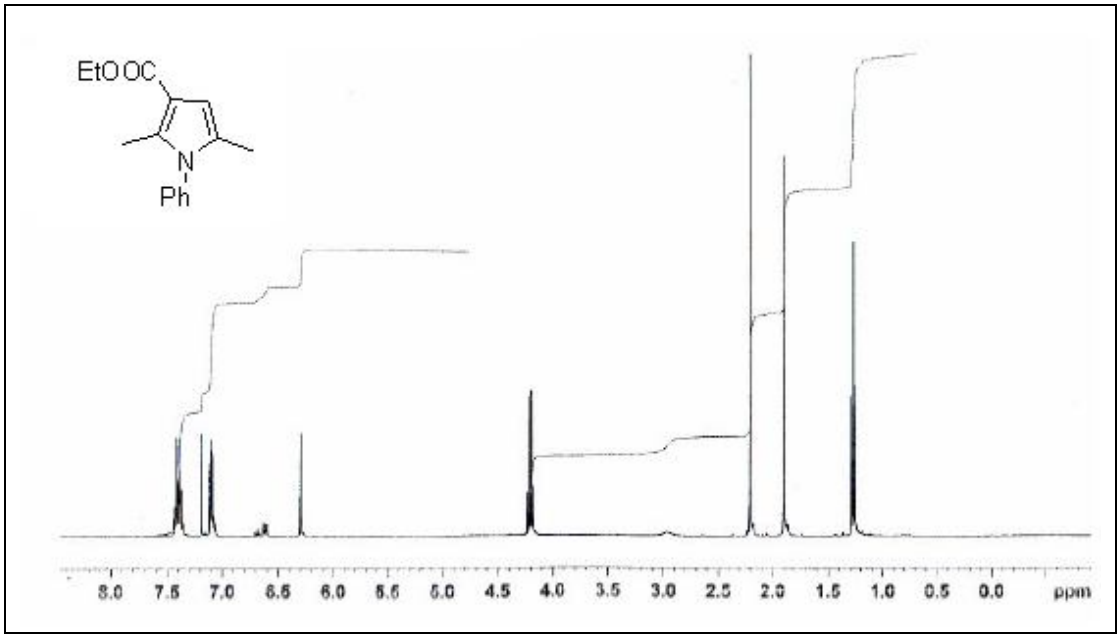


Figure 4.38. ^{1}H-NMR spectrum of ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-Carboxylate **66e**

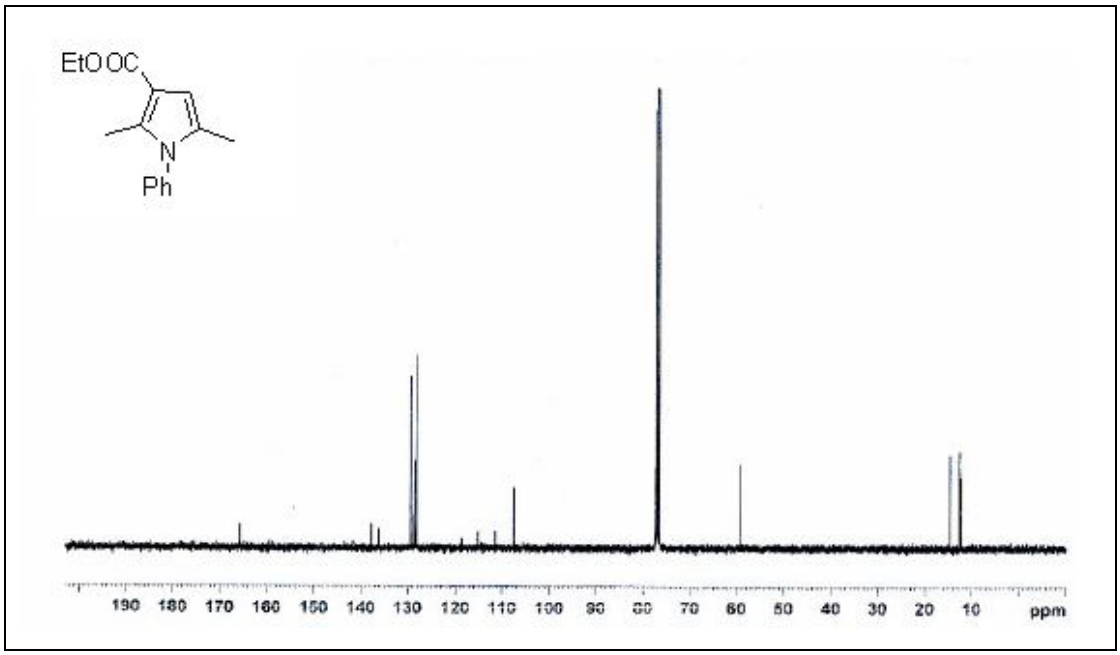


Figure 4.39. ^{13}C-NMR spectrum of ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-Carboxylate **66e**

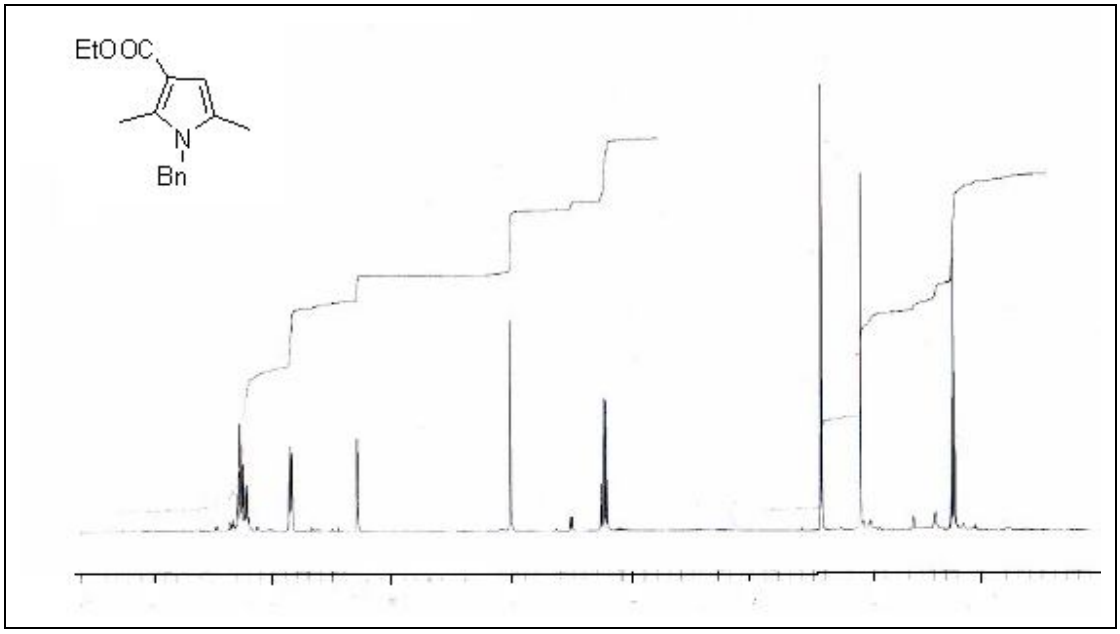


Figure 4.40. ^{1}H-NMR spectrum of ethyl 1-benzyl-2,5-dimethyl-1H-pyrrole-3-Carboxylate **66f**

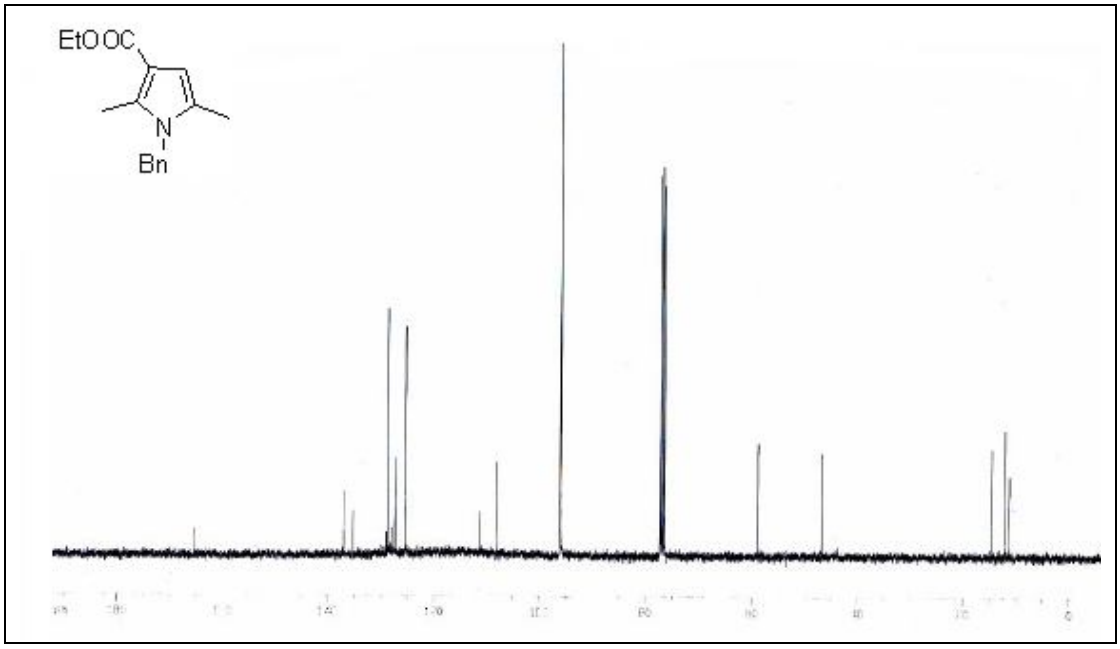


Figure 4.41. ^{13}C-NMR spectrum of ethyl 1-benzyl-2,5-dimethyl-1H-pyrrole-3-Carboxylate **66f**

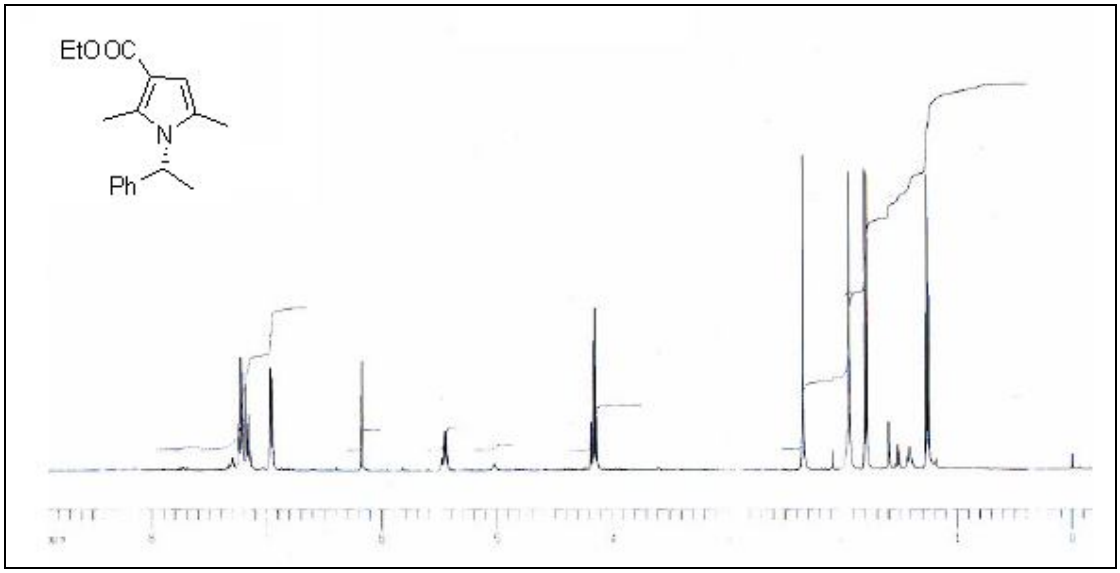


Figure 4.42. ^{1}H-NMR spectrum of (*R*)-ethyl 2,5-dimethyl-1-(1-phenylethyl)-1Hpyrrole-3-carboxylate **66g**

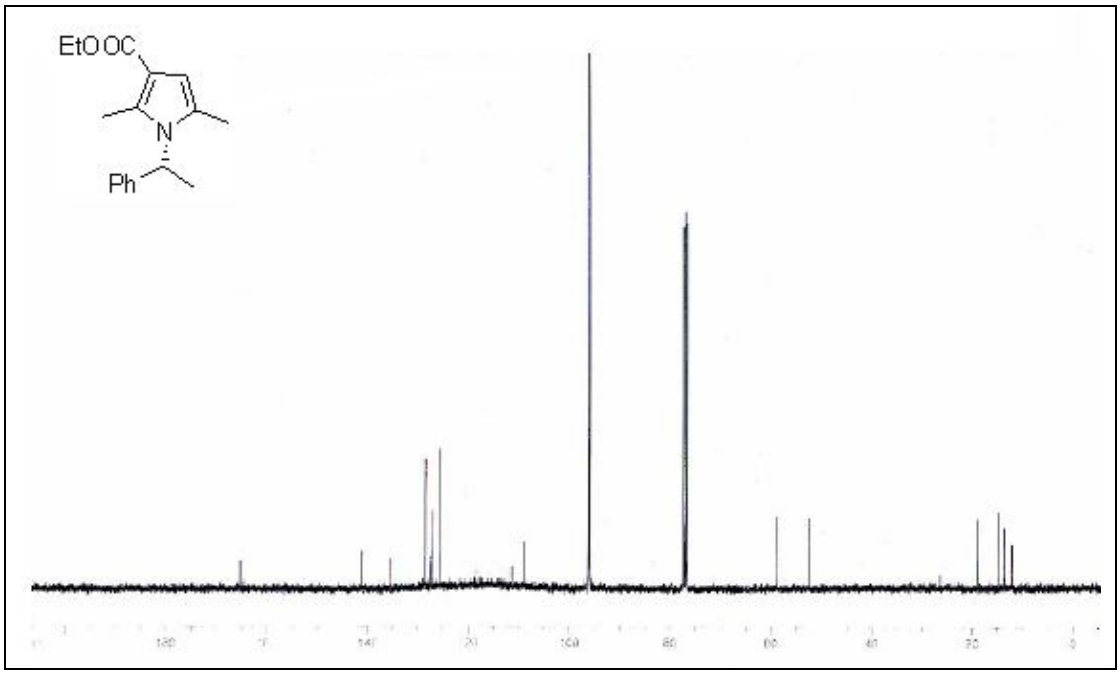


Figure 4.43. ^{13}C-NMR spectrum of (*R*)-ethyl 2,5-dimethyl-1-(1-phenylethyl)-1Hpyrrole-3-carboxylate **66g**

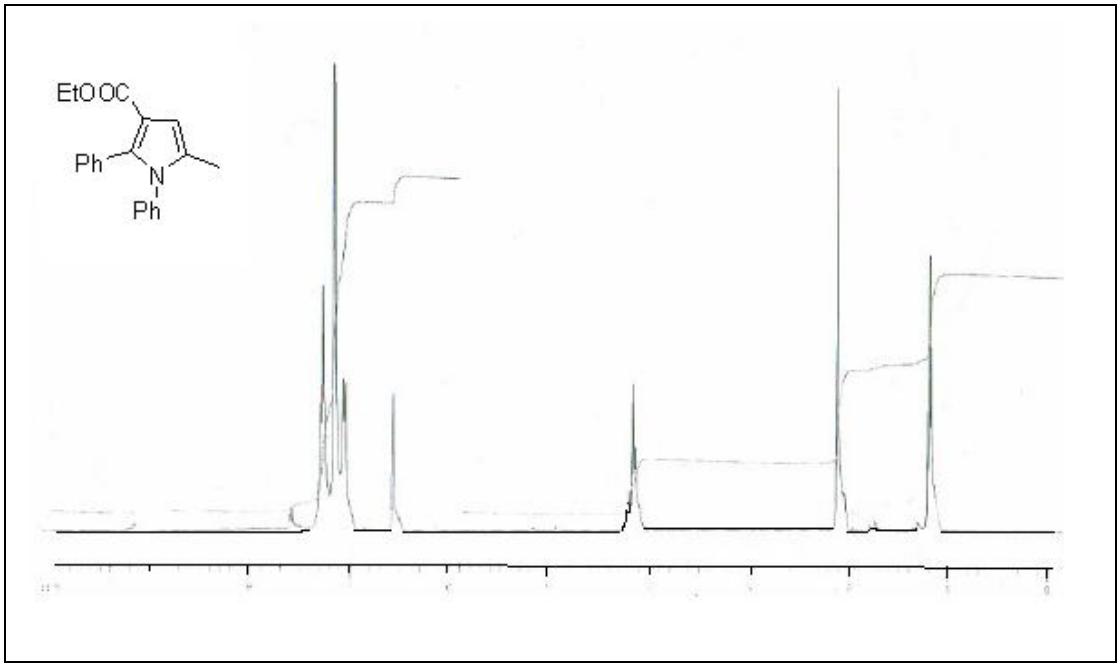


Figure 4.44. ^{1}H-NMR spectrum of ethyl 5-methyl-1,2-diphenyl-1H-pyrrole-3-Carboxylate **66b**

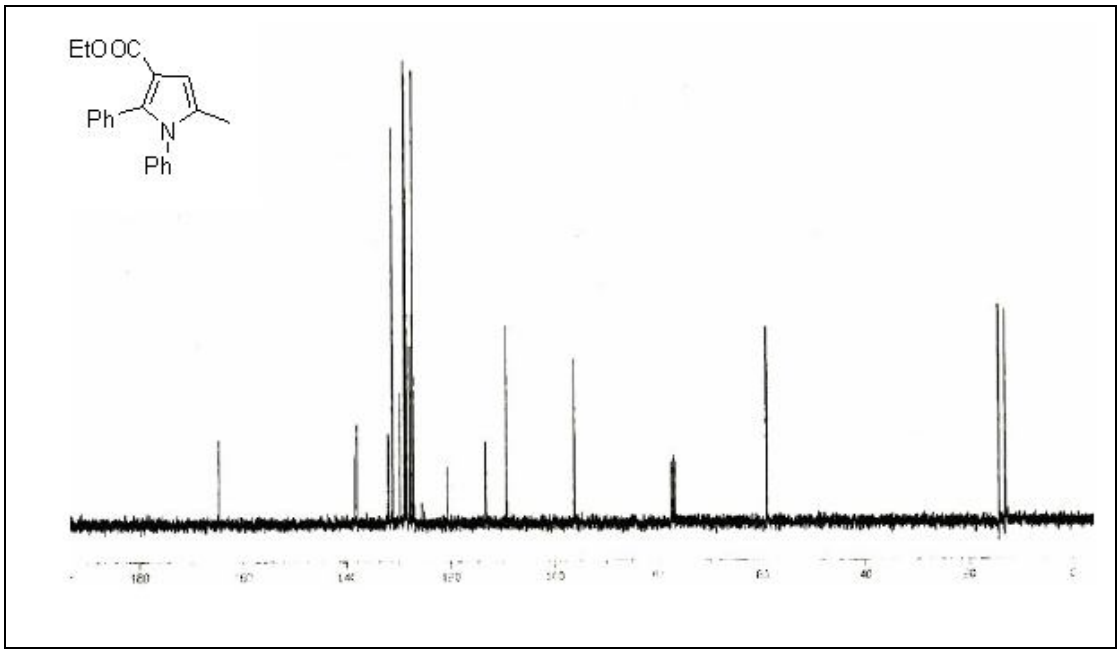


Figure 4.45. ^{13}C-NMR spectrum of ethyl 5-methyl-1,2-diphenyl-1H-pyrrole-3-Carboxylate **66b**

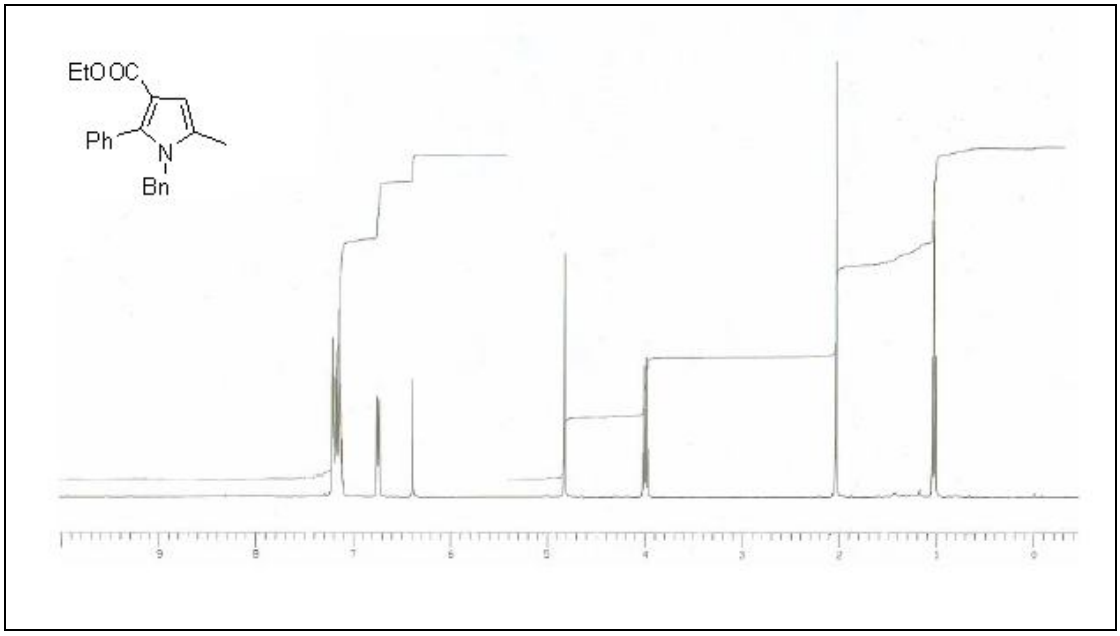


Figure 4.46. ^{1}H-NMR spectrum of ethyl 1-benzyl-5-methyl-2-phenyl-1H-pyrrole-3-Carboxylate **66c**

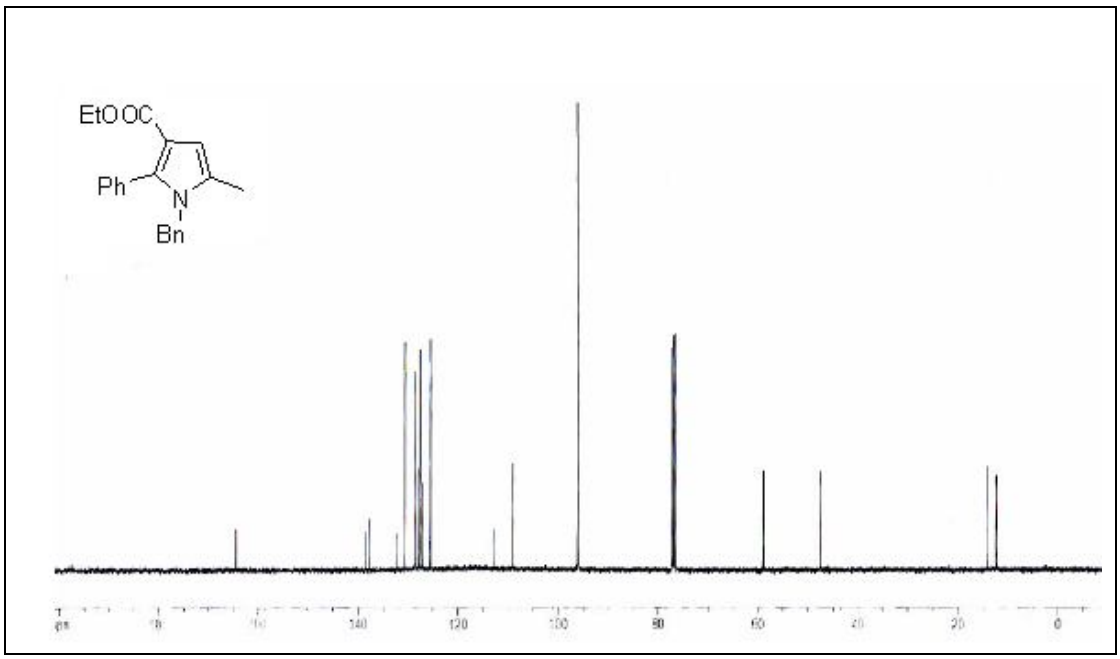


Figure 4.47. ^{13}C-NMR spectrum of ethyl 1-benzyl-5-methyl-2-phenyl-1H-pyrrole-3-Carboxylate **66c**

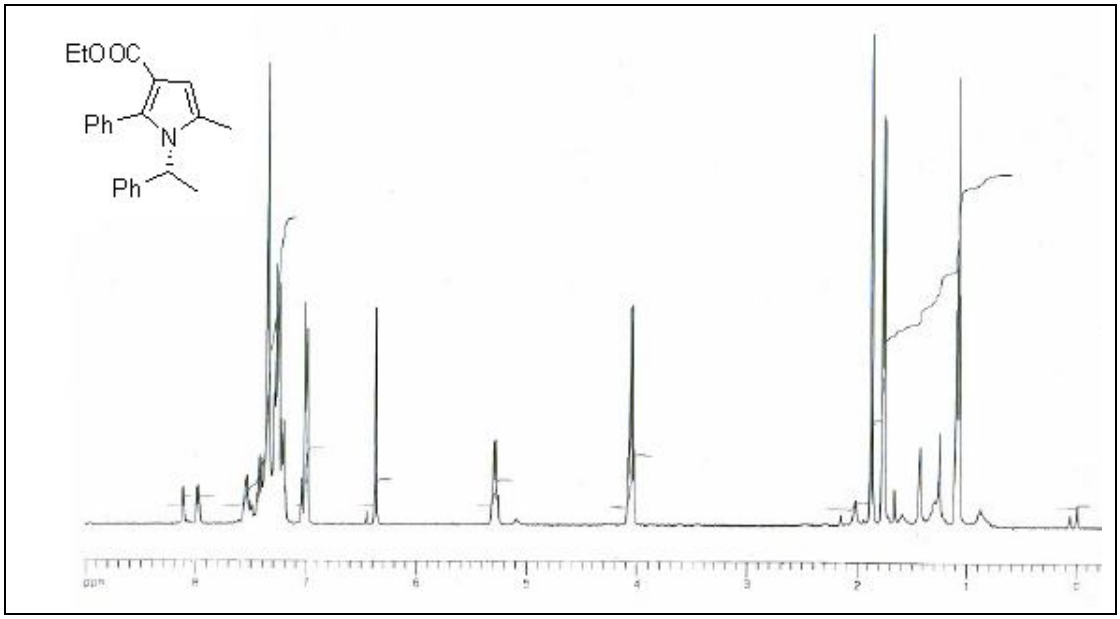


Figure 4.48. ^{1}H-NMR spectrum of (*R*)-ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1-H-pyrrole-3-carboxylate **66a**

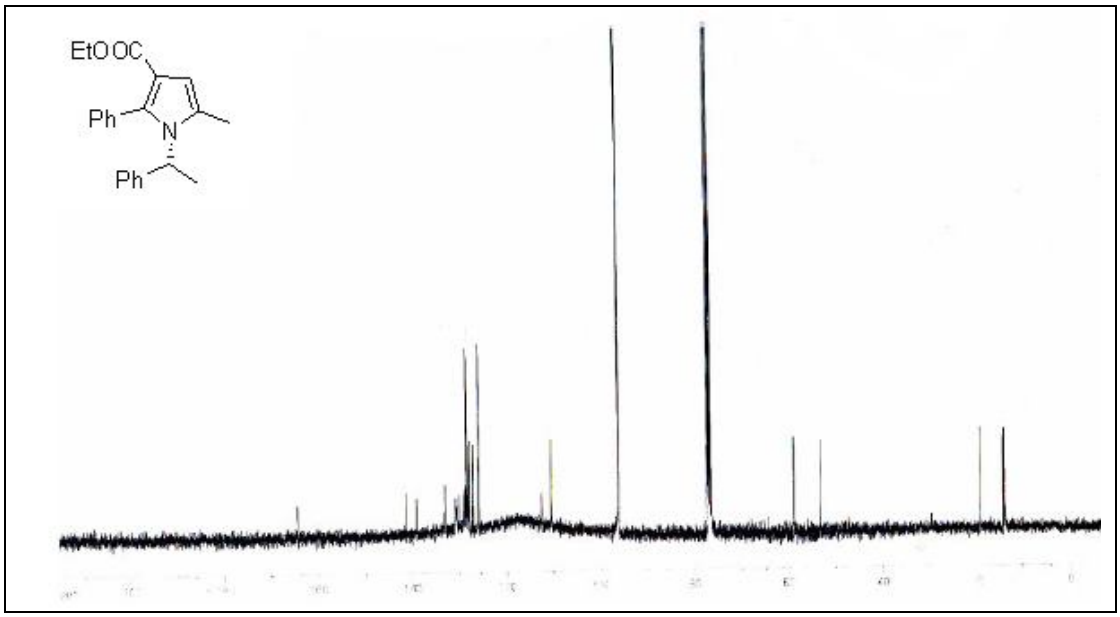


Figure 4.49. ^{13}C-NMR spectrum of (*R*)-ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1-H-pyrrole-3-carboxylate **66a**

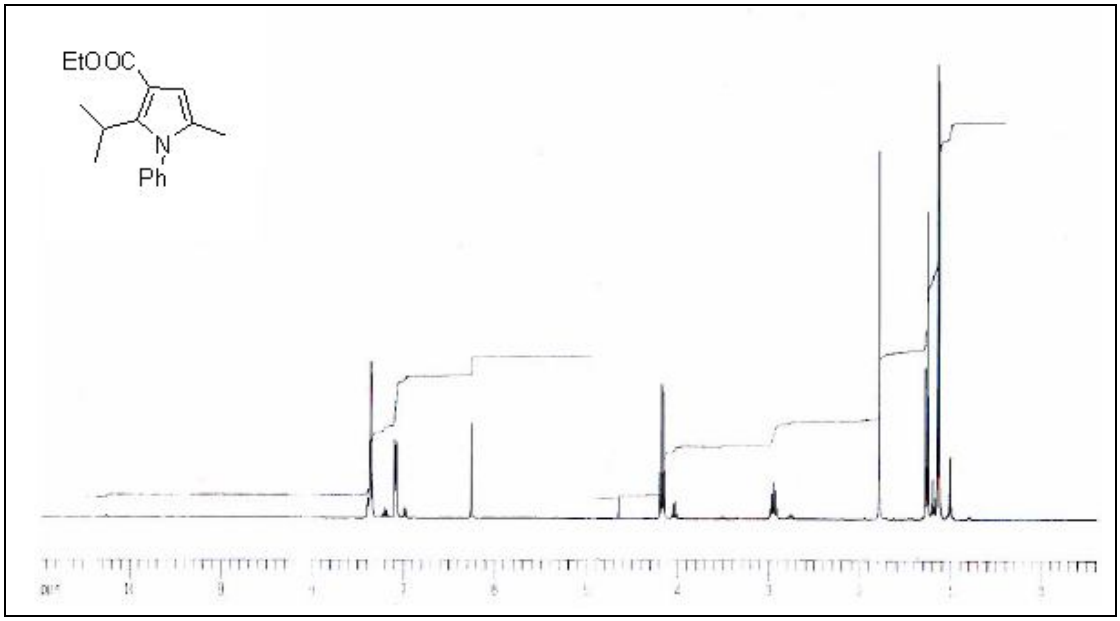


Figure 4.50. ^{1}H-NMR spectrum of ethyl 2-isopropyl-5-methyl-1-phenyl-1H-pyrrole-3-carboxylate **66j**

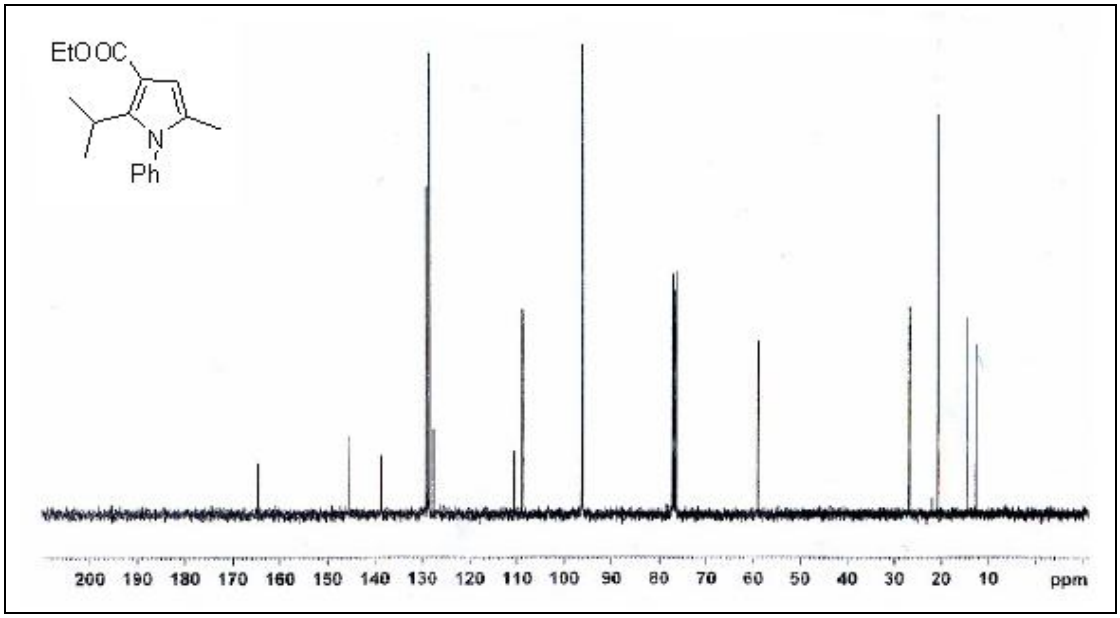


Figure 4.51. ^{13}C-NMR spectrum of ethyl 2-isopropyl-5-methyl-1-phenyl-1H-pyrrole-3-carboxylate **66j**

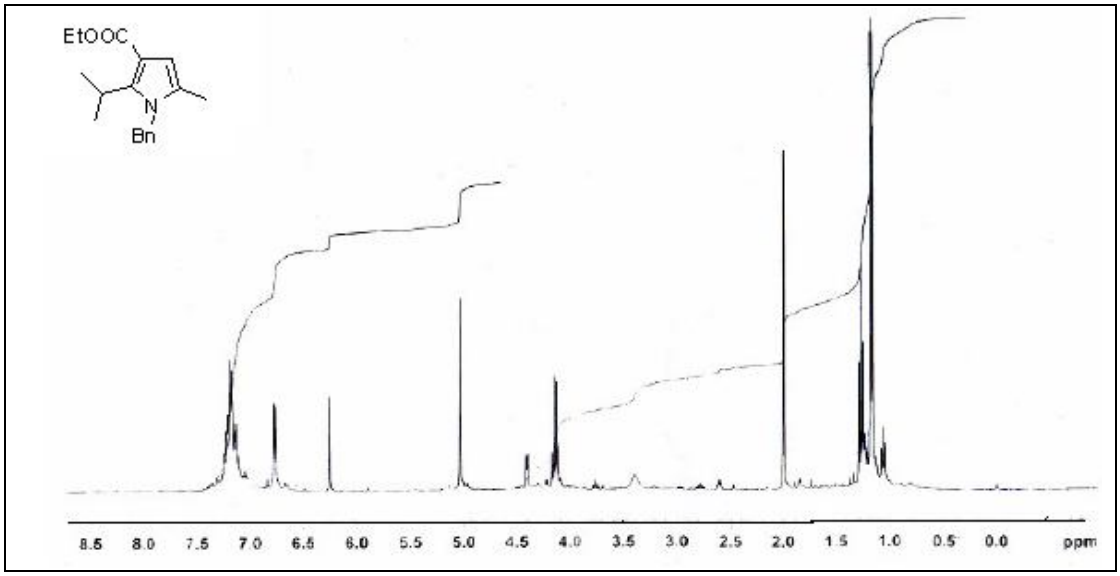


Figure 4.52. ^{1}H-NMR spectrum of ethyl 1-benzyl-2-isopropyl-5-methyl-1H-pyrrole-3-carboxylate **66k**

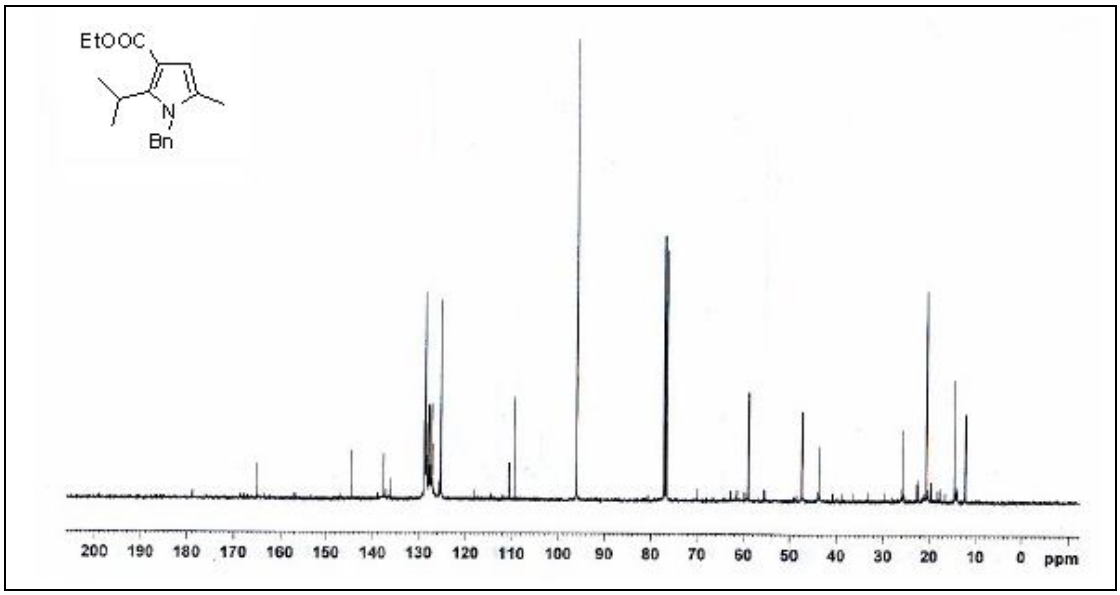


Figure 4.53. ^{13}C-NMR spectrum of ethyl 1-benzyl-2-isopropyl-5-methyl-1H-pyrrole-3-carboxylate **66k**

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