NOVEL ANNULATION REACTIONS FOR THE SYNTHESIS OF SUBSTITUTED PYRROLES

DARZENS REACTION OF ACYL PHOSPHONATES WITH α-BROMO KETONES: SELECTIVE SYNTHESIS OF *CIS*- AND *TRANS*-EPOXYPHOSPHONATES

A THESIS SUBMITTED TO
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ABSTRACT

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DARZENS REACTION OF ACYL PHOSPHONATES WITH α-BROMO KETONES: SELECTIVE SYNTHESIS OF *CIS*- AND *TRANS*-EPOXYPHOSPHONATES

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In the first part of this thesis, it is aimed to develope methods for the synthesis of tri-substituted pyrrrole derivatives. 2-Aminopyrrroles, alkoxy and sulfonyl substittitued pyrrole derivatives as well as pirolinones show interesting biological activities and are precursor of well know drugs. Although there is a number of methods for the synthesis of pyrroles, the synthesis of 2-aminopyrroles is limited to few works and is not widely known. Therefore, it is still an important goal in organic chemistry to improve methods for the synthesis of multifunctionalized pyrrole derivatives and pyrrolinones.

Alkylation of β-dicarbonyl compounds with bromoacetonitrile furnishes α-cyanomethyl-β-dicarbonyl compounds. The condensation reaction of α-

cyanomethyl-β-dicarbonyl compounds with amines catalyzed by p-TsOH affords the corresponding enamines and further base catalyzed cyclization furnishes 2-aminopyrroles in high yields, moreover, zinc perchlorate-catalyzed addition of amines, alcohols and thiols to the nitrile carbon of α-cyanomethyl-β-ketoesters followed by annulation gives the 5-alkoxy and 5-alkylsulfanylpyrrole-3-carboxylates in high yields.

In the second part of the thesis, reactions of a broad range of acyl phosphonates with α-bromo acetophenones at room temperature in the presence of different bases were described to afford two diastereomeric epoxy phosphonates in good yields and high diastereoselectivities. The diastereoselectivity of this reaction is easily controlled by changing the base. Accordingly, changing the base from Cs_2CO_3 to DBU changes the diatereomeric ratio (*trans/cis*) from 5/3 to 9/1. Furthermore, the treatment of *trans* isomer with DBU shows a complete conversion to the corresponding *cis* isomer. Additionally, these highly functionalized epoxyphosphonates are shown to be useful intermediates to give several reactions

Keywords: Darzens reaction, acyl phosphonates, epoxyphosphonates

ÖZ

SÜBSTİTÜE PİROLLERİN YENİ ANÜLAZYON REAKSİYONLARI İLE SENTEZLENMESİ

α-BROMO KETON BİLEŞİKLERİ İLE AÇİL FOSFONATLARIN DARZENS KONDENZASYON REAKSİYONLARI: *CIS*- VE *TRANS*-EPOKSİFOSFONATLARIN SEÇİCİ SENTEZİ

EMRULLAHOĞLU, Mustafa
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Ocak 2009, 175 sayfa

Tezin birinci kısmında, 2,3,4-trisübstitüe pirol türevlerinin sentezlenmesi hedef olarak seçilmistir. 2-Aminopiroller, alkil-oksi, alkil-sulfanil pirol türevleri ve pirolinonlar çok ilginç biyolojik aktivite göstermekte ve bilinen ilaçların başlangıç türevlerini oluşturmkatadır. Pirol sentezi için oldukça fazla metot bulunmasına rağmen, 2-aminopirol türevlerinin sentezlenmesi yaygın değildir. Dolayısıyla, organik kimyada, polisübstitüe pirol türevlerinin ve pirolinonların sentezlenmesi için yeni sentez metodların geliştirilmesi hala önemini korumaktadır.

β-Dikarbonil bileşiklerinin bromoasetonitril ile alkilasyonu α-siyanometil-β-dikarbonil bileşiklerini vermektedir. α-Siyanometil-β-dikarbonil bileşiklerinin p-TsOH katalizörlüğünde aminlerle kondenzasyonu sonucu enaminler ve devamında baz eşliğinde halkalaşması sonucu 2-aminopirol bileşikeleri yüksek verimlerde oluşmaktadır, buna ek olarak çinko perklorat katalizörlüğünde aminlerin, alkollerin

ve tiyol bileşiklerin α-siyanometil-β-dikarbonil bileşiğinin nitril karbonuna eklenmesi ve anülasyonu sonucu 2-aminopiroller, alkil-oksi ve alkil-sulfanil pirol türevleri yükek verimlerde sentezlenmiştir.

Tezin ikicinci kısmında, yüksek verimlerde ve yüksek diasteriyoseçicilikte epoksifosfonatların, açil fosfonatlar ile farklı bazlar varlığında α-bromo ketonların Darzen tipi tepkimesi sonucu sentezlenmesi gösterilmiştir. Tepkimenin, diasteriyoseçiciliği baz değiştirilerek kolayca kontrol edilmektedir. Bazın Cs_2CO_3'tan DBU'ya değiştirilmesi diasteriyomerik oranı (trans/cis) 3/2'den 9/1'e değiştirmektedir. Ayrıca, *trans* izomerin DBU ile muamele edildiğinde *cis* izomere dönüştüğü gösterilmiştir. Buna ek olarak, sentezlenlenen çok fonksiyonlu epoksifosfonatların tepkimeleri incelenmiştir.

Anahtar kelimeler: Darzens kondenzasyonu, açil fosfonat, epoksifosfonat

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LIST OF ABBREVIATIONS

$CHCl_3$: Chloroform

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

DCE : Dichloroethane

DMAP : Dimethylaminopyridine

DMF : Dimethyl formamide

DMSO : Dimethyl sulfoxide

KOEt : Potassium ethoxide

$NaBH_4$: Sodium borahydride

NaH : Sodium hydride

NaOEt : Sodium ethoxide

TLC : Thin layer chromatography

TsOH : *p*-Toluene sulfonic acid

$Zn(ClO_4)_2$: Zinc perchlorate

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CHAPTER 1

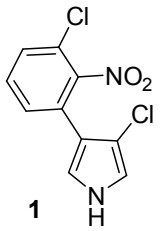
INTRODUCTION

1.1 Novel annulation reactions for the synthesis of substituted pyrroles

1.1.1 General properties of Pyrroles

Pyrrole was first isolated from bone oil, but also occurs in coal tar. It can be prepared by the dry distillation of the ammonium salt of D-galactaric acid. Pyrrole is a colorless liquid with a characteristic odor reminiscent of chloroform, of mp 24°C and bp 131°C. It is slightly soluble in water and turns to brown quickly in air.

The pyrrole ring, although not very common in nature, occurs in some very important natural products possessing biological activity beside the fact that many of them have biological activities on their own. They are versatile building blocks in organic synthesis. Moreover, they are important starting materials for various synthetic transformations. A few antibiotics contain a pyrrole ring; one of the simplest is pyrrolnitrin **1**:



1

Figure 1.1 Structure of antibiotic pyrrolnitrin **1**

The biologically important tetrapyrroles contain four pyrrole rings, which are linked by CH_2 or CH bridges. One differentiates between linear tetrapyrroles (bilirubinoids) and cyclic tetrapyrroles (porphyrins and corrins). Bilirubinoids are colored compounds occurring in vertebrates, in some invertebrates and even in algae. They are formed by the biological oxidation of porphyrins. The most important representative is the orange-colored bilirubin. Bilirubin **2** was first isolated by STAEDELER (1864) and can be purified via its crystalline ammonium salt. It is oxidized to blue-green biliverdine **3** by iron(III) chloride (Figure 1.2). The corresponding unsubstituted compounds are known as biladiene and bilin [1].

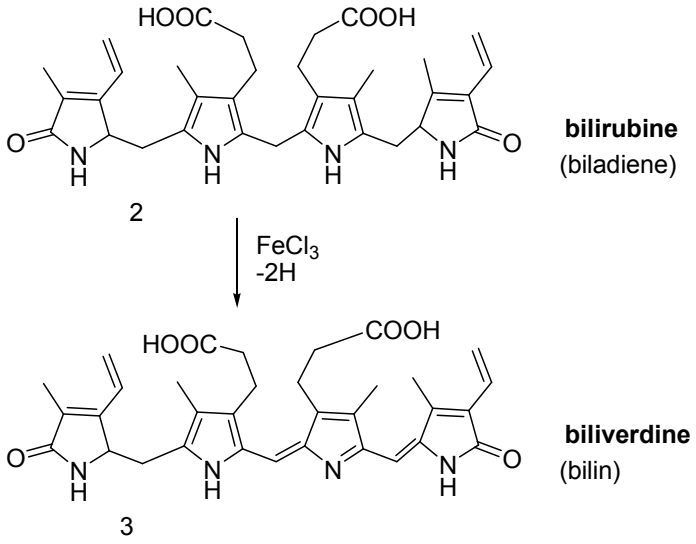


Figure 1.2 Oxidation reaction of bilirubine to biliverdine

The parent compound is the porphyrin ring system **4** in which four pyrrole units are linked by four sp^2 methine bridges forming a cyclic conjugated C_{20} structure [2]. Pyrroles being useful building blocks in organic synthesis makes them efficient starting materials for many kinds of synthetic transformations. Pyrroles take important role in the synthesis of porphyrin systems. Porphyrins and other closely

related tetrapyrrolic pigments occur widely in nature, and they play very important roles in various biological processes.

Partially hydrogenated porphyrins, such as chlorin **5** (17,18-dihydroporphyrin), phlorin **6** (15,24-dihydroporphyrin), bacteriochlorin **7** (7,8,17,18 tetrahydroporphyrin) and porphyrinogen **8** (5,10,15,20,22,24-hexahydroporphyrin), are also important (Figure 1.3).

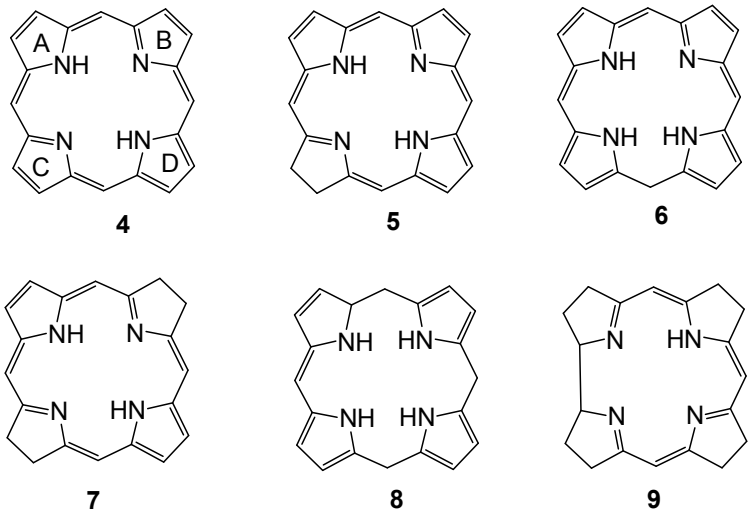


Figure 1.3 General structures of some porphyrin derivatives

All pyrrole units of the porphyrin system are partially hydrogenated in the $\mathbf{C_{19}}$ structure of corrin **9**. Two pyrrole rings are directly linked at the α-positions and not via a methine group. Porphyrins form a planar macrocycle that contains a conjugated, cyclic delocalized system of 22 π-electrons [3]. 18 Electrons can be assigned to the perimeter of a l,16-diaza[18]annulene, an arrangement which is also found in the chlorin and bacteriochlorin systems. Porphyrins and chlorins are intensely coloured (**4**: red to violet, v_{max}=500-700 nm; **5-8**: green, v_{max}=600-700 nm). The tetrapyrrolic pigments, heme **10** and chlorophyll *a* **11** play an important role for central processes of life. They are universally distributed and have therefore been named the "pigments of life" (Figure 1.4) [4].

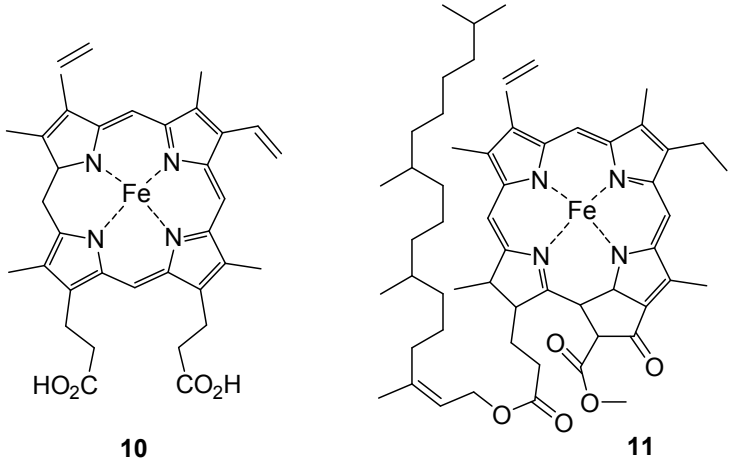


Figure 1.4 Structure of heme **10** and chlorophyll *a* **11**

A number of pharmaceuticals are derived from pyrrole, e.g. the analgesic and anti-inflammatory zomepirac **12** [5-(4-chlorobenzoyl)-l,4-dimethylpyrrol-2-ylacetic acid] (Figure 1.5).

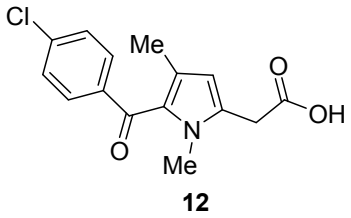
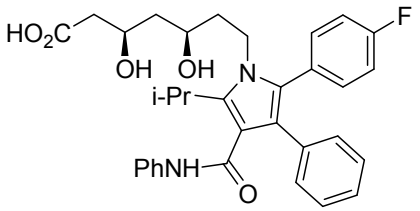


Figure 1.5 Structure of antinflammatory zomepirac **12**

Pyrrole moiety exists not only in the structure of many naturally occurring biologically active compounds, but also in the structure of some biologically active compounds with no natural source. From this point of view, pyrroles are very important building blocks in organic synthesis so in the drug industry. A good example for this case is atorvastatin calcium, the active material of famous drug named as "Atorvastatin" (**13**) (produced by Pfizer drug company) (Figure 1.6). This drug has the blood cholesterol lowering activity.



13

Figure 1.6 General structure of Atorvastatin **13**

Moreover, polymers and copolymers of pyrrole are used as organic conductors for special purposes, e.g. in photovoltaic cells [5].

1.1.2 General synthesis of Pyrrole derivatives

Concerning its *retrosynthesis,* pyrrole exhibits the function of a double enamine and can, therefore, be dissected retroanalytically in two ways (I/II). Route **I** (after retrosynthetic operations of an enamine hydrolysis **a-c**) yields 1,4-dicarbonyl compounds as potential starting materials, which should produce pyrroles by cyclocondensation with NH_3. When the intermediate I i.e. γ-keto enamine is treated according to step **d**, a bond cleavage different from that leading to **II** is possible. This reversal of an enamine alkylation gives rise to α-halocarbonyls **III** and enamines **IV** and thereby suggests alternative starting materials (Figure 1.7).

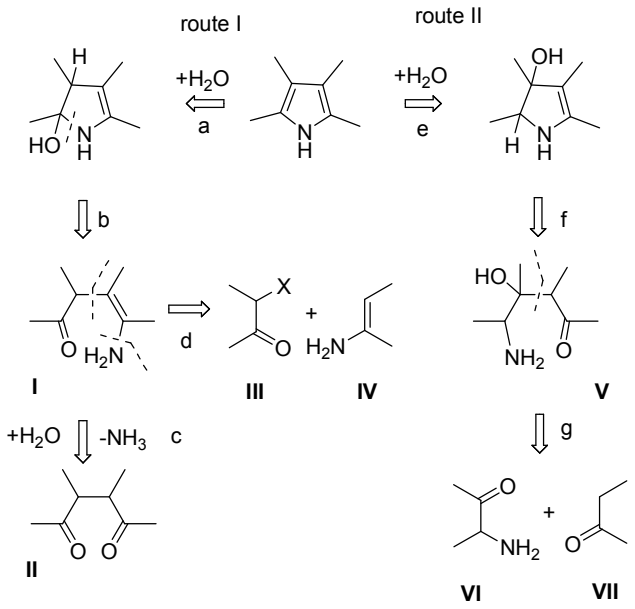


Figure 1.7 General retrosynthetic pyrrole synthesis

After H_2O addition and enamine hydrolysis (e /f), route **II** leads to the /-amino aldol intermediate **V**. Aldol fission follows (retroanalysis step **g**) resulting in the formation of α-amino carbonyl compounds **VI** and methylene ketones **VII**. These are possible starting materials for the synthesis of pyrroles.

1.1.2.1 Named reactions for Pyrrole synthesis

(1) The *Paal-Knorr synthesis,* in which 1,4-dicarbonyl compounds are treated with NH_3 or primary amines (or with ammonium or alkylammonium salts) in ethanol or acetic acid, leads to 2,5-disubstituted pyrroles, and is universally applicable. For instance, hexane-2,5-dione **14** reacts with NH_3 to yield 2,5-dimethylpyrrole **1 (**Figure 1.8).

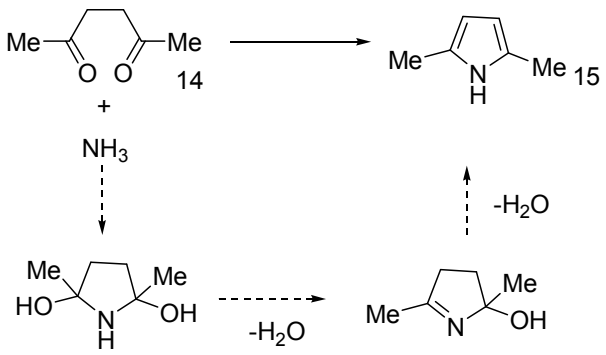


Figure 1.8 General mechanism for Paal-Knorr pyrrole synthesis

The primary step leads to the double hemiaminal **16** which, by step wise H_2O elimination, furnishes the pyrrole system **15** via the imine **17** [6].

(2). α-Halocarbonyl compounds react with β-keto esters or β-diketones and ammonia or primary amines to give 3-alkoxycarbonyl- or 3-acyl-substituted pyrrole derivatives, respectively *(Hantzsch synthesis)* (Figure 1.9).

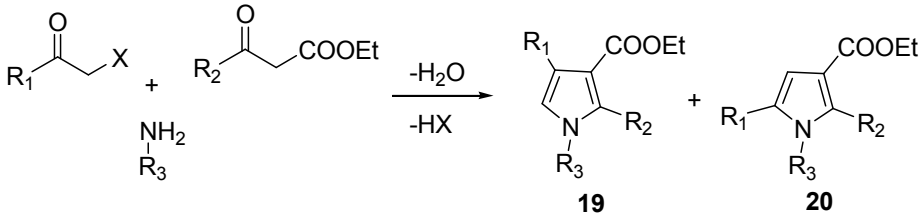


Figure 1.9 Hantzsch pyrrole synthesis

The regioselectivity depends on the substituents in the starting material but gives mainly the 1,2,3,5-tetrasubstituted pyrrole. Exhaustive investigations show that β-keto esters react with ammonia or amine to give β-aminoacrylic ester **18** as a primary step. C-Alkylation of the enamine function in **18** by the haloketone produces the 1,2,3,5-substituted pyrrole **19**, while *N*-alkylation leads to a 1,2,3,4-substituted pyrrole **20** (Figure 1.10).

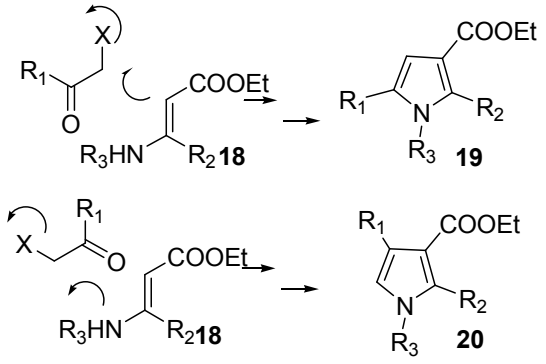


Figure 1.10 Mechanism for the formation of pyrrole **19** and **20**

(3) α-Amino ketones undergo cyclocondensation with β-keto esters or β-diketones to give 3-alkoxycarbonyl- or 3-acyl-substituted pyrroles **22** *(Knorr synthesis).*

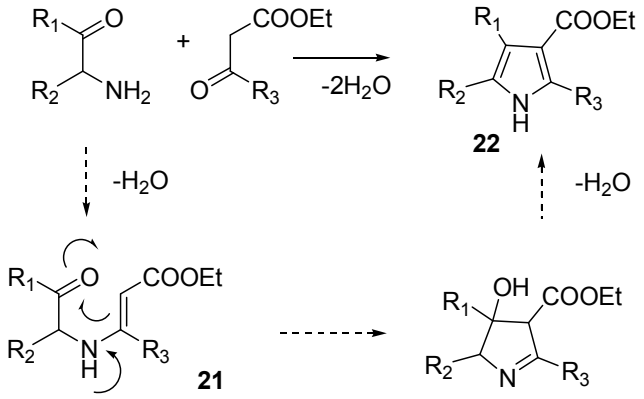


Figure 1.11 Reaction mechanism for Knorr pyrrole synthesis

The KNORR synthesis also proceeds via β-enaminone intermediates **21** [7]. Frequently, the α-amino ketones are not employed as such but generated in situ by reduction of α-oximino ketones. The latter are obtained by nitrosation of ketones with alkyl nitrites in the presence of sodium methoxide:

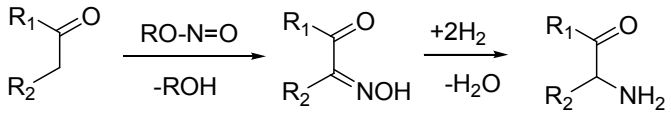


Figure 1.12 Formation reaction of α-aminoketones

For both the HANTZSCH and KNORR syntheses of pyrroles, several variations have been elaborated [8].

(4) 3-Substituted pyrrole-2-carboxylic esters **26** are synthesized from *N*-tolylsulfonyl glycine ester **24** and vinyl ketones *(Kenner synthesis*) [9]. By MICHAEL addition and intramolecular aldol addition, they first yield pyrrolidine-2-carboxylic esters **25.** These are converted into pyrroles by succesive H_2O and sulfamic acid eliminations.

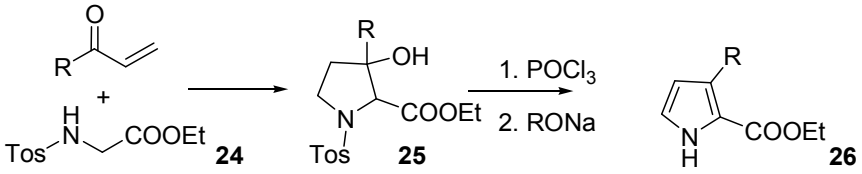


Figure 1.13 Kenner pyrrole synthesis

(5) Cyclocondensation of nitroalkenes with CH-acidic isocyanides in the presence of bases leads to the formation of trisubstituted pyrroles **27** *(Barton-Zard synthesis)* [10].

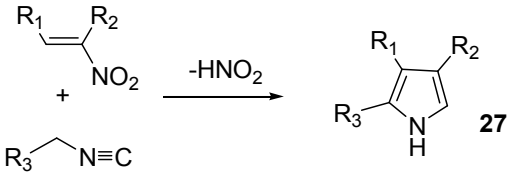


Figure 1.14 Barton-Zard pyrrole synthesis

The first step of this reaction is a MICHAEL addition of isocyanide to the nitroalkene. Cyclization and elimination of HNO_2 follow. On the other hand, α,β-unsaturated isocyanides and nitromethane yield 3-nitropyrroles **28.**

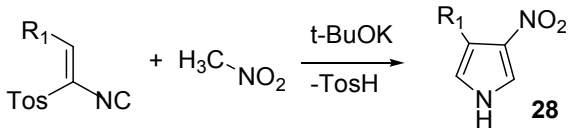


Figure 1.15 Synthesis of 3-nitropyrroles

1.1.3 Synthesis and properties of 2,4,5-substituted Pyrroles

Synthesis of 2,4,5-tetrasubstituted pyrrole derivatives include several classes of natural and unnatural compounds that exhibit a variety of biological and biomedical properties. Some excellent reviews concerning these properties have been published [11]. As a consequence, many synthetic methods are known for the construction of the pyrrole structure [12]. Whereas these methods have proven very useful for the synthesis of pyrrole derivatives, they generally involve multistep synthetic operations that limit the scope of these reactions.

Multicomponent strategies offer significant advantages over classical linear syntheses by combining a series of reactions from easily available and simple precursors without the need for isolation of the intermediates to allow the construction of complex molecules [13]. Such reactions are thus economically and environmentally attractive and have become an important area of research in organic chemistry.

Within this context, recently, an elegant four component reaction for the construction of substituted pyrroles was reported by Müller and co-workers [14]. This multicomponent approach developed on from a earlier discovery that the Sonogashira coupling reaction of 1-arylprop-2-yn-1-ols **29** with electron deficient

aryl or heteroaryl halides **30** followed by a base-catalyzed isomerization reaction of the coupled products leads to the corresponding chalcones **31** (Figure 1.16) [15].

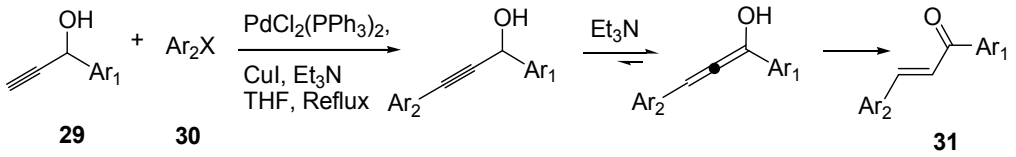


Figure 1.16 Synthesis of chalcone

Building on these results, Müller and collaborators developed an integrated procedure for the synthesis of pyrroles based on the reactivity of the newly formed enone functionality. To this end, the palladium- catalyzed enone synthesis was combined with a Stetter reaction to give 1,4-diketone intermediates [16], which were treated with primary amines in a subsequent Paal–Knorr cyclocondensation reaction.

These three reactions were efficiently integrated in a one-pot domino sequence to yield highly substituted pyrrole derivatives in rather good yields (Figure 1.17). Thus, after the reaction of various 1-arylprop-2-yn-1-ols **29** with electron-deficient aryl bromides **30** under the reaction conditions of the Sonogashira coupling–isomerization sequence in boiling triethylamine, the newly formed enones **31** were treated with an aldehyde in the presence of a catalytic amount of a thiazolium salt. After the complete conversion of **31** into the corresponding diketone **32**, the subsequent addition of primary amines and acetic acid to the reaction mixture yielded the expected tri- or tetrasubstituted pyrroles **33**.

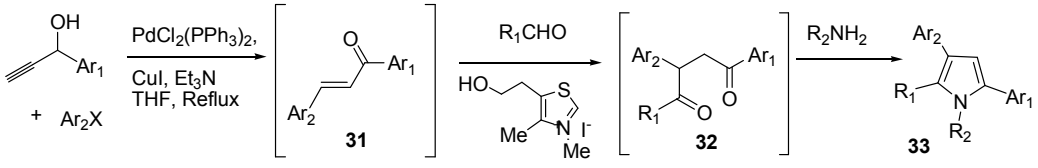


Figure 1.17 Synthsis of tetrasubstituted pyrrole **33**

Another multi-component pyrrole synthesis which was performed by Shiraishi *et al.* as illustrated in figure 1.18 [17]. The samarium(II) iodide catalyzed condensation of alkylamines **34**, aldehydes **35** and nitroalkanes **36** gave 1,2,3,4-tetrasubstituted pyrroles **37** in moderate to good yields.

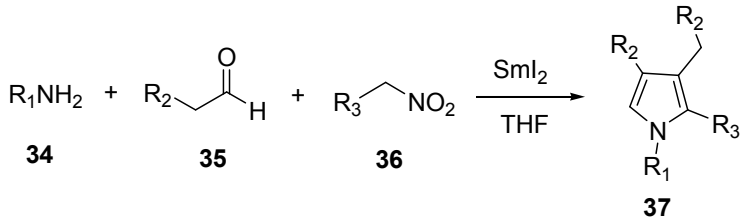


Figure 1.18 SmI_2 catalyzed synthesis of tetrasubstituted pyrrole **37**

An efficient multicomponent application is reported by Ranu *et.al.* [18] Ranu *et.al* have studied the synthesis of alkyl-substituted pyrroles by three component coupling of a carbonyl compound, amine and nitro-alkane/alkene on a solid surface of silica gel/alumina under microwave radiation. Efficient synthesis of highly substituted alkylpyrroles **41** by a three component coupling of α,β-unsaturated aldehyde/ketone **38**, amine **39** and nitroalkane **40** (Figure 1.19) on the surface of silica gel and alumina without any solvent under microwave irradiation were performed.

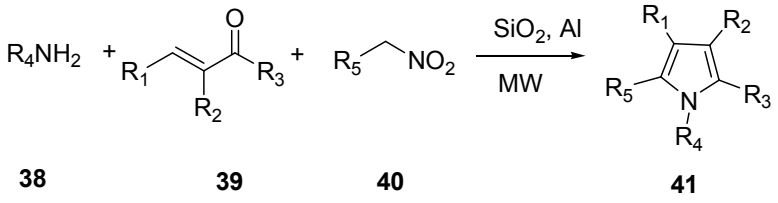


Figure 1.19 Synthesis of highly substituted alkylpyrroles **41**

Other methods, including lewis acid catalyzed cyclization reaction to afford pyrroles are also very common in the literature.

Arcadi *et.al.* [19] have synthesized functionalized pyrroles **44** in good to high yields by the reaction of **42** with benzylamine **43** (Figure 1.20). This reaction involves the formation of an imine that undergoes a *5-exo-dig* cyclization followed by isomerization to give pyrrole. In this study, 1,2,3,5-substituted pyrrole derivatives are synthesized via gold catalyzed amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds.

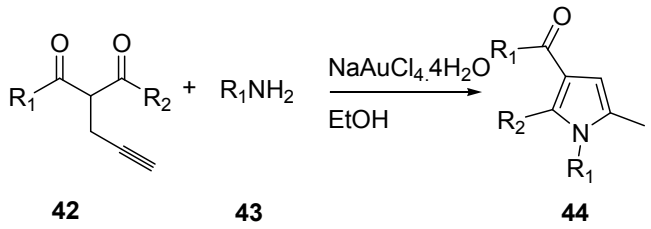


Figure 1.20 Gold catalyzed synthsis of functionalized pyrrole **44**

Another mild, gold(I)-catalyzed acetylenic Schmidt reaction of homopropargyl azides **45** gave regiospecific substituted pyrroles **46**. A mechanism in which azides serve as nucleophiles toward gold(I)-activated alkynes with subsequent gold(I)-aided expulsion of dinitrogen is proposed (Figure 1.21) [20].

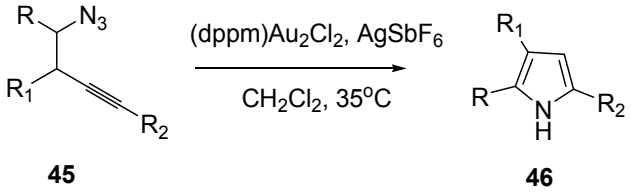


Figure 1.21 Gold(I)-catalyzed acetylenic Schmidt reaction homopropargyl azide

Propargyl vinyl ethers **47** and aromatic amines are effectively converted into tetra- and pentasubstituted 5-methylpyrroles **49** through a silver(I)-catalyzed propargyl-Claisen rearrangement to afford allene **48**, an amine condensation, and a gold(I)-

catalyzed 5-*exo*-dig heterocyclization in a convenient one-pot process (Figure 1.22) [21].

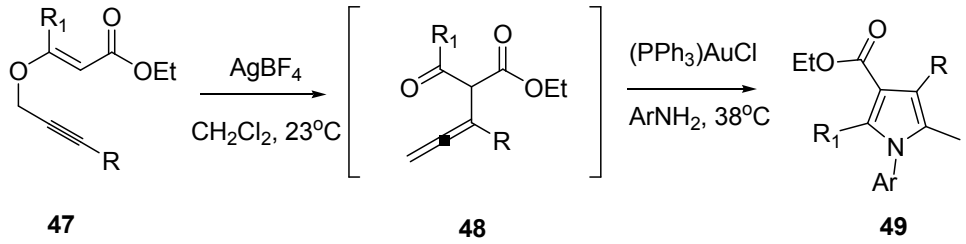


Figure 1.22 One pot synthsis of pyrrole **49**

A new microwave-assisted rearrangement of 1,3-oxazolidines scaffolds is the basis for a new, metal-free, direct, and modular construction of tetrasubstituted pyrroles from terminal-conjugated alkynes **50**, aldehydes **51**, and primary amines under very simple and environmental-friendly experimental conditions (Figure 1.23) [22].

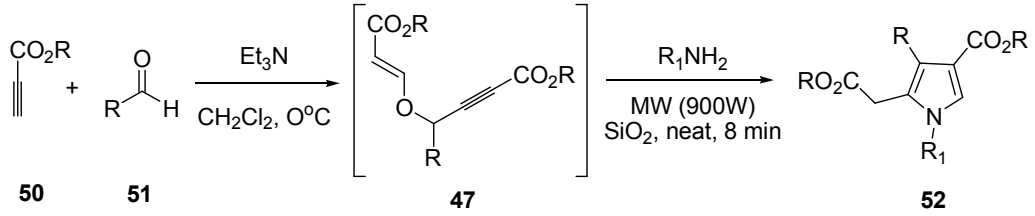


Figure 1.23 Microwave-assisted synthesis of tetrasubstituted pyrrole **52**

A silver(I)-promoted oxidative cyclization of homopropargylamines **53** at room temperature provides pyrroles **54**. Homopropargylamines **53** are readily available by the addition of a propargyl Grignard reagent to *Schiff* bases [23].

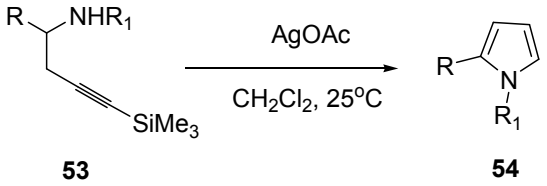


Figure 1.24 Silver(I)-promoted oxidative cyclization of homopropargylamine to give pyrrole **54**

Ferraz *et al.* described the synthesis of N-substituted pyrrole **57** and tetrahydroindole derivatives from alkenyl 1,3-dicarbonyl compounds **55** via the formation of iodo-1,3-enamino esters **56** followed by dehydroiodination (Figure 1.25) [24].

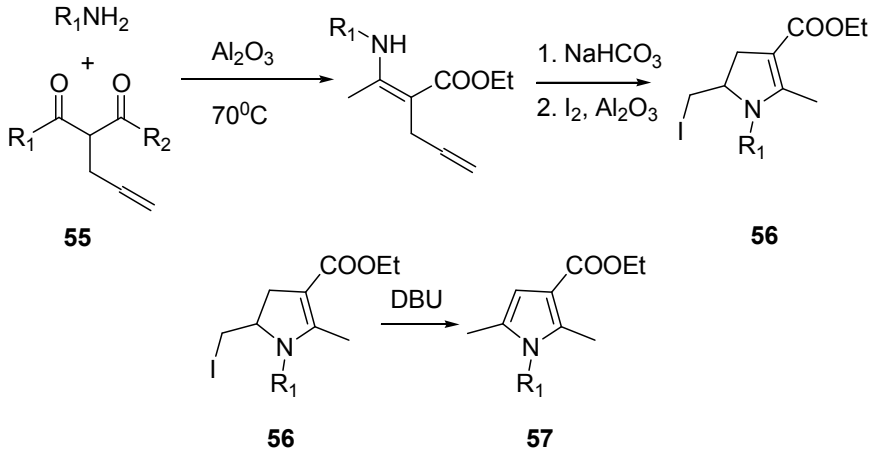


Figure 1.25 Synthesis of N-substituted pyrrole **57**

Similar studies starting with active methylene compounds to synthesize pyrroles have been carried out by Demir *et.al.* Demir *et.al* described the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives [25]. Accordingly, the corresponding 1,3-dicarbonyl compounds **58** were initially alkylated with 2,3-dibromoprop-1-ene **59** to afford compound **60** followed with enamine **61** formation. Then the isolated enamines **61** were led to the cyclization reaction to form pyrrole derivatives **62** (Figure 1.26).

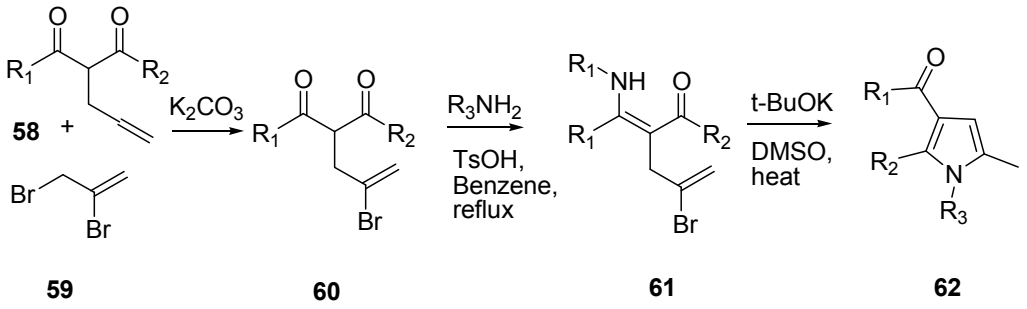


Figure 1.26 Synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives

Demir and coworkers have also shown that the condensation reaction of 2-propynyl-1,3-dicarbonyl compounds **63** with amines catalyzed by TFA which represents a new general one-pot entry into functionalized pyrroles **64**. The formation of the pyrroles was suggested to proceed through the sequential amination of carbonyl compounds followed by regioselective *5-exo-dig* cyclization of the enaminone intermediate and aromatization reaction. The reaction requires a catalyst. TFA is the most efficient and selective catalyst and its application is general, but $Cu(OAc)_2$ was also efficient catalyst when enaminones were used [27].

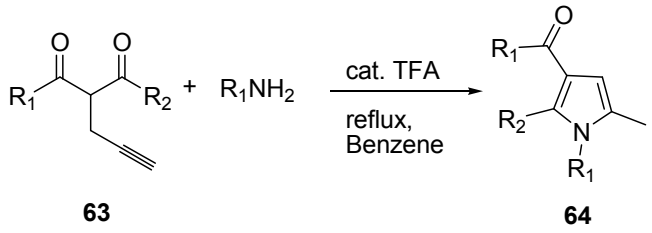
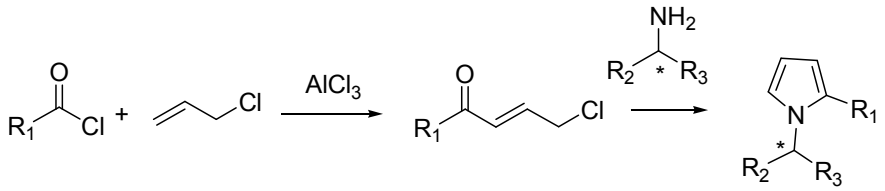


Figure 1.27 Synthsis of functionalized pyrroles

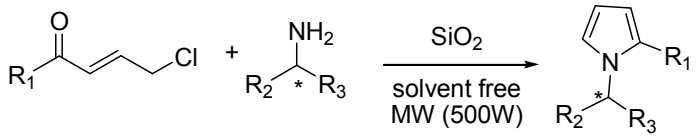
Demir *et al*. [28] have developed a convenient method for the construction of substituted pyrrole rings **68** from amines, amino alcohols and amino acids with chloroenones **67** prepared from acid chlorides **66** and allyl chlorides **65** in the presence of $AlCl_3$. Ring construction process was performed by the reaction of a specific chloroenone and amino acid ester salts, amines or amino alcohols in the presence of Et_3N (Figure 1.28).



66 **65** **67** **68**

Figure 1.28 Synthesis of pyrroles from chloroenones

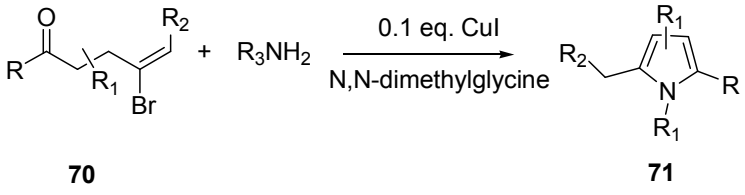
An efficient, solvent-free, microwave-assisted coupling of chloroenones **67** and amines **68** on the surface of silica gel gave 1,2-disubstituted homochiral pyrroles **69** in good yields [29].



67 **68** **69**

Figure 1.29 Microwave assisted synthsis of pyrrole **69**

The CuI/*N,N*-dimethylglycine-catalyzed reaction of amines with γ-bromo-substituted γ,δ-unsaturated ketone **70** in the presence of K_3PO_4 and NH_4OAc gave the corresponding polysubstituted pyrrole **71** in very good yields [30].

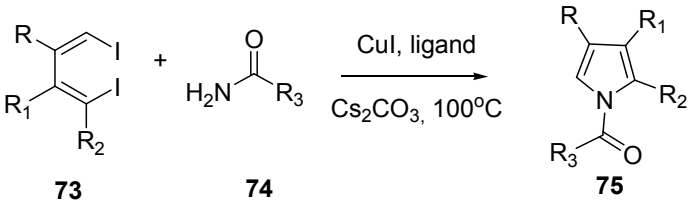


70 **71**

Figure 1.30 CuI/*N,N*-dimethylglycine-catalyzed synthe sis of polysubstituted pyrrole

An efficient copper-catalyzed double alkenylation of amides with (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes **72** affords di- or trisubstituted *N*-acylpyrroles **74** in good yields

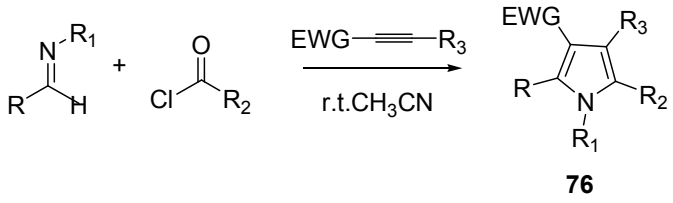
using CuI as the catalyst, Cs_2CO_3 as the base, and *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine **73** as the ligand [31].



73 **74** **75**

Figure 1.31 Copper-catalyzed double synthesis di- or trisubstituted *N*-acylpyrroles **74**

A direct synthesis of pyrroles from imines, acid chlorides, and alkynes mediated by isocyanides proceeds with a range of substrates, providing a method to generate various pyrroles in high yield. Mechanistic studies suggest a generation of imino analogues of münchnones, which can undergo in situ coupling with alkynes to liberate isocyanate and form the pyrrole product **76** [32].



76

Figure 1.32 Synthesis of pyrroles from imines

An efficient synthesis of 2,3,4-trisubstituted pyrroles **78** through a mechanism involving a distal cleavage of the C-C bond of the cyclopropane ring via intermolecular cyclization of alkylidenecyclopropyl ketones **77** with amines is presented in figure 1.3 [33].

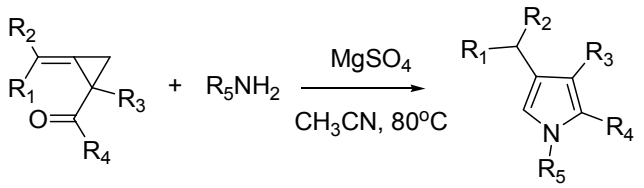


Figure 1.33 Intermolecular cyclization of alkylidenecyclopropyl ketones **77** with amines

1.1.4 Synthesis and properties of Aminopyrroles.

As it is mentioned before the pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry primarily due to the fact that many pyrroles are subunits of natural products, pharmaceutical agents and polymers [34]. The valuable and diverse biological properties of pyrroles make the development of efficient methods for the preparation of these compounds, having a defined substitution pattern, a focus of considerable synthetic effort. β-Dicarbonyl compounds are versatile intermediates for the synthesis of pyrrole derivatives [35]. Pioneering work on the synthesis of pyrroles from β-dicarbonyl compounds was carried out by Hantzsch in 1890. Many studies have been published on the synthesis of pyrroles using the principle of Hantzsch's method starting from β-dicarbonyl compounds [36].

Aminopyrroles have been found to show interesting biological properties [37] or have been used as precursors [38] for known drugs, in which they have found use as synthetic precursors for acyclic nucleoside analogues of the pyrrolo[2,3-d]pyrimidine ring system [39].

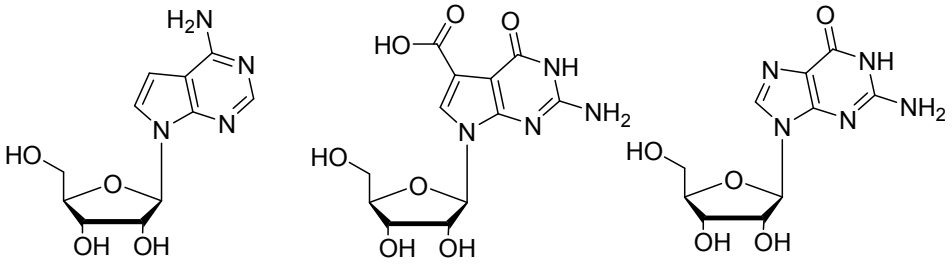


Figure 1.34 Nucleoside analogs

As constituents of cytotoxic drugs, such as netropsin and distamycin, aminopyrroles have served as principle components for constructing a diverse series of DNA-binding ligands exhibiting antibiotic, antiviral, and oncolytic properties [40].

DNA that consists of the four bases A, G, C, and T is one of the most important biomolecules by means of coding indispensable information for life. The three bases of mRNA transcribed from DNA, codon, correspond to 20 kinds of amino acids respectively, and translated to protein. Thus, if an artificial nucleobase pair could be added to the natural base pair system, the number of codons would be dramatically increased. In the past two decades, some groups reported the trial of synthesis of enzymatically replicable artificial base pairs for a functionalized protein that includes unnatural amino acids by such an approach [41]. In a recent work H. Oda et.al studied the synthesis of deoxyribonucleoside bearing 2-aminopyrrole **79** as several artificial nucleosides [42].

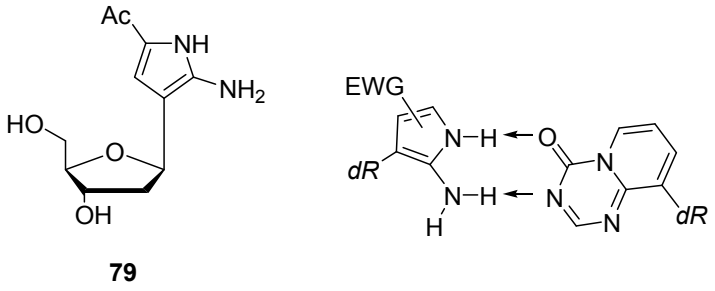
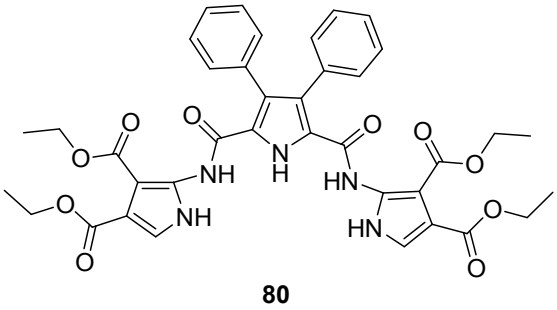


Figure 1.35 Deoxyribonucleoside bearing 2-aminopyrrole **79**

Moreover, aminopyrroles have also exhibited anticonvulsant activity by blocking sodium ion channels [43]. Effective methodology for synthesizing aminopyrroles is thus essential for furthering their application in medicinal and biological chemistry.

Supramolecular compounds including 2-aminopyrrole moiety are known to be as anion binding receptor precursors due to the pyrrolic NH groups good hydrogen bond donor property that are capable of interact with Lewis basic anions. Also, pyrrole functionalization as hydrogen bond acceptors (e.g. carbonyls) is easier than other structures such as amide and other functional groups [44]. The reported

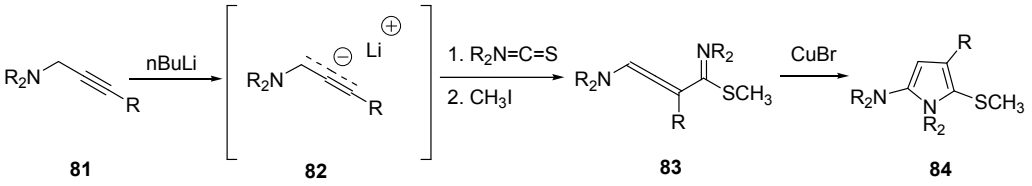
compound bispyrrole-2-yl-2,5-diamidopyrrole **80** has been used as an anion receptor [45].



80

Figure 1.36 Structure of bispyrrole-2-yl-2,5-diamidopyrrole **80**

A one-pot synthesis of 1,2,3,5-tetrasubstituted pyrroles was reported starting from 2-alkynylamines and isothiocyanates [46]. In this process, 2-alkynylamines **81** were metallated with nBuLi to produce the unsaturated carbanions **82**, which undergo regiospecific reaction with alkyl isothiocyanates followed by S-methylation leading to the azatrienes **83**. Addition of catalytic amounts of copper(I) bromide then induces cyclization to the tetrasubstituted pyrroles **84**.



81 **82** **83** **84**

Figure 1.37 Synthesis of 1,2,3,5-tetrasubstituted pyrroles from 2-alkynylamines and isothiocyanates

Most compounds of this type have been obtained by the reaction of a nitrogen-two-carbon compound with an appropriate two-carbon unit, for example, base-promoted condensation of an amino ketone or a conjugated azoalkene.

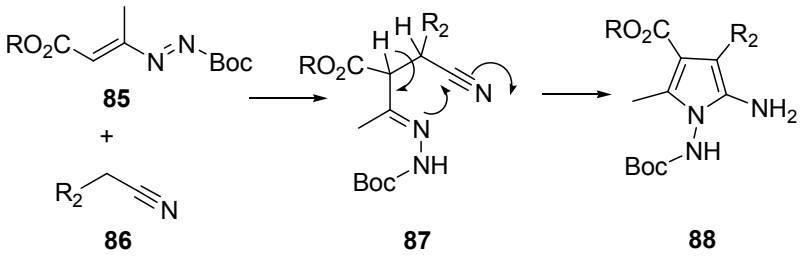


Figure 1.38 Synthsis of 1-Boc-protected 1,2-diaminopyrrole derivatives **88**

The nucleophilic attack of the activated methylene group of acetonitrile derivatives **85** at the aza–ene system of **86** affords hydrazone 1,4-adducts **87**. By means of intramolecular ring closure on the nitrile function we achieved 1-Boc-protected 1,2-diaminopyrrole derivatives **88** (Figure 1.38) [47].

Recent access to 2-(alkylamino)- and 2-(arylamino)pyrroles **89** by the addition of isocyanides to protonated 1-azabutadienes is described by Marchand et al. [48].

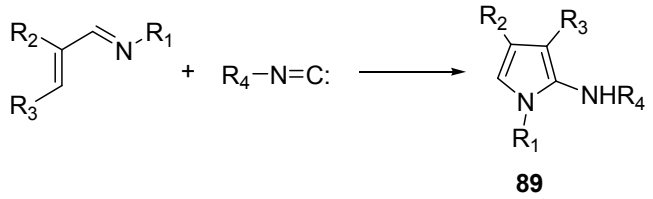
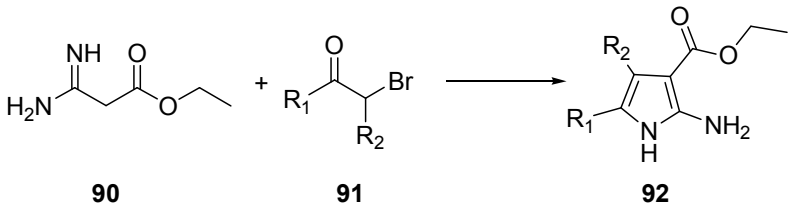


Figure 1.39 Synthesis of 2-(alkylamino)- and 2-(arylamino)pyrroles **89**

Other miscellaneous and limited methods were also described in the review by Trofimov et al. [49].

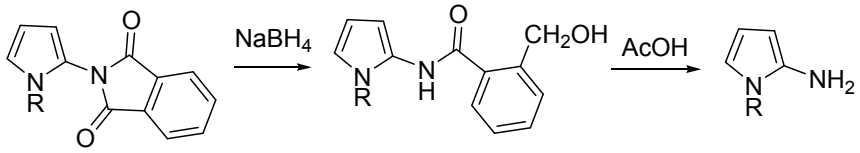
Emilio et al. reported the synthesis of 2-amino-pyrrole-3-carboxylate derivatives. The reaction of ethoxycarbonylacetamidine (**90**), obtained in situ from hydrochloride and NaOEt, with α-bromoacetone **91** derivatives was carried out in absolute EtOH. Pure 2-aminopyrrole- 3-carboxylate derivatives **92** obtained in yields ranging 25%-64% (Figure 1.40) [50].



90 **91** **92**

Figure 1.40 Synthesis of 2-amino-pyrrole-3-carboxylate

A synthetic route used to prepare 2-aminopyrroles **93** has been described by De Rosa et.al. as summarized in figure 1.41 [51]. The preparation of 2-aminopyrroles were achieved by reaction of 1-substituted pyrroles with *N*-chlorophthalimide gave an *N*-(1-substituent-1*H*-pyrrol-2-yl)phthalimide **93** by an addition–elimination reaction. Partial reduction followed by hyrolysis afforded the pure 2-aminopyrroles **94**.



93 **94**

Figure 1.41 Preparation of 2-aminopyrroles

Another synthetic way for the preparation of 2-aminopyrroles **95** in moderate yields as precursors of new pyrrolo[2,3-*b*]pyridine derivatives **96** being potent inhibitors of tumour necrosis factor is described by Mohammed et al. [52].

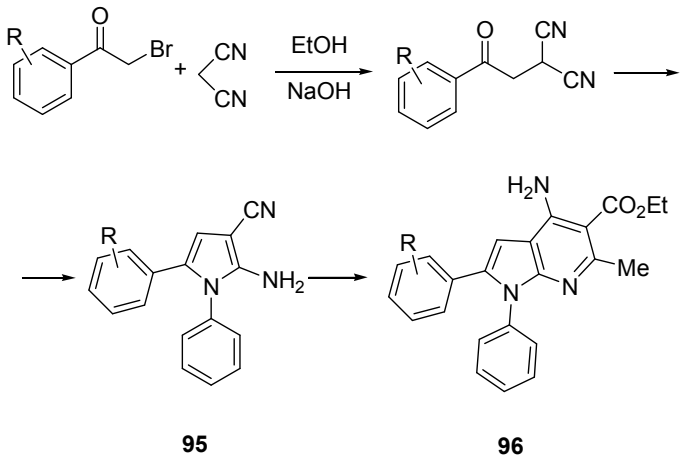


Figure 1.42 synthesis of pyrrolo[2,3-*b*]pyridine derivatives **96**

1.1.5 2-Aminopyrroles as conformationally restricted GABA analogs.

GABA is the major inhibitory amino acid transmitter of the mammalian central nervous system and it is present in some 40% of all neurones. Most of the early studies, carried out with iontophoretic application of GABA in the CNS, indicated that it generally produced inhibitory hyperpolarizing responses on neurones, which were blocked competitively by the alkaloid **bicuculline**. The hyperpolarizing response is due to an increase in the chloride conductance of the neuronal membrane allowing chloride ions to flow down their electrochemical gradient into the cell. However, in the late 1970's, Bowery and his colleagues, in attempts to identify GABA receptors on peripheral nerve terminals, noted that GABA application reduced the evoked release of noradrenaline in the rat heart and that this effect was not blocked by bicuculline. This action of GABA was mimicked by **baclofen**, 4-amino-3-(4-chlorophenyl) butanoic acid (Figure 1.44), a compound that had no effect on chloride conductance in central neurones.

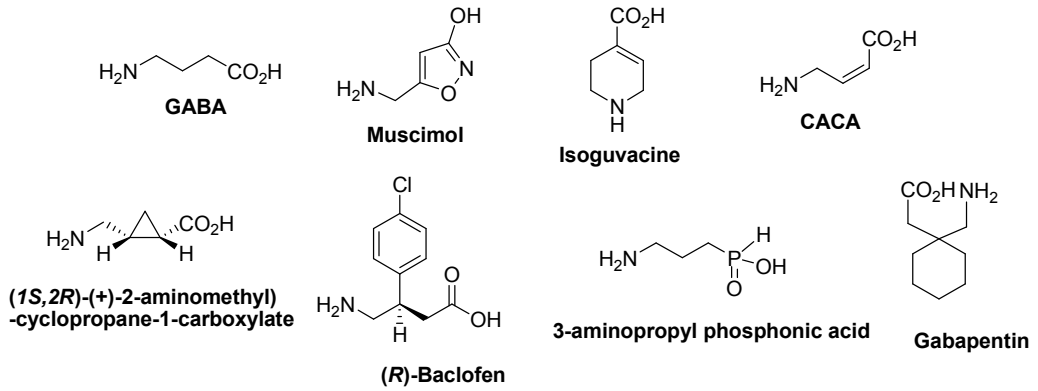


Figure 1.44 Structures of GABA analogs

The inhibitory neurotransmitter γ-amino butyric acid (GABA) has served as a structural template for a number of substances that have effects on the central nervous system [53]. Those that have advanced to the clinic include the GABA-B receptor agonist baclofen an antispastic agent, [54] the GABA transaminase inhibitor vigabatrin, [55] and the putative GABA prodrug progabide [56] which are anticonvulsant agents like gabapentin wherein the third carbon atom of GABA is incorporated into a cyclohexane ring [57].

A strategy common to the design of all of these compounds was to manipulate the molecule of GABA so as to increase its lipophilicity, restrict the conformation and thereby allow it to gain access to the CNS. From this point, 2-aminopyrrole-carboxylates serve as new conformationally restrictes analogs of GABA (Figure 1.45).

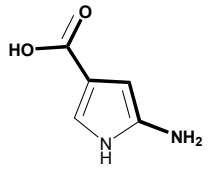


Figure 1.45 General structure of 2-aminopyrrole as GABA analogs

1.2 Darzens condensation with Acylpsphonates

1.2.1 Darzens reaction and application, synthesis of substituted epoxides

Darzens condensation is one of the most potential methodologies for the preparation of α,β-epoxy carbonyl compounds [58] and is one of the classical C-C and C-O bond forming process widely known. Moreover is used in a great number of synthesis of important biologically active natural compounds.

This reaction was discovered by the organic chemist Auguste George Darzens (1867-1954) [59-62]. It includes the Condensation of α-halo carbonyl compoundss with aldehydes and ketones in the presence of bases to afford epoxides.

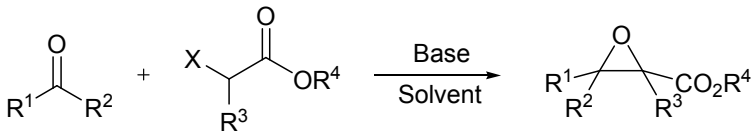


Figure 1.46 General reaction of Darzens condensation

Three possible products are observed during the darzens condensation reaction depending on the reaction conditions. Initially a halohydrin is formed as the intermediate product. Intramolecular annulation affords the epoxide halohydrin **98**. Whereas in the presence of proton source the halohydrin anion abstracts a proton to form the epoxide **99**. Another possible product is the compound **100** which is formed via elimination of the OH^- group .

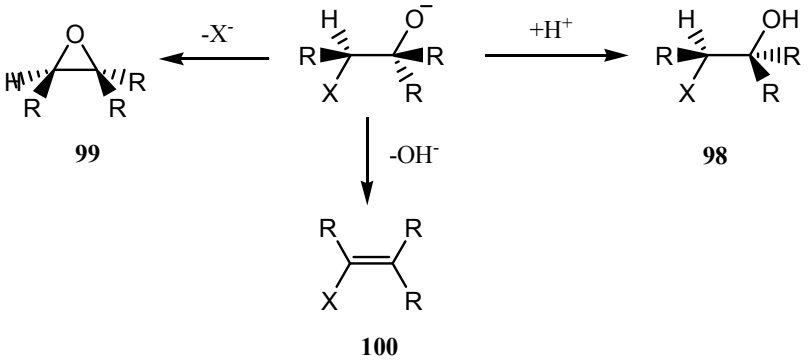


Figure 1.47 Possible products of Darzens condensation reaction

Darzens methodology for the construction of epoxides can be used for α-halo carbonyl compounds, however similar compounds that can undergo deprotonation and bear electron-withdrawing groups. In addition, the reaction can be carried out with diazoacetate, where N_2 is the leaving group, or with a sulphur ylide with SR_2 as the leaving group.

The control of diastereo- and enatioselectivities in asymmetric Darzens reactions leading to α,β-epoxy carbonyl compounds is a challenging goal. A significant problem to be solved is the establishment of an efficient catalytic cycle in which the inorganic salts or related compounds generated from both substrates and reagents are converted into effective reactive species. Past enantioselective Darzens reactions promoted by metal reagents required stoichiometric amounts of chiral sources because of the metal reagents and harsh reaction conditions employed [64].

A camphor-derived amide-stabilized ylide **101** reacts with aldehydes at -50°C in ethanol to give glycidic amides in one step with up to 99% ee and complete diastereoselectivity. In the following specific substitution pattern, the outcome of the reaction depends on the energy of the transition states of the addition, the rotation and the ring closure, as described by Aggarwal [63]. Although explanations for the

diastereoselectivity have been given, the enantioselectivity that is induced by the camphor-derived sulphonium group is not fully understood.

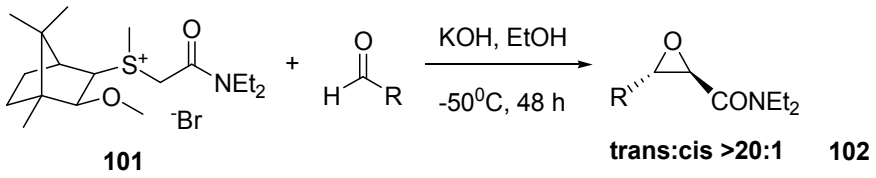
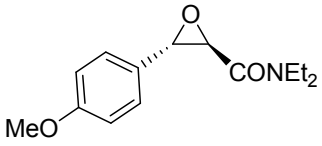
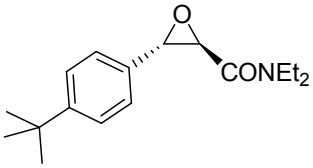
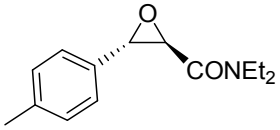
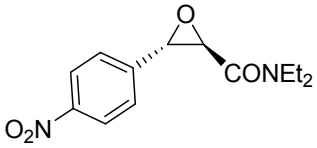


Figure 1.48 Diastereoselective synthesis of epoxyamide

Table 1.1 Reaction of camphor-derived amide-stabilized **101** ylide with aldehydes

entry	product	yield (%)	ee (%)	product	yield (%)	ee (%)
		90	97		85	63
		88	98		84	92

Another concept for highly diastereoselective and enantioselective transformations was developed by Arai et al. They successfully sythesized the desired epoxy ketones **103** with the reaction of an aldehyde **104** and α-chloro ketone **105** by using 10% PTC with yields between 32-83% and ee's between 42-79% [65].

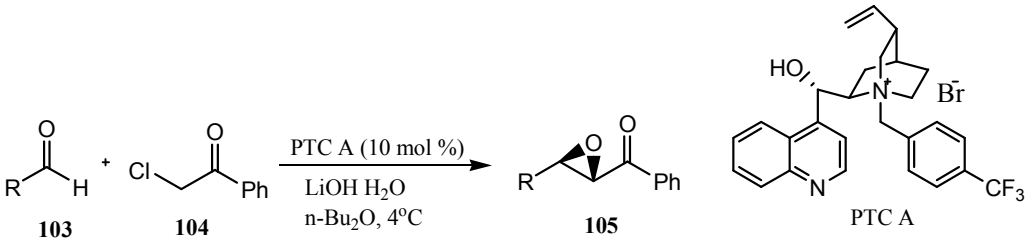


Figure 1.49 Synthesis of epoxy ketones in the presence of a PTC

In this system, the chiral phase transfer catalyst (PTC) is able to recognize one aldolate selectively. There is an equilibrium between *syn*- and *anti*-aldolates via retro-aldol addition, and the formation of a stable, chelated lithium salt blocks the non-catalyzed subsequent reaction from yielding the epoxide product.

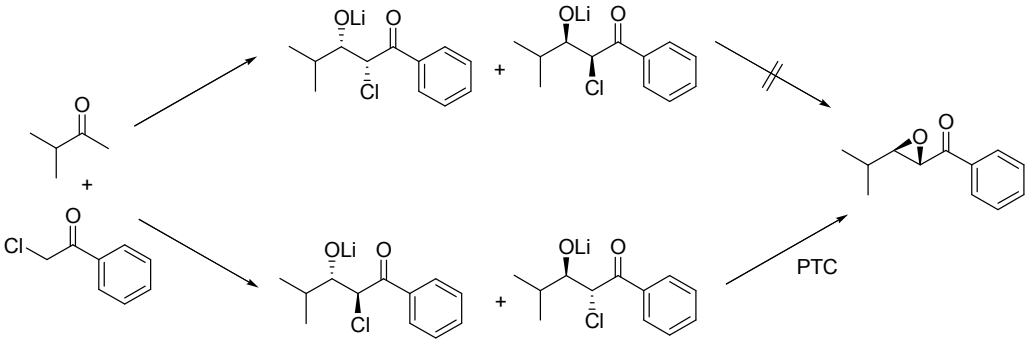
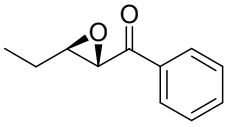
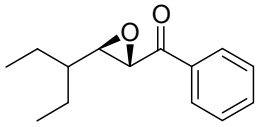
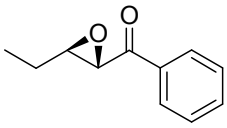
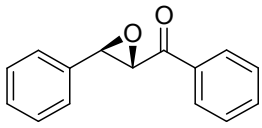
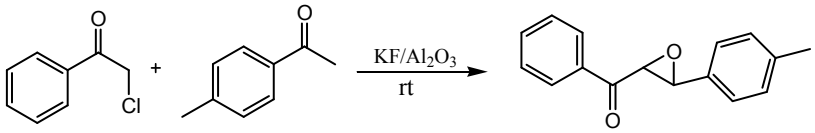


Figure 1.50 Mechanistic explanation of *trans* slectivity

Table 1.2 Reaction of α-chloroketones with aldehydes in the presence of PTC

Product	T(h)	yield (%)	ee(%)	Product	T(h)	yield (%)	ee(%)
	**117**	**32**	**79**		**117**	**76**	**58**
	**134**	**73**	**69**		**69**	**43**	**42**

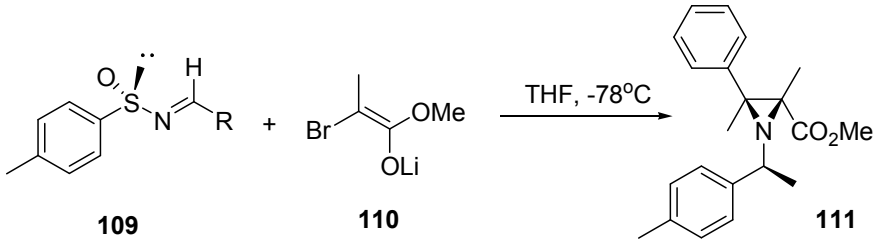
Recently, a Darzens condensation of α-chloroacetophenone **106** with various aromatic aldehydes **107** mediated by potassium fluoride on a alumina at room temperature and obtained *trans*-α,β-epoxy ketones **108** with good yields is reported by Sharifi and co. Workers [66].



106 **107** **108**

Figure 1.51 Synthesis of *trans*-α,β-epoxy ketones with KF/Al_2O_3

An asymmetric aza-Darzens reaction, in which a preformed lithium α-bromoenolate **109** reacts with a sulphinimine **110** to give an aziridine **111**, features a six-membered transition state that accounts for the high diastereoselectivity is reported by Daies et. al. [67].



109 **110** **111**

Figure 1.52 Asymmetric aza-Darzens reaction

In another work, a mild, convenient aza-Darzens protocol for the synthesis of *cis*-aziridines **112** employs a catalytic amount of Brønsted acid. Diazo compound decomposition via alkylation or homocoupling upon exposure to a proton source is slow relative to [2 + 1] annulation in the presence of a Schiff base [68].

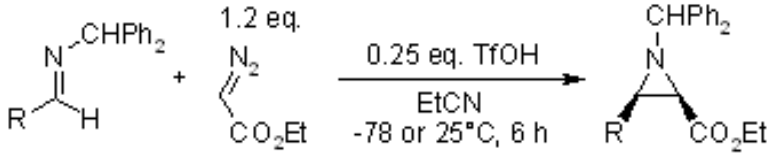
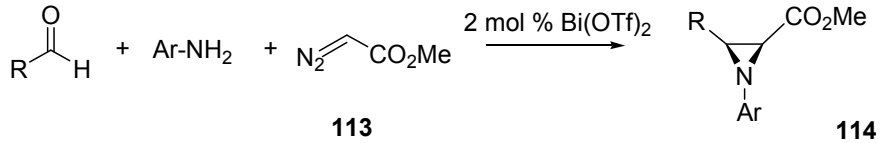


Figure 1.53 Aza-Darzens reaction for the synthesis of *cis*-aziridines **112**

Moreover, aldimines (generated in situ from aldehydes and amines) react readily with ethyl diazoacetate **113** in the presence of 2 mol% of $Bi(OTf)_3$ in $[bmim]PF_6$ (1-N-butyl-3-methylimidazolium) to produce the corresponding aryl aziridine carboxylates **114** in high yields with excellent *cis*-diastereoselectivity [69]. The proposed mechanism is as followed in figure 1.55.



113 **114**

Figure 1.54 Synthesis of aryl aziridine carboxylates **114**

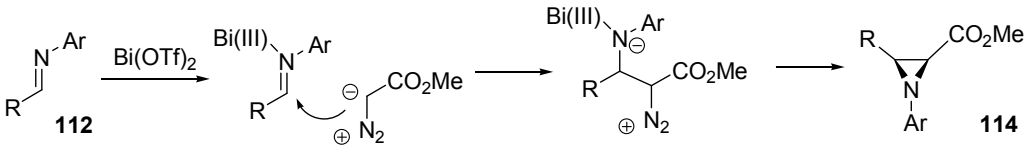


Figure 1.55 Proposed mechanism fort he synthesis of aziridine carboxylate **114**

1.2.2 Acylphsphonates and Epoxyphosphonates

1.2.2.1 Properties and synthesis of Epoxyphosphonates

1,2-Epoxyphosphonates are very important intermediates in organic synthesis. Many of their derivatives have attracted attention because of their antibacterial, antiviral, antibiotic, pesticidal, anti-cancer, and enzyme inhibitory properties. For example, (–)-(1*R*,2*S*)-(*Z*)-1,2-epoxypropylphosphonic acid, a derivative of *cis*-1,2-epoxypropylphosphonates, also called fosfomycin **115** or phosphonomycin, is a low molecular weight cell-wall active antibiotic found by Hendlin and coworkers in 1969 [70].

As a consequence of this discovery, a lot of research has resulted in the extensive development of methodologies in order to prepare analogs of fosfomycin and to diversify the syntheses. Synthesis of dialkyl 1,2-epoxyalkylphosphonates may be classified into four main categories including (a) the Darzens reaction of dialkyl chloromethylphosphonates with carbonyl compounds, (b) the reaction of sodium dialkylphosphites with α-halo ketones, (c) the reaction of dialkyl halohydrinphosphonates with bases, (d) the oxidation of 1,2-unsaturated phosphonates with a peroxide and (e) the reaction of diazobenzylphosphonates with aldehydes and ketones.

1.2.2.2 Darzens reaction of dialkyl chloromethylphosphonates with carbonyl compounds

The Darzens reaction is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds and, therefore, has been recognized as one of the most significant C–C, C-O bond forming processes in synthetic organic chemistry. It employs the base induced condensation of α-halo carbonyl compounds with aldehydes for the construction of highly functionalized oxiranes. The most general and perhaps most widely employed method for the synthesis of dialkyl 1,2-epoxyalkylphosphonates involves the reaction of dialkyl chloromethylphosphonates **116** with carbonyl compounds. Treatment of dialkyl chloromethylphosphonate with an equimolecular amount of base and the further reaction of the intermediate compound **117** with the carbonyl compounds (aromatic aldehydes and ketones) gives the corresponding 1,2-epoxyalkylphosphonates **118** [71].

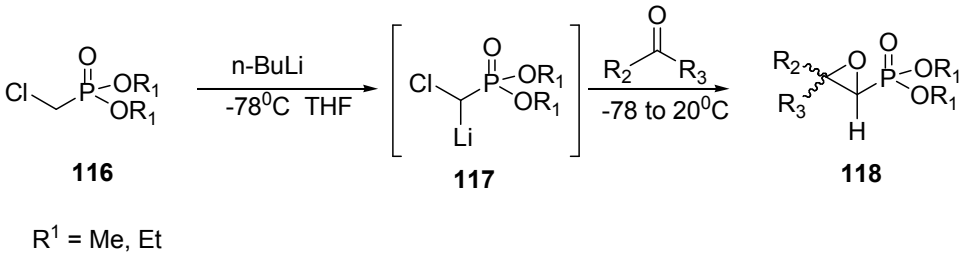


Figure 1.56 Synthesis of 1,2-epoxyphosphonates via Darzens reaction

A useful variant of the Darzens reaction has been reported for the preparation of fosfomycin **121** from diethyl chloromethylphosphonate **116** [72]. Nucleophilic substitution of chlorine in diethyl chloromethylphosphonate with dimethyl sulfide **119** gives the sulfonium salt, further converted into its stable ylide **120** by the use of NaH in DMSO. The addition of the ylide to acetaldehyde produces diethyl 1,2-epoxypropylphosphonate, thus avoiding the problems associated with the stability of chloromethylphosphonate carbanions (Figure 1.57).

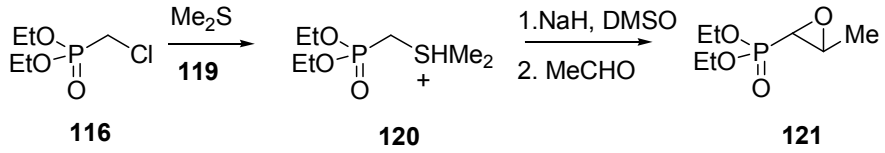


Figure 1.57 Preparation of fosfomycin **121** from diethyl chloromethylphosphonate **116**

1.2.2.3 Reactions of sodium dialkyl phosphite with α-haloketones

The use of sodium Dialkyl Phosphite as phosphorus nucleophiles by the reaction with α-halo compounds can constitute an interesting but somewhat limited method of synthesis of dialkyl 1,2-epoxyalkylphosphonates **121**. It has been reported that the treatment of metal dialkylposphite with α-halo ketone to give a mixture of the epoxide **121** and vinyl phosphate **122**, or a mixture of the epoxide and β-oxophosphonate [73].

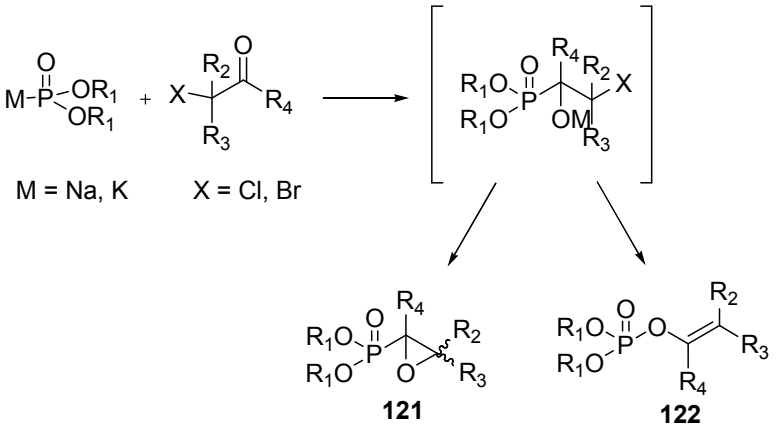


Figure 1.58 Synthesis of 1,2-epoxyphosphonates from sodium dialkylphosphites

An alternative procedure for the preparation of dialkyl 1,2-epoxyalkylphosphonates **125** from α-haloketones **123** is the action of MeONa (1eq) on a mixture of α-chloroketones and dimethyl or diethyl phosphate **124** (1eq) in MeOH at room temperature [74].

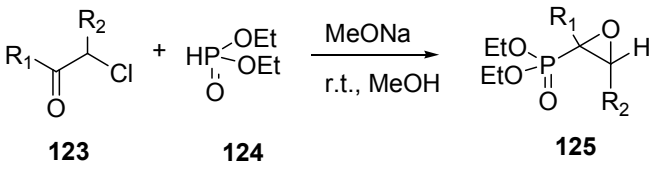


Figure 1.59 Preparation of dialkyl 1,2-epoxyalkylphosphonates **125** from α-haloketones **123**

1.2.2.4 Reactions of dialkyl 1,2-halohydrinphosphonates with bases

Halohydrins are widely used as starting materials for the synthesis of epoxides. Moreover, halohydrinphosphonates are easily converted into epoxyphosphonates by formation of an alkoxide anion. Formation of halohydrinphosphonates can be accomplished by two procedures, which exploit either the condensation of a dialkylphosphite with an α- chlorocarbonyl compound or the halohydroxylation of a vinylphosphonate. After the formation of the corresponding dialkyl halohydrinphosphonate **126**, it is converted to the epoxide **127** by the furter treatment with base (Figure 1.60)[75].

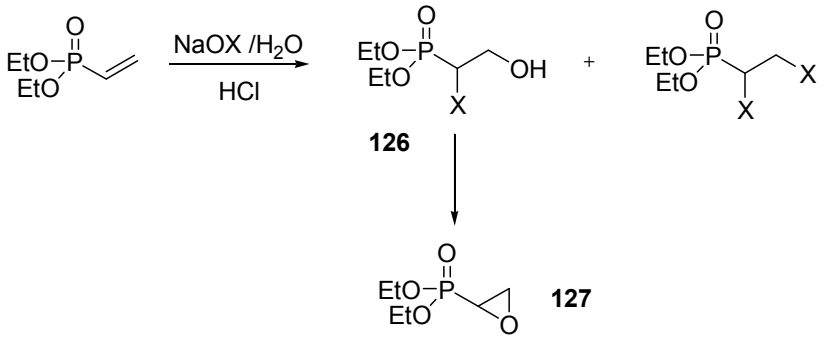
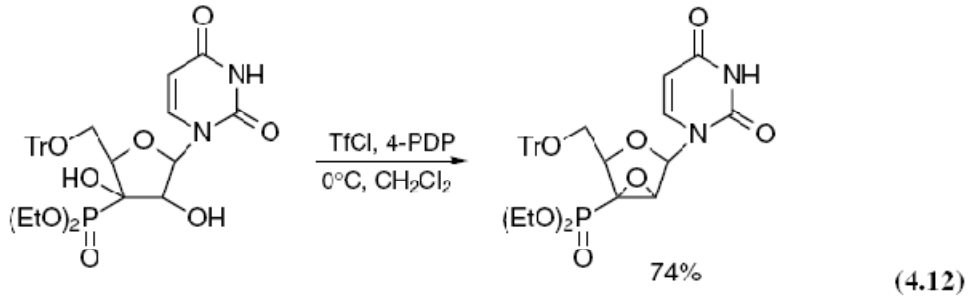


Figure 1.60 Synthesis of 1,2-epoxyphosphonates via reaction of dialkyl halohydrinphosphonates with bases

One ingenious procedure for the construction of a nucleoside epoxyphosphonate from a 1,2- dihydroxyalkylphosphonate exploits the interesting properties of triflates, which serve as good leaving groups [76]. Treatment of the 1,2-diol **128** with trifluoromethanesulfonyl chloride and 4-DMAP directly produces the nucleoside 1,2-epoxyphosphonate **129** in 31% yield via the displacement of an intermediate 2′-triflate. Unfortunately, this reaction is accompanied by the formation of the methylated uracil derivative. When the 1,2-diol is treated with trifluoromethanesulfonyl chloride and 4-PDP in CH_2Cl_2 at 0°C, the nucleoside 1,2-epoxyphosphonate is obtained in 74% yield, and no alkylated byproducts are detected (Figure 1.61).

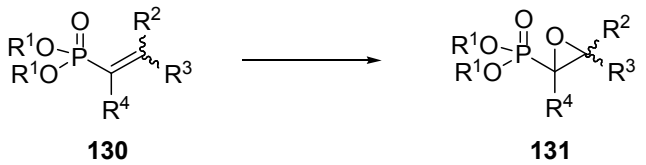


(4.12)

Figure 1.61 synthsis of nucleoside 1,2-epoxyphosphonate **129**

1.2.2.5 Epoxidation of 1,2-unsaturated phosphonates

Epoxidation of unsaturated compounds is a general way to produce epoxides. This general route appears to be an efficient way for the synthesis of dialkyl 1,2-epoxyalkylphosphonates **131** from the corresponding dialkyl vinylphosphonates **130** (Figure 1.62). The use of vinylphosphonates offers appreciable advantages however the difficulties of the preparation of vinylphosphonates is only disadvantage [77].



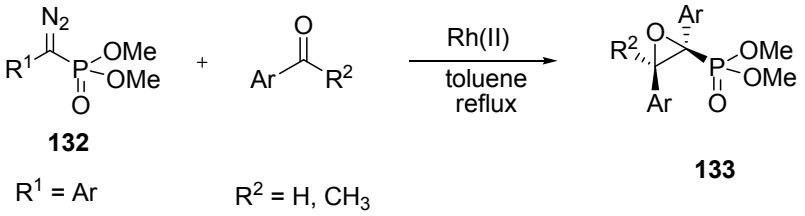
130 **131**

Figure 1.62 Synthesis of dialkyl 1,2-epoxyalkylphosphonates **131** from the corresponding dialkyl vinylphosphonates **130**

,

1.2.2.6 Reaction of diazobenzylphosphonates with aldehydes and ketones

Carbonyl ylides derived from the metal-catalyzed decomposition of diazo compounds have received much attention over the past number of years [78]. They can undergo some important reactions such as 1,3-dipolar cycloaddition reactions with a series of dipolarophiles, rearrangement reactions, and cyclizations to form three-membered ring compounds. Most of the reported carbonyl ylide reactions are 1,3-dipolar cycloadditions [79]. The cyclization of carbonyl ylides is an attractive and general method to give epoxides [80]. One of the methods to synthesize 1,2-epoxyalkylphosphonate **133** is the reaction of carbonyl and diazo compounds **132** in the presence of rhodium acetate [81].



132 **133**

R^1 = Ar R^2 = H, CH_3

Figure 1.63 Synthesis of 1,2-epoxyphosphonates via reaction of diazobenzylphosphonates with aldehydes and ketones

1.2.3 Properties and synthesis of acyl phosphonates

Acyl phosphonates (α-ketophosphonates) are very useful compounds, having interesting properties and wide application. They are the main precursors for biologically active α-aminophosphonic acids and α-hydroxyphosphonic acids. 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 [82]. Some of their properties sometimes directly compared with trihaloketones [83]. Their reactions with Grignard reagents provide the corresponding ketones upon hydrolysis that can classify them as reminiscent of secondary amides [84]. 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 [84]. 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 [85].
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. Acyl anions are available though polarity reversal (umpolung) of the carbonyl compounds and adds a dimension of flexibility to a synthetic design.

Acyl anion equivalents are available from acyl phosphonates. Cyanide or phosphite anion promoted rearrangement of acyl phosphonates in the presence of aldehydes as potent electrophiles to devise a catalytic cross benzoin reaction.

Unlike the similar reagent acylsilanes, acyl phosphonates are readily available from acyl chlorides **134** and trialkyl phosphites **135** via an Arbuzov reaction without needing any special condition or apparatus [86]. Reaction proceeds via formation of unstable intermediate **136** that eventually leads to acyl phosphonate **137** (Figure 1.64).

This apparently makes them more advantageous in terms of practical issues. Furthermore, it is a highly intriguing question as to whether acyl phosphonates can be utilized in a sequence of reactions as depicted in figure 1.64 for the generation of carbanion and their consequent reactions with carbon electrophiles as a generalized strategy for the synthesis of quaternary cyanohydrins.

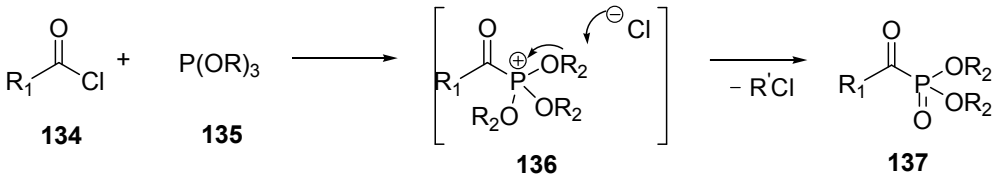


Figure 1.64 Preparation of acyl phosphonates

1.2 Aim of the work

Because of the high importance of pyrrole derivatives and the importance of development of new and efficient synthetic methods, in the first part of this thesis, it is aimed to describe the synthesis of tri-substituted pyrrrole derivatives. 2-Aminopyrrroles, alkoxy and sulfonyl substitttitued pyrrole derivatives as well as pirolinones show interesting biological activities and are precursor of well know drugs. Although there is a number of methods for the synthesis of pyrroles, the synthesis of 2-aminopyrroles is limited to few works and is not widely known. Therefore, it is still an important goal in organic chemistry to improve methods for the synthesis of multifunctionalized pyrrole derivatives and pyrrolinones.

Phosphorous containing epoxides like 1,2-epoxyphosphonates have attracted considerable interest since the first discovery of the antibiotic fosmycin.
A great number of fosmycin derivatives have been synthesized over the years with biological activities, many of which have included the synthesis of epoxyphosphonates as intermediates. The are quite a lot of strategies for their synthesis however, there is still a need for alternative synthetic approaches.

In the second part of the thesis, it is aimed to describe a novel approach for the diastereoselective synthesis of highly functionalized epoxyphosphonates as fosfomycin derivatives by applying a Darzens type reaction of α-halo ketones with acyl phosphonates.

CHAPTER 2

RESULTS AND DISCUSSION

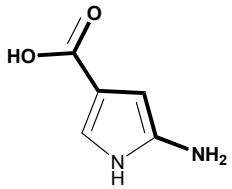
2.1 Pyrroles from α-cyanomethyl-β-ketoesters

2.1.1 Synthesis of 2,4,5-substituted pyrroles

2.1.1.1 Synthesis of 2-aminopyrrole-4-carboxylates

Aminopyrroles are not readily available through general pyrrole ring-formation methods. Despite the large number of published methods for the elaboration of various pyrroles, relatively few examples have been reported for the preparation of simple 2-amino derivatives.

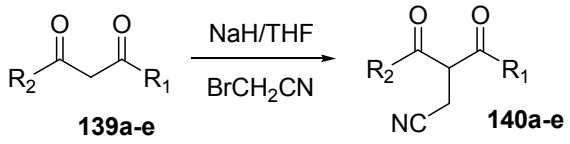
To continue our investigations that are directed towards the synthesis of substituted pyrroles and related compounds [87]. We were especially interested in obtaining 2-amino-4-carboxyl- derivatives of pyrroles. These compounds are conformationally restricted GABA structure analogous **138** (Fig. 2.1).



138

Figure 2.1 General structure of 2-aminopyrrole **138** as GABA analogs

From a synthetic point of view, 2-aminopyrroles can be synthesized via a reaction sequence involving α-alkylation of β-dicarbonyl compounds with bromoacetonitrile, enamine formation, and finally a ring closure reaction. This seems like a very attractive route because a wide variety of substituents (R_1, R_2, and R_3) can be used, originating from readily accessible starting materials. As shown in figure 2.2, α-cyanomethyl-β-dicarbonyl compounds **140a–e** were synthesized by alkylation of β-dicarbonyl compounds **139** with bromoacetonitrile (NaH/ THF and DBU/benzene) according to the literature procedure in 71–80% yields (Figure 2.2) [88].



139a-e **140a-e**

139a(R_1=Me, R_2=Me)
139b(R_1=OMe, R_2=Me)
139c(R_1=OMe, R_2=Et)
139d(R_1=OMe, R_2=Ph)
139e(R_1=OMe, R_2=p-F-C_6H_5)

Figure 2.2 General reaction for the preparation of α-cyanomethyl-β-dicarbonyl compounds

As shown in figure 2.3, the enamine derivatives **142a–i** were easily prepared from amines **141a–c** and α-cyanomethyl-β-dicarbonyl compounds **140a–e** in benzene at reflux with the addition of a catalytical amount of p-TsOH in 68–75% yields after purification of the crude products by column chromatography (Table 2.1). The formation of enamines by using ethyl 2-(cyanomethyl)-3-oxo-3-phenylpropanoate (**142d**) was not successful under the above described conditions. There are many general methods for the synthesis of β-amino-α,β-unsaturated carbonyl compounds, however, no convenient procedure is described in the literature for the formation of enamines starting from 2-alkyl-3-aryl-1,3-dicarbonyl compounds. Various reaction conditions were applied in order to find a convenient procedure for the formation of enamine **142j** (ethyl-3-(benzylamino)-2-cyanomethyl-3-phenylacrylate) with benzylamine as described below:

1. p-TsOH–Benzene (or Toluene), azeotropic removal of water. (1 equiv **140d**, 2 equiv **141c**, 10 mL solvent, 48 h): product was obtained in very low yield.
2. TFA–Benzene (1 equiv **140d**, 2 equiv diketone, 10 ml solvent, 48 h): trace amount of product formation (GC–MS).
3. BF_3–Et_2O, Toluene (1 equiv **140d**, 2equiv **141c** 10 ml solvent): no product formation.
4. Al_2O_3 supported reaction [89] (1 equiv **140d**, 1.5 equiv **141c**, Al_2O_3, at 70 ^{0}C): no product formation.
5. Al_2O_3 supported microwave reaction (1 equiv **140d**, 1.5 equiv **141c**, Al_2O_3): starting material and unidentified side products.
6. p-TsOH, silica gel or K-10 Montmorillonitrite clay supported microwave reaction [90] (1 equiv **140d**, 1.5 equiv **141c**): product was observed, but in low yield (5–7%).
7. Stefani et al.[91] described the preparation of enaminones from β-ketoesters or β-diketones and primary amines in water. Application of this procedure to **140d** (1 equiv **140d**, 2 equiv **141c**, 5 ml H_2O, stirred at room temperature for 3 h) furnished the decarboxylation product **144** in 10% yield (Figure 2.4).
8. Five equivalents **141c** was neutralized with 5 equiv acetic acid added to 1 equiv **140d** solution refluxed in ethanol for 24 h:[92] product formed with very low yield, but was not reproducible.
9. Finally the highest yield (46%) was achieved from **140d** and **141c** without a solvent and excess amine. This reaction was carried out at 140 ^{o}C for 4 h. Increasing temperature increases the amount of side products, which could not be identified. This reaction was also carried out under microwave conditions without heat and solvent, in which the product was obtained in 40% yield.

After many trials, we found that the latter procedure was the best choice for the conversion of **140d–e** to enamine **142j–l**. The cyanomethyl substituted enamines **142 a–l** were also assumed to be obtained starting from β-dicarbonyl compounds **139a–e** and amines **142**, by the formation of enamine followed by alkylation with bromoacetonitrile. In a representative reaction, **140b** was reacted with aniline in benzene at reflux with the addition of a catalytical amount of p-TsOH to give

enamine **142** in 79% yield. Deprotonation of the enamine with NaH in THF followed by alkylation with bromoacetonitrile furnished trace amount of the desired product. This method was not suitable for the synthesis of enamines **142a–l**.

Simple and efficient conditions were found for the cyclization of enamines to pyrroles. This condition involved the treatment of enamines **142a–l** with potassium ethoxide in ethanol at room temperature, in which the pyrrole derivatives **143a–l** were obtained in excellent yields in a short reaction time (5–10 min; for aryl substituted enamines 20–30 min) (Figure 2.3).

In addition to the above described experiments, many attempts were made for the direct one pot synthesis of pyrroles starting with; (a) β-dicarbonyl compound, bromoacetonitrile and amine, (b) starting from enamine, bromoacetonitrile, heating in benzene in the presence of catalytical amount of p-TsOH or TFA, but none of the reactions were successful.

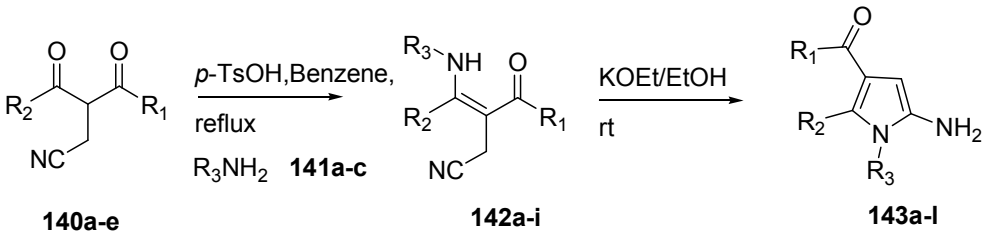


Figure 2.3 General reaction for the synthesis of 2-aminopyrroles

Table 2.1 Reaction of dicarbonyl compounds **140a-e** with amines **141a-i**

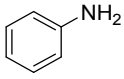
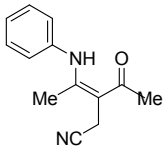
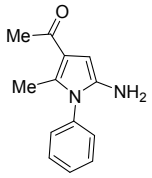
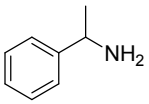
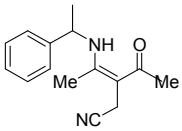
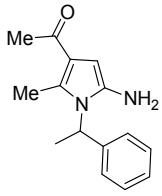
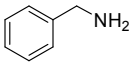
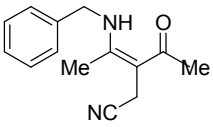
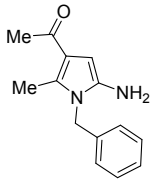
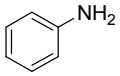
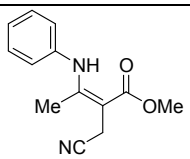
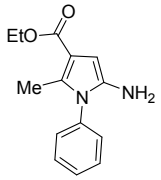
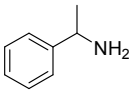
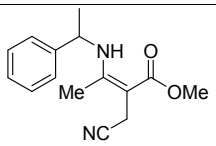
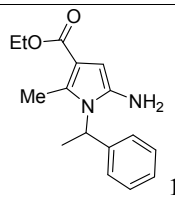
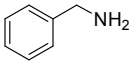
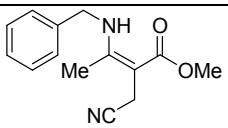
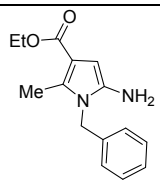
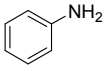
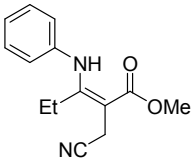
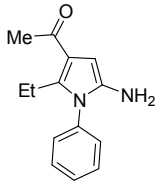
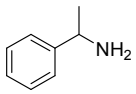
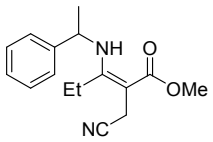
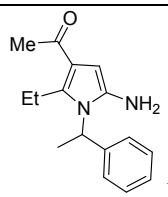
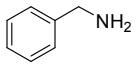
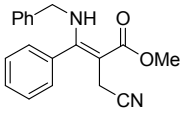
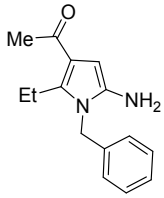
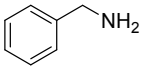
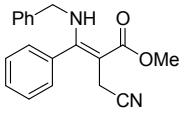
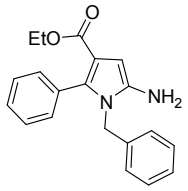
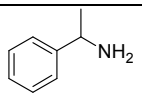
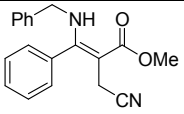
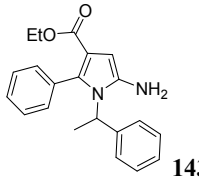
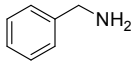
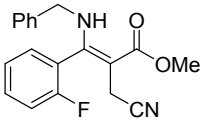
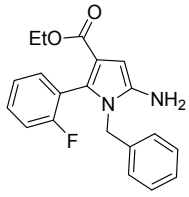
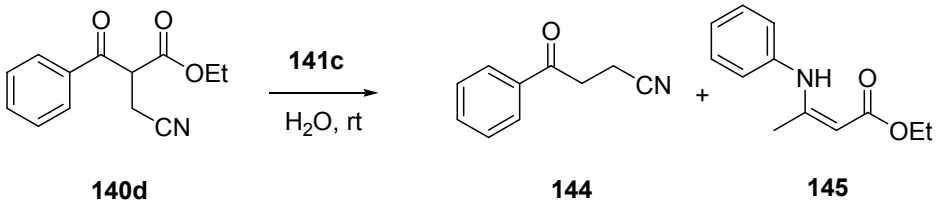
Entry	Dicarbonyl compound **140**	Amine **141**	Enamine **142**	Pyrrole **143**
1	**140a**	 **141a**		 **143a**
2	**140a**	 **141b**		 **143b**
3	**140a**	 **141c**		 **143c**
4	**140b**	 **141a**		 **143d**
5	**140b**	 **141b**		 **143e**
6	**140b**	 **141c**		 **143f**
7	**140c**	 **141a**		 **143g**

Table 2.1 continue

8	**140c**	 **141b**		 **143h**
9	**140c**	 **141c**		 **143i**
10	**140d**	 **141c**		 **143j**
11	**140d**	 **141b**		 **143k**
12	**140e**	 **141c**		 **143l**



140d **144** **145**

Figure 2.4 Decarboxylation of compound **140**

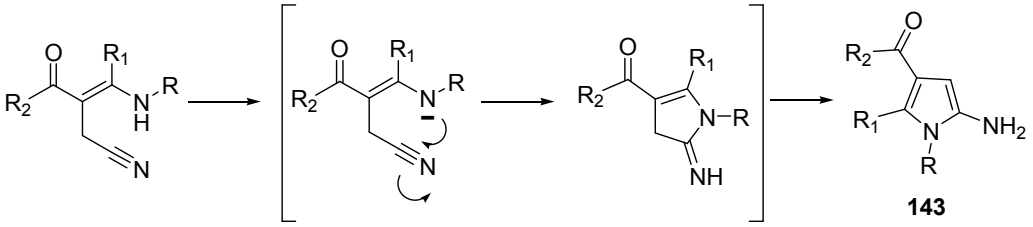


Figure 2.5 General reaction mechanism

The mechanism is assumed to involve the deprotonation of the enamine, then the addition of the amine moiety to the carbon–nitrogen triple bond to afford the cyclic intermediate (Figure 2.5). This is followed by a rearrangement to afford pyrrole **143**. The attack of nitrogen to the carbon–nitrogen triple bond is activated by the potassium ion. This mechanism is consistent with the generally accepted mechanism of the nucleophilic addition to metal-activated carbon–carbon multiple bonds [93].

This investigation has resulted in the elaboration of a convenient procedure for the preparation of 2-aminopyrrole derivatives. The condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by p-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond furnished 2-aminopyrroles in high yields [94].

2.1.1.2 Zinc perchlorate catalyzed regioselective synthesis of 2-aminopyrrole-4-carboxylates

As we have described in previous part, the condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by p-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond of nitrile furnished 2-aminopyrroles in high yields (Figure 2.6, route A) [95].

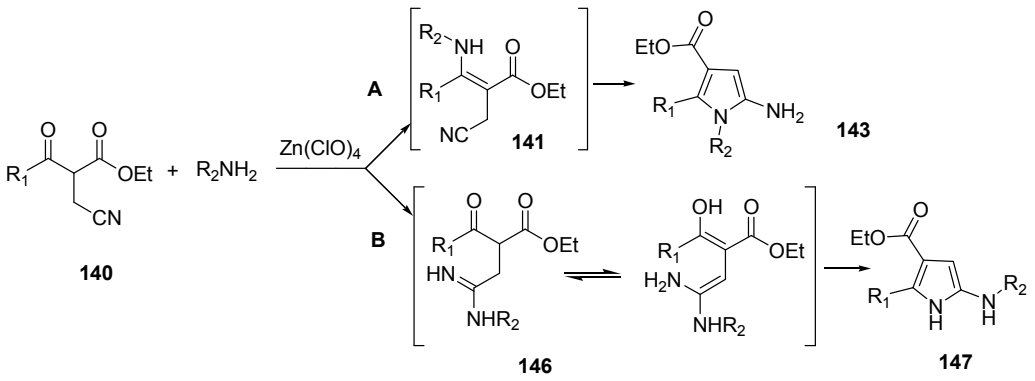


Figure 2.6 General reaction summary

The addition of nitrogen nucleophiles to CN triple bonds of nitriles is one of the most attractive transformations of nitriles. However, the reported methods are limited because of the low reactivity of nitriles. Development of a catalytic method, which proceeds under neutral and mild conditions is desired in view of the synthetic and environmental aspects. As a line of our study on the development of a synthetic methodology for exploring environmentally friendly processes, and to continue our investigations that are directed towards the synthesis of substituted pyrroles and related compounds, we were especially interested in obtaining 2-amino-4-carboxyl-derivatives of pyrroles. These principles have led us to find a novel catalytic one-pot synthesis of 2-aminopyrroles starting from α-cyanomethyl-β-ketoesters.

In the following part of this work the novel chemo- and regioselective metalperchlorate-catalyzed amination and annulation of α-cyanomethyl-β-ketoesters will be described. Metal-coordinated dicarbonyl compound **140** undergoes either C=O activation to react with amines to form enamines **141**, or CN triple bond activation of nitriles to have a direct reaction with amines to afford **146** as shown in Figure 2.6. This step determines the selective formation of pyrrole isomers **143** and **147**.

In an initial reaction, we attempted to synthesize the enamine **141** starting with β-dicarbonyl compound **140a** and aniline **100** by using 5 mol% of $Zn(ClO_4)_2$ in DCM in which the reaction was monitored by TLC. The isolated product was identified as

a pyrrole derivative **147a** in excellent yield. The structure of the product showed that pyrrole nitrogen was not from the aniline as expected but from nitrile.

We continued our study by comparing the catalytic activity of zinc perchlorate with other metallic derivatives. Among all of the catalysts tested zinc perchlorate proved to be the most efficient, and 5 mol% of zinc perchlorate showed the highest efficiency. Moreover, the effects of other zinc salts were also tested (Table 2.2).

Table 2.2 Catalyst screening

Entry	Catalyst (5mol %)	Time (h)	Yield (%)
1	$Zn(ClO_4)_2$	3	91
2	$Mg(ClO_4)_2$	3	78
3	$Cu(ClO_4)_2$	3	No product
4	$LiClO_4$	3	No product
5	$Co(ClO_4)_2$	3	52
6	$NaClO_4$	3	No propuct
7	$Mn(ClO_4)_2$	3	No propuct
8	Zinctriflate	3	75
9	$ZnCl_2$	3	27
10	$Zn(OAc)_2$	3	45

This reaction is carried out in different solvents by using 5 mol% $Zn(ClO_4)_2$ as a catalyst and as shown in Table 2.2 in which most of the solvents gave comparable yields. The highest yield was obtained with DCM and surprisingly water as a solvent gave comparable yields of DCM. The addition of α-cyanomethyl-β-ketoester and amine into water furnished a heterogen solution, which was heated at 80 ^{o}C and the reaction monitored by TLC. The product formation took longer than the DCE but with a comparable yield. Various α-cyanomethyl-β-ketoesters and amines reacted under the above described conditions and the corresponding pyrroles were obtained in high yields as summarized in Table 2.3.

Table 2.3 Reaction of diketoester **140a-e** with amine **141a-e**

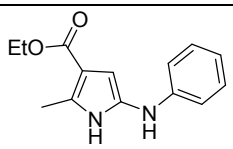
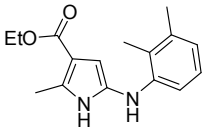
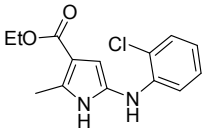
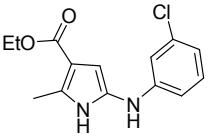
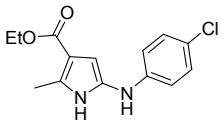
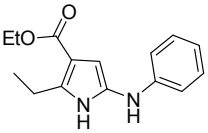
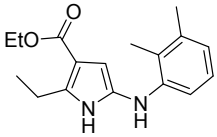
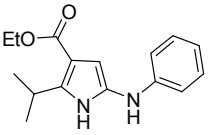
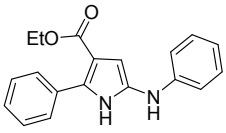
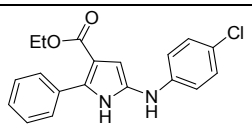
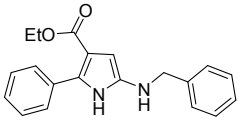
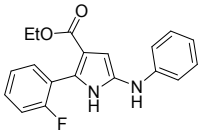
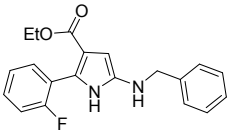
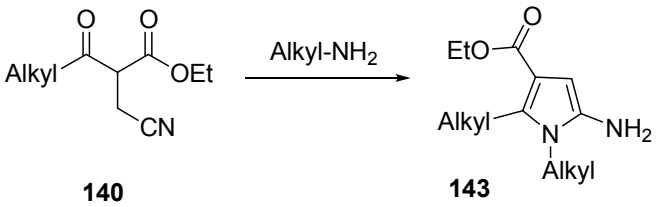
Entry	Diketoester **140**	Amine **141**	Product **147**	Solvent	Yield (%)	Reaction Time(h)
1	a	Ph a	 **147a**	DCE H_2O Benzene DMF/H_2O CH_3CN	91 80 85 40 88	3 5 4 5 4
2	a	$2,3\text{-}(CH_3)_2$-Ph b	 **147b**	DCE H_2O	78 73	5 7
3	a	2-Cl-Ph c	 **147c**	DCE H_2O	79 77	3 6
4	a	3-Cl-Ph d	 **147d**	DCE H_2O	93 81	3 6
5	a	4-Cl-Ph e	 **147e**	DCE H_2O	94 83	3 7
6	b	a	 **147f**	DCE H_2O	93 77	3 6
7	b	b	 **147g**	DCE H_2O	87 75	5 7
8	c	a	 **147h**	DCE H_2O	95 81	4 7
9	d	a	 **147i**	DCE H_2O	89 77	3 6

Table 2.3 continue

10	d	e	 **147j**	DCE H_2O	85 74	4 7
11	d	f	 **147k**	DCE H_2O	89 70	5 7
12	e	a	 **147l**	DCE H_2O	87 74	4 6
13	e	f	 **147m**	DCE H_2O	85 73	4 6

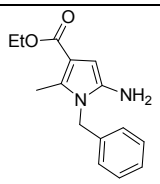
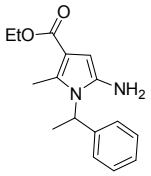
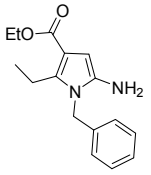
The above described selective amination and annulations reaction shows substrate dependent selectivity by the formation of aminopyrroles. As shown in Table 2.3 all representative α-cyanomethyl-β-ketoesters furnished with aromatic amines of the pyrrole products **147a–m** gave high yields (Figure 2.6, path B). Only one exception was observed when we started with aliphatic α-cyanomethyl-β- ketoesters **140a–c** and aliphatic amines **141f,g**. In this case (Figure 2.6, path A) metal-coordinated α-cyanomethyl-β-ketoester undergo C=O activation to give a dehydrative coupling between ketones and amines to form enamines **142**. The addition of a amine moiety to the carbon–nitrogen triple bond furnished 2-aminopyrroles **143a–c** (Table 2.4). Many attempts were made for the direct- one-pot synthesis of pyrroles starting with a β-dicarbonyl compound. The reaction of bromoacetonitrile and amine in the presence of catalytical amount of $Zn(ClO_4)_26H_2O$ and $Mg(ClO_4)_2$ by refluxing in DCE and H_2O furnished N-substituted β-enamino esters via the condensation of β-ketoesters with amines in a 25–32% yields [95].



140 **143**

Figure 2.7 Reaction of diketoester **140a-b** with alkylamines **141f-g**

Table 2.4 Reaction of diketoester **140a-b** with amine **141f-g**

Entry	Diketoester **140**	Amine **141**	Product **143**	Yield (%)	Reaction Time(h)
14	a	f	 **143a**	76	5
15	a	g	 **143b**	72	5
16	b	f	 **143c**	73	7

Coordination of nitriles to the Zn followed by the addition of the amine into the CN bonds would occur to afford α-cyanomethyl-β-ketoesters metal complex. Coordination of Zn to C=O followed by a dehydrative coupling between ketones and amines would give enamines **141**. Annulation of **141** and **146** would afford product pyrroles **143** and **147** to complete the catalytic cycle. For the chemo- and regioselective processes sterical and electronic factors of the substituents and the enamine–imine tautomeric ratio certainly play an important role.

Typically, when α-cyanomethyl-β-ketoesters was allowed to react with amine in the presence of $Zn(ClO_4)_2$, in addition to the CN triple bond of **140** followed by cyclocondensation afforded 2-aminopyrrole **147**. The reactions can be applied to the synthesis of various multifunctionalized aminopyrroles. The present $Zn(ClO_4)_2$ catalyzed nitrogen–carbon bond formation will provide a wide scope of selective transformations of nitriles and even other substrates under neutral conditions in water. The key point of the present reaction is the selective activation of both C=O bonds of α-cyanomethyl-β-ketoesters as electrophiles and nitriles as pronucleophiles.

2.1.1.3 Synthesis of polysubstituted pyrroles and pyrrolinones from α cyanomethyl-β-ketoesters

Alkoxy and alkylsulfanyl substituted pyrrole carboxylates and their hydrolysis product pyrrolinones (4,5-dihydro-5- oxo-1H-pyrrole-3-carboxylates) are versatile 4-carbon synthons [96], show interesting biological properties and have been used as precursors for currently known drugs [97]. Because of their multifunctional nature, these heterocycles can take part in several stereoselective transformations, such as conjugate additions [98], cycloadditions [99], acyliminium ion chemistry [100], and allylic substitutions [101].

Alkoxy and alkylsulfanyl substituted pyrrole carboxylates are not readily available through general pyrrole ring-formation methods. Many excellent methodologies have been developed for constructing pyrrole rings, although relatively few examples have been reported for the preparation of simple alkoxy and alkylsulfanyl substituted pyrrole carboxylate and substituted pyrrolinones [102]. As it is described previously, the condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by p-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond of nitrile in turn furnished 2-aminopyrroles in high yields. as discussed in the previous two parts we discovered that when α-cyanomethyl-β-ketoesters were allowed to react with amine in the presence of $Zn(ClO_4)_2$, in addition to the CN triple

bond of α-cyanomethyl-β- ketoester and subsequent to cyclocondensation, 2-aminopyrroles were afforded. It wasfound that perchlorate salts are effective catalysts for the activation of the C=O bond and CN triple bond.

The addition of heteroatom nucleophiles to CN triple bonds of nitriles is one of the most attractive transformations of nitriles [103]. The reported methods are limited, however, because of the low reactivity of nitriles. The development of a catalytic method, which proceeds under neutral and mild conditions, is desired. To continue the previously described investigations, which are directed toward the synthesis of substituted pyrroles and related compounds, it is intersitng to carry out the addition–annulation reaction to α-cyanomethyl-β-ketoesters with oxygen and sulfur nucleophiles.By this way thiols or alcohols can give alkoxy and alkylsulfanyl substituted pyrrole carboxylate and their hydrolysis products pyrrolinones (4,5-dihydro-5-oxo-1H-pyrrole-3- carboxylates).

In this part of the work the zinc perchlorate-catalyzed selective one-pot synthesis of substituted 5-alkoxypyrrole-3-carboxylates and pyrrolinone carboxylates from α-cyanomethyl-βketoesters and alcohols is described. (Figure 2.8) [104].

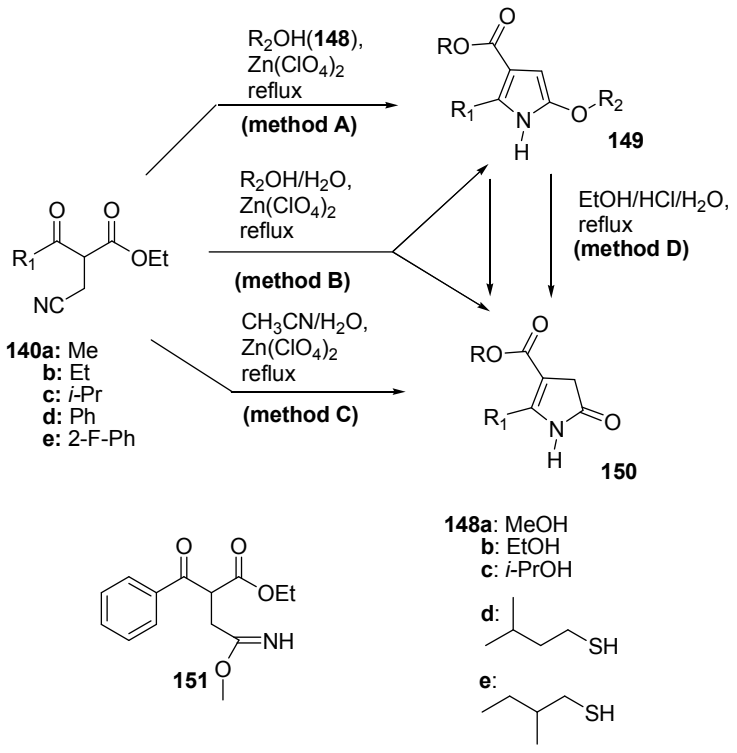


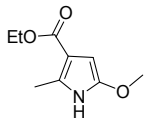
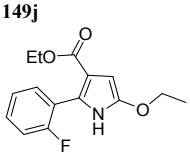
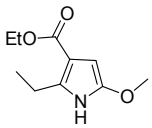
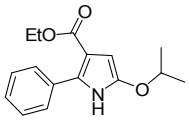
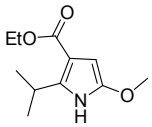
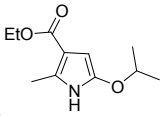
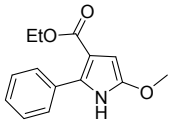
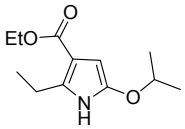
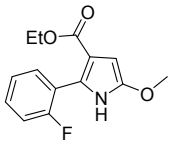
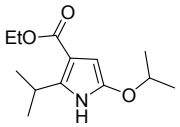
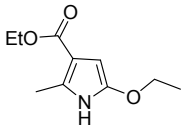
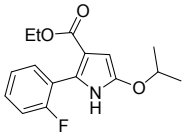
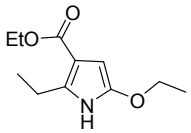
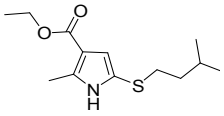
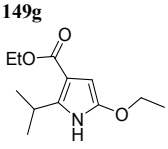
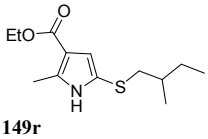
Figure 2.8 General reaction summary

As shown in figure 2.8, α-cyanomethyl-β-dicarbonyl compounds **140a–e** were synthesized by the alkylation of commercially available β-dicarbonyl compounds with bromoacetonitrile (using either NaH/THF or DBU/benzene) in 71–80% yields according to the literature procedure.

In an initial reaction α-cyanomethyl-β- ketoesters **140d** and 5 mol% of $Zn(ClO_4)_2$ were heated to reflux in methanol with the reaction being monitored by TLC. Three different products were isolated after work-up and chromatographic separation. The isolated products were identified as an addition product **151a** (minor product), pyrrole derivative **149d**, and pyrrolinone derivative **150d** (as the major products) (Figure 2.8). When this reaction is carried out in anhydrous methanol with 5 mol% of $Zn(ClO_4)_2$ the pyrrole derivative **149d** was isolated in 91% yield after chromatography (Figure 2.8, condition A).

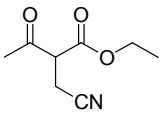
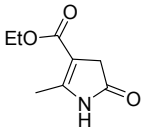
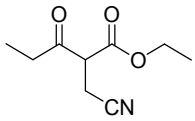
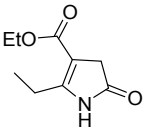
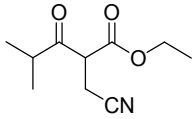
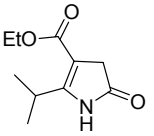
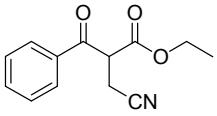
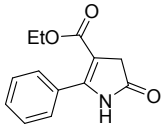
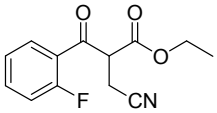
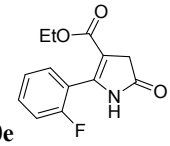
Using these conditions, various α-cyanomethyl-β- ketoesters derived from commercially available β-ketoesters and different alcohols were prepared as shown in Table 2.5. The 5-alkoxypyrrole-3-carboxylates were thus obtained in good to high yields. Using dichloroethane as a solvent (contains 10% methanol), **149d** was also furnished in 82% yield with a long reaction time (12 h). The addition–annulation process is also carried out with two representative thiols, and the corresponding 5-alkylsulfanylpyrrole- 3-carboxylates obtained in 79–80% yields (Table 2.5, entries 16 and 17); for these reaction, dichloroethane was used as the solvent.

Table 2.5 Reaction of diketoester **140a-e** with alcohols **148a-c**

Entry	**140**	**148**	Pyrrole **149**	Yield (%)/ Time (h)	Entry	**140**	**148**	Pyrrole **149**	Yield (%)/ Time (h)
1	**a**	**a**	**149a** 	93/6	10	**e**	**c**	**149j** 	80/5
2	**b**	**b**	**149b** 	90/6	11	**d**	**c**	 **149k**	78/6
3	**c**	**c**	**149c** 	89/6	12	**a**	**c**	 **149l**	75/5
4	**d**	**a**	**149d** 	91/7	13	**b**	**c**	**149m** 	77/5
5	**e**	**a**	**149e** 	82/7	14	**c**	**c**	**149n** 	73/5
6	**a**	**b**	**149f** 	86/6	15	**e**	**c**	**149o** 	70/7
7	**b**	**b**	 **149g**	88/5	16	**a**	**d**	 **149p**	79/5
8	**c**	**b**	 **149h**	79/6	17	**a**	**e**	 **149r**	80/6

As shown in Table 2.5, the use of isopropanol decreased the yields to 70–78% (Table 2.5, entries 11–15) and pyrrolinones **150a–e** (Table 2.6) were also isolated as side products. It is suggested that the presence of a small amount of water in isopropanol is the reason for the diminished yields and the formation of pyrrolinones. Thus, when a few drops of water were added to the reaction medium, pyrrole/pyrrolinone mixture **149l**:**150a** was obtained in a 2:1 ratio. After this result, the addition–annulation reaction was carried out with **140a** in a MeOH/water (2:1) mixture at reflux in the presence of $Zn(ClO_4)_2$ (Scheme 1, condition B). At the start of the reaction, only the formation of pyrrole **149a** was observed, subsequently the formation of pyrrolinone **150a** in increasing amount along with the disappearance of pyrrole **149a** was observed. The only product isolated from the reaction was identified as pyrrolinone **150a** in 95% yield. The formation of pyrrolinone must proceed via the formation of pyrrole **149a** and then undergo hydrolysis with water, as well as by the direct addition of water to nitrile carbon followed by heteroannulation.

Table 2.6 Synthesis of pyrrolinones

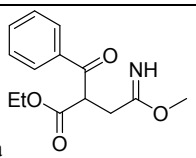
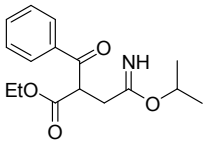
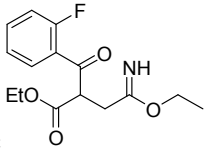
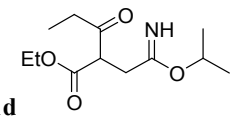
Entry	Ketoester **140**	Pyrolinone **150**	Method B Yield(%)/ Time(h)	Method C Yield(%)/ Time(h)
1	 **140a**	 **150a**	95/ 6	93/4
2	 **140b**	 **150b**	94/ 7	91/3
3	 **140c**	 **150c**	89/ 6	92/4
4	 **140d**	 **150d**	95/7	90/4
5	 **140e**	 **150e**	87/7	89/4

As shown in Table 2.6, different pyrrolinones can be synthesized according to this procedure in high yields. In order to shed light on the formation of pyrrolinone, the typical pyrrole formation reaction was carried out in a CH_3CN/water mixture (5:1) in the presence of $Zn(ClO_4)_2$ (condition C). TLC monitoring of these mixtures showed that ketoesters were completely converted into pyrrolinones (Figure 2.8, condition C). The results of this conversion with various ketoesters are summarized in Table 2.6. In the non-catalytic case, ketoester **140a** was refluxed with methanol for several hours in the absence of $Zn(ClO_4)_2$, and only a trace amount of **149a** was detected by GC–MS. As shown in figure 2.8 (condition D), the heating of pyrroles in an HCl/water/alcohol mixture (ethanol/2 NHCl; 20 mL/L) furnished the corresponding

pyrrolinones in 82–85% yields. The mechanism of pyrrole formation starting from α-cyanomethyl- β-ketoesters and anhydrous alcohols was investigated systematically. To demonstrate that alcohol attack at the nitrile is the initial step, the isolation of the corresponding iminoesters was carried out for selected examples as shown in Table 2.7. The reactions were stopped when an isolable amount of iminoesters was formed according to TLC monitoring (1–2 h). After work-up and chromatographic separation, the corresponding iminoesters **151a–d** were isolated in 12–15% yields.

The second step was carried out with **140a** in methanol and $Zn(ClO_4)_2$, and the annulations product **149d** obtained in 74% yield. In all of the cases, the products were readily separable by flash column chromatography, and the products are obtained in nearly pure form. In some cases, the pyrrolinones could be directly obtained from the crude product via crystallization. The present reaction can be rationalized by assuming that the anhydrous conditions, attack of an external alcohol on the complex substrate form an iminoester complex. However, if the alcohol is used when wet, attack of water on the formed iminoester and direct attack on the complex afford a carboximide complex, the precursor of pyrrolinones (figure 2.8).

Table 2.7 Iminoester **151-a-d** formation from diketoester **140b-e**

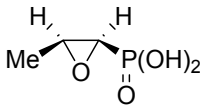
Entry	Ketoester **140**	Alcohol **148**	Iminoester 1**51**	Yield(%)/ Time (h)
1	**d**	**a**	 **151a**	12/2
2	**d**	**c**	 **151b**	15/1
3	**e**	**b**	 **151c**	13/2
4	**b**	**c**	 **151d**	12/1

In summary, typically, when α-cyanomethyl-β-ketoesters were allowed to react with alcohols, thiols, and water in the presence of $Zn(ClO_4)_2$, addition to the CN triple bond of **140** and subsequent to cyclocondensation occurred, and afforded 5-alkoxy-, 5-alkylsulfanylpyrroles, and pyrrolinones. Starting from α-cyanomethyl-β-ketoesters and alcohols in the presence of $Zn(ClO_4)_2$, the 5-alkoxypyrrole-3-carboxylate can be synthesized under water free conditions in 70–93% yields. The same reaction was carried out in water–alcohol or in water, which furnished the pyrrolinones in 87–95% yields. The pyrrolinones can also be synthesized from pyrroles in 82–85% yields with EtOH/HCl. This method opens an entry for the selective synthesis of 5-alkoxypyrroles and pyrrolinones, depending on the reaction conditions.

2.2 Acylphosphonates in Darzens Reaction; synthesis of highly functionalized epoxyphosphonates

As mentioned before epoxides are important compounds which rank among the most versatile synthetic intermediates, constituting convenient precursors for the synthesis of many products of biological interest. Phosphorus containing epoxides like 1,2-epoxyphosphonates have attracted considerable interest since the first discovery of the antibiotic fosmycin. Fosfomycin (1R, 2S)-(-)-(1,2)-Epoxypropyl phosphonic acid is an antibiotic produced by several streptomyces as well as by gram negative pseudomonas syringiae and pseıdomonas viridiflava. Despite its seemingly simple structure, fosfomycin has attracted considerable interest from a biosynthetic point of view. The epoxide functionalitiy, and particularly the extremely rare C-P bond, makes fosfomycin an attractive target for biosynthetic investigations.

A great number of fosmycin derivatives have been synthesized over the years with biological activities, many of which have included the synthesis of epoxyphosphonates as intermediates.



fosfomycin

152

Figure 2.9 Structure of fosfomycin

Direct epoxidation of the corresponding alkenyl phosphorous compound [77] is the most common method for the preparation of epoxyphosphonates, however, several other approaches are also know in the literature [71-81]. These approaches include the reaction of α-halo ketones and α-tosyl ketones with metal dialkyl phosphites, the cyclization of halohydrins in the presence of a base, the Darzens type reaction of chloromethyl phosphonates with carbonyl compounds and rhodium acetate mediated reaction of diazobenzylphosphonates with carbonyl compounds. Although there are many methods for the preparation of these important intermediates, many of these methods lack stereoselectivity, efficiency, and ease of preparation of the starting materials, so that there is still a need for alternative synthetic approaches.

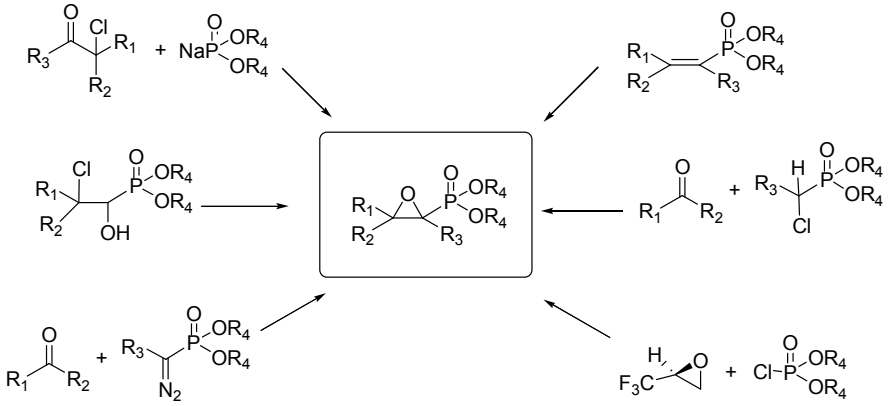


Figure 2.10 Literature methods for the synthesis of α,β-epoxyphosphonates

The Darzens reaction is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds and, therefore, has been recognized as one of the most significant C–C, C-O bond forming processes in synthetic organic chemistry. It employs the base induced condensation of α-halo carbonyl compounds with aldehydes for the construction of highly functionalized oxiranes.

2.2.1 Darzens reaction of acylphosphonates

Based on the previous studies carried out with acyl phosphonates (Figure 2.11) [104]. and the possibility to generate epoxides by the very well known Darzens reaction, a novel approach for the diastereoselective synthesis of highly functionalized epoxyphosphonates by applying a Darzens type reaction of α-halo ketones with acyl phosphonates is described.

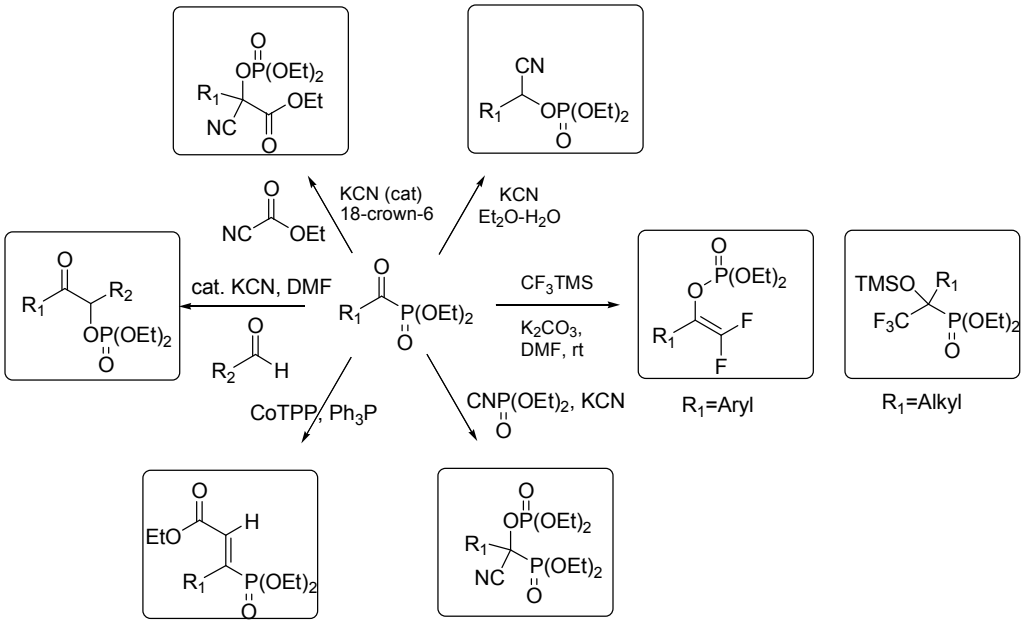


Figure 2.11 Reactions carried out with acyl phosphonates

This type of Darzens reaction including the use of acyl phosphonates has not been reported. Despite the vast number of methods for the synthesis of epoxyphosphonates[71-81], there are no examples to afford this type of highly functionalized epoxyphosphonates that could be further used as intermediates to give several reactions.

In the present work, the reactions of a broad range of acyl phosphonates containing electron withdrawing and electron donating substituents with α-halo ketones under various conditions is examined [106]. Although the classical Darzens condensation is still performed in the presence of a strong base such as RONa, ROK, and $NaNH_2$, and that it is carried out under anhydrous conditions and at low temperatures, the sensibility of acyl phosphonates to such bases prompted to use comparable milder bases such as carbonates or organic bases to prevent the hydrolysis of acyl phosphonates.

At first, the reaction of benzoylphosphonate **154a** with α-bromoacetophenone **153a** is initially carried at room temperature in the presence of K_2CO_3 and the formation of the products is monitored by TLC. At the end of the reaction (10 h), two diastereomeric epoxyphosphonates **155a** (*trans/cis*) (34 %) is isolated as a major product together with minor products **156**(5%), **157**(10%), and **158**(15%) as shown in Figure 2.1. The reaction is carried out by using different bases and solvents at room temperature. The use of bases such as KOH, NaOH, and ^{t}BuOK is avoided in order to prevent the hydrolysis of the acyl phosphonate by which acyl phosphonates easily decompose. The desired product is formed in low yield together with side products (Table 2.7, entry 7-9). The reaction time decreases at higher temperatures (6 h, 45%), whereas the conversion is very slow at low temperatures (24 h, 5%).

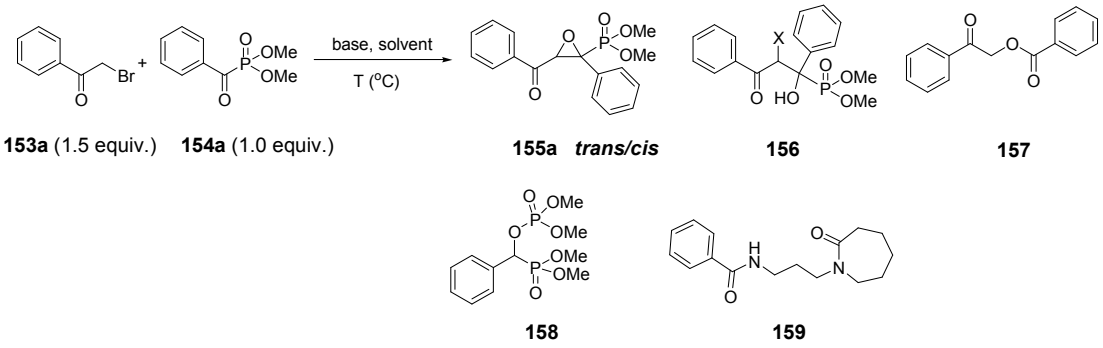


Figure 2.12 Darzens reaction of benzoylphosphonates with α-bromoacetophenone

Table 2.8 Darzens reaction of benzoylphosphonate with α-bromoacetophenone under different reaction conditions

Entry	Base	Solvent	T (°C)	**155a**[a] *cis* (%)	**155a**[a] *trans* (%)	**156**[a] (%)	**157**[a] (%)	**158**[a] (%)	**159**[a] (%)
1	K_2CO_3	CH_3CN	0	5	-	-	-	20	-
2	K_2CO_3	CH_3CN	25	29	5	5	10	15	-
3	K_2CO_3	CH_3CN	60	35	10	-	15	25	-
4	KOH	THF	25	15	10	5	15	10	-
5	^tBuOK	THF	25	12	10	-	12	20	-
6	Cs_2CO_3	CH_3CN	25	35	20	-	15	20	-
7	DMAP	CH_3CN	25	-	-	-	-	-	-
8	DBU	CH_3CN	25	45	5	-	10	5	20
9	DBU	THF	25	-	-	-	15	20	-
10	Et_3N	CH_3CN	25	-	-	-	-	80	-

[a]Isolated yields after column chromatography

By the screening of the bases, K_2CO_3 is replaced with the more active base Cs_2CO_3. The reaction is carried out at room temperature in CH_3CN. It is in this way that not only the reaction time decreased (6h) but also the reaction yield increased, and **155a** was obtained in a 55% yield together with the side products **157** and **158** (Table 2.7, entry 6). The diastereomeric ratio was found as 35/20 (*trans*/*cis*), which was

determined by using NMR spectroscopy, in which the diastereomers are easily separated by flash column chromatography.

To illustrate the generality of this reaction, a range of acyl phosphonates **154a-h** are treated with α-bromo ketones **153a** under optimized reaction conditions (Cs_2CO_3, CH_3CN, rt). The results are shown in table 2.8. By using electron donating and electron withdrawing groups furnished a comparable yield but ortho substitution decreased the yield and increased the reaction time (Table 2.8, entry 6). Acylphosphonates are treated with variously substituted α-bromo ketones **153c-b** under the same conditions to give the corresponding epoxyphosphonates **155i-l**. [107].

Table 2.9 Reaction of acyl phosphonates with α-halo ketones in the presence of bases in acetonitrile

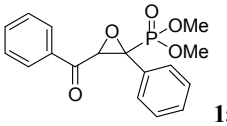
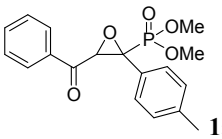
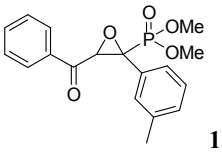
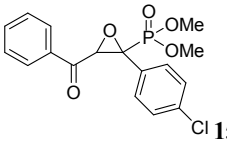
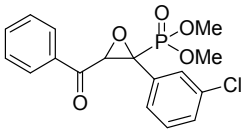
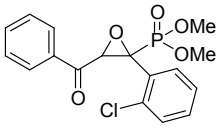
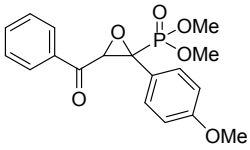
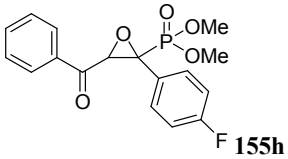
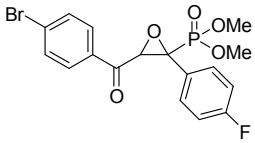
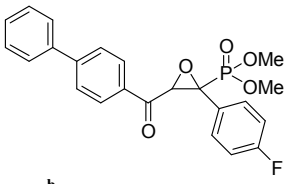
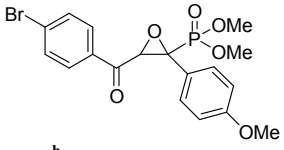
(**153**)	(**154**)	Epoxyphosphonate (**155**)	Cs_2CO_3			DBU		
R_1	R_2		time (h)	yield[a] (%)	*trans*/ *cis*	time (h)	yield[a] (%)	*trans*/ *cis*
C_6H_5 **1a**	H **2a**	 **155a**	4	49	3/2	3	50	8/1
C_6H_5 **1a**	4-CH_3 **2b**	 **155b**	5	54	3/2	5	56	7/1
C_6H_5 **1a**	3-CH_3 **2c**	 **155c**	5	44	2/1	5	45	7/1
C_6H_5 **1a**	4-Cl **2d**	 **155d**	6	48	2/1	4	45	8/1
C_6H_5 **1a**	3-Cl **2e**	 **155e**	8	41	2/1	6	42	6/1

Table 2.9 continue

C_6H_5 **1a**	2-Cl **2f**	 **155f**	12	37	2/1	9	30	5/1
C_6H_5 **1a**	4-OCH_3 **2g**	 **155g**	5	63	2/1	5	60	7/1
C_6H_5 **1a**	4-F **2h**	 **155h**	3	69	3/2	2	68	9/1
4-Br-C_6H_5 **1b**	4-F **2h**	 **155i**[b]	7	51	3/2	6	48	8/1
4-C_6H_5-C_6H_5 **1c**	4-F **2h**	 **155j**[b]	8	52	5/3	8	49	8/1
4-Br-C_6H_5 **1b**	4-OCH_3 **2g**	 **155k**[b]	7	46	5/3	6	43	7/1

[a]Isolated yields [b] [107]

For the epoxidation reactions, organic bases were also screened. Among the bases DMAP, DABCO, DBU, and triethylamine, the use of DBU in CH_3CN gives **155a** in a 50% yield **(**Table 2.7, entry 8). No product formation was observed with DBU by using THF as a solvent (Table 2.7, entry 9). Other bases such as DMAP and DABCO showed no product formation. The use of triethylamine as a base (Table 2.7, entry 10) in the reaction proceeded to give compound **158**, which is the main characteristic

behavior of acyl phosphonates in the presence of amines [108]. Dry conditions are crucial in order to prevent the formation of halohydrin **156**, which is formed by proton abstraction of the corresponding intermediate.

The promised results prompted us to carry out the examples with DBU. The reaction of acyl phosphonates with α-bromo ketones in the presence of DBU in CH_3CN at room temperature was carried out for maximum conversion (monitoring by TLC). After the work up, the desired products were obtained in 30-68% yields. The isomeric ratio of the products are determined by NMR as 5:1-9:1 *trans*/*cis*. Both isomers were easily separated by flash column chromatography and are characterized by spectroscopic methods. As from the ^{1}H-NMR the basic difference between the diastereomers arises from the chemical behavior of the single bridge proton which changes significantly according to structure of the epoxide. As in the ^{1}H NMR spectra of *cis*-**155a** the single bridge proton is observed as small doublet peak at 4.68 ppm*, whereas* the bridge proton for the *trans*-**155a** diastereomer appeared at 3.91 ppm. The splitting of the single bridge protons to a doublet for both isomers is explained by the long range phosphorous coupling.

In addition to these products, three side products were also isolated. Two of them are characterized as **157** and **158** and the last one is identified as a seven membered ring amide **159**. For the formation of **159**, DBU reacted with phosphonates, in which further hydrolysis afforded the corresponding seven membered ring amide. Similar reactions of DBU with alkyl halides have been reported in the literature (Figure 2.13) [109].

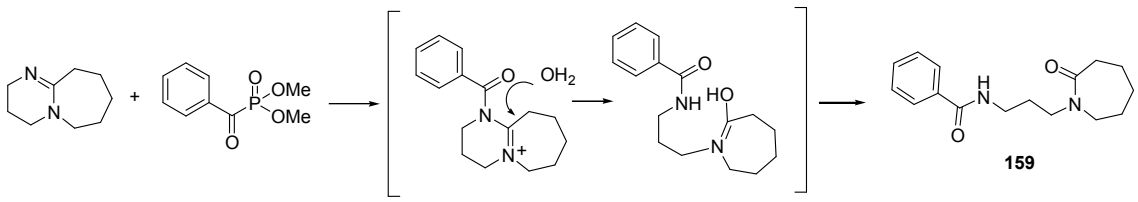


Figure 2.13 : Reaction of DBU with acyl phosphonate

Apart from the results, changing the base surprisingly changed the stereoselectiviy of this reaction. In general, the experiments performed in the presence of Cs_2CO_3 gave a

product distribution of approx. 3/2 (*trans*/*cis*), whereas the use of DBU significantly increased the selectivity up to 9/1 (*trans*/*cis*).

2.3 Regioselective synthesis of *cis-trans* epoxides

Close inspection of the reaction with DBU afforded interesting results. With the careful monitoring of the reaction by TLC, the distribution for both diastereomers in the presence of DBU is easily controlled. Initially the *trans* isomer is formed in relative excess to *cis* isomer (9/1). However, at a prolonged reaction time, the *trans* isomer isomerizes to afford the *cis* isomer. To support this observation, both of the isolated diastereomeric epoxides are treated under the same reaction conditions (1 equiv of DBU, CH_3CN, rt). As a result of this experiment, the *trans* epoxide isomerizes to afford the *cis* epoxide, whereas the reverse is not the case.

With the Darzens condensation, the formation of the epoxide is the favored course of the reaction. The carbanion of α-halo ketones can attack the carbonyl carbon of phosphonate to form the intermediate halohydrins, **160a** and **160b**. The positioning of the halide *trans* to the oxygen, which is involved in the nucleophilic attack, forms the epoxide. According to published works [110], the Darzens intermediate (Figure 2.15) is commonly formed in the rate-determining step, in which the exclusive formation of the *trans* product may be attributed to the steric inhibition in the formation of the *cis* isomer. The existence of a very large effect (in both the rates and equilibrium of the ring-forming reactions) opposing the formation of *cis* substituents on small rings constitutes a further basis for assigning greater thermodynamic stability to a *trans* versus a *cis* oxide, however, in our case the **cis-160b** intermediate is more favored. This result might be explained according to the thermodynamic stability of intermediate **cis-160b,** as the steric interaction of -COPh with $PO(OMe)_2$ is less because of the fact that C-P is long enough decrease the interaction. The steric interaction is comparable less than the interaction of –COPh with –Ph which makes intermediate **cis-160a** the kinetic intermediate.

Clearly, a *cis* halohydrin anion, **160b**, is not the intermediate in the formation of the *cis* product in the Darzens reaction [111], rather, the only possible way in which *cis* can be obtained in the Darzens reaction is through the formation of the *trans* product, followed by base-catalyzed isomerization (Figure 2.14).

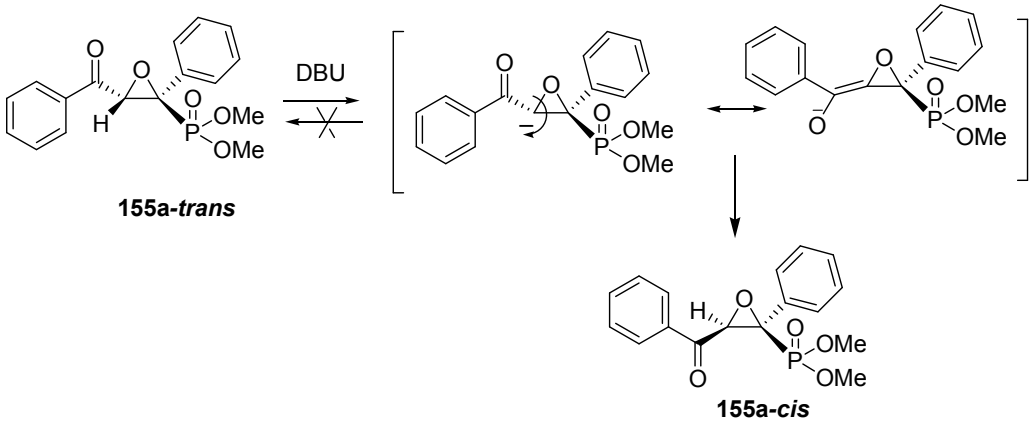


Figure 2.14 Formation of *cis*-isomer from a *trans*-isomer

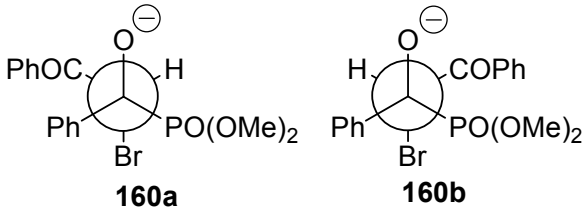


Figure 2.15 Possible transition states of compound **160**

Substituted benzoylphosphonates proceed efficiently to give epoxides; The treatment of alkyl phosphonate **154i** under the same reaction conditions failed to give the corresponding epoxides [107]. Accordingly, the reaction proceeded to give the compound **161** [112] and **162** (Figure 2.16).

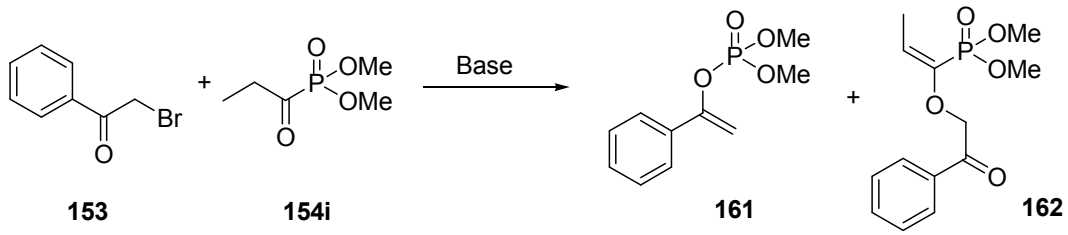


Figure 2.16 Reaction of acyl phosphonates with alkylphosphonate

For showing the application of the products two representative reactions are carried out with *cis*-3a. The methylation of ***cis*-155a** with Me_3Al yielded the corresponding epoxy alcohol **163**, with high selectivity (Figure 2.16). The same selectivity is obtained by the reduction of *cis*-3a with $LiBH_4$ or $NaBH_4$ (2 equiv of $NaBH_4$, THF, rt; or 2 equiv of $LiBH_4$, THF, rt), which furnished a mixture of diastereomeric epoxy alcohol, **164** (4/1). In both of the reactions, the epoxide ring is preserved. These types of reactions open an entry for the selective synthesis of new fosfomycin analogs. More work for the application of the epoxides is under investigation.

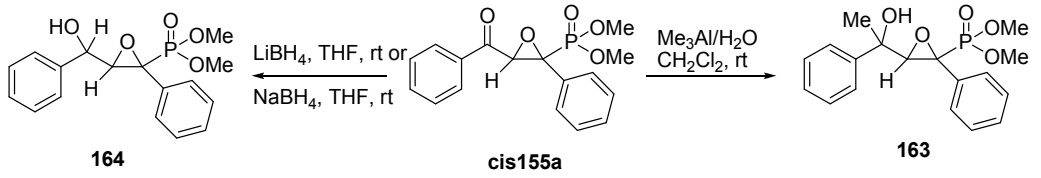


Figure 2.17 Methylation and reduction of **cis-155a**

2.4. Conclusion

As a conlusion, within this part we described here a novel synthesis of epoxyphosphonates applying a Darzens type reaction to acyl phosphonates with α-bromo ketones in the presence of different bases. The diastereoselectivity of this reaction is easily controlled by means of changing the base. These highly functionalized products with multifunctionality can be further converted to various interesting compounds. As a representative example, selective reduction of the

carbonyl group and the methylation reaction is carried out by keeping the epoxide ring.

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.

Flash column chromatography was done for purifying the products by using Merck Silica Gel 60 (partical size 40-63 μm).

3.2 General procedures

3.2.1 General Procedure for alkylation of β-Dicarbonyl Compounds

NaH (1.5 mmol) was added slowly to a stirred solution of β-dicarbonyl compound **139a-e** (1mmol) at r.t. under argon. The reaction mixture is stirred further for 1hour and then a solution of bromoacetonitrile (1.2 mmol) in THF (15 ml) was added slowly and stirred for 4 hours. Reaction is monitored by TLC. Then, water is added and the mixture is extracted with ethylacetate. The extract is dried over $MgSO_4$ and the solvent is evaporated under reduced pressure and the crude pruduct is purified by column chromotography. (hexane:ethylacetate (4:1) as eluent)

3.2.1.1 3-Acetyl-4-oxopentanenitrile (140a)

Yield: (105 mg, 76%); yellow oil. IR (neat): 2333, 2976, 1723 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.25 (s, 6H), 2.73 (d, 2H, *J*=7.13 Hz), 4.02 (t, 1H, *J*=7.15 Hz). ^{13}C- NMR (100 MHz, $CDCl_3$): δ= 15.7, 23.5, 30.0, 62.9, 117.7, 191.5, 200.1. Anal. Calcd for $C_7H_9NO_2$ (139.15): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.23; H, 6.45; N, 10.01.

3.2.1.2 Ethyl 2-(cyanomethyl)-3-oxobutanoate (140b)

Yield: (181 mg, 71%); yellow oil. IR (neat): 2331, 2978, 1725 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.32 (s, 3H), 1.27 (t, 3H, *J*=7.15 Hz), 2.32 (s, 3H), 2.74 (dd, 2H, *J*=7.05 Hz , J=2.48 Hz), 3.75 (t, 1H, *J*=7.27 Hz), 4,23 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.4, 15.8, 29.6, 55.5, 62.6, 117.4, 166.6, 198.6. Anal. Calcd for $C_8H_{11}NO_3$ (169.7): C, 56.80; H, 6.55; N, 8.28. Found**:** C, 56.76; H, 6.53; N, 8.19.

3.2.1.3 Ethyl 2-(cyanomethyl)-3-oxopentanoate (140c)

Yield: (146 mg, 80%); yellow oil. IR (neat): 2326, 2975, 1720 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.05 (t, 3H, *J*=7.25 Hz), 1.23 (t, 3H, *J*=7.10 Hz), 2.58 (m, 2H), 2.74 (d, 2H, *J*=7.24 Hz), 3.77 (t, 1H, *J*=7.26 Hz), 4,18 (q, 2H, *J*=7.13 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.7, 14.7, 22.4, 30.1, 62.2, 116.7, 192.4, 198.1**.** Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.00; H, 7.15; N, 7.65. Found C, 59.01; H, 7.13; N, 7.59.

3.2.1.4 Ethyl 2-(cyanomethyl)-3-oxo-3-phenylpropanoate (140d)

Yield: (198 mg, 78%); colorless oil. IR (neat): 2978, 2249, 1736, 1689 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.20 (t, 3H, *J*=7.13 Hz), 3.01-3.12 (m, 2H), 4.20 (q, 2H, *J*=7.15 Hz), 4.66 (t, 1H, *J*=7.27 Hz), 7.53-8.05 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 13.3, 16.1, 49.7, 62.0, 116.4, 128.3, 128.5, 133.7, 134.5, 166.0, 190.4. Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.33; N, 6.12.

3.2.1.5 Ethyl 2-(cyanomethyl)-3-(2-fluorophenyl)-3-oxopropanoate (140e)

Yield: (199 mg, 80%); yellow oil. IR (neat): 2954, 2212, 1732, 1679 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ= 1.17 (t, 3H, *J*=7.07 Hz), 2.97 (m, 2H), 4.17 (q, 2H, *J*=7.06 Hz), 4.62 (t, 1H, *J*=7.01 Hz), 7.14-7.94 (m, 4H). ^{13}C-NMR (100 MHz, CDCl3): δ= 13.3, 15.8, 53.2, 61.7, 95.7, 116.1 (d, *J*=23 Hz), 123.6 (d, J=11 Hz), 124.3 (d, *J*=3 Hz), 130.8, 135.1 (d, *J*=9 Hz), 161.3 (d, *J*=253 Hz), 166.2, 189.0. Anal. Calcd for $C_{13}H_{12}FNO_3$ (249.24): C, 62.65; H, 4.85; F, 7.62; N, 5.62. Found: C, 62.62; H, 4.86; F, 7.59; N, 5.61.

3.2.1.6 Ethyl 2-(cyanomethyl)-4-methyl-3-oxopentanoate (140f)

Yield: (155 mg, 79%), yellow oil, IR (neat): 2978 , 2249 , 1736 , 1689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, d, *J*= 6.7 Hz), 1.20 (3H, d, *J*= 7.1 Hz), 1.31 (3H, t, *J*= 7.2 Hz), 2.83 (2H, d, *J*= 7.3 Hz), 2.91 (1H, m), 3.98 (1H, t, J= 7.3 Hz), 4.27 (2H, q, J= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 15.9, 18.4, 19.2, 40.5, 52.5, 62.3, 116.9, 166.3, 204.7; Anal. Calcd for $C_{10}H_{15}NO_3$ (197,23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.89; H, 7.64; N, 7.11.

3.2.2 General Procedure For Enamine Formation

Alkylated β-dicarbonyl compound **140** (1 mmol) was dissolved in benzene (10 ml). Corresponding amine **141** (1.2 mmol) together with catalytic amount of PTSA was

added to the stirring mixture and refluxed for 6-10 hours by using Dean-Stark trap. Reaction is monitored by TLC. The reaction mixture is extracted with ethylacetate. The extract is dried over $MgSO_4$ and the solvent is evaporated under reduced pressure and the crude pruduct is purified by column chromotography (hexane:ethylacetate (4:1) as eluent).

3.2.2.1 (*Z*)-3-Acetyl-4-(phenylamino)pent-3-enenitrile (142a)

Obtained according to general procedure. Yield: (143 mg, 67%); brown oil. IR (neat): 2987, 2242, 1592, 1570 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.03 (s, 3H), 2.22 (s, 3H), 3.29 (s, 2H), 7.09-7.19 (m, 5H), 13.51 (s, 1H, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 19.0, 20.5, 30.4, 98.3, 120.6, 128.0, 128.8, 131.642, 140.6, 163.0, 196.7.Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C. 72,87; H. 6,59; N. 13,07; Found: C. 72,82; H. 6,45; N. 13,01.

3.2.2.2 (*Z*)-4-(1-Phenylethylamino)-3-acetylpent-3-enenitrile (142b)

Yield: (166 mg, 69%); white solid, mp=105 °C, $[\alpha]^{22}_D$= -586.66 (0.12, $CHCl_3$). IR (neat): 3441, 2962, 2921, 2357, 2240, 1598 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.48 (d, 3H, *J*=6.78 Hz), 1.84 (s, 3H), 2.14 (s, 3H), 3.17 (dd, 2H, *J*= 9.98 Hz, *J*= 16.02 Hz), 4.60 (q, *J*=6.81 Hz), 7.17-7.44 (m, 5H), 12.56 (d, H, *J*= 7.10 Hz , N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 16.0, 18.4, 25.2, 28.3, 54.1, 94.7, 118.8, 125.8, 127.8, 129.3, 144.2, 163.0, 193.8. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C. 74,35; H. 7,49; N. 11,56; Found: C. 74,26; H. 7,41; N. 11,48.

3.2.2.3 (*Z*)-3-Acetyl-4-(benzylamino)pent-3-enenitrile (142c)

Yield: (148 mg, 65%); brown oil. IR (neat): 3436, 3028, 2917, 2346, 2240, 1599 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.92 (s, 3H), 2.10 (s, 3H), 3.17 (s, 2H), 4.37 (d, 2H, *J*=5.97 Hz), 7.11-7.21 (m, 5H), 12.32 (s, 1H, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 15.6, 18.5, 28.3, 47.5, 119.05, 127.0, 127.9, 129.2, 137.7, 163.7, 193.8. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.90): C. 73,66; H. 7,06; N. 12,27. Found: C. 73,66; H. 7,03; N. 12,17.

3.2.2.4 (*Z*)-Ethyl 2-(cyanomethyl)-3-(phenylamino)but-2-enoate (142d)

Yield: (122 mg, 50%); colorless oil. IR (neat): 3214, 3135, 2981, 2933, 2245, 1606 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.26 (t, 3H, *J*=7.14 Hz), 2.02 (s, 3H), 3.29 (s, 2H), 4.17 (q, 2H, *J*=7.13 Hz), 6.96- 7.11 (m, 5H), 11.16 (s, 1H, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.9, 16.6, 17.9, 31.5, 60.2, 86.1, 118.0, 118.7, 119.0, 125.8, 126.1, 129.5, 130.1, 139.1, 159.0, 168.9.
Anal. Calcd. for $C_{14}H_{16}N_2O_2$ (244.29): C. 68,83; H. 6,60; N. 11,47. Found: C. 68,78; H. 6,57; N. 11,45.

3.2.2.5 (*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)but-2-enoate (142e)

Obtained according to general procedure. Yield: (187 mg, 69%); yellow oil, $[\alpha]^{22}_{D}$= -278.09 (2.1, $CHCl_3$). IR (neat): 3492, 2981, 2363, 2243, 1653 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.28 (t, 3H, *J*=7.11 Hz), 1.46 (d, 3H, *J*=6.78 Hz), 1.81 (s, 3H), 3.18 (dd, 2H, *J*=17.99 Hz, *J*=55.54 Hz), 4.11 (m, 2H), 4.57 (m, 1H), 7.13-7.22 (m, 5H), 9.88 (d, 1H, *J*=5.68 Hz, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 15.0, 16.0, 16.5, 25.4, 53.8, 59.8, 83.4, 119.4, 125.7, 127.6, 129.3, 144.9, 161,3, 169,2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.51; H, 7.42; N, 10.22.

3.2.2.6 (*Z*)-Ethyl 3-(benzylamino)-2-(cyanomethyl)but-2-enoate (142f)

Obtained according to general procedure. Yield: (142 mg, 55%); yellow oil. IR (neat): 3254, 2980, 2357, 2242, 1646, 1597 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.20 (t, 3H, *J*= 7.09 Hz), 1.90 (s, 3H), 3.20 (s, 2H), 4.07 (q, 2H, *J*=7.01 Hz), 4.31 (d, 2H, *J*=6.07 Hz), 7.11-7.21 (m, 5H), 9.82 (s, 1H, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.9, 15.6, 16.6, 47.59, 59.8, 83.6, 119.5, 125.7, 127.3, 127.9, 128.5, 129.3, 138.5, 161.7, 169.1. Anal. Calcd. for $C_{15}H_{18}N_2O_2$ (258.32): C. 69,74; H. 7,02; N. 10,84. Found: C. 69,69; H. 7,01; N. 10,81.

3.2.2.7 (*Z*)-Ethyl 2-(cyanomethyl)-3-(phenylamino)pent-2-enoate (142g)

Yield: (175 mg, 68%); colorless oil. IR (neat): 3489, 2967, 2360, 2253, 1646 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.06 (t, 3H, *J*=7.6 Hz), 1.29 (t, 3H, *J*=7.2 Hz), 2.37 (q, 2H, *J*= 7.55 Hz), 3.27 (s, 2H), 4.18 (q, 2H, *J*=7.2 Hz), 7.01-7.11 (m, 5H), 10.99 (s, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.7, 14.5, 16.0, 22.0, 59.8, 84.7, 119.0, 126.2, 126.3, 129.2, 138.9, 164.2, 169.1. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84; Found: C, 69.68; H, 7.07; N, 10.79.

3.2.2.8 (*Z*)-Ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)pent-2-enoate (142h)

Yield: (203 mg, 71%); yellow oil. $[\alpha]^{22}_{D}$= 365.71 (0.07, $CHCl_3$). IR (neat): 3321, 3127, 2978, 2142, 1423 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.97 (t, 3H, *J*=7.6 Hz), 1.28 (t, 3H, *J=7.1* Hz), 1.47 (d, 3H, *J*=6.8 Hz), 2.19 (m, 2H), 3.18 (dd, 2H, *J*=17.8 Hz, *J*= 29.4 Hz), 4.14 (m, 2H), 4.57 (m, 1H), 7.21-7.25 (m, 5H), 9.87 (s, 1H, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.1, 14.6, 15.8, 22.2, 25.3, 53.0, 59.5, 82.5, 119.3, 125.3, 127.3, 128.9, 144.9, 165.5, 169.3 ; Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78; O, 11.17. Found: C, 71.20; H, 7.71; N, 9.80.

3.2.2.9 (*Z*)-Ethyl 3-(benzylamino)-2-(cyanomethyl)pent-2-enoate (142i)

Yield: (182 mg, 67%); yellow oil. IR (neat): 3456, 3123, 2903, 2344, 1599 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.16 (t, 3H, *J*=7.6 Hz), 1.25 (t, 3H, *J*=7.1 Hz), 2.34 (q, 2H, *J*=7.7 Hz), 3.22 (s, 2H), 4.08 (q, 2H, *J*=7.1 Hz), 7.19-7.22 (m, 5H), 9.80 (s, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.1, 14.6, 15.9, 21.9, 46.8, 59.5, 82.6, 119.3, 126.2, 127.6, 128.9, 138.2, 165.8 169.2 . Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.34; H, 7.32; N, 10.21.

3.2.2.10 (*Z*)-Ethyl 3-(benzylamino)-2-(cyanomethyl)-3-phenylacrylate (142j)

Yield: (108 mg, 34%) brown oil; IR (neat): 3496, 3321, 2765, 2346, 1587 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.27 (t, 3H, *J*=7.12 Hz), 2.78 (s, 2H), 3.99 (d, 2H, *J*=6.32 Hz), 4.12 (q, 2H, *J*=7.10 Hz), 7.18-7.22 (m, 10H), 9.63 (bs, 1H, N*H*).^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.5, 17.8, 30.7, 48.5, 59.7, 84.9, 119.3, 126.7, 127.3,

127.6, 129.1, 129.4, 133.5, 138.5, 163.9, 169.0. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 75.42; H, 6.63; N, 8.38; Found: C, 75.45; H, 6.58; N, 8.32.

3.2.2.11 (*Z*)-Ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)-3-phenylacrylate (142k)

Yield: (137 mg, 40%); brown oil.$[\alpha]^{22}_D$= -420.01 (0.02, $CHCl_3$). IR (neat): 3436, 3028, 2917, 2240, 1587 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.30 (t, 3H, *J*=7.61 Hz), 1.37 (d, 3H, *J*=6.81 Hz), 2.75 (dd, 2H, *J*=17.41 Hz, *J*=23.98 Hz), 4.02 (m, 1H), 4.21 (m, 2H), 7.18-7.51 (m, 10H), 9.69 (d, 1H, *J*=8.80 Hz, N*H*).^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.5, 17.6, 24.6, 29.7, 54.3, 59.8, 84.8, 119.6, 125.5, 127.0, 127.2, 127.8, 128.5, 128.7, 129.0, 129.3, 133.7, 144.5, 163.4, 169.2. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.4): C, 70.99; H, 5.66; F, 5.61; N, 8.28; Found: C, 70.98; H, 5.70; F, 5.73; N, 8.32

3.2.2.12 (*Z*)-Ethyl 3-(benzylamino)-2-(cyanomethyl)-3-(2-fluorophenyl)acrylate (142l)

Yield: (138 mg, 41%); yellow oil. IR (neat): 3412, 3123, 2923, 2221, 1598 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.24 (t, 3H, *J*=7.12 Hz), 2.65-3.03 (dd, 3H, *J*=18.227 Hz, *J*=152.254 Hz), 3.97 (m, 2H), 4.17 (m, 2H), 7.01-7.31 (m, 9H), 9.61 (bs, 1H, N*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.5, 17.6, 48.6, 59.9, 85.5, 116.3 (d, J=20 Hz), 118.8, 120.1, 124.9, 126.9, 127.4, 128.6, 130.0, 131.7, 137.9, 157.8, 161.2 (d, *J*=252 Hz), 168.7.Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338,38): C, 70.99; H, 5.66; F, 5.61; N, 8.28. Found: C, 70.93; H, 5.63; F, 5.63; N, 8.22.

3.2.3 General Procedure for Base Catalyzed Cyclization Reaction

Enamine (1mmol) was added to potassium ethoxide in ethanol solution (5ml) and stirred for 5-30 min at rt. The reaction was monitored by TLC. Then, water is added and the mixture is extracted with ethylacetate. The extract is dried over $MgSO_4$ and the solvent is evaporated under reduced pressure and the crude pruduct is purified by column chromotography. (hexane:ethylacetate (4:1) as eluent).

3.2.3.1 1-(5-amino-2-methyl-1-phenyl-1*H*-pyrrol-3-yl)ethanone (143a)

Yield: (199 mg, 93%); brown oil. IR (neat); 3370, 2989, 1644 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.20(s, 3H), 2.28 (s, 3H), 2.95 (s, 2H, NH_2), 5.65 (s, 1H), 7.17-7.30 (m, 5H),^{13}C-NMR (100 MHz, $CDCl_3$): δ= 13.1, 28.9, 92.3, 128.7, 129.1, 130.0, 130.9, 135.2, 136.2, 194.7. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.76; H, 6.50; N, 13.01.

3.2.3.2 (*R*))-1-(5-Amino-2-methyl-1-(1-phenylethyl)-1*H*-pyrrol-3-yl)ethanone (143b)

Yield: (199 mg, 93%); oil,$[\alpha]^{22}_{D}$= 33.2 (77.0, $CHCl_3$). IR (neat): 3418, 2901, 2924, 2355, 1645 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.80 (d, 3H, *J* =7.06 Hz), 2.21 (s, 3H), 2.40 (s, 3H), 2.60 (s, 2H, NH_2), 5.53 (q, 1H, *J*=7.01 Hz), 5.61 (s, 1H), 7.14-7.23 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.1, 18.2, 50.8, 59.5, 110.4, 126.3, 127.4, 129,3, 131.3, 134.7, 141.23, 166.2. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.31; H, 7.23; N, 11.45.

3.2.3.3 1-(5-Amino-1-benzyl-2-methyl-1*H*-pyrrol-3-yl)ethanone (143c)

Yield: (198 mg, 87%); brown oil. IR (neat): 3388, 3007, 2917, 2849, 1656 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.27 (s, 3H), 2.41 (s, 3H), 2.82 (s, 2H, NH_2), 4.99 (s, 2H), 5.76 (s, 1H), 7.15-7.29 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.1, 28.9, 30.1, 45.5, 119.4, 126.1, 127.9, 129.3, 131.1, 133.8, 137.4, 194.6. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.18): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.66; H, 7.06; N, 12.27.

3.2.3.4 Ethyl 5-amino-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (143d)

Yield: (222 mg, 91%); yellow oil. IR (neat); 3315, 2982, 2926, 2336, 1687 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.24 (t, 3H, *J*= 7.11 Hz), 2.18 (s, 3H), 2.93 (s, 2H,

N*H*$_2$), 4.18 (q, 2H, *J*= 7.1 Hz), 5.68 (s, 1H), 7.13-7.30 (m, 5H).^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.59, 15.0, 59.4, 92.2, 96.5, 128.8, 128.9, 129.9, 131.3, 135.2, 136.6, 165.7. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.12): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.76; H, 6.64; N, 11.34.

3.2.3.5 (*R*)-Ethyl 5-amino-2-methyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (143e)

Yield (255 mg, 94%); yellow oil, $[\alpha]^{22}_D$= 332.46 (0.8, $CHCl_3$). IR(neat); 3243, 2923, 2854, 2342, 1688 cm^{-1} ; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.24 (t ,3H, *J* =7.10 Hz), 1.81 (d, 3H, *J*=6.76 Hz), 2.40 (s, 3H), 2.67 (s, 2H, N*H*$_2$), 4.18 (q, 2H, *J*=7.08 Hz), 5.57 (m, 1H), 5.76 (s, 1H), 7.13-7.28 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 12.2, 14.9, 18.3, 51.8, 59.5, 110.5, 126.3, 127.7, 129,1, 131.6, 134. 8, 141.3, 166.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C. 70,56; H. 7,40; N. 10,29; Found: C. 70,52; H. 7,34; N. 10,21.

3.2.3.6 Ethyl 5-amino-1-benzyl-2-methyl-1*H*-pyrrole-3-carboxylate (143f)

Yield: (229 mg, 89%); yellow oil. IR (neat); 3305, 2980, 2933, 2343, 1683 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.24 (t, 3H, *J*= 7.13 Hz), 2.34 (s, 3H), 2.82 (s, 2H, N*H*$_2$), 4.13 (q, 2H, *J*=7.12 Hz), 4.95 (s, 2H), 5.78 (s, 1H), 7.09-7.21 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 11.6, 15.0, 45.6, 59.3, 96.1, 110.3, 126.2, 127.7, 129.2, 131.4, 134.0, 137.7, 165.8. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.72; H, 7.05; N, 10.84.

3.2.3.7 Ethyl 5-amino-2-ethyl-1-phenyl-1*H*-pyrrole-3-carboxylate (143g)

Yield: (260 mg, 91%); colorless oil. IR (neat): 3375, 2970, 2913, 2340, 1681 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.91 (t, 3H, *J*=7.31 Hz), 1.27 (t, 3H, *J*=7.22 Hz), 2.59 (q, 2H, *J*=7.37 Hz), 2.86 (bs, 2H, N*H*$_2$), 4.20 (q, 2H, *J*=7.21 Hz), 5.70 (s, 1H), 7.28-7.38 (m, 5H),^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.5, 19.0, 29.7, 58.9, 92.0, 109.9, 114.9, 128.7, 129.4, 134.6, 136.3, 137.3, 165.0. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (286.37): C, 69.74; H, 7.02; N, 10.84; O. Found: C, 69.68; H, 7.01; N, 10.80.

3.2.3.8 (*R*)-Ethyl 5-amino-2-ethyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (143h).

Yield: (254 mg, 89%); colorless oil, $[\alpha]^{22}_{D}$= 197.56 (0.04, $CHCl_3$). IR (neat): 3298, 2934, 2984, 2323, 1645 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.08 (t, 3H, *J*=7.42 Hz), 1.26 (t, 3H, *J*=6.98 Hz), 1.86 (d, 3H, *J*= 7.00 Hz), 2.52 (bs, 2H, NH_2), 2.95 (q, 2H, *J*=7.41 Hz), 4.17 (q, 2H, *J*=7.08 Hz), 5.45 (q, 1H, *J*=7.04 Hz), 5.67 (s, 1H), 7.10-7.19 (m, 5H).^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.6, 15.0, 18.1, 18.7, 51,3, 58.8, 95.4, 109.4, 125.9, 127.3, 128.8, 134.1, 137.0, 141.2. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.68; N, 9.69;

3.2.3.9 Ethyl 5-amino-1-benzyl-2-ethyl-1*H*-pyrrole-3-carboxylate (143i)

Yield: (244 mg, 92%); yellow oil. IR (neat): 3323, 2979, 2934, 2334, 1675 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.02 (t, 3H, J=7.41 Hz), 1.27 (t, 3H, *J*=7.11 Hz), 2.81 (bs, 2H, NH_2), 2.86 (q, 2H, *J*=7.12 Hz), 4.21 (q, 2H, *J*=7.38 Hz), 5.12 (s, 2H), 5.72 (s, 1H), 6.81-7.38 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.6, 18.7, 29.6, 45.1, 58.8, 96.01, 109.3, 125.6, 127.3, 127.3, 133.3, 137.6, 137.6, 165.0. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (286.37): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.53; H, 7.29; N, 10.21.

3.2.3.10 Ethyl 5-amino-1-benzyl-2-phenyl-1*H*-pyrrole-3-carboxylate (143j)

Yield: (230 mg, 72%); yellow oil. IR (neat): 3312, 2978, 2923, 2332, 1679 cm^{-1}.^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.03 (t, 3H, *J*=7.10 Hz), 2.87 (bs, 2H, NH_2), 4.01 (q, 2H, *J*=7.04 Hz), 4.84 (s, 2H), 5.93 (s, 1H), 6.84-7.28 (m, 5H).^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.2, 46.4, 58.9, 95.7, 111.7, 125.7, 127.3, 127.9, 127.9, 128.8, 130.8, 132.2, 132.9, 133.9, 135.0, 137.8, 164.5. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.15): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.90; H, 6.23; N, 8.71.

3.2.3.11(R)-Ethyl-5-amino-2-phenyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (143k)

Yield: (250 mg, 75%); yellow oil, $[\alpha]^{22}_{D}$= 413.33 (0.03, $CHCl_3$). IR (neat): 3298, 2976, 2943, 2321, 1675 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.08 (t, 3H, *J*=7.09 Hz), 1.84 (d, 3H, *J*=7.08 Hz), 2.65 (bs, 2H, N*H*$_2$), 4.06 (q, 2H, *J*=7.09 Hz), 5.21 (q, 1H, *J*=7.03 Hz), 5.85 (s, 1H), 7.21-7.38 (m, 5H).^{13}C-NMR (100 MHz, $CDCl_3$): δ= 14.2, 17.8, 52.5, 58.9, 95.3, 11.5, 126.0, 127.3, 127.7, 128.0, 128.8, 130.9, 132.8, 133.8, 135.6, 141.1, 164.5. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.17): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.24; H, 6.55; N, 8.30.

3.2.3.12 Ethyl 2-methyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (147a)

Yield: (222 mg, 91%), white solid (mp=123 °C), IR (neat): 3426, 3295, 3043, 2982, 2930, 2369, 2326, 1682, 1595 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, *J*= 7.1 Hz), 2.40 (3H, s), 4.16 (2H, q, *J*= 7.1 Hz), 5.06 (1H, bs, N*H*), 6.14 (1H, d, *J*= 2.6 Hz), 6.52-7.12 (5H, m), 7.98 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 14.5, 59.1, 104.1, 111.4, 113.8, 119.3, 127.5, 129.2, 131.9, 146.4, 165.0; Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.12): C, 68.83; H, 6.60; N, 11.47; Found: C, 68.81; H, 6.62; N, 11.45.

3.2.3.13 Ethyl 5-(2,3-dimethylphenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (147b)

Yield: (212 mg, 78%), white solid (mp=130 °C), IR (neat): 3414, 3217, 2991, 2978, 2856, 2356, 2330, 1721, 1669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, t, *J*= 7.1 Hz), 2.15 (3H, s), 2.32 (3H, s), 2.51 (3H, s), 4.29 (2H, q, *J*= 7.1 Hz), 5.02 (1H, bs, N*H*), 6.21 (1H, d, *J*= 2.6 Hz), 6.49-6.93 (3H, m), 8.04 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 14.0, 15.4, 21.4, 60.0, 97.0 104.6, 112.3, 121.7, 122.4, 127.1, 129.1, 132.8, 137.7, 145.4, 166.0; Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.15): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.52; H, 7.41; N, 10.27.

3.2.3.14 Ethyl 5-(2-chlorophenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (147c)

Yield: (219 mg, 79%), white solid (mp=149 °C), IR (neat): 3673, 3304, 3052, 2930, 2895, 2353, 2326, 1682, 1591 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, *J*= 7.1 Hz), 2.44 (3H, s), 4.11 (2H, q, *J*= 7.1 Hz), 5.63 (1H, bs, N*H*), 6.24 (1H, d, *J*= 2.9 Hz), 6.62-7.21 (4H, m), 7.84 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 14.5, 59.2, 105.6, 111.8, 113.6, 118.8, 119.4, 125.7, 127.7, 129.2, 132.4, 142.7, 164.8. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.7): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.31; H, 5.41; N, 10.03.

3.2.3.15 Ethyl 5-(3-chlorophenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (147d)

Yield: (258 mg, 93%), white solid (mp=138 °C), IR (neat): 3523, 3387, 3022, 2894, 2336, 2229, 2136, 1732, 1681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, *J*= 7.1 Hz), 2.44 (3H, s), 4.18 (2H, q, *J*= 7.1 Hz), 5.15 (1H, bs, N*H*), 6.15 (1H, d, *J*= 2.6 Hz), 6.46-7.01 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.2, 14.4, 59.4, 105.1, 111.6, 111.9, 113.6, 119.2, 126.3, 130.3, 132.6, 135.1, 147.9, 165.2; Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.7): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.32; H, 5.42; N, 10.04

3.2.3.16 Ethyl 5-(4-chlorophenylamino)-2-methyl-1*H*-pyrrole-3-carboxylate (147e)

Yield: (261 mg, 94%), white solid (mp=137 °C), IR (neat): 3443, 3391, 3052, 2943, 2336, 2356, 2326, 1739, 1682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (3H, t, *J*= 7.1 Hz), 2.40 (3H, s), 4.16 (2H, q, *J*= 7.1 Hz), 5.13 (1H, bs, N*H*), 6.13 (1H, d, *J*= 2.6 Hz), 6.50 (2H, d, *J*= 8.7 Hz, Ph-H), 7.01 (2H, d, *J*= 8.7 Hz), 8.12 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.1, 14.5, 59.3, 104.3, 111.4, 114.9, 124.0, 127.1, 129.1, 132.2, 145.1, 165.2; Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.7): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.30; H, 5.41; N, 10.02.

3.2.3.17 Ethyl 2-ethyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (147f)

Yield: (239 mg, 93%), white solid (mp=125 °C), IR (neat): 3316, 3275, 3047, 2962, 2839, 2329, 2316, 1785, 1621 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, *J*= 7.5 Hz), 1.23 (3H, t, *J*= 7.2 Hz), 2.89 (2H, q, *J*= 7.5 Hz), 4.19 (2H, q, *J*= 7.2 Hz), 5.13 (1H, bs, N*H*), 6.21 (1H, d, *J*= 2.9 Hz), 6.61-7.13 (5H, m), 7.98 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 14.4, 20.5, 59.3, 104.1, 110.4, 113.8, 119.3, 127.6, 129.3, 138.1, 146.5, 165.3. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.73; H, 7.01; N, 10.83.

3.2.3.18 Ethyl 5-(2,3-dimethylphenylamino)-2-ethyl-1*H*-pyrrole-3-carboxylate (147g)

Yield: (248 mg, 87%), white solid, IR (neat): 3512, 3312, 2871, 2934, 2867, 2312, 2336, 1678, 1678 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, *J*= 7.5 Hz), 1.24 (3H, t, *J*= 7.1 Hz), 2.03 (3H, s), 2.23 (3H, s), 2.85 (2H, q, *J*= 7.5 Hz), 4.13 (2H, q, *J*= 7.1 Hz), 4.94 (1H, bs, N*H*), 6.09 (1H, d, *J*= 2.8 Hz), 6.39-6.71 (3H, m), 8.06 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 12.5, 13.6, 14.5, 20.3, 20.5, 59.1, 103.5, 110.4, 111.3, 120.8, 121.4, 126.2, 128.3, 136.8, 137.8, 144.5, 165.0. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286,37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.30; H, 7.72; N, 9.77.

3.2.3.19 Ethyl 2-isopropyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (147h)

Yield: (187 mg, 95%), white solid (mp), IR (neat): 3523, 3285, 3061, 2979, 2922, 2345, 2313, 1672, 1612 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, d, *J*= 7.0 Hz), 1.34 (3H, t, *J*= 7.1 Hz), 3.79-3.83 (1H, m), 4.27 (2H, q, *J*= 7.1 Hz), 5.21 (1H, bs, N*H*), 6.24 (1H, d, *J*= 2.8 Hz), 6.63-7.31 (5H, m), 8.07 (1H, bs. N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 22.1, 25.8, 59.2, 104.1, 109.9, 113.7, 119.3, 127.4, 129.3, 142.0, 146.5, 164.9. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.15): C, 70.56; H, 7.40; N, 10.29; Found: C, 70.54; H, 7.47; N, 10.25.

3.2.3.20 Ethyl 2-phenyl-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (147i)

Yield: (272 mg, 89%), white solid (mp=141 °C), IR (neat): 3421, 3065, 2982, 2934, 2904, 1695, 1591cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (3H, t, *J*= 7.1 Hz), 4.10 (2H, q, *J*= 7.1 Hz), 5.2 (1H, bs, N*H*), 6.31 (1H, d, *J*= 2.3 Hz), 6.53-7.55 (10H, m), 8.15 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 30.7, 59.4, 105.4, 111.9, 114.1, 119.7, 128.0, 128.8, 129.4, 129.6, 131.8, 133.6, 145.9, 164.1;
Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306,14): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.47; H, 5.90; N, 9.13.

3.2.3.21 Ethyl 5-(4-chlorophenylamino)-2-phenyl-1*H*-pyrrole-3-carboxylate (147j)

Yield: (289 mg, 85%), white solid (mp=132 °C), IR (neat): 3513, 3372, 3153, 2897, 2239, 2450, 2389, 1732, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, *J*= 7.1 Hz), 4.04 (2H, q, *J*= 7.1 Hz), 5.27 (1H, bs, N*H*), 6.25 (1H, s), 6.53-7.44 (9H, m), 8.29 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 15.1, 60.6, 105.4, 112.5, 116.1, 125.2, 128.9, 128.9, 129.7, 130.1, 130.5, 132.6, 145.2, 165.6; Anal. Calcd for $C_{19}H_{17}ClN_2O_2$ (340.8): C, 66.96; H, 5.03; N, 8.22. Found: C, 66.95; H, 5.02; N, 8.22.

3.2.3.22 Ethyl 5-(benzylamino)-2-phenyl-1H-pyrrole-3-carboxylate (147k)

Yield: (284 mg, 89%), yellow oil, IR (neat): 3413, 3272, 3142, 2787, 2199, 2421, 2298, 1752, 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, t, *J*= 7.1 Hz), 4.04 (3H, q, *J*= 7.1 Hz), 4.07 (2H, bs), 5.68 (1H, d, *J*= 2.8 Hz), 7.11-7.39 (10H, m), 8.04 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 50.6, 59.3, 92.4, 111.1, 127.3, 127.4, 127.7, 127.8, 128.1, 128.5, 128.6, 128.9, 130.8, 132.3, 139.0, 139.3, 165.1;
Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.94; H, 6.25; N, 8.76.

3.3.3.23 Ethyl 2-(2-fluorophenyl)-5-(phenylamino)-1*H*-pyrrole-3-carboxylate (147l)

Yield: (281 mg, 87%), white solid (mp=113 °C), IR (neat): 3525, 3266, 2987, 2921, 2964, 1699, 1601 cm^{-1}. ^1H NMR(400 MHz, $CDCl_3$): δ 1.16 (3H, t, *J*=7.2 Hz), 4.15 (2H, q, *J*= 7.2 Hz), 5.25 (1H, bs, N*H*), 6.39 (1H, s), 6.71-7.61 (9H, m), 8.31 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 11.1, 56.6, 99.9, 110.3, 111.1, 112.3 (*J*= 22 Hz), 116.4, 120.4, 122.8, 126.2, 126.5, 126.7, 127.6, 128.8, 142.2, 156.9 (d, *J*= 246 Hz), 161.6; Anal. Calcd for $C_{19}H_{17}FN_2O_2$ (324.35): C, 70.36; H, 5.28; N, 8.64. Found: C, 70.32; H, 5.22; N, 8.63.

3.2.3.24 Ethyl 5-(benzylamino)-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (147m)

Yield: (287 mg, 85%), yellow oil, IR (neat): 3523, 3472, 3347, 2687, 2231, 2521, 2342, 1749, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, t, *J*= 7.0 Hz), 4.04 (2H, q, *J*= 7.0 Hz), 4.07 (2H, bs), 5.73 (1H, s), 6.91-7.48 (9H, m), 8.14 (1H, bs, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 50.5, 59.5, 92.0, 113.2, 115.4 (d, *J*= 22 Hz), 120.3 (d, *J*= 13 Hz), 123.6 (d, *J*= 8 Hz), 127.4, 127.7, 128.1,128.6, 129.0, 131.9, 138.9, 139.6, 159.1 (d, *J*= 245 Hz), 164.9; Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338.38): C, 70.99; H, 5.66; N, 8.28; Found: C, 70.92; H, 5.64; N, 8.23.

3.2.4 The general procedure for the synthesis of pyrroles (3a-o) (method A):

β-Ketoester **140** (1 mmol) was dissolved in corresponding alcohol **148** (5 ml) together with a catalytic amount of $Zn(ClO_4)_2$ (5 mmol%). The reaction was refluxed for 5-6 hours and monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, and the crude product was purified by column chromotography (hexane/ethyl acetate (4:1)).

3.2.4.1 Ethyl 5-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149a).

Yield: (170 mg, 93%), white solid (mp=106-107°C), IR ($CHCl_3$): 3947, 3293, 3286, 2986, 2369, 2309, 1722, 1439 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, *J*= 7.1 Hz), 2.35 (3H, s), 3.71 (3H, s), 4.20 (2H, q, *J*= 7.1 Hz), 5.47 (1H, d, *J*= 3.0 Hz), 7.99 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 12.7, 14.5, 57.4, 59.3, 83.1, 109.5, 127.8, 146.4, 165.8; Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.00; H, 7.15; N, 7.65; Found: C, 58.88; H, 7.24; N, 7.44.

3.2.4.2 Ethyl 2-ethyl-5-methoxy-1*H*-pyrrole-3-carboxylate (149b).

Yield: (177 mg, 90%), white solid (mp= 70-71°C), IR ($CHCl_3$): 3940, 3293, 3285, 2978, 2312, 1732, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (3H, t, *J*= 7.5 Hz), 1.26 (3H, t, *J*= 7.0 Hz), 2.82 (2H, q, *J*= 7.5 Hz), 3.70 (3H, s), 4.17 (2H, q, *J*= 7.0 Hz), 5.44 (1H, d, *J*= 2.9 Hz), 7.63 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.6, 14.5, 20.1, 57.5, 59.1, 83.3, 106.5, 133.3, 146.3, 165.1; Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10; Found: C, 60.81; H, 7.55; N, 6.88.

3.2.4.3 Ethyl 2-isopropyl-5-methoxy-1*H*-pyrrole-3-carboxylate (149c).

Yield: (187 mg, 89%), white solid (mp=121-122°C), IR ($CHCl_3$): 3945, 3423, 3189, 3055, 2982, 2930, 2326, 1692, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (6H, d, *J*= 7.0 Hz), 1.26 (3H, t, *J*= 7.1 Hz), 3.71 (3H, s), 4.19 (2H, q, *J*= 7.1 Hz), 5.47 (1H, d, *J*= 2.9 Hz), 7.81 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 22.0, 25.6, 57.5, 59.3, 83.1, 107.9, 137.7, 146.3, 165.2; Anal. Calcd for $C_{11}H_{17}NO_3$ (211,26): C, 62.54; H, 8.11; N, 6.63; Found: 62.42; H, 8.23; N, 6.48.

3.2.4.3 Ethyl 5-methoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149d).

Yield: (228 mg, 91%), white solid (mp=129-131°C), IR ($CHCl_3$): 3944, 3432, 3190, 3032, 2985, 2306, 1722, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, t, *J*= 7.1 Hz), 3.78 (3H, s), 4.13 (2H, q, *J*= 7.1 Hz), 5.65 (1H, d, *J*= 2.9 Hz), 7.21-7.51 (5H, m), 7.77 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 32.8, 59.3, 85.8, 110.5, 127.7, 128.0, 128.7, 129.0, 133.3, 147.8, 168.3; Anal. Calcd for $C_{14}H_{15}NO_3$ (245.27): C, 68.56; H, 6.16; N, 5.71; Found: C, 68.48; H, 6.12; N, 5.58.

3.2.4.5 Ethyl 2-(2-fluorophenyl)-5-methoxy-1*H*-pyrrole-3-carboxylate (149e).

Yield: (215 mg, 82%), white solid (mp=122-123°C), IR ($CHCl_3$): 3966, 3701, 3433, 3055, 2988, 2370, 1684, 1595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, t, *J*= 7.1 Hz), 3.77 (3H, s), 4.11 (2H, q, *J*= 7.1 Hz), 5.73 (1H, d, *J*= 2.9 Hz), 6.99-7.52 (4H, m), 8.06 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 57.6, 59.7, 85.6, 112.4, 115.6 (d, *J*= 22 Hz), 119.7, 122.0, 123.6, 129.6 (d, *J*= 8.7 Hz), 132.0, 148.1, 160.9 (d, *J*= 245 Hz), 164.6; Anal. Calcd for $C_{14}H_{14}F\ NO_3$ (263.26): C, 63.87; H, 5.36; N, 5.32; Found: C, 63.71; H, 5.28; N, 5.12.

3.2.4.6 Ethyl 5-ethoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149f).

Yield: (169 mg, 86%), white solid (mp=114-115°C), IR ($CHCl_3$): 3932, 3290, 3294, 2982, 2366, 2334, 1732, 1421 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, *J*= 7.1 Hz), 1.21 (3H, t, *J*= 7.1 Hz), 2.35 (3H, s), 3.95 (2H, q, *J*= 7.1 Hz), 4.18 (2H, q, *J*= 7.1 Hz), 5.45 (1H, d, *J*= 2.9 Hz), 7.91 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 12.7, 14.5, 57.4, 59.2, 66.2, 83.9, 109.5, 127.5, 145.3, 165.8; Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10; Found: C, 59.51; H, 7.49; N, 6.86.

3.2.4.7 Ethyl 5-ethoxy-2-ethyl-1*H*-pyrrole-3-carboxylate (149g).

Yield: (189 mg, 86%), white solid (mp=115-116°C), IR ($CHCl_3$): 3944, 3687, 3190, 3049, 2984, 2312, 1691, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, t, *J*= 7.1 Hz), 1.15 (3H, t, *J*= 7.5 Hz), 1.25 (3H, t, *J*= 7.2 Hz), 2.81 (2H, q, *J*= 7.5 Hz), 4.06 (2H, q, *J*= 7.2 Hz), 4.11 (2H, q, *J*= 7.1 Hz), 5.41 (1H, d, *J*= 3.1 Hz), 7.61 (1H, bs, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): 13.5, 14.5, 14.6, 20.0, 58.9, 65.8, 84.0, 108.7, 133.0, 145.1, 165.0; Anal. Calcd for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63; Found: C, 62.43; H, 8.04; N, 6.49.

3.2.4.8 Ethyl 5-ethoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate (149h).

Yield: (177 mg, 79%), white solid (mp=101-103°C), IR ($CHCl_3$): 3947, 3809, 3291, 3043, 2986, 2301, 1733, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (6H, d, *J*= 6.9 Hz), 1.25 (3H, t, *J*= 7.1Hz,), 1.29 (3H, t, *J*= 7.1 Hz), 3.65 (1H, m), 3.93 (2H, q,

J= 7.1 Hz), 4.17 (2H, q, *J*= 7.1 Hz), 5.44 (1H, d, *J*= 2.4 Hz), 7.74 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 14.7, 22.0, 25.5, 59.2, 66.1, 83.7, 107.9, 137.4, 145.2, 165.4; Anal. Calcd for $C_{12}H_{19}NO_3$ (225.28): C, 63.98; H, 8.50; N, 6.22; Found: C, 63.86; H, 8.45; N, 6.11.

3.2.4.9 Ethyl 5-ethoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149i).

Yield: (212 mg, 82%), white solid (mp=129-131°C), IR ($CHCl_3$): 3939, 3295, 3045, 2982, 2369, 1702, 1593 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, *J*= 7.1 Hz), 1.34 (3H, t, *J*= 7.0 Hz), 4.03 (2H, q, *J*= 7.1 Hz), 4.15 (2H, q, *J*= 7.0 Hz), 5.68 (1H, d, *J*= 2.9 Hz), 7.22-7.51 (5H, m), 7.88 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 14.6, 59.6, 66.4, 86.4, 110.3, 127.7, 128.0, 128.6, 128.8, 132.0, 147.0, 164.9; Anal. Calcd for $C_{15}H_{17}NO_3$ (259.3): C, 69.48; H, 6.61; N, 5.40; Found: 69.32; H, 6.59; N, 5.11.

3.2.4.10 Ethyl 5-ethoxy-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (149j).

Yield: (221 mg, 80%), white solid (mp=104-105°C), IR ($CHCl_3$): 3945, 3693, 3416, 3189, 3053, 2985, 1691, 1421 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, t, *J*= 7.1 Hz), 1.32 (3H, t, *J*= 7.0 Hz), 4.10 (2H, q, *J*= 7.0 Hz), 4.12 (2H, q, *J*= 7.1 Hz), 5.71 (1H, d, *J*= 2.9 Hz), 7.01-7.56 (4H, m), 8.05 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 14.6, 59.6, 66.5, 86.3, 122.4, 115.4 (d, *J*= 22 Hz), 119.6 (d, *J*= 13 Hz), 121.8, 123.6, 129.4 (d, *J*= 8.8 Hz), 132.0, 147.1, 160.9 (d, *J*= 245 Hz), 164.7; Anal. Calcd for $C_{15}H_{16}F\,NO_3$ (277.29): C, 64.97; H, 5.82; N, 5.05; Found: C, 64.82; H, 5.71; N, 5.21.

3.2.4.11 Ethyl 5-isopropoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149k)

Yield: (201 mg, 78%), oil, IR (neat): 3939, 3422, 3295, 3193, 3045, 2982, 2369, 1702, 1593 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, *J*= 7.1 Hz), 1.37 (6H, d, *J*= 6.1 Hz), 4.19 (2H, q, *J*= 7.1 Hz), 4.43 (1H, m), 5.68 (1H, d, *J*= 2.9 Hz), 7.25-7.57 (5H, m), 7.77 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 21.9, 59.2, 73.7, 87.6, 110.4, 127.8, 128.4, 128.6, 128.7, 132.0, 145.6, 164.4; Anal. Calcd for $C_{16}H_{19}NO_3$ (273.3): C, 70.31; H, 7.01; N, 5.12; Found: 70.15; H, 6.88; N, 4.89.

3.2.4.12 Ethyl 5-isopropoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149l).

Yield: (140 mg, 75%), white solid (mp=121-122°C), IR ($CHCl_3$): 3934, 3273, 3279, 2977, 2356, 2322, 1735, 1423 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (6H, d, *J*= 6.1 Hz), 1.25 (3H, t, *J*= 7.1 Hz), 2.35 (3H, s), 4.16 (2H, q, *J*= 7.1 Hz), 4.27 (1H, m), 5.45 (1H, d, *J*= 2.8 Hz), 7.63 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 12.8, 14.5, 21.9, 59.2, 74.0, 85.6, 109.7, 127.2, 144.0, 165.7; Anal. Calcd for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63; Found: C, 62.33; H, 8.01; N, 6.42.

3.2.4.13 Ethyl 2-ethyl-5-isopropoxy-1*H*-pyrrole-3-carboxylate (149m).

Yield: (173 mg, 77%), yellow oil, IR (neat): 3941, 3682, 3429, 3293, 3043, 2990, 2332, 1692, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, t, *J*= 7.5 Hz), 1.25 (6H, d, *J*= 6.2 Hz), 1.26 (3H, t, *J*= 7.0 Hz), 2.82 (2H, q, *J*= 7.5 Hz), 4.18 (2H, q, *J*= 7.0 Hz), 4.25 (1H, m), 5.49 (1H, d, *J*= 3.0 Hz), 7.76 (1H, bs, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.4, 13.4, 20.8, 49.7, 60.0, 72.7, 84.1, 107.6, 132.1, 143.0, 164.4; Anal. Calcd for $C_{12}H_{19}NO_3$ (225.28): C, 63.98; H, 8.50; N, 6.22; Found: C, 63.69; H, 8.45; N, 6.08.

3.2.4.14 Ethyl 5-isopropoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate (149n).

Yield: (174 mg, 73%), yellow oil, IR (neat): 3945, 3426, 3193, 3055, 2984, 2300 1722, 1427 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (6H, d, *J*= 6.2 Hz), 1.24 (3H, t, *J*= 7.1 Hz,), 1.25 (6H, d, *J*= 7.0 Hz), 3.65 (1H, m), 4.11 (2H, q, *J*= 7.1 Hz), 4.23 (1H, m), 5.46 (1H, d, *J*= 3.0 Hz), 7.74 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 14.5, 21.9, 22.0, 59.6, 74.2, 83.1, 107.9, 137.7, 146.3, 165.7; Anal. Calcd for $C_{13}H_{21}NO_3$ (239.31): C, 65.25; H, 8.84; N, 5.85; Found: C, 65.12; H, 8.71; N, 5.71.

3.2.4.15 Ethyl 2-(2-fluorophenyl)-5-isopropoxy-1*H*-pyrrole-3-carboxylate (149o).

Yield: (202 mg, 70%), white solid (mp=116-117°C), IR ($CHCl_3$): 3899, 3690, 3425, 3143, 2979, 2369, 2326, 1682, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, t, *J*= 7.1 Hz), 1.30 (6H, d, *J*= 6.0 Hz), 4.12 (2H, q, *J*= 7.1 Hz), 4.35 (1H, m), 5.72

(1H, d, *J*= 2.9 Hz), 7.02-7.56 (4H, m), 7.85 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 21.9, 59.3, 73.8, 87.6, 112.4, 115.3 (d, *J*= 22 Hz), 119.6, 121.4, 123.4 (d, *J*= 3 Hz), 129.5 (d, *J*= 85 Hz), 132.0, 145.8, 160.9 (d, *J*= 246 Hz), 164,2; Anal. Calcd for $C_{16}H_{18}FNO_3$ (291.32): C, 65.97; H, 6.23; N, 4.81; Found: C, 65.82; H, 6.11; N, 4.71.

3.2.5 The general procedure for the synthesis of pyrroles (149p,149r):

β-Ketoester **140** (1 mmol) was dissolved in DCE (5 ml). The corresponding thiol **148** (2 mmol) along with a catalytic amount of $Zn(ClO_4)_2$ (5 mmol%) was added to the stirring mixture. The reaction was refluxed for 5-6 hours and monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, and the crude product was purified by column chromotography (hexane/ethyl acetate (4/1)).

3.2.5.1 Ethyl 5-(isopentylthio)-2-methyl-1*H*-pyrrole-3-carboxylate (149p).

Yield: (196 mg, 79 %), white solid (129-131°C) , IR ($CHCl_3$): 3956, 3293, 3286, 3041, 2986, 2303, 2316, 1721, 1439 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (6H, d, *J*= 6.5 Hz), 1.39 (3H, t, *J*= 7.0 Hz), 1.52 (2H, m), 1.71 (1H, m), 2.49 (3H, s), 2.76 (2H, t, *J*= 7.6 Hz), 4.30 (2H, q, *J*= 7.0 Hz), 6.44 (1H, s), 8.17 (1H, bs, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 14.4, 22.3, 27.4, 32.1, 37.7, 59.2, 111.9, 116.1, 117.6, 136.1, 164,6; Anal. Calcd for $C_{13}H_{21}NO_2S$ (249.24): C, 61.14; H, 8.29; N, 5.48; Found: C, 61.03; H, 8.17; N, 5.22.

3.2.5.2 Ethyl 5-(2-methylbutylthio)-2-methyl-1*H*-pyrrole-3-carboxylate (149r).

Yield: (199 mg, 80%), white solid (127-129°C) IR ($CHCl_3$): 3951, 3299, 3289, 3045, 2996, 2308, 2320, 1722, 1443 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, *J*= 7.0 Hz), 0.93 (3H, d, *J*= 10.5 Hz), 1.16 (1H, m), 1.30 (3H, t, *J*= 7.0 Hz), 1.46-1.62 (2H, m), 2.44 (3H, s), 2.52-2.71 (2H, m), 4.20 (2H, q, *J*= 7.0 Hz), 6.39 (1H, s), 8.32 (1H, bs, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 10.3, 13.0, 13.5, 27.9, 33.2, 40.4, 58.3, 110.8, 114.9, 117.0, 135.3, 163.8; Anal. Calcd for $C_{13}H_{21}NO_2S$ (249.24): C, 61.14; H, 8.29; N, 5.48; Found: C, 61.19; H, 8.44; N, 5.31.

3.2.6 The general procedure for the synthesis of pyrolidones (150a-e) (method B):

The corresponding β-Ketoester (1mmol) together with a catalytic amount of $Zn(ClO_4)_2$ (5mol %) was dissolved in a water/isopropanol mixture (10ml/4ml). The reaction was refluxed for 6-7 hours and was monitored with TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, and the crude product was purified by column chromotography (hexane–ethyl acetate (3/1)).

3.2.6.1 Ethyl 4,5-dihydro-2-methyl-5-oxo-1*H*-pyrrole-3-carboxylate (150a).

Yield: (160 mg, 95%), white solid (mp=124-125°C), IR ($CHCl_3$): 3691, 3416, 3297, 2984, 2306, 2326, 1691, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, *J*= 7.1 Hz), 2.21 (3H, s), 3.23 (2H, d, *J*= 2.1 Hz), 4.15 (2H, q, *J*= 7.1 Hz), 8.91 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 14.4, 37.5, 59.8, 104.4, 151.7, 164.1, 178.5; Anal. Calcd for $C_8H_{11}NO_3$ (169.18): C, 56.80; H, 6.55; N, 8.28; Found: C, 56.64; H, 6.43; N, 8.15.

3.2.6.2 Ethyl 2-ethyl-4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (150b).

Yield: (172 mg, 94%), white solid (mp=99-100°C), IR ($CHCl_3$): 3692, 3434, 3295, 2984, 2326, 2326, 1726, 1474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (3H, t, *J*= 7.6 Hz), 1.22 (3H, t, *J*= 7.1 Hz), 2.78 (2H, q, *J*= 7.6 Hz), 3.32 (2H, s), 4.13 (2H, q, *J*= 7.1 Hz), 9.07 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 11.6, 14.4, 20.4, 37.6, 59.5, 103.3, 157.2, 163.5, 178.9; Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.0; H, 7.15; N, 7.65; Found: C, 58.74; H, 7.12; N, 7.59.

3.2.6.3 Ethyl 4,5-dihydro-2-isopropyl-5-oxo-1*H*-pyrrole-3-carboxylate (150c).

Yield: (175 mg, 89%), white solid (mp=128-129°C), IR ($CHCl_3$): 3657, 3425, 3191, 3053, 2983, 1723, 1593 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (6H, d, *J*= 7.0

Hz), 1.29 (3H, t, *J*= 7.0 Hz), 3.27 (2H, s), 3.90 (1H, m), 4.18 (2H, q, *J*= 7.0 Hz), 9.62 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 20.0, 25.7, 37.6, 59.5, 102.1, 161.2, 163.4, 178.9; Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10; Found: 60.79; H, 7.62; N, 6.88.

3.2.6.4 Ethyl 4,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (150d).

Yield: (210 mg, 95 %), (mp=173-174°C), IR ($CHCl_3$): 3660, 3426, 3198, 3053, 2987, 2361, 1701, 1438 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, *J*= 7.1 Hz), 3.41 (2H, s), 4.05 (2H, q, *J*= 7.1 Hz), 7.35-7.56 (5H, m), 8.62 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 14.9, 39.2, 60.0, 104.2, 128.1, 128.7, 129.4, 130.4, 152.3, 163.4, 178.6; Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06; Found: 67.49; H, 5.62; N, 5.81.

3.2.6.5 Ethyl 2-(2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (150e).

Yield: (221 mg, 87 %), white solid (mp=116°C), IR ($CHCl_3$): 3653, 3194, 3045, 2987, 2303, 1689, 1498 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, t, *J*= 7.1 Hz), 3.44 (2H, s), 4.09 (2H, q, *J*= 7.1 Hz), 7.11-7.51 (4H, m), 8.76 (1H, bs, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 37.9, 59.8, 107.0, 115.8 (d, *J*= 21 Hz), 123.7, 130.6, 132.0 (d, *J*= 8.6 Hz), 145.1, 162.3 (d, *J*= 246 Hz), 176.8; Anal. Calcd for $C_{13}H_{12}FNO_3$ (249.24): C, 62.65; H, 4.85; N, 5.62; Found: C, 62.76; H, 4.81; N, 5.56.

3.2.7 The general procedure for the synthesis of pyrolidones (method C) (150a-e):

The corresponding β-ketoester (1mmol) together with a catalytic amount of $Zn(ClO_4)_2$ (5 mol %) was dissolved in a water/acetonitrile mixture (10ml/2.0 ml). The reaction was refluxed for 3-4 hours and was monitored with TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, and the crude product was purified by column chromotography (hexane/ethyl acetate (3:1)).

3.2.8 The general procedure for the synthesis of pyrolidones (method D) (150a-e):

The corresponding pyrrole (**3b)** (1 mmol) was dissolved in ethanol/1N HCl mixture (10 ml/0.5 ml). The reaction was refluxed for 1-2 hours and monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, and the crude product was purified by column chromotography (hexane/ethyl acetate (3:1)).

3.2.8.1 3-(Ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid methyl ester (151a):

Yield: (26 mg, 12%), oil, IR (neat): 3866, 3538, 3197, 2990, 1745, 1419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, t, *J*= 7.1 Hz), 3.02 (2H, m), 3.69 (3H, s), 4.12 (2H, q, *J*= 7.1 Hz), 4.80 (1H, t, *J*= 7.1 Hz), 7.45-8.01 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.8, 32.7, 49.4, 51.7, 61.4, 128.4, 128.7, 133.2, 135.9, 168.2, 171.3, 193.4; Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32; Found: C, 63.81; H, 6.64; N, 5.19.

3.2.8.2 3-(Ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid isopropyl ester (151b):

Yield: (43 mg, 15%), oil, IR (neat): 3856, 3532, 3195, 2985, 1722, 1412 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, t, *J*= 7.1 Hz), 1.21 (6H, d, *J*= 6.2 Hz), 2.98 (2H, m), 4.14 (2H, q, *J*= 7.1 Hz), 4.81 (1H, t, *J*= 7.1 Hz), 5.13 (1H, m), 7.44-8.02 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.8, 21.6, 33.4, 49.5, 61.3, 68.1, 128.4, 128.7, 133.2, 136.0, 168.3, 170.3, 193.5; Anal. Calcd for $C_{16}H_{21}NO_4$ (291.34): C, 65.96; H, 7.27; N, 4.81; Found: C, 65.93; H, 7.31; N, 4.71.

3.2.8.3 3-(Ethoxycarbonyl)-4-(2-fluorophenyl)-4-oxobutanoxylimidic acid ethyl ester (151c):

Yield: (31 mg, 13%), oil, IR (neat): 3866, 3552, 3192, 2982, 1752, 1432 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, t, *J*= 7.2 Hz), 1.29 (3H, t, *J*= 7.1 Hz), 2.87-

3.11 (2H, m), 4.13 (2H, q, *J*= 7.1 Hz), 4.14 (2H, q, *J*= 7.2 Hz), 4.68 (1H, t, *J*= 5.7 Hz), 7.12-7.91 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.8, 14.1, 32.8, 53.4, 60.7, 61.3, 116.5 (d, *J*= 23 Hz), 124.4, 125.0, 131.2, 134.7, 161.5 (d, *J*=253 Hz), 168.5, 170.7, 191.7; Anal. Calcd for $C_{15}H_{18}FNO_4$ (295.31): C, 61.01; H, 6.14; N, 4.74; Found: C, 61.12; H, 6.25; N, 4.61.

3.2.8.4 3-(Ethoxycarbonyl)-4-oxohexanoxylimidic acid isopropyl ester (151d):

Yield: (35 mg, 12%), oil, IR (neat): 3846, 3539, 3198, 2991, 1744, 1418 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, t, *J*= 7.2 Hz), 1.14 (6H, d, *J*= 6.2 Hz), 1.22 (3H, t, *J*= 7.1 Hz), 2.58 (2H, m), 2.90 (2H, m), 3.89 (1H, m), 4.13 (2H, q, *J*= 7.1 Hz), 4.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 7.6, 14.0, 21.7, 32.8, 36.1, 53.7, 61.7, 68.5, 168.6, 170.8, 204.7; Anal. Calcd for $C_{12}H_{21}NO_4$ (243.3): C, 59.24; H, 8.70; N, 5.79; Found: C, 59.31; H, 8.55; N, 5.66.

3.2.9 General procedure for the preparation of epoxyphosphonates 155a-l:

DBU (2 mmol) is added very slowly to a stirred solution of **154a-h** (1 mmol) and α-bromo ketone **153a-c** (2 mmol) in anhydrous acetonitrile at room temperature under an argon atmosphere. The reaction mixture is stirred for several hours (2-12 h). The reaction is monitored by TLC. Water is added, and the mixture is extracted with ethyl acetate, in which the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford **155a-l** (ether- petroleum ether) (5–1)).

Benzoylphosphonate **154a-h** (1 mmol) is added to a mixture of α-bromo ketone **153a-c** (1.2 mmol) and Cs_2CO_3 (1.5 mmol) in anhydrous acetonitrile at room temperature under an argon atmosphere. The reaction mixture is stirred for several hours (2-12 h). The reaction was monitored by TLC. Water is added, the mixture is extracted with ethyl acetate, and the combined organic layers are dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product is purified on silica gel to afford **3a-l** (ether- petroleum ether) (5–1)).

3.2.9.1 Dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate (*trans*-155a):

Yield: (100 mg, 30 %), white solid (mp=125 °C), IR (KBr): 3007, 2352, 1650, 1220, 1059 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 3.53 (3H, s), 3.91 (1H, d, *J*=4.16 Hz), 7.28-8.05 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.6 (d, J_{C-P}=7.4 Hz), 54.3 (d, J_{C-P}=6.9 Hz), 61.8 (d, J_{C-P}=202 Hz), 66.0, 126.7 (d, J_{C-P}=2.7 Hz), 128.6, 128.7, 129.0, 134.0 (d, J_{C-P}=14.5 Hz), 134.4, 134.9, 190.6. ^{31}P NMR: 16.121. Anal. calcd for. $C_{17}H_{17}O_5P$: C, 61.45; H, 5.16. Found: C, 61.32; H, 5.17.

3.2.9.2 Dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate (*cis*-155a):

Yield: (64 mg, 19 %), white solid (mp=120-122 °C), IR (KBr): 2968, 2360, 1688, 1258, 1059 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (3H, d, *J*=10.7 Hz), 3.81 (3H, d, *J*=10.5 Hz), 4.68 (1H, d, *J*=5.6 Hz), 7.13-7.81 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 54.4 (d, J_{C-P}=7.2 Hz), 54.5 (d, J_{C-P}=6.5 Hz), 61.2 (d, J_{C-P}=198 Hz), 61.7, 127.6 (d, J_{C-P}=2.7 Hz), 128.1, 128.2, 128.8, 128.9, 129.6, 129.7, 133.9, 135.0, 189.7; ^{31}P NMR: 16.638. Anal. calcd. for $C_{17}H_{17}O_5P$: C, 61.45; H, 5.16. Found: C, 61.42; H, 5.20.

3.2.9.3 Dimethyl 3-benzoyl-2-p-tolyloxiran-2-ylphosphonate (*trans*-155b):

Yield: (114 mg, 33%), white solid (mp=110 °C), IR (KBr): 3001, 2336, 1642, 1227, 1057 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (3H, s), 3.57 (3H, s), 3.59 (3H, s), 3.89 (1H, d, *J*=3.6 Hz), 7.23 (2H, m), 7.51 (2H, m), 7.59 (3H, m), 8.11 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 21.3, 53.4 (d, J_{C-P}=6.6 Hz), 54.1 (d, J_{C-P}=6.2 Hz), 61.5 (d, J_{C-P}=202 Hz), 65.9, 126.7 (d, J_{C-P}=2.7 Hz), 128.6, 128,7, 129.2, 131.5 (d, J_{C-P}=15 Hz), 133.6, 135.1, 138.6, 190.2. ^{31}P NMR: 16.853. Anal. calcd. for $C_{18}H_{19}O_5P$: C, 62.43; H, 5.53. Found: C, 62.36; H, 5.57.

3.2.9.4 Dimethyl 3-benzoyl-2-p-tolyloxiran-2-ylphosphonate (*cis*-155b):

Yield: (73mg, 21%), white solid (mp=129 °C), IR (KBr): 3003, 2362, 1656, 1233, 1041 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (3H, s), 3.66 (3H, d, *J*=10.7 Hz), 3.79 (3H, d, *J*=10.5 Hz), 4.66 (1H, d, *J*=5.5 Hz), 6.92-7.82 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 21.2, 54.1 (d, J_{C-P}=7.4 Hz), 54.2 (d, J_{C-P}=6.9 Hz), 61.1 (d, J_{C-P}=197

Hz), 62.0, 65.9, 126.7, 127.5 (d, J_{C-P}=2.8 Hz), 128.6, 128.7, 133.6, 135.1, 138.3, 189.7. ^{31}P NMR: 16.799. Anal. calcd. for $C_{18}H_{19}O_5P$: C, 62.43; H, 5.53. Found: C, 62.46; H, 5.51.

3.2.9.5 Dimethyl 3-benzoyl-2-m-tolyloxiran-2-ylphosphonate (*trans*-155c):

Yield: (100mg, 29%), white solid (mp=112 °C), IR (KBr): 2999, 2344, 1631, 1246, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 3.50 (3H, s), 3.53 (3H, s), 3.90 (1H, d, *J*=4.1 Hz), 7.13-8.05 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 21.6, 54.1 (d, J_{C-P}=7.2 Hz), 54.8 (d, J_{C-P}=6.5 Hz), 62.5 (d, J_{C-P}=202 Hz), 66.4, 124.7 (d, J_{C-P}=3.0 Hz), 128.6 (d, J_{C-P}=3.2 Hz), 129.4, 129.6, 130.7, 134.9, 135.1, 135.7, 139.5, 192.2. ^{31}P NMR: 16.271. Anal. calcd. for $C_{18}H_{19}O_5P$: C, 62.43; H, 5.53. Found: C, 62.49; H, 5.47.

3.2.9.6 Dimethyl 3-benzoyl-2-m-tolyloxiran-2-ylphosphonate (*cis*-155c):

Yield: (52mg, 15%), white solid (mp=120 °C), IR (KBr): 2989, 2339, 1640, 1240, 1043 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (3H, s), 3.67 (3H, d, *J*=10.5 Hz), 3.80 (3H, d, *J*=10.5 Hz), 4.64 (1H, d, *J*=5.6 Hz), 6.91-7.82 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 21.3, 54.2 (d, J_{C-P}=6.1 Hz), 54.3 (d, J_{C-P}=6.4 Hz), 61.1 (d, J_{C-P}=198 Hz), 61.6, 124.7 (d, J_{C-P}=2.9 Hz), 127.9, 128.2, 128.6, 129.6, 133.6, 135.2, 137.6, 189.8; ^{31}P NMR: 16.799. Anal. calcd. for $C_{18}H_{19}O_5P$: C, 62.43; H, 5.53. Found: C, 62.45; H, 5.46.

3.2.9.7 Dimethyl 3-benzoyl-2-(4-chlorophenyl)oxiran-2-ylphosphonate (trans-155d):

Yield: (104mg, 31%), white solid (mp=123 °C), IR (KBr): 3005, 2357, 1663, 1255, 1068 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (3H, d, *J*=3.0 Hz), 3.62 (3H, d, *J*=3.0 Hz), 3.90 (1H, d, *J*=4.0 Hz), 7.41-8.01 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.5 (d, J_{C-P}=7.5 Hz), 54.2 (d, J_{C-P}=6.1 Hz), 61.0 (d, J_{C-P}=202 Hz), 65.9, 128.2 (d, J_{C-P}=2.7 Hz), 128.6, 128.7, 128.9, 132.8 (d, J_{C-P}=15.3 Hz), 133.8, 134.9, 135.1, 189.9; ^{31}P NMR: 15.552. Anal. calcd. for $C_{17}H_{16}ClO_5P$: C, 55.68; H, 4.40. Found: C, 55.73; H, 4.36.

3.2.9.8 Dimethyl 3-benzoyl-2-(4-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155d):

Yield: (58mg, 17 %), white solid (mp=126 °C), IR (KBr): 3010, 2359, 1669, 1253, 1063 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (3H, d, *J*=10.7 Hz), 3.83 (3H, d, *J*=10.7 Hz), 4.68 (1H, d, *J*=5.5 Hz), 7.11-7.80 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 54.2 (d, $J_{C\text{-}P}$=7.4 Hz), 54.3 (d, $J_{C\text{-}P}$=7.4 Hz), 60.8 (d, $J_{C\text{-}P}$=195 Hz), 61.7, 127.6, 127.9, 128.3, 128.5 (d, $J_{C\text{-}P}$=2.9 Hz), 134.4, 134.5, 188.9; ^{31}P NMR: 16.231. Anal. calcd. for $C_{17}H_{16}ClO_5P$: C, 55.68; H, 4.40. Found: C, 55.63; H, 4.43.

3.2.9.9 Dimethyl 3-benzoyl-2-(3-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155e):

Yield: (91mg, 27%), white solid (mp=124 °C), IR (KBr): 3012, 2347, 1651, 1243, 1067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, d, *J*=4.4 Hz), 3.54 (3H, d, *J*=4.6 Hz), 3.81 (1H, d, *J*=3.91 Hz), 7.28-7.99 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.5 (d, $J_{C\text{-}P}$=7.4 Hz), 54.2 (d, $J_{C\text{-}P}$=6.2 Hz), 60.9 (d, $J_{C\text{-}P}$=202 Hz), 65.9, 125.0 (d, $J_{C\text{-}P}$=2.6 Hz), 126.6 (d, $J_{C\text{-}P}$=3.2 Hz), 128.6, 128.7, 129.2, 129.8, 133.8, 134.8 (d, $J_{C\text{-}P}$=4.6 Hz), 136.6, 189.8; ^{31}P NMR: 15.466. Anal. calcd. for $C_{17}H_{16}ClO_5P$: C, 55.68; H, 4.40. Found: C, 55.55; H, 4.31.

3.2.9.10 Dimethyl 3-benzoyl-2-(3-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155e):

Yield: (47mg, 14%), white solid (mp=129-130 °C), IR (KBr): 3004, 2356, 1659, 1255, 1071 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (3H, d, *J*=10.7 Hz), 3.84 (3H, d, *J*=10.7 Hz), 4.67 (1H, d, *J*=5.5 Hz), 7.06-7.80 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 54.2 (d, $J_{C\text{-}P}$=7.5 Hz), 54.3 (d, $J_{C\text{-}P}$=7.5 Hz),60.4(d, $J_{C\text{-}P}$=198 Hz), 61.7, 125.8, 127.8 (d, $J_{C\text{-}P}$=2.8 Hz), 128.1, 128.7, 129.1 (d, $J_{C\text{-}P}$=10.9 Hz), 131.8, 132.0, 133.9, 134.2, 135.0, 189.4; ^{31}P NMR: 16.147. Anal. calcd. for $C_{17}H_{16}ClO_5P$: C, 55.68; H, 4.40. Found: C, 55.59; H, 4.34.

3.2.9.11Dimethyl 3-benzoyl-2-(2-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155f):

Yield: (88mg, 24%), white solid (mp=127 °C), IR (KBr): 3017, 2369, 1685, 1246, 1064 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56 (3H, d, *J*=11.0 Hz), 3.59 (3H, d, *J*=13.0 Hz), 4.11 (1H, d, *J*=5.0 Hz), 7.19-8.14 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.7 (d, J_{C-P}=7.1 Hz), 54.3 (J_{C-P}=6.2 Hz), 61.5 (d, J_{C-P}=205 Hz), 64.7, 126.9, 128.6, 128.9, 129.6, 130.4, 130.7 (d, J_{C-P}=2.0 Hz), 133.5, 133.7, 135.7, 191.5; ^{31}P NMR: 16.234. Anal. calcd. for $C_{17}H_{16}ClO_5P$: C, 55.68; H, 4.40. Found: C, 55.59; H, 4.46.

3.2.9.12 Dimethyl 3-benzoyl-2-(2-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155f):

Yield: (48mg, 13%), white solid (mp=130 °C), IR (KBr): 3011, 2361, 1679, 1241, 1059 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (3H, d, *J*=11.0 Hz), 3.83 (3H, d, *J*=11.0 Hz), 5.12 (1H, d, *J*=5.0 Hz), 7.11-7.94 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 54.4 (d, J_{C-P}=7.5 Hz), 54.6 (d, J_{C-P}=6.4 Hz), 59.8, 62.6 (d, J_{C-P}=203 Hz), 126.9, 128.5, 128.6, 129.2, 129.7 (d, J_{C-P}=12.2 Hz), 130.2, 131.5 (d, J_{C-P}=2.6 Hz), 133.0, 133.7, 135.9, 189.8; ^{31}P NMR: 16.206. Anal. calcd. for $C_{17}H_{16}ClO_5P$: C, 55.68; H, 4.40. Found: C, 55.61; H, 4.36.

3.2.9.13 Dimethyl 3-benzoyl-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155g):

Yield: (149mg, 41%), white solid (mp=121 °C), IR (KBr): 3015, 2341, 1661, 1253, 1055 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 (3H, s), 3.51 (3H, s), 3.74 (3H, s), 3.83 (1H, d, *J*=3.9 Hz), 6.86-8.02 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.3 (d, J_{C-P}=7.2 Hz), 54.1 (d, J_{C-P}=6.5 Hz), 55.0, 61.3 (d, J_{C-P}=202 Hz), 65.9, 114.0, 126.2 (d, J_{C-P}=14.3 Hz), 128.2 (d, J_{C-P}=2.7 Hz), 128.5, 128.7, 133.6, 135.0, 160.1, 190.3; ^{31}P NMR: 16.853. Anal. calcd. for $C_{18}H_{19}O_6P$: C, 59.67; H, 5.29. Found: C, 59.75; H, 5.23.

3.2.9.14 Dimethyl 3-benzoyl-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155g):

Yield: (80mg, 22%), white solid (mp=127 °C), IR (KBr): 3009, 2351, 1654, 1257, 1065 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.67 (3H, d, *J*=10.6 Hz), 3.79 (3H, d, *J*=10.6 Hz), 4.65 (1H, d, *J*=5.4 Hz), 6.64-7.81 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 54.1 (d, J_{C-P}=2.8 Hz), 54.2 (d, J_{C-P}=3.0 Hz), 54.7, 60.8 (d, J_{C-P}=199 Hz), 61.8, 113.5, 121.4 (d, J_{C-P}=15 Hz), 128.1, 128.6, 128.9 (d, J_{C-P}=2.7 Hz), 133.6, 135.1, 159.8, 189.7; ^{31}P NMR: 16.826. Anal. calcd. for $C_{18}H_{19}O_6P$: C, 59.67; H, 5.29. Found: C, 59.71; H, 5.33.

3.2.9.15 Dimethyl 3-benzoyl-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-155h):

Yield: (147 mg, 42 %), white solid (mp=116-117 °C), IR (KBr): 2969, 2320, 1658, 1220, 1061 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49 (3H, s), 3.52(3H, s), 3.80 (1H, d, *J*=3.9 Hz), 7.10-8.01 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.3 (d, J_{C-P}=7.2 Hz), 54.1 (d, J_{C-P}=6.5 Hz), 61.3 (d, J_{C-P}=204 Hz), 66.5, 116.4 (d, J_{C-P}=21.7 Hz), 129.4, 129.5, 129.6, 131.0 (d, J_{C-P}=15.1 Hz), 135.0, 135.6, 164.1 (d, J_{C-F}=248 Hz), 191.7. ^{31}P NMR: 15.891 Anal. calcd. for. $C_{17}H_{16}FO_5P$: C, 58.29; H, 4.60. Found: C, 58.21; H, 4.50.

3.2.9.16 Dimethyl (Z)-3-benzoyl-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-155h):

Yield: (95 mg, 27 %), white solid (mp=123 °C), IR (KBr): 2981, 2335, 1660, 1229, 1046 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, d, *J*=10.6 Hz), 3.84 (3H, d, *J*=10.6 Hz), 4.69 (1H, d, *J*=5.4 Hz), 6.83-7.82 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 54.3 (d, J_{C-P}=7.2 Hz), 54.4 (d, J_{C-P}=7.2 Hz), 60.6 (d, J_{C-P}=199 Hz), 61.7, 115.3 (d, J_{C-P}=21.8 Hz), 125.5 (d, J_{C-P}=14.8 Hz), 128.2, 128.8, 129.6 (d, J_{C-P}=7.6 Hz), 133.9, 135.0, 163.1(d, J_{C-F}=249 Hz), 189.8; ^{31}P NMR: 16.476. Anal. calcd. for. $C_{17}H_{16}FO_5P$: C, 58.29; H, 4.60. Found: C, 58.26; H, 4.46.

3.2.9.17 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-155i):

Yield: (136mg, 31%), white solid (mp=115 °C), IR (KBr): 3001, 2348, 1657, 1213, 1049 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (3H, s), 3.55 (3H, s), 3.84 (1H, d, *J*=4.0 Hz), 7.03-7.90 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.6 (d, J_{C-P}=7.4 Hz), 54.4 (d, J_{C-P}=6.3 Hz), 61.2 (d, J_{C-P}=203 Hz), 65.7, 115.9 (d, J_{C-P}=21.7 Hz), 128.7 (d, J_{C-P}= 9.4 Hz) , 129.4, 129.8 (d, J_{C-P}=15.1 Hz), 130.2, 132.2, 133.7, 163.1 (d, J_{C-F}=247 Hz), 189.9; ^{31}P NMR: 15.976. Anal. calcd. for $C_{17}H_{15}BrFO_5P$: C, 47.58; H, 3.52. Found: C, 47.46; H, 3.61.

3.2.9.18 Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2ylphosphonate (*cis*-155i):

Yield: (88mg, 20%), white solid (mp=121 °C), IR (KBr): 2990, 2363, 1644, 1227, 1067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (3H, d, *J*=11.0 Hz), 3.81 (3H, d, *J*=11.0 Hz), 4.66 (1H, d, *J*=6.0 Hz), 6.82-7.72 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.4 (d, J_{C-P}=4.9 Hz), 53.6 (J_{C-P}=7.0 Hz), 58.8 (d, J_{C-P}=200 Hz), 60.7, 114.4 (d, J_{C-P}=21.8 Hz), 124.3, 124.5, 128.5, 128.6, 131.2, 132.6, 160.7 (d, J_{C-F}=247 Hz), 188.5; ^{31}P NMR: 16.288. Anal. calcd. for $C_{17}H_{15}BrFO_5P$: C, 47.58; H, 3.52. Found: C, 47.51 ; H, 3.44.

3.2.9.19 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-155j):

Yield: (141mg, 33%), white solid (mp=119 °C), IR (KBr): 3011, 2344, 1660, 1226, 1045 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (3H, d, *J*=2.4 Hz), 3.66 (3H, d, *J*=2,4 Hz), 4.01 (1H, d, *J*=4.2 Hz), 7.14-8.20 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.7 (d, J_{C-P}=7.1 Hz), 54.4 (J_{C-P}=6.4 Hz), 61.2 (d, J_{C-P}=203 Hz), 66.1, 115.8 (d, J_{C-P}=21.6 Hz), 127.3, 127.4, 128.5, 128.8 (d, J_{C-P}=2.7 Hz), 128.9 (d, J_{C-P}=2.7 Hz), 129.0, 129.3, 133.6, 139.7, 146.8, 163.1 (d, J_{C-F}=247 Hz), 190.2; ^{31}P NMR: 16.62. Anal. calcd. for $C_{23}H_{20}FO_5P$: C, 64.58; H, 4.73. Found: C, 64.62 ; H, 4.65.

3.2.9.20 Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-155j):

Yield: (81mg, 19%), white solid (mp=125-126 °C), IR (KBr): 2995, 2351, 1671, 1231, 1054 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, d, *J*=10.0 Hz), 3.83 (3H, d, *J*=11.0 Hz), 4.75 (1H, d, *J*=5.0 Hz), 6.82-7.90 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.4 (d, J_{C-P}=6.3 Hz), 53.5 (d, J_{C-P}=7.2 Hz), 58.8 (d, J_{C-P} =198 Hz), 60.8, 114.4 (d, J_{C-P}=21.8 Hz) 126.2, 126.4, 127.5, 127.8, 128.0, 128.6 (d, J_{C-P}=2.7 Hz), 128.7 (d, J_{C-P}=2.7 Hz), 132.7, 138.5, 145.8, 162.9 (d, J_{C-F}=247 Hz), 188.7; ^{31}P NMR: 16.288. Anal. calcd. for $C_{23}H_{20}FO_5P$: C, 64.58; H, 4.73. Found: C, 64.45; H, 4.80.

3.2.9.21 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155k):

Yield: (132 mg, 30%), white solid (mp=121 °C), IR (KBr): 2987, 2359, 1675, 1241, 1047 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 3.54 (3H, s), 3.76 (3H, s), 3.86 (1H, d, *J*=4.0 Hz), 6.87-7.92 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 52.6 (d, J_{C-P}=7.5 Hz), 53.3 (J_{C-P}=6.2 Hz), 54.4, 60.5 (d, J_{C-P}=202 Hz), 64.7, 113.2, 124.9 (d, J_{C-P}=14.9 Hz), 127.3, 128.3, 129.2, 131.1, 132.8, 159.3 189.2; ^{31}P NMR: 17.028. Anal. calcd. for $C_{18}H_{18}BrO_6P$: C, 49.00; H, 4.11. Found: C,49.12 ; H, 4.16.

3.2.9.22 Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155k):

Yield: (71mg, 16%), white solid (mp=128 °C), IR (KBr): 2990, 2365, 1673, 1248, 1044 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (3H, s), 3.67 (3H, d, *J*=11.0 Hz), 3.80 (3H, d, *J*=11.0 Hz), 4.64 (1H, d, *J*=5.0 Hz), 6.65-7.70 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 53.4 (d, J_{C-P}=5.5 Hz), 53.5 (d, J_{C-P}=2.8 Hz), 54.1, 59.1, 60.1 (d, J_{C-P}=200 Hz), 112.8, 120.3 (d, J_{C-P}=13.8 Hz), 127.9 (d, J_{C-P}=2.9 Hz), 128.4, 128.7, 131.2, 132.8, 159.0, 188.4; ^{31}P NMR: 16.741. Anal. calcd. for $C_{18}H_{18}BrO_6P$: C, 49.00; H, 4.11. Found: C, 49.08; H, 4.21.

3.2.9.23 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155l):

Yield: (118mg, 27%), white solid (mp=123 °C), IR (KBr): 3000, 2341, 1679, 1243, 1052 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.51 (3H, d, *J*=1.0 Hz), 3.56 (3H, d, *J*=1.0 Hz), 3.76 (3H, s), 3.92 (1H, d, *J*=4.0 Hz), 6.88-8.12 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$): 54.1 (d, J_{C-P}=7.2 Hz), 54.8 (d, J_{C-P}=6.5 Hz), 55.7, 61.9 (d, J_{C-P}= 204 Hz), 66.6, 114.9, 126.9 (d, J_{C-P}=14.8 Hz), 128.1, 128.2, 129.1 (d, J_{C-P}=3.1 Hz), 129.3, 129.8, 130.2, 134.4, 140.6, 147.6, 161.2, 191.7; ^{31}P NMR: 20.800. Anal. calcd. for $C_{24}H_{23}O_6P$: C, 65.75; H, 5.29. Found: C, 65.67; H, 5.21.

3.2.9.24 Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155l):

Yield: (66mg, 15%), white solid (mp=128 °C), IR (KBr): 3012, 2361, 1682, 1255, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.68 (3H, d, *J*=11.0 Hz), 3.82 (3H, d, *J*=11.0 Hz), 4.74 (1H, d, *J*=6.0 Hz), 6.66-7.93 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8 (d, J_{C-P}=5.8 Hz), 55.9 (J_{C-P}=4.8 Hz), 56.5, 62.6 (d, J_{C-P}=200 Hz), 63.3, 115.2, 122.9 (d, J_{C-P}=14.8 Hz), 128.7 (d, J_{C-P}=15.1 Hz), 129.9, 130.2, 130.4 (d, J_{C-P}=14.8 Hz), 130.5, 133.6, 135.3, 140.9, 148.0, 161.4, 191.4; P NMR: 17.594. Anal. calcd. for $C_{24}H_{23}O_6P$: C, 65.75; H, 5.29. Found: C, 65.79; H, 5.33.

3.2.9.25 N-(3-(2-oxoazepan-1-yl)propyl)benzamide (159):

Oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.64 (8H, m), 2.45 (3H, s), 2.48 (2H, m), 3.29 (4H, m), 3.42 (2H, m), 7.12 (2H, d, *J*=7.9 Hz), 7.74 (2H, *J*=7.9 Hz), 7.79 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$): 21.4, 23.4, 27.1, 28.5, 30.0, 35.2, 37.0, 45.0, 49.5, 127.1, 128.9, 131.8, 140.9, 166.4, 176.7. Anal. calcd for. $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21; Found: C, 70.10; H, 8.11; N, 10.18.

3.2.9.26 Dimethyl-1-(1-phenyletanonxy-prop-1-ene phosphonate(162):

Oil, ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, dd, *J*= 2.6 Hz, *J*=6.8 Hz), 3.65 (3H, s), 3.67 (3H, s), 5.13 (2H, s), 6.07 (1H, m), 7.38-7.91 (5H, m); ^{13}C NMR (100 MHz,

$CDCl_3$): 11.1, 11.3, 52.7, 76.7, 127.8, 128.7, 128.9, 129.9, 133.6, 134.6, 143.2, 145.3, 194.2.^{31}P NMR: 14.08. Anal. calcd for. $C_{13}H_{17}O_5P$: C, 54.93; H, 6.03; Found: C, 54.89; H, 6.10.

3.2.9.27 Dimethyl 3-(1-hydroxy-1-phenylethyl)-2-phenyloxiran-2-ylphosphonate (163):

Oil, IR (neat): 3430, 3010 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (3H, s), 3.48 (3H, s), 3.65 (3H, d, *J*=10.6 Hz), 3.82 (3H, d, *J*=10.6 Hz), 3.93 (1H, d, *J*=5.0 Hz), 6.99 (H, bs, *OH*) 7.11-7.25 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 30.6, 53.7 (d, J_{C-P}=6.5 Hz), 53.9 (J_{C-P}=6.9 Hz), 56.5, 60.1 (d, J_{C-P}=201 Hz), 66.5, 71.6, 124.7, 127.2, 127.8, 127.9, 128.1,128.4 (d, J_{C-P}=14.8 Hz),131.5 (d, J_{C-P}=11.5 Hz), 144.0. ^{31}P NMR: 17.594. Anal. calcd. for $C_{18}H_{21}O_5P$: C, 62.07; H, 6.08; Found: C, 62.10; H, 6.15.

3.2.9.28 Dimethyl 3-(hydroxy(phenyl)methyl)-2-phenyloxiran-2-ylphosphonate (164):

Oil, IR (Neat): 3495, 2996 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (1H, d, *J*= 4.2 Hz, *major*-isomer), 2.71 (1H, d, *J*=3.2 Hz, *minor*-isomer), 3.49 (3H, d, *J*=10.5 Hz, *minor*-isomer), 3.58 (3H, d, *J*=10.7 Hz, *major*-isomer), 3.62 (H, d, *J*=8.3 Hz, *major*-isomer), 3.63 (3H, d, *J*=10.5 Hz, *minor*-isomer), 3.67 (3H, d, *J*=10.7 Hz, *major*-isomer), 3.74 (H, d, *J*=8.3 Hzi *major*-isomer), 3.75 (H, d, *J*=8.3 Hz, *minor*-isomer), 3.91 (H, d, *J*=8.3 Hz, *minor*-isomer), 7.01-7.71 (20H, m, both-isomers). ^{13}C NMR (100 MHz, $CDCl_3$): 53.9-54.0 ($4CH_3$, m, both-isomers), 61.2 (d, J_{C-P}=197 Hz, *minor*-isomer), 61.3 (d, J_{C-P}=197 Hz, *major*-isomer), 64.0 (*major*-isomer), 65.0 (*minor*-isomer), 70.5 (*major*-isomer), 72.0 (*minor*-isomer), 126.1 (*major*-isomer), 126.7 (*minor*-isomer), 127.8 (d, J_{C-P}=3.1 Hz, minor-isomer), 128.0 (d, J_{C-P}=3.1 Hz, *major*-isomer), 128.1 ,128.2, 128.4, 128.5, 128.71, 128.75, 131.4 (d, J_{C-P}=13.6 Hz, *minor*-isomer), 131.7 (d, J_{C-P}=13.8 Hz, *major*-isomer), 138.5 (*minor*-isomer), 140.8 (*major*-isomer); ^{31}P NMR: 16.638, 16.567

CHAPTER 4

CONCLUSION

As a conlusion, in the first part of this thesis we were concentrated on the synthesis of highly functionalized pyrroles. Apart from this idea we described some novel methods for the synthesis of new 2-aminopyrroles, 5-alkoxypyrroles and pyrrolinones.

A convenient procedure for the preparation of 2-aminopyrrole derivatives is developed including the condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by p-TsOH to afford the corresponding enamines and subsequent base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond furnished 2-aminopyrroles in high yields.

Similarly, the reaction of α-cyanomethyl-β-ketoesters with amines in the presence of $Zn(ClO_4)_2$, results in the formation 2-aminopyrrole via the selective addition of the amine to nitrile with subsequent heteroannulation, likewise, when α-cyanomethyl-β-ketoesters reacts with alcohols, thiols or water, this reactions affords 5-alkoxy-, 5-alkylsulfanylpyrroles, and pyrrolinones respectively. The key point of these reactions is the selective activation of both C=O and CN bonds of α-cyanomethyl-β-ketoesters as electrophiles and nitriles as pronucleophiles.
Eventually all of these developed methods opens an entry for the selective synthesis of highly substituted pyrroles as well as pyrolinones, depending on the reaction conditions.

In the second part of this thesis we described a novel synthesis of epoxyphosphonates applying a Darzens type reaction to acyl phosphonates with α-bromo ketones in the

presence of different bases. The diastereoselectivity of this reaction is easily controlled by meas of chaniging the base. Apparently, changing the base from Cs_2CO_3 to DBU changed the diatereomeric ratio (*trans/cis*) from 3/2 to 9/1. Additionally, the treatment of *trans* isomer in the presence of DBU showed a complete conversion to the corresponding *cis* isomer. Moreover, these highly functionalized epoxyphosphonates are useful intermediates to give several reactions. These products with multifunctionality can be further converted to various interesting compounds. As a representative example, selective reduction of the carbonyl group and the methylation reaction is carried out by keeping the epoxide ring. We are currently investigating the precise origin of the diasterocontrol, in which the further application of these epoxides are currently under way.

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APPENDIX A

COPY OF ^{1}H and ^{13}C NMR SPECTRA

For all new compounds the spectral data is also available in corresponding publications [94, 95, 104, 106]

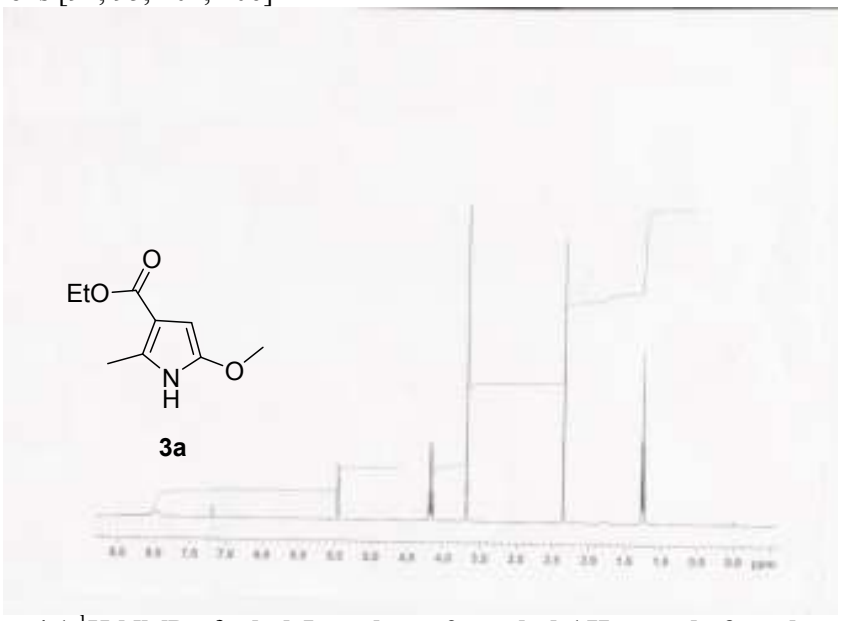

Figure 4.1 ^{1}H-NMR of **ethyl 5-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149a)**

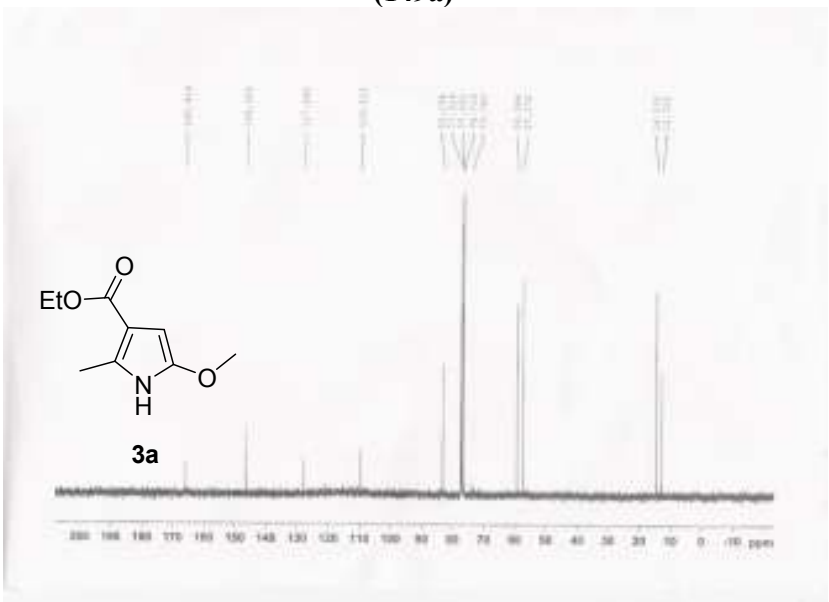

Figure 4.2 ^{13}C-NMR of **ethyl 5-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149a)**

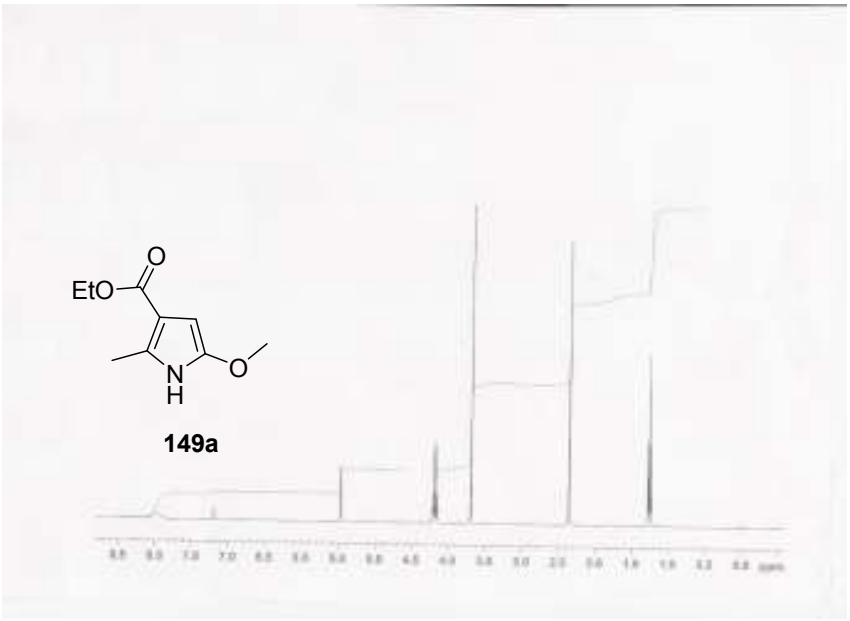

Figure 4.3 ^{1}H-NMR of **ethyl 5-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149a)**

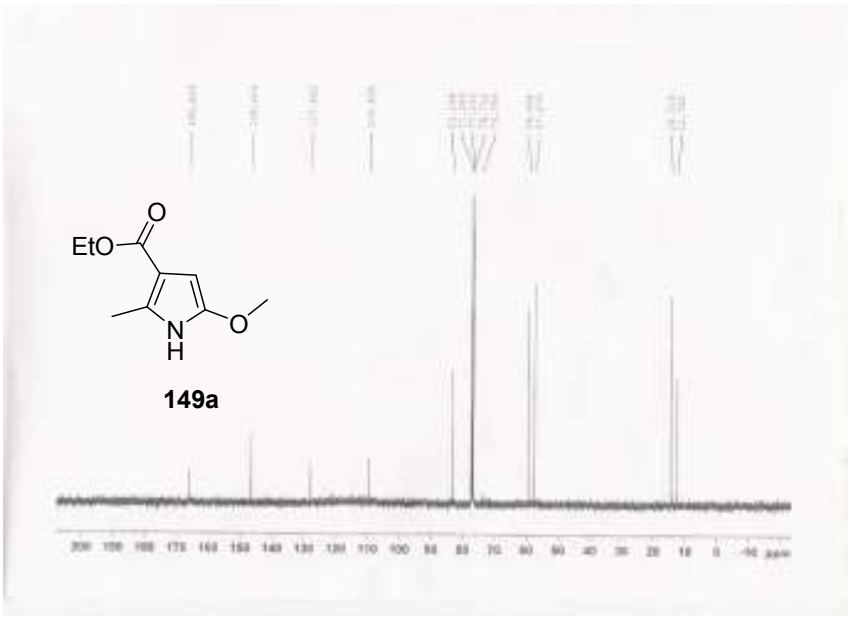

Figure 4.4 ^{13}C-NMR of **ethyl 5-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149a)**

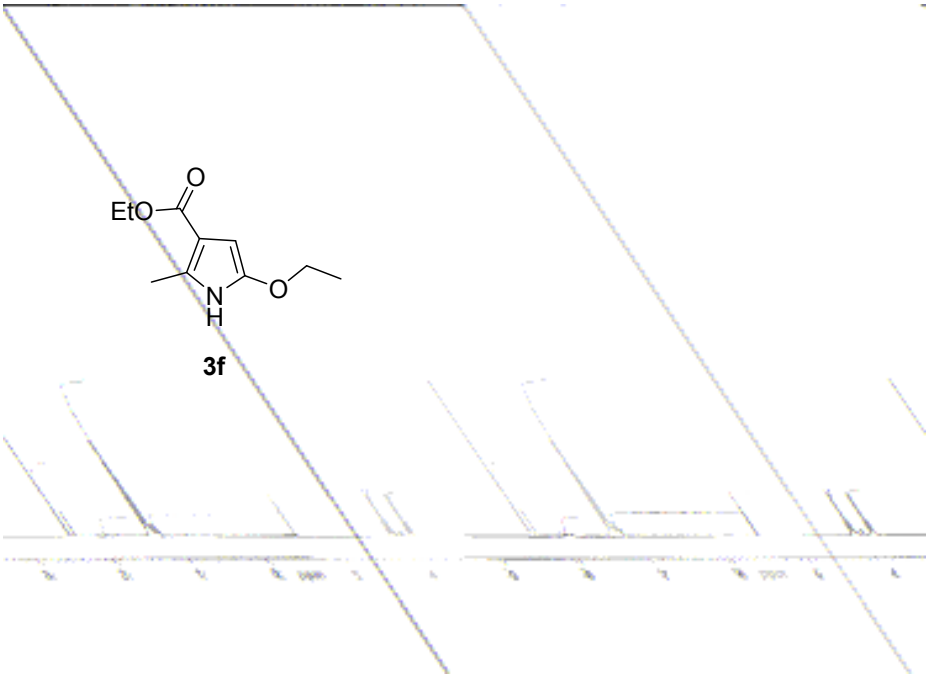

Figure 4.5 ^{1}H-NMR of **ethyl 5-ethoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149f)**

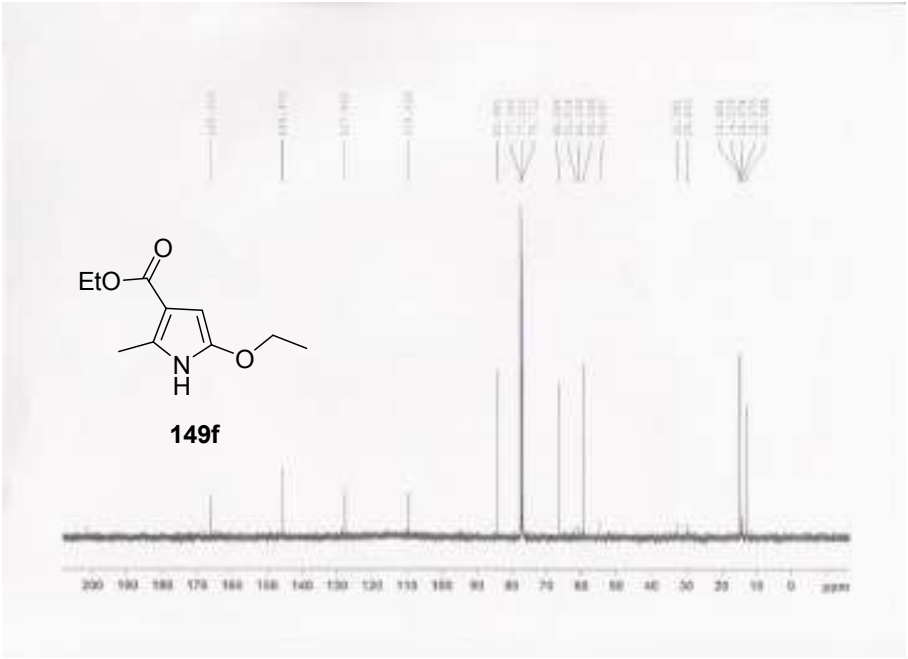

Figure 4.6 ^{13}C-NMR of **ethyl 5-ethoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149f)**

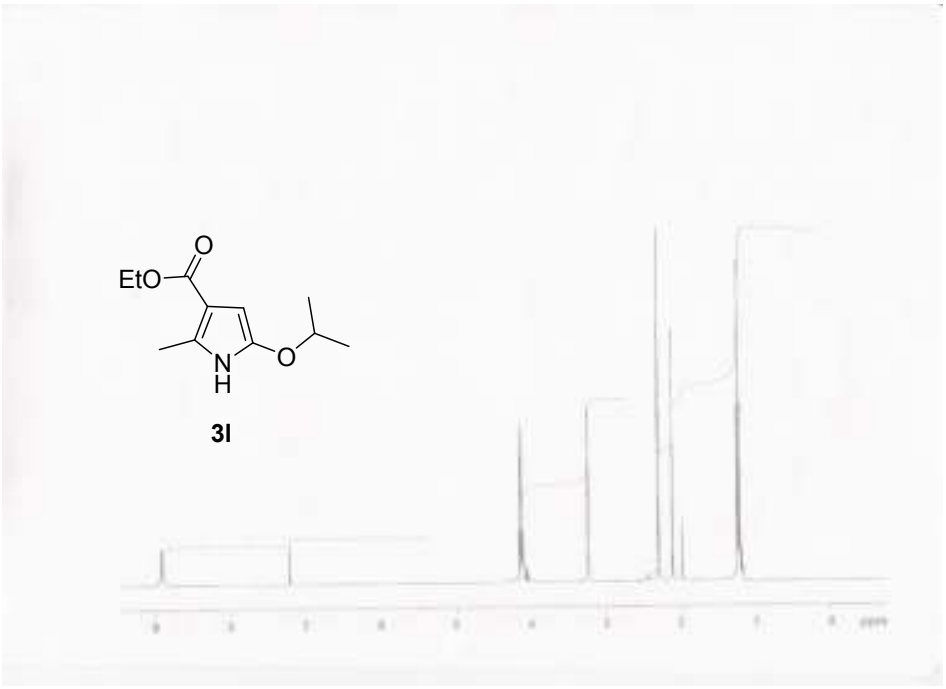

Figure 4.7 ^{1}H-NMR of **ethyl 5-isopropoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149l)**

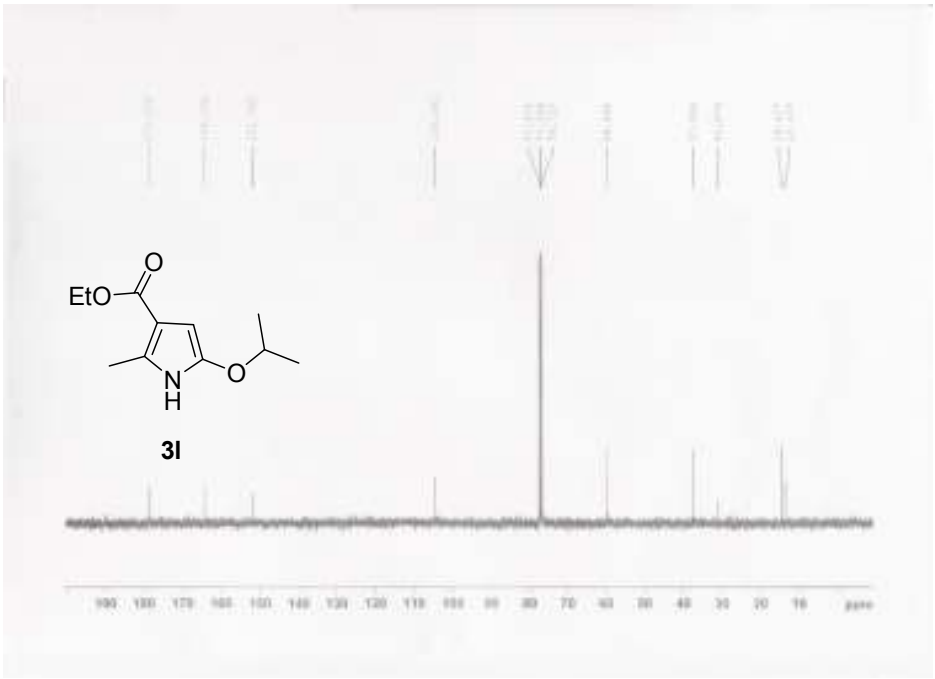

Figure 4.8 ^{13}C-NMR of **ethyl 5-isopropoxy-2-methyl-1*H*-pyrrole-3-carboxylate (149l)**

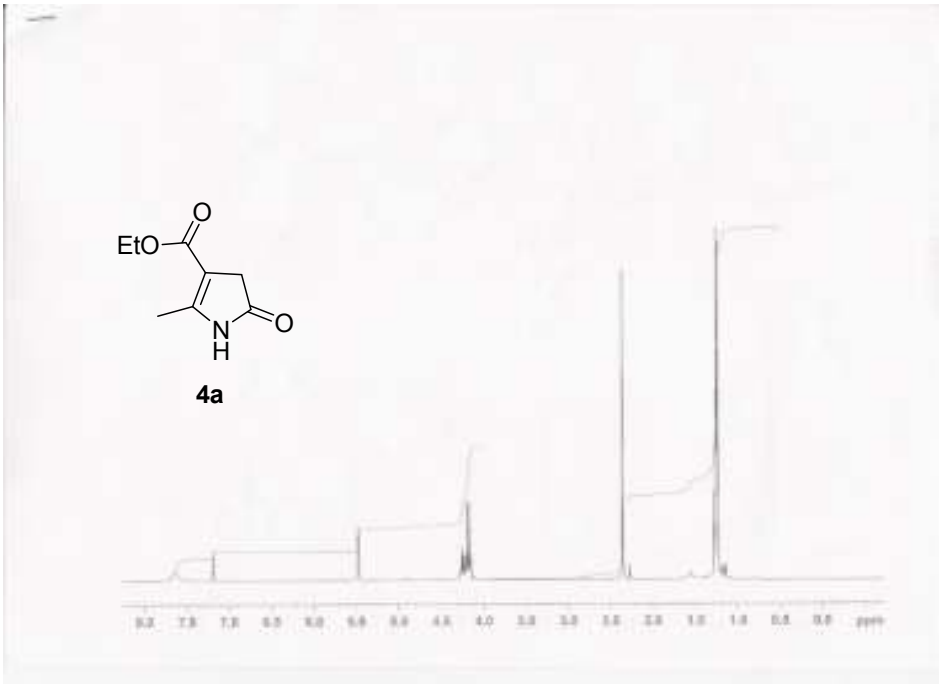

Figure 4.8 ^{1}H-NMR of **ethyl 4,5-dihydro-2-methyl-5-oxo-1*H*-pyrrole-3-carboxylate (150a)**

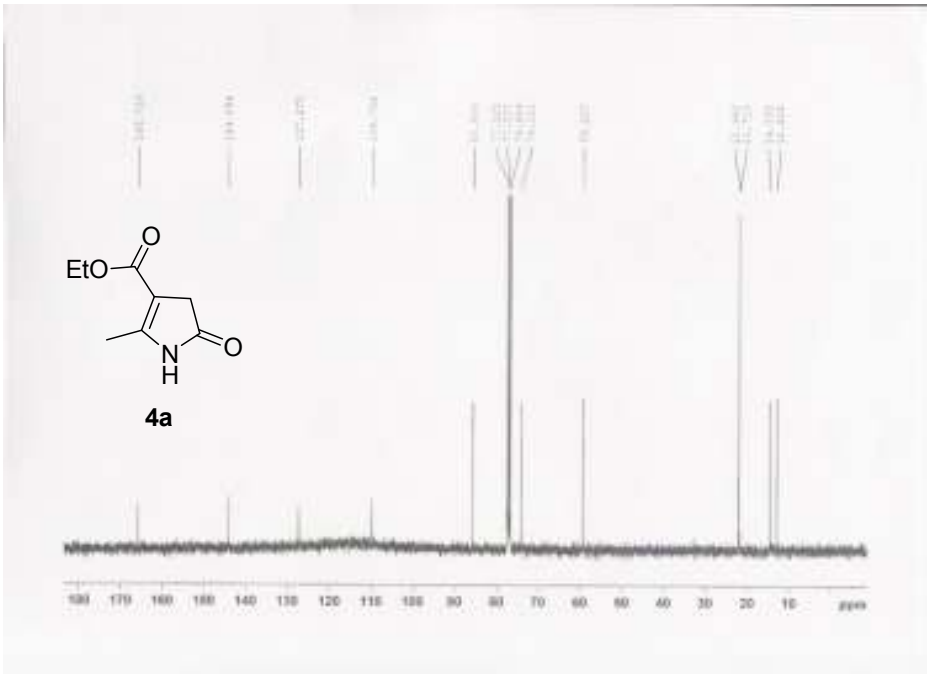

Figure 4.9 ^{13}C-NMR of **ethyl 4,5-dihydro-2-methyl-5-oxo-1*H*-pyrrole-3-carboxylate (150a)**

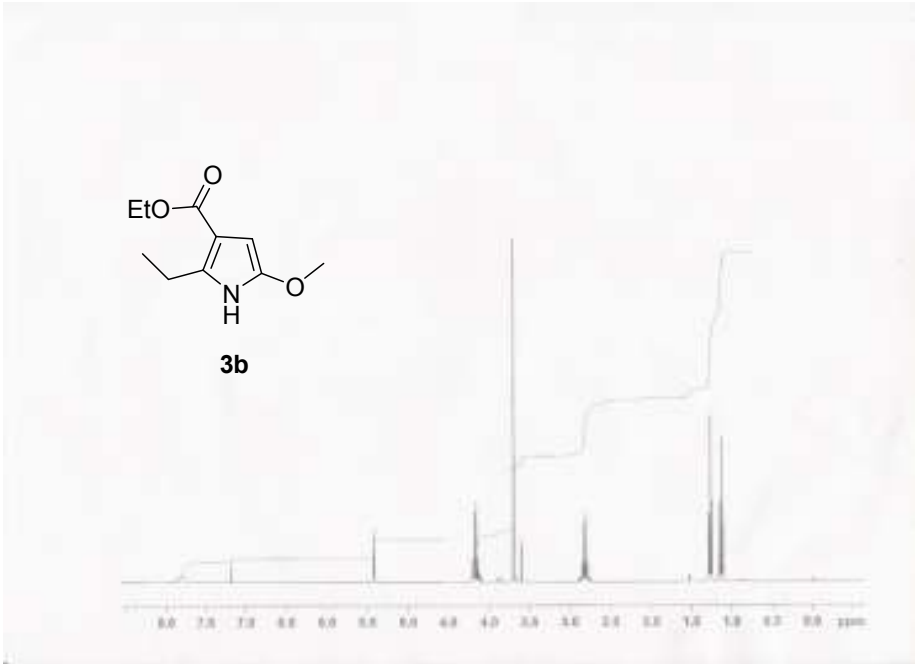

Figure 4.10 ^{1}H-NMR of **ethyl 2-ethyl-5-methoxy-1*H*-pyrrole-3-carboxylate (149b).**

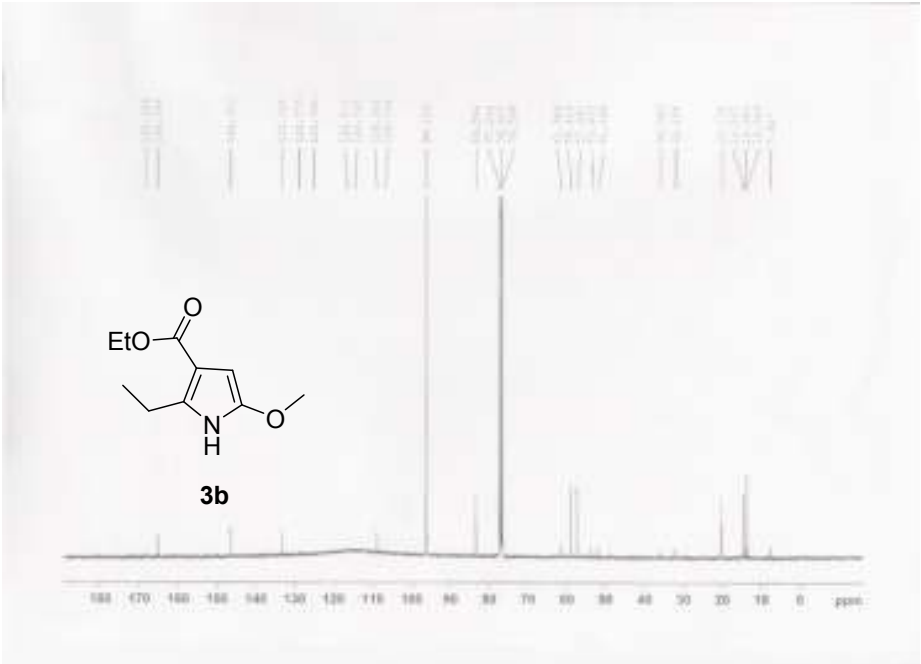

Figure 4.11 ^{13}C-NMR of **ethyl 2-ethyl-5-methoxy-1*H*-pyrrole-3-carboxylate (149b).**

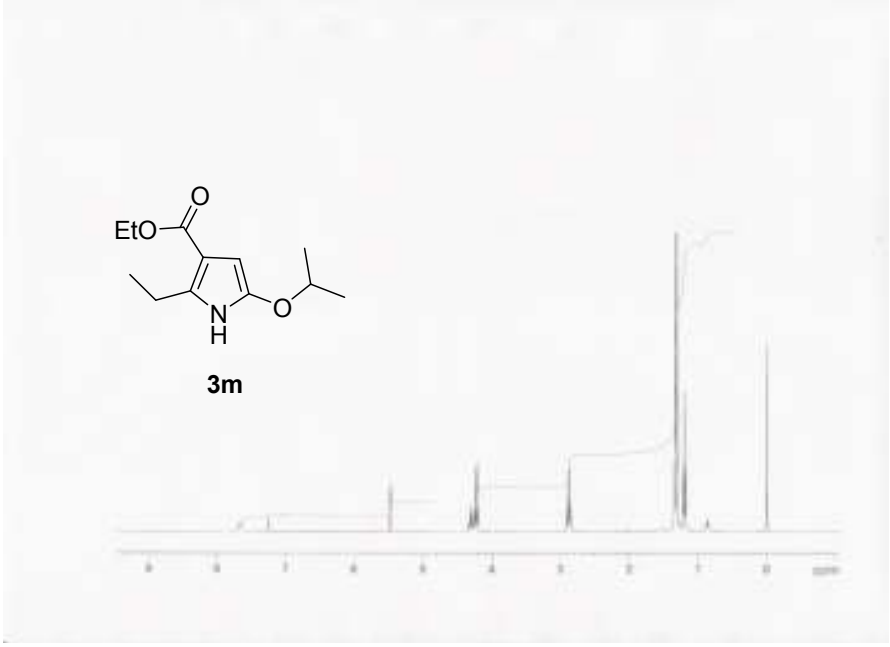

Figure 4.12 ^{1}H-NMR of **ethyl 2-ethyl-5-isopropoxy-1*H*-pyrrole-3-carboxylate (149m).**

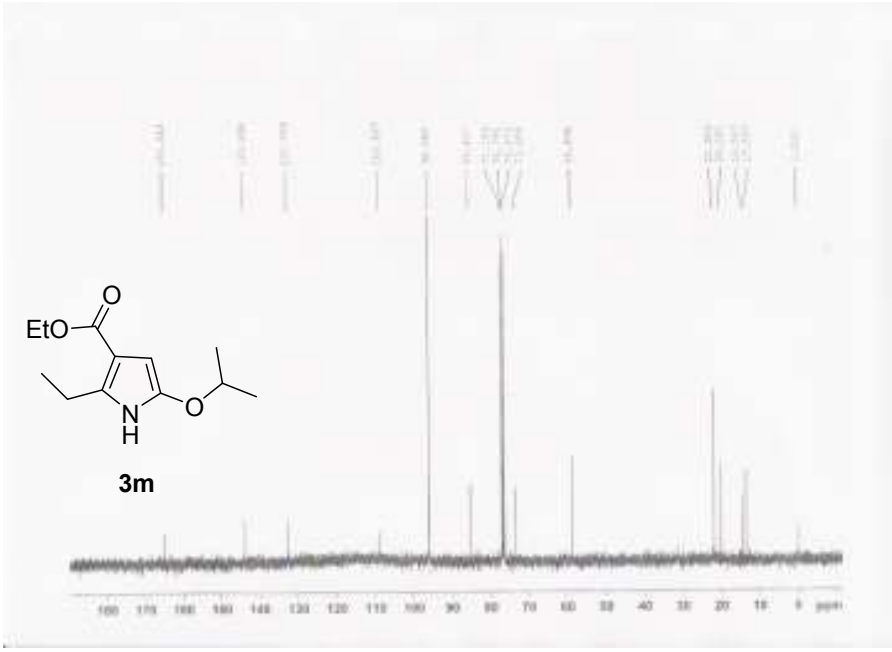

Figure 4.13 ^{13}C-NMR of **ethyl 2-ethyl-5-isopropoxy-1*H*-pyrrole-3-carboxylate (149m).**

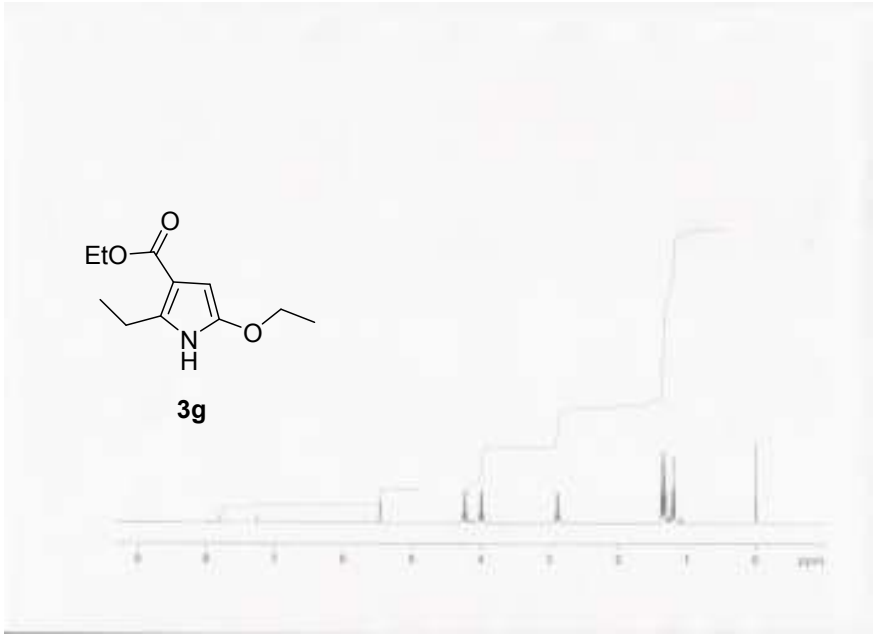

Figure 4.15 ^{1}H-NMR of **ethyl 5-ethoxy-2-ethyl-1*H*-pyrrole-3-carboxylate (149g).**

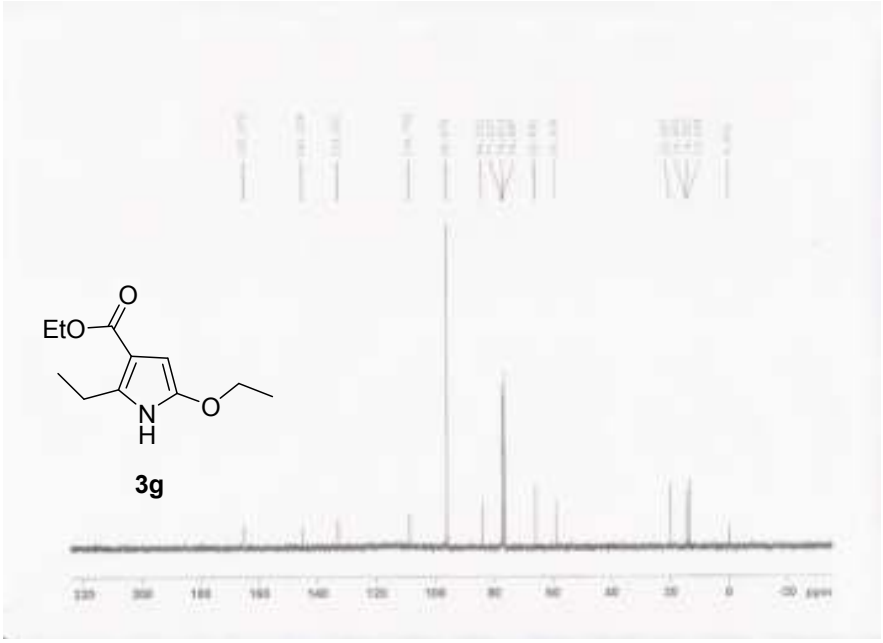

Figure 4.15 ^{13}C-NMR of **ethyl 5-ethoxy-2-ethyl-1*H*-pyrrole-3-carboxylate (149g).**

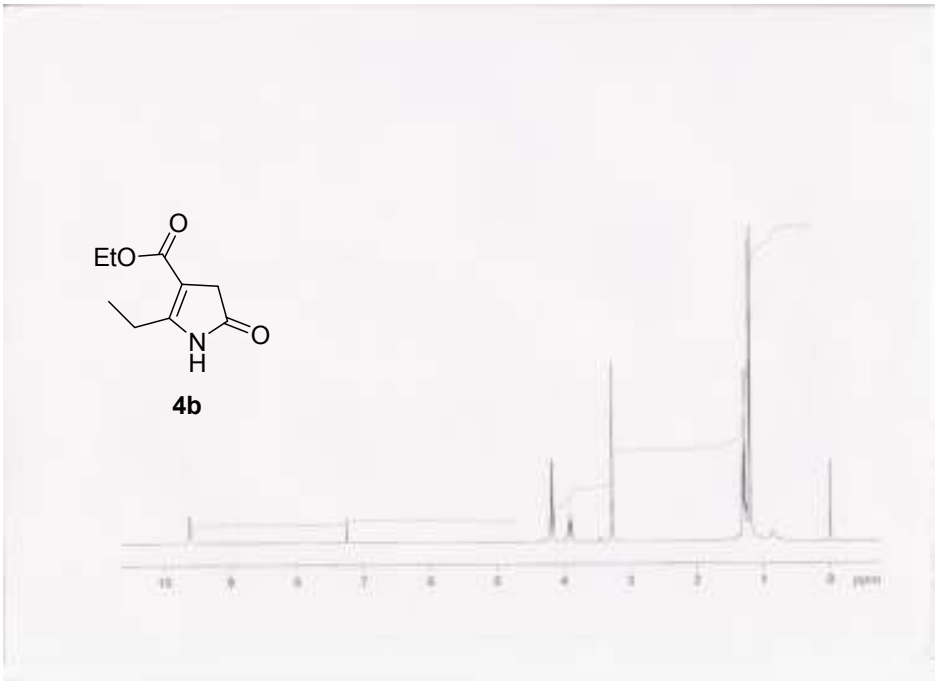

Figure 4.16 ^{1}H-NMR of **ethyl 2-ethyl-4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (150b).**

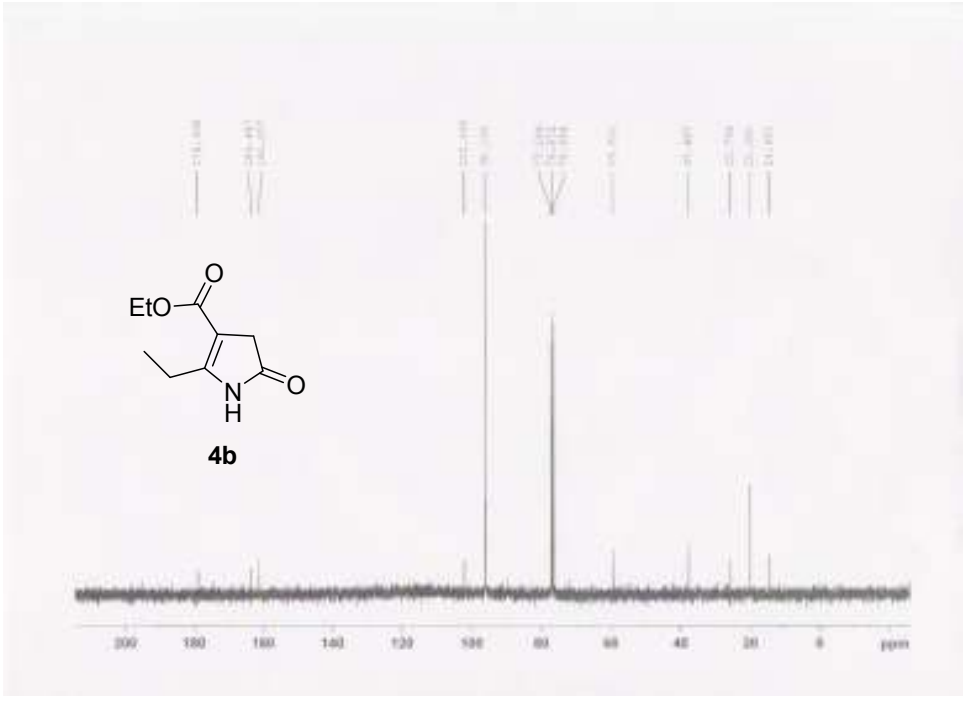

Figure 4.17 ^{13}C-NMR of **ethyl 2-ethyl-4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (4b).**

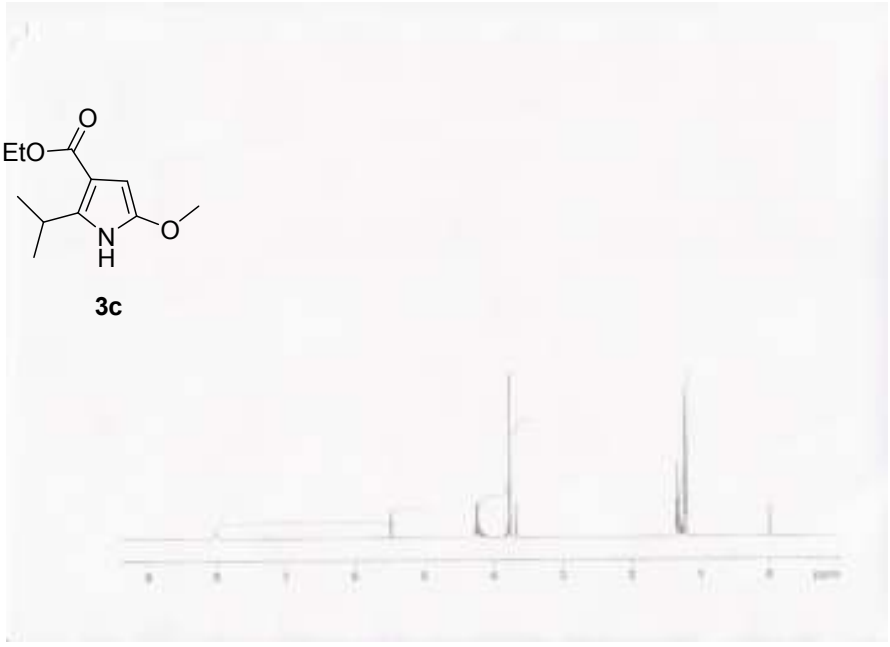

Figure 4.18 ^{1}H-NMR of **Ethyl 2-isopropyl-5-methoxy-1*H*-pyrrole-3-carboxylate (149c).**

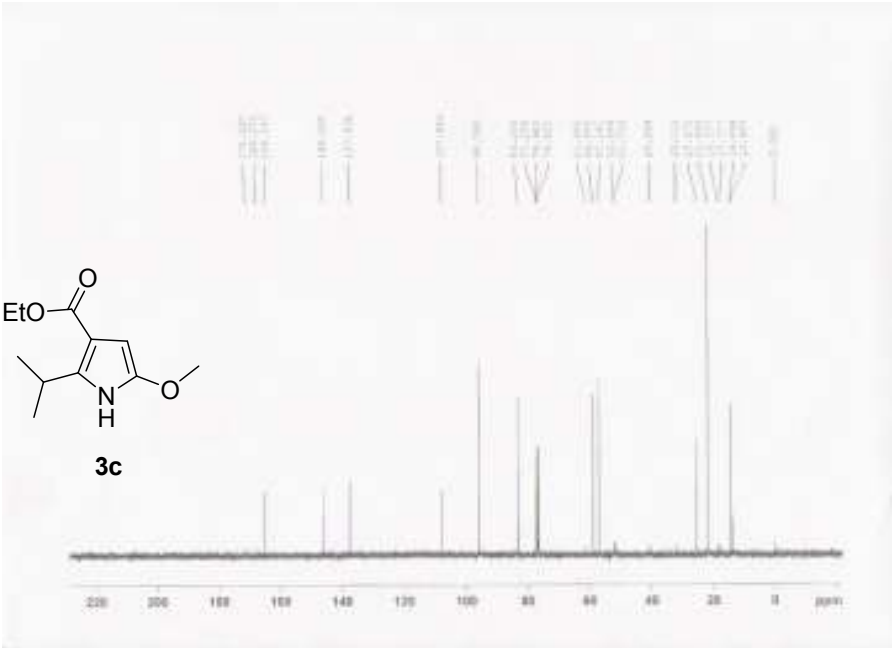

Figure 4.19 ^{13}C NMR of **Ethyl 2-isopropyl-5-methoxy-1*H*-pyrrole-3-carboxylate (149c).**

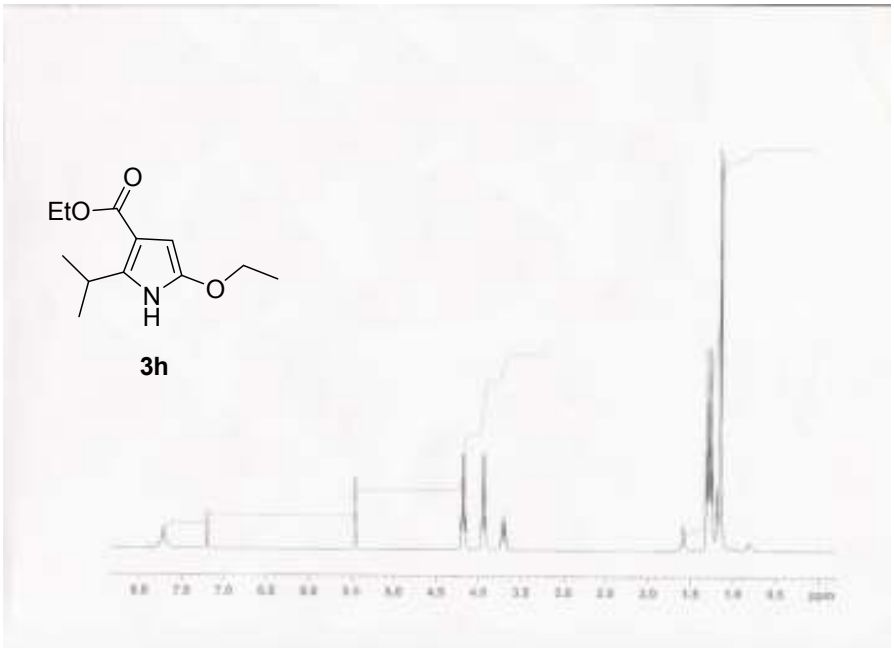

Figure 4.20 ^{1}H-NMR of **Ethyl 5-ethoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate (149h).**

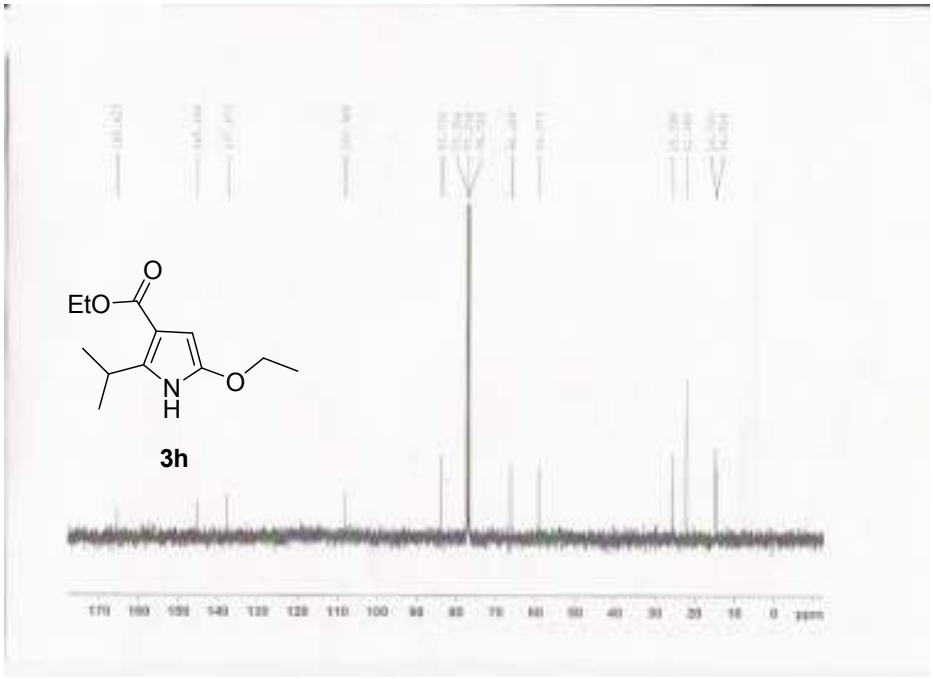

Figure 4.21 ^{13}C-NMR of **Ethyl 5-ethoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate (149h).**

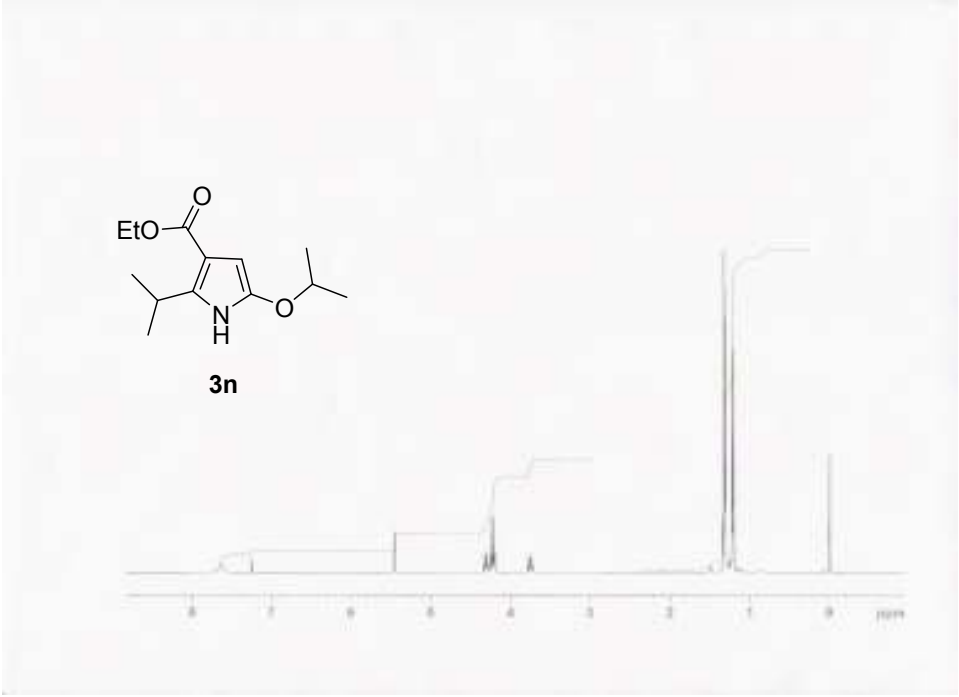

Figure 4.22 ^{1}H-NMR of **ethyl 5-isopropoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate (149n).**

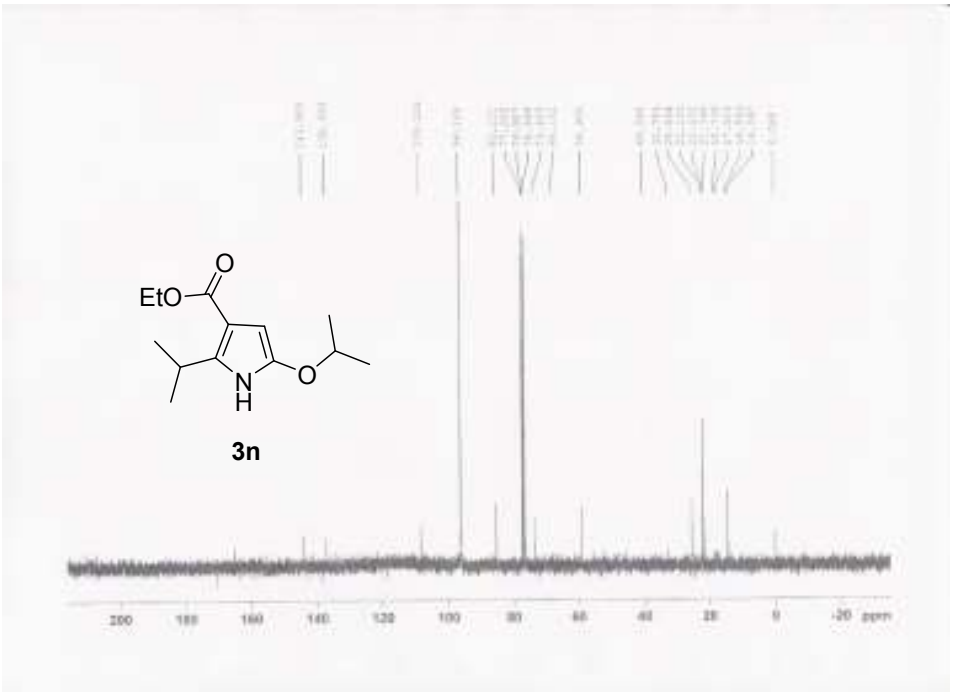

Figure 4.23 ^{13}C NMR of **ethyl 5-isopropoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate (149n).**

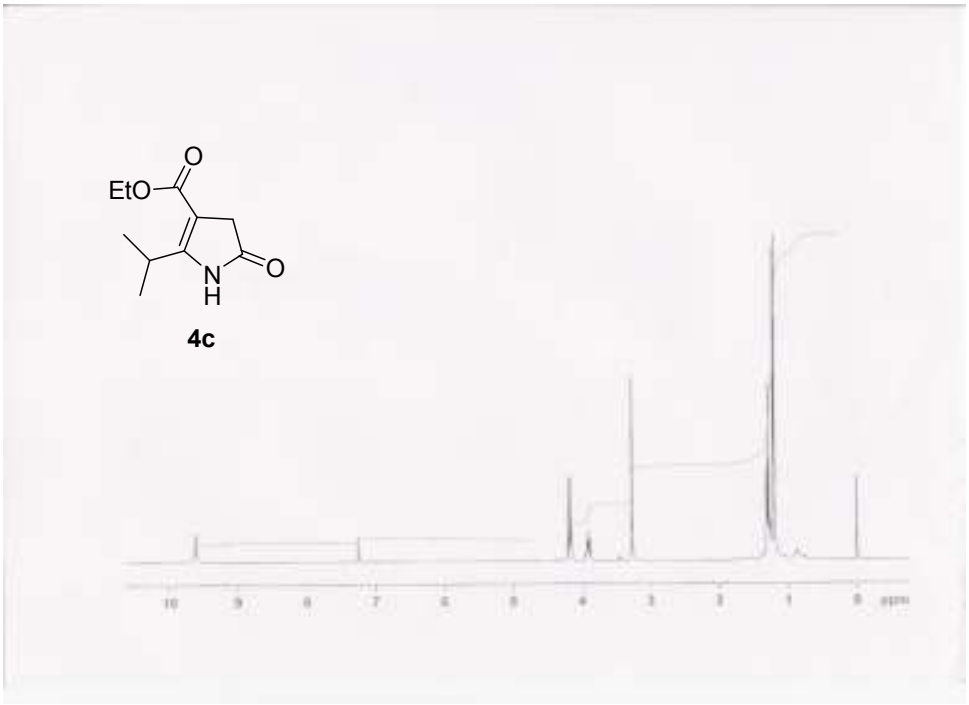

Figure 4.24 ^{1}H-NMR of **Ethyl 4,5-dihydro-2-isopropyl-5-oxo-1*H*-pyrrole-3-carboxylate (150c).**

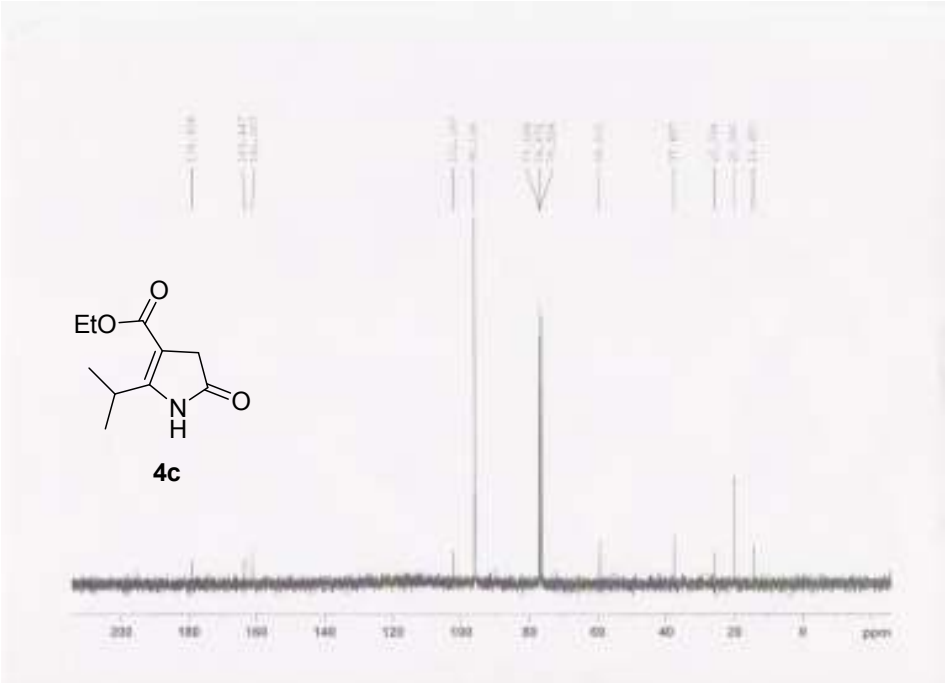

Figure 4.25 ^{13}C-NMR of **Ethyl 4,5-dihydro-2-isopropyl-5-oxo-1*H*-pyrrole-3-carboxylate (150c).**

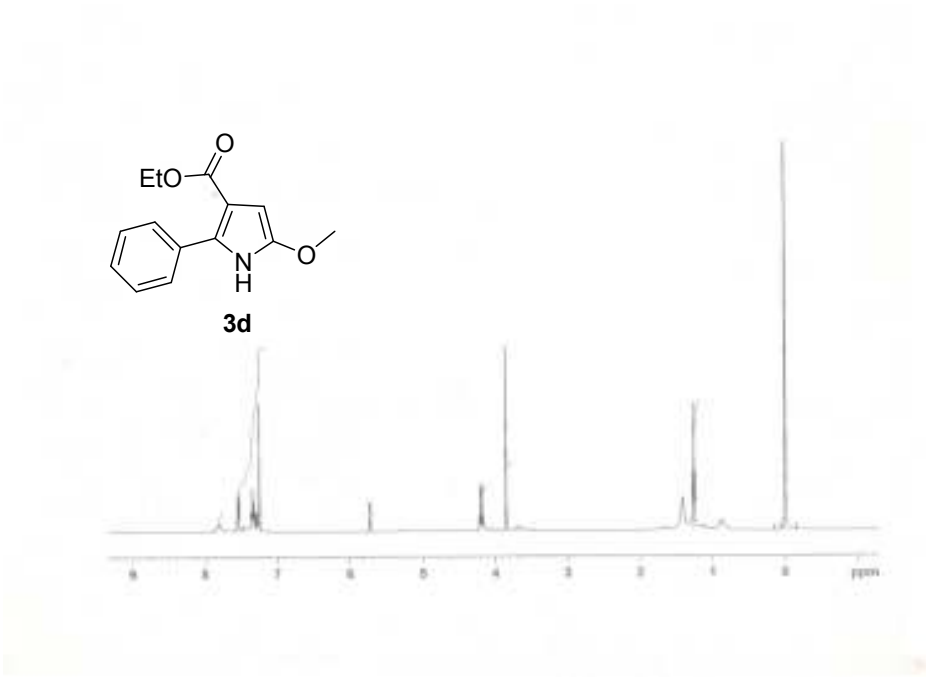

Figure 4.26 ^{1}H-NMR of **Ethyl 5-methoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149d).**

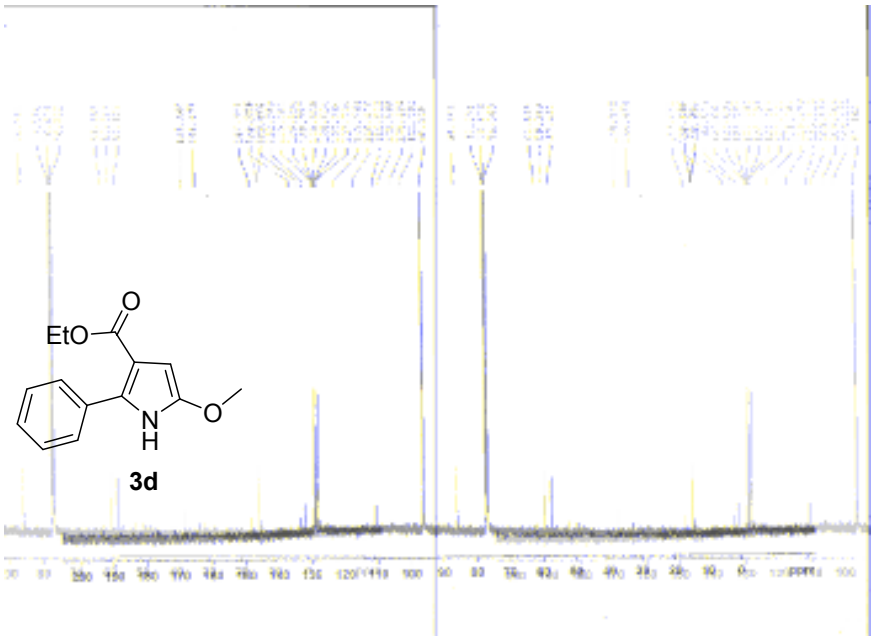

Figure 4.27 ^{13}C-NMR of **5-methoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149d).**

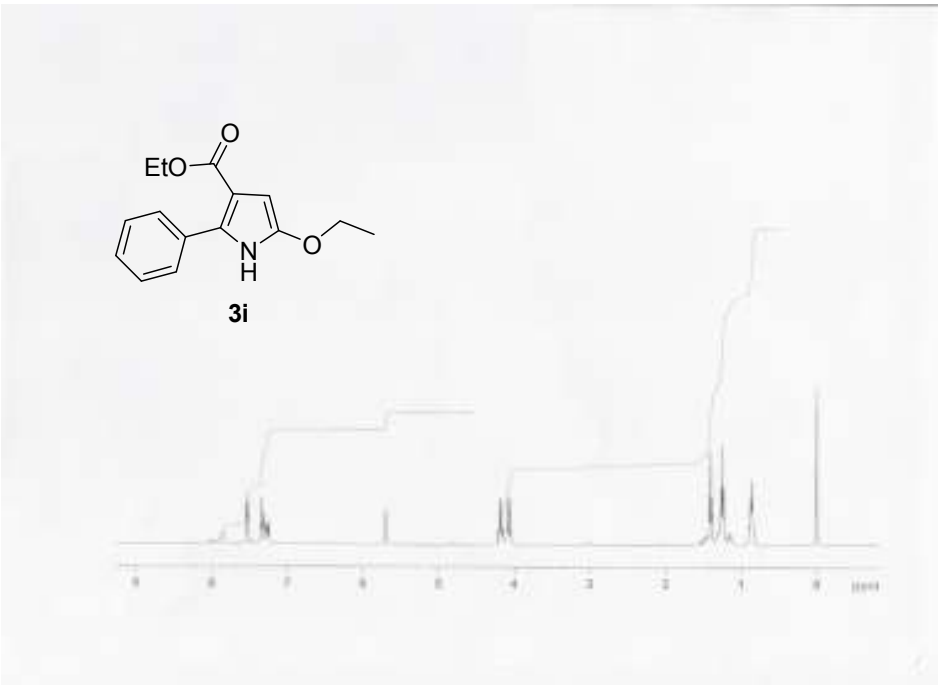

Figure 4.28 ^{1}H-NMR of e**thyl 5-ethoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149i).**

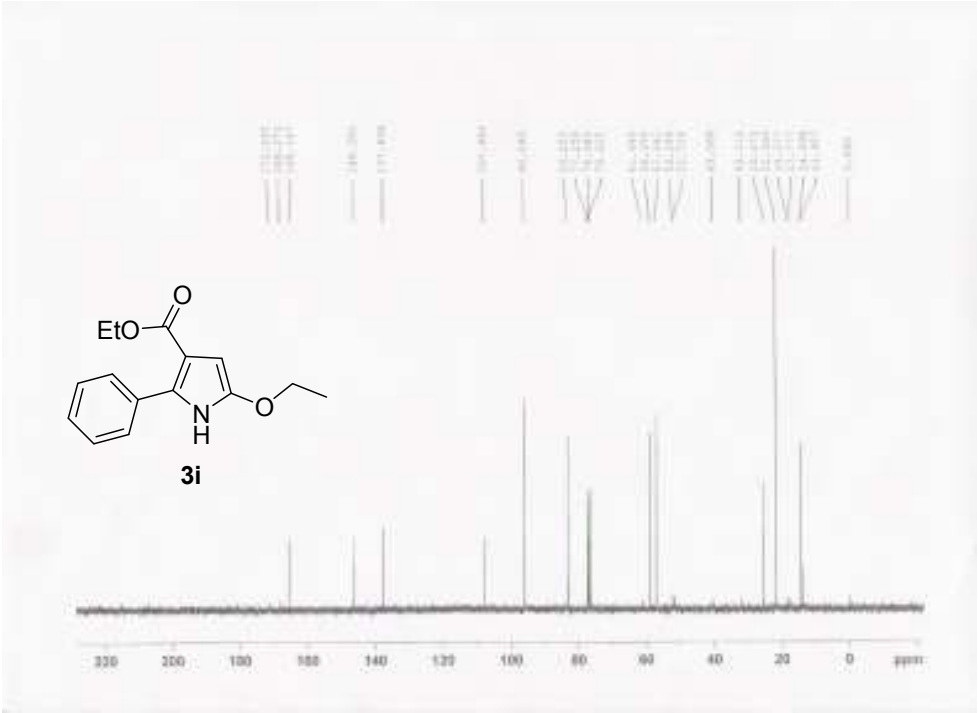

Figure 4.29 ^{13}C-NMR of **ethyl 5-ethoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149i).**

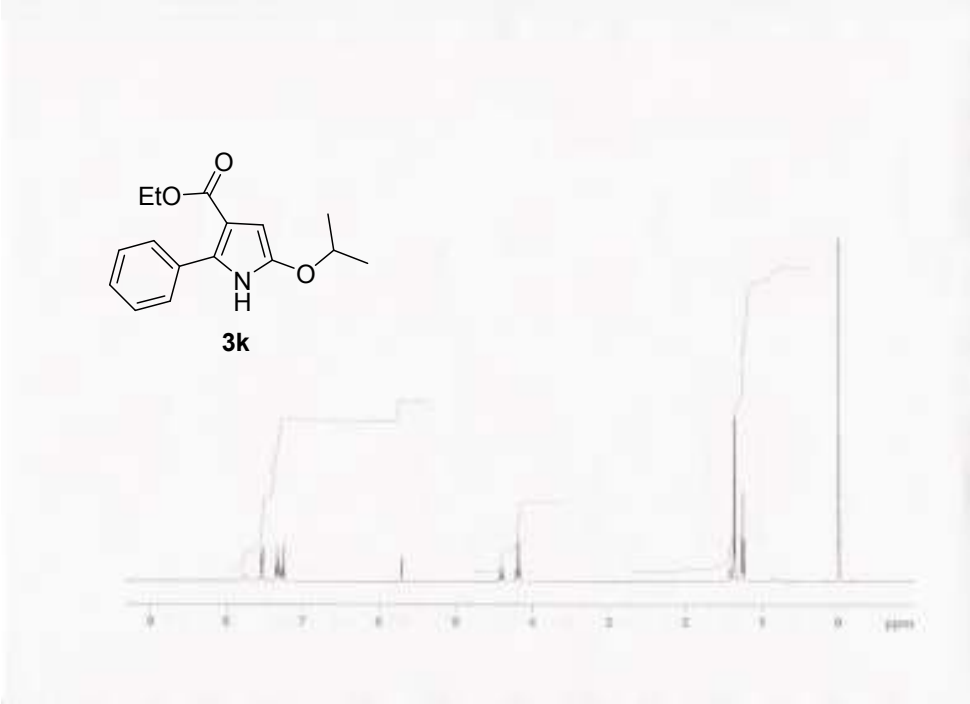

Figure 4.30 ^{1}H-NMR of e**thyl 5-isopropoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149k)**

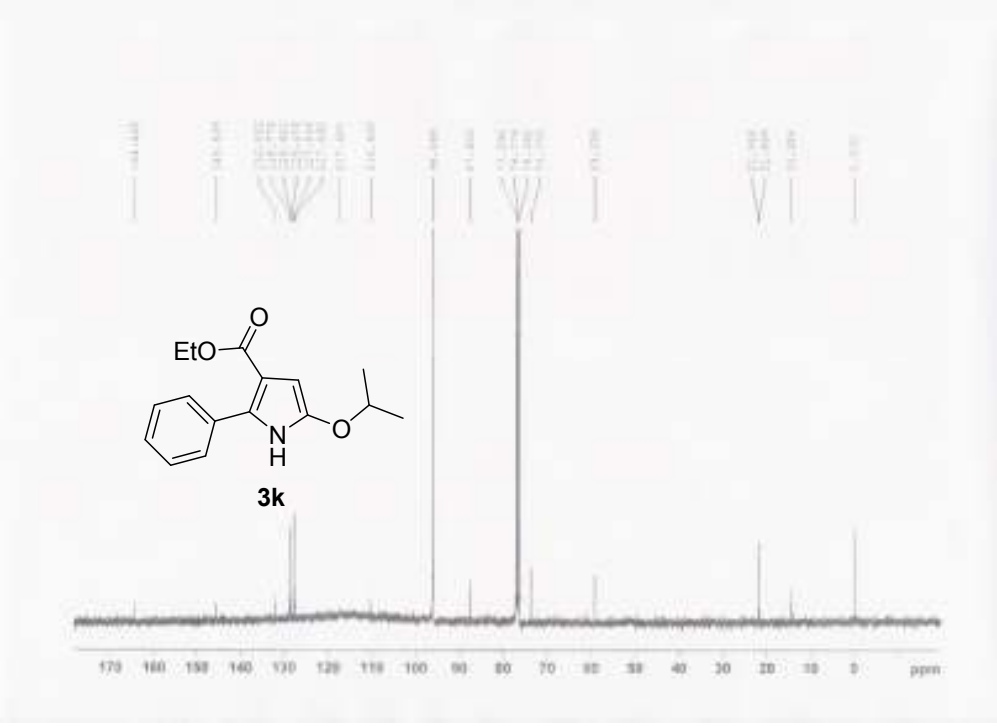

Figure 4.31 ^{13}C-NMR of **ethyl 5-isopropoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (149k)**

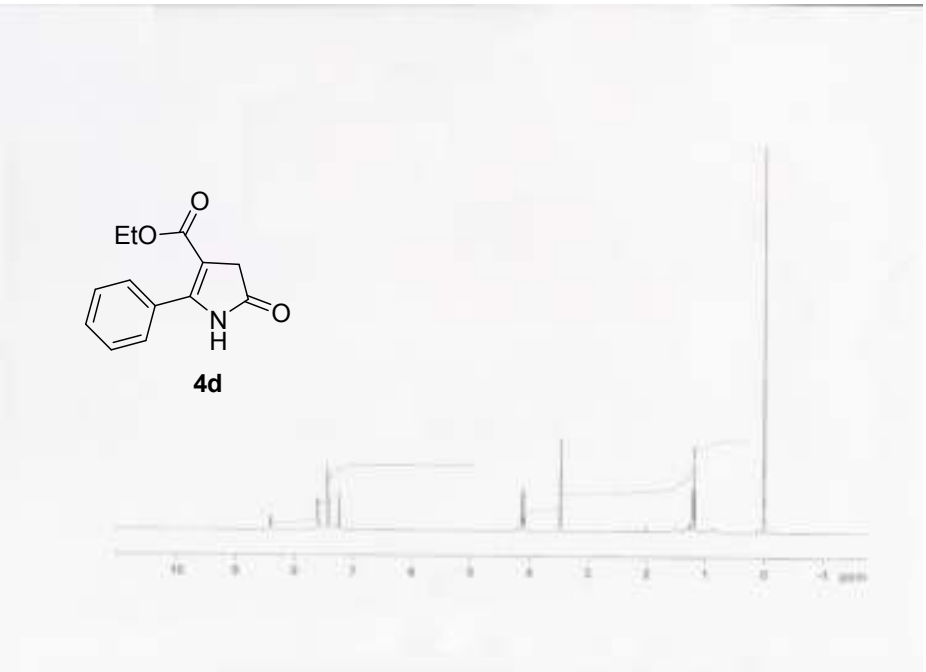

Figure 4.32 ^{1}H-NMR of **ethyl 4,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (150d).**

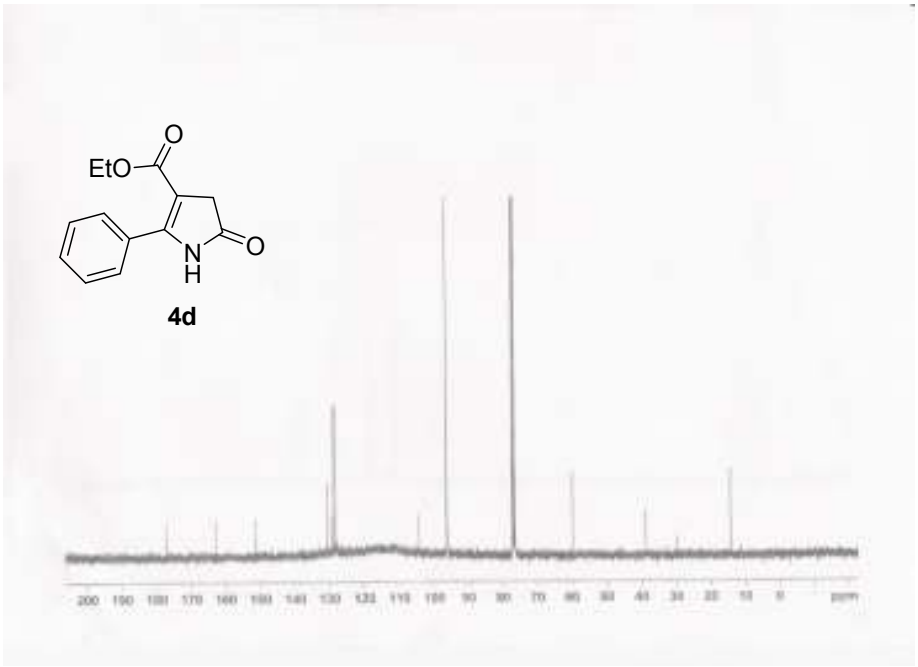

Figure 4.33 ^{13}C-NMR of **ethyl 4,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (150d).**

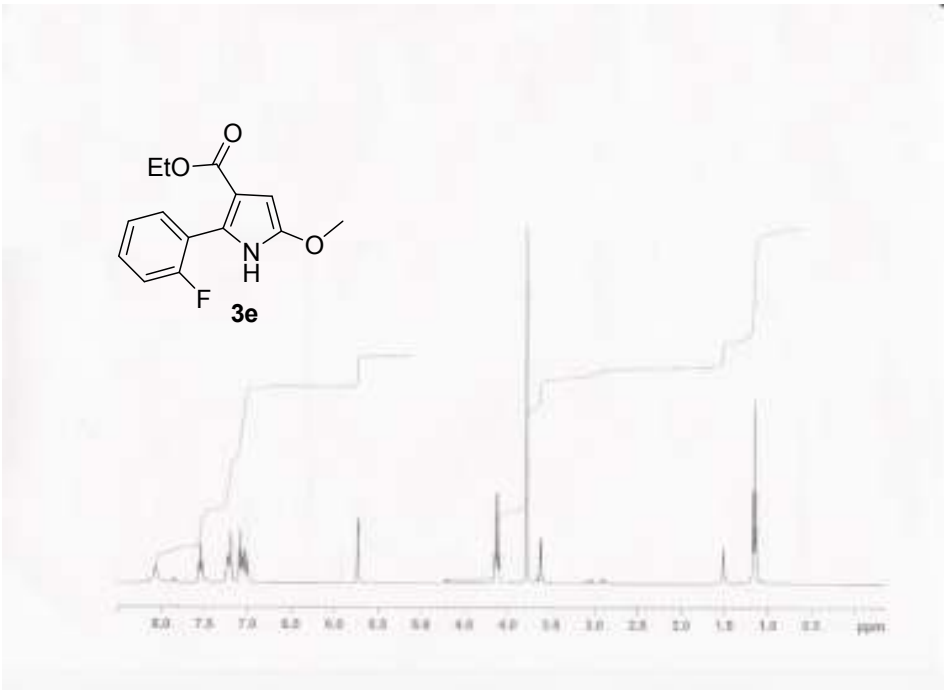

Figure 4.34 ^{1}H-NMR of **ethyl 2-(2-fluorophenyl)-5-methoxy-1*H*-pyrrole-3-carboxylate (149e).**

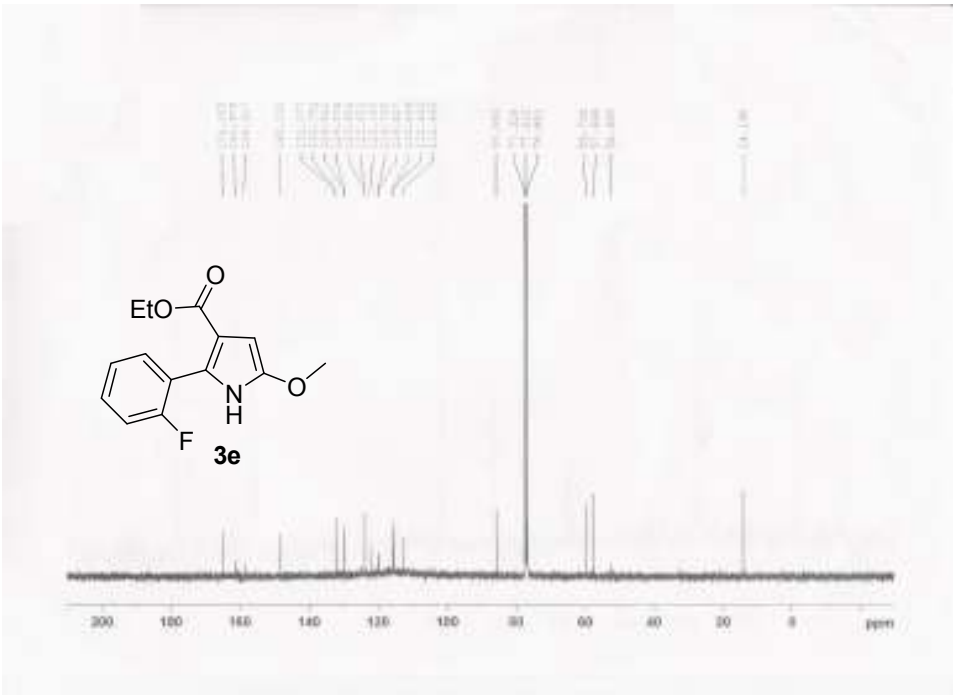

Figure 4.35 ^{13}C-NMR of **ethyl 2-(2-fluorophenyl)-5-methoxy-1*H*-pyrrole-3-carboxylate (149e).**

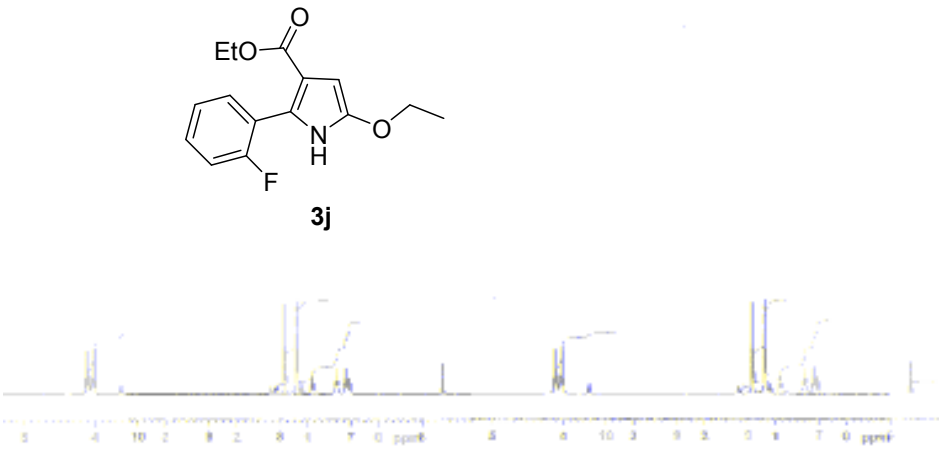

Figure 4.36 ^{1}H-NMR of **ethyl 5-ethoxy-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (149j)**

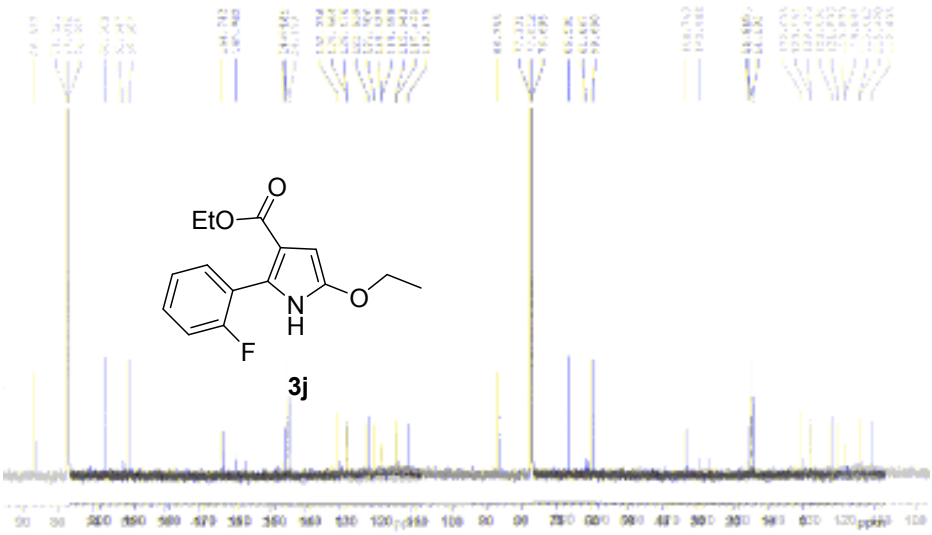

Figure 4.37 ^{13}C-NMR of ethyl 5-ethoxy-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (149j)

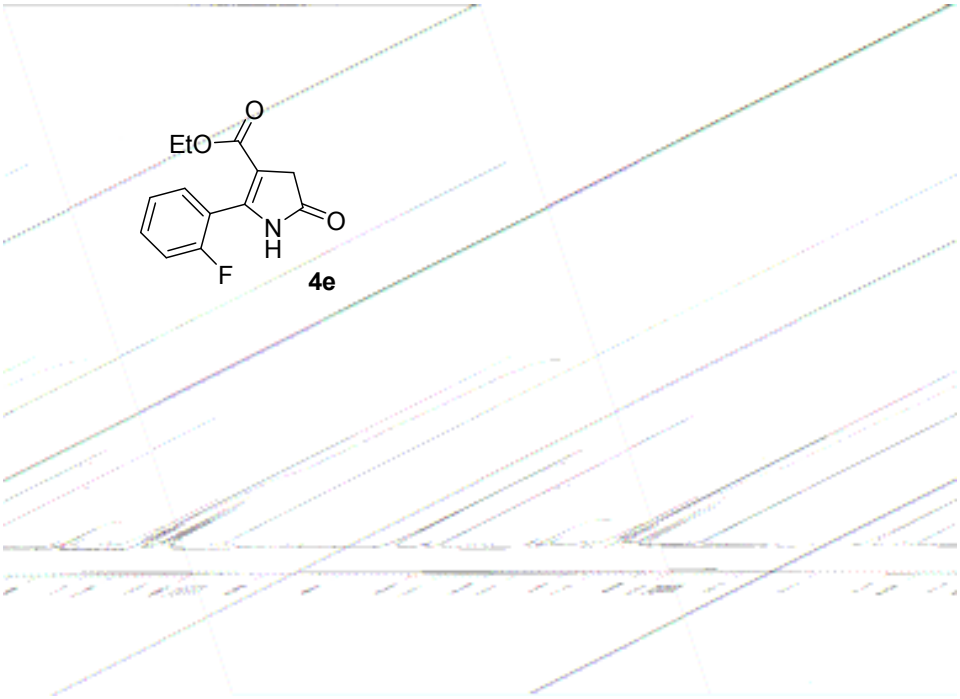

Figure 4.38 ^{1}H-NMR of **ethyl 2-(2-fluorophenyl)-4,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (150e)**

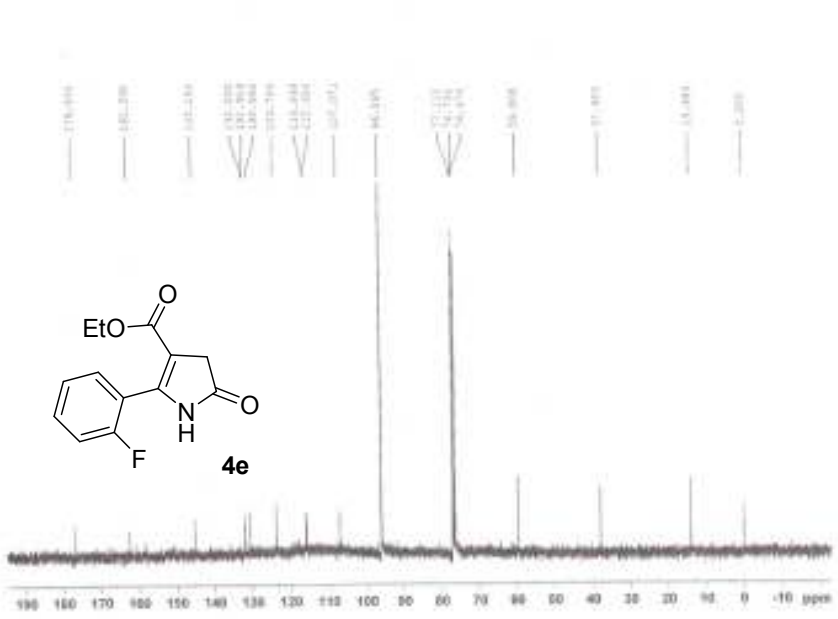

Figure 4.39 ^{13}C-NMR of **ethyl 2-(2-fluorophenyl)-4,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (150e)**

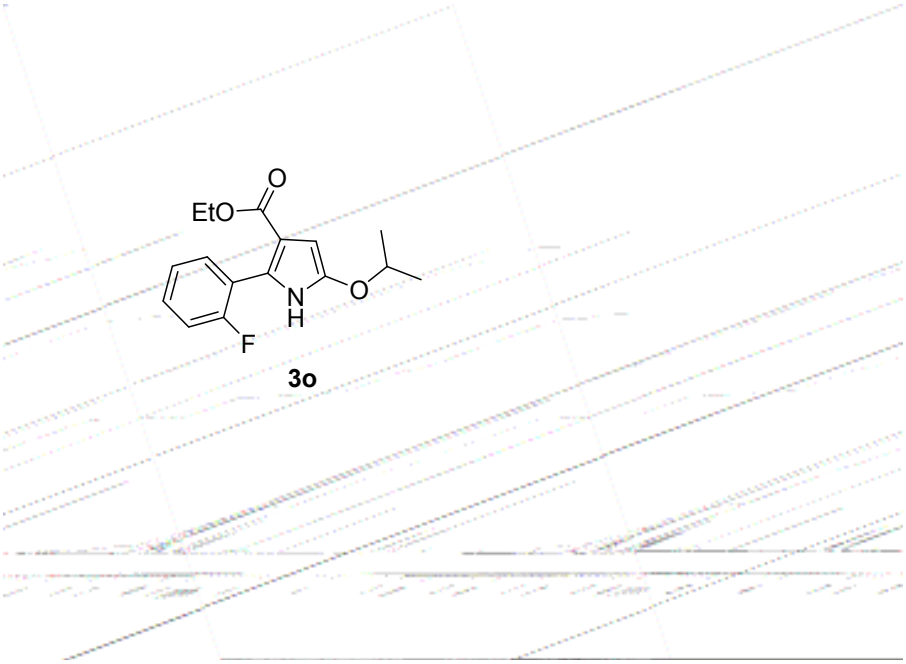

Figure 4.40 ^{1}H-NMR of **ethyl 2-(2-fluorophenyl)-5-isopropoxy-1*H*-pyrrole-3-carboxylate (149o).**

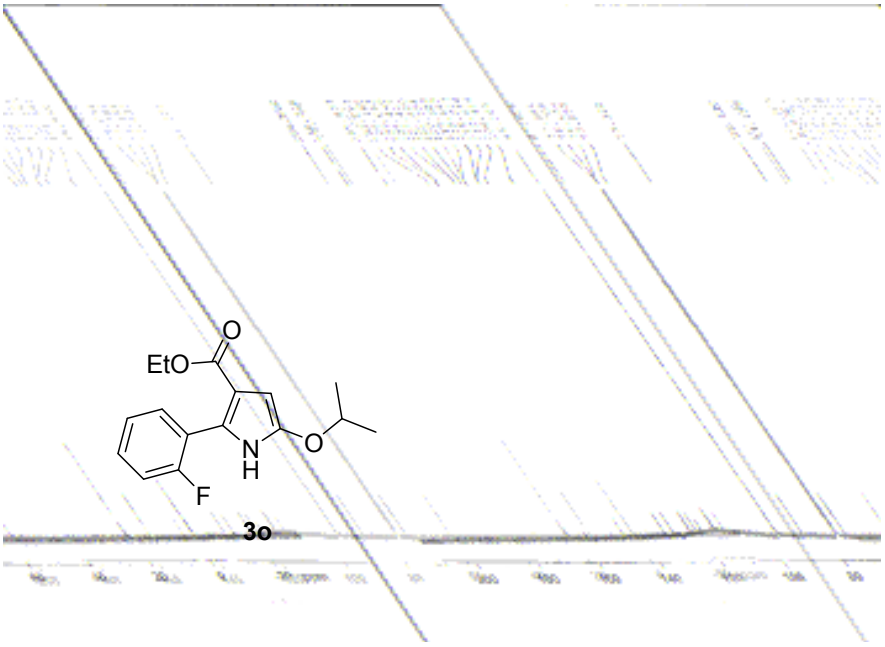

Figure 4.41 ^{13}C-NMR of **ethyl 2-(2-fluorophenyl)-5-isopropoxy-1*H*-pyrrole-3-carboxylate (149o)**

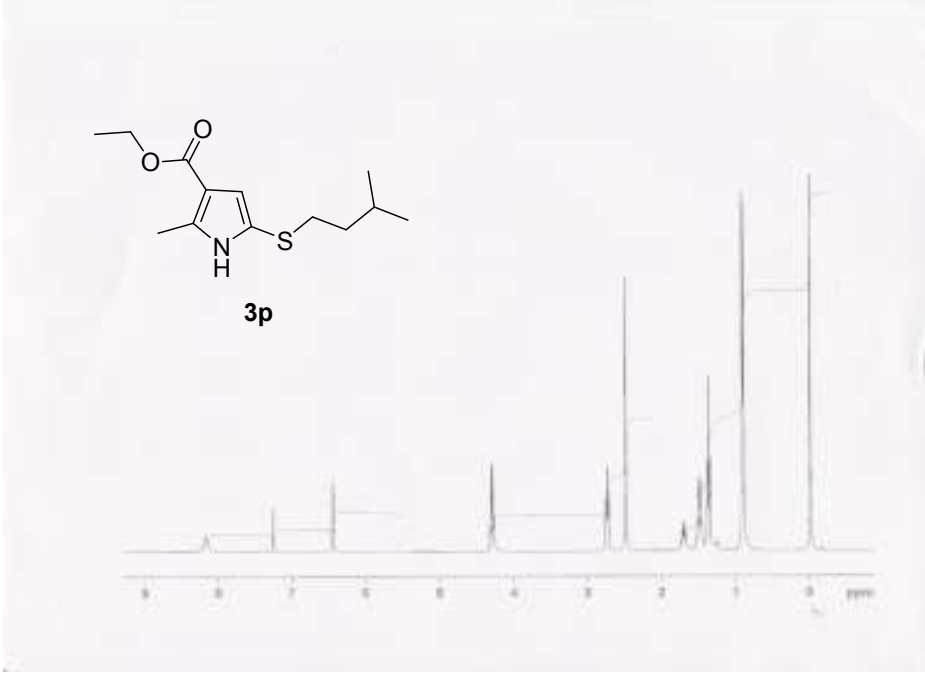

Figure 4.42 ^{1}H-NMR of **ethyl 5-(isopentylthio)-2-methyl-1*H*-pyrrole-3-carboxylate (149p).**

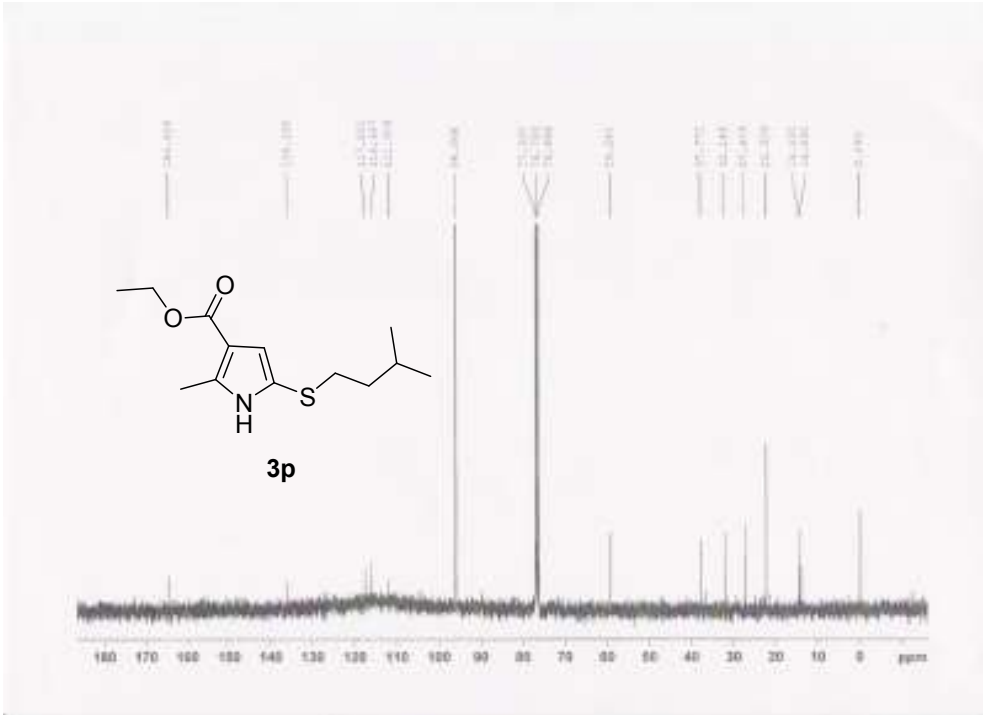

Figure 4.43 ^{13}C-NMR of **ethyl 5-(isopentylthio)-2-methyl-1*H*-pyrrole-3-carboxylate (149p).**

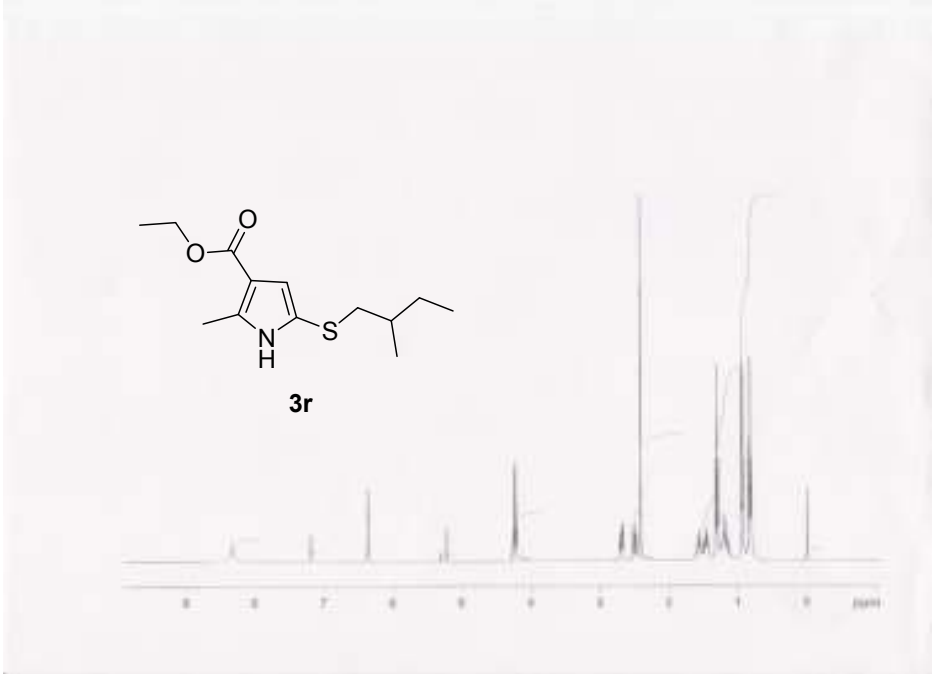

Figure 4.44 ^{1}H-NMR of **ethyl 5-(2-methylbutylthio)-2-methyl-1*H*-pyrrole-3-carboxylate (149r).**

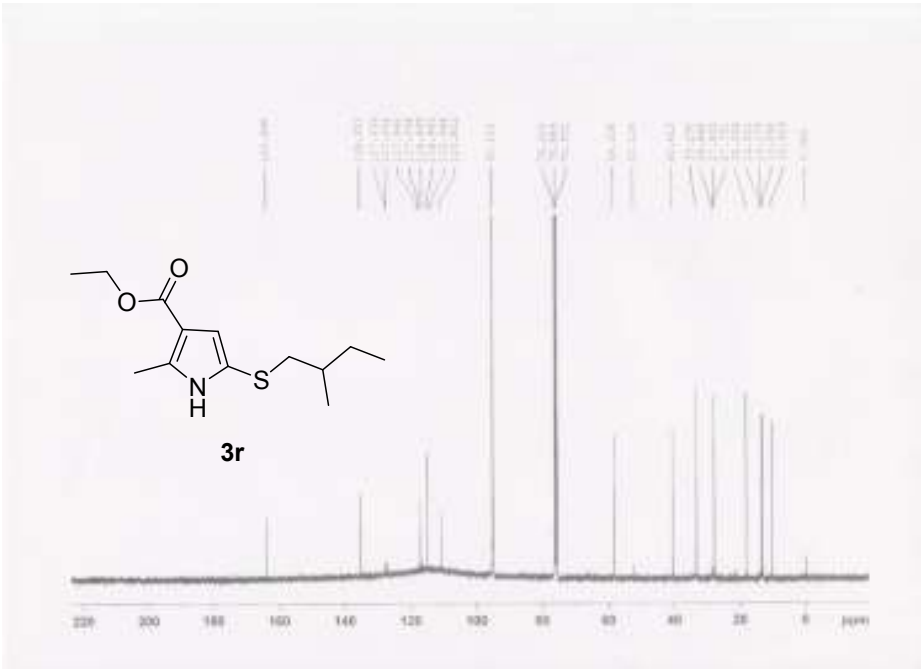

Figure 4.45 ^{13}C-NMR of **ethyl 5-(2-methylbutylthio)-2-methyl-1*H*-pyrrole-3-carboxylate (149r).**

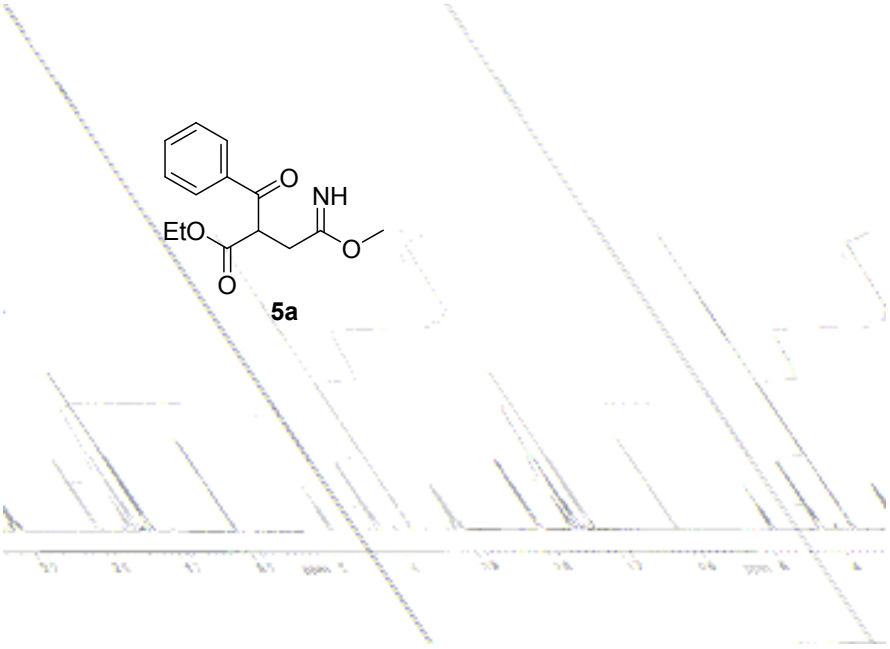

Figure 4.46 ^{1}H-NMR of **3-(ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid methyl ester (151a)**

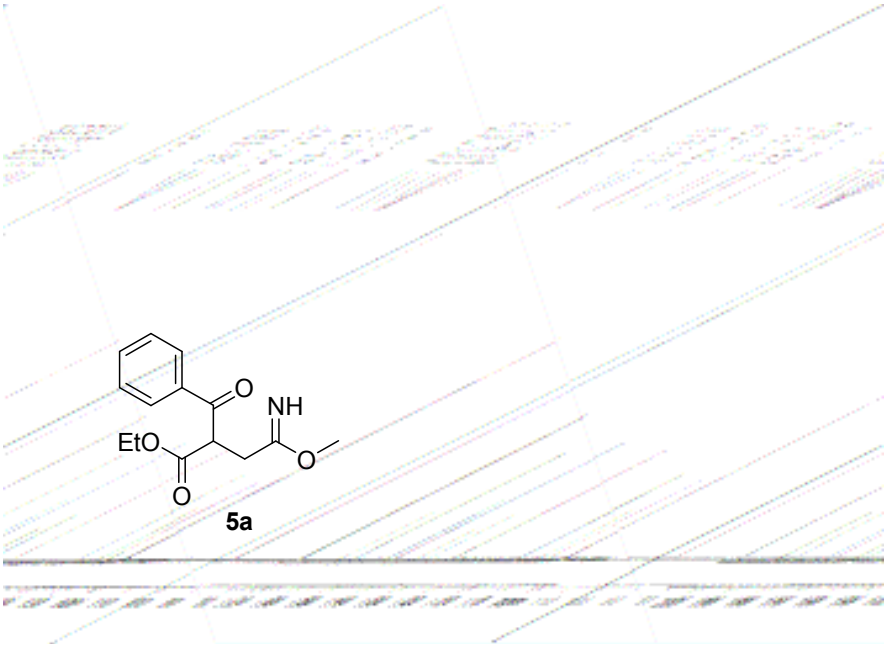

Figure 4.47 ^{13}C-NMR of **3-(ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid methyl ester (151a)**

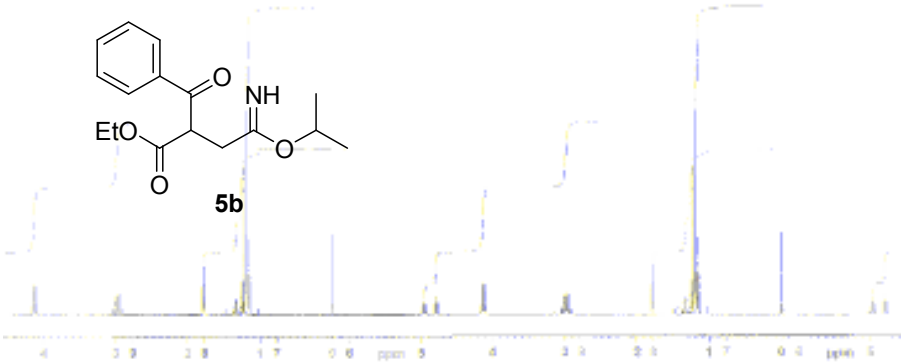

Figure 4.48 ^{1}H-NMR of **3-(ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid isopropyl ester (151b)**

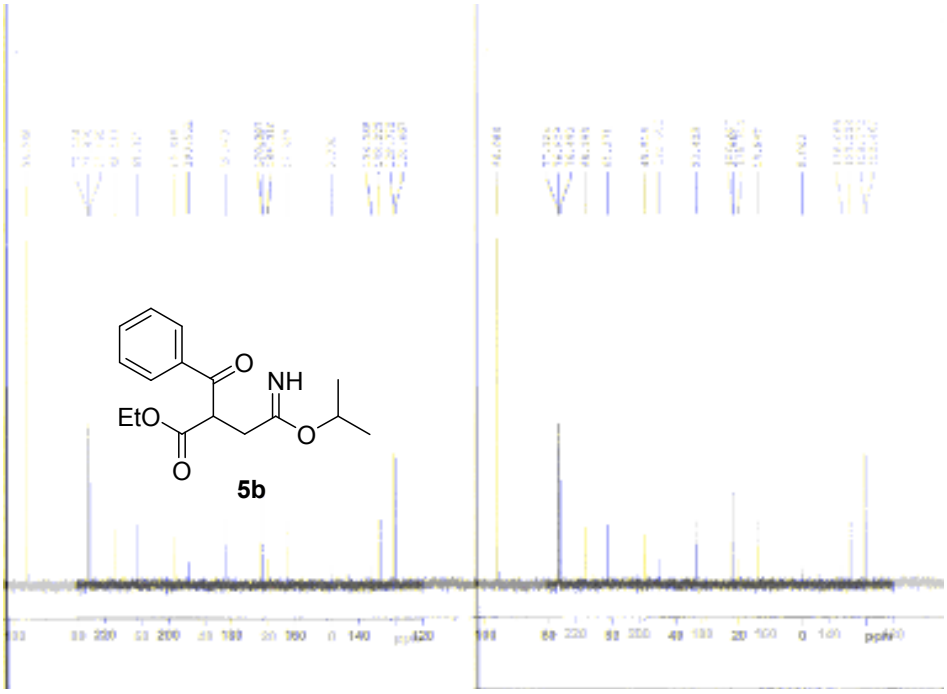

Figure 4.49 ^{13}C-NMR of **3-(ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid isopropyl ester (151b)**

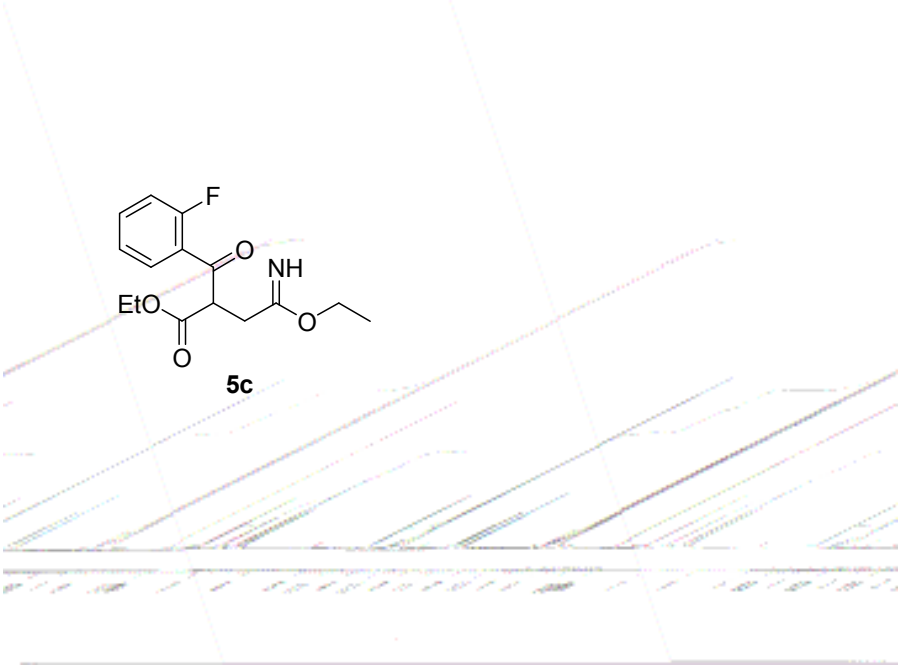

Figure 4.50 ^{1}H-NMR of **3-(ethoxycarbonyl)-4-(2-fluorophenyl)-4-oxobutanoxylimidic acid ethyl ester (151c)**

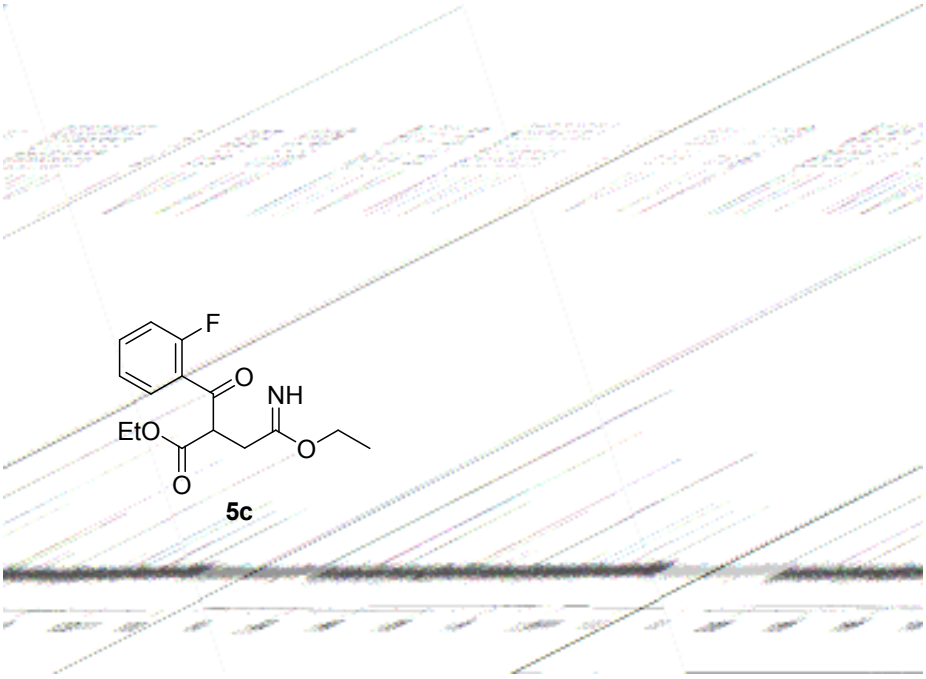

Figure 4.51 ^{13}C-NMR of **3-(ethoxycarbonyl)-4-(2-fluorophenyl)-4-oxobutanoxylimidic acid ethyl ester (151c)**

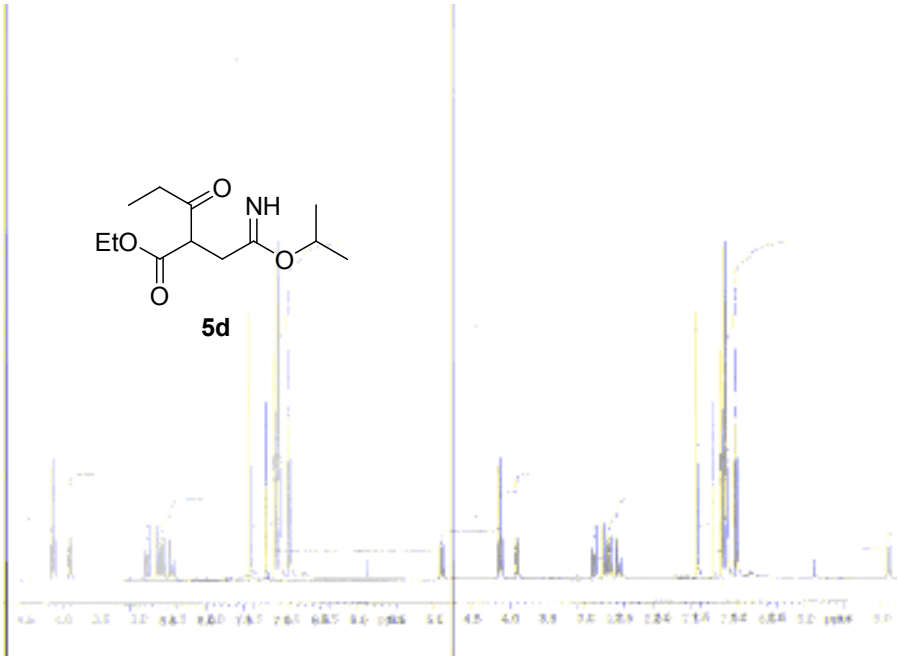

Figure 4.52 ^{1}H-NMR of **3-(ethoxycarbonyl)-4-oxohexanoxylimidic acid isopropyl ester (5d)**

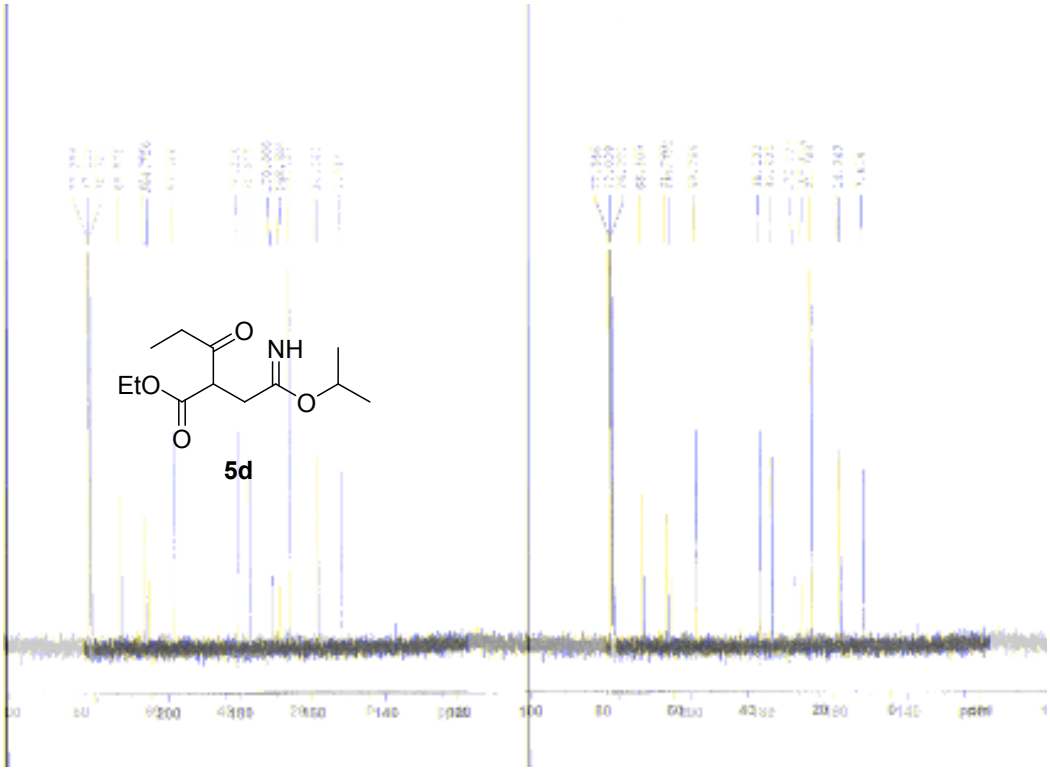

Figure 4.53 ^{13}C-NMR of **3-(ethoxycarbonyl)-4-oxohexanoxylimidic acid isopropyl ester (5d)**

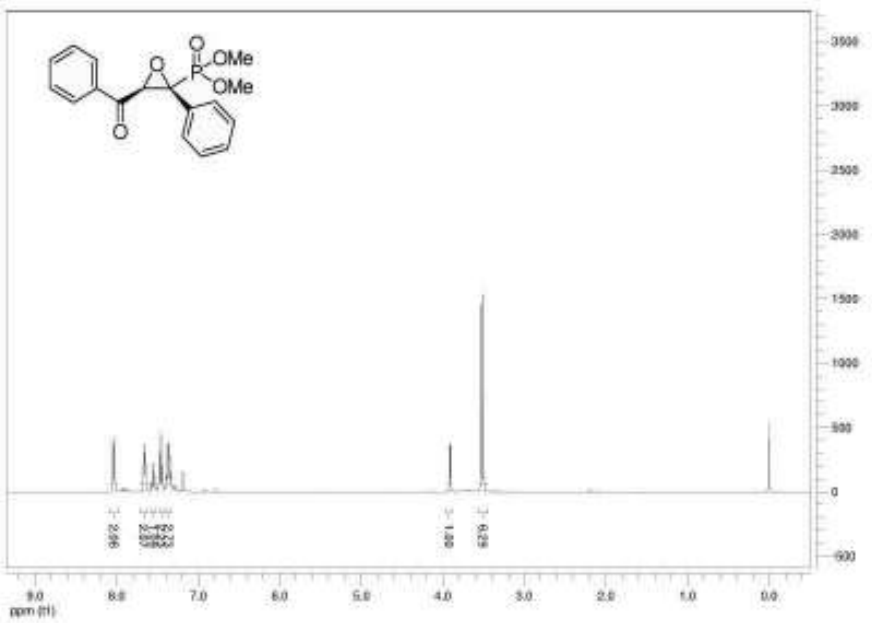

Figure 4.54 ^{1}H NMR of **dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate (*trans*-155a)**

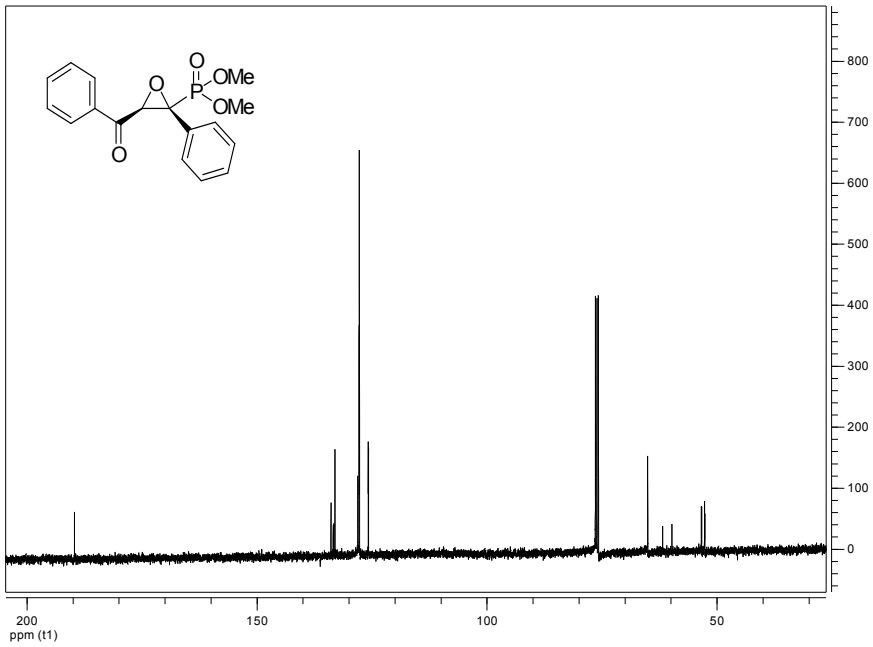

Figure 4.55 ^{13}C NMR of **dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate (*trans*-155a)**

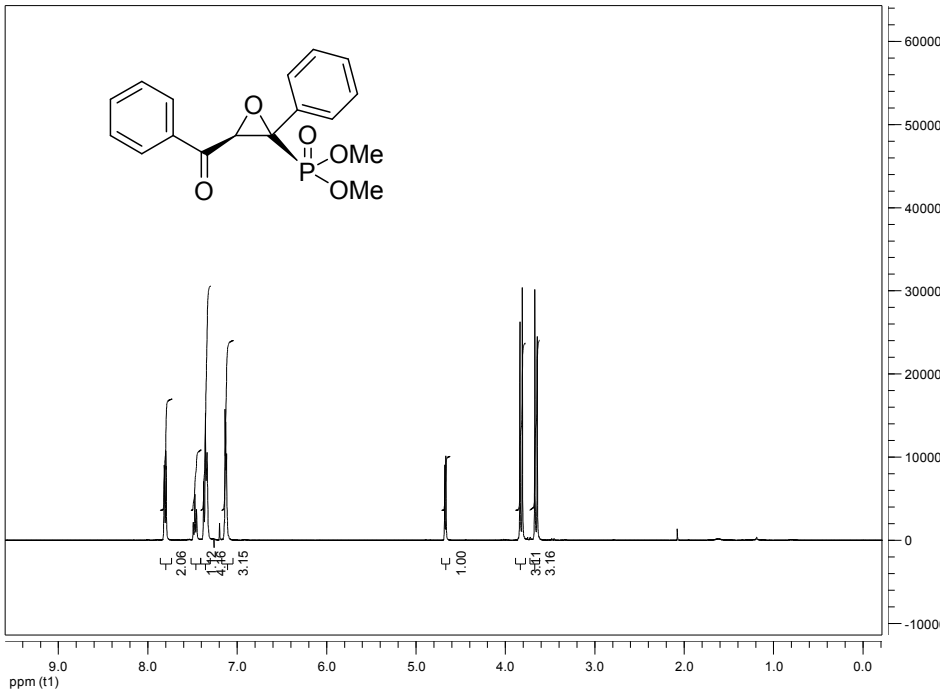

Figure 4.56 ^{1}H NMR of **Dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate (*cis*-155a)**

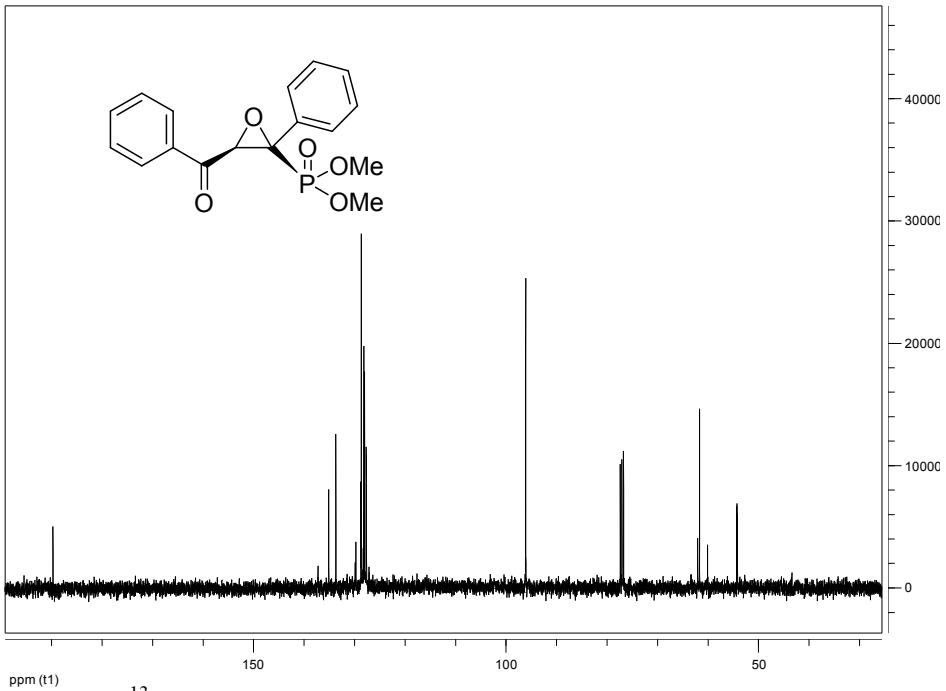

Figure 4.57 ^{13}C NMR of **Dimethyl 3-benzoyl-2-phenyloxiran-2-ylphosphonate (*cis*-155a)**

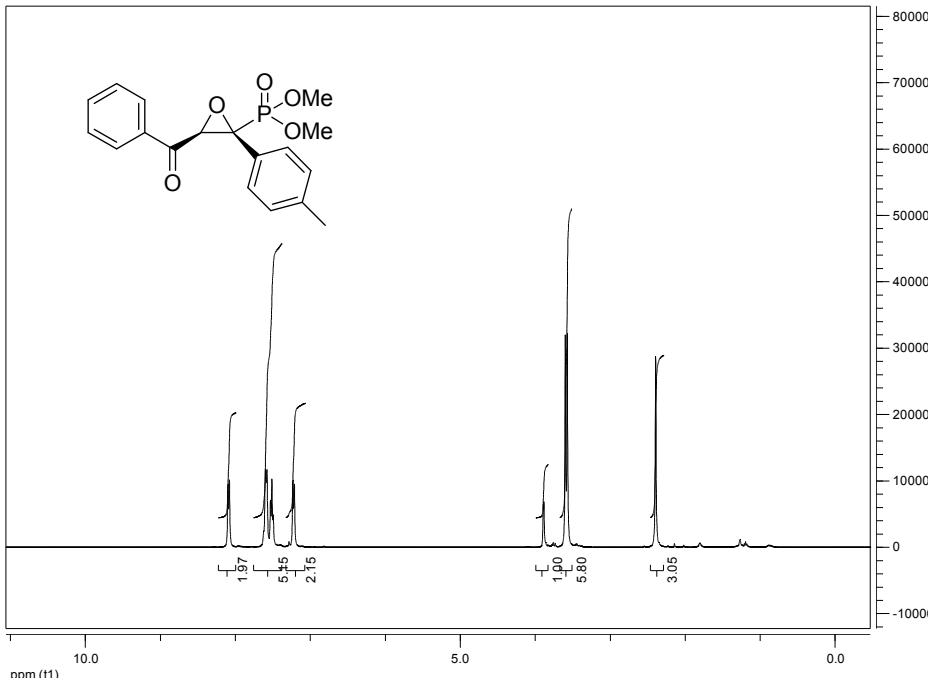

Figure 4.58 ^{1}H NMR of **Dimethyl 3-benzoyl-2-p-tolyloxiran-2-ylphosphonate (*trans*-155b)**

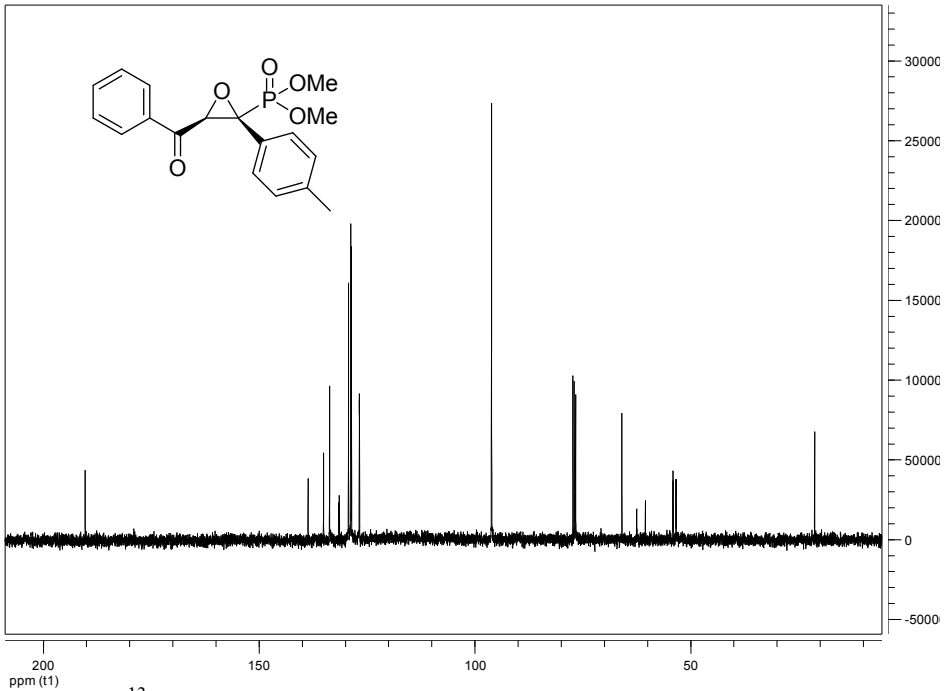

Figure 4.59 ^{13}C NMR of **Dimethyl 3-benzoyl-2-p-tolyloxiran-2-ylphosphonate (*trans*-155b)**

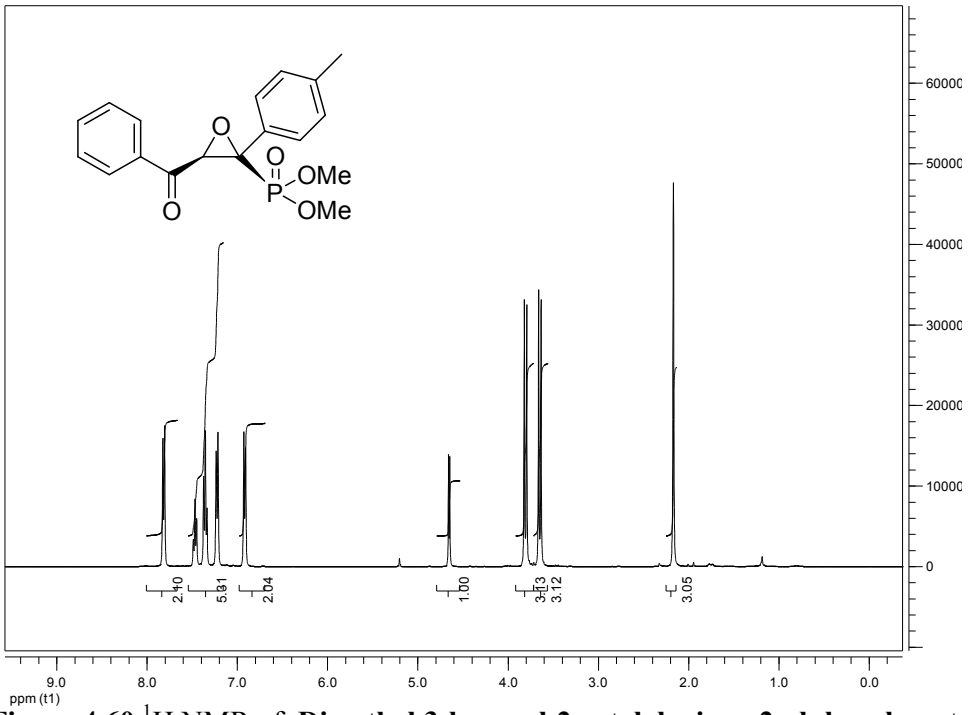

Figure 4.60 ^{1}H NMR of **Dimethyl 3-benzoyl-2-p-tolyloxiran-2-ylphosphonate (*cis*-155b)**

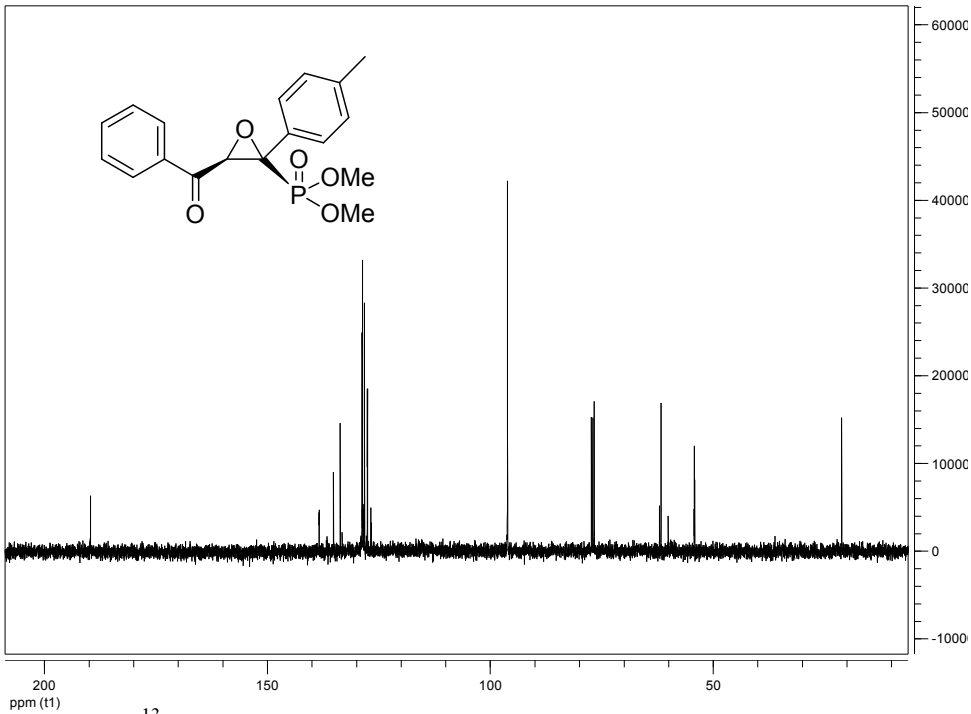

Figure 4.60 ^{13}C NMR of **Dimethyl 3-benzoyl-2-p-tolyloxiran-2-ylphosphonate (*cis*-155b)**

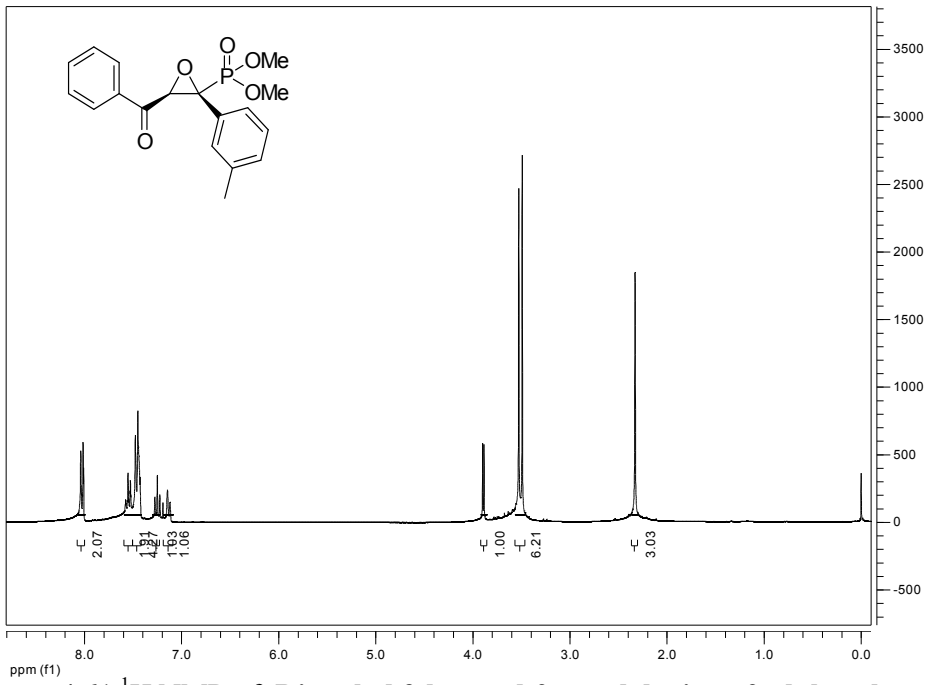

Figure 4.61 ^{1}H NMR of **Dimethyl 3-benzoyl-2-m-tolyloxiran-2-ylphosphonate (*trans*-3c)**

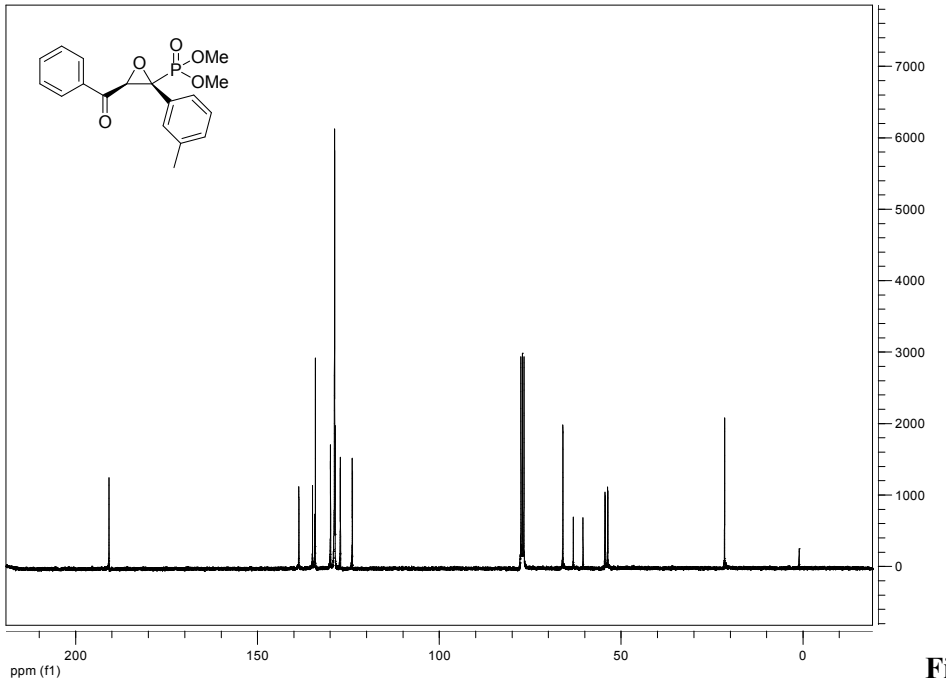

Figure 4.62 ^{13}C NMR of **Dimethyl 3-benzoyl-2-m-tolyloxiran-2-ylphosphonate (*trans*-155c)**

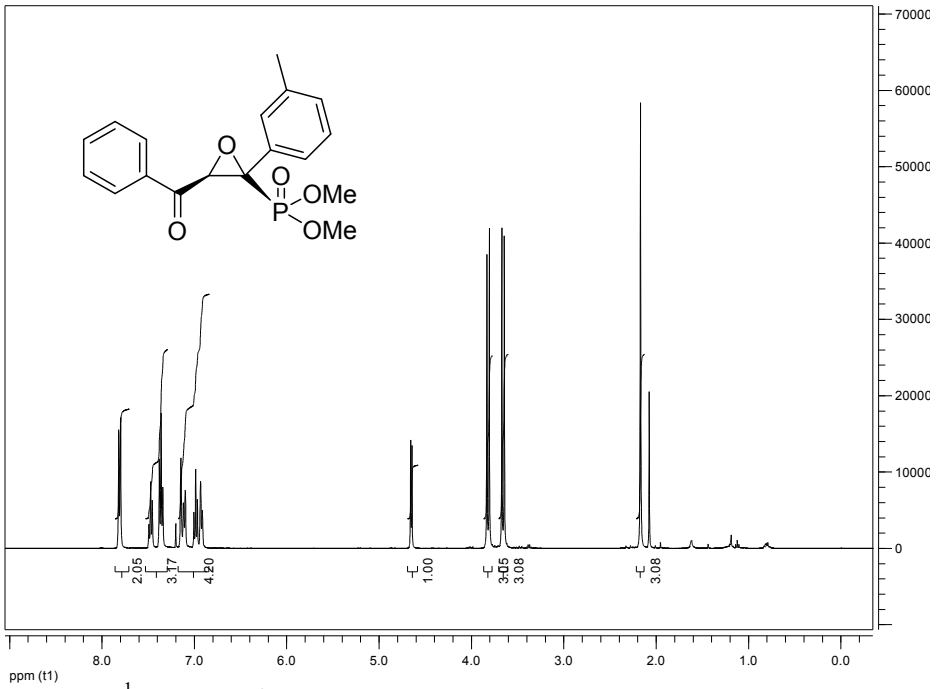

Figure 4.63 ^{1}H NMR of **Dimethyl 3-benzoyl-2-m-tolyloxiran-2-ylphosphonate (*cis*-155c)**

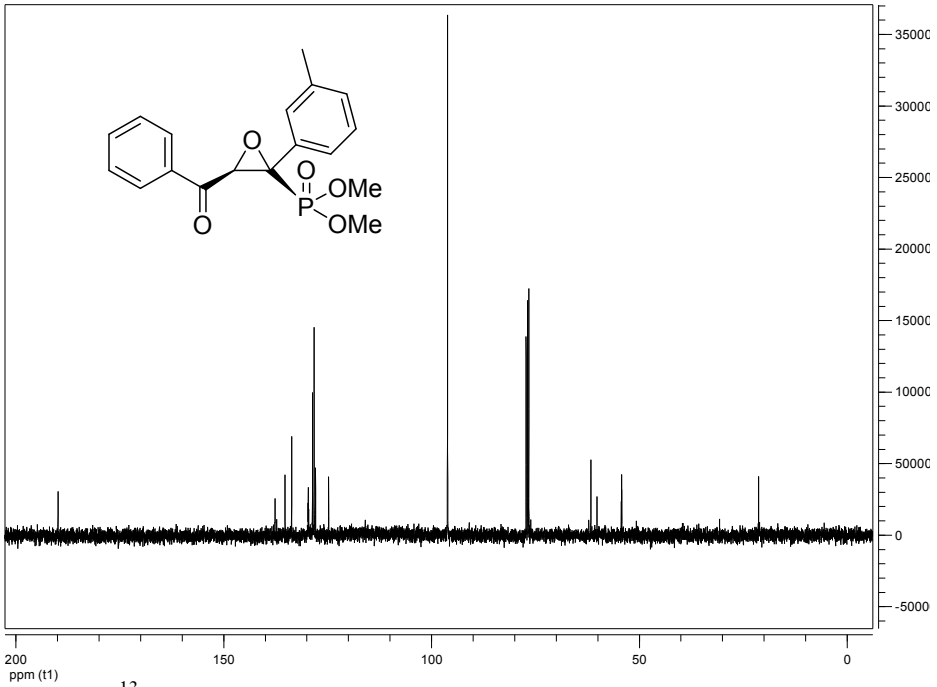

Figure 4.64 ^{13}C NMR of **Dimethyl 3-benzoyl-2-m-tolyloxiran-2-ylphosphonate (*cis*-155c)**

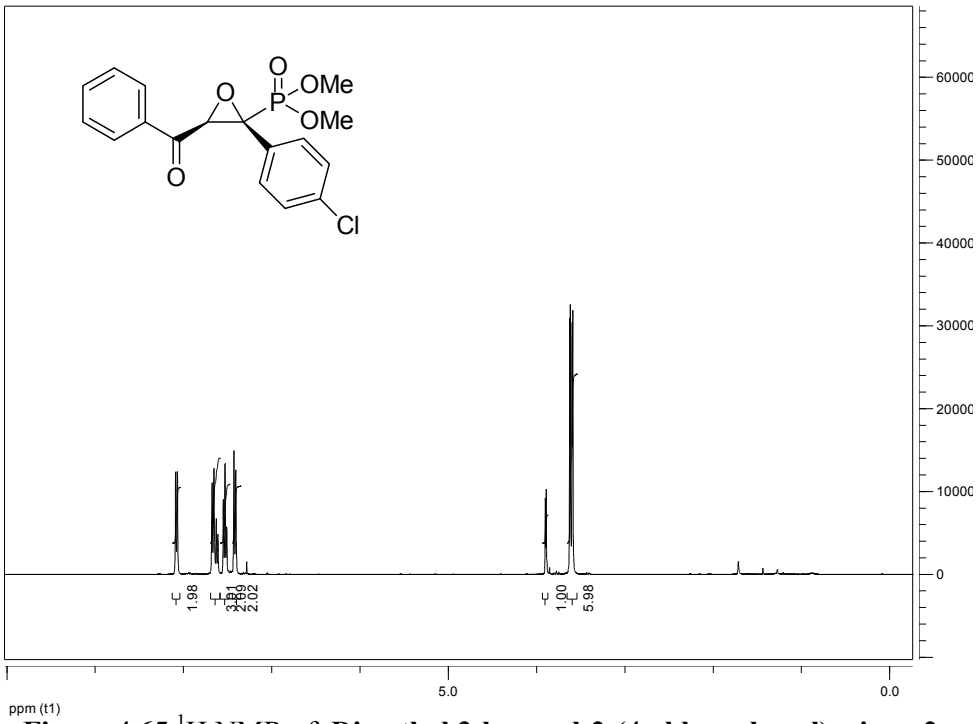

Figure 4.65 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(4-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155d)**

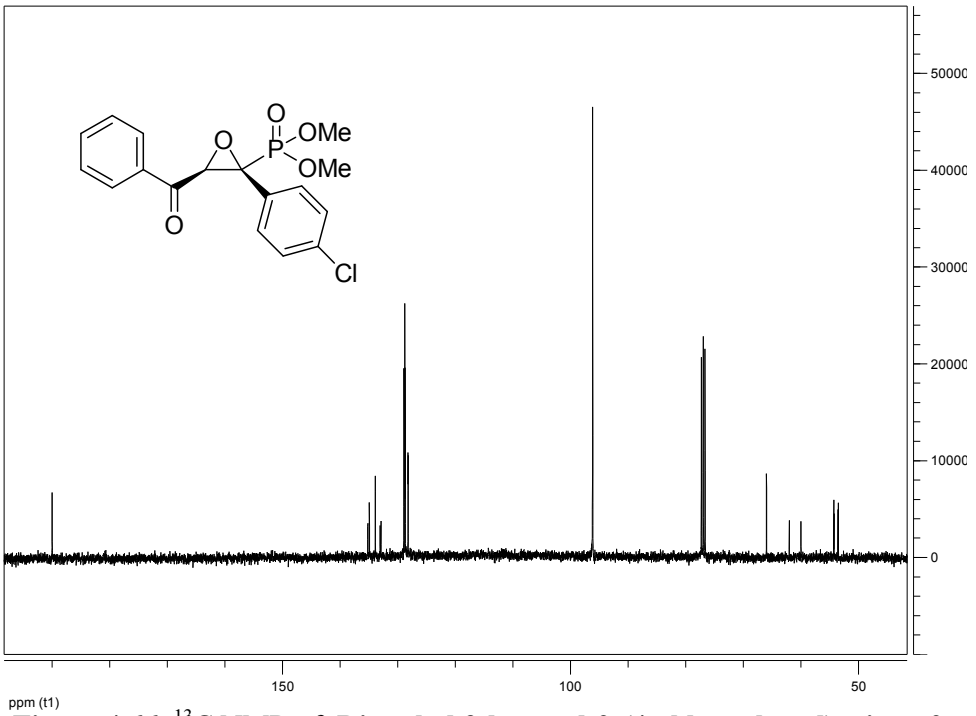

Figure 4.66 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(4-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155d)**

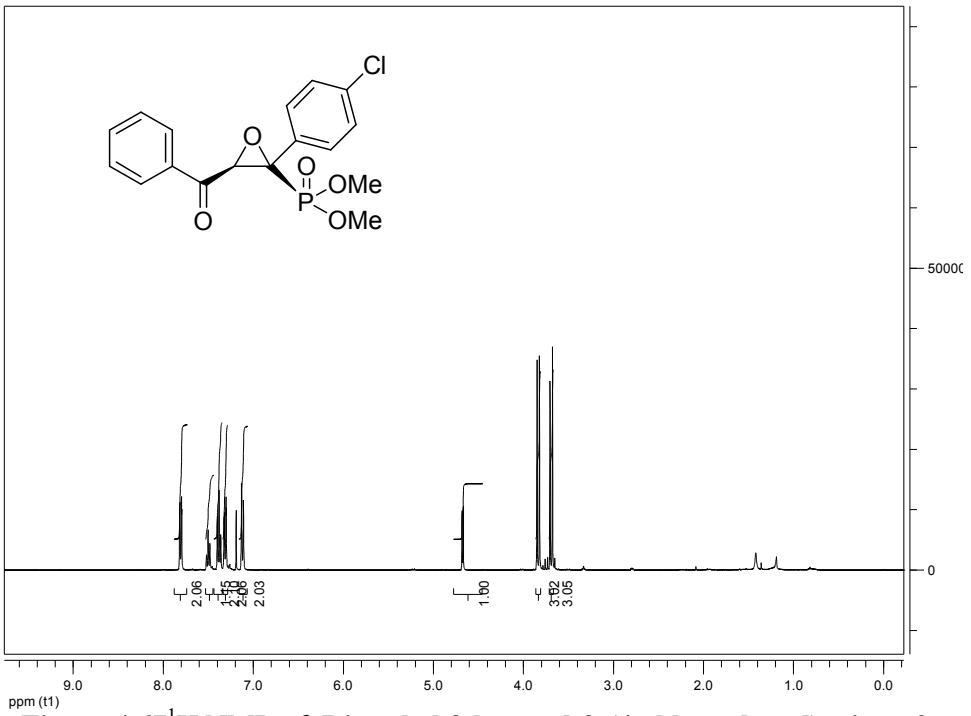

Figure 4.67 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(4-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155d)**

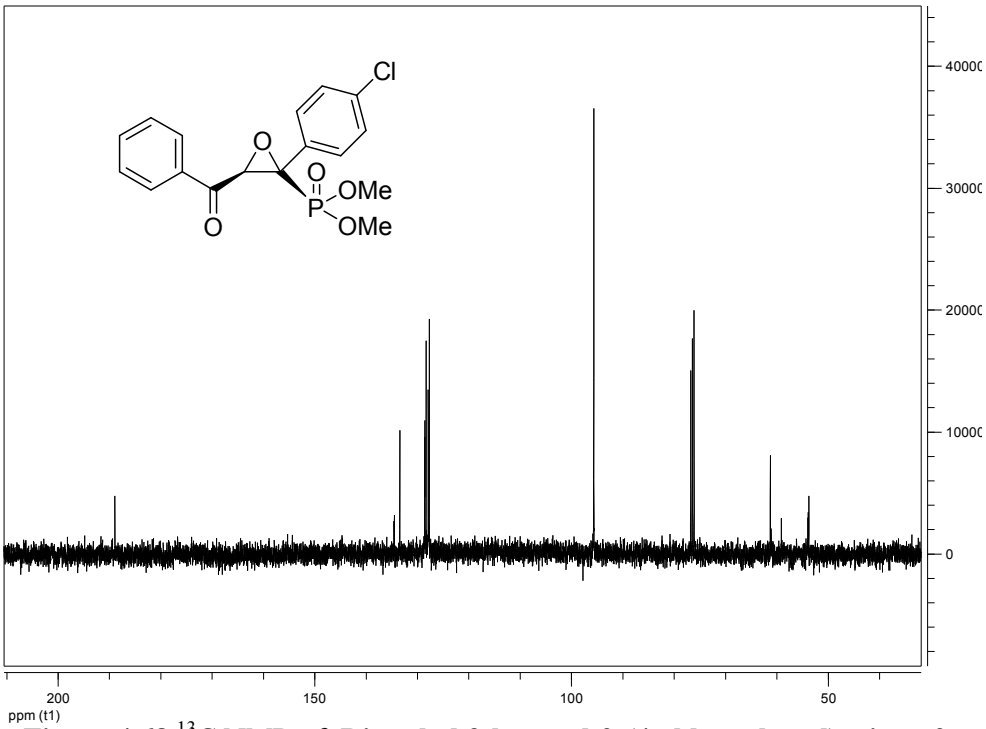

Figure 4.68 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(4-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155d)**

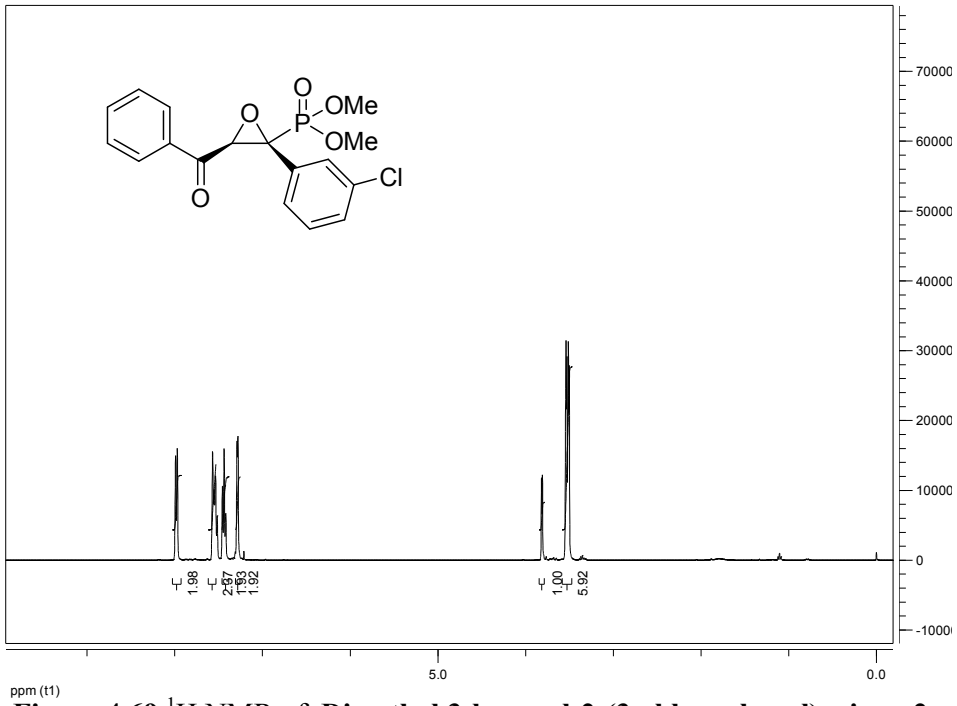

Figure 4.69 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(3-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155e)**

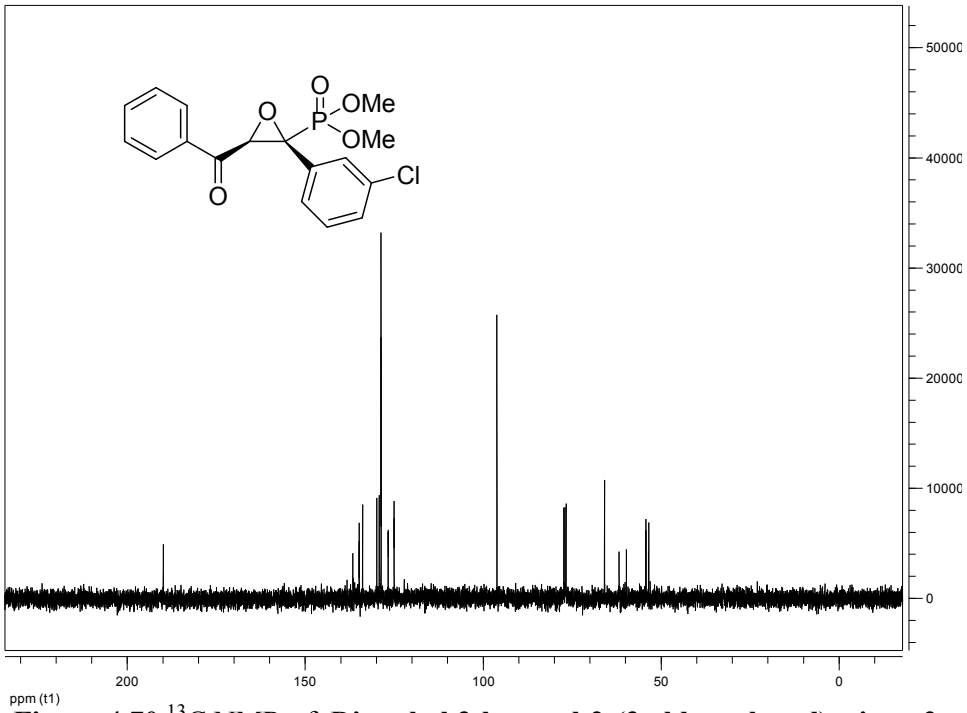

Figure 4.70 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(3-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155e)**

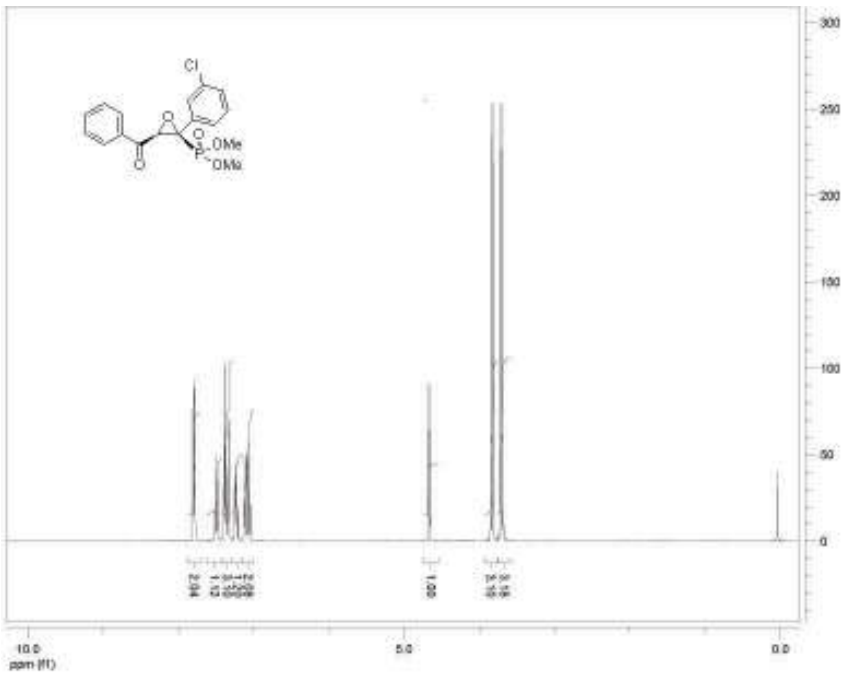

Figure 4.71 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(3-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155e)**

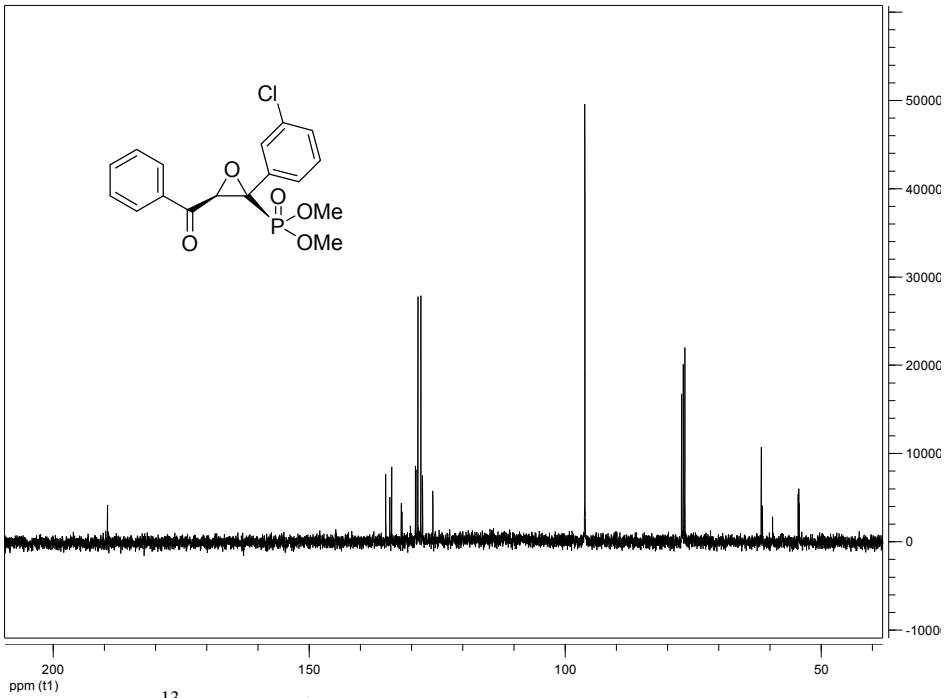

Figure 4.72 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(3-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155e)**

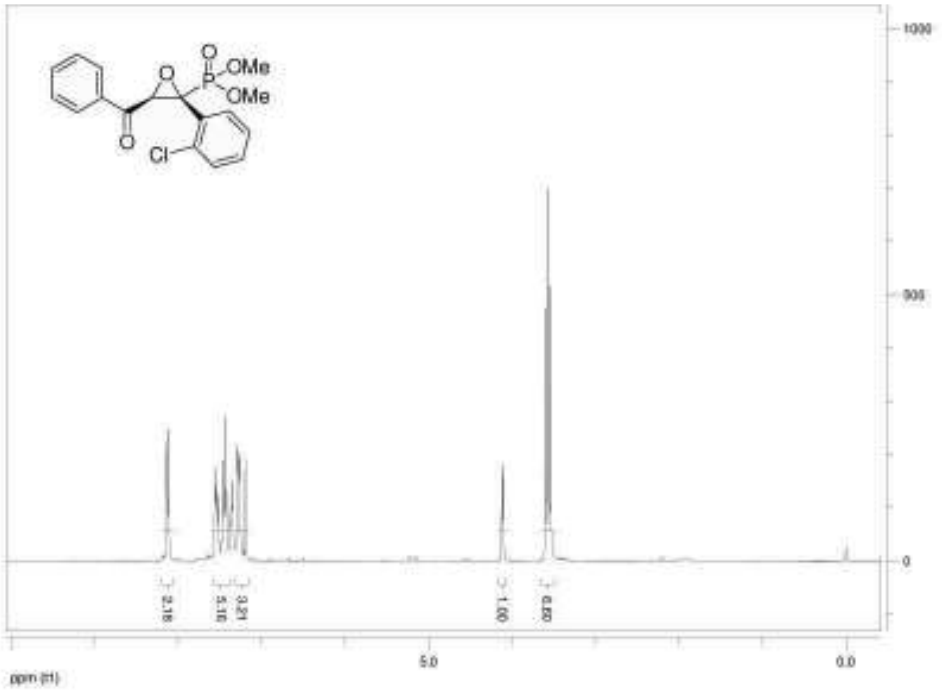

Figure 4.73 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(2-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155f)**

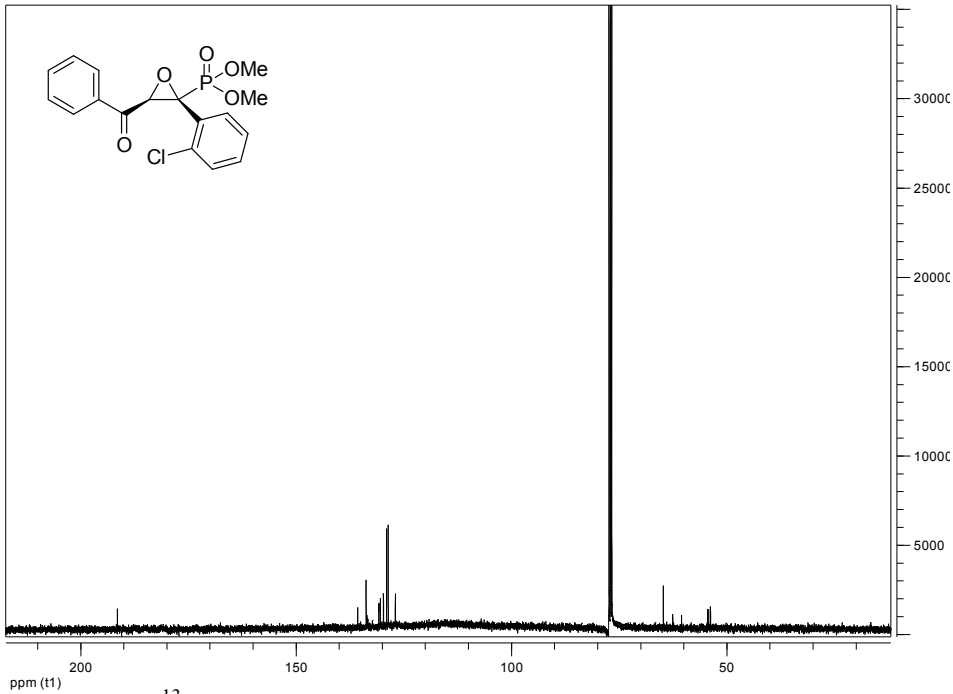

Figure 4.74 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(2-chlorophenyl)oxiran-2-ylphosphonate (*trans*-155f)**

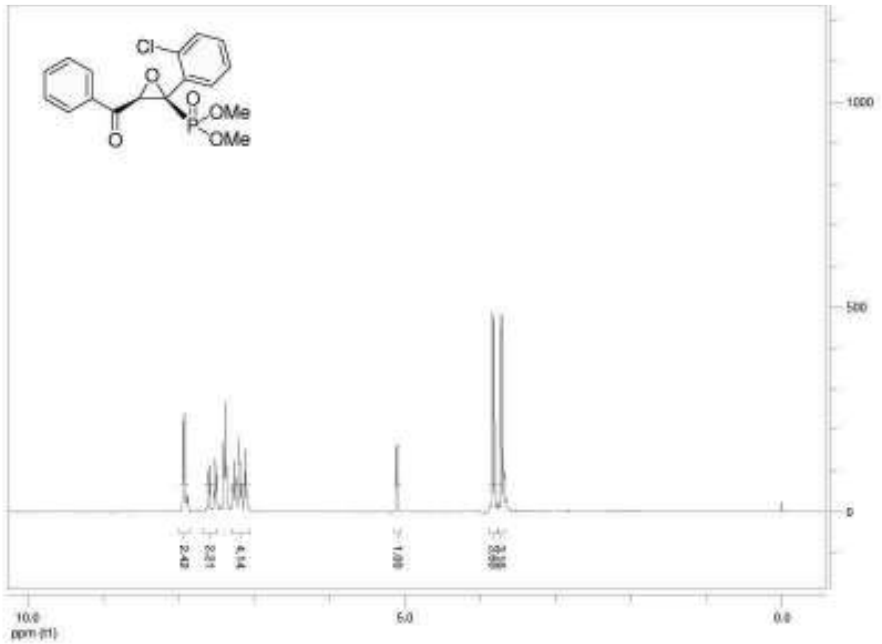

Figure 4.75 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(2-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155f)**

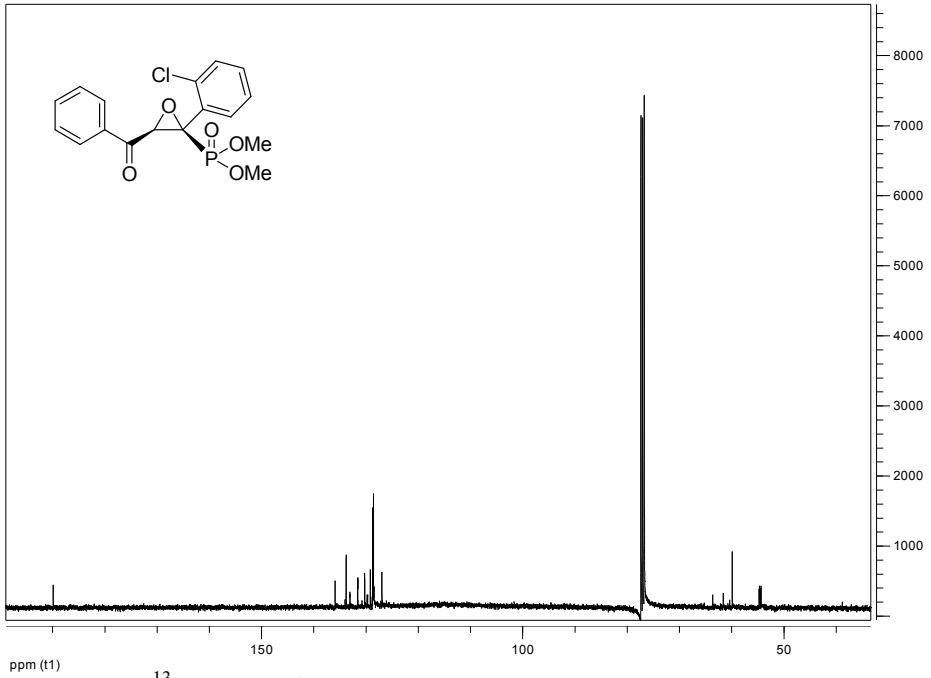

Figure 4.76 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(2-chlorophenyl)oxiran-2-ylphosphonate (*cis*-155f)**

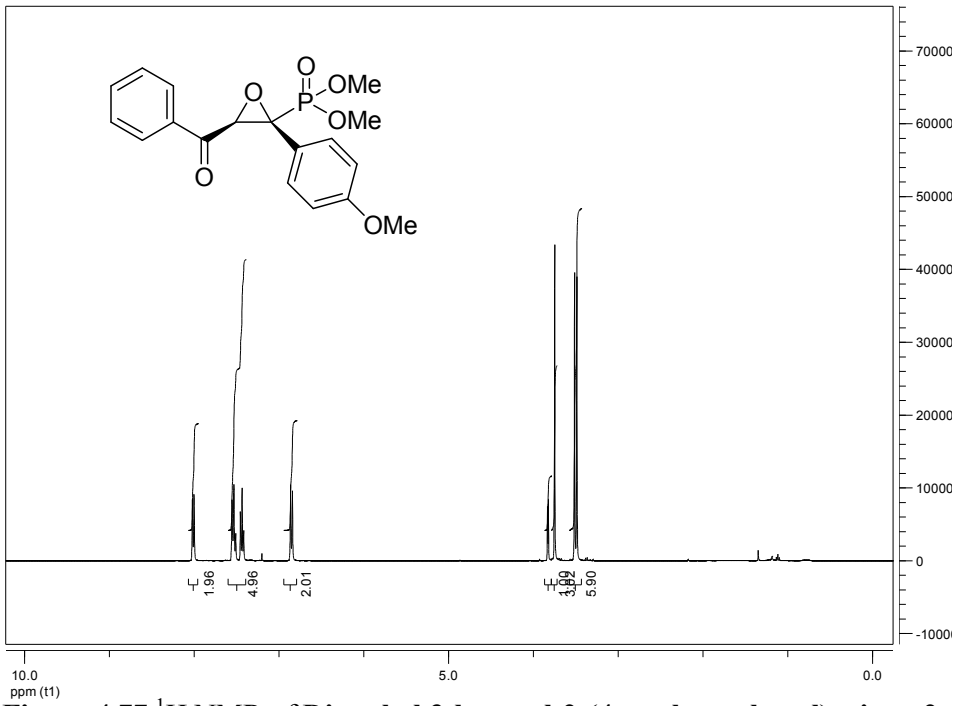

Figure 4.77 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-3g)**

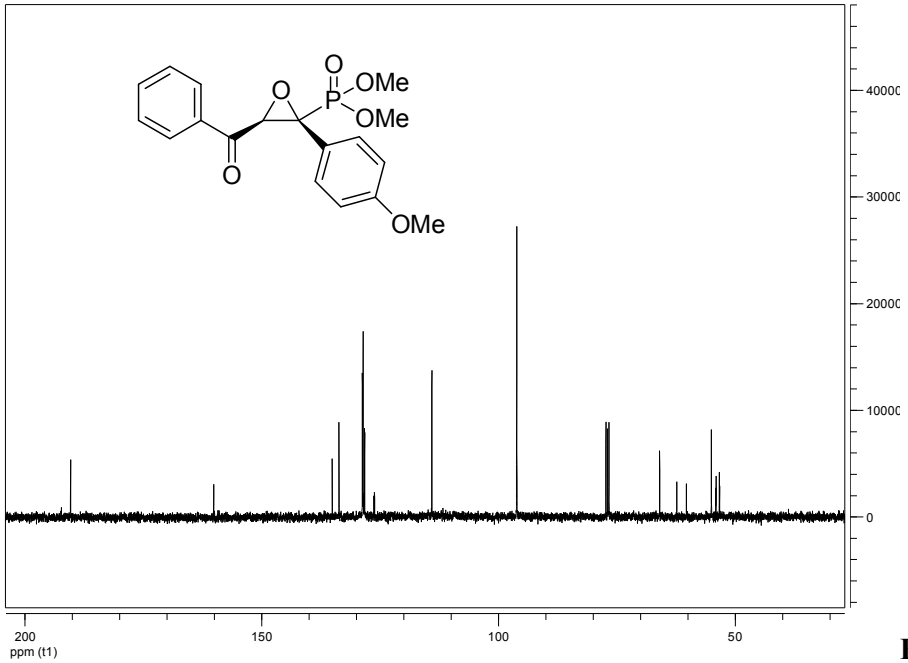

Figure 4.78 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155g)**

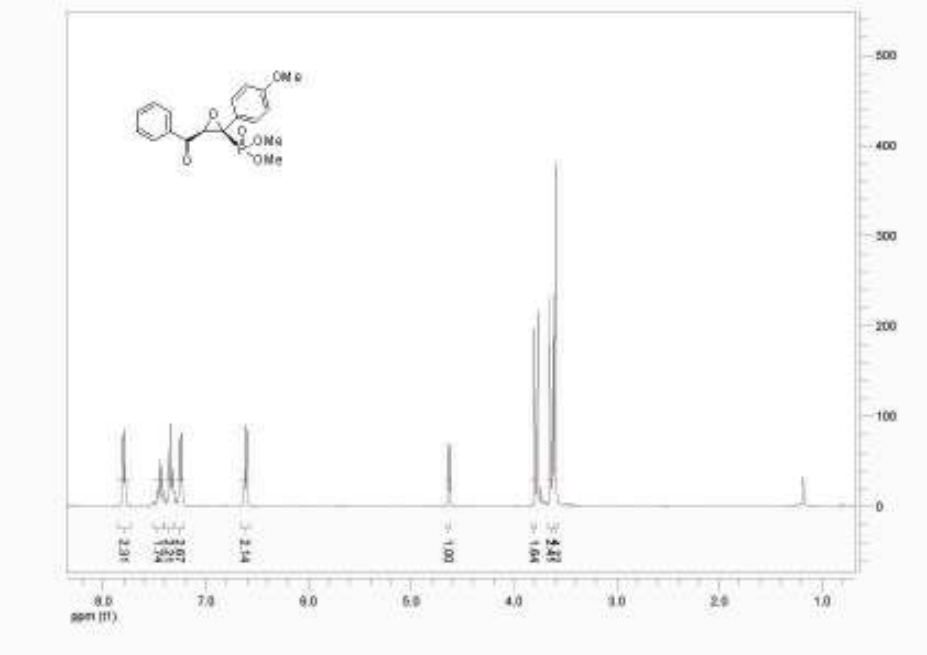

Figure 4.79 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155g)**

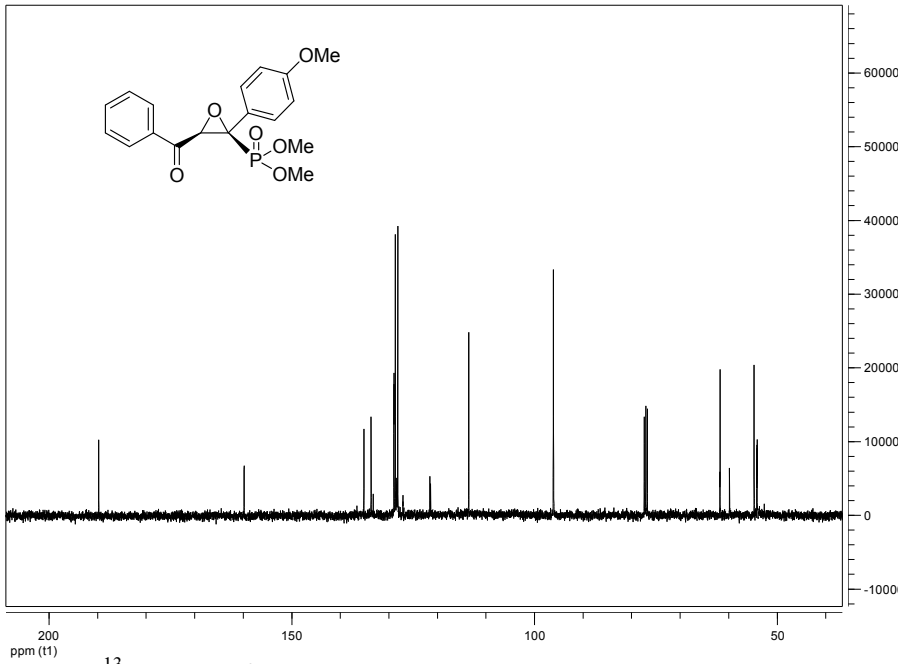

Figure 4.80 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155g)**

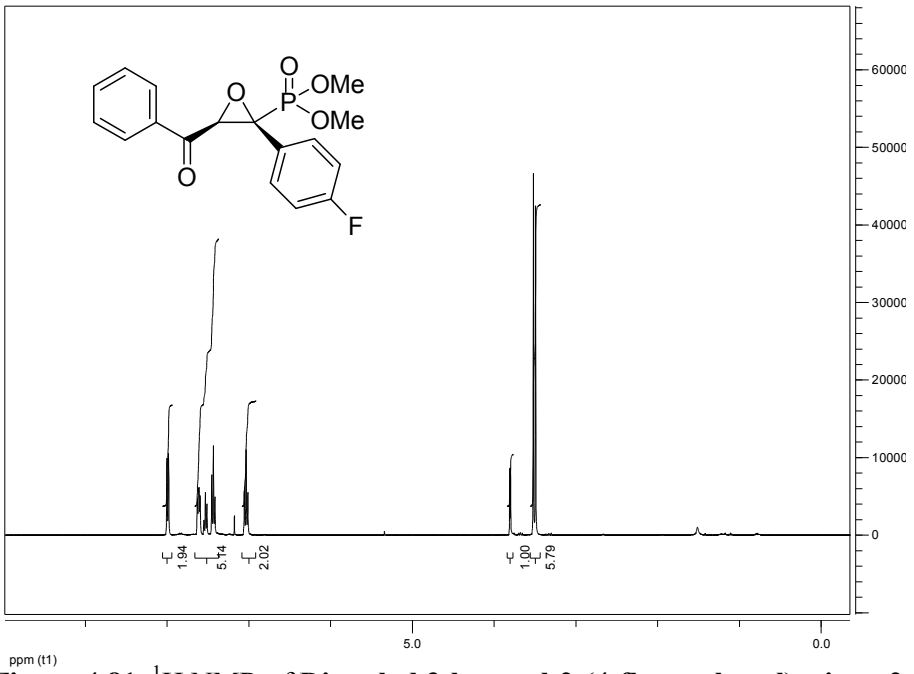

Figure 4.81 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-3h)**

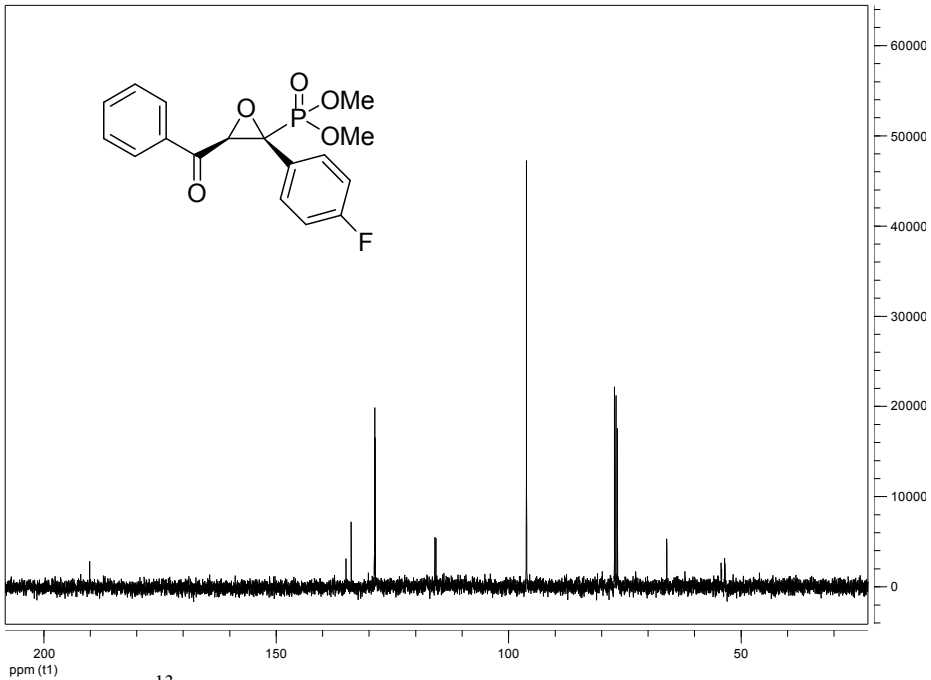

Figure 4.82 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-155h)**

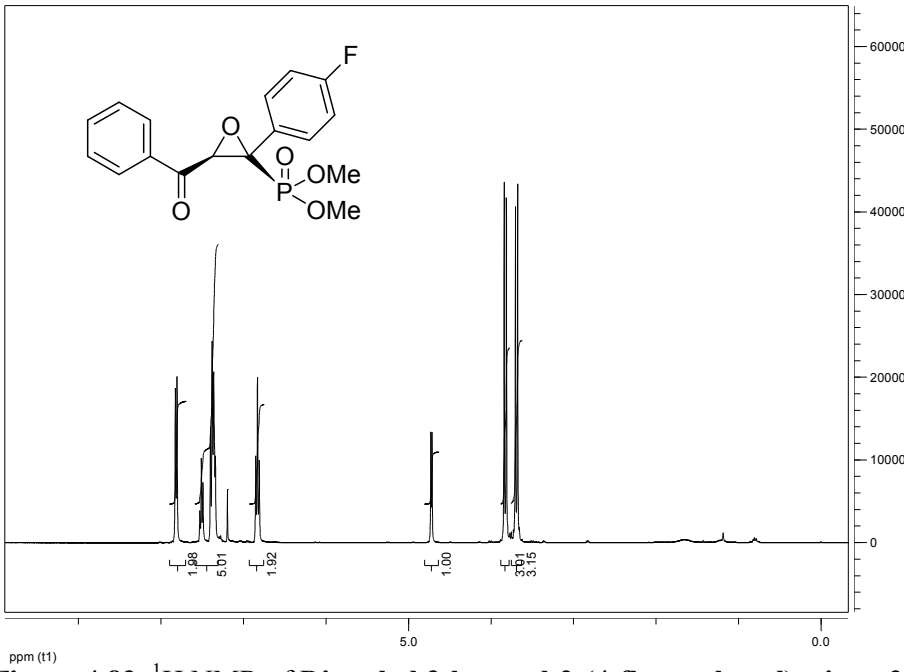

Figure 4.83 ^{1}H NMR of **Dimethyl 3-benzoyl-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-155h)**

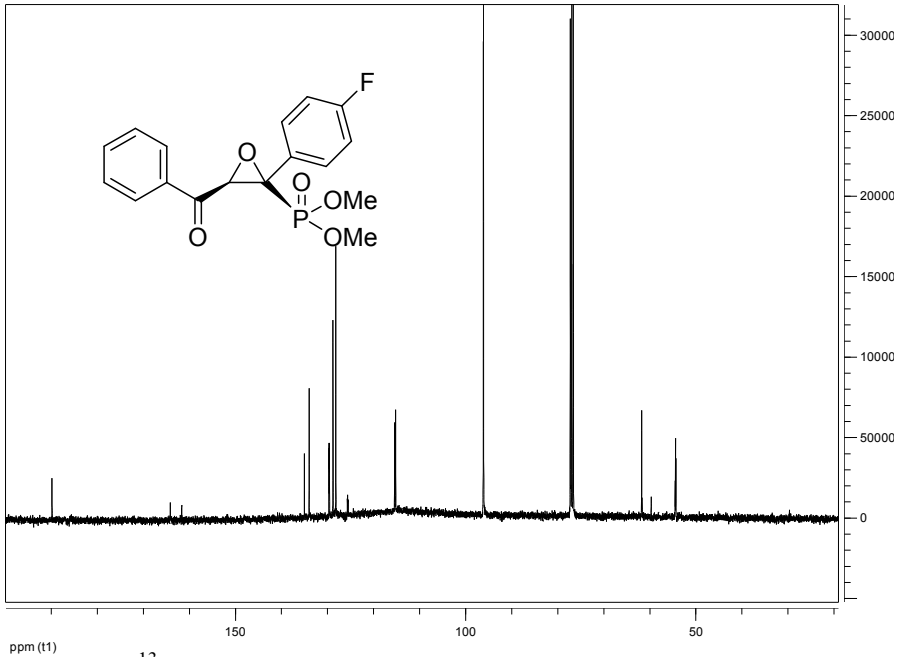

Figure 4.84 ^{13}C NMR of **Dimethyl 3-benzoyl-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-3h)**

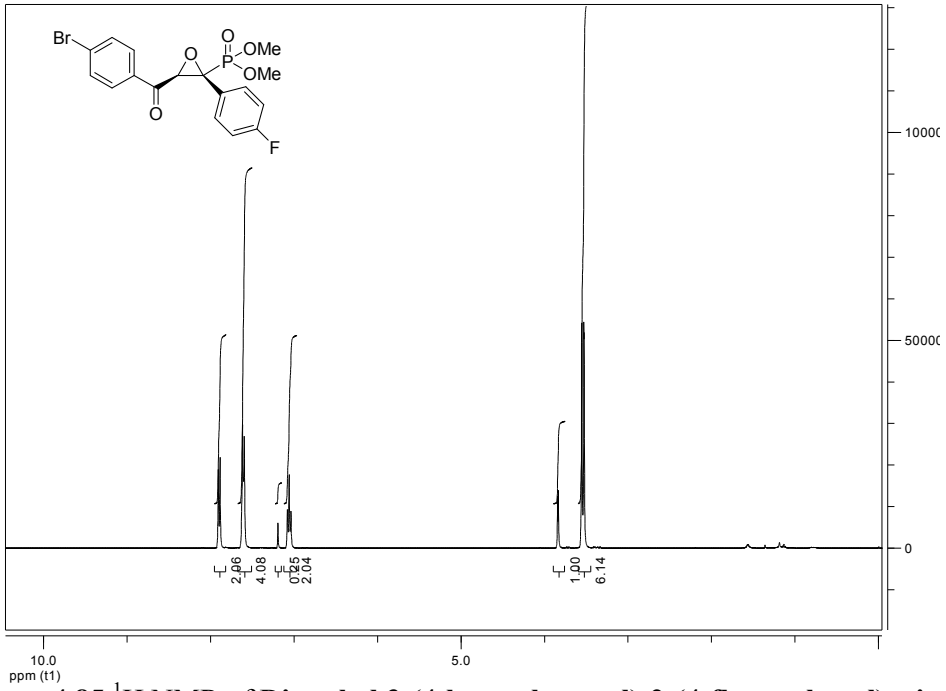

Figure 4.85 ^{1}H NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-155i)**

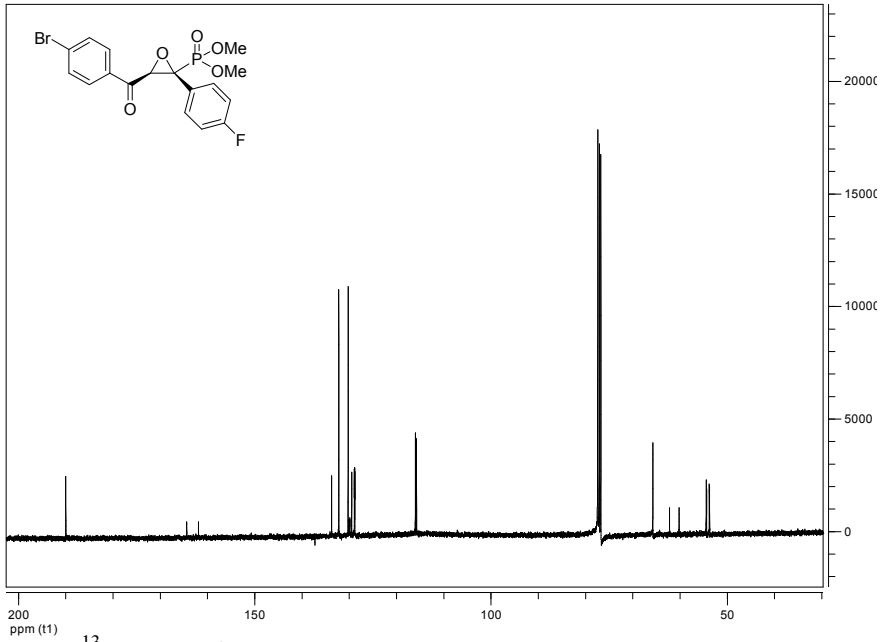

Figure 4.86 ^{13}C NMRof **Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-155i)**

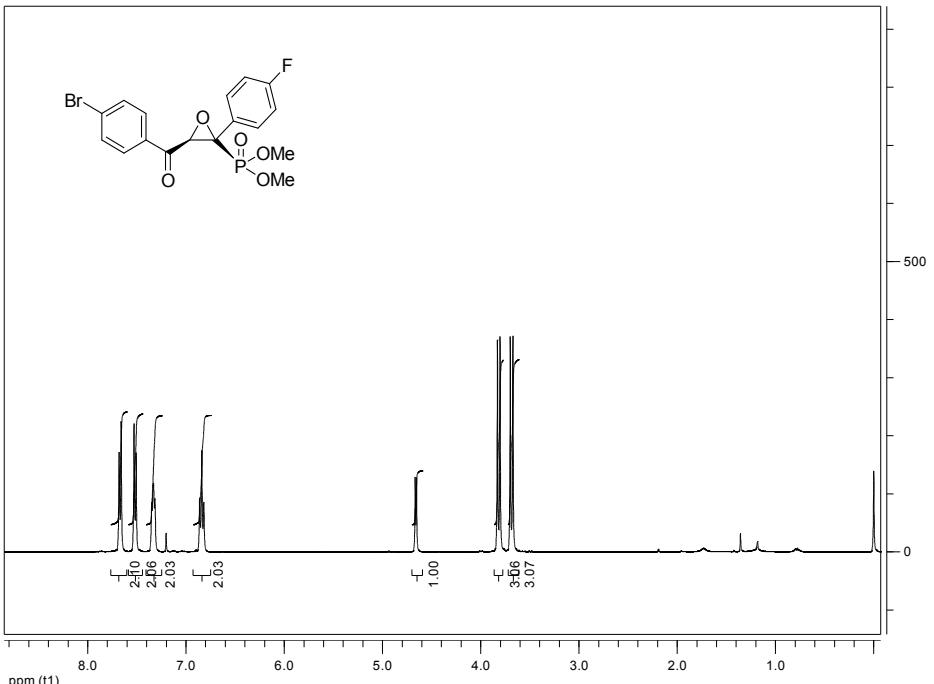

Figure 4.87 ^{1}H NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-155i)**

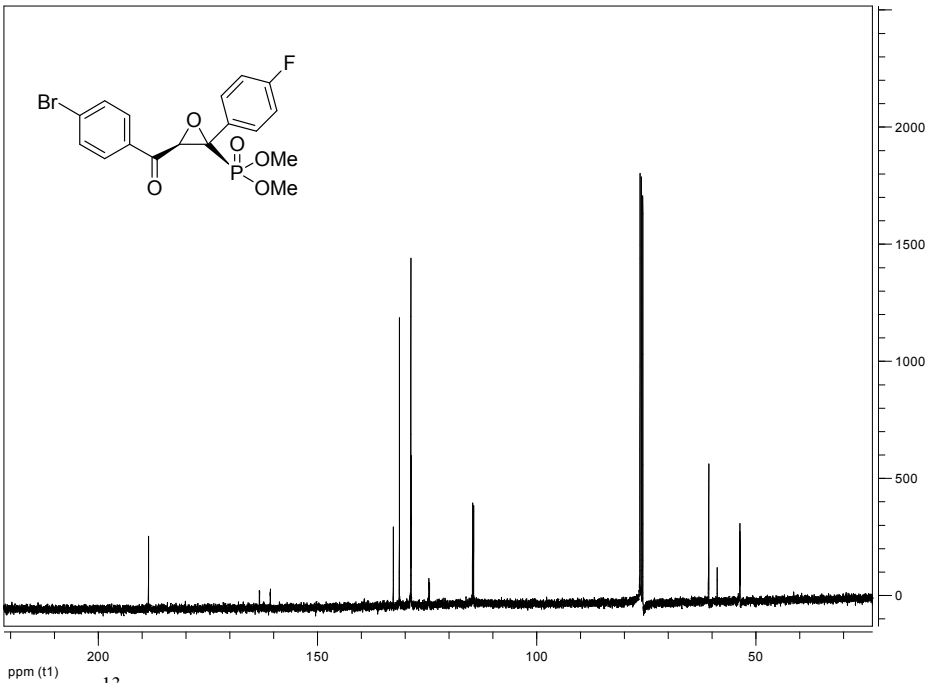

Figure 4.88 ^{13}C NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-3i)**

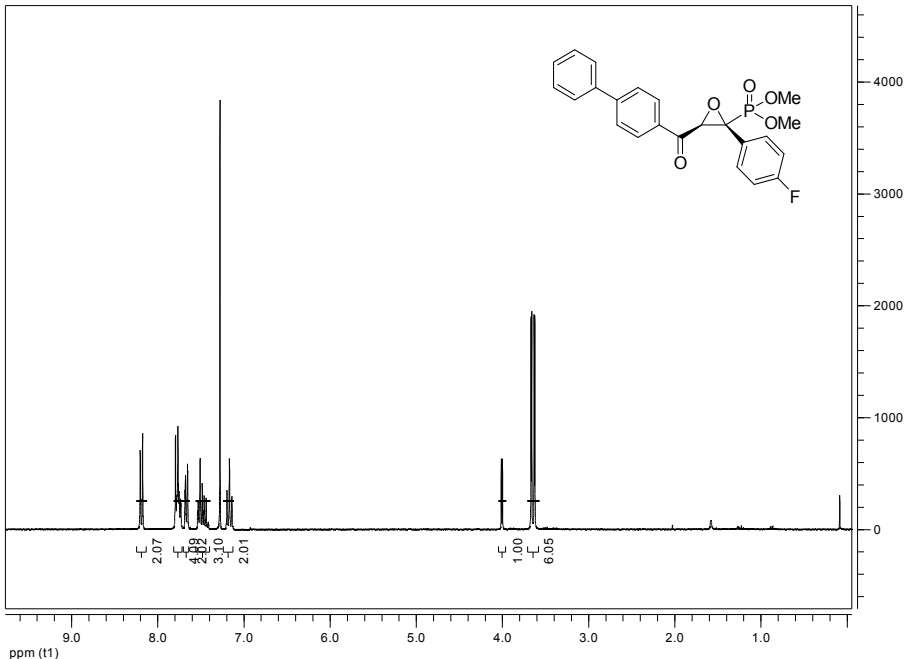

Figure 4.89 ^{1}H NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-3j)**

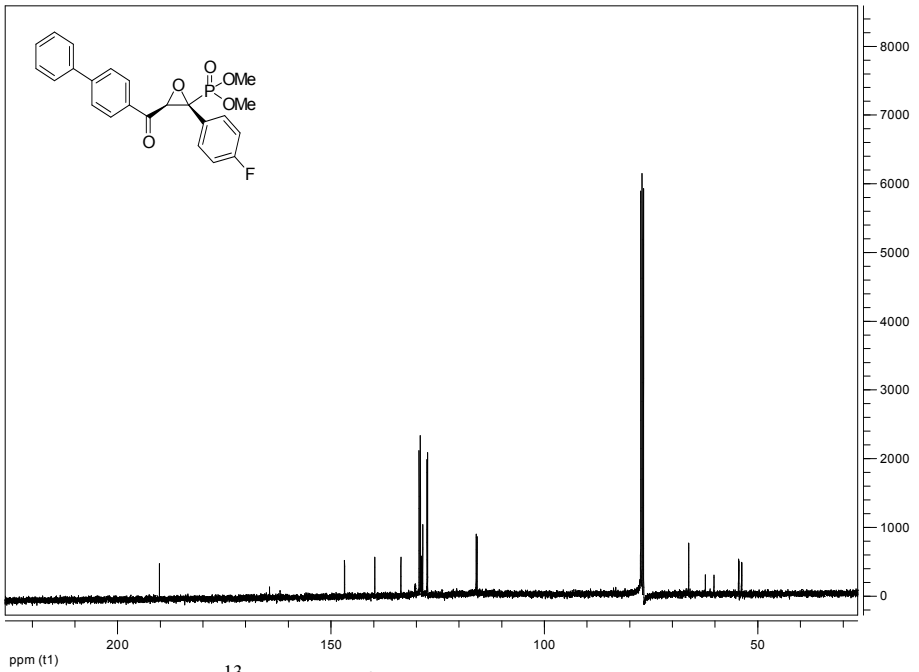

Figure 4.90 ^{13}C NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*trans*-3j)**

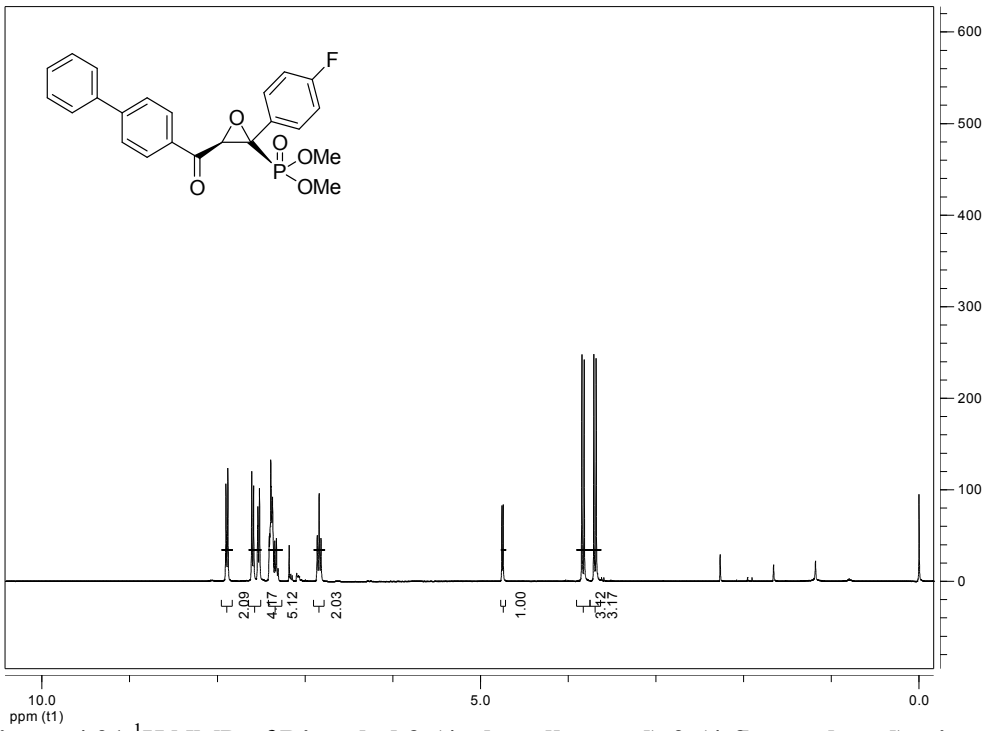

Figure 4.91 ^{1}H NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-3j**

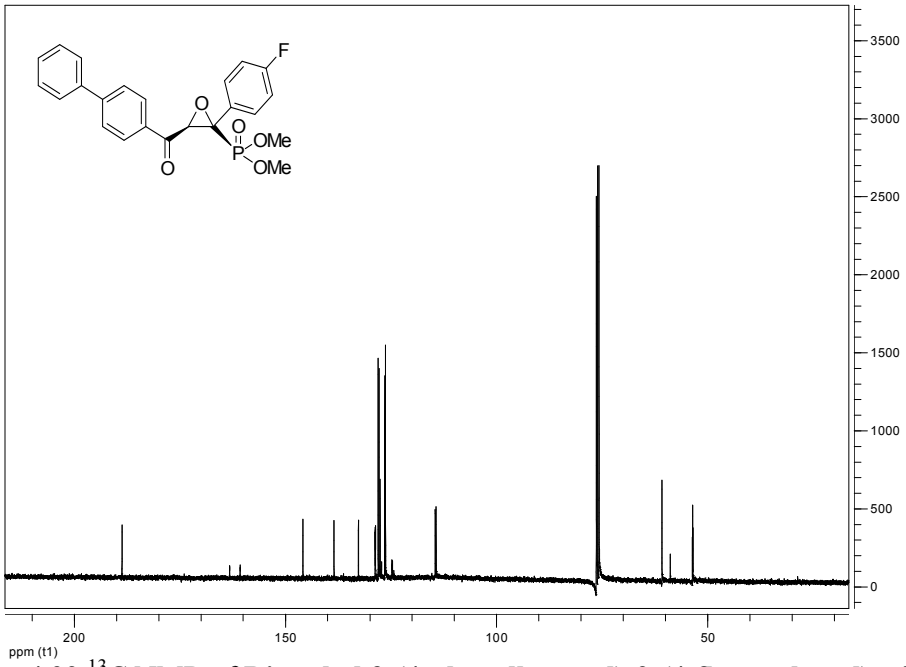

Figure 4.92 ^{13}C NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-fluorophenyl)oxiran-2-ylphosphonate (*cis*-155j)**

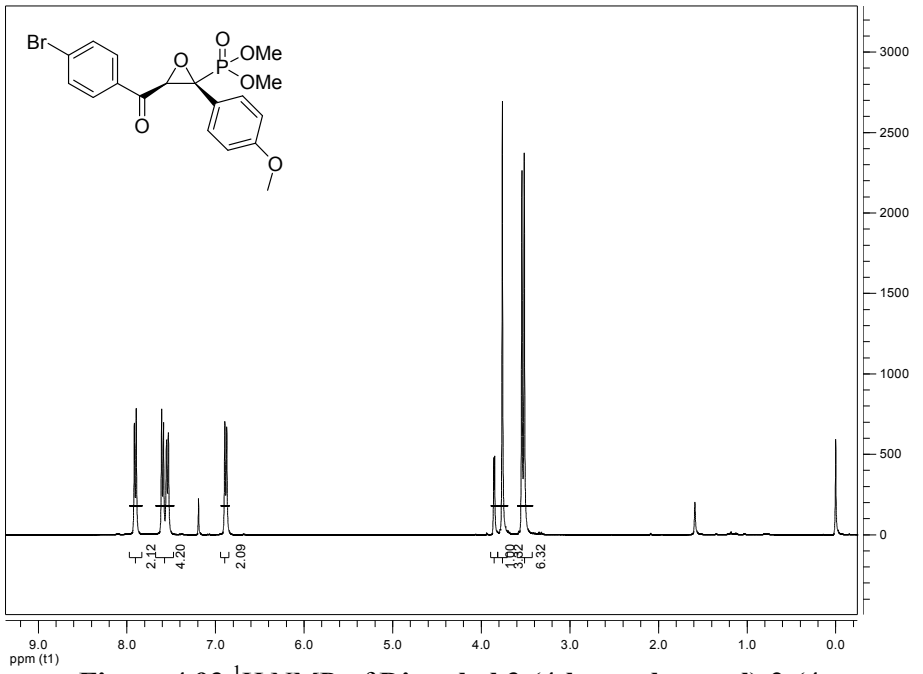

Figure 4.93 ^{1}H NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155k)**

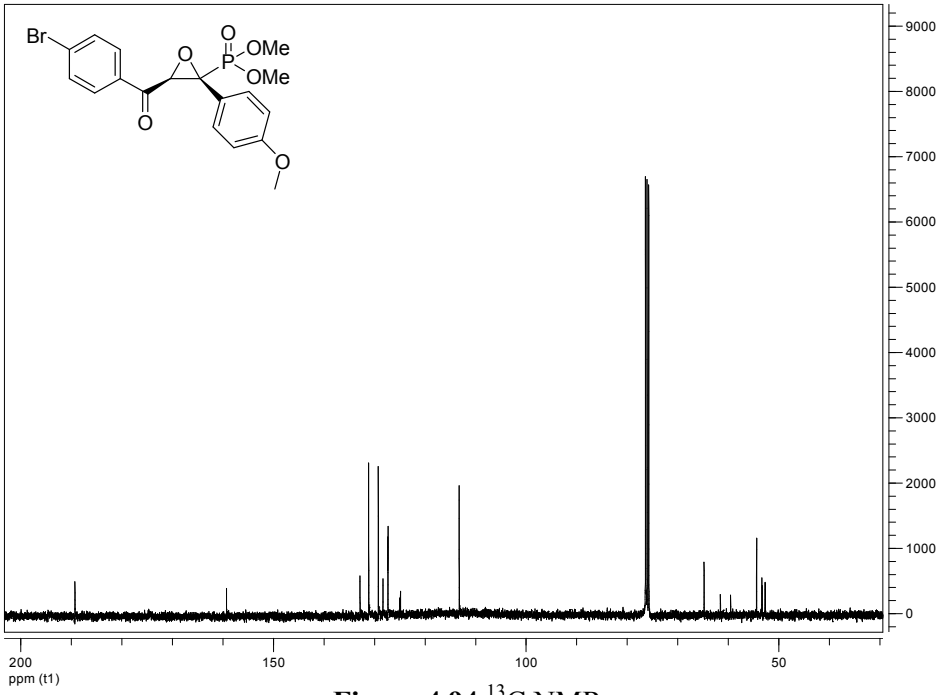

Figure 4.94 ^{13}C NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155k)**

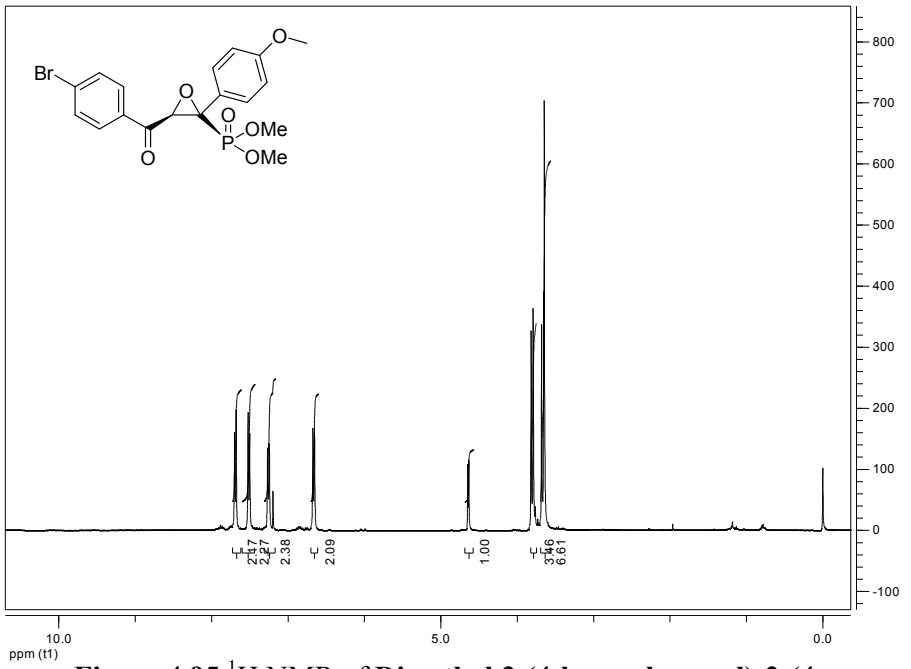

Figure 4.95 ^{1}H NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155k)**

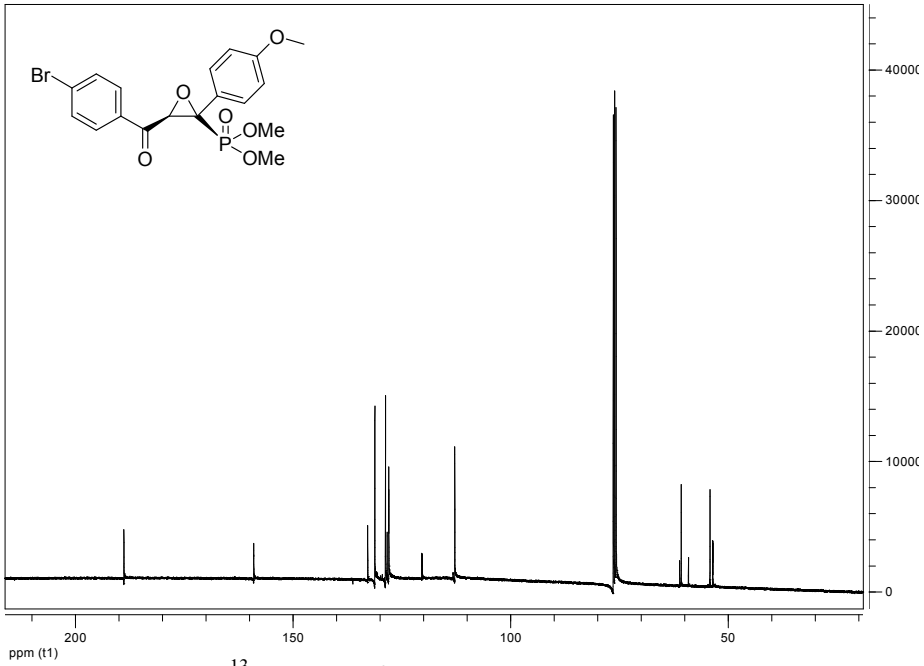

Figure 4.96 ^{13}C NMR of **Dimethyl 3-(4-bromobenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155k)**

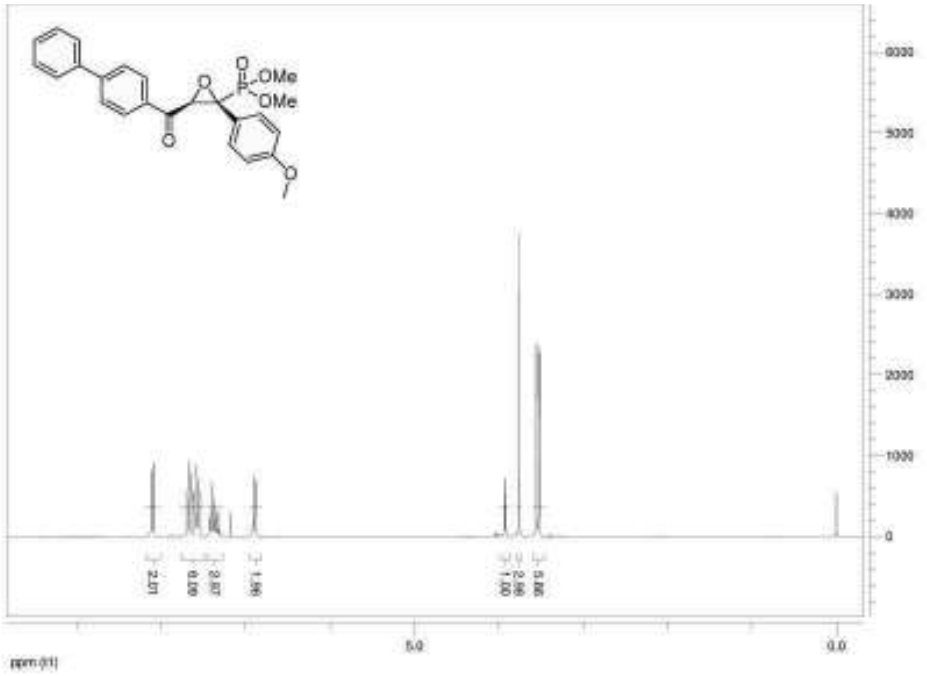

Figure 4.97 ^{1}H NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155l)**

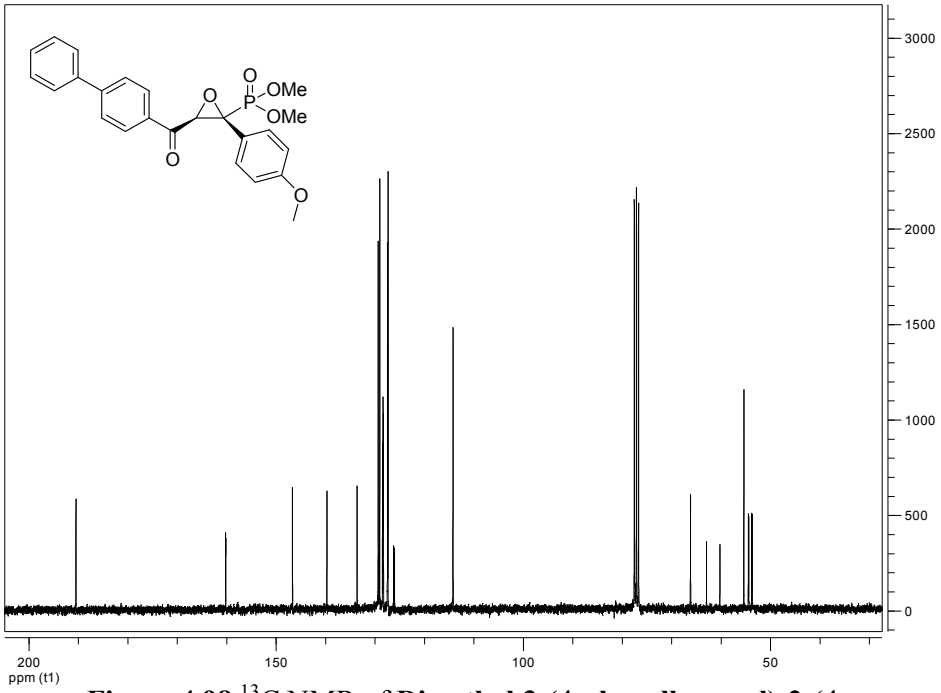

Figure 4.98 ^{13}C NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*trans*-155l)**

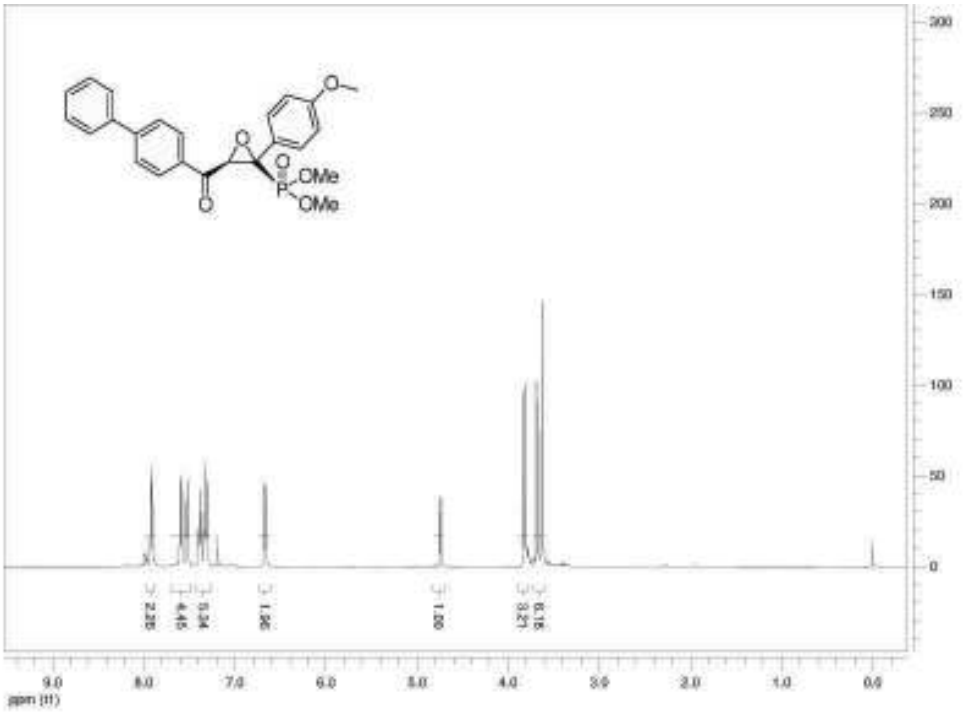

Figure 4.99 ^{1}H NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155l)**

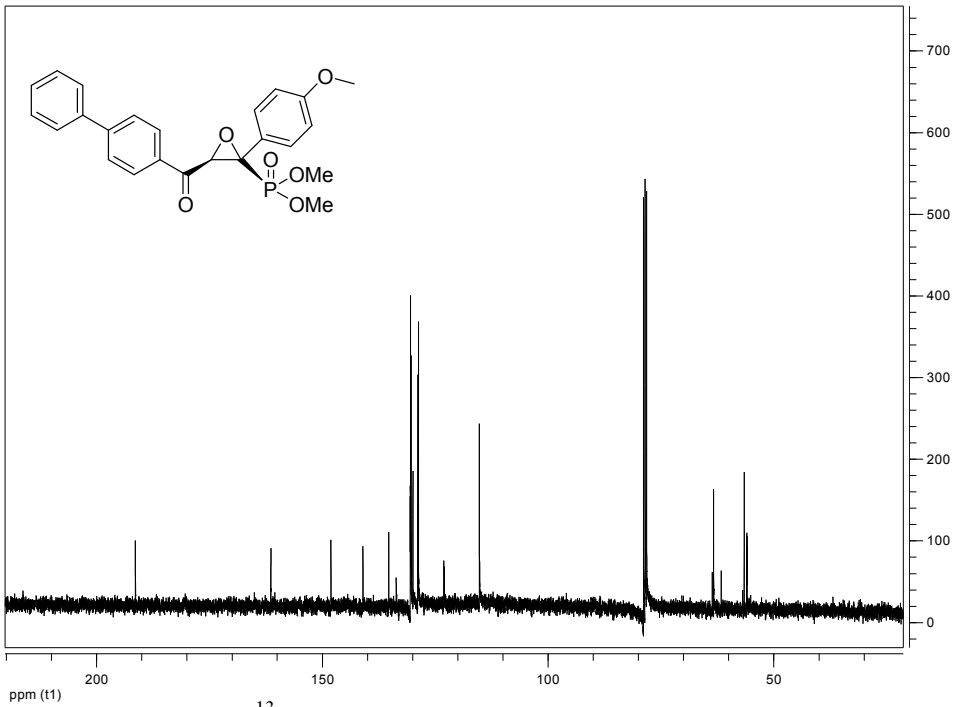

Figure 4.100 ^{13}C NMR of **Dimethyl 3-(4-phenylbenzoyl)-2-(4-methoxyphenyl)oxiran-2-ylphosphonate (*cis*-155l)**

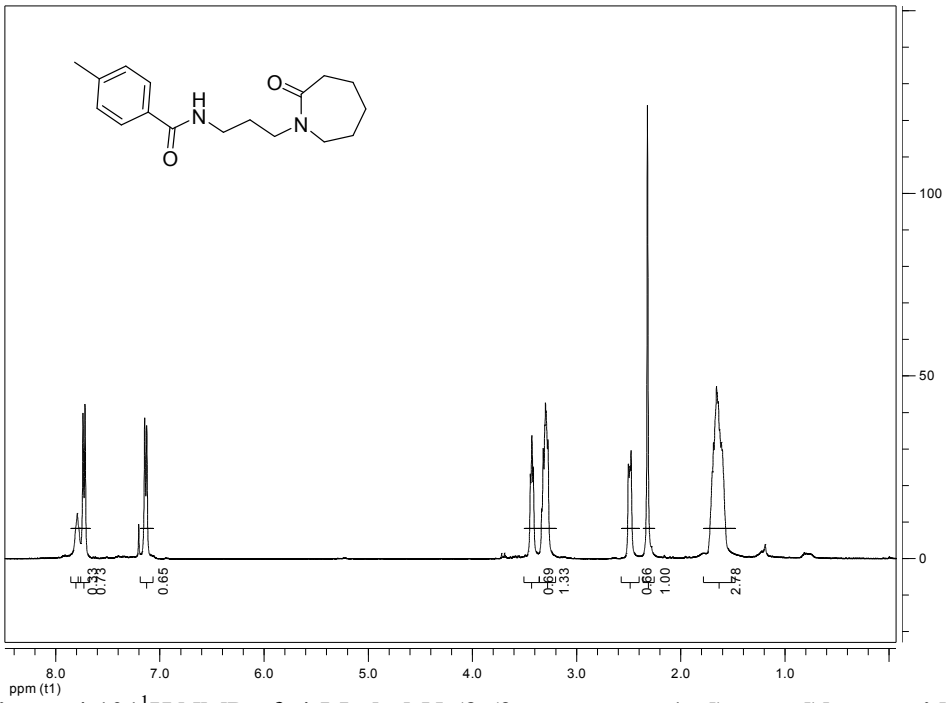

Figure 4.101 ^{1}H NMR of **4-Methyl-N-(3-(2-oxoazepan-1-yl)propyl)benzamide (159)**

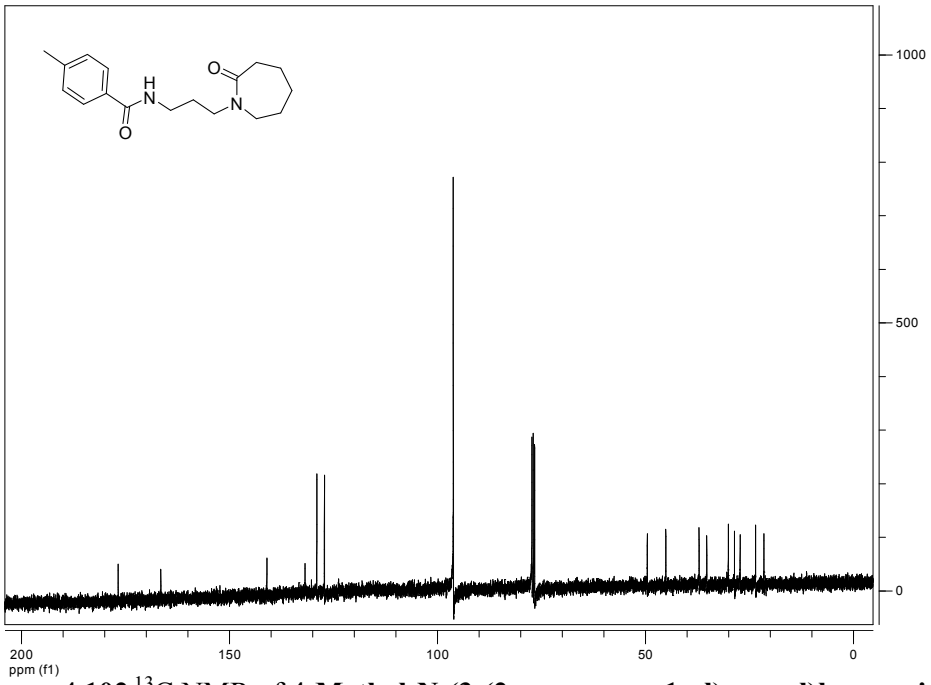

Figure 4.102 ^{13}C NMR of **4-Methyl-N-(3-(2-oxoazepan-1-yl)propyl)benzamide (159)**

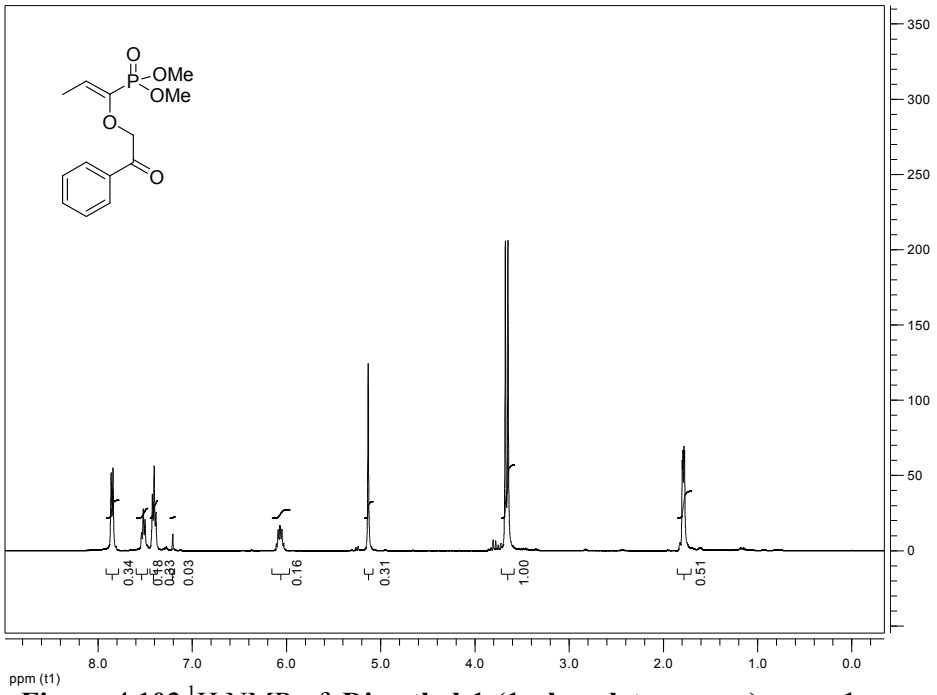

Figure 4.103 ^{1}H NMR of **Dimethyl-1-(1-phenyletanonoxy)-prop-1-ene phosphonate (162)**:

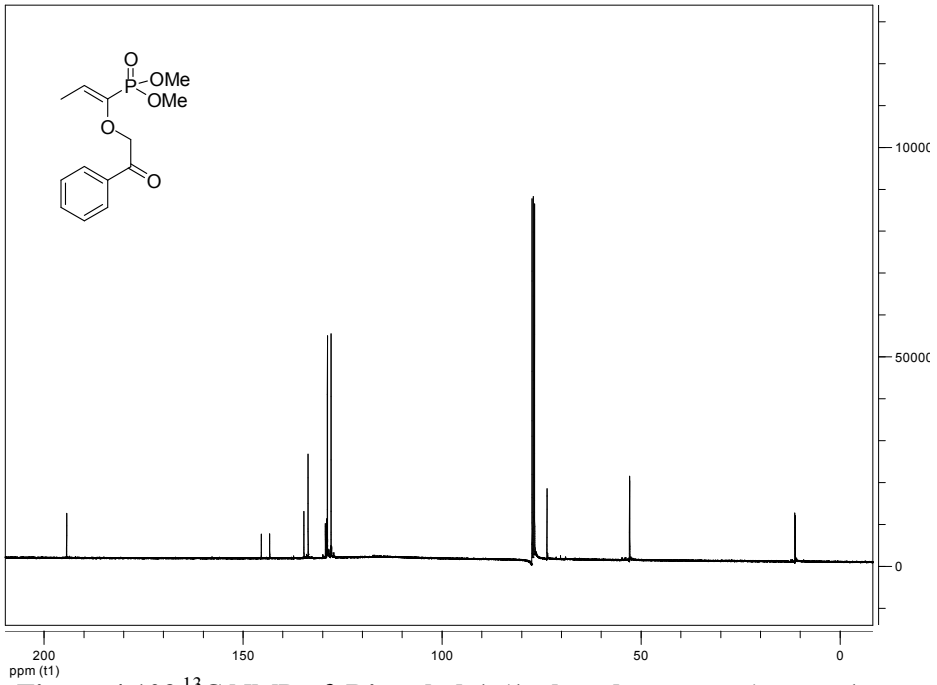

Figure 4.103 ^{13}C NMR of **Dimethyl-1-(1-phenyletanonoxy)-prop-1-ene phosphonate (162)**:

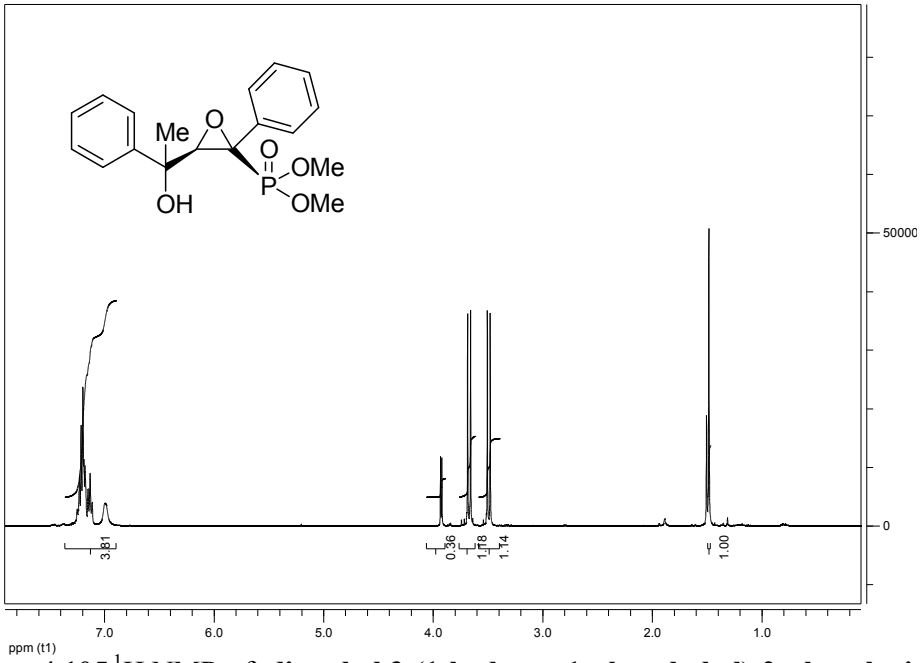

Figure 4.105 ^{1}H NMR of **dimethyl 3-(1-hydroxy-1-phenylethyl)-2-phenyloxiran-2-ylphosphonate (163)**

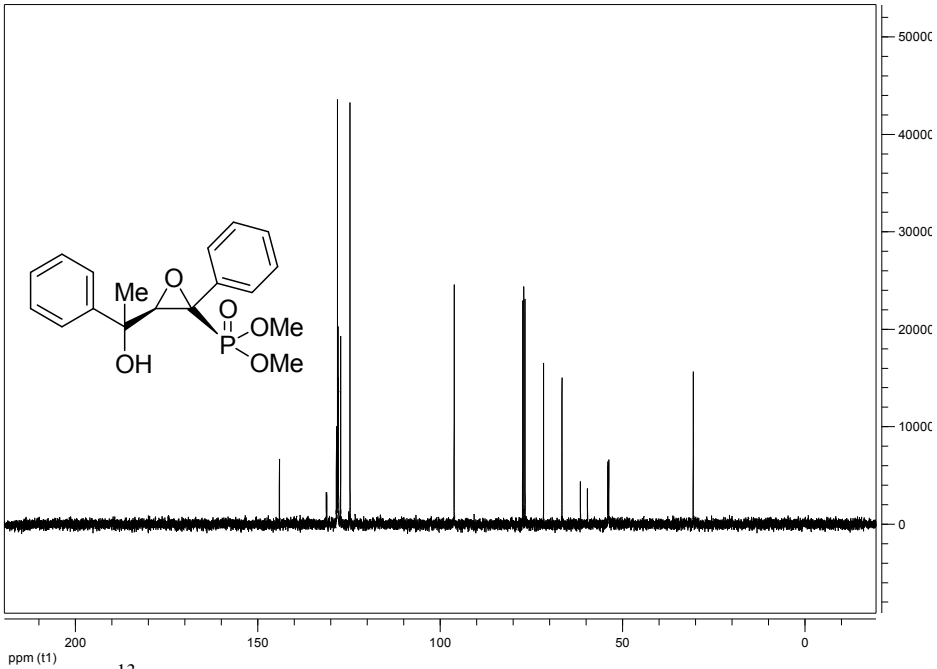

Figure 4.106 ^{13}C NMR of **dimethyl 3-(1-hydroxy-1-phenylethyl)-2-phenyloxiran-2-ylphosphonate (163)**

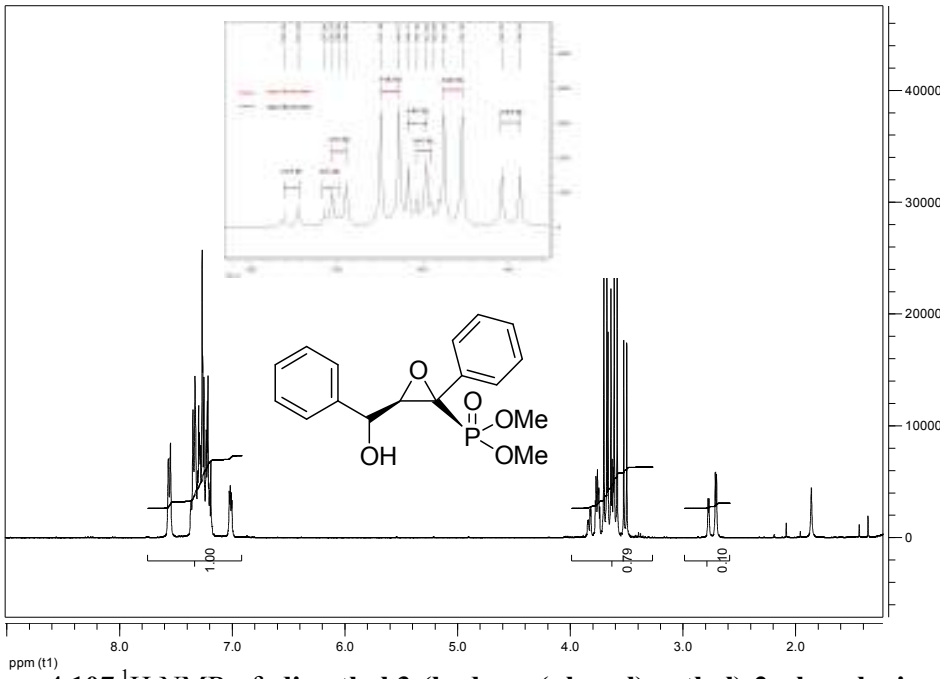

Figure 4.107 ^{1}H NMR of **dimethyl 3-(hydroxy(phenyl)methyl)-2-phenyloxiran-2-ylphosphonate (164)**

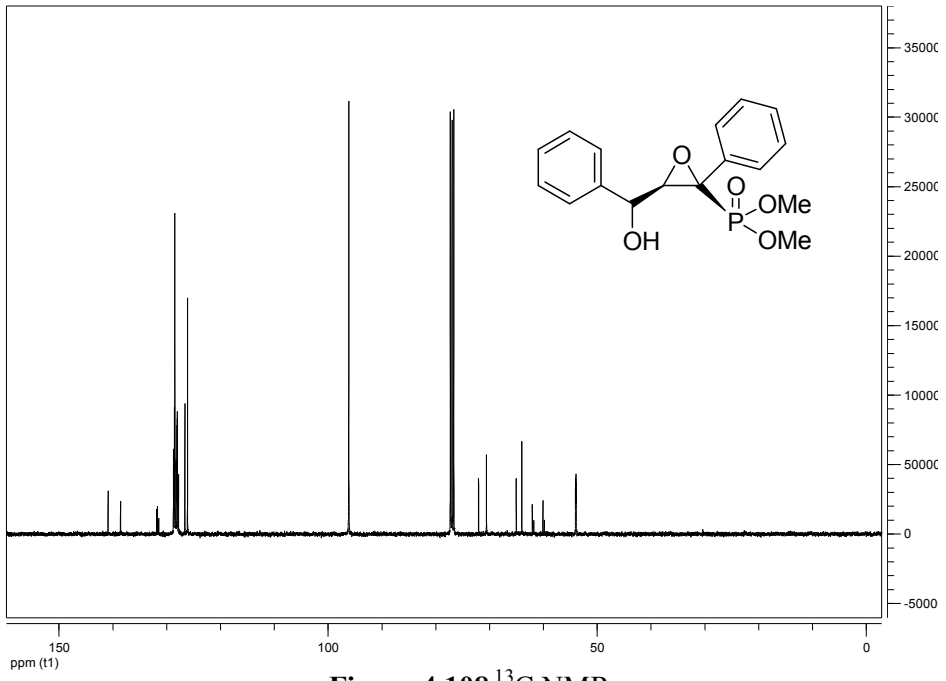

Figure 4.108 ^{13}C NMR
of **dimethyl 3-(hydroxy(phenyl)methyl)-2-phenyloxiran-2-ylphosphonate (164)**

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8.Manganese(III) Acetate-mediated oxidative coupling of phenylhydrazines with furan and thiophene: a novel method for heterobiaryl coupling, Emrullahoğlu, M., Reis, O., Demir, A. S.; *Tetrahedron***, 2002, 58, 8055**