NOVEL SYNTHETIC METHODOLOGIES FOR HETEROCYCLES AS BUILDING BLOCKS IN DRUG SYNTHESIS

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NURİYE TUNA SUBAŞI

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Approval of the thesis:

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submitted by **NURİYE TUNA SUBAŞI** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan Özgen _____
Dean, Graduate School of **Natural and Applied Sciences**

Prof. Dr. İlker Özkan _____
Head of Department, **Chemistry**

Prof. Dr. Ayhan S. Demir _____
Supervisor, **Chemistry Dept., METU**

Examining Committee Members:

Prof. Dr. Bekir Peynircioğlu _____
Chemistry Dept., METU

Prof. Dr. Ayhan S. Demir _____
Chemistry Dept., METU

Prof. Dr. Özdemir Doğan _____
Chemistry Dept., METU

Assoc. Prof. Dr. Nezire Saygılı _____
Faculty of Pharmacy., Hacettepe University

Assist. Prof. Dr. Sıdıka Polat Çakır _____
Chemistry Dept., Nevşehir University

Date:

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

Name, Last name : Nuriye Tuna Subaşı

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ABSTRACT

NOVEL SYNTHETIC METHODOLOGIES FOR HETEROCYCLES AS BUILDING BLOCKS IN DRUG SYNTHESIS

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Subaşı, Nuriye Tuna

Ph.D., Department of Chemistry

Supervisor: Prof. Dr. Ayhan S. Demir

Nitrogen containing heterocycles have always constituted a subject of great interest due to their wide presence in biologically important compounds so the development of efficient methods for the preparation of pyrrole derivatives and formation of new pyrrole-based heterocyclic compounds are an attractive goal in heterocyclic chemistry. In this study, starting from dimethoxytetrahydrofurane and amino acid esters, unsubstituted pyrrole derivatives, and treatment of amino acid esters with convenient chloroenones 1,2-disubstituted and 1,2,4-trisubstituted pyrrole derivatives were synthesized without racemization. Reaction of unsubstituted pyrrole derivatives with norephedrine toward inter- and intramolecular cyclizations give new interesting heteropolycylic compounds with oxazole-pyrrole-pyrazine structures. Study continued with cyclization reaction of these synthesized substituted and unsubstituted pyrrole derivatives with BBr_3 and new bicyclic pyrrole derivatives were obtained in moderate yield.

Keywords: Substituted pyrrole derivatives, chloroenone, norephedrine, BBr_3 cyclization.

ÖZ

İLAÇ BAŞLANGIÇ MADDELERİ HETEROSİKLİK BİLEŞİKLERİN SENTEZLERİ İÇİN YENİ YÖNTEMLER GELİŞTİRİLMESİ

Ocak 2011, 123 sayfa

Subaşı, Nuriye Tuna

Doktora, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Azot içeren heterosiklik moleküller biyolojik aktivite gösteren maddelerin yapılarında bulunduğundan daima büyük ilgi çeken bir konu olmuştur. Bu nedenle pirol türevlerinin ve pirol tabanlı heterosiklik bileşiklerin sentezlenmesi için etkili yöntemlerin geliştirilmesi heterosiklik kimyada ilgi çekici bir hedeftir. Bu çalışmada öncelikle dimetoksitetrahidrofuran ve amino asit esterleri kullanılarak sübstitüe olmayan pirol türevleri, uygun kloroenonların amino asitlerle etkileştirilmesi sonucunda da 1,2-disübstitüe ve 1,2,4-trisübstitüe pirol türevleri sentezlenmiştir. Sübstitüe olmayan pirol türevlerinin norefedrin ile molekül içi halkalaşma reaksiyonu sonucu yeni oksazol-pirol-pirazin yapısında ilginç heteropolisiklik bileşikler elde edilmiştir. Çalışma, sentezlenen sübstitüe ve sübstitüe olmayan bu pirol türevlerinin BBr_3 ile halkalaşma reaksiyonuyla devam etmiş ve yeni bisiklik pirol türevleri iyi bir verimle elde edilmiştir.

Anahtar kelimeler: Sübstitüe pirol türevleri, kloroenon, norefedrin, BBr_3 ile halkalaşma reaksiyonu.

To my husband Kenan Canbaz and precious family

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CHAPTER 1

INTRODUCTION

1.1 The Importance of Pyrroles in Pharmaceutical Chemistry

1.1.1 Pyrroles as Natural Products

Almost half of the all known compounds contain a heterocyclic ring, and many of these are aromatic heterocyclic rings. Heteroaromatics are found in many of the products such as drugs, pest control agents, colouring agents and flavourings. They involve the basic building blocks for many new materials such as porphyrines, semi-conducting polymers and as ligands for homogeneous asymmetric catalysis. Due to their vital importance, heteroaromatic compounds still represent a very active area of current research.

Heterocycles have played an important role in the evalution of life. Most of the coenzymes and vitamins contain heterocycles. The heterocyclic ring is often the central constituent necessary to fulfill the biological function of the coenzymes, thiamine pyrophosphate **1**, NAD^+ **2** and Vitamin B_6 **3**

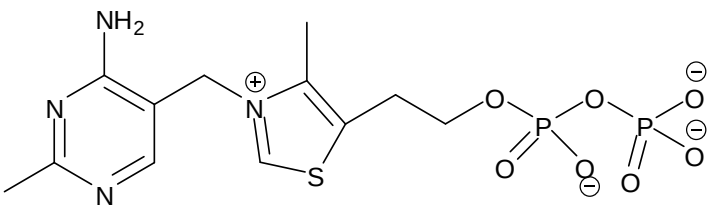


Figure 1. Structure of thiamine pyrophosphate

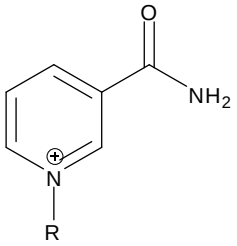


Figure 2. Structure of NAD^+

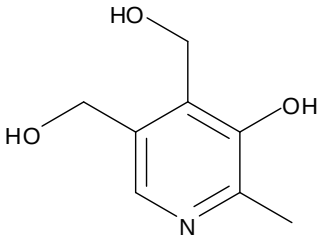


Figure 3. Structure of Vitamin B_6

Compounds containing a pyrrole ring occur in a large number of natural products and they have been found to be useful for applications in medicine and agriculture [1]. They display various physiological activities [2] in particular, 1,2,3,5-tetrasubstituted pyrrole derivatives [3] which are biologically active and have been proven to display antibacterial [4], antiviral [5], anti-inflammatory [6] and antioxidant activities and to inhibit cytokine-mediated diseases [7]. Additionally, they have been found to show potent inhibit platelet aggregation [8] and antihypertensive activities [9].

In particular, the biological importance of pyrroles and their derivatives is emphasized because several natural pigments, such as heme, chlorophyll, or enzymes like the various cytochromes include the pyrrole ring [10]. In addition to this, amino acids such as proline and hydroxypyroline also contain the hydrogenated pyyrole ring which is a pyrroline framework [11].

Some examples to pyrrolic natural products are given below **4-9**.

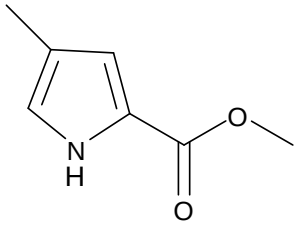


Figure 4.
Trail phremone of leaf-cutting ant *Acromyrmex*

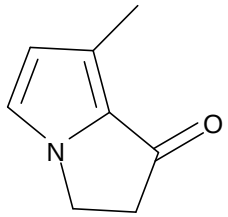


Figure 5.
Male sex pheromone from butterfly family *Danainae*

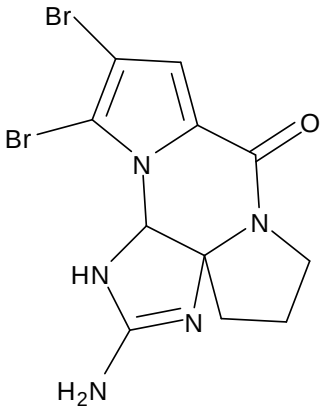


Figure 6.
Dibromophakellin from marine sponge *Phakellia flabellat*

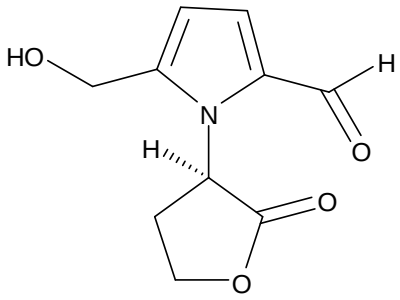


Figure 7.
Regulator of trigonelline-induced G2 arrest from *Pisum sativum*

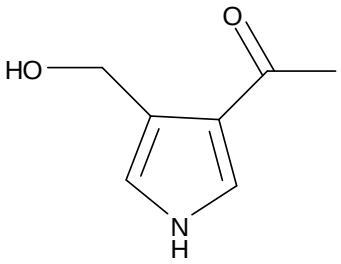


Figure 8.
verrucarin E from the fungus *Myrothecium verroceire*

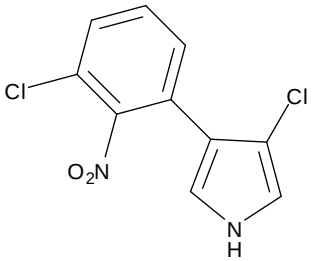


Figure 9.
Pyrrolnitrin antibiotic from *Peudomonas pyrrocinia*

Their biological functions are as variable as their structures **4-9** [12-14]. Some natural pyrroles are pheromones **4** [15,16], plant hormones **7** [17] or act as an antibiotics **9** [18].

Besides monopyrrolic natural products there are also polypyrrolic natural products. Two important examples of pyrole derived from natural products containing more than one pyrrole ring are Neotropsin **10** and Distamycin A **11** which bind to the minor groove of DNA [19]. They contain a series of pyrrole rings which are linked by amide bonds.

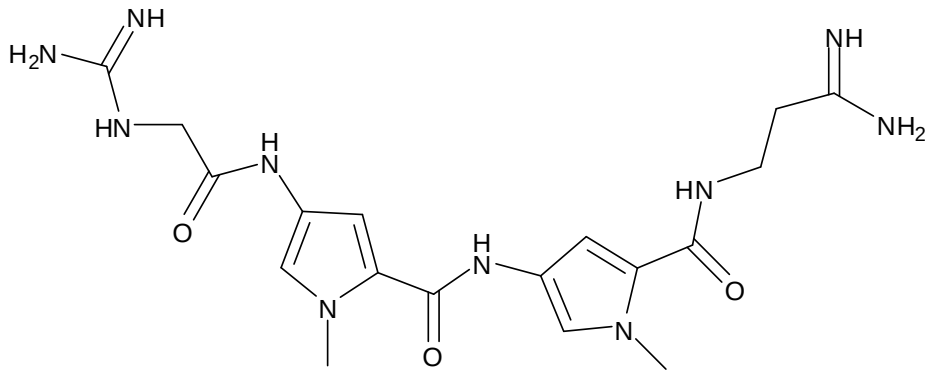


Figure 10. Structure of Neotropsin

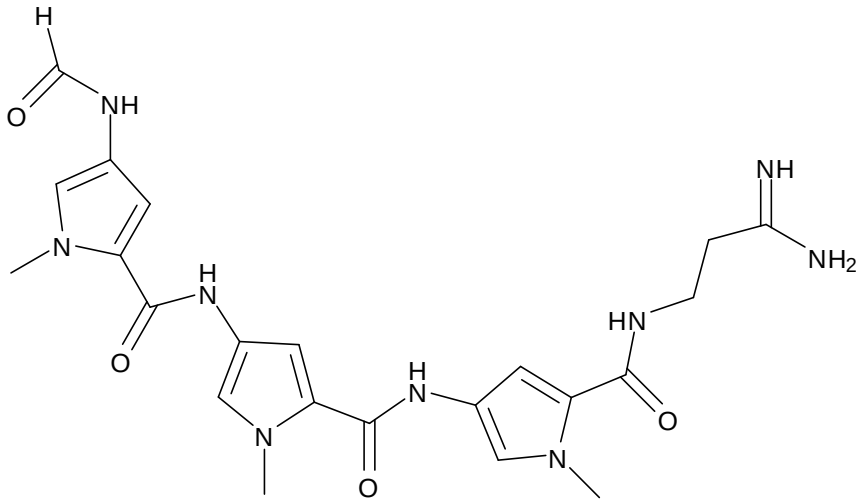


Figure11. Structure of Distamycin A

Porphobilinogen (PBG) **12**, the aromatic pyrrole play vitally important role in fundemental metabolism is a dedicated intermediate in the biosynthesis of tetrapyrroles [20-22].

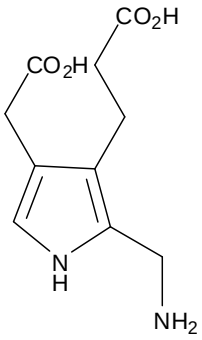


Figure 12. Structure of porphobilinogen

The tetrapyrrolic pigments heme **13** and chlorophyll α **14** play an important role for major parts of life. They are universally distributed and have therefore been named the “pigments of life” [23,24].

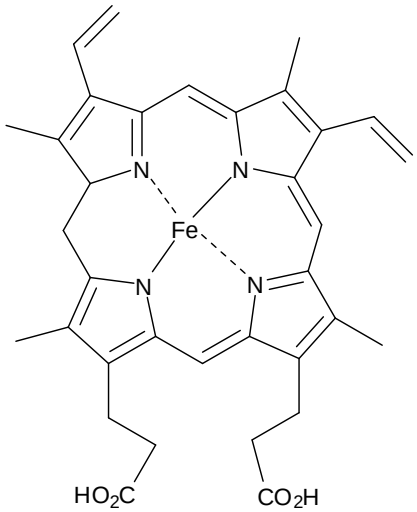


Figure 13. Structure of heme

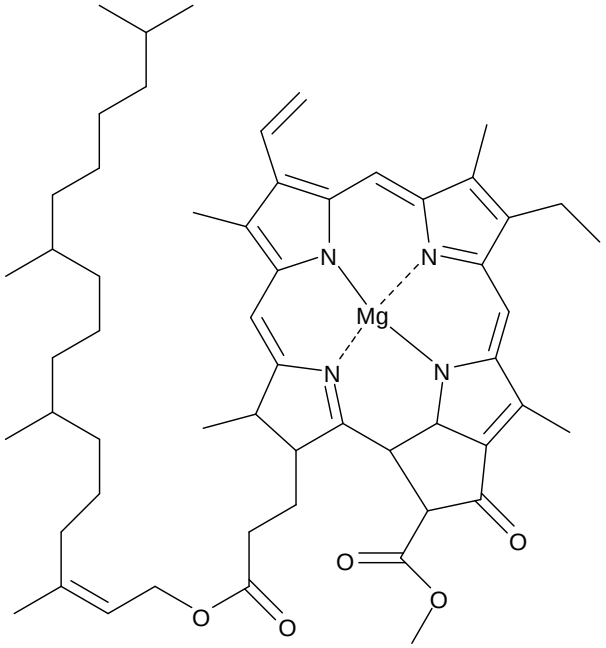


Figure 14. Structure of chlorophyll α

Anti-cholesterol drug, atorvastatin **15** is also very important pharmaceutical compound that contains a pyrrole ring.

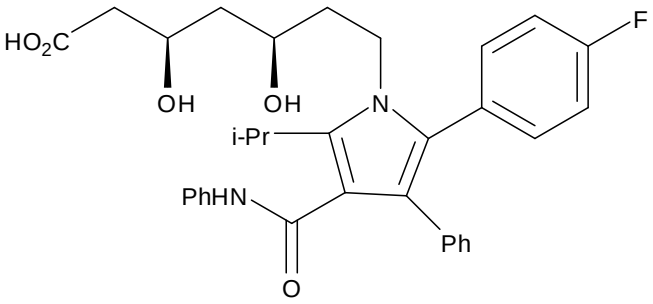


Figure 15. Structure of atorvastatin

The alkaloid nicotine **16** contains a pyrrolidine ring as well as pyridine ring.

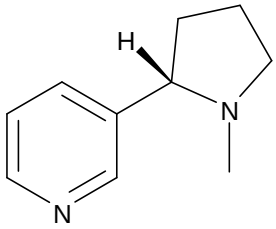


Figure 16. Structure of nicotine

1.1.2 Pyrroles as Aromatase Inhibitors

Aromatase inhibitors are a class of drugs used in the treatment of breast cancer and ovarian cancer in postmenopousal women. Some cancers require estrogen to grow and aromatase is an enzyme that synthesizes estrogen. Aromatase inhibitors block the synthesis of estrogen. This lowers the estrogen level and slows the growth of cancer.

Cytochrome P450 aromatase inhibitor is one of the therapeutic agents used for the treatment of breast cancer which is an estrogen dependent diseases [25]. In the recent times antisense oligodeoxynucleotides which are used as aromatase inhibitors and several nonsteroidal inhibitors of aromatase have been reported to inhibit human aromatase gene expression [26]. Most of these reported aromatase inhibitors consist of azole-type compound and they are commercially available or still under clinical research [27-29]. However, according to the latest results received in vivo and side effects of these compounds [30,31], the synthesis of more powerful and more specific aromatase inhibitors still remains a challenge.

For that purpose Bayer et al. [32-35] designed and synthesized some benzocycloalkene-type inhibitors. After that, Sonnet et al. [36] described the synthesis and the biological evaluation of a new 3-amino-2-arylmethyl indenones. They showed that MR20814 **17** inhibits efficiently human aromatase in vitro towards equine aromatase which is used as a useful comparative model to understand the active side of enzyme.

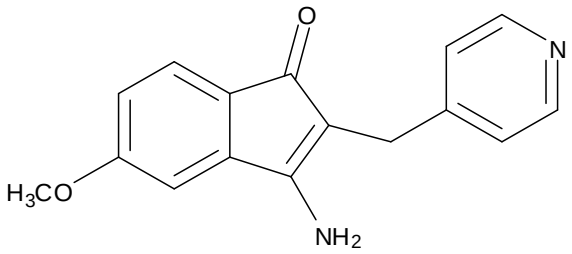


Figure 17. Structure of MR 20814

Sonnet et al. [36] showed that an interaction between the pyridine nitrogen atom of **17** and the heme iron atom of the human enzyme, led to dispose of the amino group of **17** at the entry of an extra-hydrophobic pocket. Also they proposed that the primary structure and the conformation of the enzyme cannot allow this position.

In order to confirm this hypothesis and to improve the activity of some compounds they replaced the amino group with the extra hydrophobic pocket which is phenyl ring and they synthesized compound **18** (MR 20496). By introducing the phenyl ring, its pyridin moiety was frozen in a Z geometry and this compound inhibits strongly human aromatase in vitro.

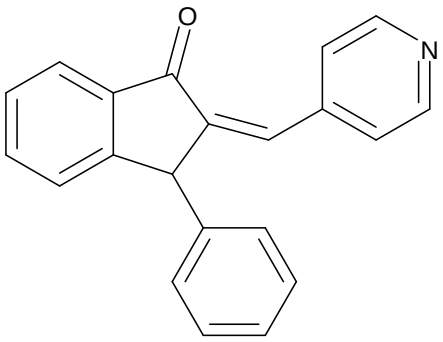


Figure 18. Structure of MR 20496

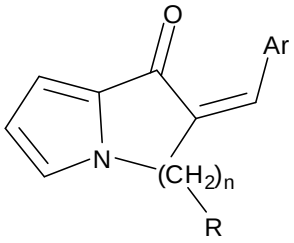


Figure 19. Structure of new aryl-substituted pyrrolizine and indolizidine derivatives (n=1,2)

Sonnet et al. evaluated these results and they designed a hypothetical pharmacore structure which is responsible for the aromatase inhibition and they reported the synthesis and the biological evaluation of new aryl-substituted pyrrolizine and indolizidine derivatives **19**, fitting this model. For that purpose they synthesized a series of pyrrolizinone compounds as shown Figure 20.

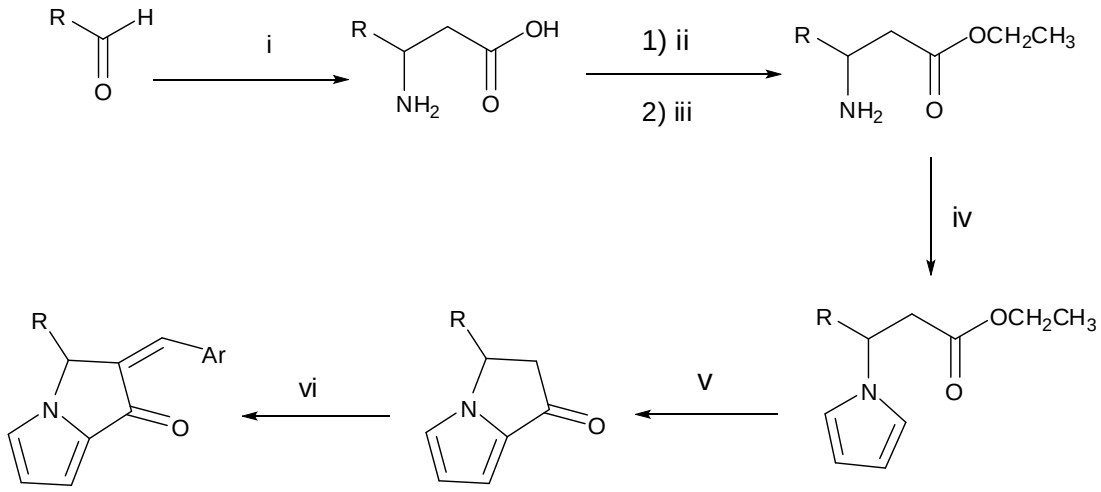
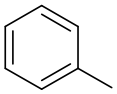
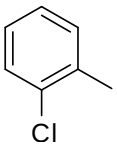
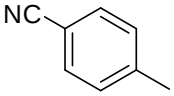
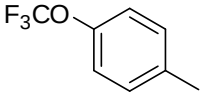
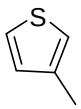
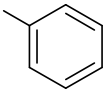
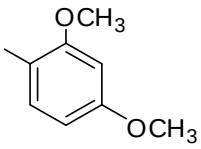
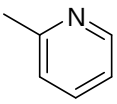
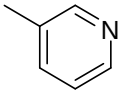
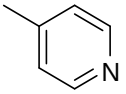


Figure 20. Synthesis of new aryl-substituted pyrrolizine and indolizine derivatives. (i) $CH_2(COOH)_2$, $AcONH_4$, EtOH or MeCN; (ii) $SOCl_2$, EtOH; (iii) NH_3 gas, EtO_2; (iv) 2,5-dimethoxytetrahydrofurane, AcOH; (v) BBr_3, CH_2Cl_2; (vi) Ar-CHO, NaOH, EtOH.

R					
Ar					

These ligands interact with the receptor using the coordination bond between the nitrogen of pyridine group and the heme iron [36]. As a conclusion these results confirm the presence of the extrahydrophobic surface explaining the activities of these series.

1.1.3 Pyrroles as Pyrrolopyrazinones

Micheli et al. [37] developed and reported pyrrolo[1,2-α]pyrazinones, a new class of mGluR1 antagonists, which is produced by a cyclization of the C-2 position on the pyrrole N-1 nitrogen.

In the central nervous system glutamate is a key neurotransmitter that shows its activity through ionotropic (NMDA, AMPA and kainate) and metabotropic receptors (mGluRs) [38,39]. mGluRs belong to the C family of G-protein-

coupled receptors (GPCRs) which are characterized by a large amino-terminal domain where the agonists bind.

According to the succession on molecular cloning, eight mGluRs have been identified and named mGluRs 1-8 and also these mGluRs are classified into three main groups on the basis of sequence similarity, pharmacology and transduction. Group I includes mGluR1 and mGluR5; group II consists of mGluR2 and mGluR3; group III contains mGluR4, mGluR6, mGluR7 and mGluR8.

Micheli et al. studied mainly group I and especially mGluR1 antagonist and they described selective molecules Figure 21 which involve pyrrole ring [40-42].

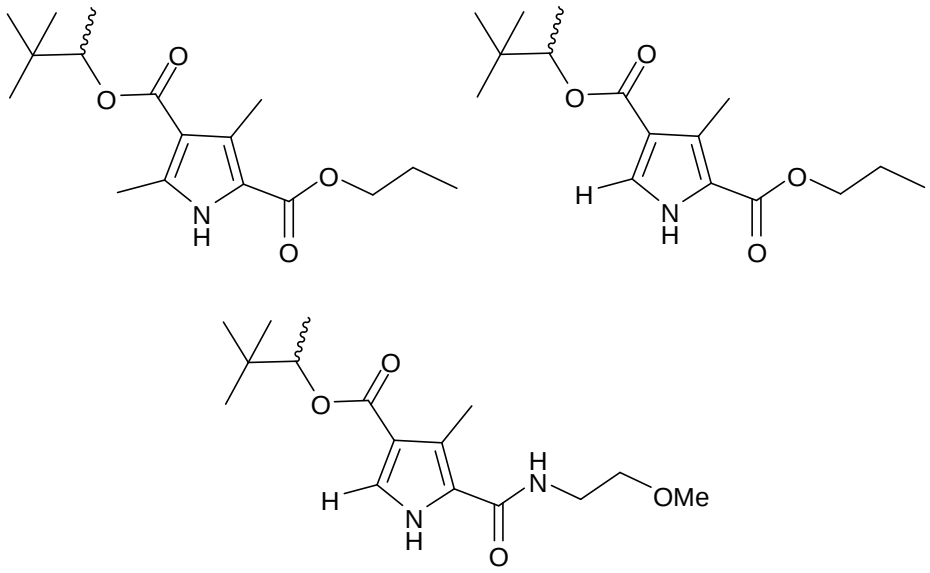


Figure 21. Examples of mGluR1 antagonist

The pyrrole class has great potency and selectivity for the mGluR1receptor. The intrduction of amides in C2 position caused the improvement in the PK (pharmacokinetic) profile of the pyrrole class and compounds show impressive bioavailability in different animal species. For all a few

compounds containing amide function showed unexpected high clearance (Clb) when studying in vivo. Different reasons could cause this problem and one of the possibility is mainly in metabolic instability of the C2 lipophilic side chain. Another possibility could be ‘amino acidic’ moiety masked with in the 2-carboxy pyrrole structure. In order to overcome this problem a new class of potent and selective mGluR1 noncompetitive antagonists which is pyrrolo[1,2,α]pyrazinones Figure 22 was developed by Micheli et al. [37].

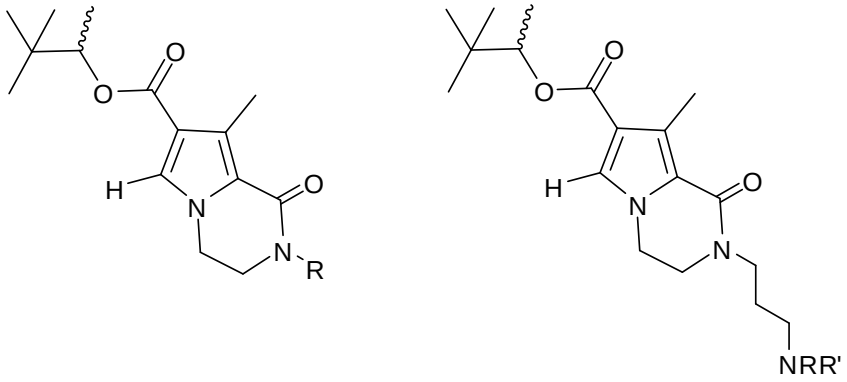


Figure 22. A new class selective mGluR1 noncompetitive antagonists, pyrrolo[1,2,α]pyrazinones

1.1.4 Pyrroles for Indolizidine Alkaloids

In recent years, indolizidine alkaloids especially which are derived from amphibians and ants are important targets for total synthesis for both conformation of structure and investigation of the potent biological activity [43]. Therefore, development of a new synthetic route to synthesize indolizidine alkaloids gains importance and they are simple enough to use as models for developing new synthetic methadologies. Many of the isolated alkaloids have alkyl substituents around the bicyclic structure such as the 5-alkyl substituted derivative named as indolizidine 209D[2] **23** and the Pharaoh’s ant trail pheromone (+)-monomorine **24** [44] which is a 3,5-dialkyl indolizidine as shown below.

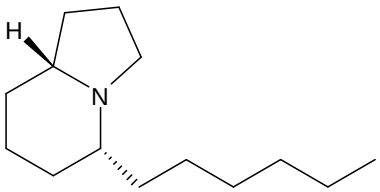


Figure 23. Indolizidine 209D[2]

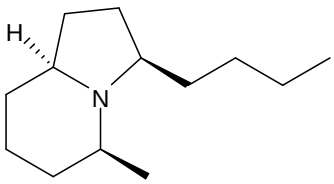


Figure 24. 3,5-dialkyl indolizidine

Also many alkaloids have been partyl or fully characterized from the skin secrations of amphibians. Indolizidine alkaloids which are the largest class within the alkaloids come up in dendrobatid frogs from Central and South America. Pumiliotoxins and allopumiliotoxins are entirely described indolizidines. But recently discovered 5-alkylindolizidines and 3,5- and 5,8-disubstituted indolizidines have attracting increasing attention. There is still uncertainity about the relative and absolute stereochemistry of many of these alkaloids because of their low natural abundance.

Jefford et al. [45] reported an effective and stereoselective approach for the synthesis of biologically active indolizidine alkaloids which are based on reduction of bicyclic pyrrole derivatives. Their biological activity and their exotic provenance make them an attractive targets for their synthesis. Indolizidine 167B **25** which is a constituent of the skin of a dendrobatid frog and (+)-monomorine **26**, a trail pheromone of the ant are two well known examples of indolizidine alkaloids.

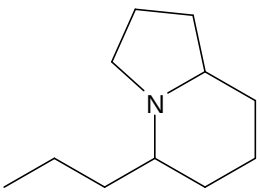


Figure 25. Indolizidine 167B

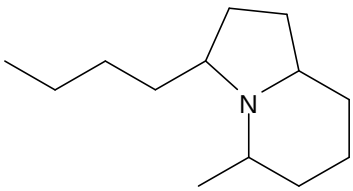
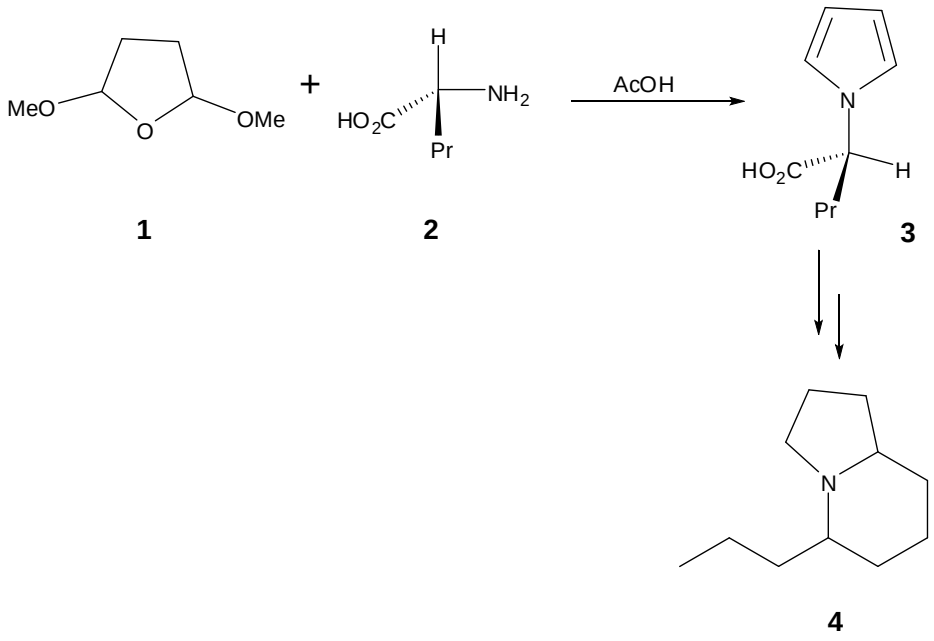


Figure 26. (+)-monomorine

Constituents containing in genus Dendrobates skins and closely related to indolizidine 167B are noncompetitive blockers of neuromascular transmission. That's why the efficient synthesis of these rare compounds is quite important but most methods in the literature are multistep procedures which give the product in poor yields.

Jefford et al. [45] developed and described a three-part method to synthesize enantiomerically pure indolizidine alkaloids. This method involved condensation of chiral α-amino acid, D-norvaline **2** with 2,5-dimethoxytetrahydrofurane **1** to produce the corresponding pyrrole derivative **3** as shown Figure 27. After that homologation and cyclization followed by catalytic hydrogenation, give indolizidine 167B **4**.



1 **2** **3** **4**

Figure 27. Synthesis of indolizidine 167B

Also (+)-monomorine **5** was synthesized by the same synthetic route as illustrates Figure 28.

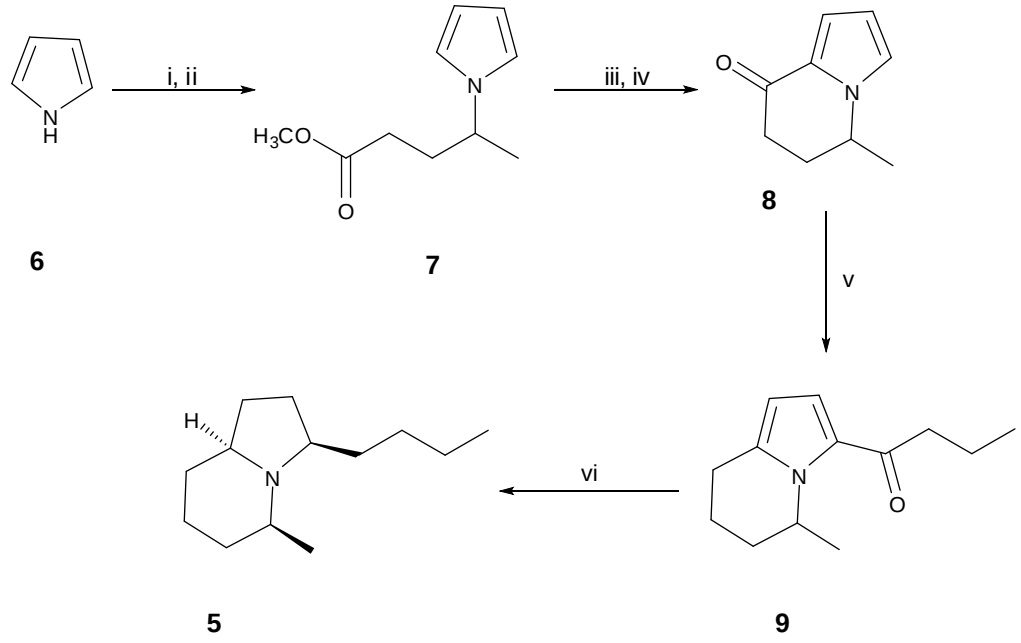


Figure 28. Synthesis of (+)-monomorine. Reagents: (i) KH, 0°C; and then γ-valerolactone, 160°C, 4h; (ii) K_2CO_3, DMF, CH_3I (excess) 18°C; (iii) BBr_3 (1.1 equiv), CH_2Cl_2, 0°C; (iv) $NaBH_3CN$, ZnI_2, CH_2Cl_2, 45°C; (v) butyryl chloride, AgOTf, CH_2Cl_2, 0°C; (vi) Pd/C, H_2 (55 psi), CH_3OH, catalytic H_2SO_4.

1.2. General Synthesis of Pyrroles

1.2.1 General Properties of 5-membered Ring System

Pyrrole is an aromatic heterocyclic compound which is defined as composing of planar pentagons with sp^2-hybridized carbon atoms. Every carbon atoms has 1 electron in a p_z orbital, while the nitrogen atom has 2 electron in the same orbital. These p orbitals overlap to result in π-clouds below and above the ring. Because of its containing 6 electrons in the π-clouds, pyrroles obey Huckel's 4n+2 rule. Neverthless, pyrroles extend of aromaticity which is determined by resonance energies different from benzene rings and so it is the predictive factor for their chemistry [46,47].

Resonance energies:

Pyrrole : 100 $KJmol^{-1}$

Benzene : 151 $KJmol^{-1}$

Pyrrole is a very weak base compared to known amines and some aromatic compounds like pyridine. Protonation ends up with loss of aromaticity because it is unwanted.

1.2.2 Reactivity of Pyrroles

The NH proton of pyrrole is partially acidic with a pKa of 16,5. It can be easily deprotonated with strong bases such as butyllithium and sodium hydride. The resonance structure of pyrrole enables the reactivity of the pyrrole.

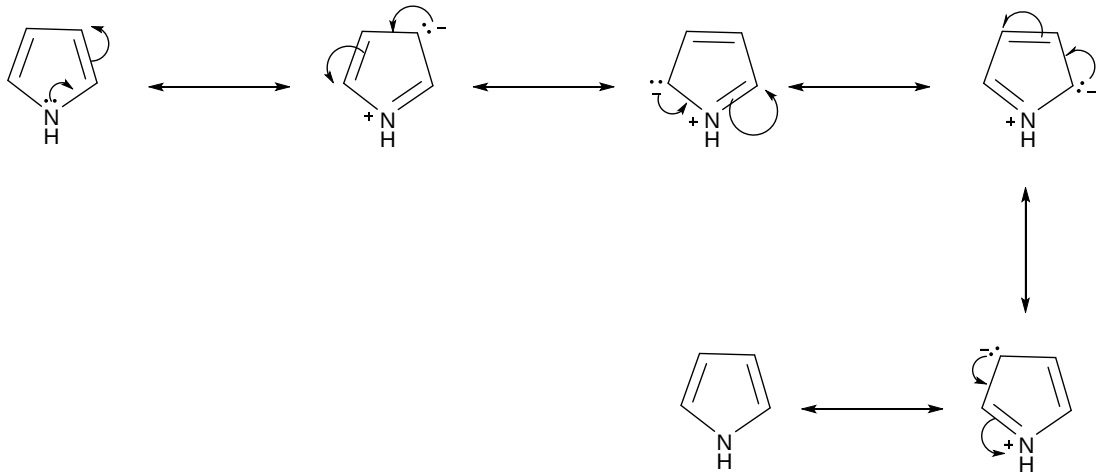


Figure 29. Resonance structures of pyrrole

Pyrrole is more reactive than benzene against eleptrophilic aromatic substitution since pyrrole is able to stabilize the positive charge of the carbocation. Pyrroles give electrophilic aromatic substitution mostly at the C2 and C5 positions. The Vilsmeier-Haack reaction [48] and the Mannich reaction are important reactions for obtaining functionalized pyrrole derivatives.

1.2.3 Synthesis of Pyrroles

1.2.3.1 General Remarks

The various biological properties of pyrroles set focus on the development of efficient methods for the preparation of pyrrole derivatives which are having a defined substitution pattern [49-57]

Pyrroles play an important role in heterocyclic chemistry [58-63] and for their preparation there are various synthetic routes. Although, many procedures exist in the literature, they remain incapable for pyrroles from the point of substituents and substitution pattern [64] and also most of the procedures involve multistep reaction which lower the overall yield [65-75]. In recent years, a small number of one-step procedures [76,77,11] have been reported; but these are not satisfactory in terms of reaction conditions (long reaction period), yield and scope of substitution at the ring. After all, developing simple and efficient method is still needed for the synthesis of pyrroles [64,78-83].

In the literature there are many methods which have their own name for the preparation of heteroaromatic ring system but they are typically synthesized by using small number of well known reaction types. These reaction types are:

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

1.2.3.2 Classical Methods for the Synthesis of Pyrroles

There are three classical methods in the literature:

1. **Paal-Knorr** Synthesis

In this synthesis 1,4-dicarbonyl compounds and ammonia or primary amines are used for the preparation of pyrroles. It is a very successful, if the appropriate dicarbonyl compounds are readily available. Besides ammonia and primary amines, hydroxylamines and hydrazines can be used as the nitrogen source.

2. **Knorr** Synthesis

This synthesis involves condensation reaction between α-aminoketones and β-ketoesters. After hydrolysis and decarboxylation, pyrroles are obtained. It is the most important and widely used method for the formation of pyrroles.

3. **Hantzsch** Synthesis

The reaction of an α-haloketone with β-ketoesters and ammonia or primary amine is named as Hantzsch synthesis.

1.2.3.2.1 Paal-Knorr Synthesis

Cyclisation of 1,4-dicarbonyl compounds **10** with ammonia or primary amines **11** give pyrroles **12** and **13** (Figure 30) [84,85].

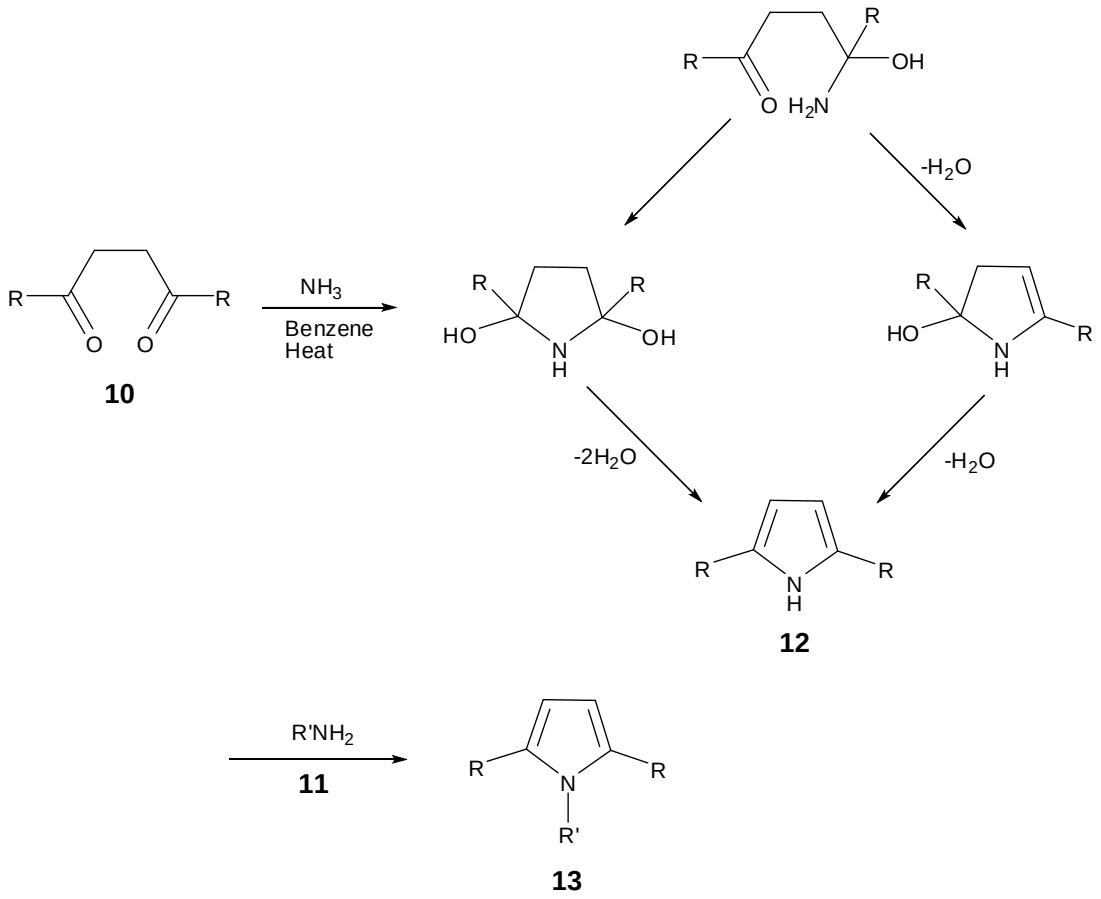


Figure 30. Synthesis of pyrroles starting from 1,4-dicarbonyl compounds with primary amines

Paal-Knorr synthesis also a very good method for the formation of alkyl-bridged and fused pyrroles, such as **14** and **15** (Figure 31) [86].

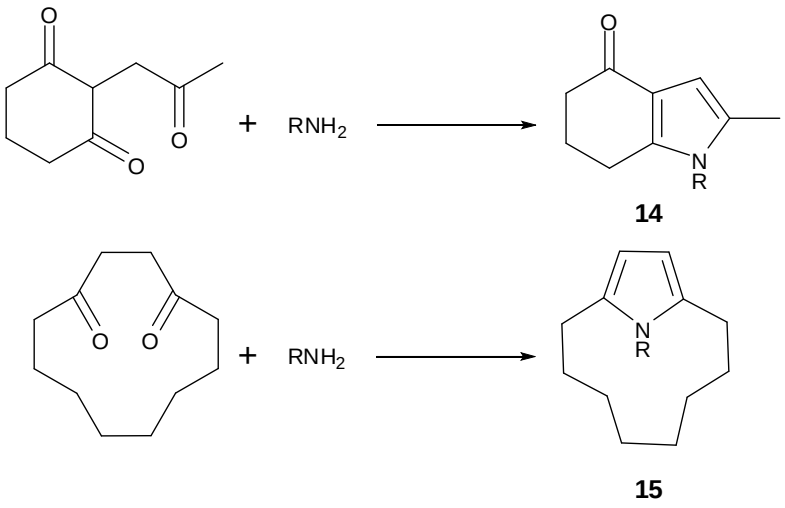


Figure 31. Examples of Paal-Knorr synthesis

Moreover, Paal-Knorr synthesis can be carried out by using primary amines **11**, aminoacids **2** and the masked equivalents of 1,4-dicarbonyl compounds [45,88,89] such as 2,5-dimethoxytetrahydrofurane **1** to synthesize the corresponding pyrrole derivatives **16** and **3** (Figure 32).

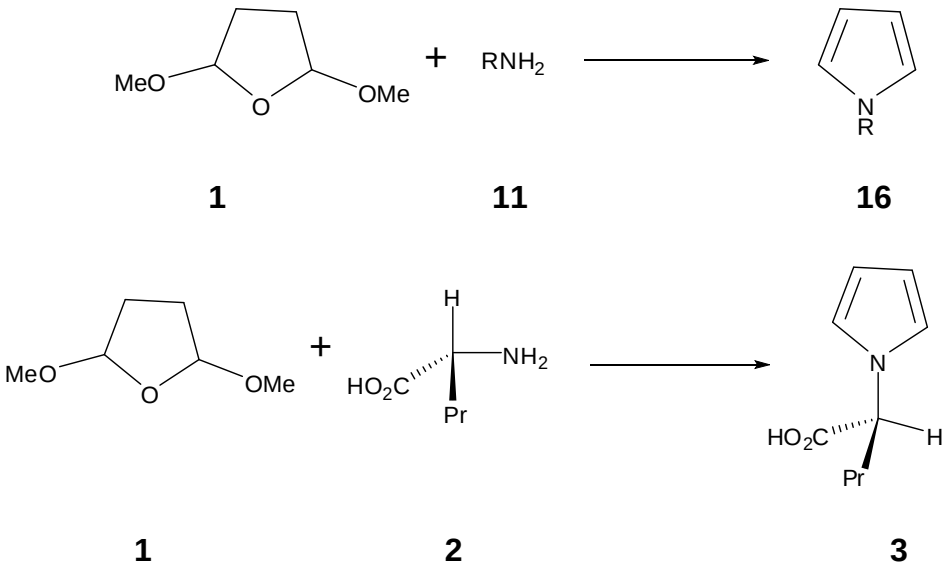


Figure 32. Examples of Paal-Knorr synthesis by using the masked equivalents of 1,4-dicarbonyl compounds

In this synthesis using amino acids often cause partial racemization during the condensation reaction for the formation of pyrrole ring. This racemization limits the usage of this method in the aymmetric synthesis.

1.2.3.2.2 Knorr Synthesis

In this method, the condensation of either α-amino ketones **17** or in situ generated from isonitrosoketones with β-ketoesters **18** which contain active α-methylene groups give pyrrole derivatives **19** (Figure 33) [90-92].

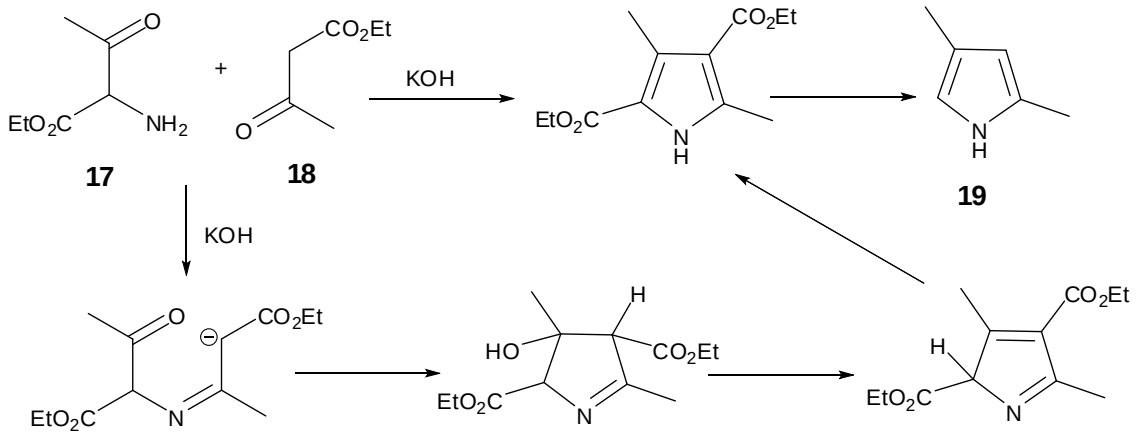


Figure 33. Knorr synthesis

Many variations of this reaction have been used but the Knorr synthesis works well with only using the further activated methylene group of second β-ketoesters to give pyrrole. Otherwise, α-aminoketone gives self-condensation reaction to produce pyrazine **20** [93] (Figure 34).

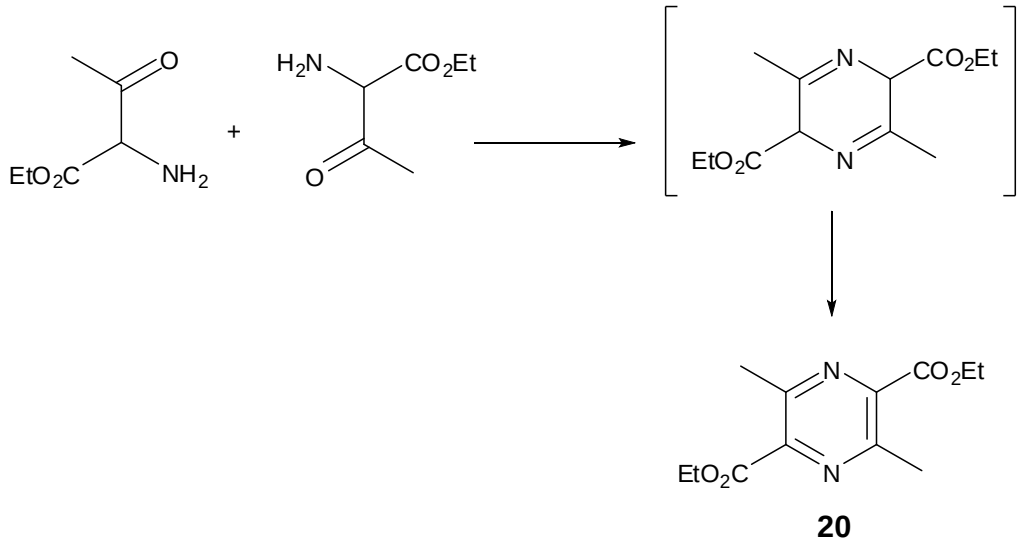
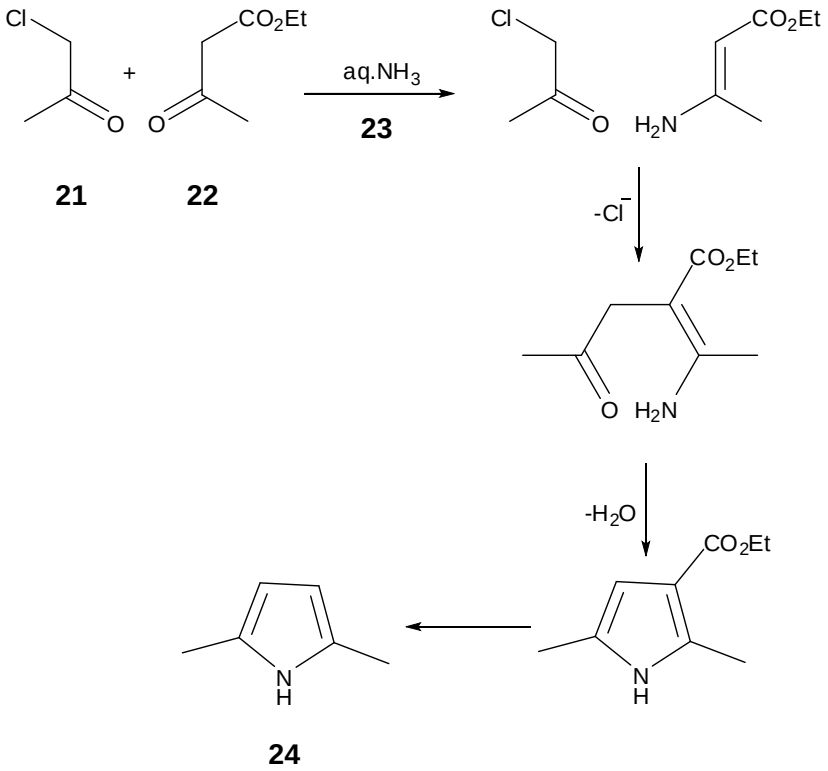


Figure 34. Knorr synthesis of β-ketoesters

1.2.3.2.3 Hantzsch Synthesis

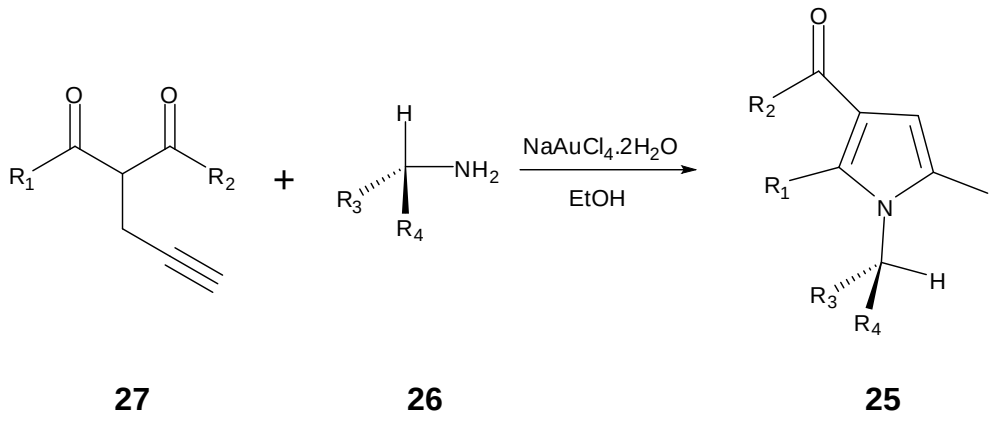
Hantzsch synthesis is a reaction between α-chloromethyl ketones **21**, with β-ketoesters **22** in the presence of either ammonia or amines **23** to give corresponding pyrrole derivatives **24** (Figure 35) [94]. Generally this reaction has been used to prepare 2,5-dialkylpyrrole-3-carboxylates **25**.



24

Figure 35. Hantzsch synthesis

Arcadi et al. [95] develop the synthesis of chiral 1,2,3,5-tetrasubstituted pyrrole derivatives **25** by using gold-catalysed amination/annulation reactions. In this purpose, primary amines, amino alcohols and α-amino esters **26** reacted with 2-propynyl-1,3-dicarbonyl compounds **27** to give homochiral 1,2,3,5-tetrasubstituted pyrrole derivatives (Figure 36).



27 **26** **25**

Figure 36. Synthesis of chiral 1,2,3,5-tetrasubstituted pyrrole derivatives by using gold-catalysed amination/annulation reactions

As shown in Figure 37, the reaction mechanism involves the addition of primary amines to 2-propynyl-1,3-dicarbonyl compounds to give enaminone derivatives [96] **28** follows by $NaAuCl_4.2H_2O$ catalyzed 5-exo-dig cyclisation reaction to obtain desired pyrrole ring.

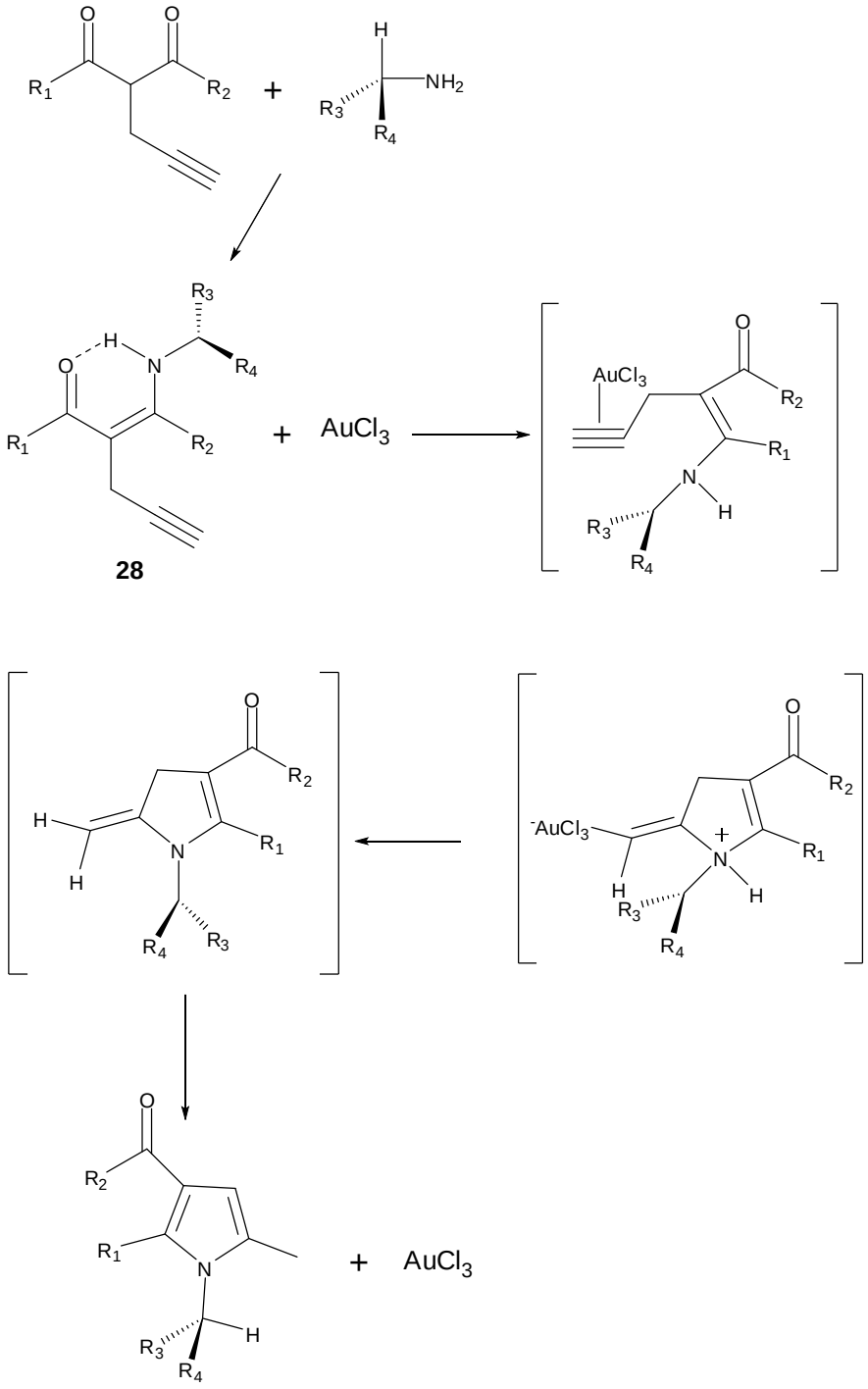


Figure 37. Formation reaction mechanism of 1,2,3,5-tetrasubstituted pyrrole derivatives

In a previous study, Shioiri et al. [97] discovered the reaction of lithium trimethylsilyldiazomethane ($TMSC(Li)N_2$) with carbonyl compounds to give

alkylidene carbenes without any problems. They performed the reaction of TMSC(Li)N_2 (which is used for an alkylidene carbene generator) with N-substituted β-amino ketones **29** and it was found that TMSC(Li)N_2 reacted seamlessly with **29** in THF to generate alkylidene carbene intermediates **30**. After the intramolecular N-H insertion of alkylidene carbene intermediates, 2-pyrrolines **31** were obtained. Lastly, obtained 2-pyrrolines were easily converted to the corresponding achiral pyrroles **32** with the help of MnO_2 (CMD, chemical manganese dioxide) [98], as shown in Figure 38 [99].

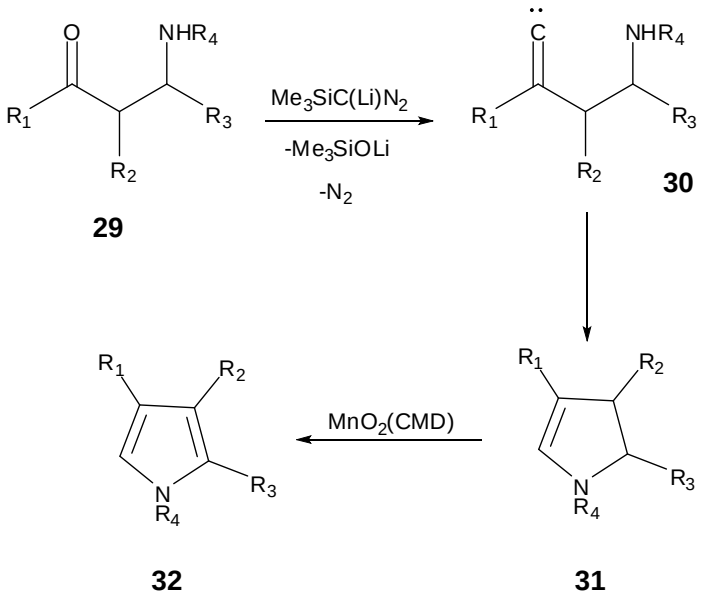
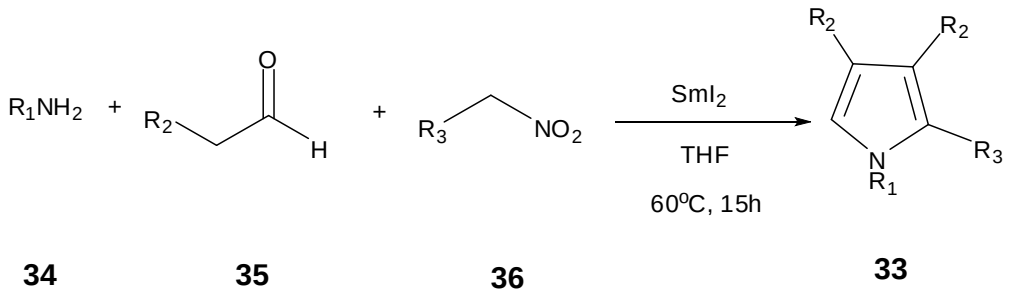


Figure 38. Synthesis of achiral pyrroles

Shiraishi et al. performed a three-component-pyrrole synthesis (Figure 39) [76]. 1,2,3,4-tetrasubstituted pyrroles **33** were obtained by condensation reaction of alkylamines **34**, aldehydes **35** and nitroalkanes **36** in good yield. The samarium (II) iodide was used as a catalyst in this reaction.



34 **35** **36** **33**

Figure 39. A three-component-pyrrole synthesis

On the basis of these results, Shiraishi et al. revealed the reaction path for these coupling reaction (Figure 40). The most important step in the three-component coupling reaction was the formation of *α,β*-unsaturated imine **37** which was obtained by the aldol-type condensation of the imine derived from amine **34** and aldehyde **35** in the presence of SmI_2 catalyst. Then *α,β*-unsaturated imine **37** coupled with nitroalkane **36** to give an intermediate **38**. Proton transfer and intramolecular cyclization of **38** to **39** followed by elimination of H_2O and NO from the intermediate **39** gave pyrrole **33**.

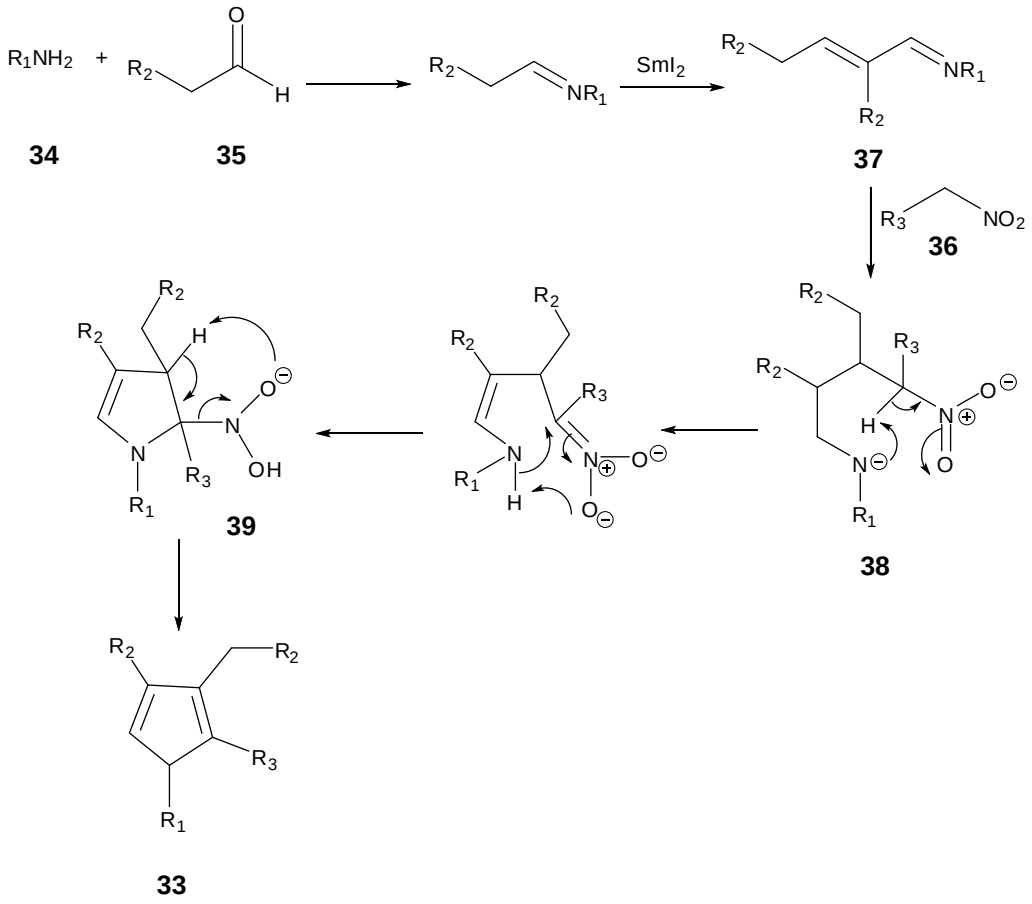
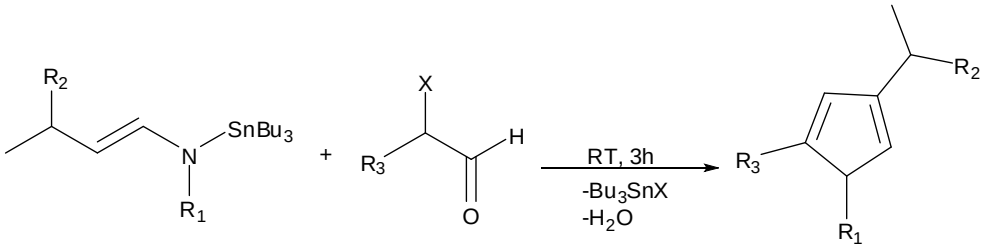


Figure 40. Mechanism of a three-component-pyrrole synthesis

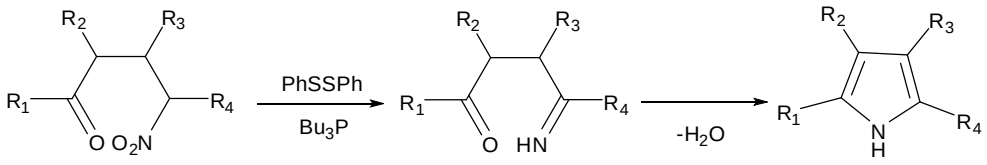
Synthesis of 2,4-disubstituted N-alkyl pyrroles **40** by using the coupling reaction of organotin (IV) enamines **41** and *α*-haloaldehydes **42** was reported by Yasuda et al. [100] In this reaction [3+2] cyclization-dehydration took place (Figure 41). For pyrrole synthesis [3+2] cyclization process is a very common method but in the dehydration step generation of water sometimes causes a serious problem and generated pyrroles are not chiral.



41 **42** **40**

Figure 41. Synthesis of 2,4-disubstituted N-alkyl pyrroles

Nitro compounds especially nitro-olefins are useful starting material for the formation of pyrroles [101]. Zard et al. performed a reaction that 1,4-nitroketones **43** was reduced by tributylphosphine-diphenyl disulfide deoxygenating system to give an intermediate imino-ketone **44**. After the spontaneous cyclisation and dehydration of imino ketone corresponding pyrroles **45** were formed in good yields. (Figure 42).



43 **44** **45**

Figure 42. Synthesis of pyrroles by using nitro compounds

Nitro group has strong ability to activate an olefins against Michael adition reactions and also it acts as a leaving group in situations where $E1_{CB}$ type eliminations are favorable. This property of nitro groups is used for the synthesis of pyrrole building blocks for porphyrin synthesis. These opinion is clarified and displayed in Figure 43, where the nucleophile in the Michael addition is an activated isocyano derivative **46** reacts with the nitro-olefin **47** to give **48** which can cyclize to **49** through internal attack of the nitronate on

the isocyano group. Proton abstraction leads to form cyclic intermediate **50** which can eliminate a nitronate ion through a vinylogous $E1_{CB}$ mechanism and then aromatization through a [1,3] sigmatropic shift of the hydrogen gives the pyrrole ring **51** [102].

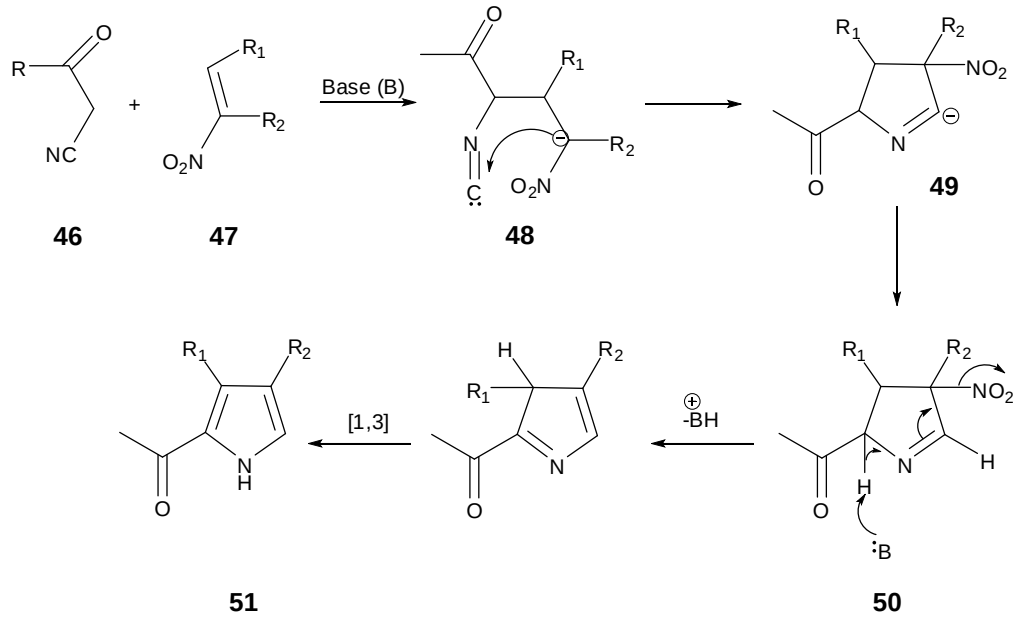


Figure 43. Formation mechanism of pyrroles by using nitro compounds

2-(2-Pyridyl) pyrroles are useful compounds because they have been known to be antioxidants and P38 kinase inhibitors. 3,5-Disubstituted and 3,4,5-trisubstituted-2-(2-pyridyl) pyrroles **52** were synthesized by Klappa et al. [103] from 2-(amino methyl) pyridine **53** and 1,3-diones **54** that is illustrated in Figure 44. The reaction looks like to go through from β-imino ketone that forms in situ.

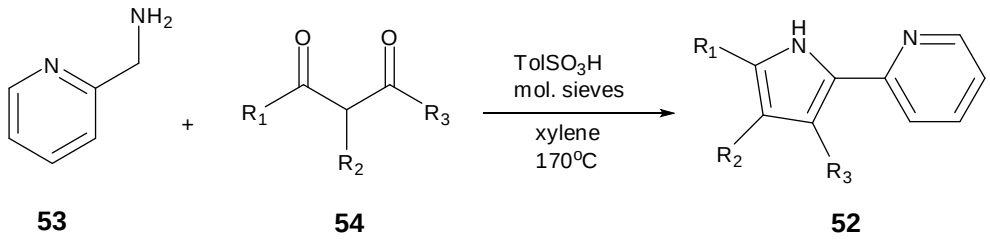


Figure 44. Synthesis of 3,4,5-trisubstituted-2-(2-pyridyl) pyrroles

From the mechanistic view, cyclisation is thought to occur by nucleophilic attack on the ketone carbonyl by the carbon atom *α* to the pyridine (Figure 45). It is proposed that the nucleophilicity of the (2-pyridyl)methyl carbon consists of the enamine tautomer **55**. Lastly, [1,3] sigmatropic shift gives the corresponding pyrrole **52**.

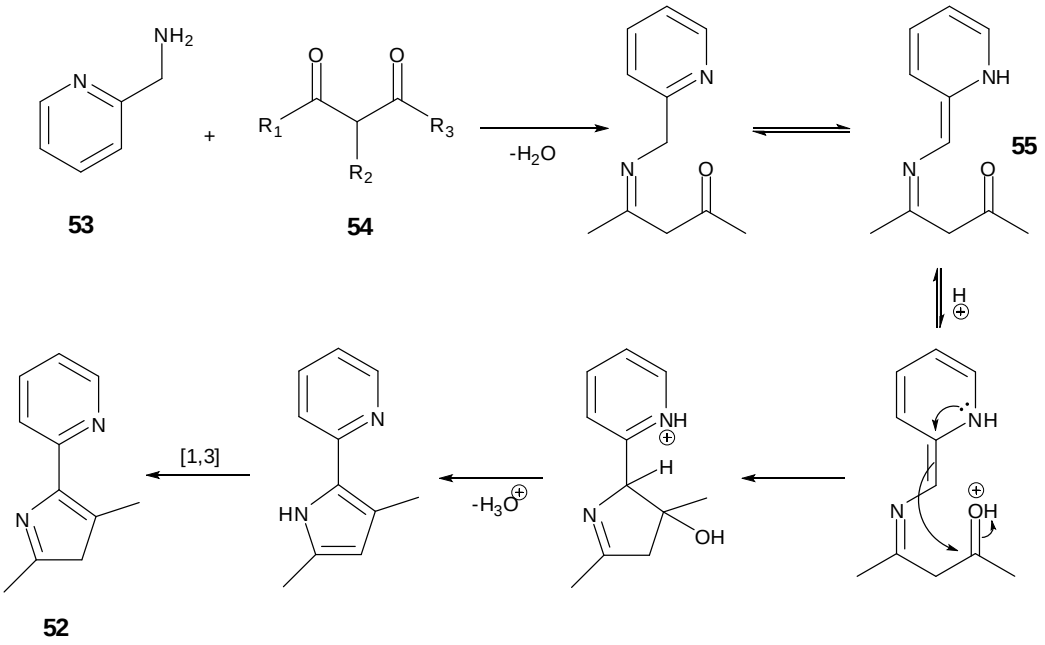


Figure 45. Formation mechanism of 3,5-disubstituted-2-(2-pyridyl) pyrroles

This hypothesis is supported by the fact that 4-(aminomethyl) pyridine **57** also gives this reaction to produce **58** because it can tautomerize to an enamine structure. However 3-(amino methyl) pyridine **59** and benzylamine **60** which cannot tautomerize to an enamine unable to form **58** under the same reaction conditions (Figure 46).

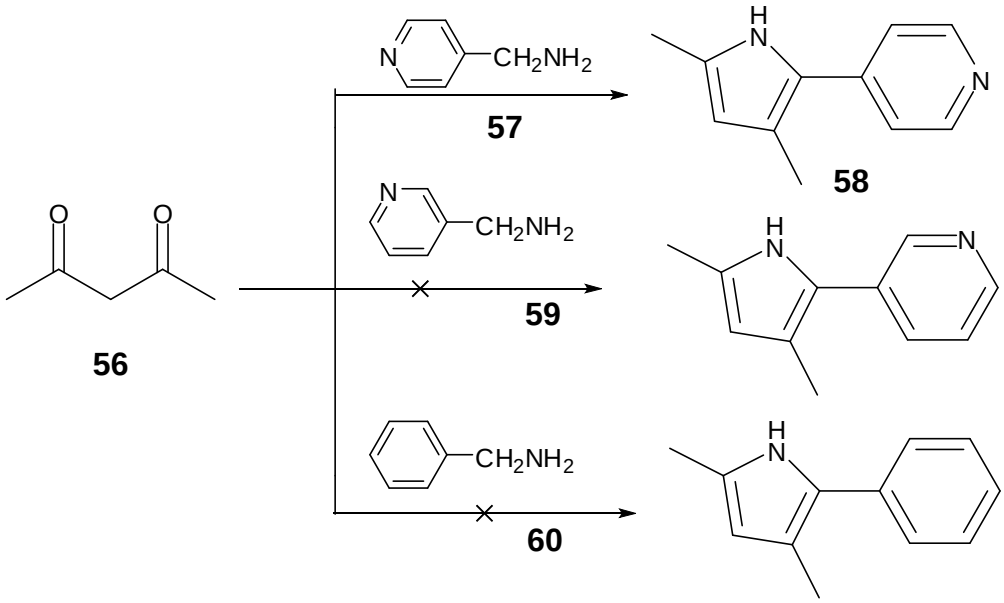
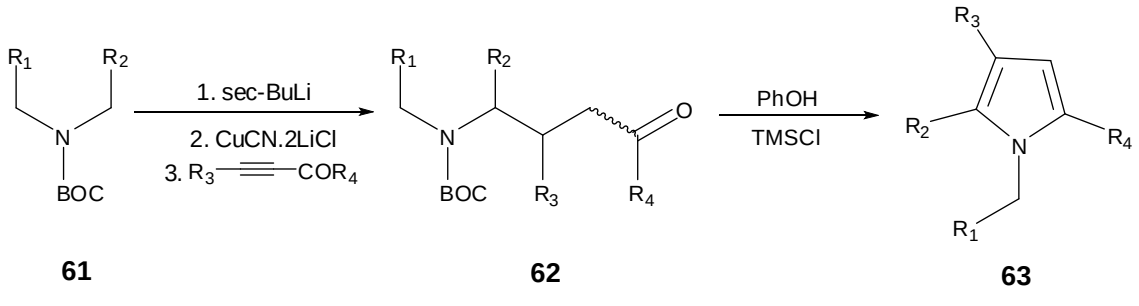


Figure 46. Synthesis of 3,5-disubstituted-2-(2-pyridyl) pyrroles by using 4-(aminomethyl) pyridine

Two step synthesis of substituted pyrroles has been studied by Dieter et al. [64]. The first step of synthesis consists of deprotonation of *tert*-butoxycarbonyl (BOC) amines **61** followed by addition of CuX-2LiCl (X=Cl,CN) to give α-aminoalkyl cuprates. This generated cuprates undergo conjugate addition reaction to α,β-alkynyl ketones producing α,β-enones **62** give carbamate deprotection and intramolecular cyclization reaction to form the corresponding pyrroles **63** (Figure 47).



61 **62** **63**

Figure 47. Two step synthesis of substituted pyrroles

A new pyrrole synthesis was reported by Cushman et al. [104] which consists of reaction between (N-BOC)-α-amino aldehydes (**64**, R_2=H) or ketones (**64**, R_2=CH_3) lithium enolates **65** that is derived from ketones **66** to produce aldol intermediates **67**. Aldol intermediates cyclize to generate desired pyrroles **68** after the treatment with mild acidic conditions (Figure 48).

Even though, this synthesis conceptually is similar to the Knorr synthesis, where α-oximino ketones are reduced to α-amino ketones and then reacted with β-diketones or β-keto esters to give substituted pyrroles. This method would offer the advantage of usage of BOC-α-amino either aldehydes or ketones **64** which are readily available from a wide variety of amino acids.

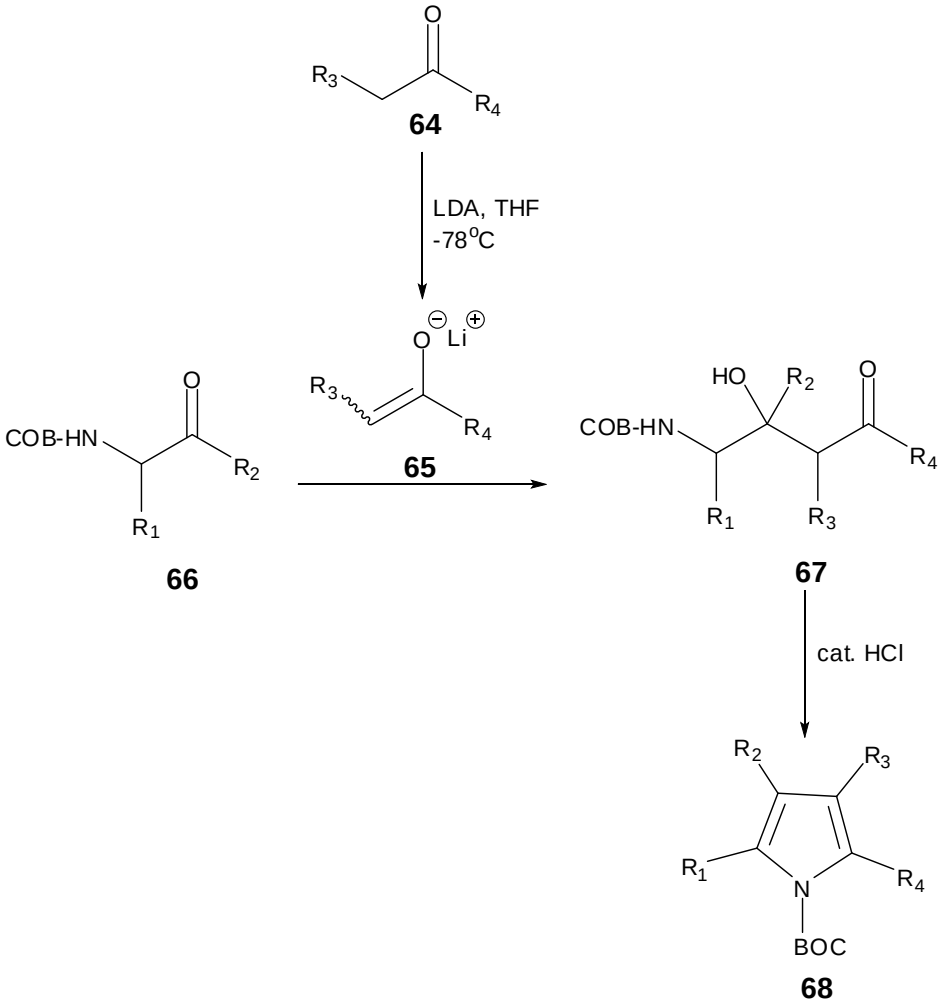


Figure 48. Synthesis of substituted pyrroles by using BOC-α-amino aldehydes or ketones

Readily available of the starting material, mild conditions and the number substituents at R_1, R_2 and R_3 are significant features for this synthetic route but the yields of this route are rather modest (5-40%). A rapid polymerization of the resulting pyrroles under the acidic condition could be the possible explanation [104]. Another disavantage of using this synthetic route is that pyrroles with alkyl substituents on the nitrogen cannot be synthesized in all cases.

Lagu et al. [105] have suggested a solution for the low yields in Cushman's synthesis. If the tert-butoxycarbonyl group on the nitrogen is replaced with other protecting group which can be easily removed under moderately neutral conditions, the yields of pyrroles could be increased and also a number of substituents to be introduced on the pyrrole nitrogen. In accordance with this purpose a benzyl group was used instead of *tert*-butoxycarbonyl group on the nitrogen of the *α*-amino aldehydes to be used in the aldol reactions. Lithium enolates **65** which was derived from ketones **64** react with benzyl protected aldehydes or ketones **69** to give **70**. It was thought that deprotection of the benzyl group generates an iminium ion **71** which could undergo a deprotection reaction to form an enamine **72**, and then dehydration reaction of enamine gives pyrrole **73** (Figure 49).

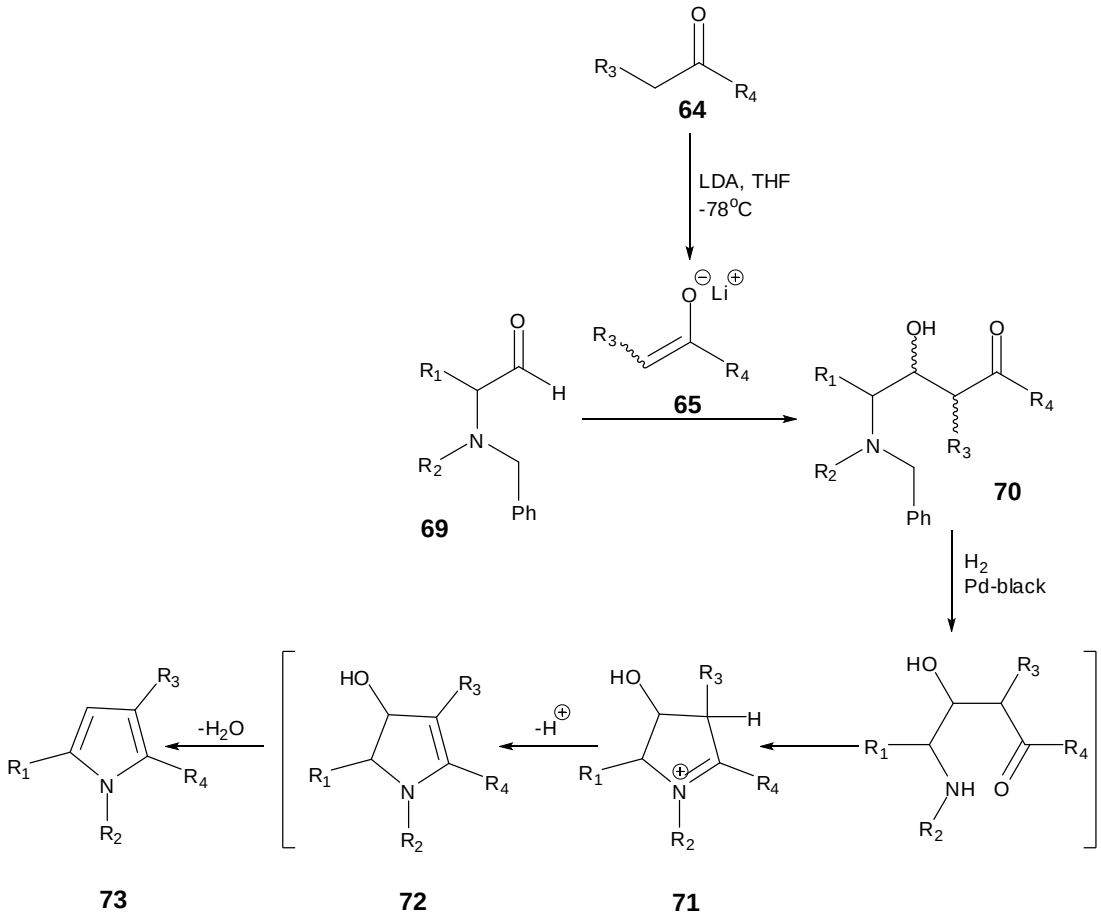
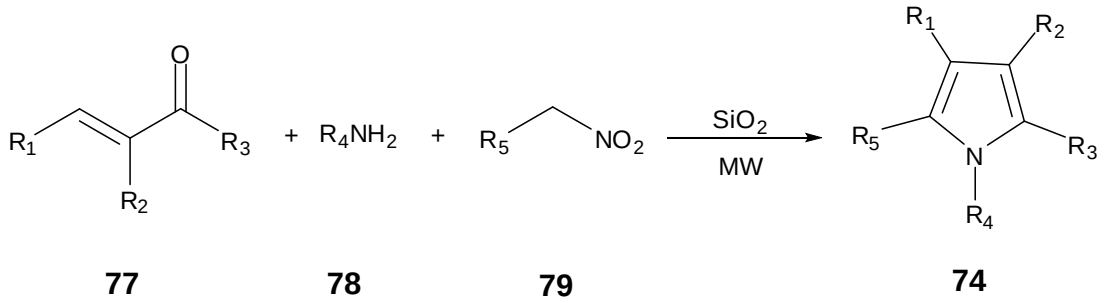


Figure 49. Synthesis of substituted pyrroles by using BOC-α-amino aldehydes or ketones

Lagu et al. described the synthetic methadology which is flexible enough to yield a various of substituent combination and by using this 1,2-di, 1,2,3-tri, 1,2,5-tri and 1,2,3,5-tetra substittent pyrroles can be synthesized. Briefly, this methodology provides opportunity for the introduction of a number of alkyl and aryl substituents on the nitrogen of pyrroles that cannot be synthesized by using known procedures. Apart from that pyrroles without a substituent on the nitrogen cannot be synthesized by using this methodology.

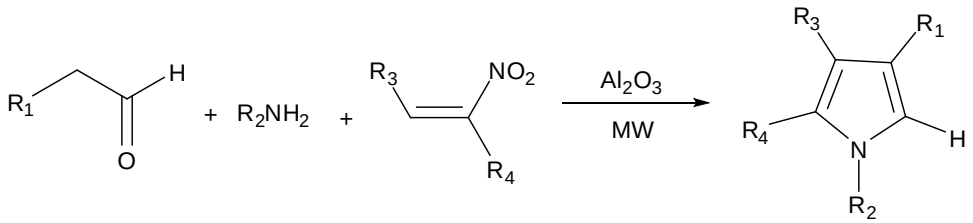
Ranu et al. [78] have shown the synthesis of alkyl-substituted pyrroles by three-component coupling which involves a carbonyl compound, amine and either nitro alkane or nitro alkene on a solid surface of silica gel/alumina

under microwave radiation. They have synthesized highyl substituted alkylpyrroles **74** and **75** and fused pyrroles **76** by using a three component coupling of *α,β*-unsaturated aldehyde/ketone **77**, amine **78** and nitro alkane **79** (Figure 50) on the surface of silica gel and alumina without using any solvent under microwave irradiation. In case of fused pyrrole formation, they performed a reaction with cyclic ketones **80**, amine **81**, and α,β-unsaturated nitroalkane **82** (Figure 51) with the same reaction conditions.

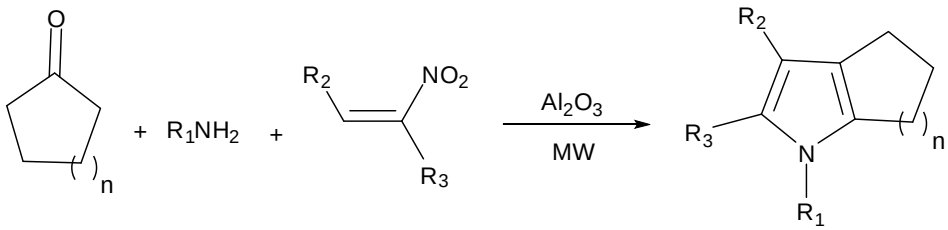


77 **78** **79** **74**

Figure 50. The synthesis of alkyl-substituted pyrroles by three-component coupling



75



80 **81** **82** **76**

Figure 51. The synthesis of alkyl-substituted pyrroles by three-component coupling under microwave irradiation

Microwave irradiation reactions were very fast and clean. The yields were quite good (60-86%) for a three-componet coupling. Also, this reaction performed without any necessity for strong acid, base and solvent [78].

Demir et al. [106] have studied an efficient one-pot two component synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives via acid-cataylzed cyclisation of 2-propynyl-1,3-dicarbonyl compounds **83**. In this study 2-propynyl-1,3-dicarbonyl compounds **83**converted to their enaminones **84** followed by metal mediated cyclisation to give the desired pyrrole derivatives **85**. With this design, they performed reaction between 2-propynyl-1,3-dicarbonyl compounds **83** and (R)-phenylethylamine in the presence of p-TsOH which is used catalytical amount to form enaminone **84**. After that, enaminone reacted with catalytical amount of $Cu(OAc)_2$ in 1,2-dichloroethane to generate corresponding pyrrole derivative **85** (Figure 52).

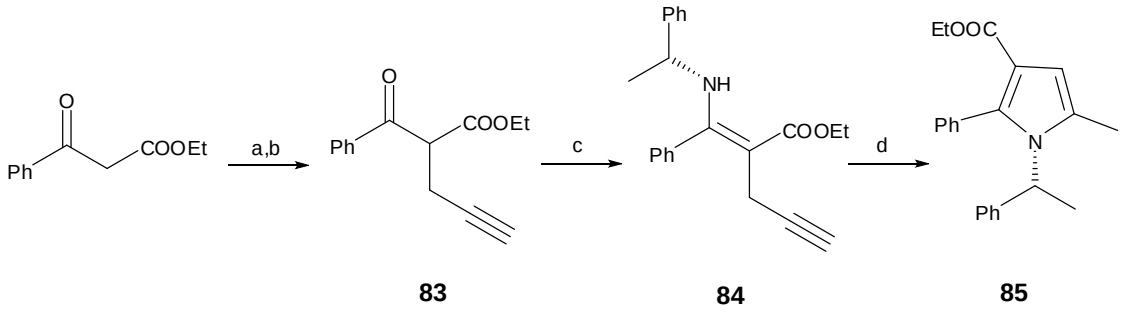


Figure 52(A). a) NaH, THF; b) Propargylbromide; c) (R)-Phenylethanamine; *p*-TsOH, benzene, reflux; d) $Cu(OAc)_2$, 1,2-Dichloroethane

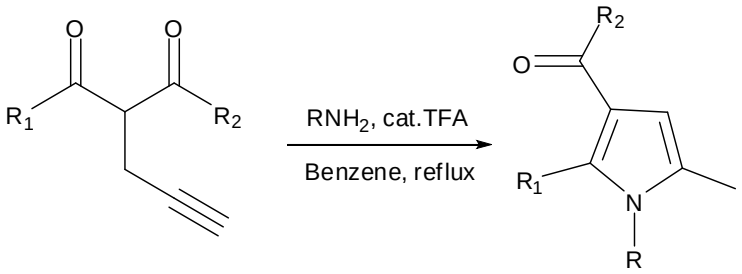


Figure 52(B). One-pot two component synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives

The attack of nitrogen to the activated triple bond leads to *5-exo-dig* cyclisation which constructs to pyrrole derivative. In this reaction pyrrole derivative was the only product, the rest of the compounds were the unreacted starting materials. In this synthesis 6-endo-dig type cyclisation product was not observed.

Demir et al. performed reactions to combine enaminone formation with cyclisation step and during the screening reactions they found convenient conditions for the formation of enaminones and their cyclisations. For that purpose they used TFA whose catalytical amount was able to convert enaminones to pyrroles **85** (Figure 52(B)). For the attack of nitrogen activation of triple bond is required so catalytical amount of TFA was used as a proton source both activation of triple bond and formation of enaminone.

As a result, a new general one pot two component synthesis which consists of condensation reaction of 2-propynyl-1,3-dicarbonyl compounds **83** with amines catalyzed by TFA is described by Demir et al. In this reaction catalyst is needed. TFA is the most efficient and selective catalyst and its application is general. Furthermore $Cu(OAc)_2$ was also efficient catalys when the enaminones were used. It was monitored that pyrroles were obtained without racemization [106] when the optical purity of the products was compared with the racemic compounds using chiral HPLC column.

Alkoxy and alkylsulfanyl substituted pyrrole carboxylates and their hydrolysis product pyrrolinones are important heterocyclic compounds because they show interesting biological properties and they have been used as precursor for currently known drugs [107]. Also these heterocyclic compounds can involve in several stereoselective transformations, such as conjugate additions [108], cycloadditions [109], acyliminium ion chemistry [110] and allylic substitutions [111]. Although alkoxy and alkylsulfanyl substituted pyrrole carboxylates and substituted pyrrolinones are significant compounds,

there are relatively few examples of them in the literature. Because it is difficult to synthesize them by using general pyrrole ring formation methods.

Demir et al. [112] reported a new approach which consist of the efficient, regioselective one-pot synthesis of 5-alkoxy and 5-alkylsulfanylpyrrole-3-carboxylates in high yields by means of the zinc perchlorate-catalyzed addition of alcohols and thiols to the nitrile carbon of α-cyanomethyl-β-ketoesters followed by annulation that is summarized in Figure 53. *α*-cyanomethyl-*β*-ketoester were synthesized by the alkylation of commercialy available β-dicarbonyl compounds with bromoacetonitrile by using either NaH/THF or DBU/benzene according to the literature procedure [113].

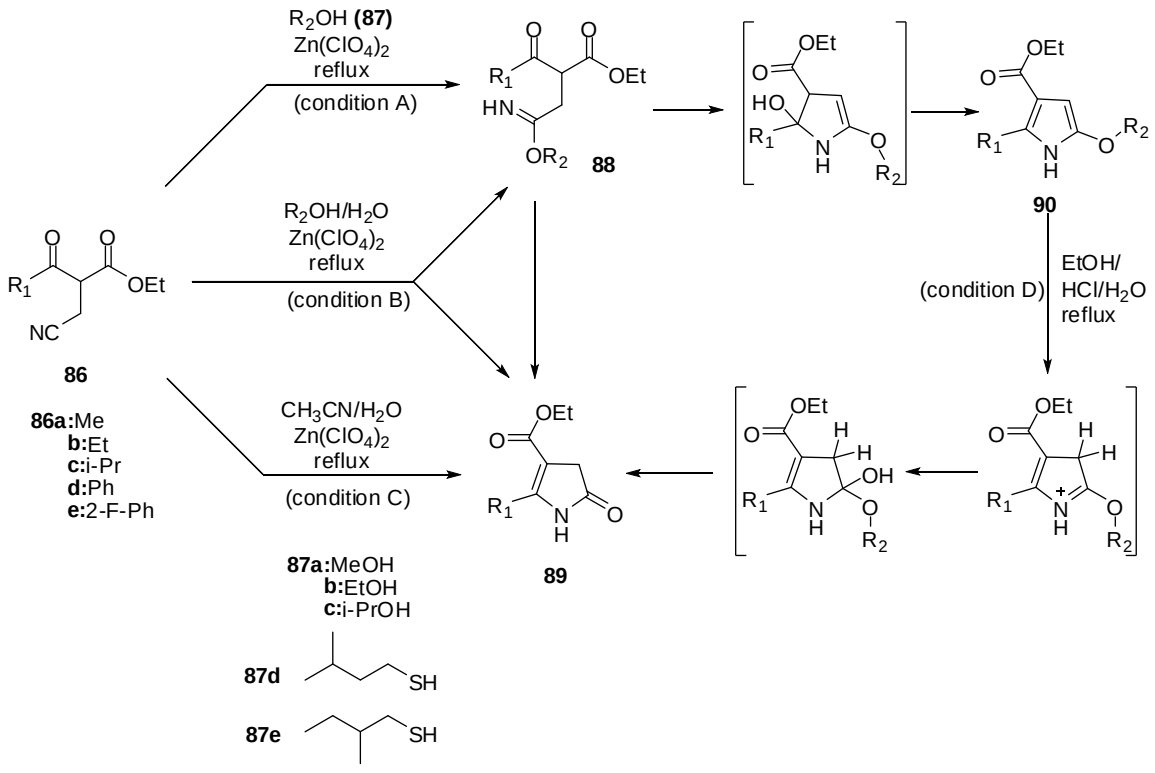


Figure 53. One-pot synthesis of 5-alkoxy and 5-alkylsulfanylpyrrole-3-carboxylates

After synthesizing 5-alkoxy and 5-alkylsulfanylpyrrole-3-carboxylates Demir et al. extended this chemistry to synthesize 5-alkoxypyrrole-3-phosphonates. They reported [114] a one-step synthesis of 5-alkoxypyrrole-3-phosphonates starting from suitable α-cyanomethyl-β-ketophosphonates. This synthesis involves the zinc perchlorate-catalyzed addition of alcohols to the nitrile carbon of α-cyanomethyl-β-ketophosphonates followed by annulation furnished 5-alkoxypyrrole-3-phosphonates. The addition-annulation process was carried out in the presence of water and pyrrolinones are obtained in good yields as shown in Figure 54.

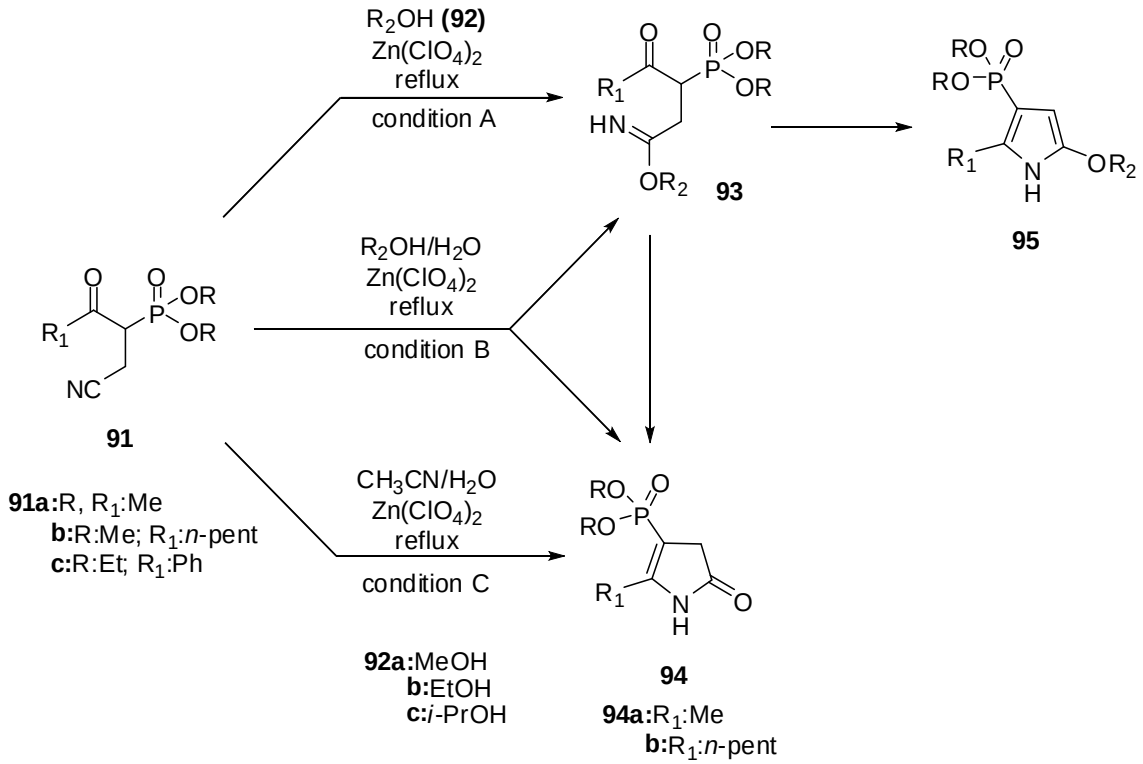


Figure 54. Synthesis of 5-alkoxypyrrole-3-phosphonates

Lastly Demir et al. developed and reported [115] an Au(I)/Zn(II) catalyzed tandem cyclisation of 4-pentyne-nitriles with various amines that provided an efficient and general route to synthesize pyrroles with a wide range of substituents. This is the only report in which Au(I) has been combined with

Zn (II) salts, which cooperatively catalyzes the hydroamination/annulation reaction of 4-yne-nitriles (Figure 55).

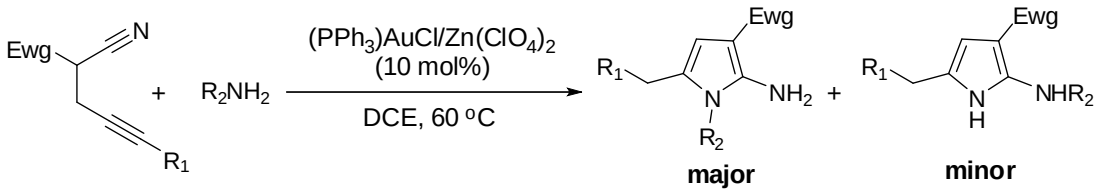


Figure 55. Au(I)/Zn(II) catalyzed tandem cyclisation of 4-pentyne-nitriles

During the recent years aliphatic nitro compounds are important and useful starting materials and intermediates in organic synthesis because they are easily available, they give various carbon-carbon bond forming reactions and nitro group can be easily converted to many other functional groups.

Ballini et al. [116] evaluated the work which was done with nitro alkanes in Michael reactions so far and they found that the nitro group can behave as an electron withdrawing and as a leaving group simultaneously. By using this discovery they suggested a new methadology to synthesize tri-alkylated pyrroles from 2,5-dialkylfuranes and nitroalkanes. In the first step of this strategy by using nitro compound **96** nitronate is synthesized and it is added to cis-3-hexen-2,5-dione **97** which is a masked equivalent of 2,5-dimethylfurane in acetonitrile with DBU (1eq) as base to obtain enones **98**. After this step chemoselective hydrogenation (10% Pd/C as catalyst) of the C-C double bond of the enones were carried out and in this way enones were converted to alkylated γ-diketones **99** (70-88%). The last step of this synthesis Paal-Knorr reaction was performed under acid-catalyzed conditions and/or thermal conditions which led to the corresponding pyrrole **100** (Figure 56).

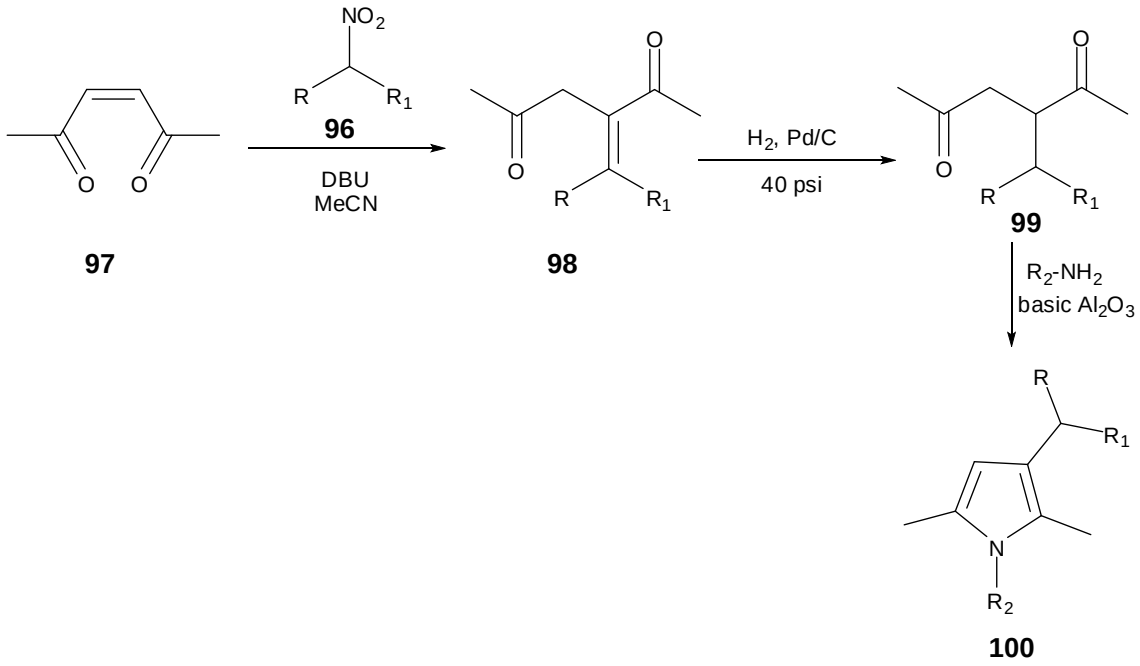
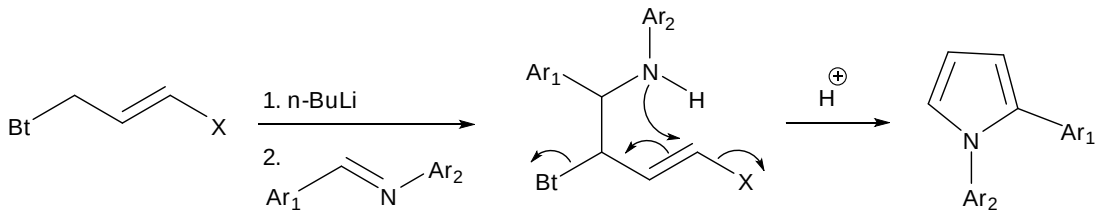


Figure 56. Synthesis of tri-alkylated pyrroles

Katrizky et al. [117] studied two-step procedure from N-allybenzotriazoles to form 1,2-diaryl (heteroaryl) pyrroles by means of intramolecular acid-catalyzed oxidative cyclisation. For the preparation of various 1,2-diaryl pyrroles strong electron withdrawing ability of benzotriazolyl group have been used successfully. N-allylbenzotriazoles **101** which have the general formula $BtCH_2CH=CHX$, where X is a second leaving group, undergo lithiation at the allylic carbon and generate anion. Acid-catalyzed cyclisation carried out by using this anion and diarylimine followed by elimination of boyh benzotriazolyl and X groups give 1,2-diarylpyrroles **102** in good yields (Figure 57). The yield of the final product does not be affected by the nature of the leaving group X (OEt or morpholino).



101 **102**

Figure 57. Intramolecular acid-catalyzed oxidative cyclisation

As was previously mentioned that the most important and widely used method for pyrrole synthesis is Paal-Knorr synthesis which involves 1,4-dicarbonyl compounds and their masked equivalents 2,5-dimethoxytetrahydrofurane are cyclized with amonia or primary amines to form pyrrole rings. In this purpose also amino acids are used as a starting material for the formation of pyrroles but with amino acids generally partial racemization occurs during the condensation reaction which is an unwanted situation for asymmetric pyrrole synthesis. As a result, to obtain such compounds development of a selective and flexible method is needed. Demir et al. [118] have developed a convenient method for the formation of substituted pyrrole rings **103**. For this purpose amine, amino alcohols and amino acid ester salts reacted with chloroenones **104** in the presence of triethylamine (Figure 58) to obtain pyrrole rings. Chloroenones were prepared from acid chlorides **105** and allyl chlorides **106** in the presence of $AlCl_3$. Demir et al. solved the racemization problem observed in Paal-Knorr synthesis and other synhetic routes in which racemization occurs by this study because in this method the cyclisation performs without racemization.

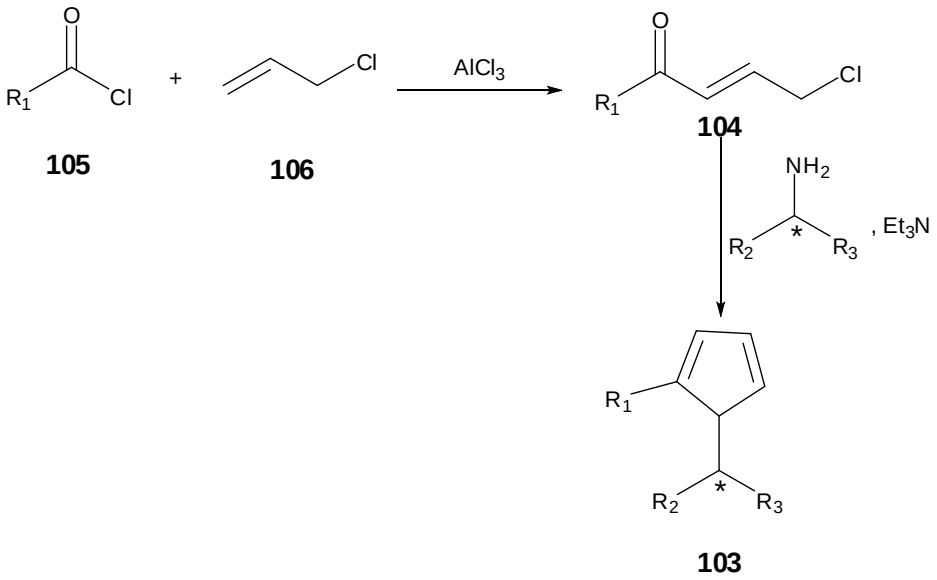


Figure 58. Synthesis of pyrroles starting from chloroenones

By using this method Demir et al. [119] synthesized 2-methyl, 2-isopropyl, 2-cyclohexyl and 2-phenyl substituted pyrrole derivatives.

1.3. Aim of the work

As I mentioned in the previous part nitrogen-containing heterocycles especially pyrrole derivatives are an important heterocyclic compound because of their wide presence in biologically important compounds. Because of this reason, the development of efficient methods for the preparation of pyrrole derivatives and formation of new pyrrole-based heterocyclic compounds are an attractive goal in heterocyclic chemistry. Thus, our aim is to synthesize biologically active, pyrrole based, new heterocylic compounds.

CHAPTER 2

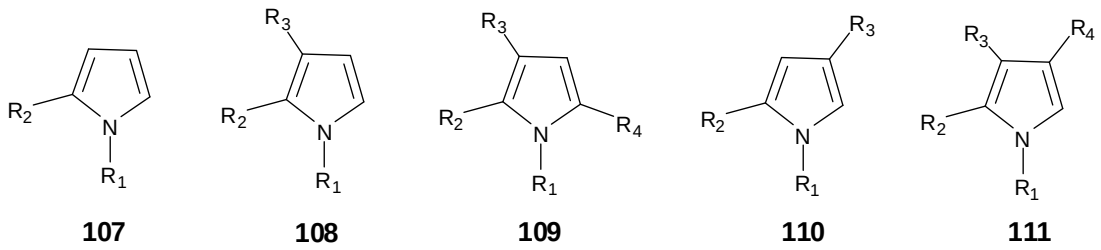
RESULTS AND DISCUSSION

2.1 Synthesis of Chiral Pyrrole Derivatives from Chloroenones

During recent years, emphasis of asymmetric synthesis of heterocyclic compounds especially chiral pyrrole derivatives is on the increase due to the fact that many pyrrole derivatives are subunits of natural products, pharmaceutical agents and polymers [120]. On the pharmaceutical industry to market chiral drugs as a single enantiomers [121] enantiospecificity shown by biological systems is significant [122]. Chiral pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of various biologically active compounds. Enantiogenic synthesis which has been reported [45] of (-)-indolizidine 167B, (+)-monomorine and indolizidine alkaloids [88] depend on the reaction of pyrrole derivatives of amino acids. Preparation of the enantiomers of pyrrole derivatives which have 1-*N* directly attached to the stereogenic center are limited in the literature [119,123]. Most of the methods developed in the literature include the formation of alky- or aryl- substituted pyrrole derivatives but there is no substituent on nitrogen atom in the pyrrole ring.

Until Demir et al. described a convenient route to synthesize 1,2- **(107)**, 1,2,3- **(108)**, 1,2,3,5- **(109)**, 1,2,4- **(110)**, 1,2,3,4- **(111)** substituted pyrrole derivatives by using reaction of amines, amino alcohols and amino acids with

accesible haloenones [119,117,124-126], there is no flexible and selective method to obtain pyrroles with a various of substituents in the literature.



107 **108** **109** **110** **111**

Figure 59. Structures of substituted pyrrole derivatives

These type of pyrroles can be easily used for the synthesis of indolizidine and pyrolizidine alkaloids as shown Figure 60a.

N-conjugates pyrrole-amino acids are used as an effective $^1O_2$ quenchers. Their quenching ability toward $^1O_2$ favorably compares with natural antioxidants such as vitamin E and C [127,128]. Besides this 1,2,4-trisubstituted pyrroles are found to be a new class of synthetic hystone deacetylase inhibitors in the recent years [129,130].

In the light of such information, our aim is to synthesize new chiral substituted pyrrole derivatives from amino acid esters **112** and convenient chloroenone **113** after that convert synthesized substituted pyrrole derivatives **114** to corresponding indolizidine **115** and pyrrolizidine **116** structures (Figure 60b).

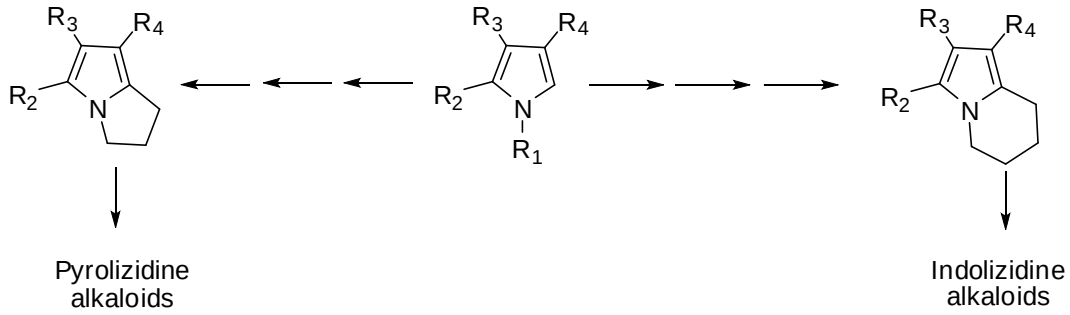


Figure 33a. Synthesis of indolizidine and pyrrolizidine alkaloids

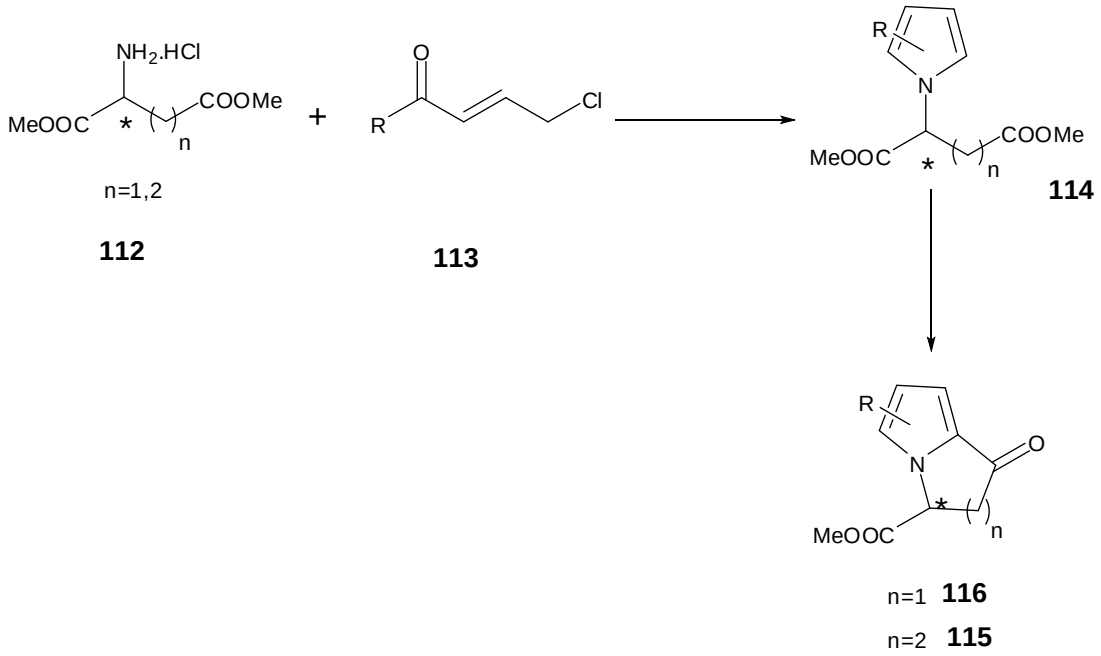


Figure 60b. Synthesis of indolizidine and pyrrolizidine structures

The chloroenone moiety contains four carbon atom. Amino group first reacted with carbon atom on which the chloride is bound and then reacts with carbonyl function and should afford pyrrole ring after the elimination of water and hydrochloric acid. This reaction should proceed without racemization because the reaction takes place under mild condition and in a way no bonds directly linked to the stereocenter are broken or formed.

2.1.1 The Synthesis of Chloroenones

To synthesize substituted pyrrole ring, chloroenones were chosen as starting material in this studies. For this purpose, chiral amino acid esters were reacted with a suitable chloroenone in the presence of triethylamine to give 1,2-disubstituted pyrrole derivatives.

5-Chloropent-3-en-2-one **119** the simplest chloroenone is synthesized by using acetyl chloride **117** and 3-chloropropene (allyl chloride) **118**. Acetyl chloride was added very slowly to $AlCl_3$ suspention in CH_2Cl_2 at 0^oC. While this mixture was stirring 3-chloropropene dissolved in CH_2Cl_2 was added dropwise to mixture at this temperature. The reaction mixture was stirred for 30 minutes at 0^oC after addition was completed. According to the ^1H-NMR data, the reaction produce 5-chloropent-3-en-2-one **119** as a major product (76% yield) and also the isomer **120** was obtained (18% yield) (Figure 61).

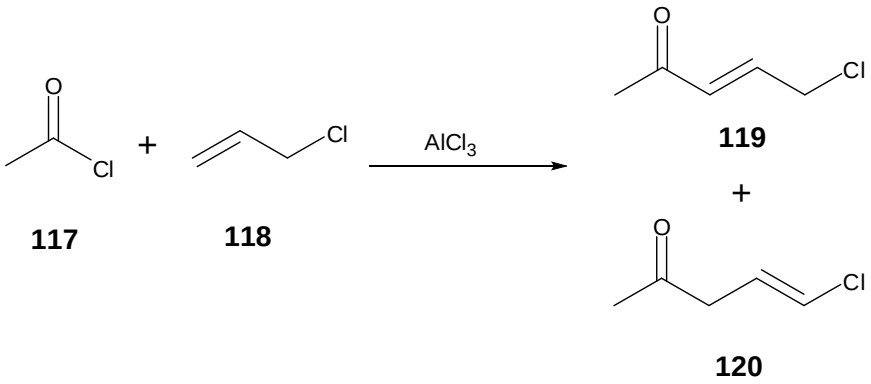


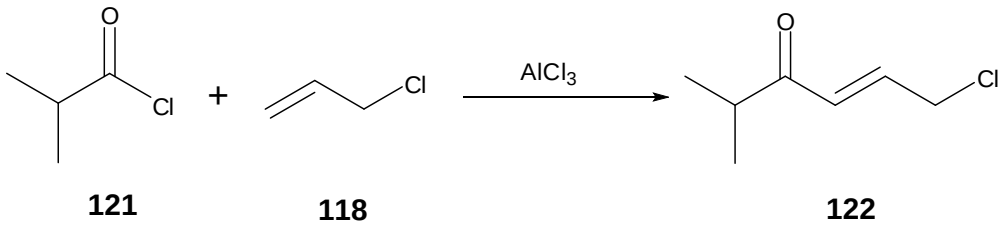
Figure 61. Synthesis of simplest chloroenones

Reaction temperature and reaction time affected the yields of the reaction. Amount of **119** has increased at low temperatures (-5^oC-0^oC) and short reaction time (30 minutes). High reaction temperature caused decomposition and the polymerization of the product.

After completion of reaction, crude product was tried to be purified by using vacuum distillation. But during distillation decomposition was observed because products are temperature sensitive. Also the desired product **119** was gained in very low yield (17%).

Both isomers (**119** and **120**) give the same reaction with amino acids, amino alcohols and amino acid esters to produce 2-substituted pyrrole derivatives because the crude product was used without further purification.

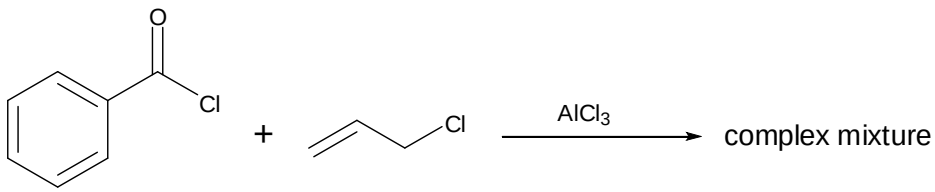
We have planned to synthesize 2-isobutyryl and 2-phenyl substituted pyrrole derivatives as a representative example. For this purpose, it is needed to synthesize 6-chloro-2-methylhex-4-en-3-one and 4-chloro-1-phenylbut-2-en-1-one as of starting material respectively. We have applied a similar reaction to synthesize 6-chloro-2-methylhex-4-en-3-one (Figure 62). Isobutyryl chloride **121** reacted with allyl chloride (3-chloropropene) **118** in the presence of $AlCl_3$ at -5^oC and **122** is obtained as a major product (72%) according to the ^1H-NMR spectrum.



121 **118** **122**

Figure 62. Synthesis of 6-chloro-2-methylex-4-en-3-one

In the case of 4-chloro-1-phenylbut-2-en-1-one synthesis, benzoylchloride **123** was reacted with allyl chloride **118** in the presence of $AlCl_3$ at -5^oC but a complex mixture of unidentified products and polymerized materials were obtained (Figure 63). To solve this problem, different reaction conditions (temperature -10^oC to 10^oC; reaction time 30 min to 2,5 hr) were applied [119] but none of them gave the desired chloroenones. The solution to this problem will be explained in section **2.1.2.1.**

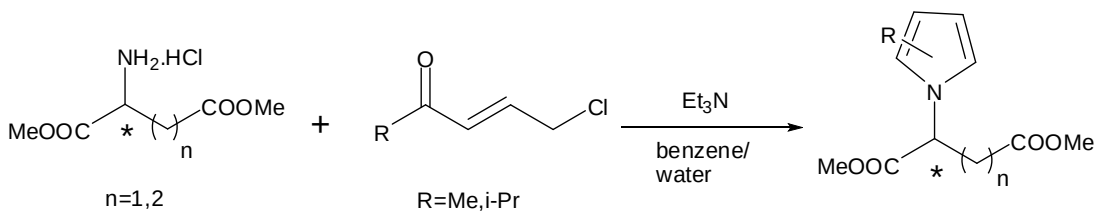


123 **118**

Figure 63. Reaction of benzoylchloride with allyl chloride

2.1.2 Formation of 1,2-Disubstituted Chiral Pyrrole Derivatives

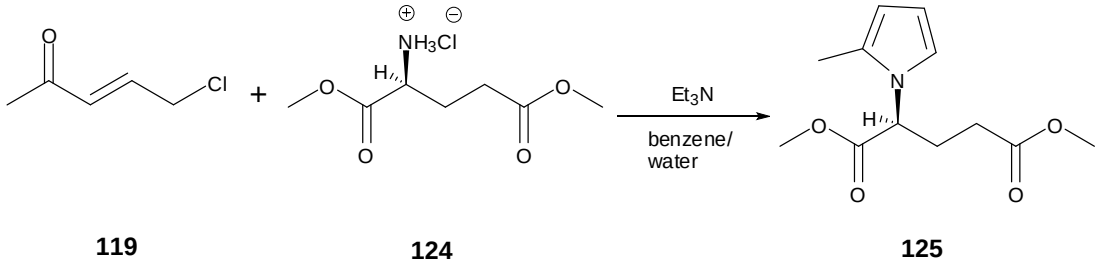
After the synthesis of methyl- and isobutryl- substituted chloroenone, we have extended this chemistry for the conversion of amino acid esters to their chiral 2-methyl- and 2-isobutryl- substituted pyrrole derivatives (Figure 64) [119].



112 **113** **114**

Figure 64. Synthesis of substituted pyrrole derivatives

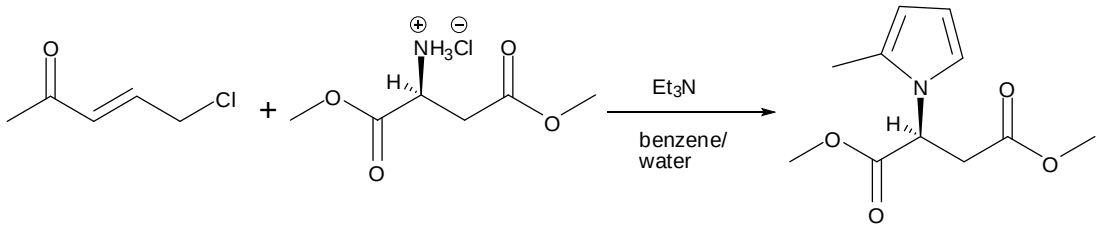
Methyl substituted chloroenone **119** was refluxed with (L)-glutamic acid methyl ester hydrochloride **124** in benzene and water for 4 hours and during this time the reaction was monitored by TLC. After the purification, the desired pyrrole derivative of (L)-glutamic acid methyl ester **125** was obtained in high yield as a colorless oil (Figure 65).



119 **124** **125**

Figure 65. Synthesis of methyl-substituted pyrrole derivative of (L)-glutamic acid methyl ester

By using the same reaction conditions mentioned above (L)-aspartic acid methyl ester hydrochloride **126** was also converted to corresponding 2-methyl substituted pyrrole derivative **127** in high yield (Figure 66).



119 **126** **127**

Figure 66. Synthesis of methyl-substituted pyrrole derivative of (L)-aspartic acid methyl ester

Afterwards the same reaction was also carried out between isobutyryl substituted chloroenone **122** and (*L*)-glutamic acid methyl ester hydrochloride, **124** (*L*)-aspartic acid methyl ester hydrochloride **116** to obtain corresponding pyrrole derivatives (*S*)-**128** and (*S*)-**129** (Figure 67).

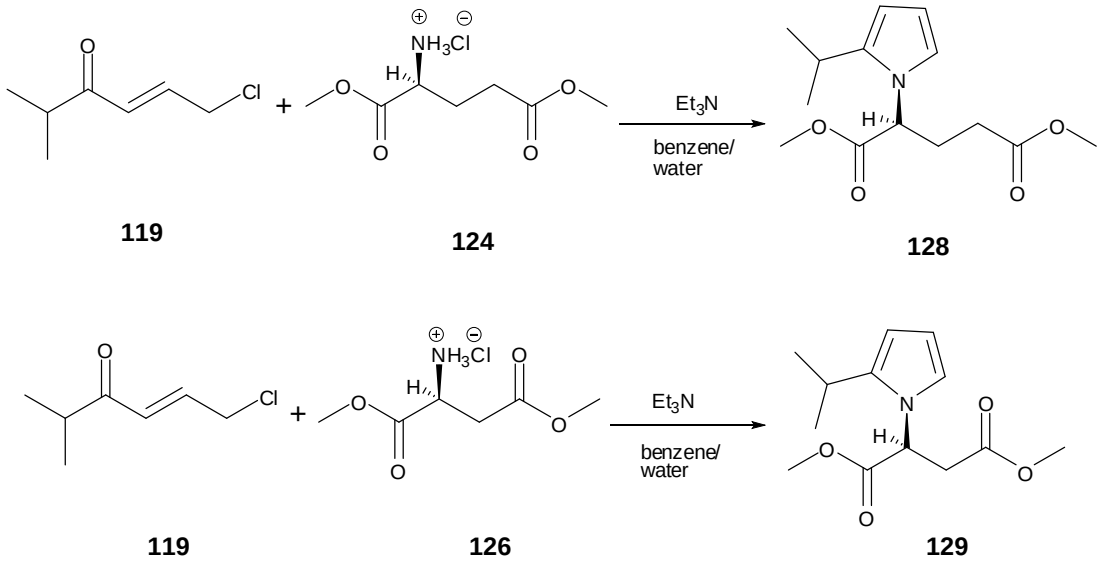


Figure 67. Synthesis of isobutryl-substituted pyrrole derivatives

As a result of previous studies which were done in our group the esters of amino acids gave higher yields than their free acids. By using different R groups on chloroenone, comparable yields were obtained and this showed that chloroenone does not affect the yield of the products so much [119].

Optical rotation values of synthesized pyrrole derivatives were measured by polarimeter; and this showed that no racemization has occured during the formation of pyrrole ring as we expected, which is proved by the following reaction (Figure 68).

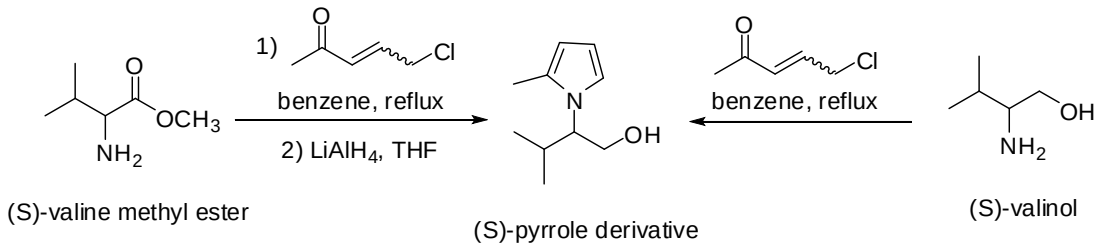


Figure 68. Synthesis of substituted pyrrole derivatives from valine methyl ester and valinol

2.1.2.1 Synthesis of 2-Phenyl-substituted Chiral Pyrrole Derivatives

We could not use phenyl substituted chloroenone for the synthesis of 2-phenyl substituted pyrrole derivative because the reaction allyl chloride **118** with benzoyl chloride **123** in the presence of $AlCl_3$ gave the corresponding chloroenone in very low yield (4-6%, ^{1}H-NMR). New synthetic route was needed to synthesize 2-phenyl derivative of pyrrole. For this purpose we used dibromo compound **130** to obtain desired pyrrole derivatives.

According to Figure 69, benzaldehyde **131** reacted with allyl bromide **132** to get the alcohol **133** in 75% yield by using a literature procedure [131]. The bromination of alcohol **134** followed by subsequent CrO_3-mediated oxidation of dibromo alcohol **134** formed the desired dibromo compound **130** in 80% yield. Then dibromo compound **130** refluxed with (L)-glutamic acid methyl ester hydrochloride **124** for 6 hours in benzene and water in the presence of triethylamine to produce corresponding 2-phenyl substituted pyrrole derivative **135** (Figure 69).

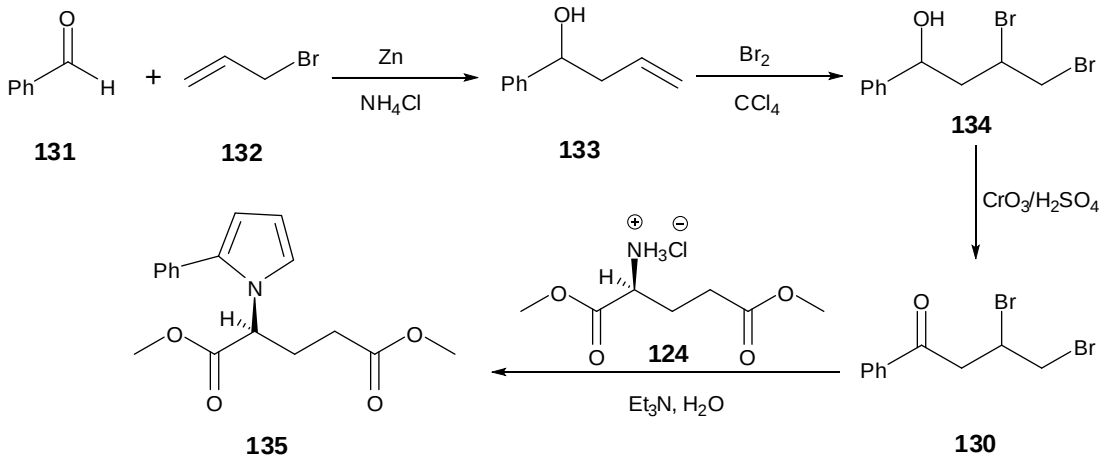


Figure 69. Synthesis of phenyl-substituted pyrrole derivative of (L)-glutamic acid methyl ester

The similar reaction carried out with (L)-aspartic acid methyl ester hydrochloride **126** and it was converted to its 2-phenyl pyrrole derivative **136** (Figure 70).

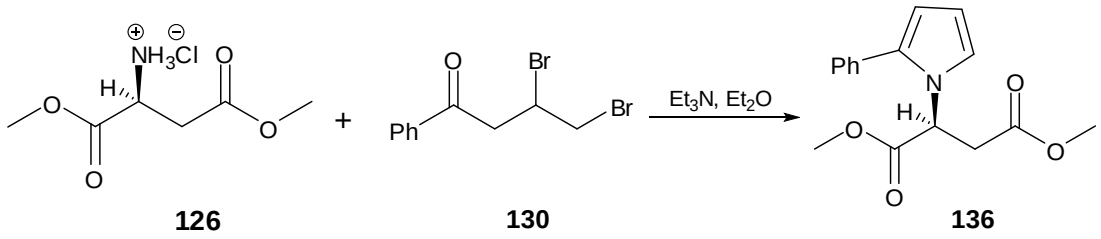


Figure 70. Synthesis of phenyl-substituted pyrrole derivative of (L)-aspartic acid methyl ester

2.1.3 Formation of 1,2,4-trisubstituted Chiral Pyrrole Derivatives

After synthesizing 1,2-disubstituted chiral pyrrole derivatives, we have extended to this chemistry to the conversion of (L)-glutamic acid ethyl ester hydrochloride **124** and (L)-aspartic acid methyl ester hydrochloride **126** to their chiral 1,2,4-trisubstituted pyrrole derivatives **139** and **140**. For this purpose at first, appropriate chloroenone **138** which is an important starting material and provide a four carbon unit with a carbonyl and halide functionality for the formation of pyrrole were synthesized according to the Figure 71.

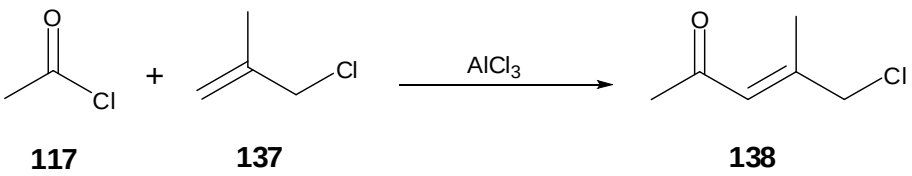


Figure 71. Synthesis of (E)-5-chloro-4-methylpent-3-en-2-one

Then the synthesized chloroenone **138** that was used without any purification reacted with (L)-glutamic acid methyl ester hydrochloride **124** and (L)-aspartic acid methyl ester hydrochloride **126** in benzene and water in the presence of triethylamine in order to obtain 1,2,4-trisubstituted chiral pyrrole derivatives **139** and **140** respectively as shown in Figure 72.

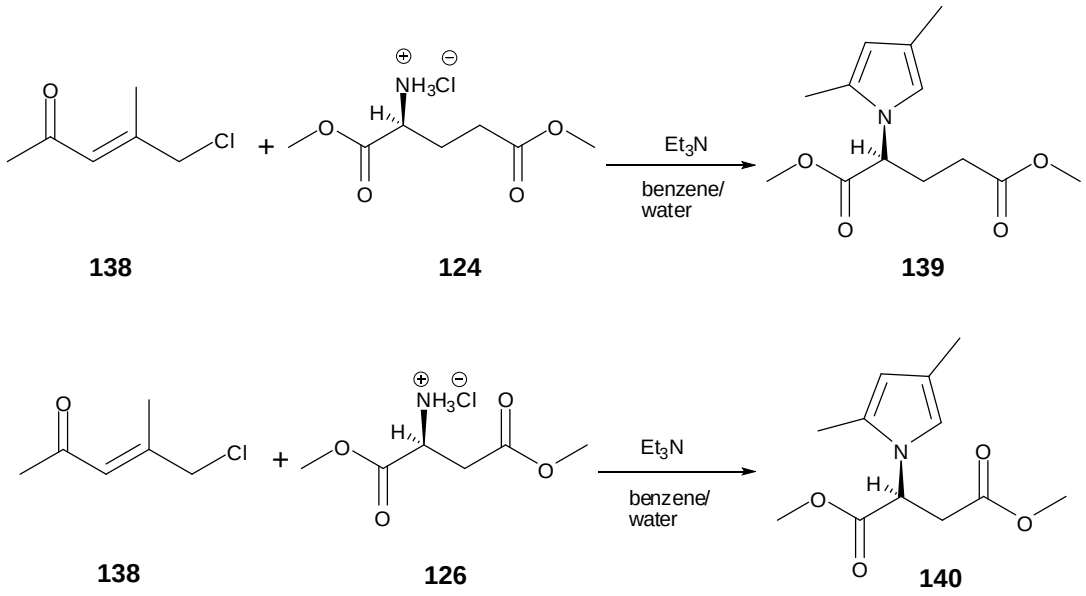


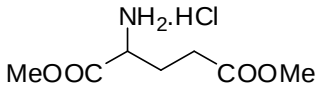
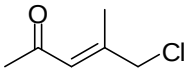
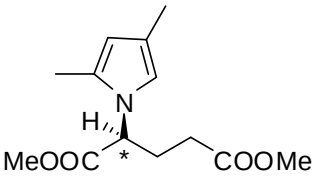
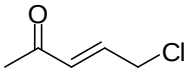
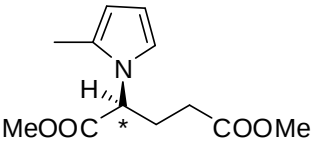
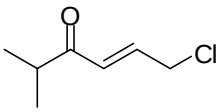
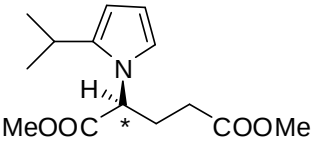
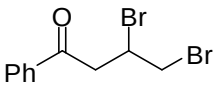
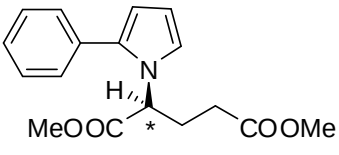
Figure 72. Synthesis of 1,2,4-trisubstituted chiral pyrrole derivatives

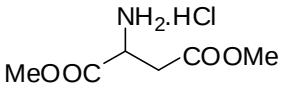
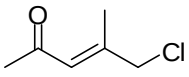
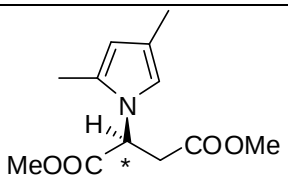
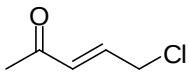
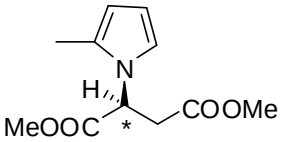
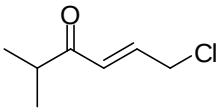
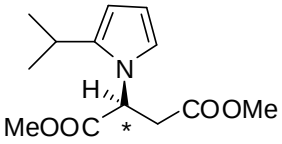
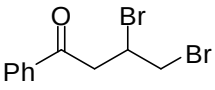
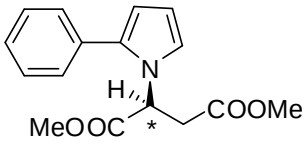
2.1.4 Comparison of the Result

Comparable yields are obtained between the reactions of different chloroenone and amino acid esters as illustrated in Table 1. This shows that the yield of the products are not affected so much by chloroenones.

All synthesized pyrroles are chiral because they are produced starting from corresponding (L)-glutamic acid methyl ester hydrochloride and (L)-aspartic acid methyl ester hydrochloride. Also measurement of optical rotation shows that no racemization occurs during the formation of pyrrole ring.

Table 1. Representative examples of synthesized substituted pyrrole derivatives

Amino acid esters	Chloroenones	Pyrroles
 **124**	 **138**	 **139**
	 **119**	 **125**
	 **122**	 **128**
	 **130**	 **135**

 **126**	 **138**	 **140**
	 **119**	 **127**
	 **122**	 **129**
	 **130**	 **136**

2.1.5 Proposed Mechanism for the Formation of Pyrrole Ring

The suggested two mechanism for the formation of pyrroles **141** is shown in Figure 73a and 73b [132]. According to first mechanism, the amine compound **142** reacts initially with the chloroenone **143** to form **144**. The cyclisation onto ketone followed by elimination of water give the product **141**.

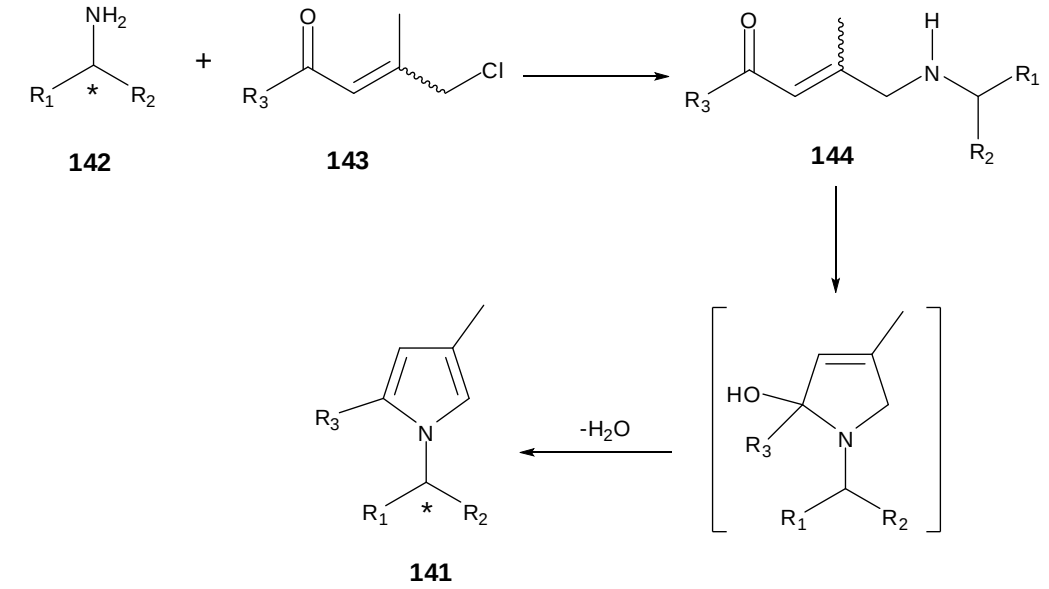


Figure 73a. Proposed mechanism for the formation of pyrrole ring I

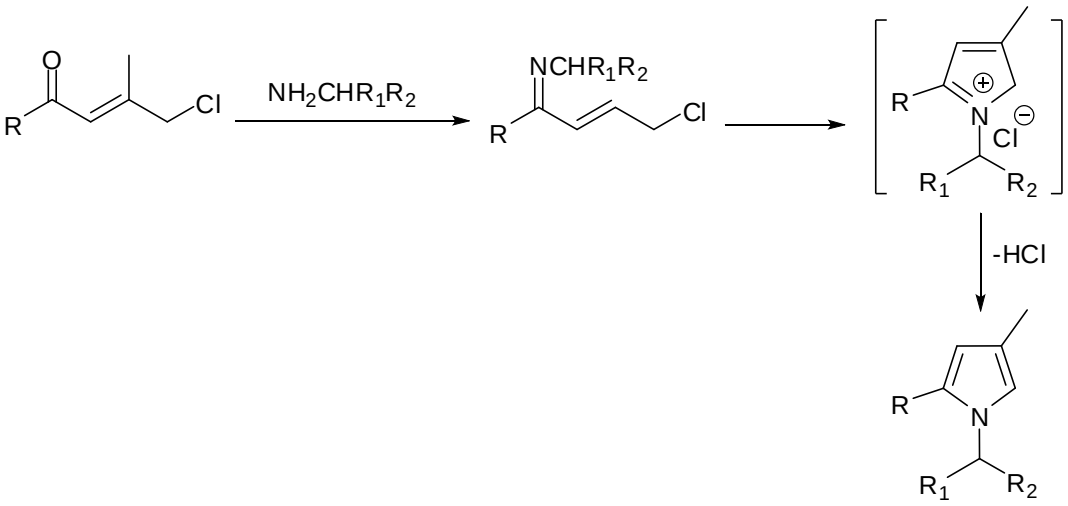


Figure 73b. Proposed mechanism for the formation of pyrrole ring II

2.2 Synthesis of Pyrrole Derivatives from Dimethoxytetrahydrofurane

Nitrogen-containing heterocycles especially pyrrole derivatives are important because of their wide presence in biologically important compounds [133]. Because of this reason, the development of efficient methods for the preparation of pyrrole derivatives and formation of new pyrrole-based heterocyclic compounds are an attractive goal in heterocyclic chemistry. In our group efficient methods have already been reported for the formation and functionalization of pyrrole derivatives [134] and still we have interest to construct new pyrrole-based heterocycles. To that end we designed a route to synthesize a new interesting heteropolycyclic compounds **145** [135] which will be explained in detail in section 2.3.2.

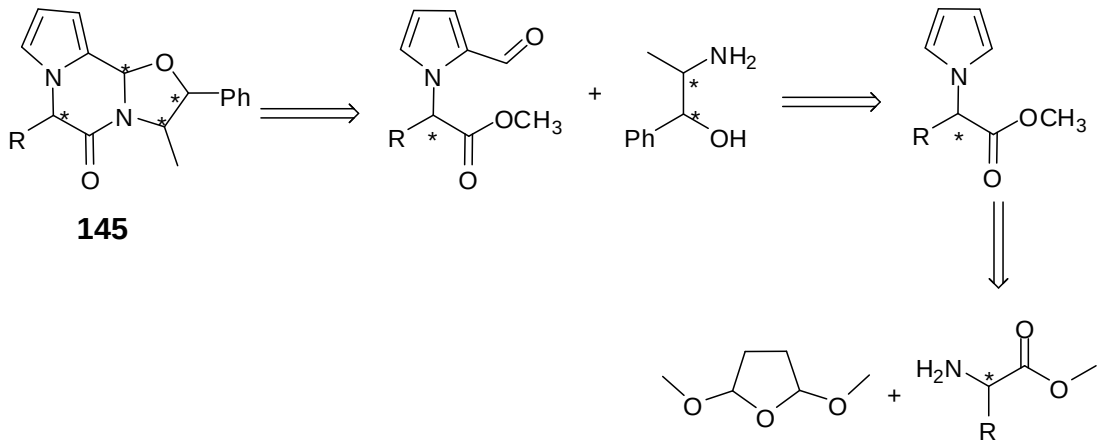
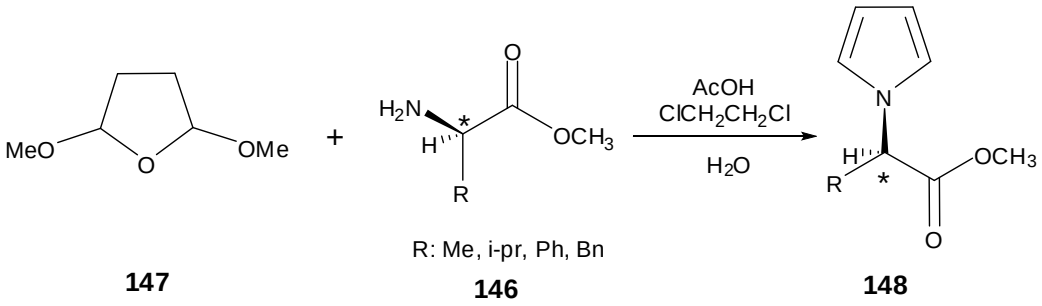


Figure 74. Retrosynthetic pathway for the formation of new pyrrole-based heterocyclic compounds

To synthesize these heterocyclic compounds of the type **145** as shown in retrosynthetic pathway firstly it is needed to synthesize unsubstituted pyrrole derivatives by Clauson-Kaas Procedure [136]. With this design, amino acid esters **146** were refluxed 3h with dimethoxytetrahydrofurane **147** in the presence of acetic acid in dichloro ethane-water and reaction monitored by TLC. After work-up crude product was purified by using column chromatograpy. As a result, this condensation reaction furnished 1-N-pyrrole

derivatives of amino acid esters **148** in high yields (95-98% yield) as shown in Figure 75.



147 **146** **148**

Figure 75. Synthesis of unsubstituted chiral pyrrole derivatives

The formation mechanism of pyrrole from dimethoxytetrahydrofurane **147** and amino acid ester **146** is outlined in Figure 76. According to the Figure 49 amino group of amio acid ester attack to the furane carbon which is attached to the protonated methoxy group followed by ring opening reaction. Then nitrogen of amino acid group reacted with carbonyl moiety and elimination of water and acetic acid give the desired pyrrole ring **148**.

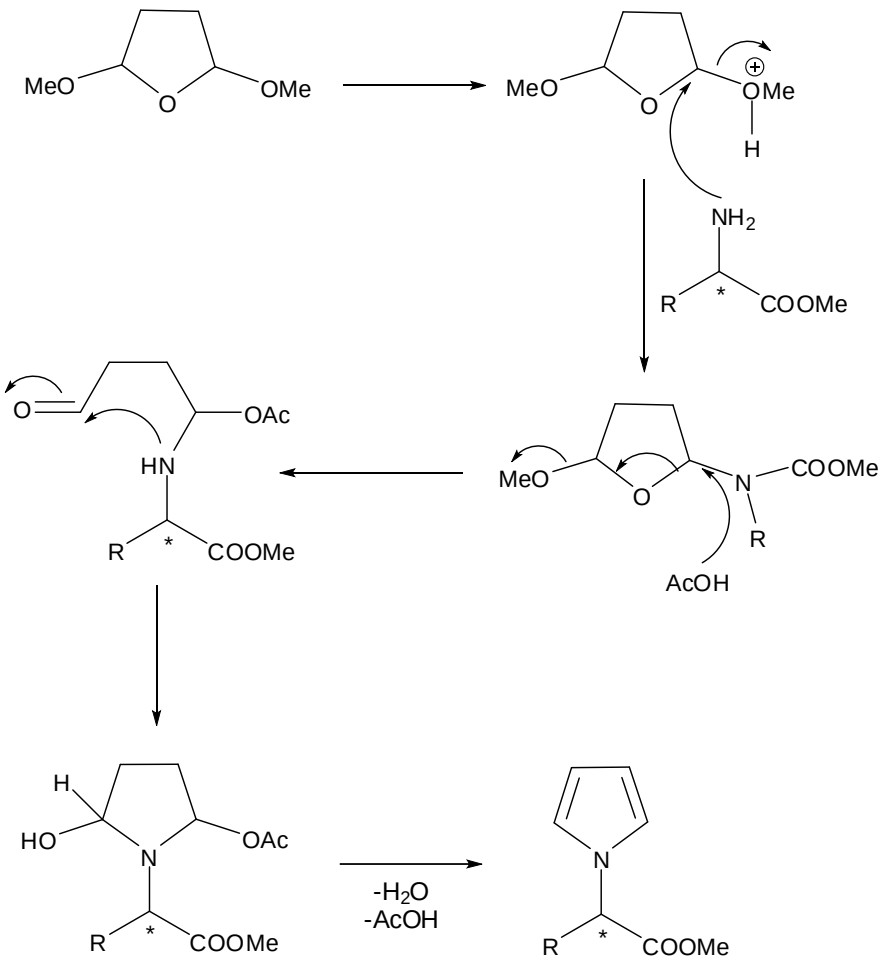
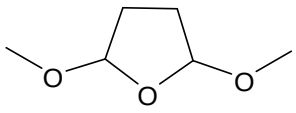
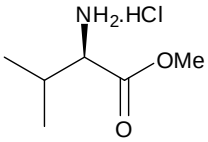
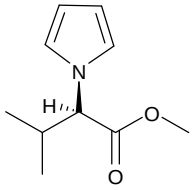
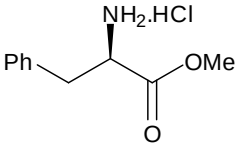
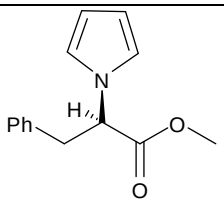
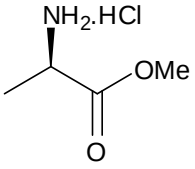
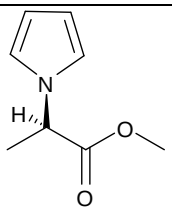
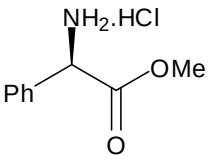
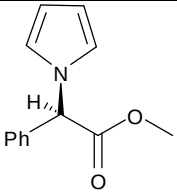
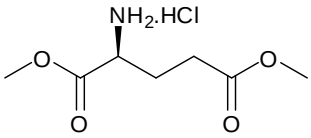
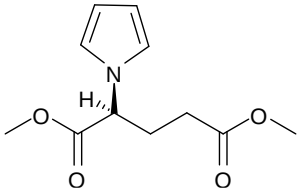
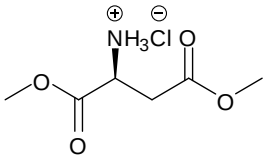
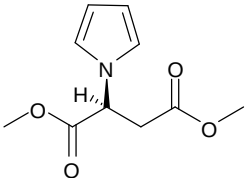


Figure 76. Formation mechanism of unsubstituted chiral pyrrole derivatives

Under the same reaction conditions chiral valine methyl ester, phenylalanine methyl ester, alanine methyl ester, phenylglycine methyl ester, glutamic acid methyl ester and aspartic acid methyl ester were converted to the corresponding chiral pyrrole derivatives in high yields as shown Table 2. No racemization was observed during the condensation reaction. All of the synthesized product was determined by using ^{1}H-NMR experiment. According to ^{1}H-NMR all peaks are in aggreement with their structure. Generally pyrrole protons give a singlet signal at between 6.02-6.65 ppm, chiral center proton (-CH) which comes from amino acid moiety gives peak at 4.40 ppm, ester protons give singlet signal at 3.64 ppm.

Table 2. Representative examples of synthesized unsubstituted pyrrole derivatives

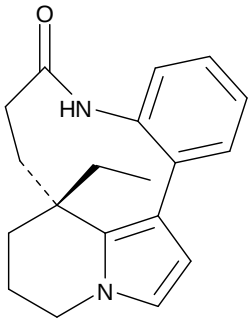
2,5-dimethoxyTHF	Amino acid esters	Pyrroles
 **147**	 **(S)-149** **(R)-151**	 **(S)-150** **(R)-152**
	 **(S)-153** **(R)-155**	 **(S)-154** **(R)-156**
	 **(S)-157** **(R)-159**	 **(S)-158** **(R)-160**
	 **(S)-161** **(R)-163**	 **(S)-162** **(R)-164**

	 **(S)-124**	 **(S)-165**
	 **(S)-126**	 **(S)-166**

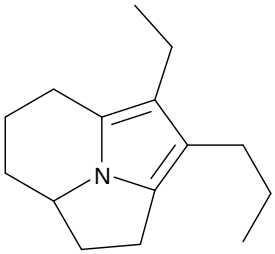
2.3 Functionalization of Pyrroles

2.3.1 Indolizidine Structures (5,6) and Pyrolizidine Structures (5,5)

The indolizidine alkaloids have great interest due to their exotic provenance and potent biological activity [137]. Especially, alkaloids containing isolated pyrrole ring are found as secondary metabolities in diversity of sources such as; plants, invertebrates, fungi and bacteria [138]. Most of the natural products contain fused bicyclic or policyclic system in which pyrrole rings form a part of them. Naturally-occurring 5,6,7,8-tetrahydroindolizidines in which the pyrrole ring remains unaffected have been found recently such as anticancer alkaloid (-)-rhazinilam **167** and ant alkaloid myrmicarin **168**.



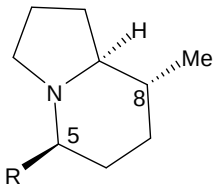
167



168

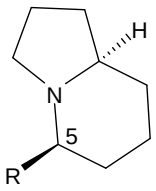
Figure 77. Anticancer alkaloid (-)-rhazinilam and myrmicarin

Recently, 5-substituted indolizidines have also great interest because of their biological activity. Alkaloids **169** which consist of *trans* 8-methyl substituent have been isolated from dendrobatid frogs and have been shown that these alkaloids were the most potent non-competitive blockers for nicotinic receptor channels [139]. In addition to this, 5-substituted alkaloids **170** which exhibit antimicrobial activity against several fungi and gram-positive bacteria [140] have also been isolated from frogs [141].



169

R= pentyl, pentenyl, pentynyl



170

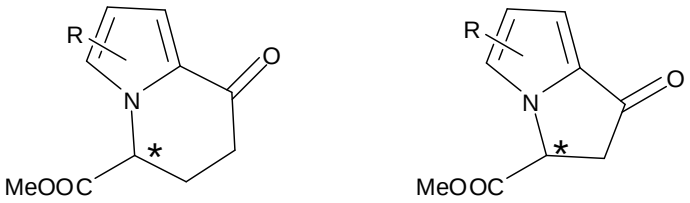
R= propyl, decenyl, decadienyl, decatrienyl

Figure 78. Examples of alkaloids

Although there are many synthetic routes for the formation of naturally occurring 5-substituted and 5,8-disubstituted indolizidines in the literature, these syntheses generally have undesirable effects. These drawbacks are:

(1) Generally incorporated R side chains in the first step of the syntheses prevents easy production of analogues. (2) Most of the synthetic routes are too long to be practical due to very low yields [142].

When we consider the importance of the pyrrole derivatives we aimed to form the substituted and unsubstituted pyrrole derivatives and their reactions with BBr_3 in order to synthesize new bicylic indolizidine **115** and pyrrolizidine **116** structures.



115 **116**

Figure 79. New bicylic indolizidine and pyrrolizidine structures

For this purpose, the esters of amino acids were treated with dimethoxytetrahydrofuran to synthesize unsubstituted pyrrole derivatives. Then substituted pyrrole derivatives were synthesized from aminoacid esters with chloroenones. By using L-glutamic acid methyl ester hydrochloride, L-aspartic acid methyl ester hydrochloride and different chloroenones corresponding substituted pyrrole derivatives were synthesized. These synthesized substituted and unsubstituted pyrrole derivatives treated with BBr_3 and new bicyclic pyrrole derivatives were obtained in modarate yield (75-85%) as shown Table 3. Before Table 3, general reaction scheme of substituted and unsubstituted bicyclic pyrrole derivatives is illustrated in Figure 80. In the cyclisation step we have also tried another method where dry HCl gas was bubbled through a solution of pyrrole derivatives in dry methanol for 3 h. After work-up and purification step bicyclic pyrole compound was obtained in 50% yield which is too smaller than BBr_3 process. Due to this result, we continued cyclisation step with BBr_3. During the

cyclisation reaction the chirality of ester-C is protected. Typically we observed ^{1}H-NMR signals at 6.21-6.90 ppm which belong to pyrrole peaks, 4.88-4.93 ppm which belongs to chiral center coming from amino acid, 3,50-3.65 ppm for OCH_3. In IR, carbonyl absorption of ketone and ester appears at 1730 cm^{-1} and 1755 cm^{-1}. In ^{13}C-NMR spectra, C=O peak of both group is present in pyrrole derivatives, one of the ester group is disappeared in cyclisation product.

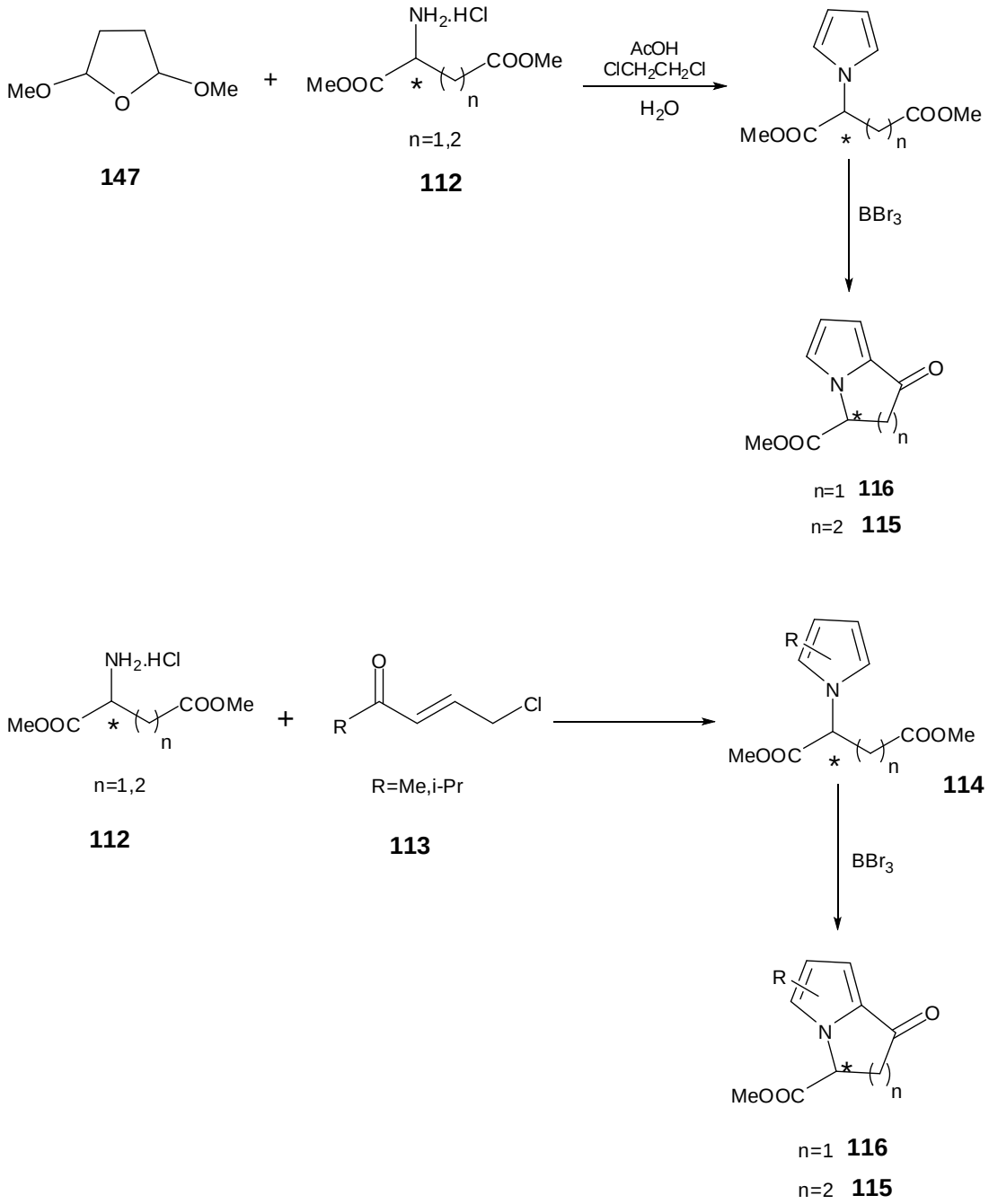
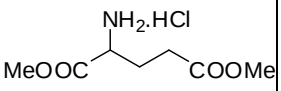
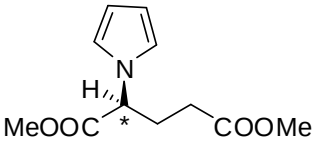
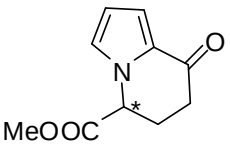
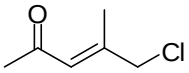
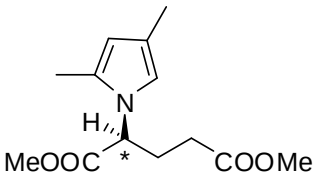
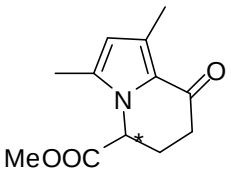
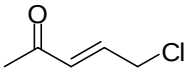
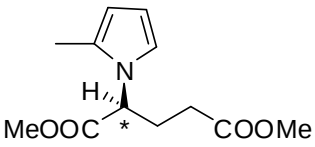
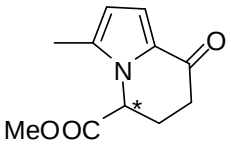
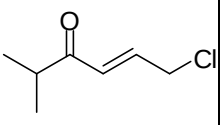
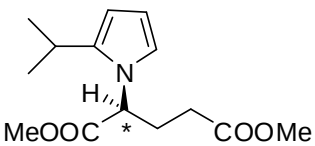
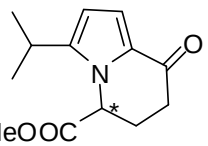
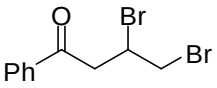
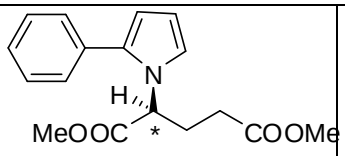
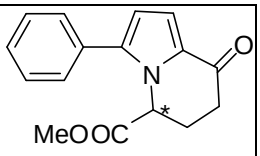
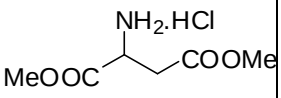
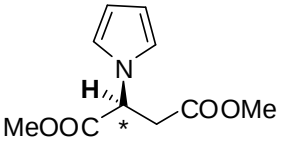
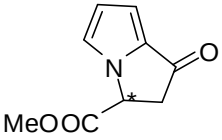
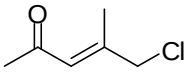
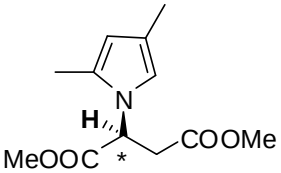
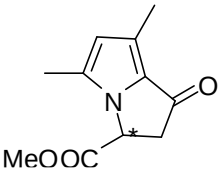
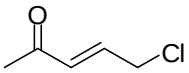
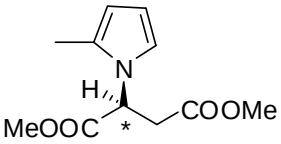
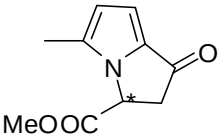
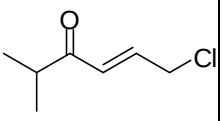
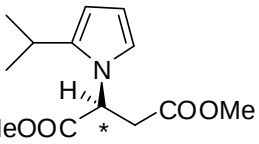
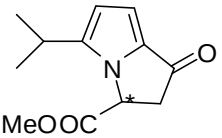
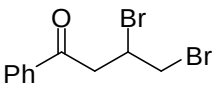
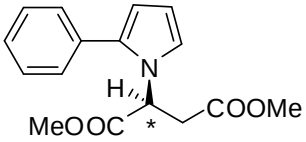
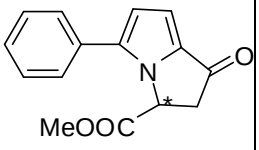


Figure 80. Synthesis of new bicylic indolizidine and pyrrolizidine structures

The chirality origin of the bicyclic 5,5 and 5,6 systems is coming from the nature of the amino acids and R group can be in several positions. This shows the flexibility of the method. Representative examples are summarized in Table 3.

Table 3. Representative examples of synthesized bicyclic pyrrole derivatives

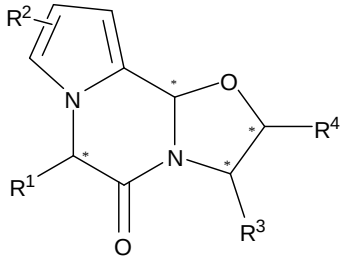
Amino acid esters	Chloroenones	Pyrroles	Bicyclic pyrrole derivatives
 **124**	-	 **165**	 **171**
	 **138**	 **139**	 **172**
	 **119**	 **125**	 **173**
	 **122**	 **128**	 **174**

	 **130**	 **135**	 **175**
 **126**	-	 **166**	 **176**
	 **138**	 **140**	 **177**
	 **119**	 **127**	 **178**
	 **122**	 **129**	 **179**
	 **130**	 **136**	 **180**

We described here the asymmetric synthesis of new bicyclic chiral pyrrole derivatives which can be suitably functionalized for converting to the naturally occurring 5-substituted and 5,8-disubstituted indolizidines. Besides this, our method has some advantages: (1) The starting materials are L-glutamic acid methyl ester and L-aspartic acid methyl ester which are commercially available and low-priced compounds. (2) R group (COOMe) of resulting bicyclic compounds can be easily functionalized. (3) By using selective hydrogenation reaction we can obtain either 5-substituted or 5,8-disubstituted indolizine alkaloids. Also, 8-substituent (OH group) is suitable for converting a number of analogues by using nucleophiles.

2.3.2 Oxazolo-Pyrrolo-Pyrazine Structures

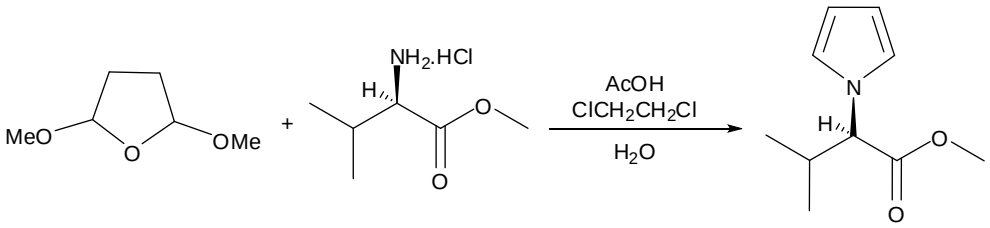
After the synthesis of unsubstituted pyrrole derivatives we have extended the work to synthesize interesting heteropolycyclic compounds with oxazolo-pyrrole-pyrazine fused structures. The reaction of pyrrole derivatives with norephedrine toward inter- and intramolecular cyclisations is carried out in order to obtain novel heterocyclic compounds **145** as shown below. These polycyclic structures are very important because they are existing in natural products [143].



145

Figure 81. Oxazolo-Pyrrolo-Pyrazine Structure

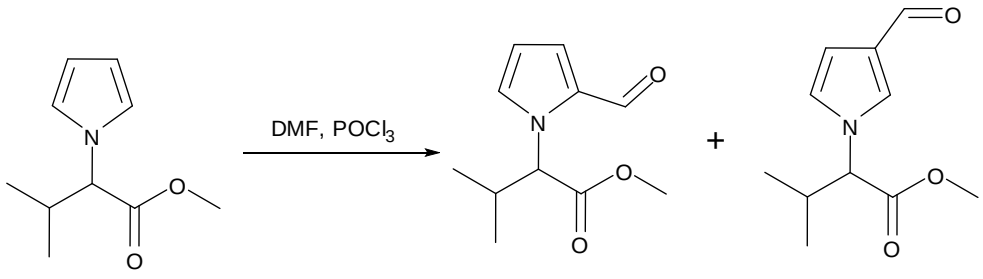
To synthesize these novel compounds we designed a practical route. Firstly, valine methyl ester **(S)-149** and **(R)-151** reacted with dimethoxytetrahydrofuran **147** in the presence of acetic acid in dichloro ethane and water to form the pyrrole derivative of valine **(S)-150** and **(R)-152** according to Clauson-Kaas procedure [136] as shown Figure 82. This pyrrole formation process was carried out without racemization.



147 **(S)-149** **(R)-151** **(S)-150** **(R)-152**

Figure 82. Reaction of valine methyl ester with dimethoxytetrahydrofuran

The second step is Vilsmeier-Haack formylation. Although several procedures were described in the literature for the formylation of a pyrrole ring we carried out the Vilsmeier-Haack formylation reaction of pyrrole to obtain the highest yield for the desired isomer of the product. By this reaction two isomeric pyrrole carbaldehydes, 2-formylpyrrole (**(S)-181** and **(R)-182**) and 3-formylpyrrole (**(S)-183** and **(R)-184**), are obtained in 77% and 23% yields which are separated easily by column chromatography as shown Figure 83.



(S)-150 **(R)-152** **(S)-181** **(R)-182** **(S)-183** **(R)-184**

Figure 83. Vilsmeier-Haack formylation reaction

The mechanism of Vilsmeier-Haack formylation is outlined in Figure 84. According to the Figure 84 first of all dimethylformamide treated with phosphorus oxychloride to give corresponding DMF-$POCl_3$ complex followed by pyrrole addition to this complex and then formylated pyrrole derivative is obtained.

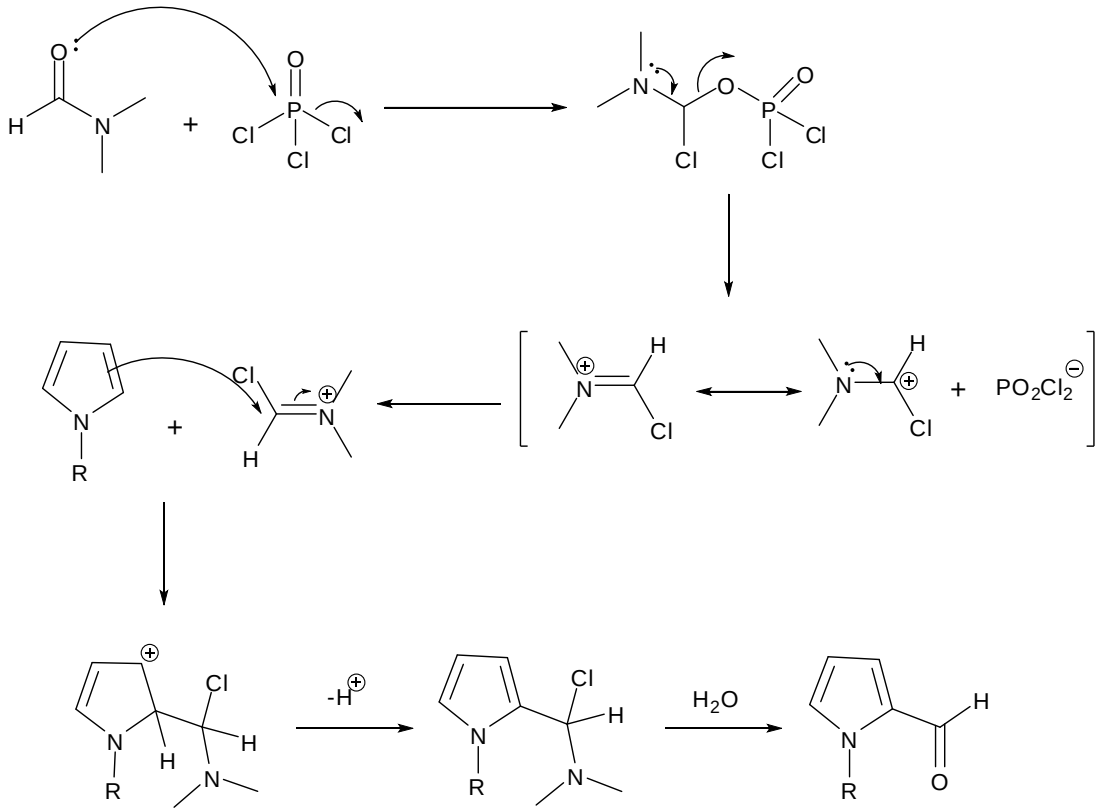
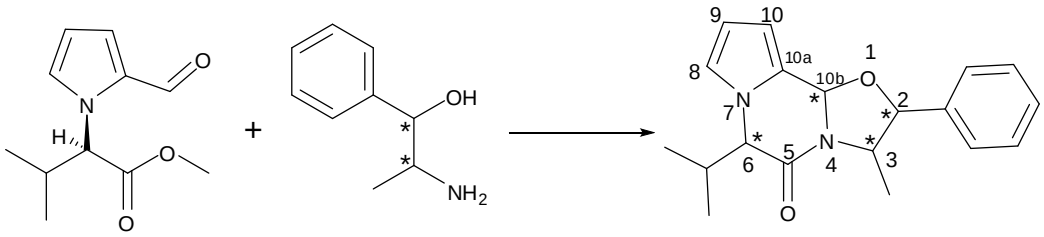


Figure 84. Mechanism of Vilsmeier-Haack formylation reaction

After Vilsmeier-Haack formylation reaction 2-formyl pyrrole derivatives **(S)-181** and **(R)-182** refluxed with (1R,2S) **185** and (1S,2R)-norephedrine **186** in benzene to give the corresponding amine via the reduction of the intermediate imine to synthesize the norephedrine based chiral ligands with multiple stereogenic centers as we expected. But we obtained the tricyclic fused structures by refluxing 2-formylpyrrole with norephedrine. Spectral analysis of the product showed that imine formation was occured and the

product was identified as a tricyclic pyrrole-pyrazine-oxazole fused structure **187** as shown Figure 85. This reaction was repeated several times with the enantiomers of valine and (1R,2S) **185** and (1S,2R)-norephedrine **186**. Thus stereoisomeric products were obtained in comparable yields (72%-75%).



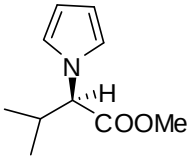
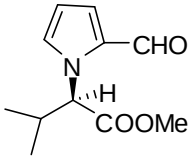
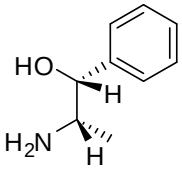
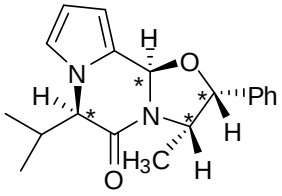
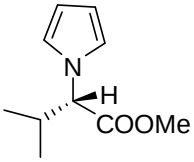
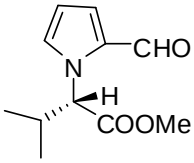
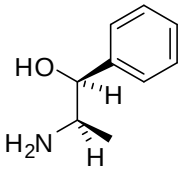
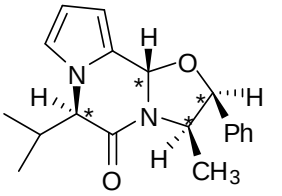
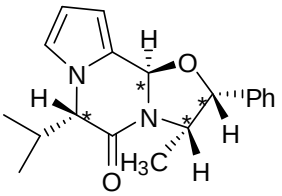
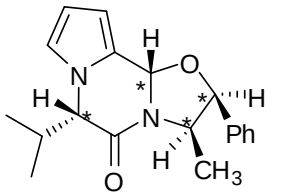
181 **(1R,2S)- 185** **(1S,2R)- 186** **187**

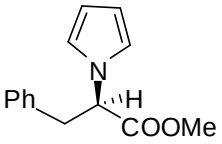
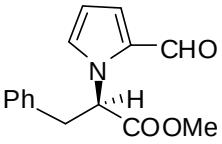
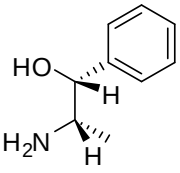
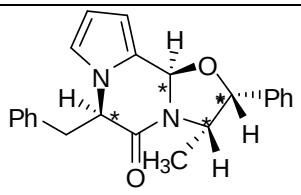
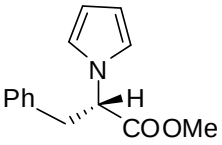
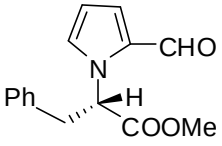
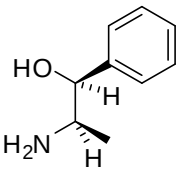
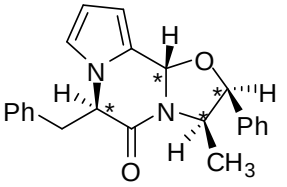
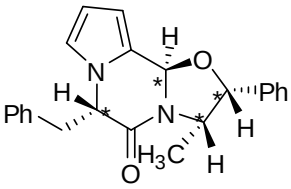
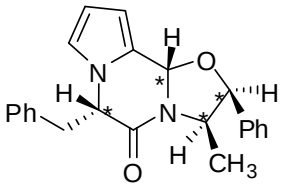
Figure 85. Synthesis of tricyclic pyrrole-pyrazine-oxazole fused structure

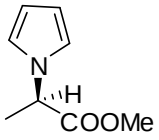
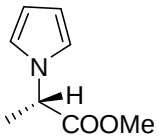
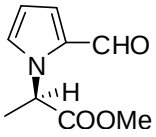
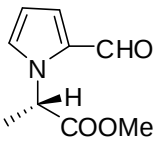
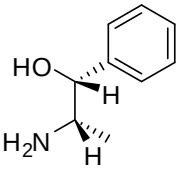
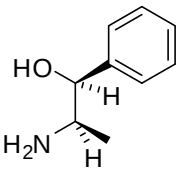
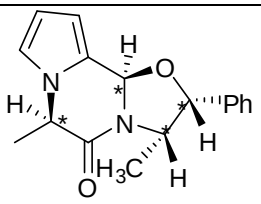
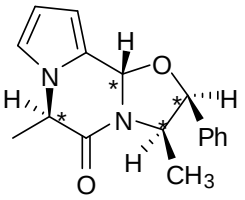
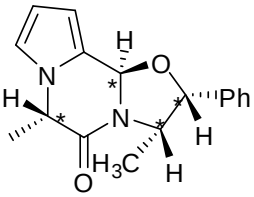
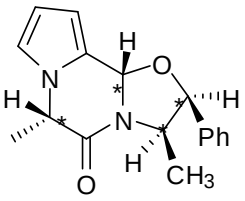
Under the same reaction conditions phenylalanine methyl ester, alanine methyl ester and phenylglycine methyl ester were converted to the corresponding tricyclic pyrrole-pyrazine-oxazole fused structures which have a newly formed stereogenic center as shown Table 4.

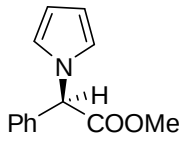
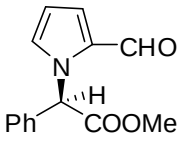
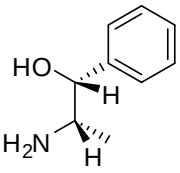
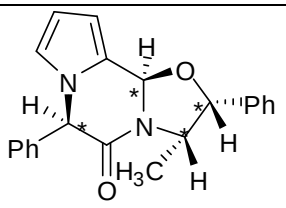
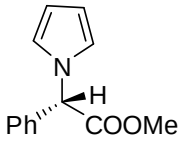
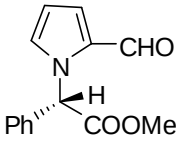
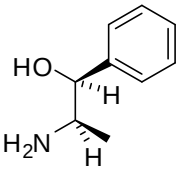
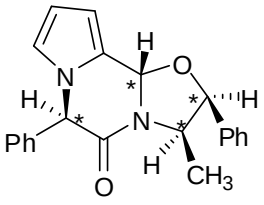
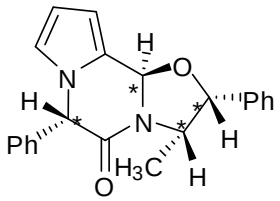
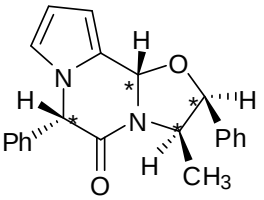
The configuration of the new stereogenic center was assigned on the basis of the NMR spectroscopic data. The NOE and NOESY experiment showed that in all four isomers of fused structures which was derived from phenylglycine methyl ester, the (C-10b)-H lies on the same side as the CH_3 and the phenyl groups of norephedrine, any positive NOE being not registered between C-10b)-H and (C-2)-H nor(C-3)-H. The structural determination experiments were carried out with other amino acid derived products with the stereochemical results in agreement with what was found for valine derived products. The assignment of the stereochemistry of the newly formed center was also assigned from the X-ray crystallographic data from (R,S,S,R)-**207**, as shown in Figure 86. It seems that the stereocenters of norephedrine are responsible for the stereochemical outcome of the products at the newly formed center, but not the stereocenter of the amino acid moiety [135].

Table 4. Representative examples of synthesized pyrrole-pyrazine-oxazole structures and **Table 4** continued following pages (72, 73, 74).

Pyrrole	2-Formylpyrrole	Norephedrine	Pyrrole-pyrazine-oxazole product
 **(R)-152**	 **(R)-182**	 (1R,2S) **185**	 **187**
 **(S)-150**	 **(S)-181**	 (1S,2R) **186**	 **188**
			 **189**
			 **190**

 **(R)-156**	 **(R)-191**	 (1R,2S) **185**	 **193**
 **(S)-154**	 **(S)-192**	 (1S,2R) **186**	 **194**  **195**  **196**

 **(R)-160**  **(S)-158**	 **(R)-197**  **(S)-198**	 (1R,2S) **185**  (1S,2R) **186**	 **199**  **200**  **201**  **202**

 **(R)-164**	 **(R)-203**	 (1R,2S) **185**	 **205**
 **(S)-162**	 **(S)-204**	 (1S,2R) **186**	 **206**  **207**  **208**

The configuration of the tricyclic structure (R,S,S,R)-**207** was determined by X-ray crystal structure analysis in Figure 86. The compound crystallizes in the non-centrosymmetric chiral space group $P2_12_12_1$ (no. 19) with Z=4; it contains the C10(R), C16(S), C8(S), C7(R) chiral centers. Although it is generally not a stable form, pyrazine ring has the boat conformation; C16 and C10 lie out of the plane and on the same side of the plane containing C15, N2, C11, and N1. Deviation for C16 and C10 from the least square plane is 0.169 and 0.135 Å, respectively the pyrrole ring is planar but the oxazole ring has a slightly distorted envelope conformation. Maximum deviation from the mean plane is 0.167 Å for C8 [Cremer and Pople puckering parameters [144] *Q*(2) = 0.273(3) Å, phi(2) = 261.1(5)°]. The chains of molecules running

parallel to the short *a* axis are linked by conventional hydrogen bonds (Figure 86).

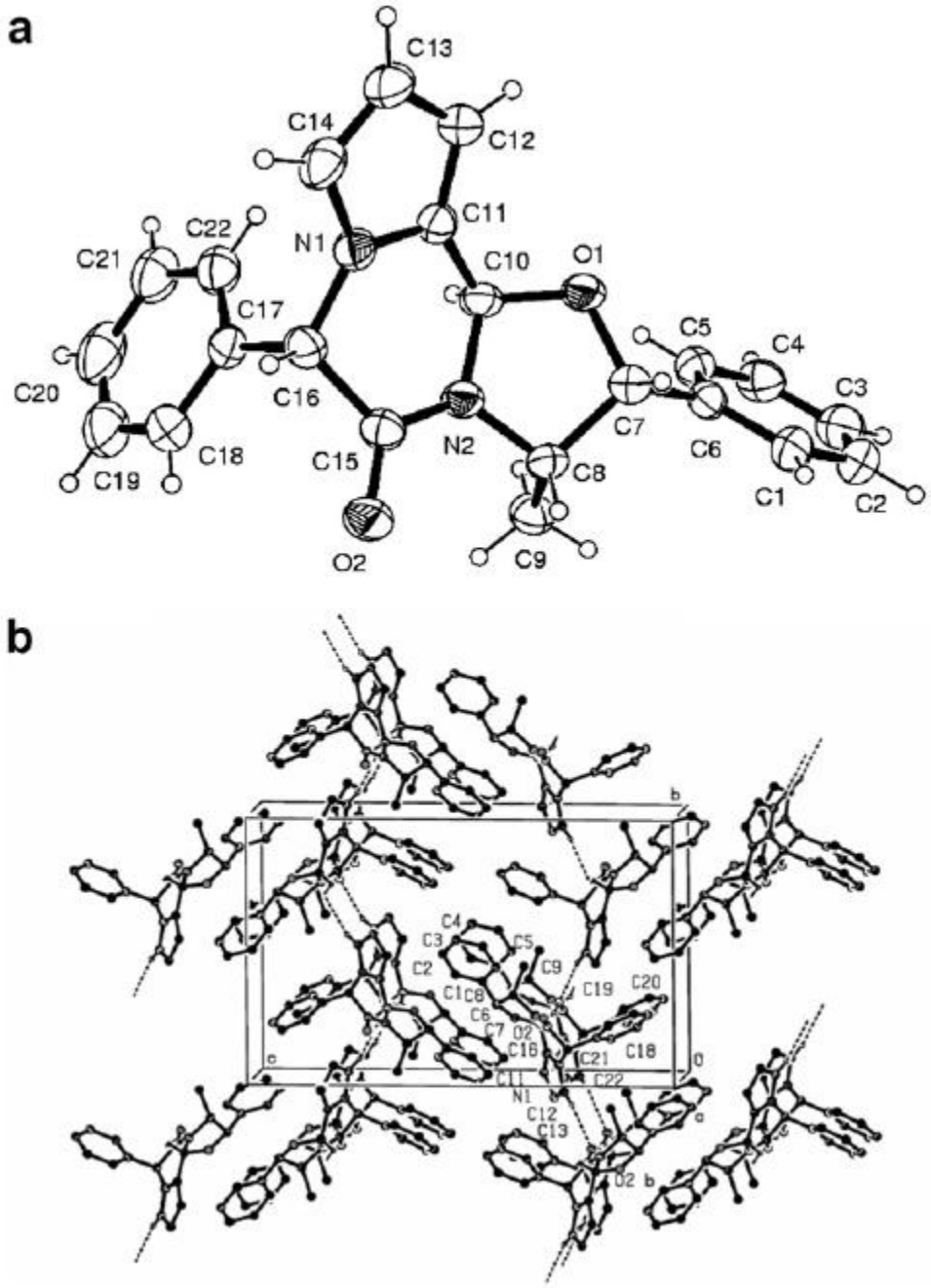


Figure 86. (a) ORTEP view of (R,S,S,R)-**234** with displacement ellipsoids drawn at the 50% probability level. (b) Hydrogen bonded chains, viewed along the *b* axis. Dashed lines represent C-H···O bonds. H atoms not involved in hydrogen bonding have been omitted. Selected bond lengths (Å), bond angles (°) and torsion angles (°): C10-O1 1.403(3), C10-N2 1.460(3), O2-C15

1.231(3), C7-C6 1.513(4), C1-C6 1.379(3), N1-C16 1.449(3), C10-O1-C7 110.7(2), N1-C16-C15 110.2(2), C10-N2-C8 109.8(2), O2-C15-N2 123.1(3), C5-C6-C7-O1 -33.0(2), C7-O1-C10-N2 4.6(2), N2-10-C11-N1 -25.9(3), C10-C11-N1-C14 179.5(2).

Most probably, during the cyclisation of the imine intermediate, the OH attack preferentially occurs on the *Si* face of the $>C{=}N-$ planar group. Thus, during the formation of the oxazoline ring, the bulky phenyl and pyrrole can be arranged in the *trans* position, to avoid steric interactions as shown in Figure 56.

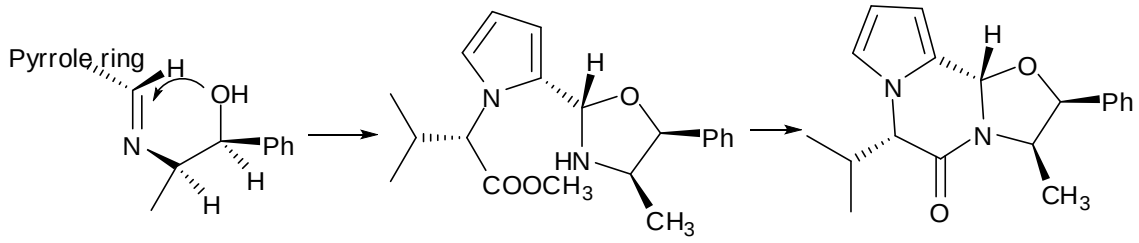
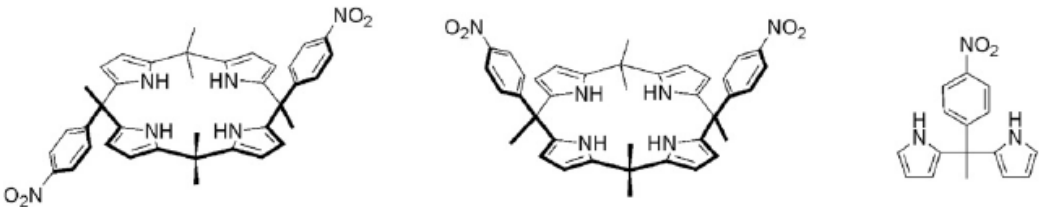


Figure 87. Formation reaction mechanism of tricyclic pyrrole-pyrazine-oxazole fused structure

2.3.3 Synthesis of Pyrrole Derivatives as Organocatalysts

The term *organocatalysis* describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound. The interest in this field has increased spectacularly in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standarts of established organic reactions. Organocatalytic reactions are becoming powerful tools in the construction of complex molecular skeletons [165].

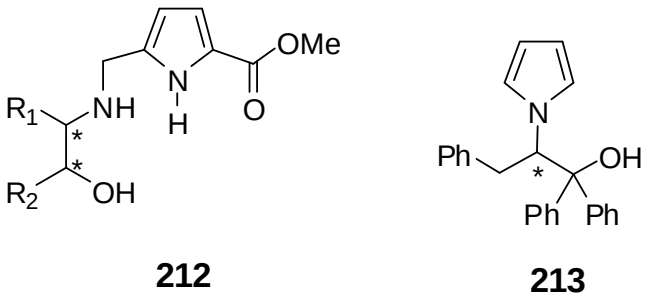
Pyrrole derivatives also can be use as an organocatalyst in the literature. Kohnke et al. [145] found and reported that, the 10α,20β-bis(4-nitrophenyl)-calix[4]pyrrole act as an effective organocatalyst for the hetero Diels-Alder reaction of Danishefsky's diene with aromatic aldehydes. Calixpyrroles has ability to bind anions as well as neutral molecules [146] bearing hydrogen-bond acceptor sites. Also due to their hydrogen-bond donor ability, calixpyrroles have the potential to act as an organocatalysts [147]. For that purpose Kohnke et al. they used stereoisomeric calix[4]pyrrole derivatives of **209, 210** and dipyrromethane **211** for the hetero Diels-Alder reaction of Danishefsky's diene with p-nitrobenzaldehyde and they obtained good result with **209**.



209 **210** **211**

Figure 88. Examples of organocatalyst

Organocatalysts play an important role for the synthesis of some key building blocks and each passing day the need of organocatalyst for the asymmetric synthesis is increased. We consider all of this and we decided to synthesize two different pyrrole derivatives **212** (norephedrine-based pyrrole derivative) and **213** as an organocatalyst.



212 **213**

Figure 89. Pyrrole derivatives as organocatalyst

For the synthesis of norephedrine-based pyrrole derivative **212** we designed a synthetic route as shown Figure 90. Pyrrole is used as a starring material and it is formylated by using Vilsmeier Haack Formylation reaction. Then pyrrole carbaldehyde oxidize with Ag_2O followed by esterification reaction and **217** was obtained. Again Vilsmeier Haack Formylation reaction was performed to obtain 5-formyl pyrrole derivative **218**. Lastly, **218** was reflux with norephedrine in the presence of benzene and Na_2CO_3 to form the corresponding imine and then the intermediate imine was reduced to form the norephedrine-based pyrrole derivative **212**.

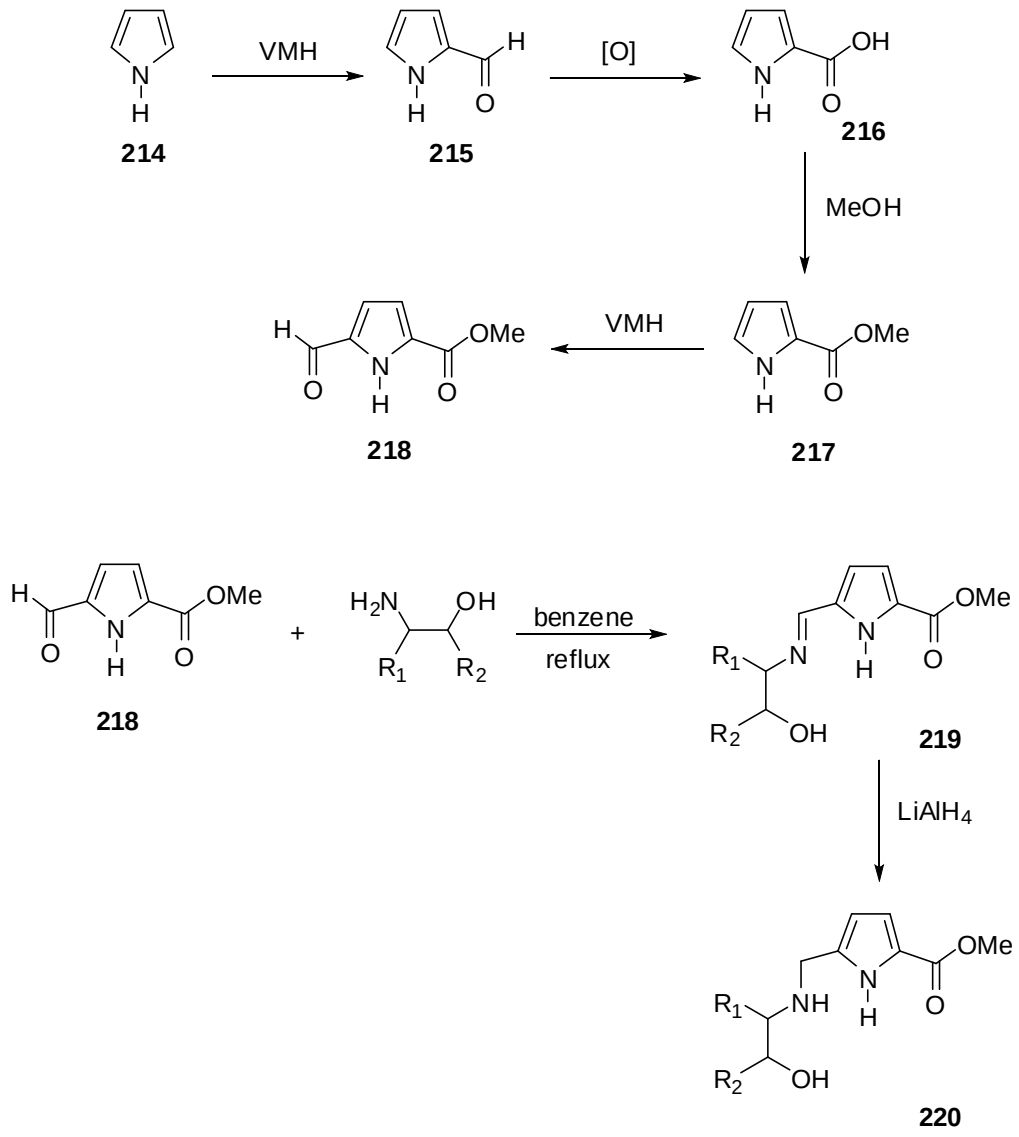
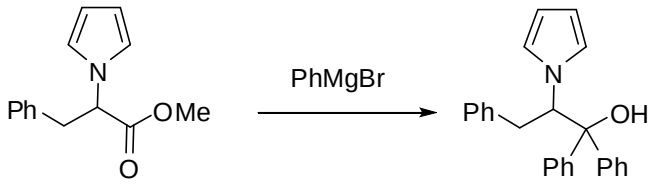


Figure 90. Synthesis of norephedrine-based pyrrole derivative

The second catalyst was synthesized in a short way as shown Figure 58 starting from amino acid ester. For this purpose, phenyl alanine methyl ester hydrochloride converted the corresponding pyrrole derivative and then Grignard reaction was carried out to form the pyrrole derivaties **213**.



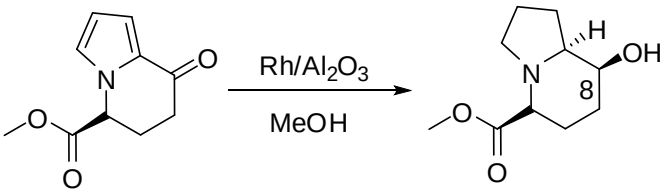
220 **213**

Figure 91. Synthesis of catalyst

These two compounds used as catalyst in oxazoboralidine reactions but we could not get any result.

2.3.4 Hydrogenation of Indolizidine and Pyrolizidine Structures

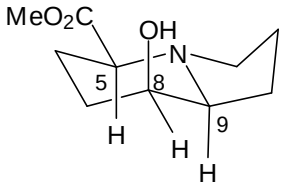
After synthesizing (5,6) and (5,5) bicyclic product selective hydrogenation was carried out and we succeeded hyrogenation of only (5,6) bicyclic system. Hydrogenation was performed in the presence of catalyst on a Paar shaker hydrogenator. For this purpose we tried three different literature procedure which involves acetic acid, Pd/C; methanol, H_2SO_4, Pd/C and Rh/Al_2O_3, methanol but only Rh/Al_2O_3, methanol system gave a positive result. Pd/C systems failed for the hydrogenation of bicyclic system and unidentified products were obtained (Fiure 92).



171 **221**

Figure 92. Hydrogenation of bicyclic system

According to the literature [142] the stereochemistry of C-8 was depend on which catalyst was used, rhodium yielded predominantly the (*S*)-alcohol and palladium reduced to the fully indolizidine. The IR and ^{1}H-NMR spectra of compound **221** confirmed that the relative stereochemistries of C-5, C-8 and C-9 were as expected as shown below.



221

Figure 93. Structure of methyl 8-hydroxyoctahydroindolizine-5-carboxylate

The observation of Bohlmann bands at 2810 cm^{-1} in the IR spectrum is diagnostic of a trans ring junction with the nitrogen lone-pair and 9-H in axial positions [148]. The lack of trans couplings to 8-H in the ^{1}H-NMR spectrum as evidenced by a small (8Hz) line width of the unresolved multiplet indicates that this proton is in an equatorial positon [142].

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

All reagents were of commercial quality and reagent quality solvents were used without further purification. IR spectra were determined on a Thermo Scientific smart iTR. NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ were reported in ppm relative to $CHCl_3$ (^1H: δ = 7.27), $CDCl_3$ (^{13}C: δ = 77.0) and CCl_4 (^{13}C: δ = 96.4) as internal standards. Column chromatography was conducted on silica gel 60 (mesh size 40-63 µm). TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (λ = 254 nm). Optical rotations were measured with a Krüss P3002RS automatic polarimeter. Evaporation refers to the removal of solvent under reduced pressure.

3.2 General Procedures

3.2.1 General procedure for the synthesis of chloroenones

Chloroenones were synthesized according to literature procedures. Aluminum chloride (55 mmol) was dissolved in 110 mL dichloromethane at RT and the solution was quickly filtered to move away the undissolved aluminum salt. To this solution acid chloride (50 mmol) was added dropwise. Then the homogeneous solution was cooled to 0°C and the unsaturated

compound (50mmol) diluted in 20 ml dichloromethane was added over 20 min at this temperature. The mixture was strirred at 0°C for 30 min and poured into 10 g of ice and 10 g of water. The precipitate was dissolved with HCl and aqueous layer was extracted with dichloromethane. After separating the layers, organic phase was washed with saturated sodium bicarbonate solution. The mixture was shaken until the colour changes from green to yellow, filtered and dried over magnesium sulfate and concentrated under reduced pressure. The crude product was used without any futher purification.

3.2.2 General procedure for the synthesis of 1,2-disubstituted and 1,2,4-trisubstituted pyrrole derivatives

To the solution of amino acid hydrochloride (10 mmol) was added 10 mmol chloroenone, 20 mmol of triethylamine, 5 mL of water and 15 mL of benzene. The mixture was refluxed for 3 hours. The reaction was monitored by TLC. The mixture was cooled to RT and organic layer was separated. Aqueous layer was extracted with dichloromethane (2x15 mL). The combined organic layer were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography.

3.2.3 General procedure for the synthesis of indolizidine structures (5,6) and pyrolizidine structures (5,5)

To solution of pyrrole derivatives (10 mmol) in dry CH_2Cl_2 (30 mL) cooled to 5°C by using ice-water bath was added dropwise BBr_3 in CH_2Cl_2 (3 mL). The cooling bath was removed and the solution stirred for an additional 30 min. The solution was quenched with saturated aq. $NaHCO_3$ solution (10 mL) with cooling and vigorously stirred for a few min. Then the aq. layer was extracted

with CH_2Cl_2, organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography.

3.2.3.1 Methyl 7-oxo-4,5,6,7-tetrahydro-3a*H*-indene-4-carboxylate (171)

Colorless oil (80% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.93 (dd, J = 4.04, 1.50 Hz, 1H), 6.80 (dd, J = 2.45, 1.59 Hz, 1H), 6.21 (dd, J = 4.03, 2.56 Hz, 1H), 4.88 (dd, J = 4.44, 3.03 Hz, 1H), 3.68 (s, 3H), 2.53-2.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 185.7, 169.9, 130.4, 126.5, 114.5, 110.9, 56.4, 52.8, 33.1, 26.2.

3.2.3.2 Methyl 1,3-dimethyl-7-oxo-4,5,6,7-tetrahydro-3a*H*-indene-4-carboxylate (172)

Yellowish oil (70% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.82 (s, 1H), 4.69 (s, 1H), 3.73 (s, 3H), 2.66-2.43 (m, 4H), 2.31 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl^3$) δ (ppm): 183.3, 168.1, 131.6, 128.2, 124.3, 110.5, 51.7, 50.8, 31.1, 24.2, 11.4, 9.9.

3.2.3.3 Methyl 3-methyl-7-oxo-4,5,6,7-tetrahydro-3a*H*-indene-4-carboxylate (173)

Yellowish oil (77% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.02 (d, J = 3.98 Hz, 1H), 6.08 (d, J = 3.78 Hz, 1H), 4.93-4.82 (m, 1H), 3.78 (s, 3H), 2.78-2.38 (m, 4H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl^3$) δ (ppm):

3.2.3.4 Methyl 3-isopropyl-7-oxo-4,5,6,7-tetrahydro-3a*H*-indene-4-carboxylate (174)

Yellow oil (72% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09 (d, J = 4.04 Hz, 1H), 6.15 (d, J = 4.12 Hz, 1H), 5.12-4.86 (m, 1H), 3.77 (s, 3H), 2.86-2.60 (m, 4H), 2.60-2.38 (m, 1H), (t, J = 6.52 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.2, 154.7, 154.4, 112.8, 107.3, 53.6, 53.0, 52.1, 51.5, 32.6, 26.5, 25.8, 23.4, 22.2.

3.2.3.5 Methyl 3-oxo-1,2,3,6a-tetrahydropentalene-1-carboxylate (176)

Colorless oil (85% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.10 (d, J = 1.53 Hz, 1H), 6.69 (dd, J = 3.98, 0.88 Hz, 1H), 6.49 (dd, J = 3.95, 2.39 Hz, 1H), 5.05 (dd, J = 8.40, 4.10 Hz, 1H), 3.78 (s, 3H), 3.24, (ddd, J_1 = 22.28, J_2 = 18.18, J_3 = 6.26 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 186.2, 169.2, 132.3, 123.8, 117.4, 108.3, 55.3, 53.1, 43.1.

3.2.3.6 Methyl 4,6-dimethyl-3-oxo-1,2,3,6a-tetrahydropentalene-1-carboxylate (177)

Yellowish oil (70% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.38 (s, 1H), 4.05 (q, J = 7.12 Hz, 1H), 3.36 (s, 3H), 2.55 (S, 3H), 2.37 (t, J = 6.37 Hz, 1H), 2.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 187.7, 186.1, 142.1, 121.8, 117.1, 108.5, 66.1, 54.6, 29.7.

3.2.3.7 Methyl 6-methyl-3-oxo-1,2,3,6a-tetrahydropentalene-1-carboxylate (178)

Yellowish oil (71% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.64 (d, J = 3.91 Hz, 1H), 6.21 (d, J = 3.77 Hz, 1H), 4.94 (dd, J_1 = 8.85, J_2 = 3.24 Hz, 1H), 3.75 (s, 3H), 3.15 (ddd, J = 21.25, J_2= 18.00, J_3 = 6.06 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 186.2, 169.7, 134.8, 131.3, 116.5, 109.1, 53.9, 52.9, 44.1, 11.7.

3.2.3.8 Methyl 6-isopropyl-3-oxo-1,2,3,6a-tetrahydropentalene-1-carboxylate (179)

Yellow oil (69% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.06 (d, J = 4.12 Hz, 1H), 6.13 (d, J = 4.13 Hz, 1H), 5.08-4.87 (m, 1H), 3.77 (s, 3H), 2.94-2.59 (m, 2H), 2.59-2.43 (m, 1H), 1.25 (t, J = 6.46 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 186.2, 169.7, 134.8, 131.3, 116.5, 109.1, 53.9, 52.9, 44.1, 11.7.

3.2.3.9 Methyl 3-oxo-6-phenyl-1,2,3,6a-tetrahydropentalene-1-carboxylate (180)

Orange oil (69% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46-7.15 (m, 5H), 6.81 (d, J = 4.05 Hz, 1H), 6.63 (d, J = 4.06 Hz, 1H), 5.34 (dd, J = 8.75, 3.24 Hz, 1H), 3.64 (s, 3H), 2.99 (dtd, J = 24.63, 17.33, 4.33 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 166.3, 132.1, 128.9, 127.5, 126.6, 117.0, 109.8, 105.3, 55.7, 53.1, 49.2, 44.2, 36.3.

3.2.4 General procedure for the synthesis of unsubstituted pyrrole derivatives

Amino acid ester (10 mmol) was dissolved in 5 mL of water. To this solution 2,5-dimethoxytetrahydrofuran (12 mmol), glacial AcOH (4 mL), and dichloroethane (30 mL) were added at room temperature. The reaction mixture was refluxed for 3 h. Then the two layers were separated and the aqueous layer extracted three times with $CHCl_3$. The organic phases were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (1:3, EtOAc/hexane).

3.2.4.1 (*S*)-methyl 3-methyl-2-(1H-pyrrol-1-yl)butanoate ((*S*)-150)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.67 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 2.34 (m, 1H), 3.64 (s, 3H), 4.00 (d, 1H), 6.02 (s, 2H), 6.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.7, 19.5, 32.1, 51.9, 68.8, 108.6, 121.0, 170.5.

3.2.4.2 (*S*)-methyl 3-phenyl-2-(1H-pyrrol-1-yl)propanoate ((*S*)-154)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.30 (ddd, J_1 = 5.6 Hz, J_2 = 14.1 Hz, J_3 = 19.7 Hz, 2H), 3.66 (s, 3H), 5.99 (s, 1H), 6.12 (m, 1H), 6.79 (m, 1H), 6.92 (m, 2H), 7.09 (m, 3H), 9.36 (s , 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 40.0, 52.7, 63.9, 109.3, 120.3, 121.5, 122.3, 126.1, 127.4, 127.4, 128.9, 129.2, 136.7, 170.6, 170.7.

3.2.4.3 (S)-methyl 2-(1H-pyrrol-1-yl)propanoate ((*S*)-158)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.24 (d, J = 7.3 Hz, 3H), 3.62 (s, 3H), 4.63 (q , J_1 = 7.3 Hz , J_2 = 14.5 Hz, 1H), 6.05 (t, J = 2.0 Hz, 2H) , 6.60 (t, J = 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.4, 52.4, 56.86 , 108.7, 119.9, 171.3.

3.2.4.4 (S)-methyl 2-phenyl-2-(1H-pyrrol-1-yl)acetate ((*S*)-162)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.65 (s, 3H), 5.71 (s, 1H), 6.04 (t, J = 2.1 Hz, 2H), 6.59 (t, J = 2.1 Hz, 2H), 7.22 (m, 3H), 7.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 52.5, 65.3, 109.0, 120.8, 127.7, 128.1, 128.8, 128.9, 135.7, 169.7.

3.2.5 General procedure for the synthesis of pyrrole-2-carboxaldehyde derivatives

Phosphoryl chloride (10 mmol) was added to ice-cold DMF (10 mmol) over 15 min. The reaction mixture was allowed to warm to room temperature diluted with CH_2Cl_2 (20 mL) and cooled again to 0°C. Pyrrole (5 mmol) was dissolved in 10 mL CH_2Cl_2 and this solution added dropwise over 1 h, while the temperature was kept at 0°C. After the addition was complete, the reaction mixture was refluxed for 30 min. After the reflux was completed, the reaction mixture was cooled to 10°C and hydrolyzed with sodium acetate solution (3.15 g NaOAc in 15 mL water). The phases were separated and the aqueous phase was extracted three times with ether. The combined organic layer was washed with a saturated sodium carbonate until no CO_2 evolved. Then the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography (1:5, EtOAc/hexane).

3.2.5.1 *(S)*-Methyl-2-(2-formyl-1H-pyrrol-1-yl)propanoate (*(S)*-198)

Orange oil (1.40 g, 77% yield). $[\alpha]_D^{25}$ = -87:5 (c 0.2, $CHCl_3$). IR (neat): 2846, 1660, 1412, 1214, 1085, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67

(d, *J* = 7.4 Hz, 3H), 3.67 (s, 3H), 5.82 (q, *J* = 7.3 Hz, 1H), 6.22 (t, *J* = 3.3 Hz, 1H), 6.88 (d, *J* = 3.5 Hz, 1H), 7.07 (s, 1H), 9.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.0, 52.4, 55.2, 110.2, 113.5, 125.1, 128.5, 171.2, 179.3.

3.2.5.2 *(S)*-Methyl-2-(2-formyl-1H-pyrrol-1-yl)-3-methylbutanoate (*(S)*-181)

Yellow oil (1.59 g, 76% yield). $[\alpha]_D^{25}$ = +1.5 (c 1.1, $CHCl_3$). IR (neat): 2966, 1662, 1208, 1030, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.71 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 2.31 (m, 1H), 3.68 (s, 3H), 5.91 (d, *J* = 9.5 Hz, 1H), 6.21 (dd, J_1 = 2.9 Hz, J_2 = 3.7 Hz, 1H), 6.82 (dd, J_1 = 1.6 Hz, J_2 = 3.9 Hz, 1H), 7.30 (s, 1H), 9.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 18.5, 19.2, 33.1, 52.1, 63.7, 110.6, 125.0, 129.7, 132.0, 170.9, 179.5.

3.2.5.3 *(R)*-Methyl-2-(2-formyl-1H-pyrrol-1-yl)-2-phenyl acetate (*(R)*-203)

White solid (1.80 g, 74% yield). Mp = 88.7–89.7 °C. $[\alpha]_D^{25}$ = -104:4 (c 0.2, $CHCl_3$). IR (KBr): 3116, 2960, 2847, 1755, 1651, 1466, 1381, 1212, 1000, 763 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl^3$) δ (ppm): 3.79 (s, 3H), 6.18 (t, *J* = 3.1 Hz, 1H), 6.84 (s, 1H), 6.97 (m, 2H), 7.35 (m, 2H), 7.41 (m, 3H), 9.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 52.4, 63.2, 109.9, 125.2, 128.8, 129.1, 130.1, 131.7, 134.1, 169.8, 179.4.

3.2.5.4 *(S)*-Methyl-2-(2-formyl-1H-pyrrol-1-yl)-3-phenylpropanoate (*(S)*-192)

Yellow oil (1.95 g, 76% yield). $[\alpha]_D^{25}$ = + 8.8 (c 0.2, $CHCl_3$). IR (neat): 3116, 2960, 1658, 1412, 1080, 751, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.30 (ddd, J_1 = 5.6 Hz, J_2 = 14.1 Hz, J_3 = 19.7 Hz, 2H), 3.66 (s, 3H), 5.99 (s, 1H), 6.12 (m, 1H), 6.79 (m, 1H), 6.92 (m, 2H), 7.09 (m, 3H), 9.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 40.1, 52.8, 63.9, 109.3, 120.3, 121.6, 122.3, 126.2, 127.4, 127.5, 128.9, 129.3, 136.7, 170.7, 170.8.

3.2.6 General procedure for the synthesis of pyrrole-pyrazine-oxazole fused cyclic structures

Formylated pyrrole (3 mmol) was dissolved in 10 mL of dry benzene. To this solution was added norephedrine (503 mg, 3.33 mmol) in 10 mL dry benzene under argon. The reaction mixture was refluxed under a Dean Stark trap apparatus and monitored by TLC (24–36 h). The organic layer was separated and dried over MgSO4. After evaporation of solvent, the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6).

3.2.6.1 (2*R*,3*S*,6*R*,10b*R*)-3,6-Dimethyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]-oxazolo[3,2-α]pyrrolo[2,1-*c*]pyrazin-5[6*H*]-one (199)

Yellow oil (610 mg, 72% yield). $[\alpha]_D^{25}$ = -7:2 (c 0.2, $CHCl_3$). IR (neat): 2962, 1659, 1413, 1260, 1087, 802 cm-1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (d, *J* = 7.0 Hz, 3H), 1.55 (d, *J* = 7.2 Hz, 3H), 4.63 (q, *J* = 7.1 Hz, 1H), 4.76 (p, *J* = 6.7 Hz, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 6.15 (t, *J* = 3.2 Hz, 1H), 6.20 (broad s, 1H), 6.24 (s, 1H), 6.56 (s, 1H), 7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.0, 21.4, 54.3, 55.9, 80.6, 81.0, 105.1, 110.0, 118.1, 124.1, 126.2, 127.9, 128.4, 136.4, 166.3.

3.2.6.2 (2*R*,3*S*,6*S*,10b*R*)-3,6-dimethyl-2-phenyl-2,3-dihydro-10b*H*[1,3]-oxazolo[3,2-a]- pyrrolo[2,1-c]pyrazin-5[6*H*]-one (201)

Yellow oil (627 mg, 74% yield). $[\alpha]_D^{25}$ = -58.1 (c 0.1, $CHCl_3$). IR (neat): 2962, 1659, 1413, 1260, 1087, 802 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (d, *J* = 7.0 Hz, 3H), 1.56 (d, *J* = 7.2 Hz, 3H), 4.64 (q, *J* = 7.1 Hz, 1H), 4.76 (p, J = 6.7 Hz, 1H), 5.10 (d, *J* = 5.5 Hz, 1H), 6.16 (t, *J* = 3.2 Hz, 1H), 6.20 (broad s, 1H), 6.24 (s, 1H), 6.58 (s, 1H), 7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.1, 21.4, 54.3, 55.9, 80.5, 81.0, 105.1, 110.0, 119.7, 123.3, 126.2, 127.9, 128.4, 136.3, 166.4.

3.2.6.3 (2*R*,3*S*,6*S*,10b*R*)-3-Methyl-6-isopropyl-2-phenyl-2,3-dihydro10b*H*-[1,3]oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-5[6*H*]-one (189)

Yellow oil (661 mg, 71% yield). $[\alpha]_D^{25}$ = -57:4 (c 0.4, $CHCl_3$). IR (neat): 2969, 1666, 1452, 1358, 1200, 1068, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (dd, J_1 = 6.8 Hz, J_2 = 9.5 Hz, 6H), 1.0 (d, J = 6.9 Hz, 3H), 2.12 (sextet, J = 6.7, 1H), 4.29 (d, J = 6.2 Hz, 1H), 4.75 (p, J = 6.8 Hz, 1H), 5.05 (d, J = 5.6 Hz, 1H), 6.12 (t, J = 3.1 Hz, 1H), 6.19 (d, J = 3.3 Hz, 1H), 6.24 (s, 1H), 6.54 (t, J = 1.8 Hz, 1H), 7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.1, 17.4, 18.4, 33.1, 53.1, 65.2, 79.3, 80.3, 103.6, 108.1, 118.9, 124.7, 125.1, 126.8, 127.3, 135.3, 164.1.

3.2.6.4 (2*R*,3*S*,6*R*,10b*R*)-3-Methyl-6-isopropyl-2-phenyl-2,3-dihydro10b*H*-[1,3]oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-5[6*H*]-one (187)

Yellow oil (707 mg, 76% yield). $[\alpha]_D^{25}$ = -28.2 (c 0.1, $CHCl_3$). IR (neat): 2969, 1666, 1452, 1358, 1200, 1068, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82 (d, J = 6.4 Hz, 3H), 0.96 (dd, J = 6.9 Hz, 6H), 2.21 (sextet, J = 6.7, 1H), 4.31 (d, J = 5.8 Hz, 1H), 4.77 (p, J = 6.3 Hz, 1H), 5.07 (d, J = 5.6 Hz, 1H), 6.14 (t, J = 2.9, 1H), 6.22 (br s, 1H), 6.25 (s, 1H), 6.56 (s, 1H), 7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 18.9, 20.2, 34.4, 55.9, 67.3, 82.7, 82.4, 104.2, 109.4, 120.4, 126.6, 126.6, 128.5, 128.7, 135.4, 165.3.

3.2.6.5 (2*R*,3*S*,6*R*,10b*R*)-2,6-Diphenyl-3-methyl-2,3-dihydro-10b*H*-[1,3]-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-5[6*H*]-one (205)

White solid (723 mg, 71% yield). Mp = 140.5–141.5 °C. $[\alpha]_D^{25}$ = -63.0 (c 0.1, $CHCl_3$). IR (KBr): 3059, 1664, 1449, 1313, 1199, 1071, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.79 (d, J = 6.8 Hz, 3H), 4.77 (p, J = 6.6 Hz, 1H), 5.16 (d, J = 5.5 Hz, 1H), 5.78 (s, 1H), 6.14 (s, 1H), 6.29 (m, 1H), 6.34 (br s, 1H), 6.68 (s, 1H), 6.98 (d, J = 7.3 Hz, 2H), 7.31 (m, 8H). ^{13}C NMR (100 MHz, CDCl3) δ (ppm): 14.0, 54.5, 63.5, 80.6, 81.2, 105.1, 110.3, 125.1, 125.3, 126.2, 126.6, 127.9, 128.2, 128.4, 128.4, 129.0, 129.1, 136.2, 136.6, 164.4.

3.2.6.6 (2*R*,3*S*,6*S*,10b*R*)-2,6-Diphenyl-3-methyl-2,3-dihydro-10b*H*-[1,3]-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-5[6*H*]-one (207)

White solid (754 mg, 73% yield). Mp = 139.8–140.8 °C. $[\alpha]_D^{25}$ = -75.4 (c 0.1, $CHCl_3$). IR (KBr): 3059, 1664, 1449, 1313, 1199, 1071, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82 (d, *J* = 6.9 Hz, 3H), 4.77 (p, *J* = 6.7 Hz, 1H), 5.16 (d, *J* = 5.4 Hz, 1H), 5.79 (s, 1H), 6.14 (s, 1H), 6.31 (m, 1H), 6.35 (br s, 1H), 6.70 (s, 1H), 6.98 (d, *J* = 7.5 Hz, 2H), 7.31 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9, 54.5, 63.5, 80.5, 81.2, 105.1, 110.3, 119.6, 125.1, 126.2, 126.5, 127.9, 128.4, 128.4, 128.9, 129.0, 129.0, 136.2, 136.5, 164.4.

3.2.6.7 (2*R*,3*S*,6*R*,10b*R*)-6-Benzyl-3-methyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]-oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-5[6*H*]-one (193)

Orange oil (795 mg, 74% yield). $[\alpha]_D^{25}$ = -8.3 (c 0.8, $CHCl_3$). IR (neat): 3059, 1660, 1451, 1214, 1079, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.64 (d, *J* = 6.8 Hz, 3H), 3.22 (ddd, J_1 = 4.2 Hz, J_2 = 13.5 Hz, J_3 = 47.2 Hz, 2H), 4.67 (m, 2H), 4.88 (t, *J* = 4.4 Hz, 1H), 4.98 (d, *J* = 5.7 Hz, 1H), 6.03 (m, 1H), 6.19 (t, *J* = 3.4 Hz, 1H), 6.58 (t, *J* = 2.1 Hz, 1H), 6.66 (d, *J* = 7.1 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 2H), 7.18 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.3, 41.6, 53.9, 60.7, 80.2, 80.6, 104.4, 110.4, 117.7, 125.9, 126.2, 126.4, 127.1, 127.6, 127.8, 128.2, 128.3, 129.1, 134.4, 136.6, 163.7.

3.2.6.8 (2R,3S,6S,10bR)-6-Benzyl-3-methyl-2-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo[3,2-a]pyrrolo[2,1-c]pyrazin-5[6*H*]-one (195)

Orange oil (763 mg, 71% yield). $[\alpha]_D^{25}$ = -23.0 (c 0.3, $CHCl_3$). IR (neat): 3059, 1660, 1451, 1214, 1079, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.73 (d, *J* = 6.9 Hz, 3H), 3.32 (ddd, J_1 = 4.1 Hz, J_2 = 13.5 Hz, J_3 = 49.6 Hz, 2H), 4.76 (m, 2H), 4.99 (t, *J* = 4.3 Hz, 1H), 5.07 (d, *J* = 5.8 Hz, 1H), 6.14 (m, 1H), 6.30 (t, *J* = 3.1 Hz, 1H), 6.69 (m, 1H), 6.76 (d, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.4

Hz, 2H), 7.30 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.3, 41.6, 53.8, 60.6, 80.1, 80.6, 104.4, 110.4, 117.7, 125.9, 126.2, 126.4, 127.1, 127.6, 127.8, 128.2, 128.3, 129.1, 134.4, 136.6, 163.7.

CHAPTER 4

CONCLUSION

In this work, we have described the synthesis of new bicyclic chiral pyrrole derivatives which can be suitably functionalized for converting to the naturally occurring 5-substituted and 5,8-disubstituted indolizidines. This method has some advantages: (1) The starting materials are L-glutamic acid methyl ester and L-aspartic acid methyl ester which are commercially available and low-priced compounds. (2) R group (COOMe) of resulting bicyclic compounds can be easily functionalized. (3) By using selective hydrogenation reaction we can obtain either 5-substituted or 5,8-disubstituted indolizine alkaloids. Also, 8-substituent (OH group) is suitable for converting a number of analogues by using nucleophiles.

We have also synthesized pyrrole derivative of amino acid esters followed by Vilsmeier-Haack formylation to give C-2 formylated pyrrole derivatives of amino acid esters as the major products. The C-2 formylated pyrroles were refluxed with norephedrine and the products identified as tricyclic pyrrole-pyrazine-oxazole fused structures which includes four chiral center in high yield. According to the NMR and X-ray experiment, the oxazole ring formation step proceeds selectively to give only one stereoisomer. The configuration of the newly generated stereogenic center in the oxazole ring depends on the chirality centers of norephedrine.

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APPENDIX A

NMR DATA

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards.

^1H and ^{13}C NMR spectra of products are given below.

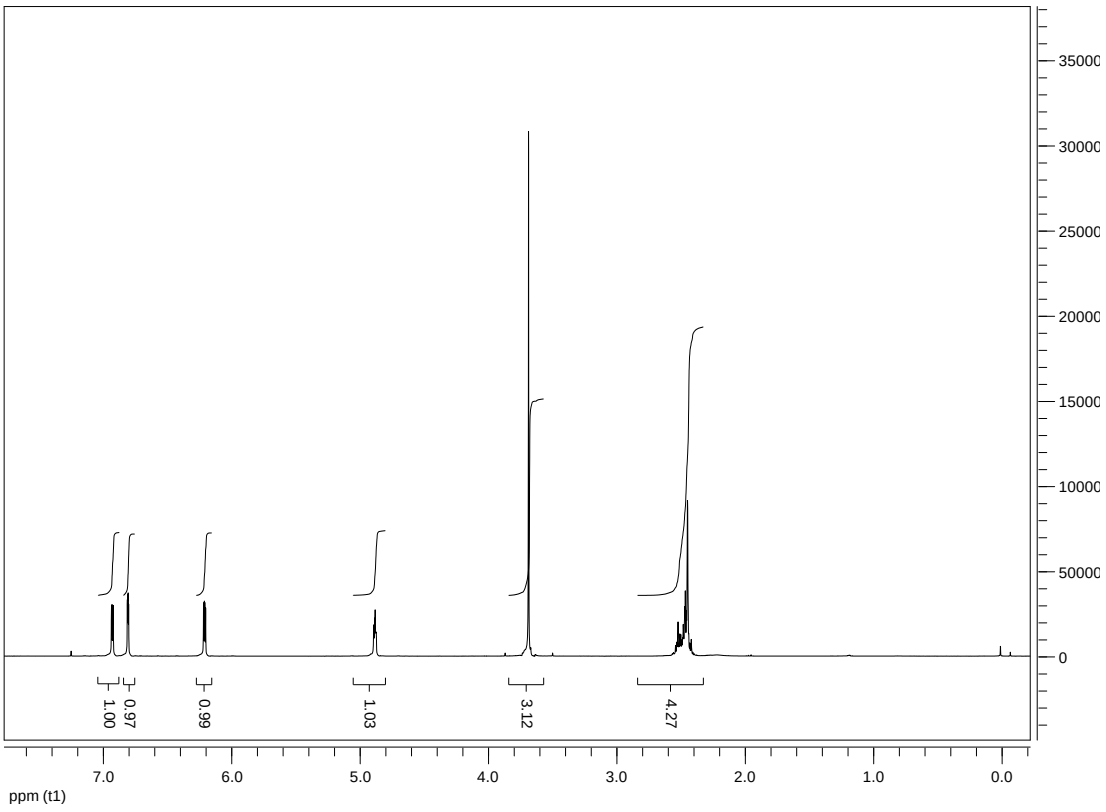

Figure A. 1 ^1H-NMR Spectrum of **171**

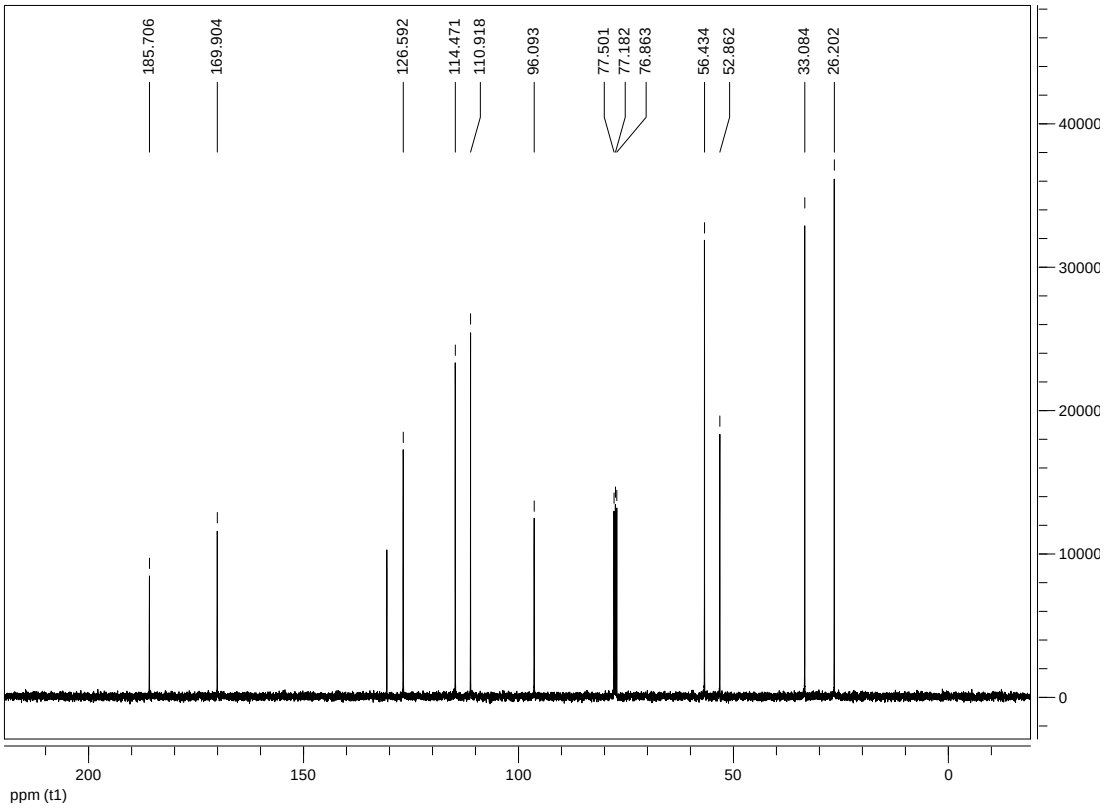

Figure A. 2 ^{13}C-NMR Spectrum of **171**

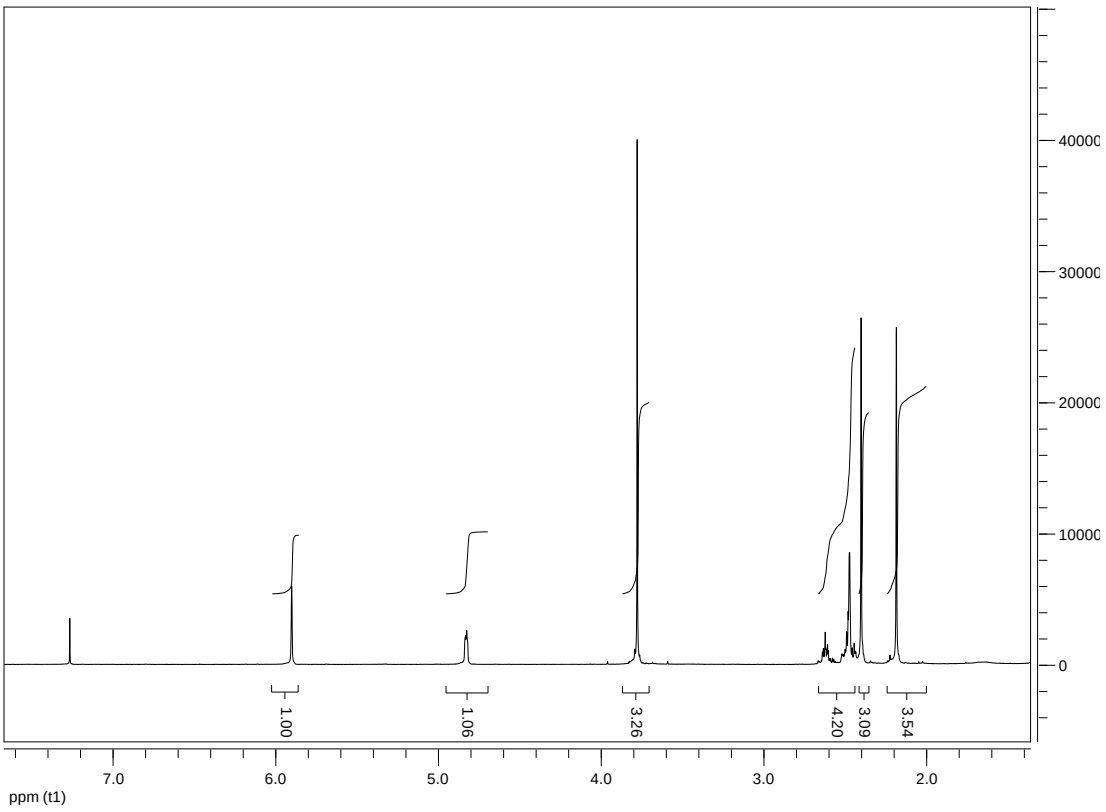

Figure A. 3 ^{1}H-NMR Spectrum of **172**

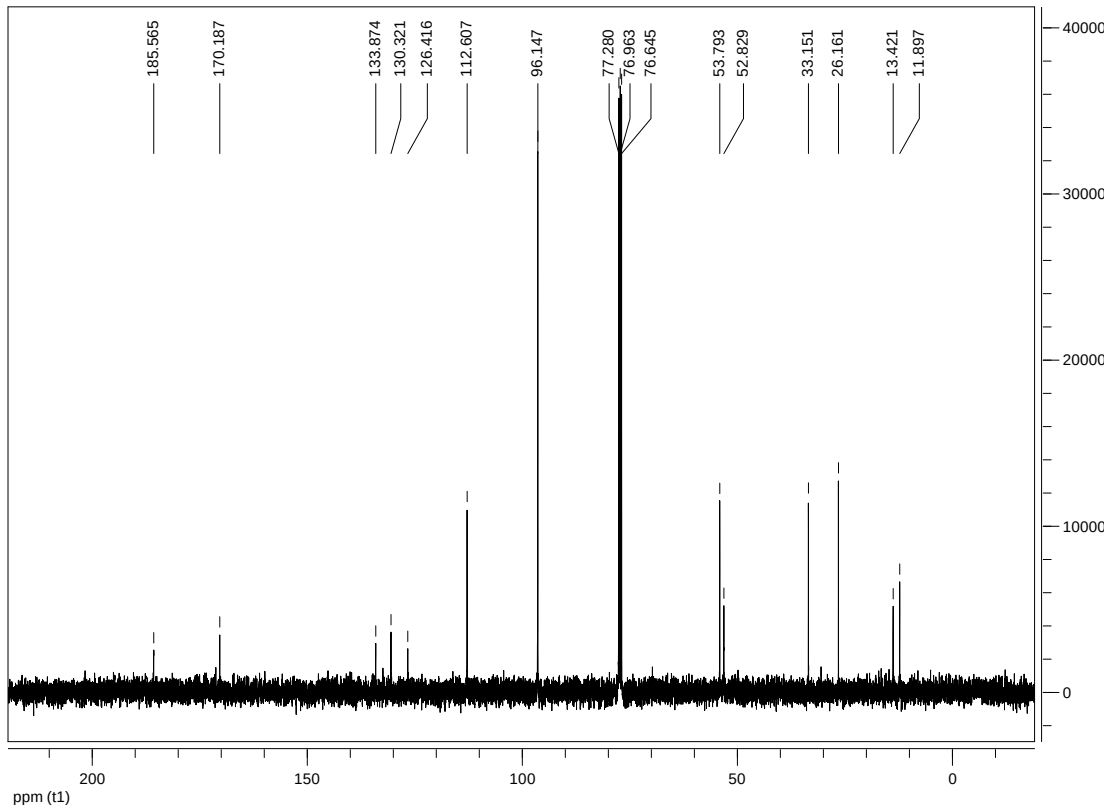

Figure A. 4 ^{13}C-NMR Spectrum of **172**

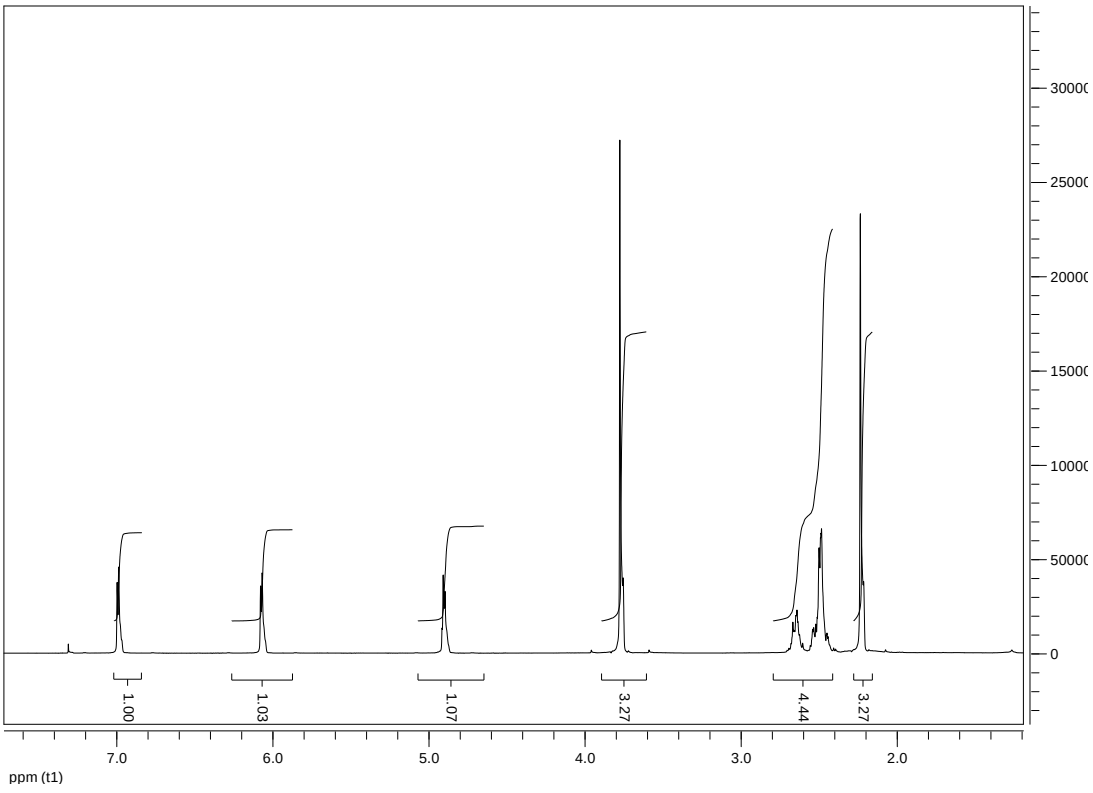

Figure A. 5 ^{1}H-NMR Spectrum of **173**

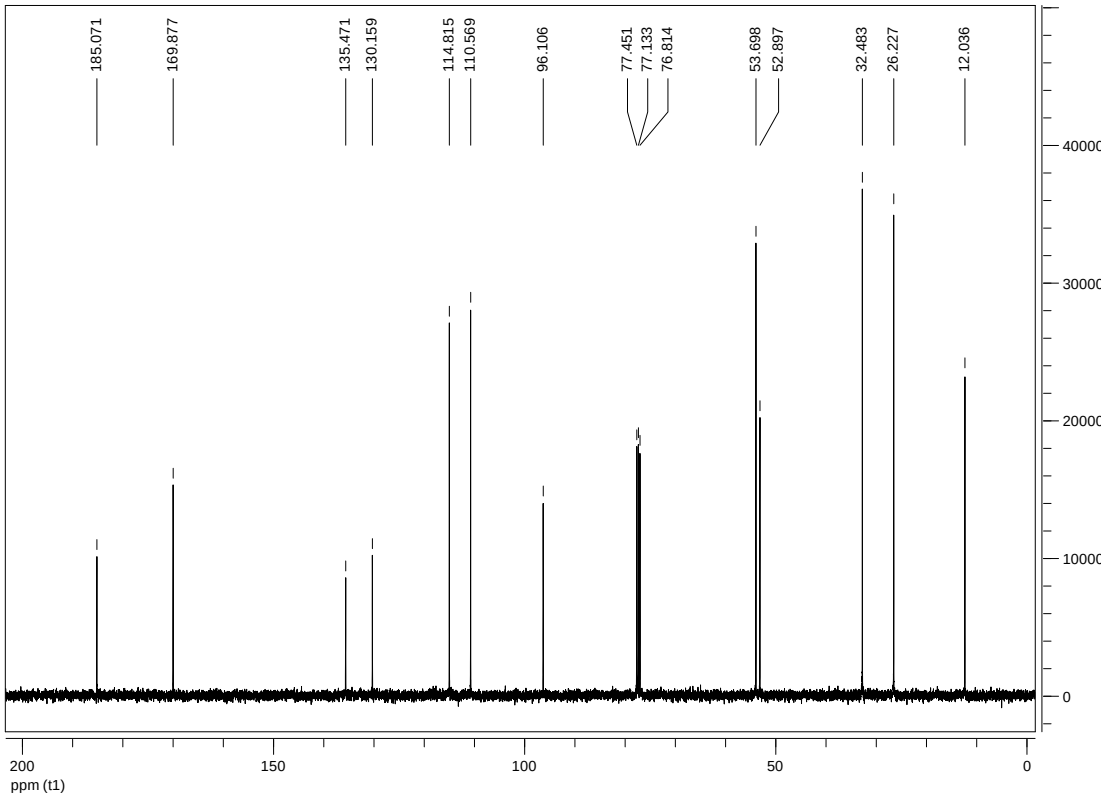

Figure A. 6 ^{13}C-NMR Spectrum of **173**

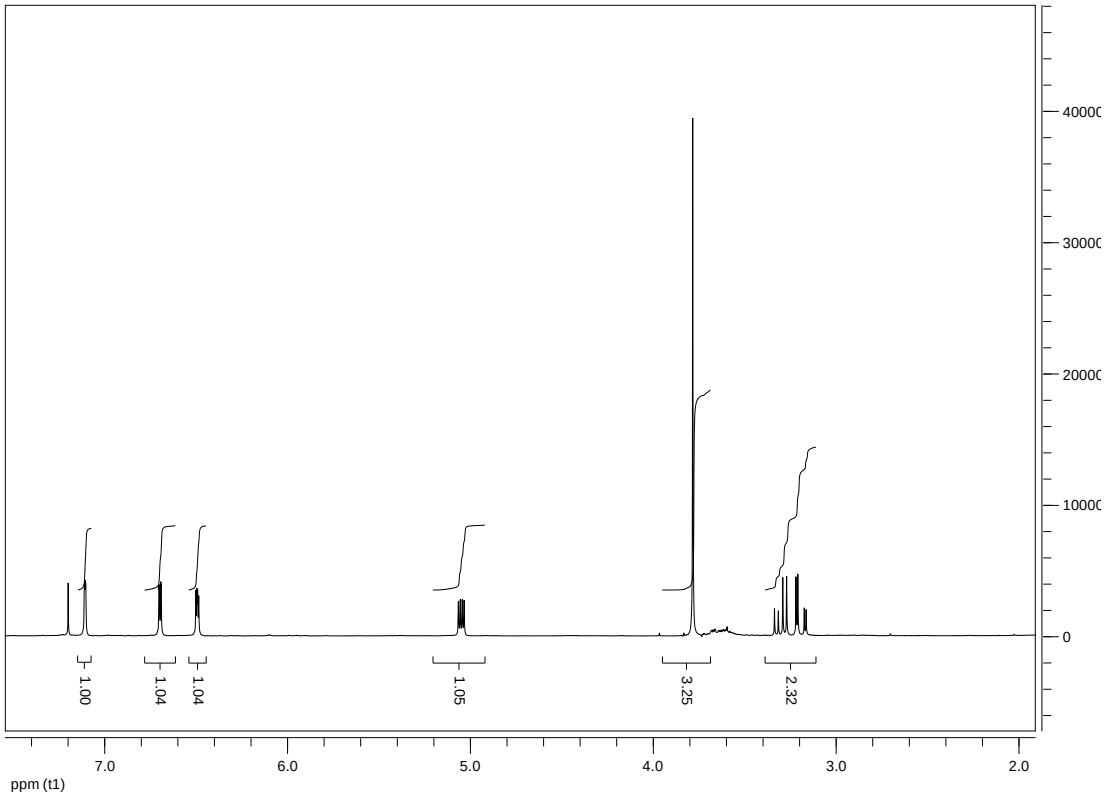

Figure A. 7 ^{1}H-NMR Spectrum of **176**

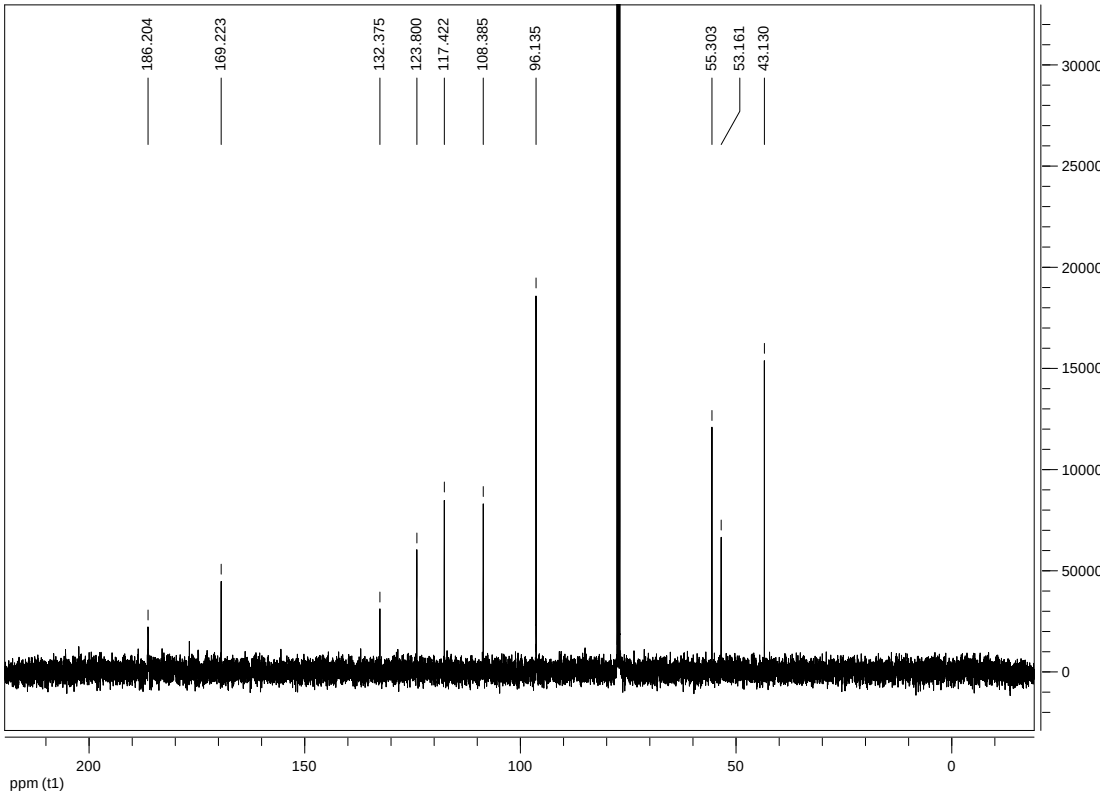

Figure A. 8 ^{13}C-NMR Spectrum of **176**

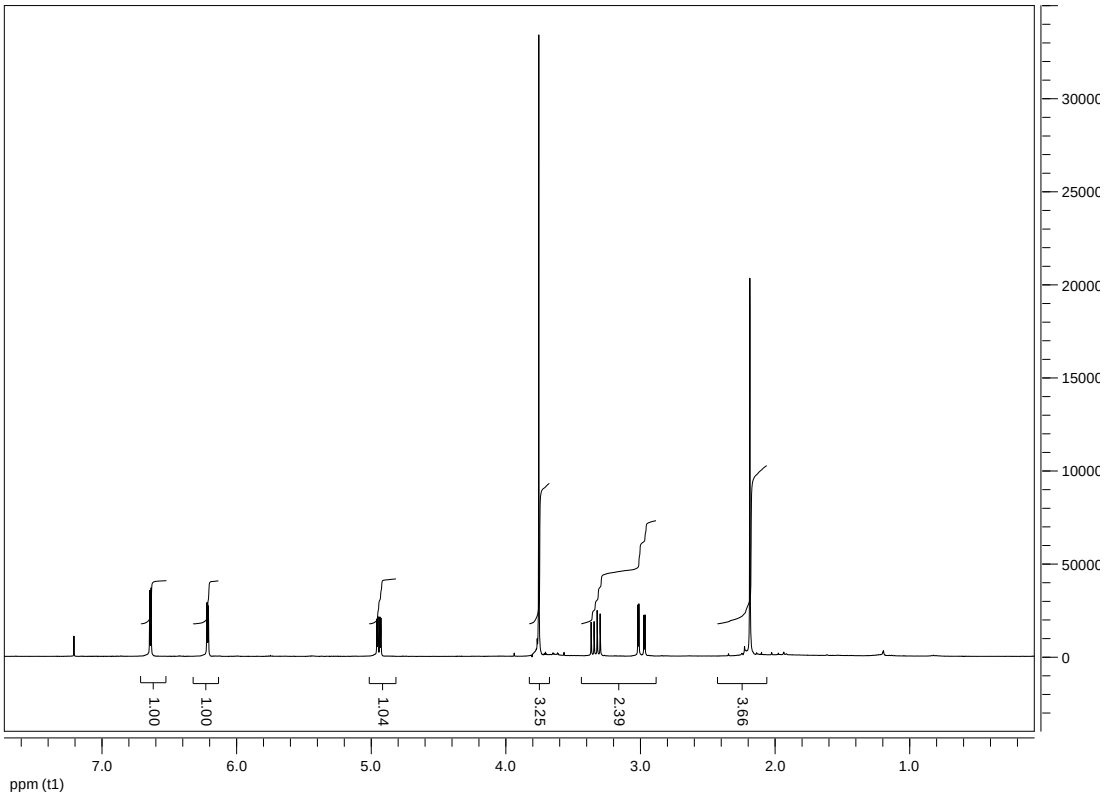

Figure A. 9 ^{1}H-NMR Spectrum of **178**

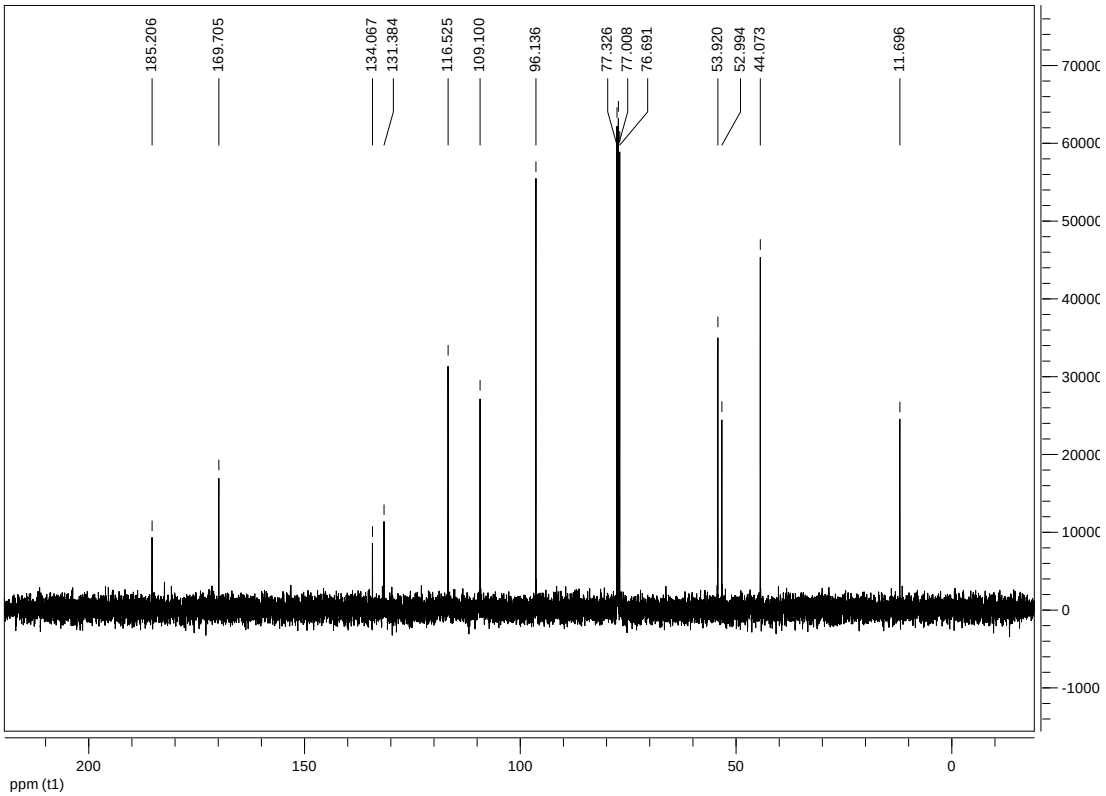

Figure A. 10 ^{13}C-NMR Spectrum of **178**

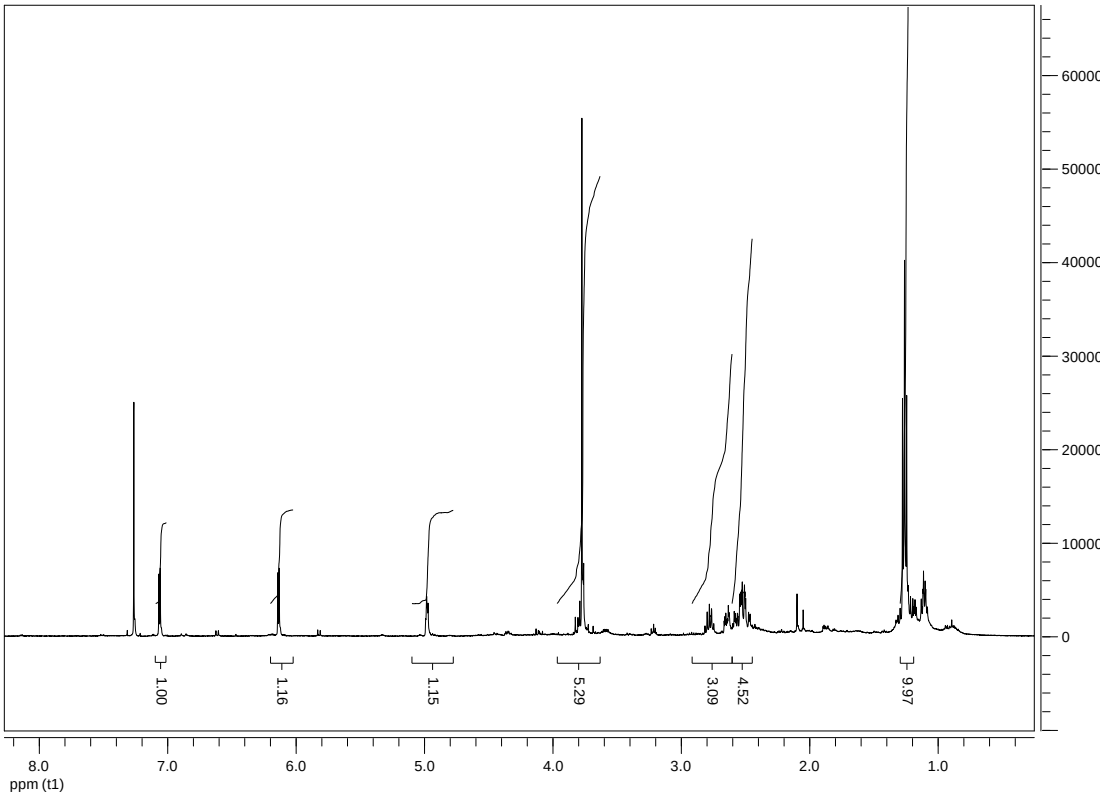

Figure A. 11 ^{1}H-NMR Spectrum of **179**

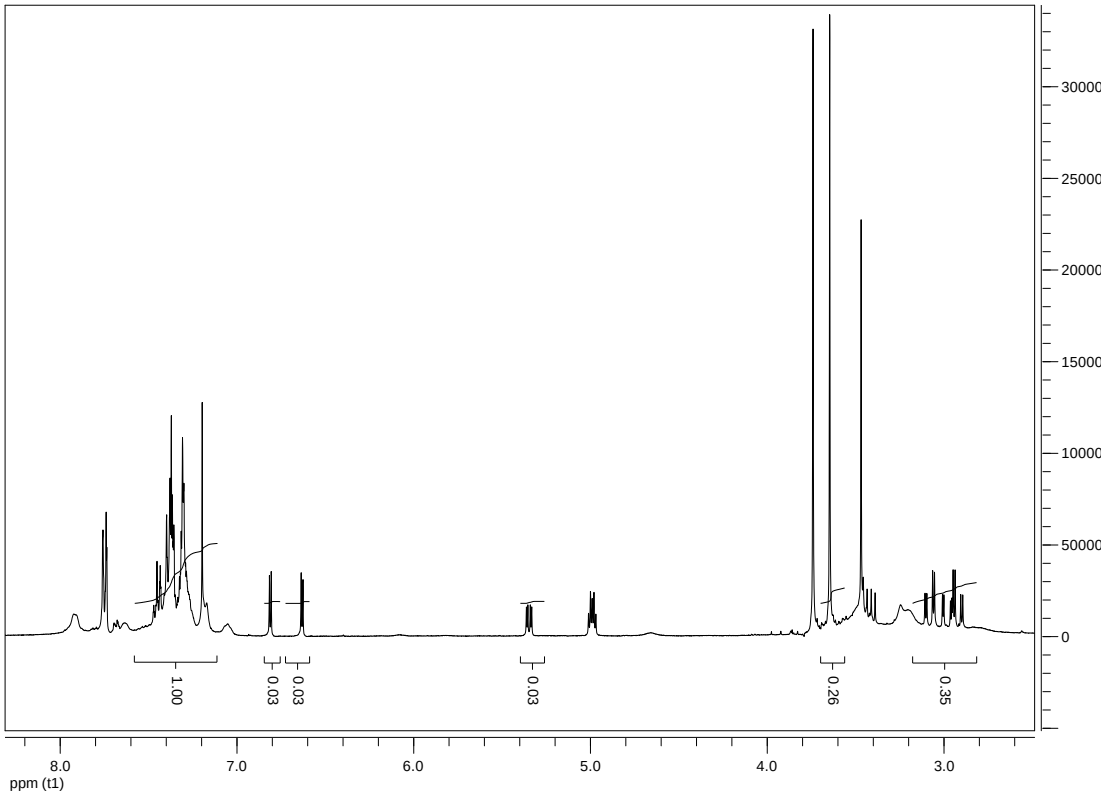

Figure A. 12 ^{1}H-NMR Spectrum of **180**

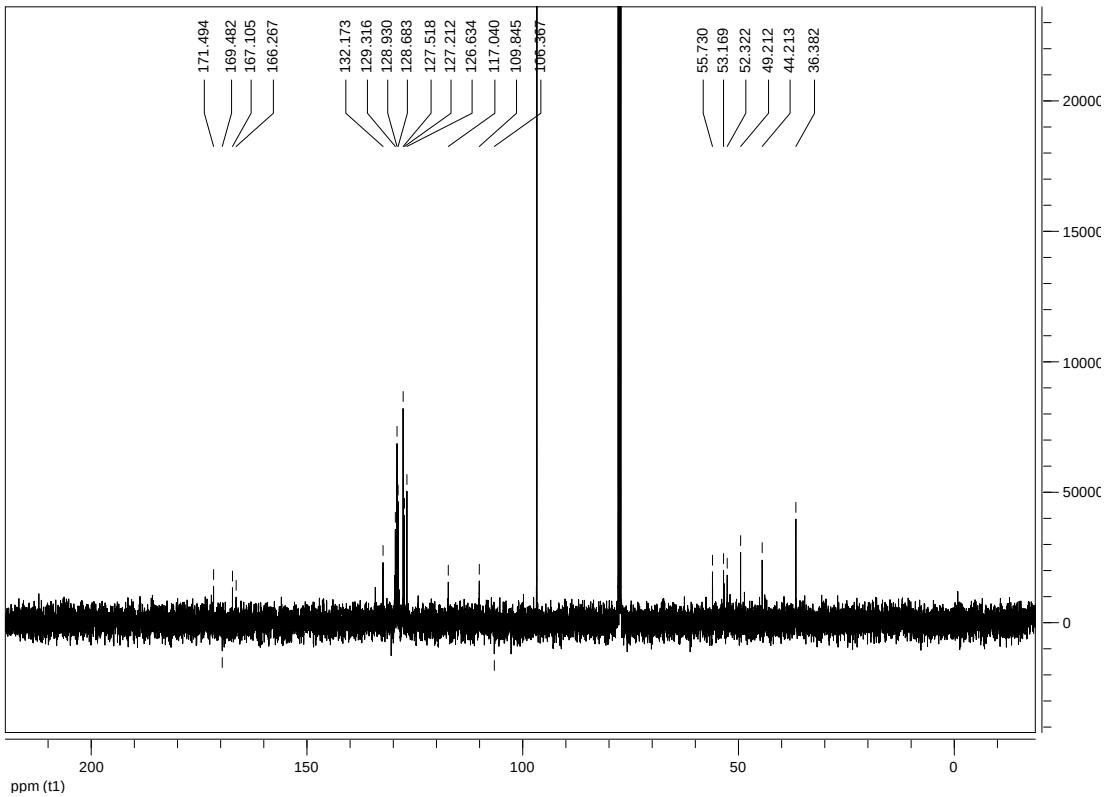

Figure A. 13 ^{13}C-NMR Spectrum of **180**

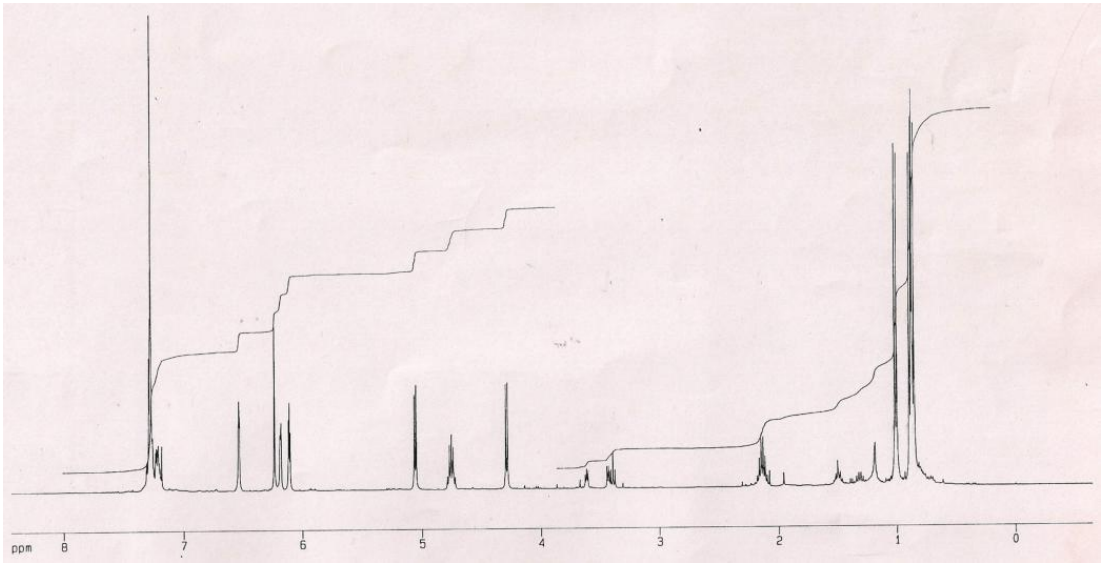

Figure A. 14 ^{1}H-NMR Spectrum of **189**

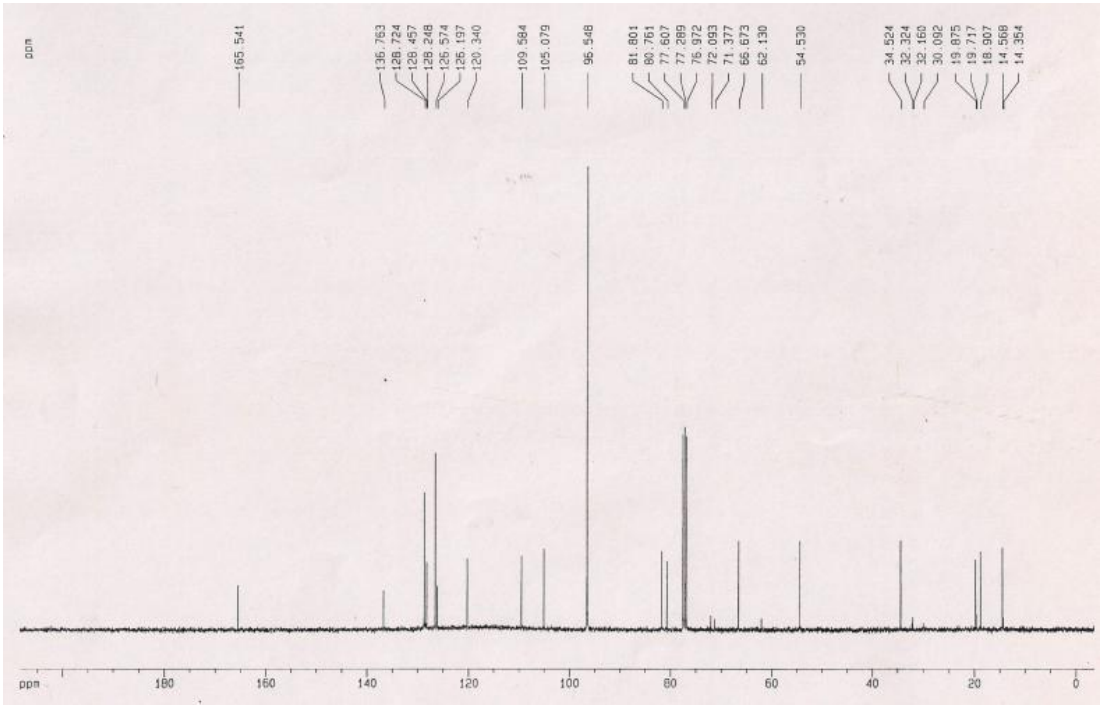

Figure A. 15 ^{13}C-NMR Spectrum of **189**

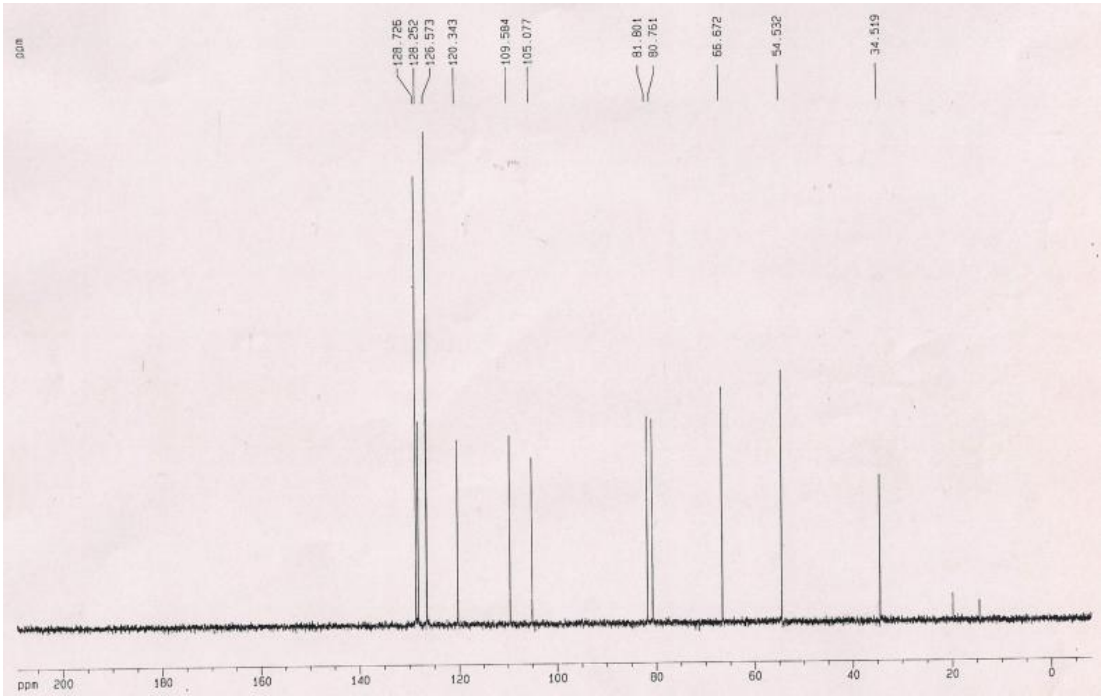

Figure A. 16 DEPT-90 Spectrum of **189**

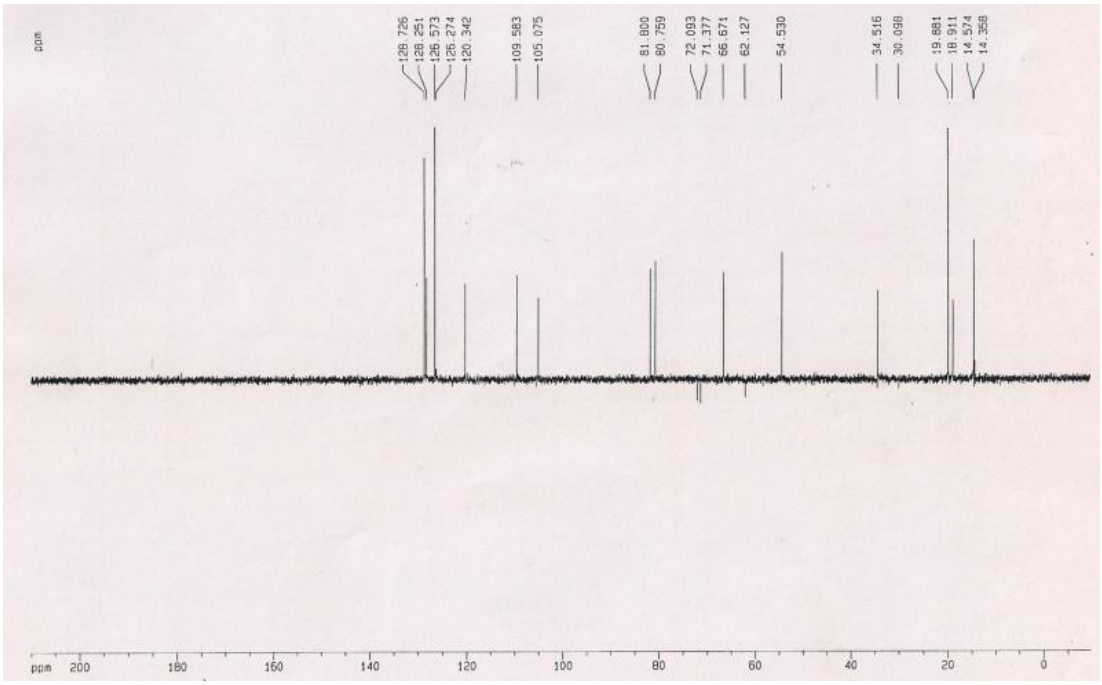

Figure A. 17 DEPT-135 Spectrum of **189**

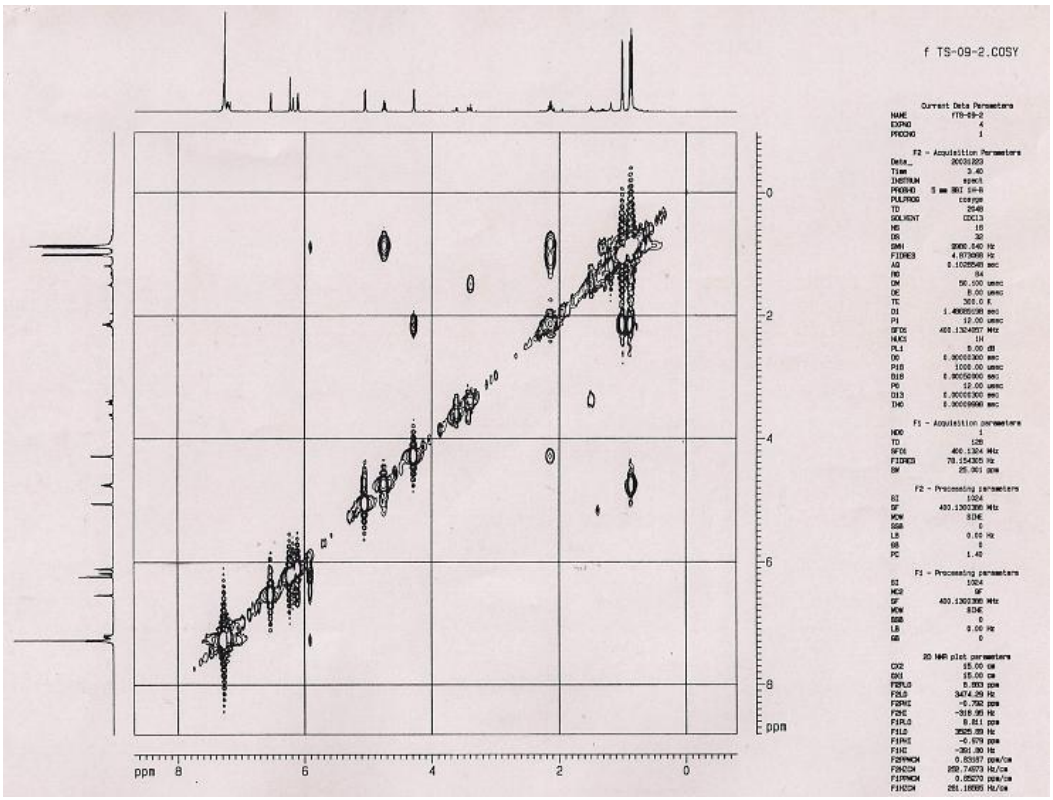

Figure A. 18 COSY Spectrum of **189**

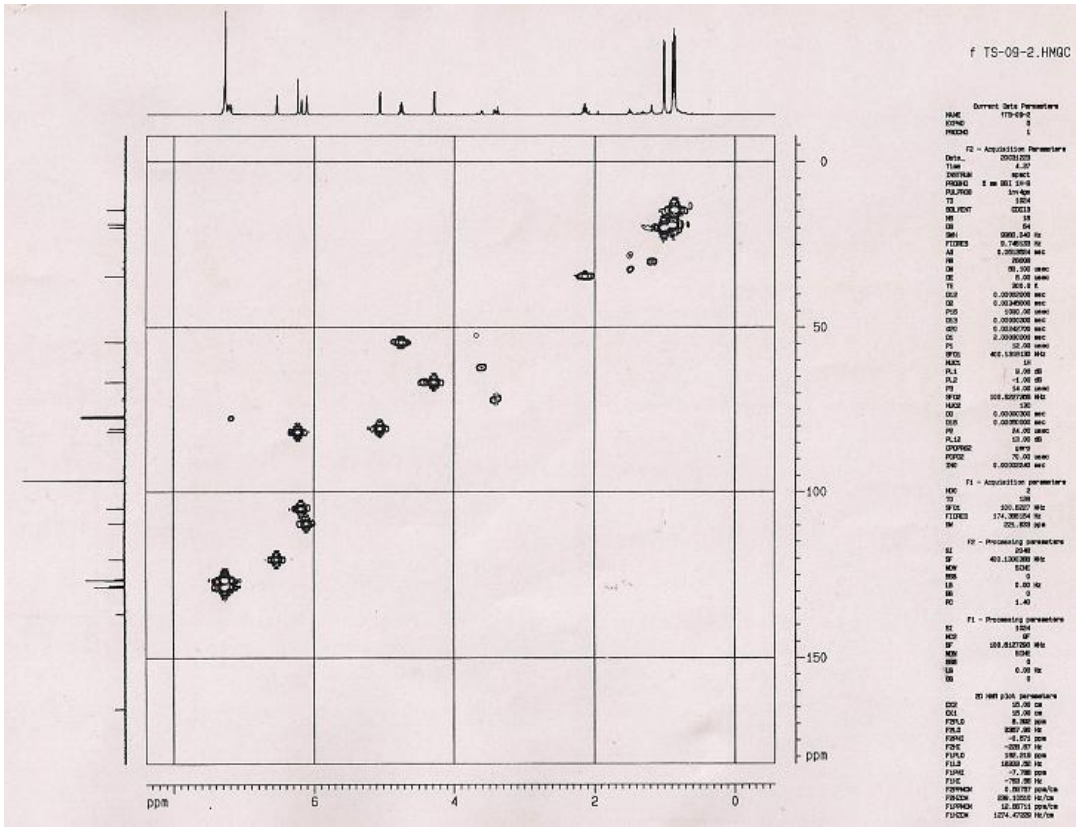

Figure A. 19 HMQC Spectrum of **189**

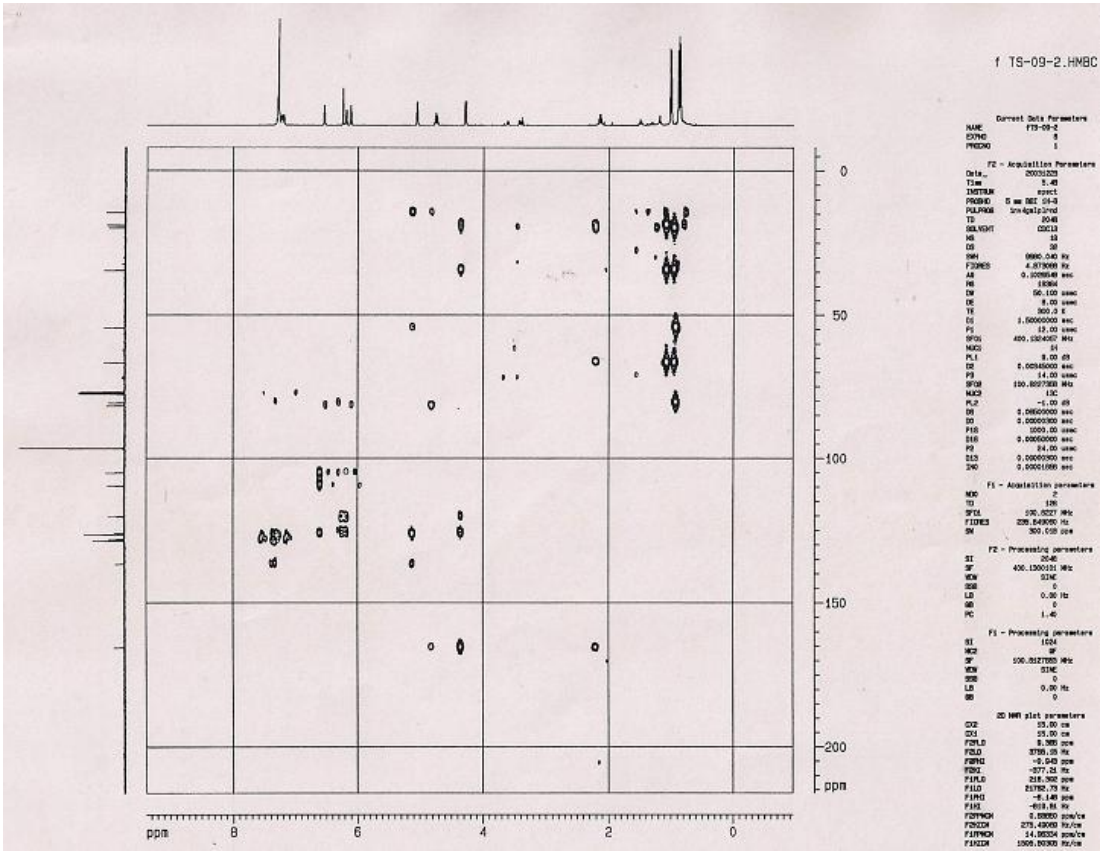

Figure A. 20 HMBC Spectrum of **189**

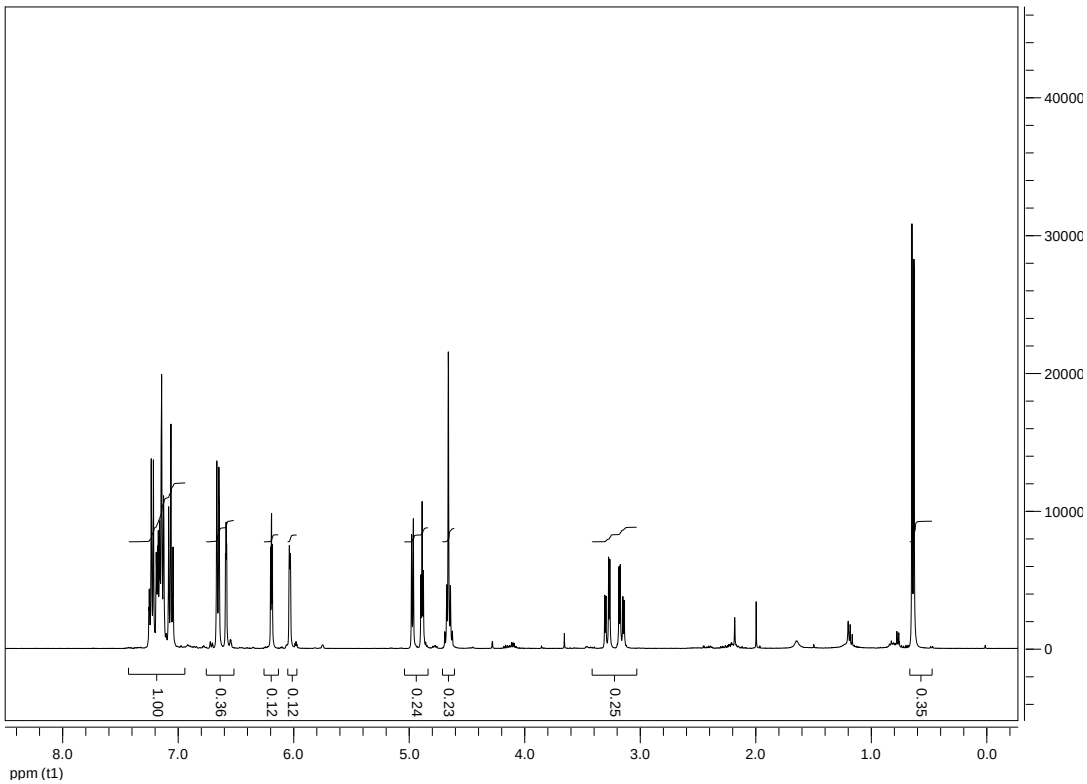

Figure A. 21 ^{1}H-NMR Spectrum of **195**

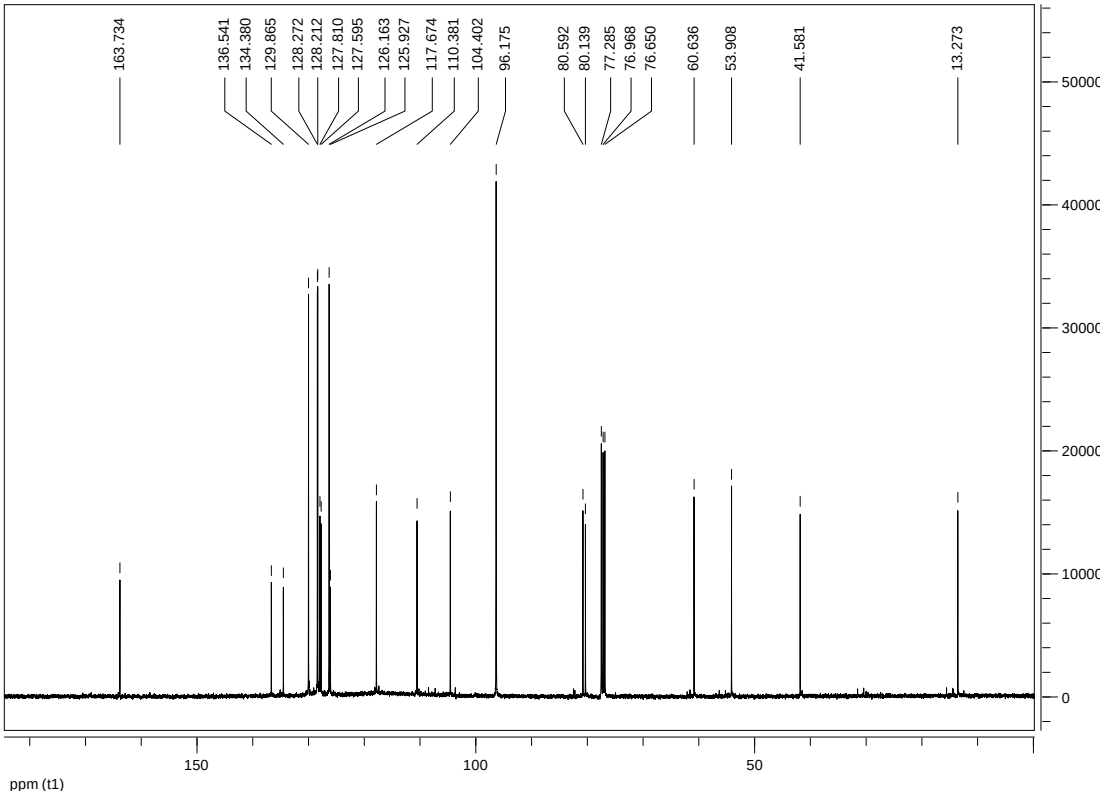

Figure A. 22 ^{13}C-NMR Spectrum of **195**

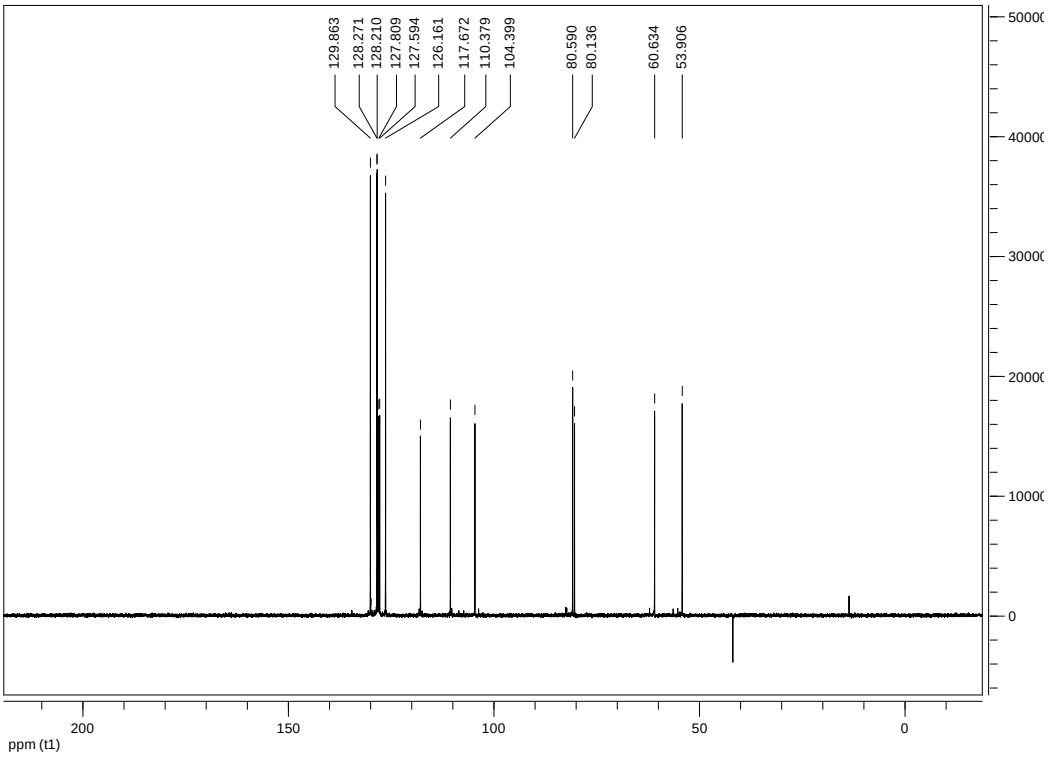

Figure A. 23 DEPT-90 Spectrum of **195**

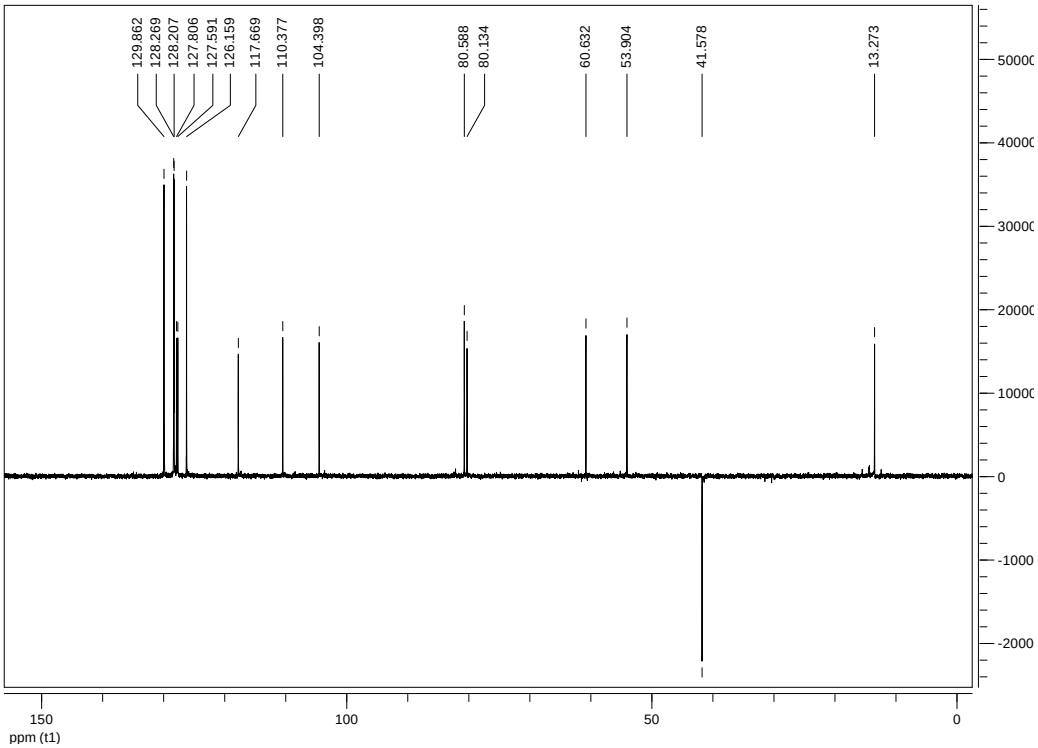

Figure A. 24 DEPT-135 Spectrum of **195**

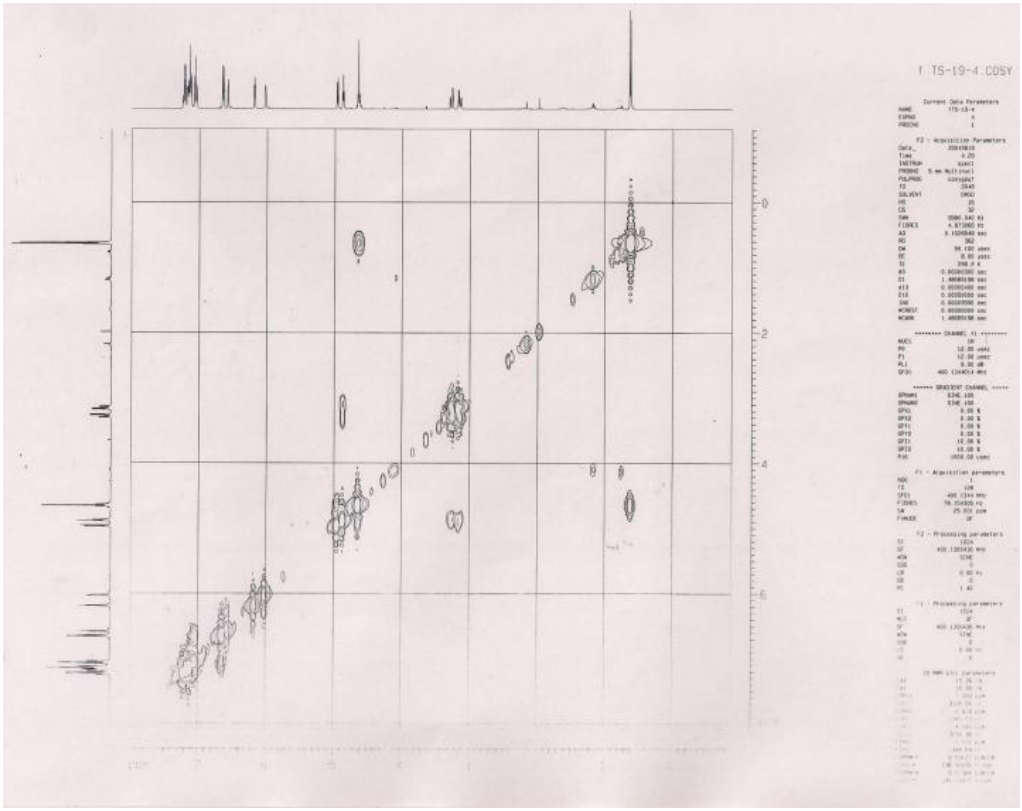

Figure A. 25 COSY Spectrum of **195**

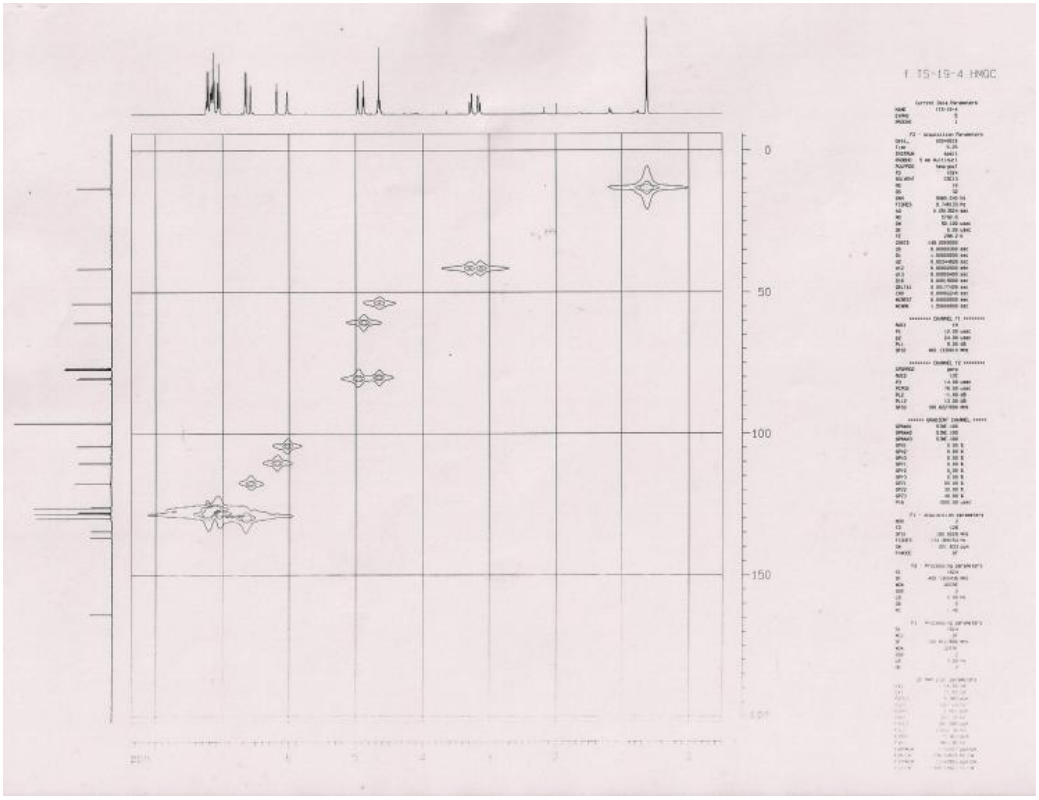

Figure A. 26 HMQC Spectrum of **195**

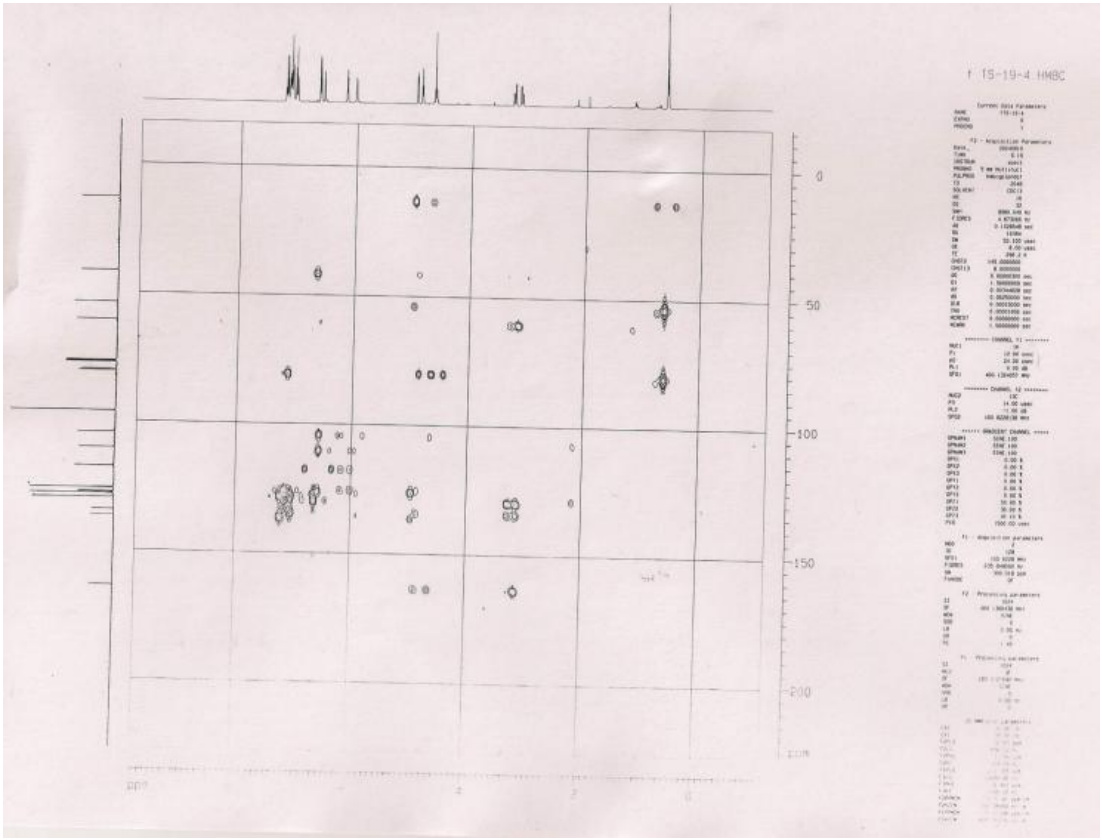

Figure A. 27 HMBC Spectrum of **195**

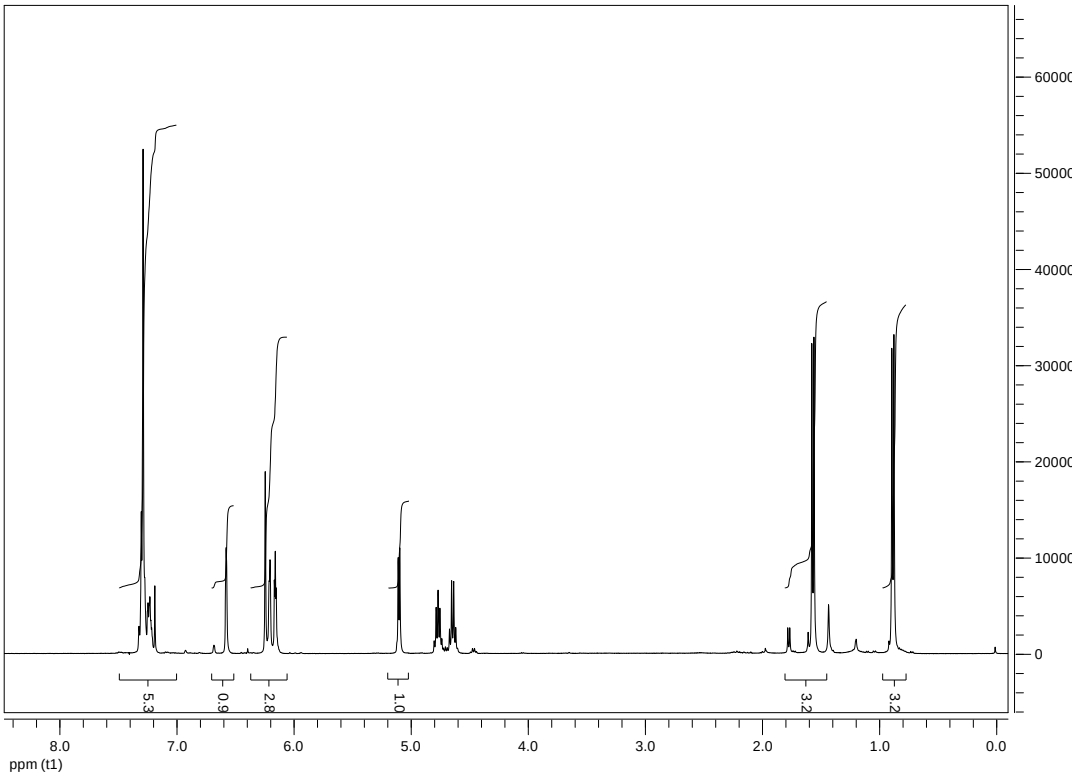

Figure A. 28 ^{1}H-NMR Spectrum of **199**

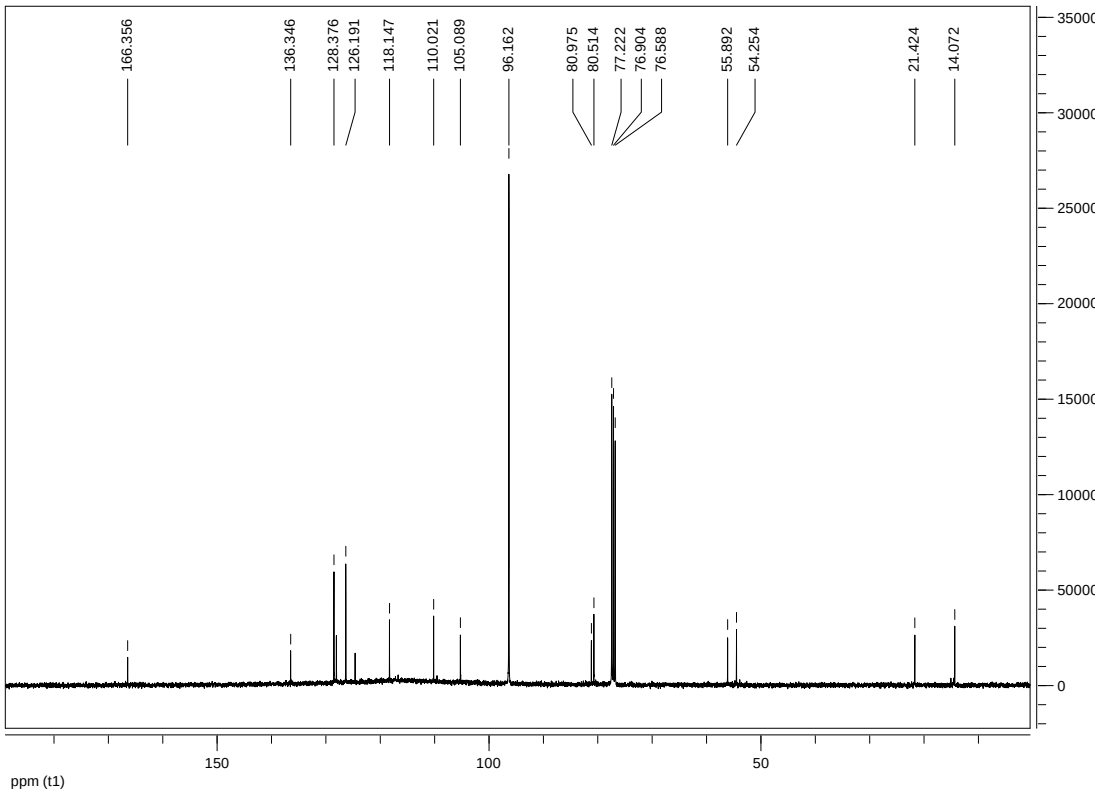

Figure A. 29 ^{13}C-NMR Spectrum of **199**

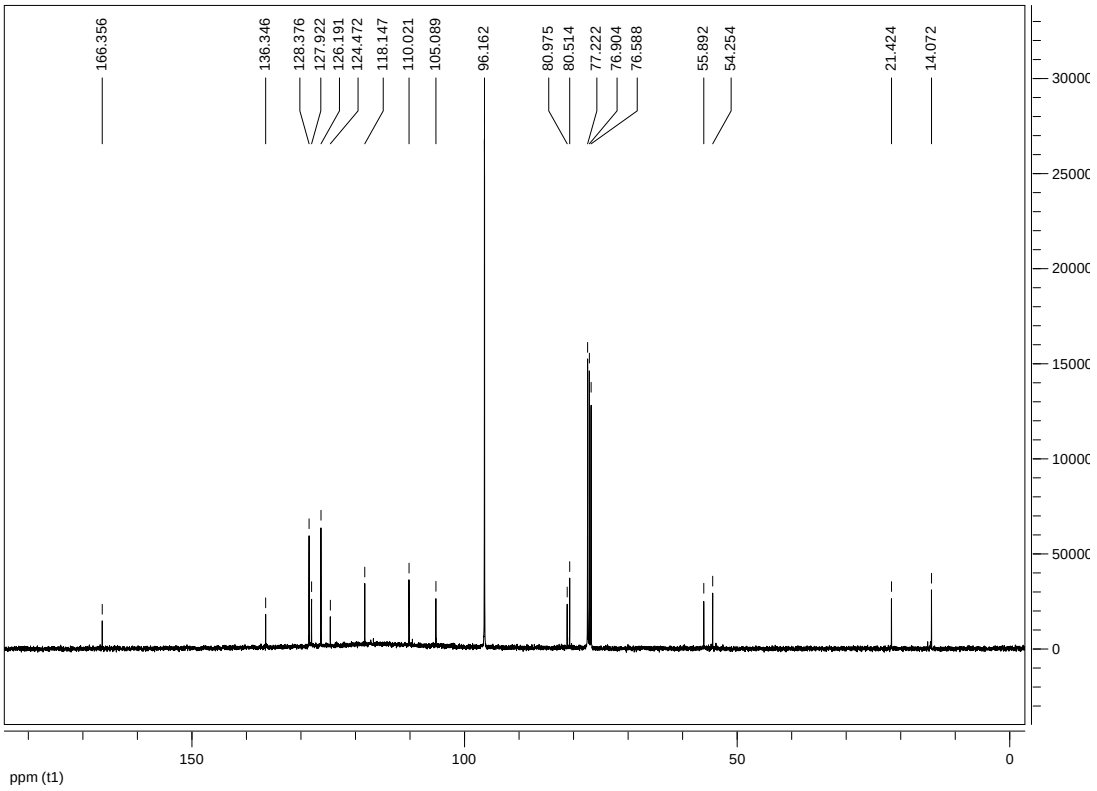

Figure A. 30 DEPT-9O Spectrum of **199**

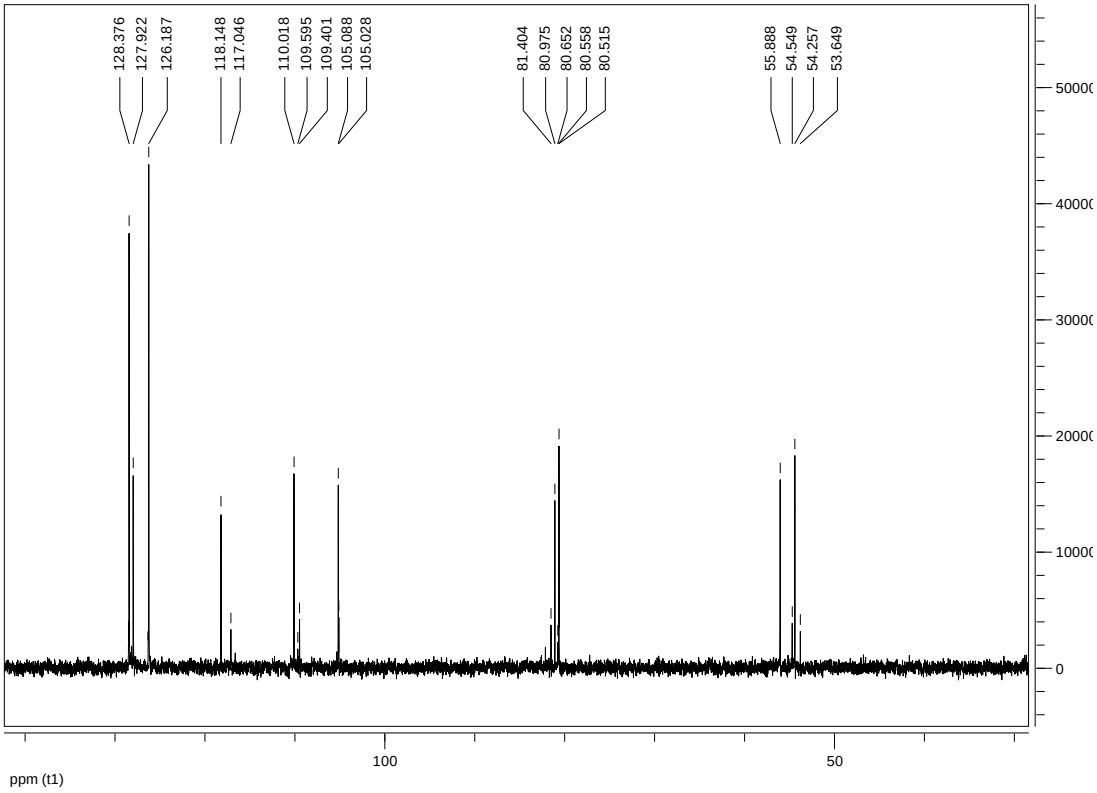

Figure A. 31DEPT-135 Spectrum of **199**

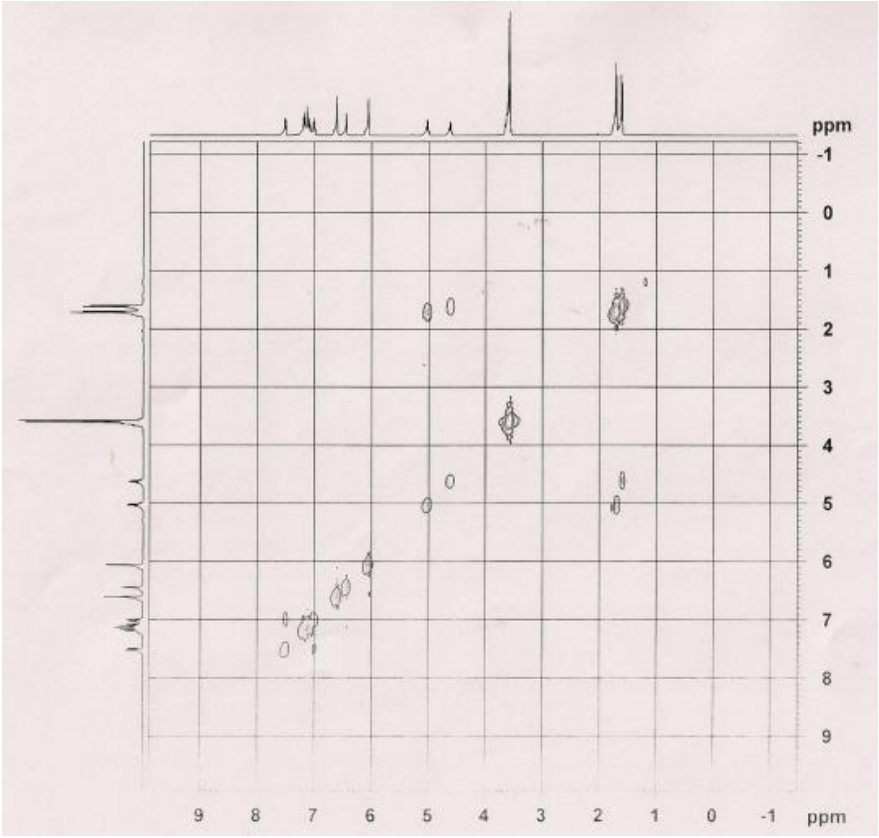

Figure A. 32 COSY Spectrum of **199**

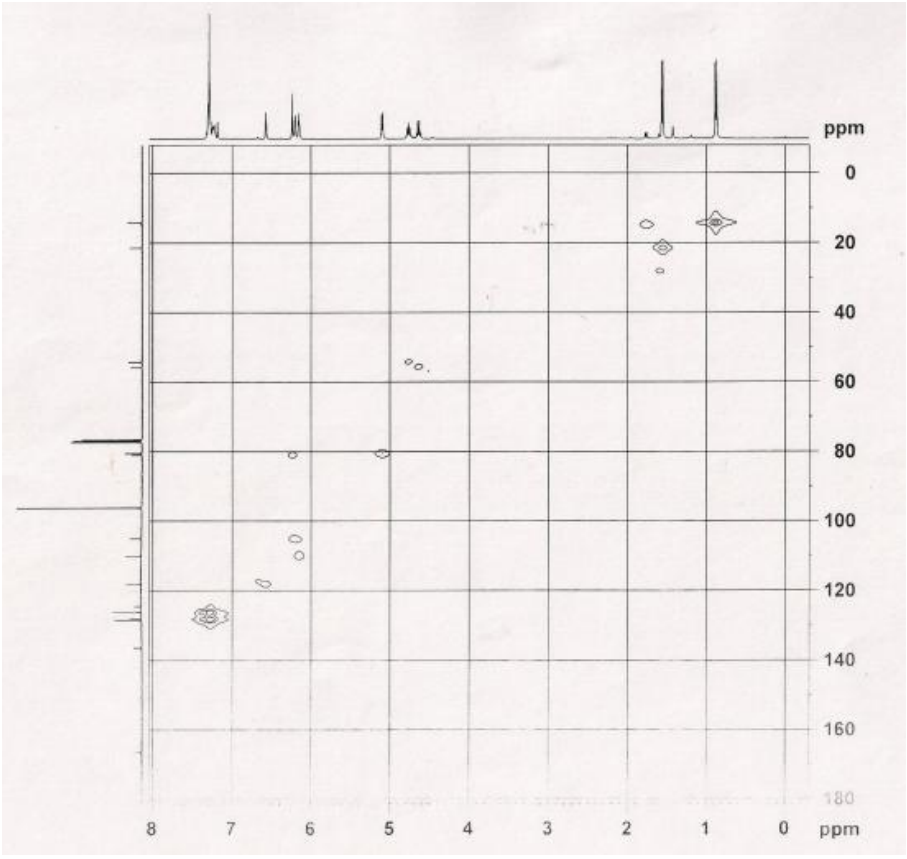

Figure A. 33 HMQC Spectrum of **199**

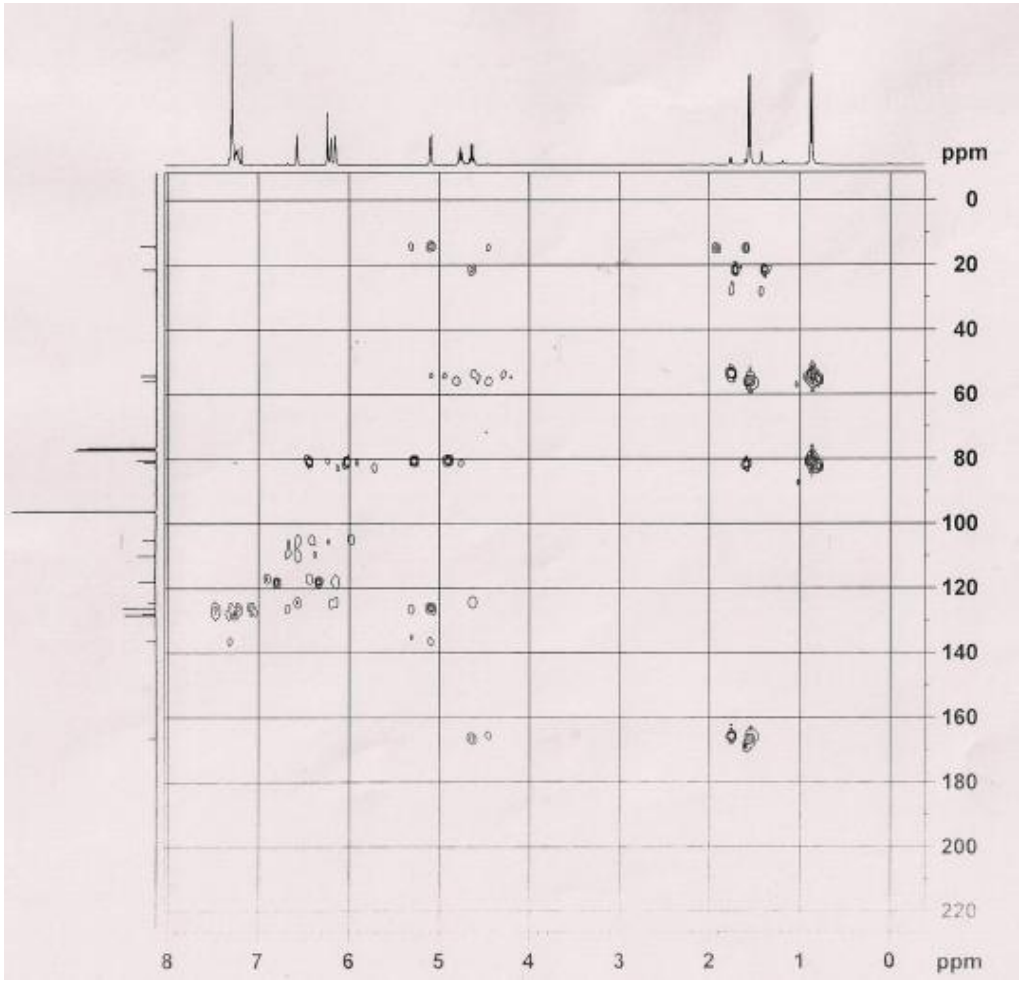

Figure A. 34 HMBC Spectrum of **199**

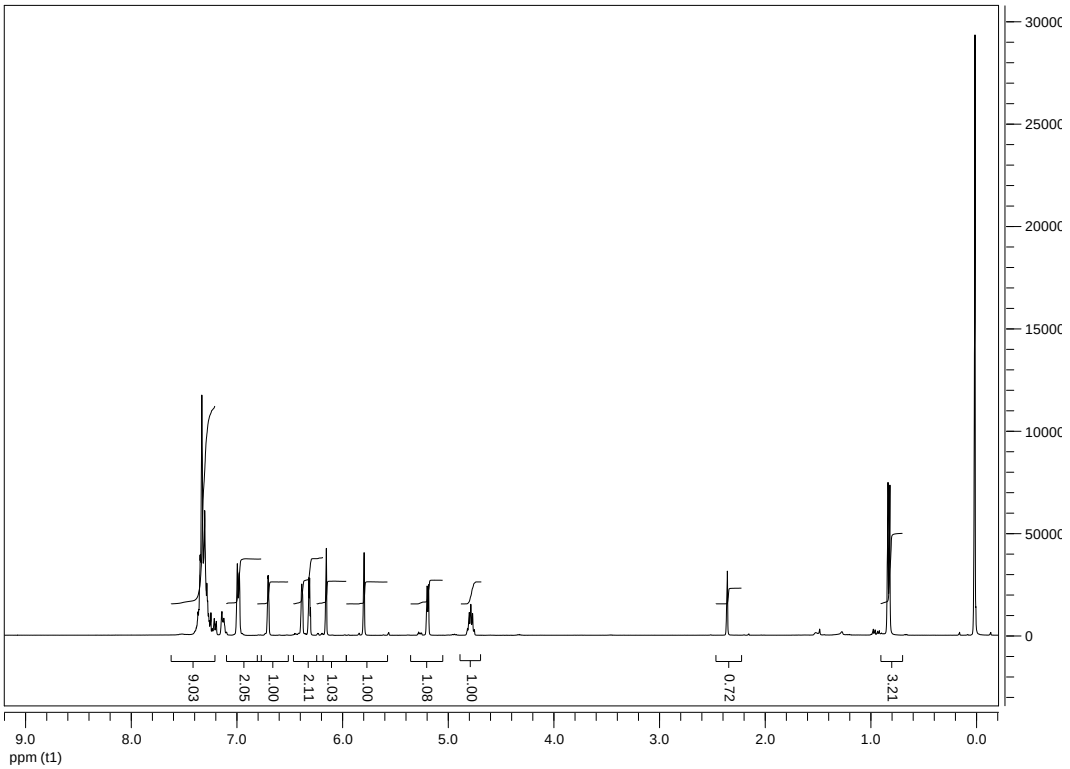

Figure A. 35 ^{1}H-NMR Spectrum of **205**

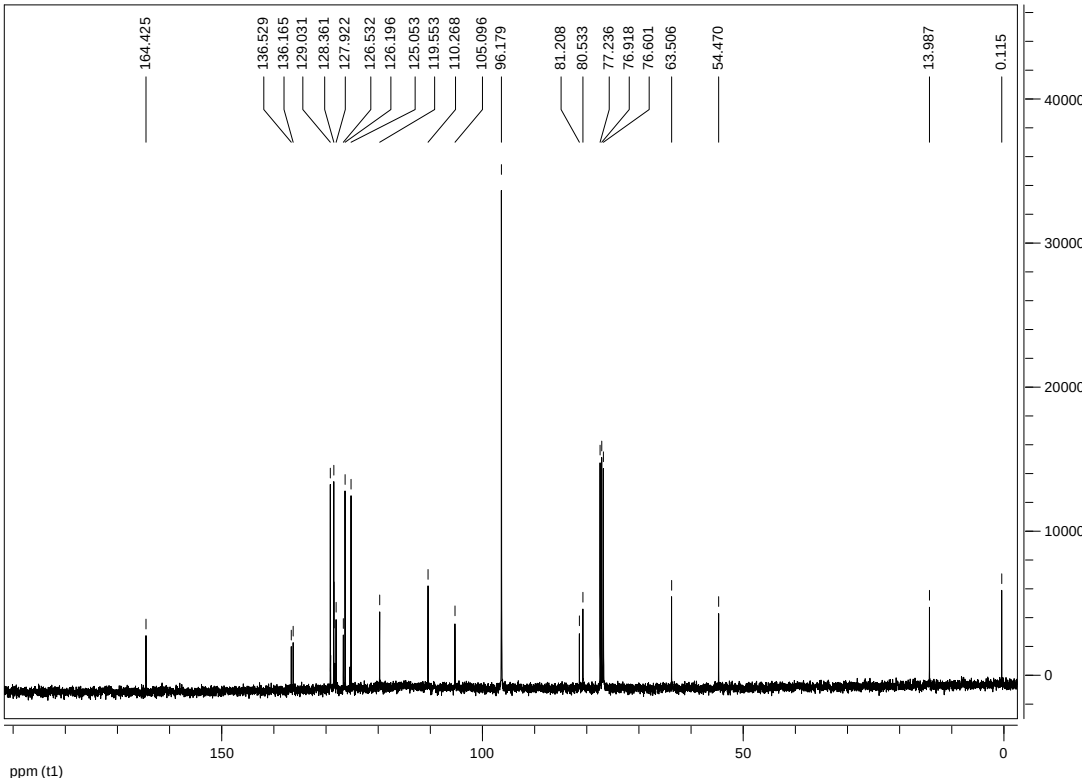

Figure A. 36 ^{13}C-NMR Spectrum of **205**

CURRICULUM VITAE

Name : Nuriye Tuna SUBAŞI

Date of Birth : September 16, 1978

Place of Birth : Ankara/TURKEY

Status : Married

Education:

January 2004-Present	**PhD in Chemistry (Organic Chemistry)** Department of Chemistry, Middle East Technical University, Ankara, Turkey **Thesis Title:** Novel Synthetic Methodologies for Heterocycles as Building Blocks in Drug Synthesis **Supervisor:** Prof. Dr. Ayhan Sıtkı DEMİR
September 1996-July 2000	**BS in Chemistry** Faculty of Arts and Sciences Ankara University, Ankara, Turkey

---

Positions:

2004-2005	Teaching Assistant In General Chemistry Laboratory, METU, Turkey
2005-Present	Teaching Assistant In Organic Chemistry Laboratory, METU, Turkey

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Publications:

2. Demir, A. S.; Findik, H.; Saygili, N.; Subasi, N. T. Manganese(III) acetate-mediated synthesis of biaryls under microwave irradiation, *Tetrahedron*, 2010, 66(6), 1308-1312.

1. Demir, A. S.; Subasi, N. T.; Sahin, E. Intermolecular one-pot cyclization of formyl-pyrroles of amino acid esters with norephedrine: stereoselective routes to new tricyclic pyrrole–pyrazine–oxazole fused structures, *Tetrahedron: Asymmetry* **2006**, *17*, 2625.

National Symposiums:

5. Subaşı, N. T., Demir, A. S. Yeni Bisiklik Pirol Türevlerinin Sentezi, 24. Ulusal Kimya Kongresi, 29 Hazirn-02 Temmuz 2010, Zonguldak (Sözlü Sunum).

4. Subaşı, N. T., Demir, A. S. Yeni Bisiklik Pirol Türevlerinin Sentezi, 23. Ulusal Kimya Kongresi, 16-20 Haziran 2009, Sivas (Poster Sunum).

3. Subaşı, N. T., Demir, A. S. Yeni Stereoseçici Pirol-Pirazin-Oxazol yapılarının Sentezi, 22. Ulusal Kimya Kongresi, 6-10 Ekim 2008, Kıbrıs, Gazimağusa (Poster Sunum).

2. Subaşı, N. T., Demir, A. S. Aminoasit Esterlerinden Türetilmiş Formil-Pirollerin Tek Basamakta Norephedrin İle Halkalaşması:Yeni Stereoseçici Pirol-Pirazin-Oxazol Yapılarının Sentezi 21. Ulusal Kimya Kongresi, 23-27 Ağustos 2007, Malatya (Poster Sunum).

1. Subaşı, N. T., Demir, A. S. Yeni Trisiklik Kiral Pirazin Türevleri, 18. Ulusal Kimya Kongresi, 5-9 Temmuz 2004, Kars (Poster Sunum).