SYNTHESIS OF VARIOUS CAMPHOR-BASED CHIRAL PYRIDINE DERIVATIVES

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MURAT IŞIK

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Approval of the Graduate School of Natural and Applied Sciences

Prof. Dr. Canan Özgen
Director

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

Prof. Dr. Hüseyin İşçi
Chairman of the Department

We certify that we have read thesis and in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

Prof. Dr. İdris Mecidoğlu Akhmedov	Prof. Dr. Cihangir Tanyeli
Co-supervisor	Supervisor

Examining Committee Members

Prof. Dr. Metin Balcı	(METU, CHEM)	_____
Prof. Dr. Cihangir Tanyeli	(METU, CHEM)	_____
Prof. Dr. İdris Mecidoğlu Akhmedov	(METU, CHEM)	_____
Prof. Dr. Lemi Türker	(METU, CHEM)	_____
Prof. Dr. Fatma Sevin Düz	(Hacettepe Univ., CHEM)	_____

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ABSTRACT

SYNTHESIS OF VARIOUS CAMPHOR-BASED CHIRAL PYRIDINE DERIVATIVES

Işık, Murat

M.S., Department of Chemistry

Supervisor: Prof. Dr. Cihangir Tanyeli

Co-supervisor: Prof. Dr. İdris Mecidoğlu Akhmedov

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Chiral aromatic nitrogen heterocycles are finding many applications in asymmetric organic synthesis, particularly as ligands in the preparation of chiral metal complexes. Since camphor-based chiral auxiliaries are known to be especially effective, a number of pyridines fused to the camphor skeleton have been reported. It is well known that nicotinic acid and its derivatives exhibiting qualitatively the biological activity of nicotinamide, which acts as an electron acceptor in many biological redox reactions. In connection to our works, we attempted to develop short and convenient way to prepare various camphor-derived chiral pyridine or nicotinic acid derivatives. Here we report our results obtained from the annulation of (+)-β-hydroxymethylenecamphor as the feasible chiral pool with various enamines derived from active methylene compounds. (+)-β-Hydroxymethylenecamphor prepared from cheap and easily available natural (+)-camphor and enamines were transformed into chiral camphor-based pyridine derivatives via tandem condensation reaction in good yields.

Key words: Chiral pyridine, nicotinic acid, enamines.

ÖZ

KAMFOR TEMELLİ ÇEŞİTLİ KİRAL PİRİDİN TÜREVLERİNİN SENTEZİ

Işık, Murat
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli
Ortak Tez Yöneticisi: Prof. Dr. İdris Mecidoğlu Akhmedov
Ocak 2005, 77 sayfa

Azotlu kiral aromatik heterohalkalar, özellikle ligant olarak kiral metal komplekslerinin hazırlanmasında asimetrik organik sentezde bir çok uygulama alanı bulmaktadır. Kamfor temelli kiral piridinlerin özellikle etkili bir ligant olduğu bilindiği için, kamfor iskeletine birleştirilmiş bir çok piridin literatürde bulunmaktadır. Nikotinik asit ve türevlerinin, bir çok biyolojik redoks tepkimelerde elektron alıcı olarak işlev gören nikotinamidin biyolojik aktivitesini kalitatif olarak gösterdiği iyi bilinmektedir. Çalışmamızla bağlantılı olarak, çeşitli kamfor temelli kiral piridin veya nikotinik asit türevlerinin kısa ve uygun sentezini geliştirmeye çalıştık. Burada makul kiral havuzumuz olan (+)-β-hidroksimetilenkamfor ile aktif metilen bileşiklerinden elde edilmiş çeşitli enaminlerlerin halkalaşması sonucu elde ettiğimiz sonuçları sunuyoruz. Ucuz ve kolayca bulunabilen doğal (+)-kamfordan elde edilmiş olan (+)-β-hidroksimetilenkamfor ve çeşitli enaminler, peş peşe gerçekleşen siklokondansasyon reaksiyonu aracılığıyla kamfor temelli kiral piridin türevlerine yüksek verimle dönüştürülmüştür.

Anahtar kelimeler: Kiral piridin, nikotinik asit, enaminler.

To Everybody

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First I would like to thank to Prof. Dr. Cihangir Tanyeli and Prof. Dr. İdris Mecidoğlu Akhmedov for their skillful guidance, patience and encouragement throughout this study.

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LIST OF ABBREVIATIONS

DMF: *N*,*N*-Dimethyl formamide

BED: 2-(2-Bromoethyl)-1,3-dioxolane

Bpy: 2,2'-Bipyridine

DMH: *N*,*N*-Dimethylhdrazone

LDA: Lithium diisopropylamide

m-CPBA: *m*-Chloroperbenzoic acid

MVK: Methyl vinyl ketone

Phens: 1,10-Phenanthrolines

THF: Tetrahydrofuran

CHAPTER I

INTRODUCTION

1.1. History of Pyridine

Names often give fascinating insights into what they describe and in the case of pyridine, we learn of its history and nature: “pyr” is Greek word for fire and “idine” is a suffix used at one time for all aromatic bases. Pyridine bases were first obtained from the pyrolysis of bone by the condensation of simple aldehydes and ketones with ammonia, which are thought to be formed from the decomposition of glycerol and nitrogenous material in bone oil under these conditions.[1,2]

Anderson isolated the first pyridine base, picoline, from bone oil in 1846, but the correct structure of pyridine was not proposed until Körner (1869) and Dewar (1871) independently formulated a mono-aza-analogue of benzene.[1-5] With this understanding of the structure of pyridine, synthetic routes appeared from the latter half of the 19th century starting with Ramsay in 1876,[6] although pyridine derivatives were of little commercial importance for decades and required quantities could be obtained from coal tar distillation. Since the middle of the last century, pyridine has assumed an important role in our understanding of the chemistry of biological systems. It plays a key role catalysing both biological and chemical systems. Pyridines came to prominence in the 1930s with the recognition of the importance of niacin (nicotinamide) **1** (Figure 1) for the prevention of dermatitis and dementia.[6]

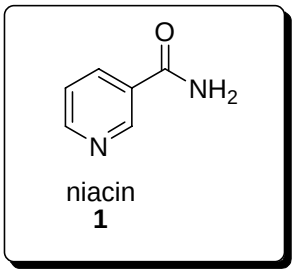


Figure 1: Chemical structure of niacin

It is well known that nicotinic acid and its derivatives exhibiting qualitatively the biological activity of nicotinamide, which acts as an electron acceptor in many biological redox reactions. The demand for pyridine and its derivatives has further increased over the last 50 years by the discovery of many biologically active pyridine containing compounds by several companies.[7]

1.2. Pyridines as Nitrogen Containing Ligands for Asymmetric Catalysis

Practical asymmetric catalysis using transition metal complexes was inspired by the work of Kagan[8] and Knowles.[9] Their important results, based on the use of chiral phosphines as ligands for asymmetric hydrogenation, have induced a tremendous amount of work dealing with the synthesis and use of new chiral phosphine-containing complexes as catalysts. Numerous catalytic reactions allowing the enantioselective formation of C-H, C-C, C-O, C-N, and other bonds have been discovered over the last 30 years, often with spectacular results in terms of efficiency and selectivity. More recently, asymmetric catalysis has been developed on a practical scale, since some very efficient catalytic industrial processes are currently carried out to produce chiral building blocks. For economic, environmental, and social reasons, interest in the preparation of enantiomerically pure compounds is growing. More than 30 years after the discovery of the above-mentioned methods,

however, most chiral synthons are still produced from natural chiral building blocks or by performing racemic resolution (either diastereomer separation or kinetic resolution). There is, indeed, no simple and versatile method for the preparation of chiral molecules: numerous competitive methodologies have to be tested to offer, in each particular case, an optimal solution. It appears that the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected, which is surprising given the huge amount of work devoted to this subject, in both academic and industrial research centers. Several factors are responsible for this lack of practical application, particularly the price of the catalyst precursor (both precious metal and optically pure ligand) and the difficulties encountered in the separation and recycling of the catalyst. A few processes have, however, permitted high turnovers. In these cases, the cost of the catalyst was considered to be negligible and so the catalyst was sacrificed during the workup procedure.[10]

Although chiral phosphines have enjoyed a longtime popularity in the design of enantioselective catalytic systems, there has been a recent renaissance in the use of nitrogen ligands for this same purpose.[10] This renaissance partly arises from several distinct advantages presented by nitrogen-containing ligands. First, they can often be employed in catalytic processes where the use of phosphines may be incompatible with the reaction conditions. Second, many nitrogen ligands are now available in enantiomerically pure form. Third, ligands that bind through nitrogen are known to coordinate with a wide variety of metal ions, and considerable progress has been made in understanding the role which these ligands play in affecting catalytic processes.[11] In this context, the most important nitrogen-containing ligands are those that involve the pyridine ring (Figure 2).[12-14]

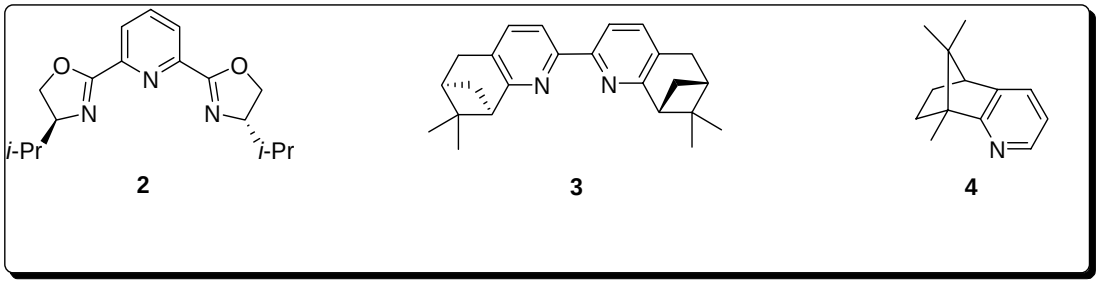


Figure 2: Examples of pyridine-containing ligands used in asymmetric catalysis

1.3. Camphor-based Chiral Pyridines in Asymmetric Catalysis

Chiral aromatic nitrogen heterocycles are finding many applications in asymmetric organic synthesis, particularly as ligands in the preparation of chiral metal complexes.[10,11] Since camphor-based chiral auxiliaries are known to be especially effective[15], a number of pyridines fused to the camphor skeleton have been reported.[16-25]

In camphor-based chiral pyridines, the bicyclic bridged system adds a further constraint to the aliphatic portion of the molecule and this is expected to result in a higher stereodifferentiating ability of the chiral ligands derived from these pyridines.[17] These compounds are also the most convenient starting products for the synthesis of the corresponding optically active 2.2'-bipyridines, a new class of chiral ligands for asymmetric reactions.[18] Additionally, chiral tetrahydroquinolines (Figure 3) are well suited substances for the study of the chirooptical properties of the pyridine chromophore: the stiffening of the chiral array determined in the molecule by the ring constraint cuts down drastically the number of the possible conformers that may contribute to the optical activity, resulting in an enhancement of the dissymmetry factor and allowing a more reliable attribution of the circular dichromism (c.d.) bands observed.[19]

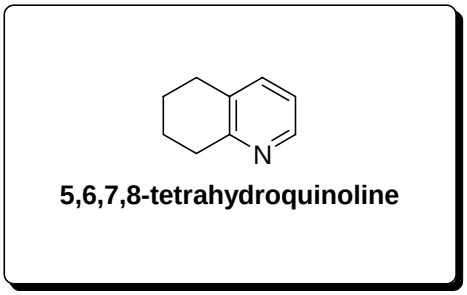
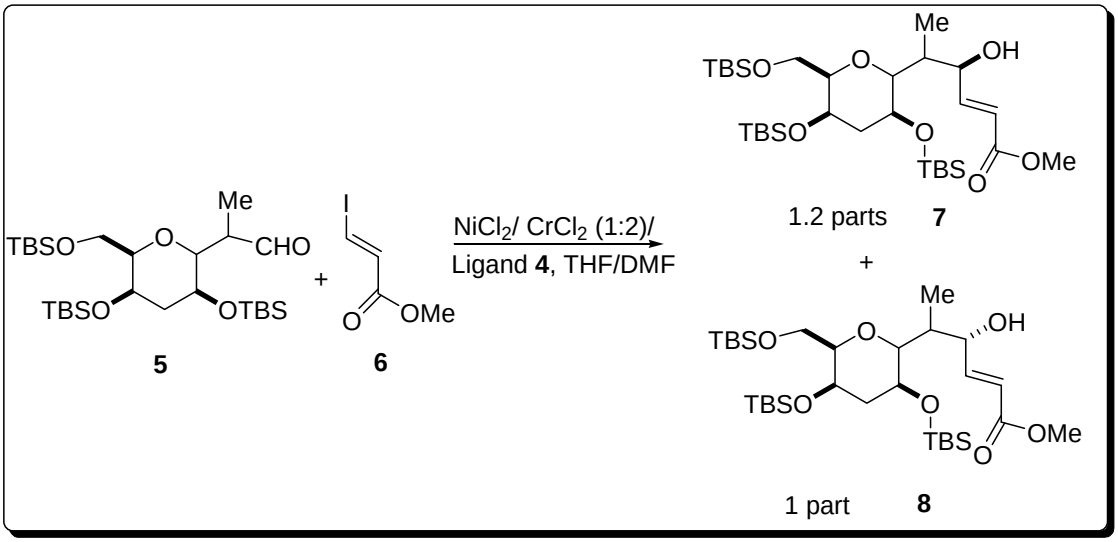


Figure 3: Chemical structure of 5,6,7,8-tetrahydroquinoline

To our knowledge, in catalytic asymmetric organic synthesis, camphor-based chiral pyridines has been used once as chiral ligand by Kishi et al. in the coupling of **5** with **6** in THF:DMF (4:l) at room temperature yielded the two possible diastereomers **7** and **8** in a 1.2:l ratio (Scheme 1).[14] They also used pinene-based chiral bipyridines and results showed that these bipyridine derivatives worked better than camphor-based pyridine **4.**



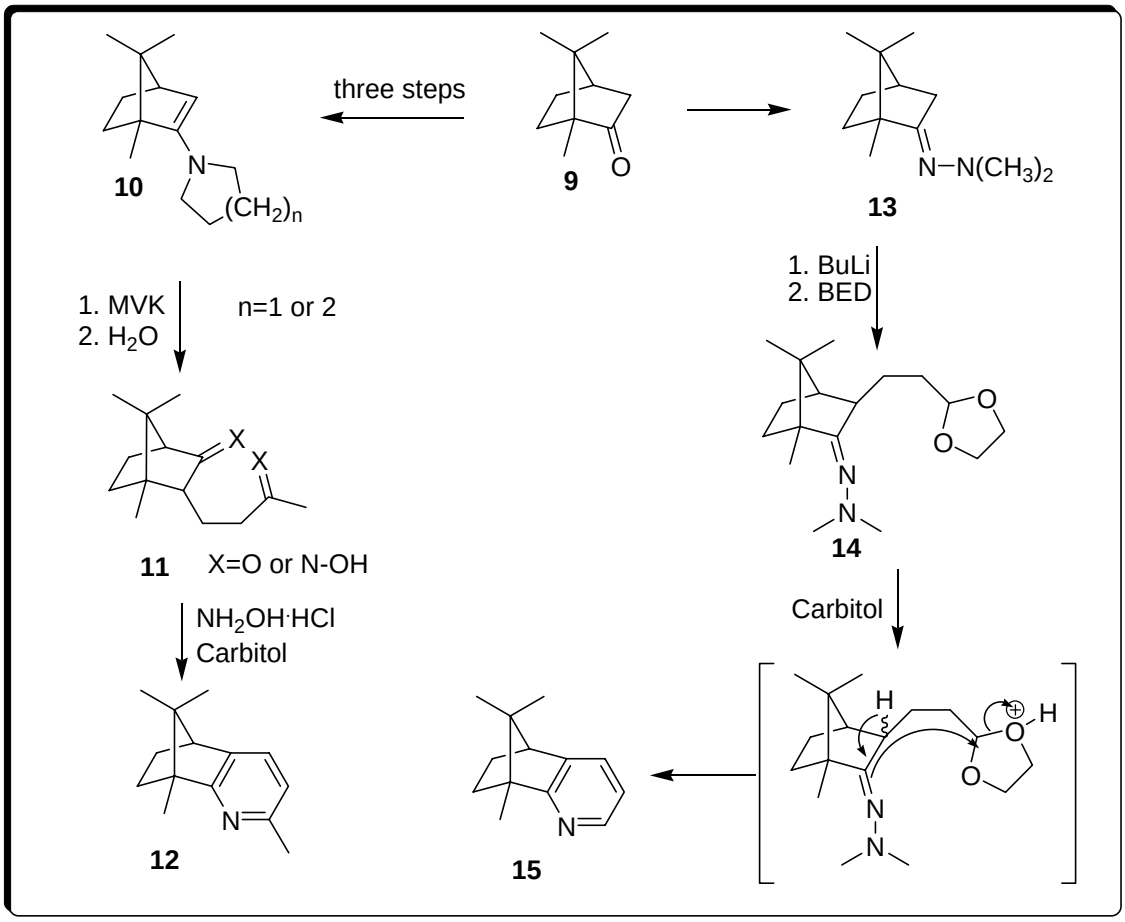
Scheme 1

1.3.1. Literature Synthesis of Camphor-based Chiral Pyridines

To our knowledge, the first synthesis of camphor-based chiral pyridine was achieved by the Gladiali et al. in 1986.[17] The synthetic method they used was defined as pyridoannelation: defined as the elaboration of a pyridine nucleus onto an α-methylene carbonyl compound ((+)-camphor **9** in their first attempt) in such a manner that the carbonyl becomes adjacent to the nitrogen in the final product. They have synthesized camphor-based chiral pyridines **12** and **15**, with 14% and 45 % overall chemical yield starting from (+)-camphor **9** (Scheme 2). According to Scheme 2, camphor enamine **10**, readily available through aminolysis of the relevant *N*-nitroimine, can be alkylated with the suitable α,β-unsaturated carbonyl compound (MVK: methyl vinyl ketone) affording a masked 1,5-dioxocompound **11** to be cyclized to chiral pyridine **12** by treatment with hydroxylamine hydrochloride.

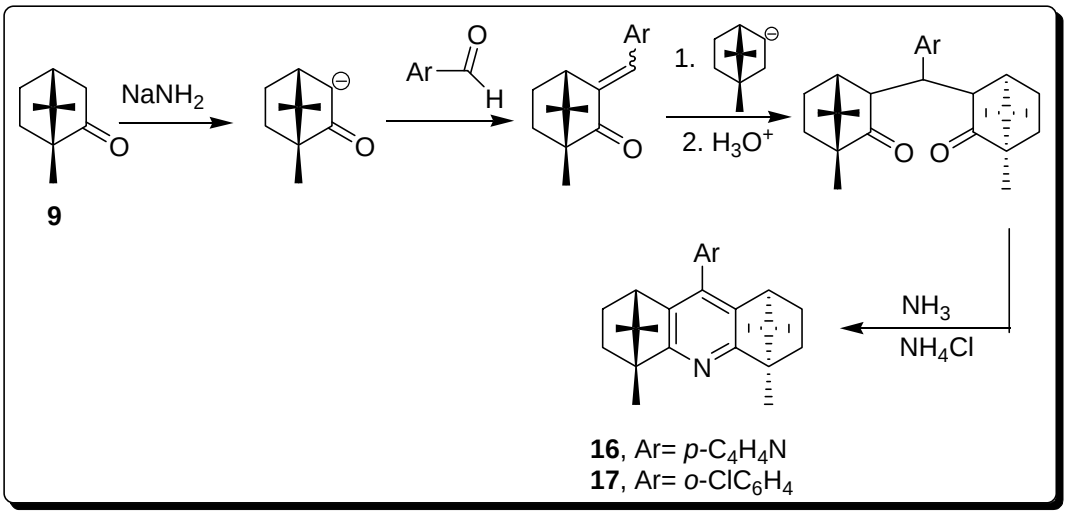
In the other synthetic route, towards chiral pyridine **15,** camphor *N,N*-dimethylhydrazone **13** was deprotonated with butyllithium and subsequently alkylated at -78 ºC with 2-(2-bromoethyl)-1,3-dioxolane **14** in good yield. Heating this compound in carbitol in the presence of one drop of hydrochloric acid resulted in a clean conversion in to the tetrahydroquinoline (camphor-based chiral pyridine) **15** that could be isolated in pure form.

It is well seen from the Scheme 2 that synthesis of target compounds **12** and **15** were accomplished with at least three steps and the overall yields are not satisfactory. In spite of these low chemical yields, this achievement was perceived even very impressive since a rather hindered substrate is involved.



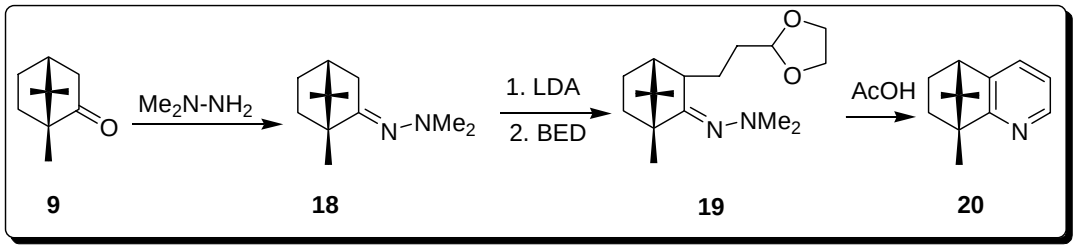
Scheme 2

One year after publication of previous work, Sotiropoulos et al. published another synthetic method to prepare camphor-based chiral pyridines **16** and **17** from (+)-camphor **9** (Scheme 3).[20]



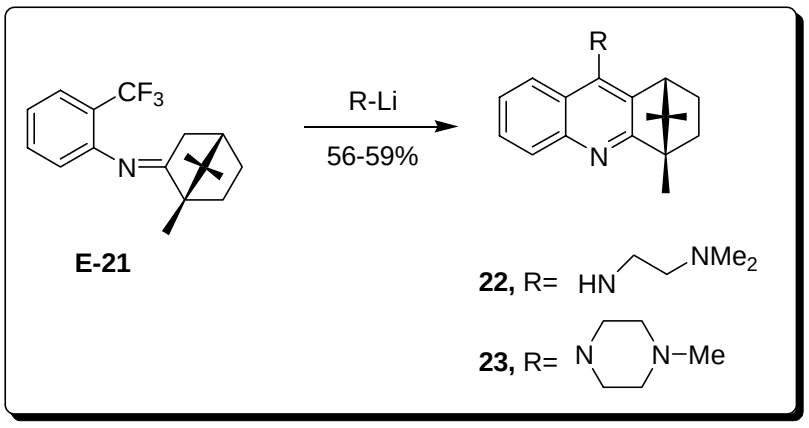
Scheme 3

In 1988, Gladiali et al. achieved a three step pyridoannelation of (+)-camphor **9** with a new method.[19] This new method relies upon a three step reaction sequence involving alkylation of the *N,N*-dimethylhdrazone (DMH) **18** of (+)-camphor **9** with 2-(2-bromoethyl)-1,3-dioxalane (BED) followed by acid catalyzed cyclization of the iminoacetal **19** to form optically active pyridine **20** with 55% chemical yield based on the yield from **18** (Scheme 4). This new method useful not only for the synthesis of chiral camphor-based pyridines but also for the synthesis of both 2- and 3-monoalkyl- as well as 2,3-dialkylpyridines, the final product being dependent only on the structure of the carbonyl substrate. This valuable feature is a direct consequence of the regiospecificity displayed by *N,N*-dimethylhdrazones (DMH's) in the alkylation step where unsymmetrical ketones DMH's are alkylated exclusively at the less substituted carbon.



Scheme 4

A stable ketimine[22] **E-21** derived from (+)-camphor **9** was cyclized to bornane-fused quinolines **22** and **23**, which can be considered as camphore-based chiral pyridines, in high yields (56-59%) by Strekowski et al. in 1992 (Scheme 5).[23] With enantiomerically pure (+)-camphor **9** the absolute values of specific rotations were virtually identical for all pairs of enantiomers of **21-23** and were not affected by changes in conditions of the reactions. These results strongly suggest that both the condensation and cyclization-reactions occur without any racemization.[23]



Scheme 5

Following the previous work, another work on camphore-based chiral pyridines has been published in 1995 by Love and Ren.[24] In this work a number of chiral quinolines **24a-e** fused to the camphor skeleton have been prapared (Figure 4)

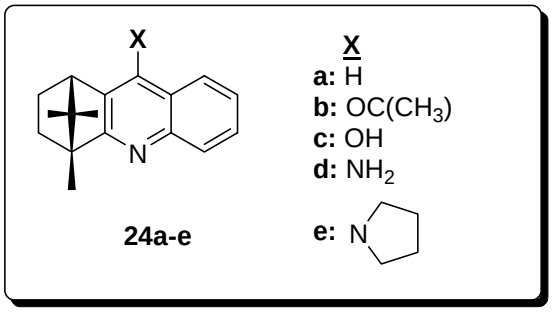
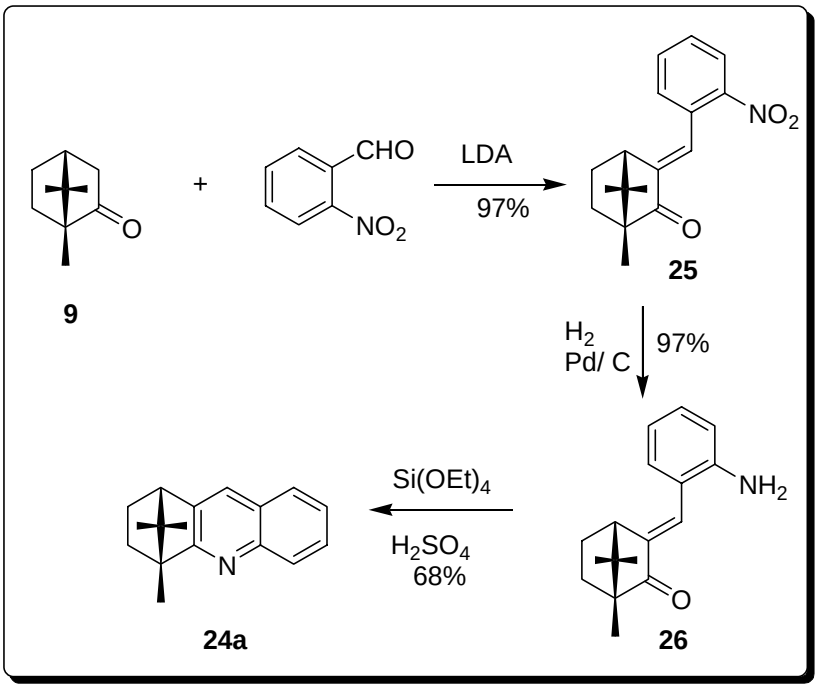


Figure 4: Derivatives of chiral quinolines **24a-e**

Quinoline **24a** was prepared by condensing (+)-camphor **9** with *o*-nitrobenzaldehyde to yield **25** (Scheme 6). Only one geometric isomer was observed, which is known to be the E isomer shown.[25] The nitro group in **25** was reduced by catalytic hydrogenation to give primary amine **26**. Previously they have shown that camphor imines can be prepared in high yield by reacting camphor with primary amines in the presence of tetraethyl orthosilicate and a catalytic amount of H_2SO_4,[26] and these conditions were used to convert **26** into **24a**.



Scheme 6

The conversion of **26** to **24a** is remarkable though, in that it requires isomerization of **26** to the less substituted *Z* isomer before cyclization. They have proposed a mechanism to explain how that isomerization takes place (Figure 5).

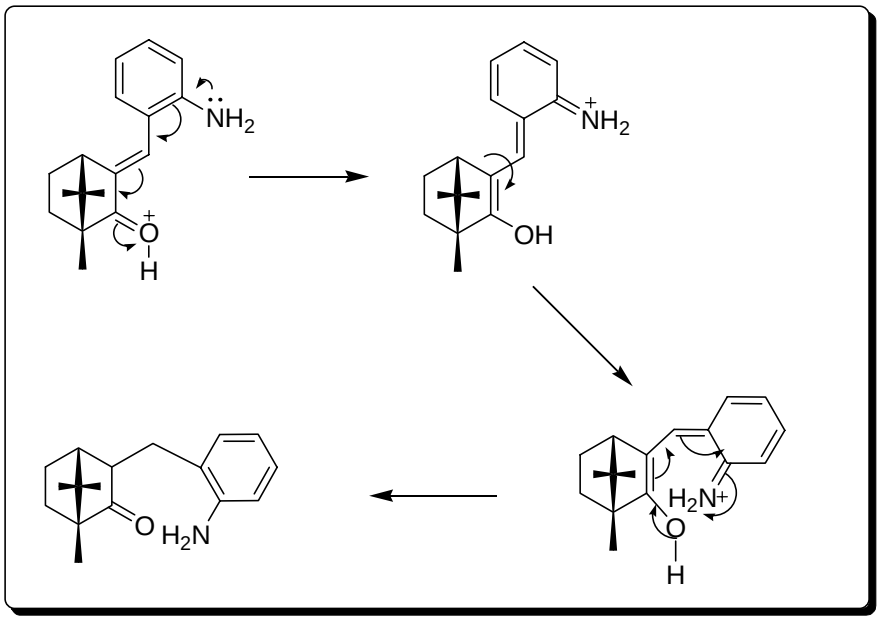
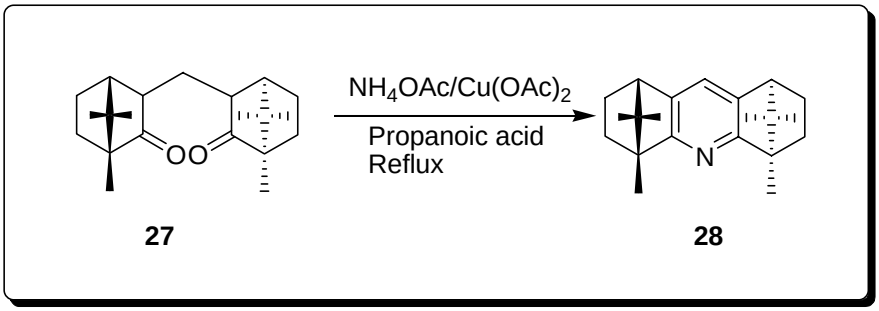


Figure 5: Proposed a mechanism for isomerization

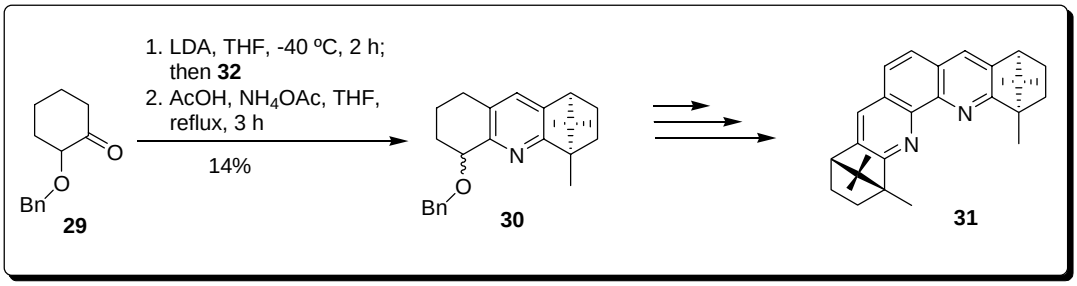
Another work on the synthesis of the camphor-based chiral pyridines published by Shiro et al. in 2000.[27] They have achieved the synthesis of highly sterically hindered C_2-symmetric chiral pyridine **27** from camphor-derived 1,5-diketone **28** by the action of $NH_4OAc/Cu(OAc)_2$ in refluxing propionic acid (Scheme 7).



Scheme 7

The reaction of (+)-camphor with *N,N*-dimethylformamide (DMF) in the presence of potassium hydride stereoselectively gave bis[1R,3S,4R)-2-oxo-3-bornyl]methane **27**.

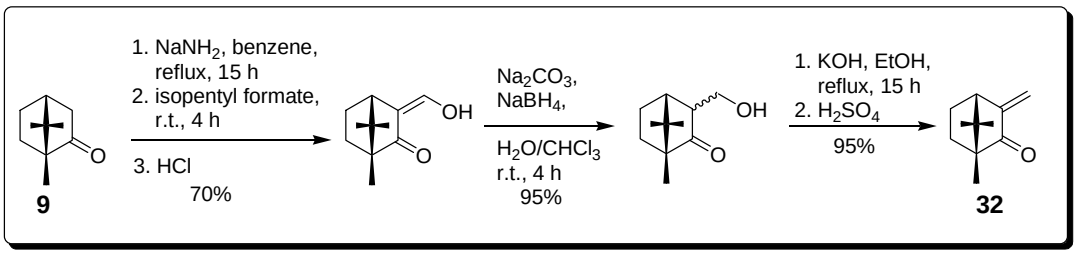
Recently, G. Chelucci et al. have been published a paper for the synthesis of chiral C_2-symmetric 1,10-phenanthrolines from naturally occurring monoterpenes such as (–)-β-pinene, (+)-α-pinene, (–)-isopinocampheol, and (+)-camphor (Scheme 8).[28] In the context of nitrogen based ligands,[10] there has been considerable work involving the synthesis and application of chiral 1,10-phenanthrolines[11] (phens) in asymmetric catalysis. The studies were, however, limited to C_1-symmetric derivatives owing to the difficulties associated with the preparation of the C_2-symmetric counterpart. In fact, only one example of this kind of phens has been reported and used in asymmetric catalysis.[29]



Scheme 8

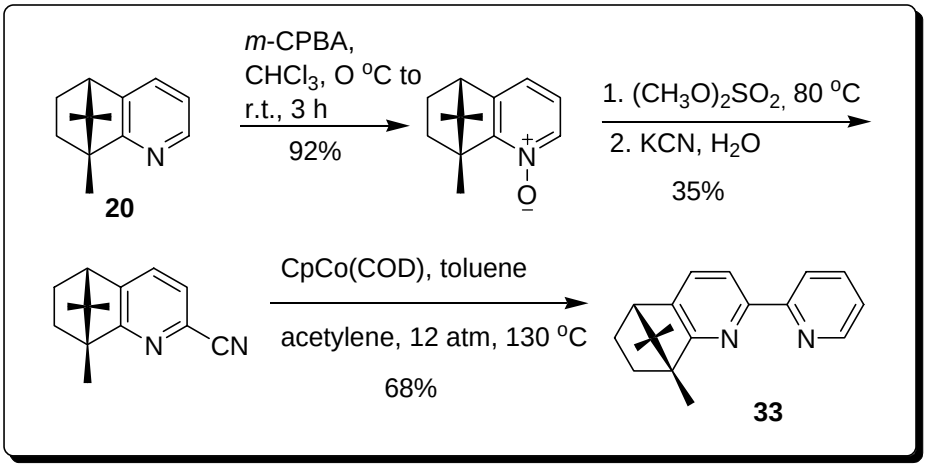
The lithium enolate of 2-benzyloxycyclohexanone **29** (LDA, one equivalent, THF, –40°C, 2h) was treated with (+)-1,7,7-trimethyl-3-methylenebicyclo[2.2.1]heptan-2-one **32** to give a 1,5-dicarbonyl intermediate by conjugate addition, which was not isolated. This intermediate underwent azaanulation-aromatization in the usual way to afford the chiral pyridine **30**, which were used as an intermediate product for the synthesis of chiral C_2-symmetric 1,10-phenanthroline **31** within several steps.

Compound **32** was derived from (+)-camphor **9** with three steps with the 63% overall yield (Scheme 9).



Scheme 9

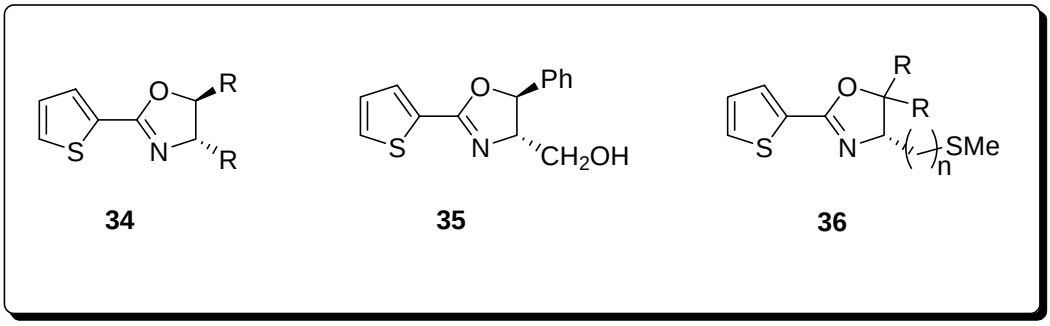
It is also reported in the literature that camphor-based chiral pyridines are valuable starting materials for the synthesis of chiral 2,2'-bipyridines (Scheme 10). In scheme 10, the synthesis of bpy **33** in which the chiral auxiliary, (+)-camphor is present in the form of cycloalkeno-condensed substituent is outlined .[11]



Scheme 10

1.3.2. Literature Synthesis of Camphor-based Chiral Thienylpyridines

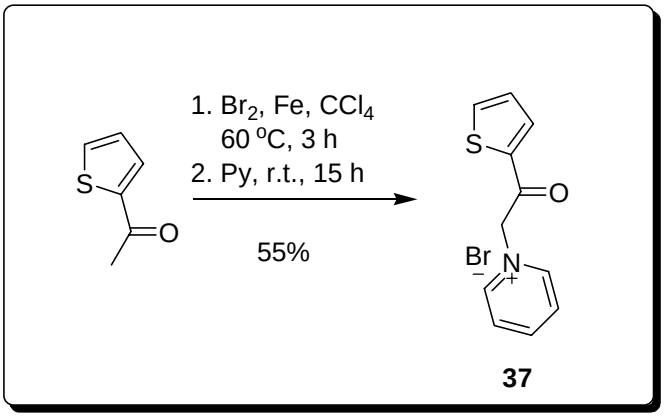
Although thiophene is known to form complexes with a variety of metals,[30] few attempts have been made to employ chiral thiophene derivatives as ligands for asymmetric catalysis. The most representative examples are those in which the thiophene sulphur is one of the donor atoms in bidentate or terdentate ligands such as thienyloxazolines **34**–**36** (Figure 6).[31-33]



34 **35** **36**

Figure 6: The most representative examples of thienyloxazolines **34**–**36**

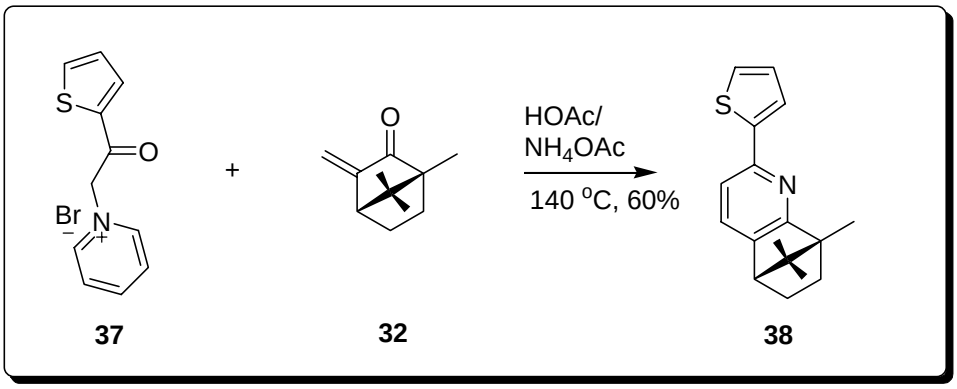
Recently, it has been described an effective procedure for obtaining chiral thienylpyridines from naturally occurring monoterpenes, making available a new class of chiral ligands by Zelewsky and Gianini (Scheme 11).[34] On treatment with ammonium acetate, α,β-unsaturated ketones can easly undergo condensation with acetylpyridinium salts, which is known as Kröhnke reaction. They prepared chiral thienylpyridine ligand choosing (+)-camphor as the chiral pool with the use of Kröhnke reaction (Scheme 11 and Scheme 12).



Scheme 11

Scheme 11 shows the synthesis of (2-thienylacetyl)pyridinium bromide **37**. The first step, bromination of 2-acetylthiophene, was performed by following a modified method of Kipnis.[35] For reasons of instability, 2-bromoacetylthiophene was not isolated but immediately transformed into the pyridinium salt **37** by the addition of pyridine.

Scheme 12 illustrates the synthetic method to obtain ligand **38**. It is well seen from the Scheme 12 that the ligand **38** was formed by condensation of salt **37** with **32** (the synthetic route is same as in Scheme 9) in an acetic acid/ammonium acetate solution.



Scheme 12

1.3.3. Camphor-based Chiral Thienylpyridines as *N*-*S* Lidands for Asymmetric Catalysis

Since it has been recently reported an effective procedure for the synthesis of chiral thienylpyridines from naturally occurring monoterpenes,[34] Chelucci et al. have been intrigued to explore their potentiality as chiral controllers for asymmetric catalysis.[36] In that work, they have reported the synthesis of some new chiral thienylpyridines and the results obtained with this kind of ligands in two reactions frequently investigated as a probe for the effectiveness of new ligands, namely, the palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[37,38] and the copper-catalyzed cyclopropanation of styrene with ethyl diazoacetate.[39]

1.3.3.1. Palladium-Catalyzed Allylic Alkylation

Enantioselective reactions based on palladium-catalyzed allylic substitutions are currently an actively pursued research area.[37,38] In contrast to the great variety of ligands based on the pyridine framework, which have proven to give very good levels of enantioselectivity in the catalyzed asymmetric C–C bond forming reactions with allylic compounds,[10] rare examples of application in this reaction of sulphur-containing pyridine ligands have been reported.[40-43] In order to define the scope and limitations of thienylpyridines as chiral controllers for asymmetric catalysis, Chelucci et al. have first examined these *N–S* ligands in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enylacetate with dimethyl malonate, which serve as a model substrate and reagent to compare the outcome of different ligands(Figure 7).[36]

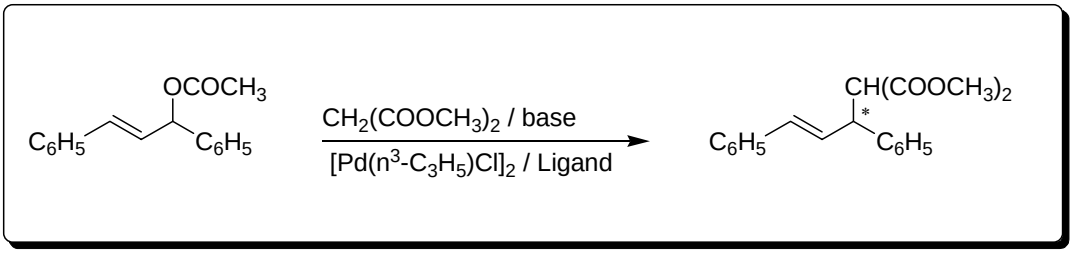


Figure 7: Enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enylacetate with dimethyl malonate

Allylic substitution of *rac*-1,3-diphenylprop-2-enylacetate was initially performed in CH_2Cl_2 at temperature in the presence of (π-allyl)palladiumligand complex generated in situ from 2.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 10 mol% of the appropriate thienylpyridine ligands. Under these conditions, thienylpyridines

provided insufficiently reactive palladium catalysts affording only a very low conversion of the starting material (5–10%).

Though the protocol using the malonate anion obtained by Trost's procedure is generally the best way to carry out allylic substitution reactions, the use of preformed sodium dimethyl malonate, generated by the use of sodium hydride in THF, may in some cases offer best results.[45] Therefore, thienylpyridine ligands were employed to test the effectiveness of this procedure. Also under these conditions the reaction failed at room temperature, but partial conversion (53%) occurred after 4 days at reflux temperature. However, the reaction was not enantioselective. The results obtained with thienylpyridines were rather disappointed in account of the satisfactory catalytic activity and good levels of asymmetric induction imparted in the palladium catalysed allylic substitution reaction by the related thienyloxazoline ligand **34** (shown in Figure 6).[31]

They were wondering whether the unexpected results could be ascribed to the possibility that the thienylpyridine behaves as a monodentate ligand binding to the palladium by the pyridine-*N* (in this case two molecules bind to the palladium by the pyridine-*N*) rather than as a bidentate ligand by the thiophene-*S* and pyridine-*N*.

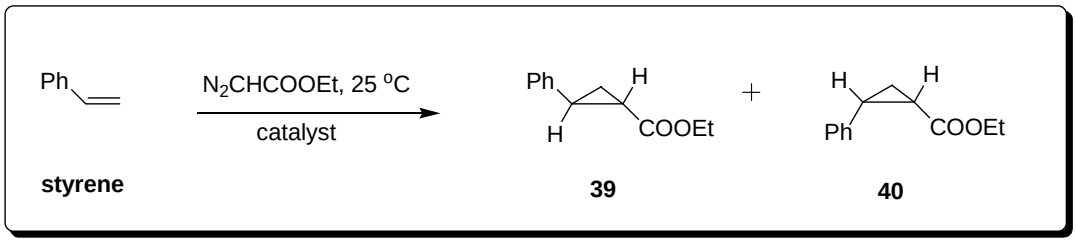
In order to obtain some information about the structure of the cationic palladium(II)-thienylpyridine complex, they tried to crystallize the complex for X-ray analysis but all attempts to crystallize it failed. Then structural assignment of the complex was performed by ^{1}H and ^{13}C NMR analysis. Integration of the ^{1}H NMR spectrum indicated that there is one thienylpyridine molecule per allylpalladium complex fragment. Also the ^{1}H NMR spectrum of the complex showed that the resonances of both the pyridine and thiophene protons are shifted downfield with respect to those of the thienylpyridine itself. Coordination of the sp^2-hybridized

electrons pair of the pyridine-*N* and thiophene-*S* causes a reduction of charge density on both the heterocycles determining the down field shift of ^{1}H NMR signals.

Though these observations are consistent with a structure for the intermediate π-allyl palladium complex in which both pyridine and thiophene are coordinated to the palladium, at present the reasons why these ligands do not work in this catalytic process are obscure.

1.3.3.2. Copper-Catalyzed Cyclopropanation

Again Chelucci et. al. performed this reaction in the article mentioned above.[36] To evaluate the efficiency of these thienylpyridine ligands in the copper-catalyzed asymmetric cyclopropanation, they first examined the cyclopropanation of styrene using copper(II)-thienylpyridine catalysts prepared in situ from copper(II) triflate and the proper ligand.



Scheme 13

The copper(II)-thienylpyridine complexes exhibited high efficiency and afforded the *trans*- and *cis*-cyclopropanes **39** and **40** in good yields (83–93%). These diastereomeric cyclopropanes were however obtained with low *trans*:*cis* diastereoselectivity (about 65:35) and they did not show significant enantioexcesses (3–8%). Then, assessed thienylpyridines in the copper(I)-catalyzed asymmetric cyclopropanation of styrene (Scheme 13).

As a result, these two reaction types in that paper showed that the thienylpyridines are poorly suitable catalysts for the enantioselective palladium-catalyzed allylic substitution. On the contrary, these ligands are good catalysts for the Cu-catalyzed cyclopropanation of styrene giving high yield of cyclopropanes though with low enantioexcesses.

1.4. Aim of the work

Chiral aromatic nitrogen heterocycles are finding many applications in asymmetric organic synthesis, particularly as ligands in the preparation of chiral metal complexes.[10,11] Since camphor-based chiral auxiliaries are known to be especially effective,[15] a number of pyridines fused to the camphor skeleton have been reported.[16-25]

In camphor-based chiral pyridines, the bicyclic bridged system adds a further constraint to the aliphatic portion of the molecule and this is expected to result in a higher stereodifferentiating ability of the chiral ligands derived from these pyridines.[17] However, due to bridge methyl group of camphor, usually the synthesis becomes a hard task producing low chemical yields and so many steps for the synthesis of these chiral pyridines. These compounds are also the most convenient starting products for the synthesis of the corresponding optically active 2.2'-bipyridines, a new class of chiral ligands for asymmetric reactions.[18]

Additionally, pyridines came to prominence in the 1930s with the recognition of the importance of niacin (nicotinamide) **1** for the prevention of dermatitis and dementia. It is also well known that nicotinic acid and its derivatives exhibiting

qualitatively the biological activity of nicotinamide, which acts as an electron acceptor in many biological redox reactions.[1,6,7]

Natural (+)-camphore is known to be used in the manufacture of cellulose nitrate, polyvinyl chloride, plastics and also serves as medicine, antiseptic, insecticide, etc.

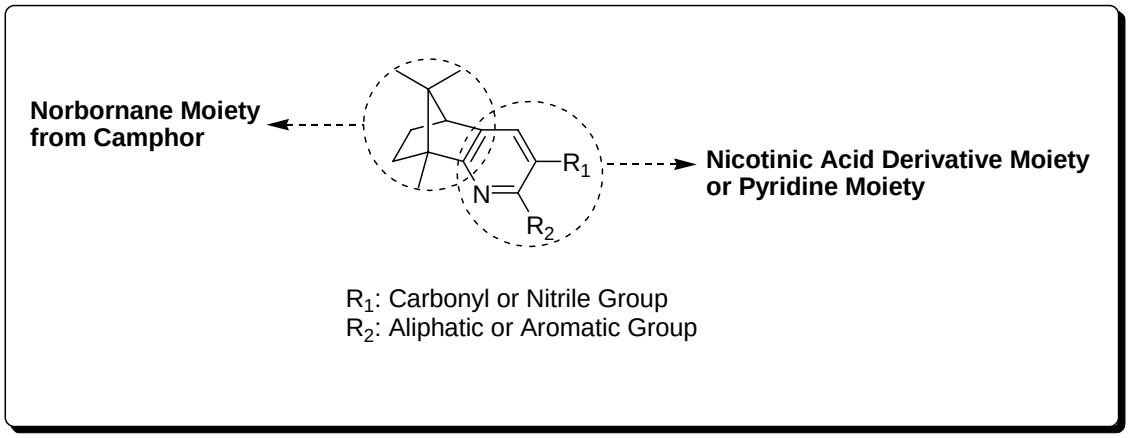
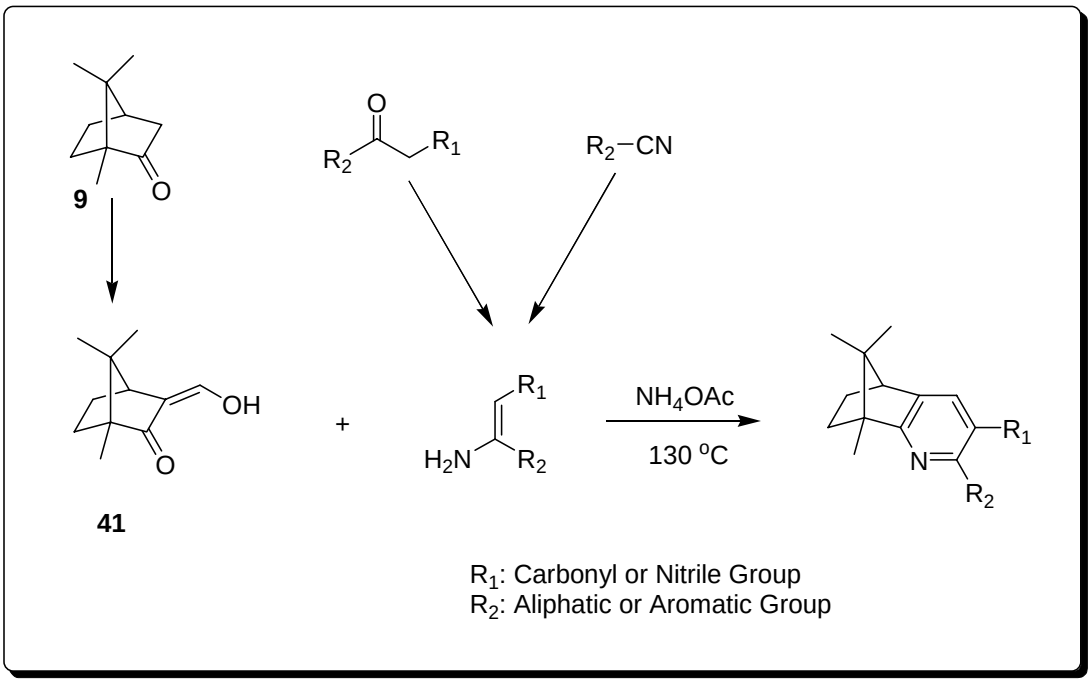


Figure 8: General example for a camphor-based chiral pyridine

A brief survey of the literature given above revealed that camhor-based chiral pyridines finds interest as nitrogen-containing ligands since they have pyridine unit which forms stable comlexes with transition metals very well and can be considered as potent biologically active compounds, since they contain both camphor unit and nicotinic acid moiety (Figure 8).

Factors outlined above drew our attention and encouraged us for the short and facile synthesis of camphor-based chiral pyridines. Natural (+)-camphor **9** was chosen as the chiral pool since it is easily available and cheap. Natural (+)-camphor was planed to react with ethyl formate to form (+)-β-hydroxymethylenecamphor **41**

which have two reactive sides (β-dicarbonyl compound) for the construction of pyridine ring. In order to construct the pyridine ring on camphor moiety we planed to prepare enamines derived from active methylene compounds and react them with (+)-β-hydroxymethylenecamphor **41**. Here we report our results obtained from the annulation of (+)-β-hydroxymethylenecamphor **41** with various enamines derived from active methylene compounds with 10% mol of NH_4OAc (Scheme 14).



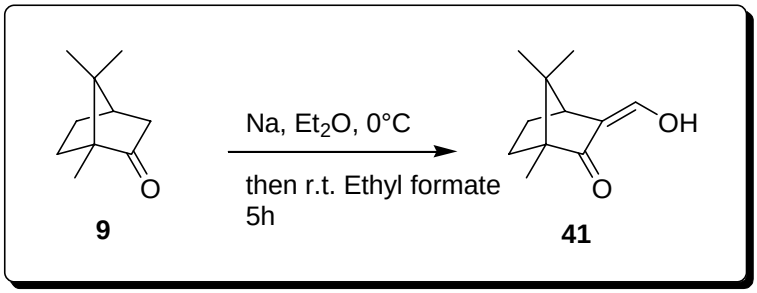
Scheme 14

CHAPTER II

RESULTS AND DISCUSSION

2.1. Synthesis of (+)-β-Hydroxymethylenecamphor (41)

(+)-β-hydroxymethylenecamphor **41** was chosen as the feasible chiral pool since it was readily assembled from (+)-camphor **9**. In our synthetic approach, hydroxymethylene unit was anchored to the host camphor system by a modified procedure given in the literature (Scheme 14).[46,47] In this procedure, one equivalent (+)-camphor **9** dissolved in dry ether is added to stirring mixture of one equivalent of Na in dry ether at 0 °C. After stirring vigorously for 30 min., ethyl formate is added dropwise at room temperature and resulting mixture stirred for 5 hours. At the end of the reaction, work-up is done. Product **41** was obtained in 30% yield as a white solid without any further purification.



Scheme 15

2.1.1. Characterization of (+)-β-hydroxymethylenecamphor (41)

The structure elucidation of (+)-β-hydroxymethylenecamphor **41**, was done by ^{1}H NMR and ^{13}C NMR spectroscopy.

In figure 10, ^{1}H NMR of (+)-β-hydroxymethylenecamphor **43** is seen. The complexity of the spectrum results from the keto-enol tautomers of the product (Figure 9). The structure of compound **41** has been studied before and it is stated that the product has three tautomers contributing to its structure.[46,47] The presence of the intense olefinic signal at 6.70 ppm strongly supports that the compound is mainly in the form of enol as drawn throughout this work.

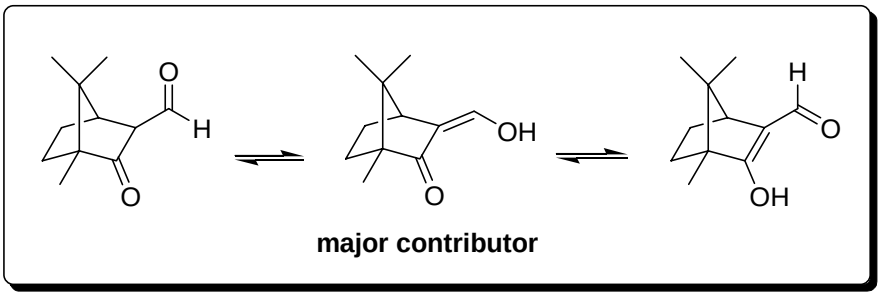


Figure 9: Tautomeric forms of (+)-β-hydroxymethylenecamphor **41**

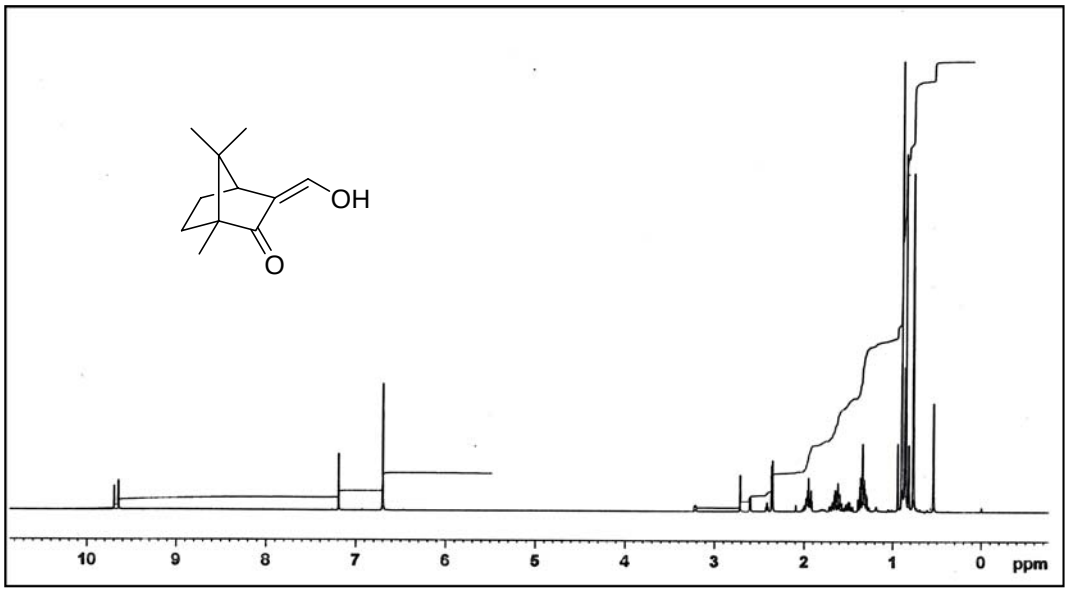


Figure 10: ^{1}H NMR spectrum of (+)-β-hydroxymethylenecamphor **41**

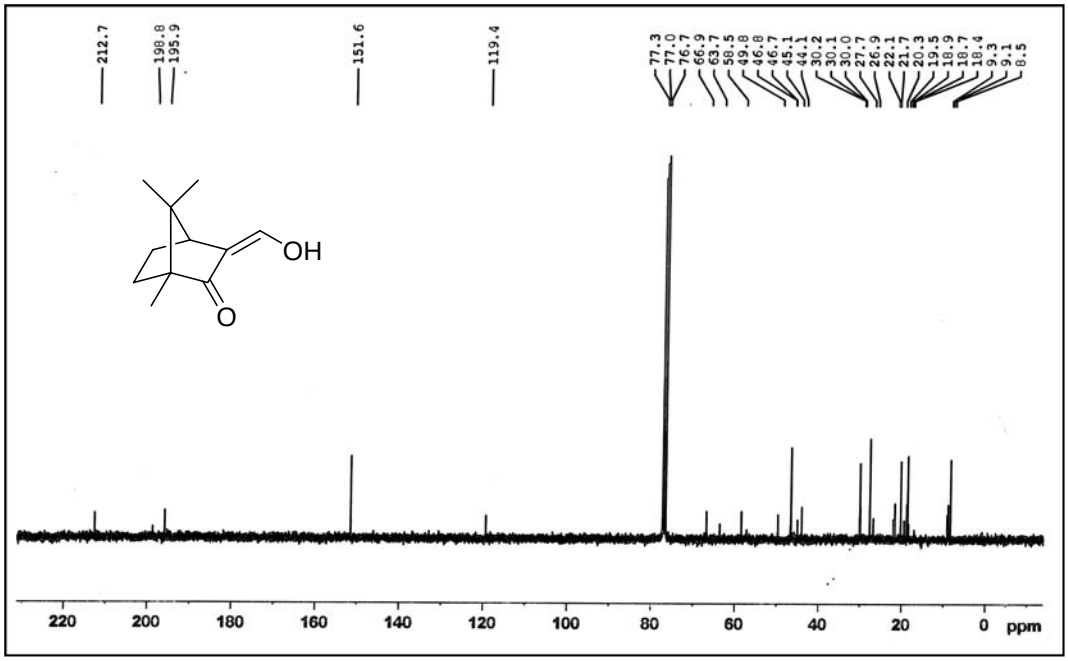


Figure 11: ^{13}C NMR spectrum of (+)-β-hydroxymethylenecamphor **41**

^{13}C NMR spectrum of (+)-β-hydroxymethylenecamphor **41** is shown in figure 11. It must give thirty three carbon peaks since each tautomer must contribute 11 peaks to the spectrum. However we see 28 peaks in the spectrum,

which means that some carbon peaks coincides or olefinic carbons of low degree tautomers does not appear.

2.2. Synthesis of Enamines

Enamines were prepared from the corresponding active methylene compounds using literature procedure.[48,49] Synthesis of enamines can be grouped into two routes according to their starting materials as:

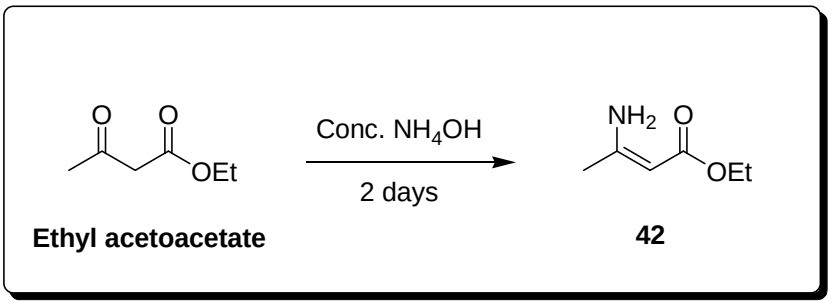
- Synthesis of enamines having carbonyl moiety
- Synthesis of enamines having nitrile moiety.

2.2.1. Synthesis of enamines having carbonyl moiety

Starting materials for the enamines having carbonyl moiety was synthesized from their corresponding β-dicarbonyl compounds.

2.2.1.1. Synthesis and characterization of ethyl 3-aminocrotonate 42

For the synthesis ethyl 3-aminocrotonate **42**, procedure given in the work of Miller[48] in 1984 was used. We used column chromatography instead vacuum distillation and got the same yield as reported in the article. Ethyl acetoacetate was choosen as the starting material. Scheme 16 shows the reaction to obtain the product **42**.



Scheme 16

When 250 mL of concentrated ammonium hydroxide was added to ethyl acetoacetate (0,5 mole) at room temperature, a solid immediately formed in a mildly exothermic reaction. The reaction mixture was allowed to stand for 2 days and then dissolved in chloroform and washed with water. After drying organic phase on $MgSO_4$, the solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to yield 90 % pale yellow solid **42** .

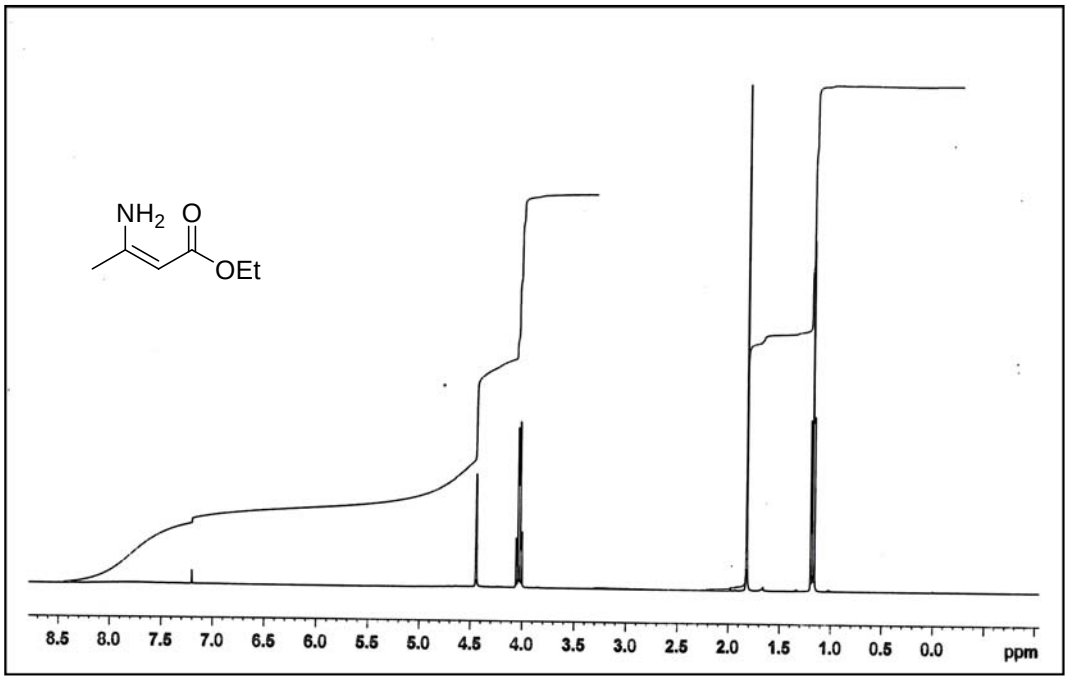


Figure 12: ^{1}H NMR spectrum of ethyl 3-aminocrotonate **42**

The ^{1}H NMR spectrum of ethyl 3-aminocrotonate **42** is seen in figure 11. Methyl protons of -OEt appear at 1.18 ppm as a triplet with the coupling constant, *J*= 7.1 Hz. Methylene group of -OEt appears as quartet at 4.04 ppm with the coupling constant, *J*= 7.1. Methyl group attached to C=C double bond resonates at 1.82 ppm as a singlet. The singlet exhibited at 4.45 ppm is arising from olefinic proton. Coming to the protons of amine, we see two broad signals at different frequencies. This is the evidence for the intramolecular hydrogen bonding between one of amine proton with the carbonyl oxygen. The one in H-bonding is shielded strongly to downfield appearing at arround 7.80 ppm as a very broad signal. The other N-H proton was observed at 4.48 ppm again as a very broad signal.

The observation of H-bonding in compound **42** proves that the product is in *cis*-geometry (*Z*). mp: 33-35 °C.

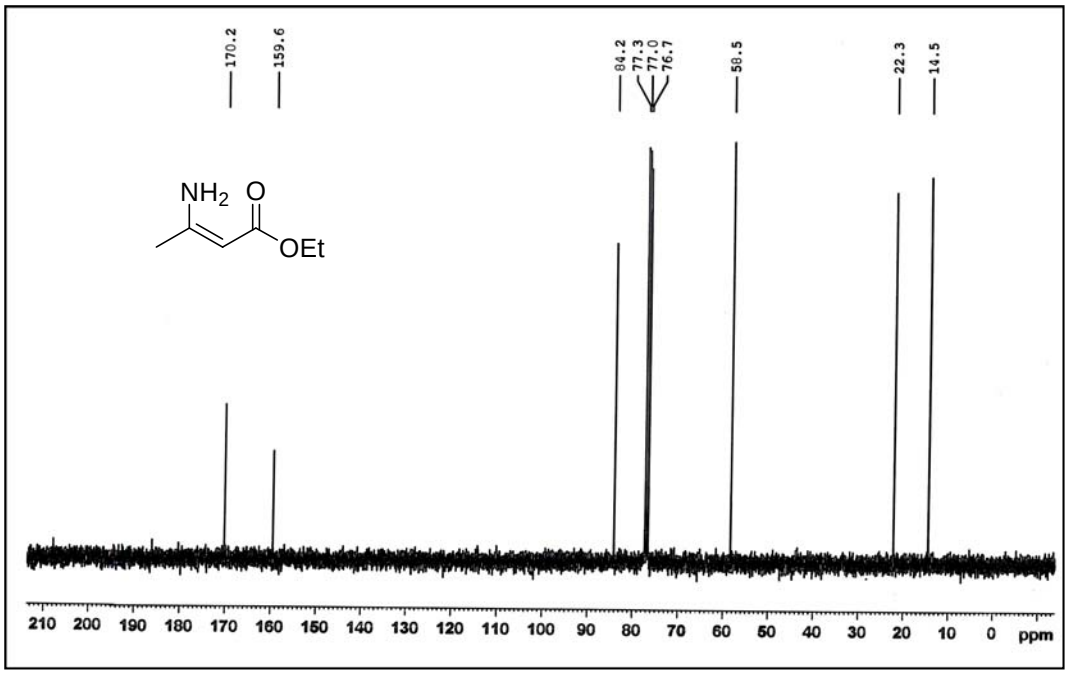
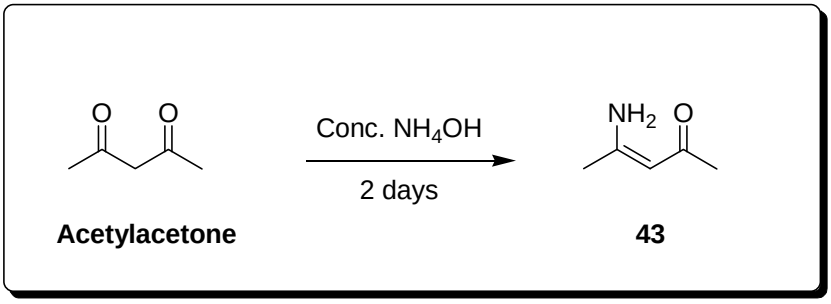


Figure 13: ^{13}C NMR spectrum of ethyl 3-aminocrotonate **42**

In figure 13, ^{13}C NMR spectrum of ethyl 3-aminocrotonate **42** is seen. The spectrum is consistent with the structure of the molecule. There are six carbons appearing in the spectrum. Carbonyl carbon appears at 172.2 ppm. Olefinic carbon bearing -NH_2 group resonates at 159.6 ppm, whereas the other olefinic carbon atom appears at 84.2 ppm as expected. Methylene carbon appears at 58.5 ppm due to electronegativity of oxygen. Methyl group of -OEt and that of bearing olefin comes at 22.3 ppm and 14.5 ppm.

2.2.1.2. Synthesis and characterization of (Z)-4-aminopent-3-en-2-one (Fluoral-P) 43

The same methodology was used in the synthesis of (Z)-4-aminopent-3-en-2-one (Fluoral-P) **43**. The starting material is an easily available material, acetylacetone, a widely used β-dicarbonyl.

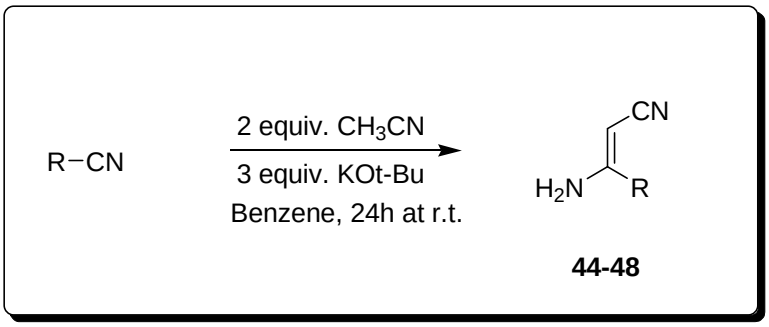


Scheme 17

When the reaction was carried out, the product, Fluoral-P **43** was obtained with the 70 % chemical yield as a pale yellow solid. mp: 37-43 °C (Scheme 17).

2.2.2. Synthesis of enamines having nitrile moiety

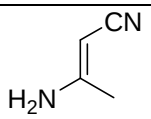
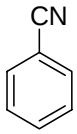
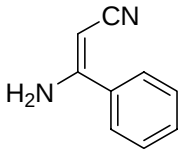
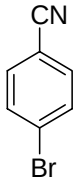
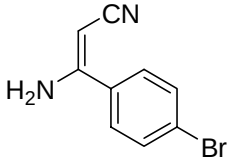
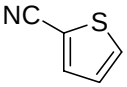
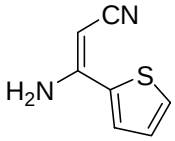
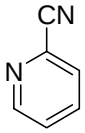
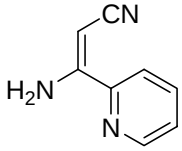
We have synthesized all enamines having nitrile group according to the literature procedure given (Scheme 18).[49]



Scheme 18

Reaction proceeds via the removal of active methyl protons of acetonitrile, consequently created carbanion attacks the nitrile group of aliphatic or aryl nitrile. To prevent self-condensation of acetonitrile, potassium tert-butoxide is used one equivalent excess. We have synthesized enaminonitriles **44** to **48** with this method in high yields. For the characterization of these enamines we benefited from their ^{1}H NMR and ^{13}C NMR spectra shown in Appendix. In the structure elucidation by NMR spectroscopy, characteristic broad singlets of $–NH_2$ protons and olefinic protons resonating between 4-5 ppm were helpful to understand whether the product was formed or not at first glance. Enaminonitriles synthesized **44-48** are indicated in Table 1 with their chemical yields.

Table 1: Synthesized Enaminonitriles

Entry	R-CN	Product	% Yield
1	CH_3CN	 **44**	80
2		 **45**	98
3		 **46**	97
4		 **47**	98
5		 **48**	85

2.3. Cyclocondensation of (+)-β-Hydroxymethylenecamphor (41) with Various Enamines (42-48)

For more than a century, many diverse methods have been developed to synthesize pyridines with new substitution patterns arround the ring. The greatest access do diverse substitution naturally comes with disconnection of the ring into

a maximum number of fragments, which should be readily available for the method to be of general value. These methods are grouped according to the nature of the ring-disconnection, for example:

[5+1]

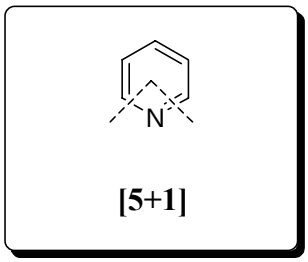


Figure 14: [5+1] ring-disconnection of pyridines

In figure 14, [5+1] ring-disconnection of pyridines is seen. [5+1] means that the ring can be divided into two parts, one with five ring atoms and the other with one ring atom.[1] Some of the most used ring-disconnections are seen in figure 15.

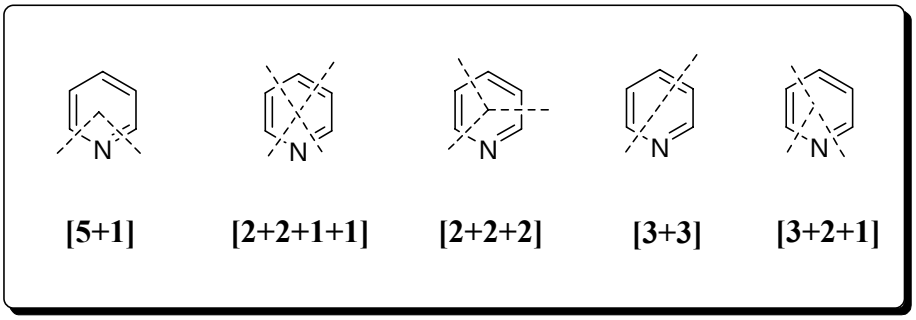


Figure 15: Some of the most used pyridine ring-disconnections

Probably the most famous ring-disconnection given in figure 15 is [2+2+1+1], the classical Hantzsch pyridine synthesis, first published by Hantzsch in 1882.[50] Symmetrical pyridines are normally generated via this method, by the interaction of ammonia, an aldehyde and 2 equiv. of a 1,3-dicarbonyl compound.

The ring-disconnection method we applied for the synthesis of camphor-based chiral pyridines is [3+3] one given in figure 15, since nitrogen atom and two carbons comes from various enamines and remaining three carbon unit from camphor moiety (Figure16).

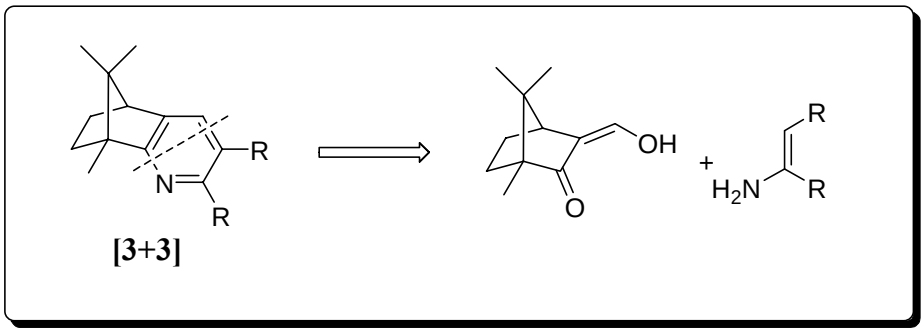
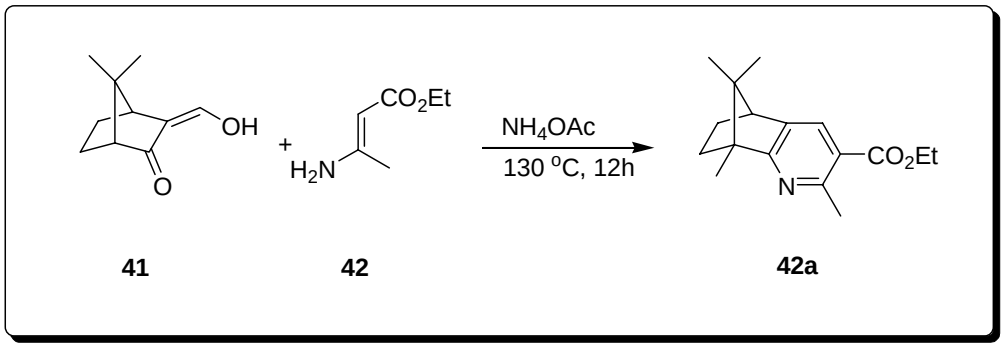


Figure 16: The ring-disconnection method we applied.

[3+3] ring-disconnection method is based on the reaction of 1,3-dicarbonyl compounds and 3-amino-enones or nitriles. This method one of the most versatile and useful, since it allows the construction of unsymmetrically substituted pyridines from relatively simple precursors (Figure16).

2.3.1. Synthesis of (*5S*,*8R*)-(+)-42a: Cyclocondensation of (+)-β-Hydroxymethylenecamphor (41) with Ethyl 3-aminocrotonate (42)

As a starting point, we studied the annulation reaction of (+)-β-hydroxymethylenecamphor **41** with ethyl 3-aminocrotonate **42** chosen as a model compound. Ethyl 3-aminocrotonate **42** reacted with the (+)-β-hydroxymethylenecamphor **41** efficiently, allowing the preparation of the desired chiral pyridine **42a** in good yield (Scheme 19).



Scheme 19

In the annulation reactions, the general procedure given below was applied: A mixture of (+)-β-hydroxymethylenecamphor **41** (360 mg, 2.00 mmol) and enamine **42** (439 mg, 3.40 mmol) containing a catalytic amount of ammonium acetate (10 mg, 0,13 mmol) was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated 12 h at 130 °C. The crude product was purified by flash column chromatography to afford 73% of (*5S,8R*)-(+)-**42a** (EtOAc/hexane, 1:6). When the same reaction was carried out in toluene used as solvent, the isolated yield of product **42a** was drastically decreased to 27%. Reason for the failure or low yield of the condensation reaction in toluene could be explained with the following two factors. First the annulation reaction may need high temperature (using toluene one can reach at most 115 ^{o}C, via refluxing) and the second reason could be the nonpolarity of the toluene compared with the polarities of the reactants.

Since it is known that (+)-β-hydroxymethylenecamphor **41** has three tautomeric form we expected two possible products. The reason is that the attack of lone pair electrons of nitrogen could attack both from ketone side or aldehyde side. Thus in our point of view, the annulation reaction could yield two possible products as **42a** and **42b** (Figure 17).

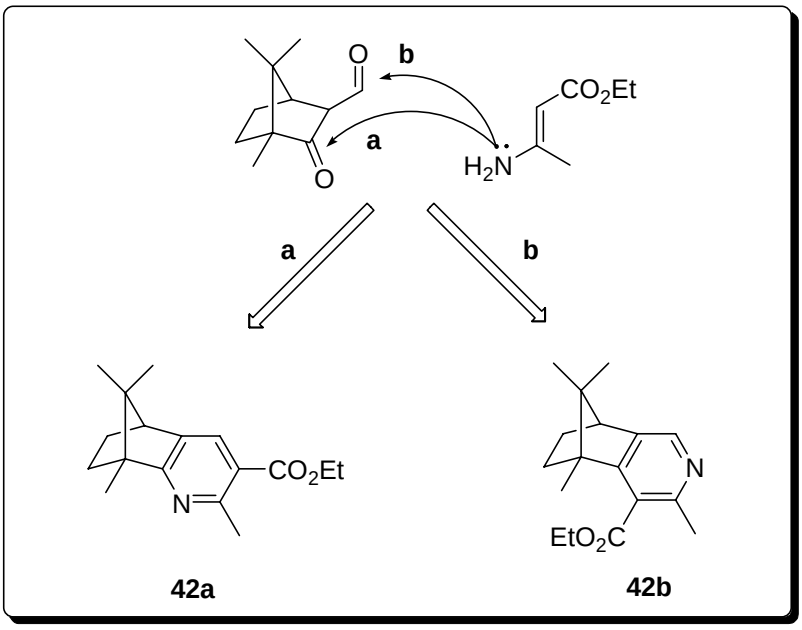


Figure 17: Possible products expected from annulation reaction.

It was seen from TLC monitoring that only one compound was formed! To clarify the structure of that product we first took its ^{1}H NMR (Figure 18) and ^{13}C NMR (Figure 19) spectra.

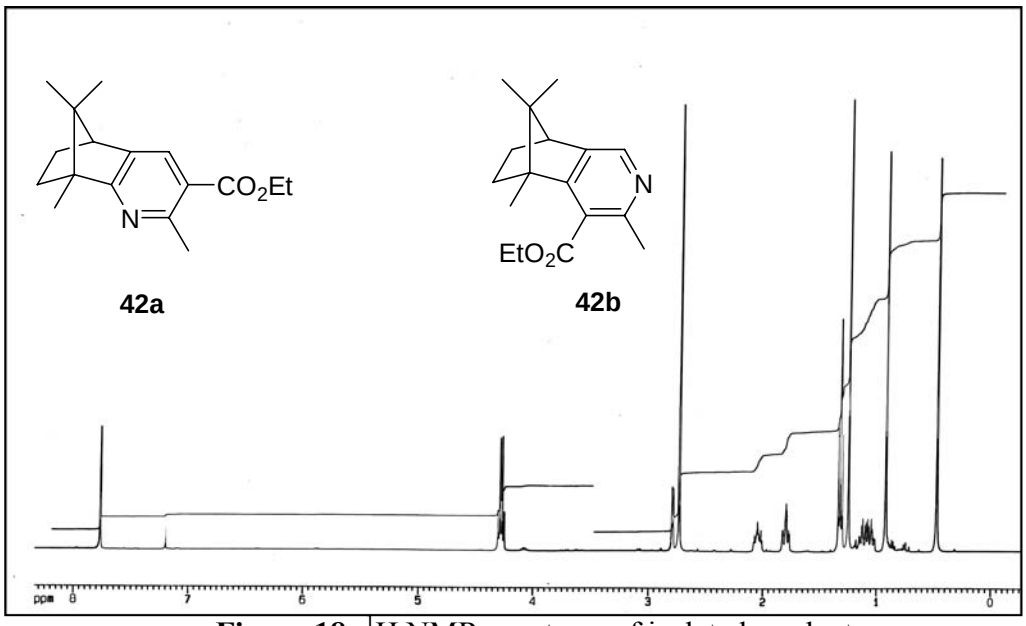


Figure 18: ^{1}H NMR spectrum of isolated product

From the ^{1}H NMR spectrum of isolated product, it is easily understood that the annulation reaction occured to form camphor-based chiral pyridine due to the presence of newly formed aromatic proton resonating at 7.77 ppm. The other evidences for aromatization are the absence of olefinic protons of both (+)-β-hydroxymethylenecamphor **41** and ethyl 3-aminocrotonate **42** whereas all other protons present in the structure of the product presumably shifted due to aromatization.

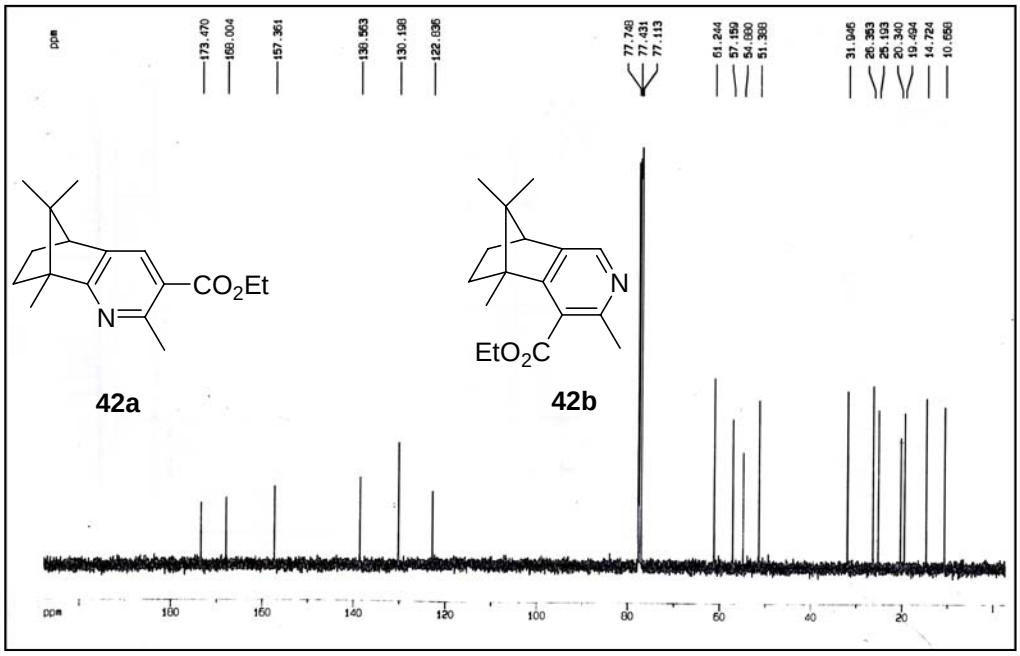


Figure 19: ^{13}C NMR spectrum of isolated product

Figure 19 shows that ^{13}C NMR spectrum of the isolated product consists of 17 carbon peaks as expected. It is proved also by ^{13}C NMR spectrum that the reactants transformed into chiral pyridine. However, we were not able to distinguish between those isomers **42a** or **42b** by analysing ^{1}H- and ^{13}C NMR. We needed more powerful tecniques (HMQC and HMBC) to make clear the structure of the isolated product.

The structure of the isolated product was elucidated with the help of HMQC (Figure 20) and HMBC (Figure 21) techniques.

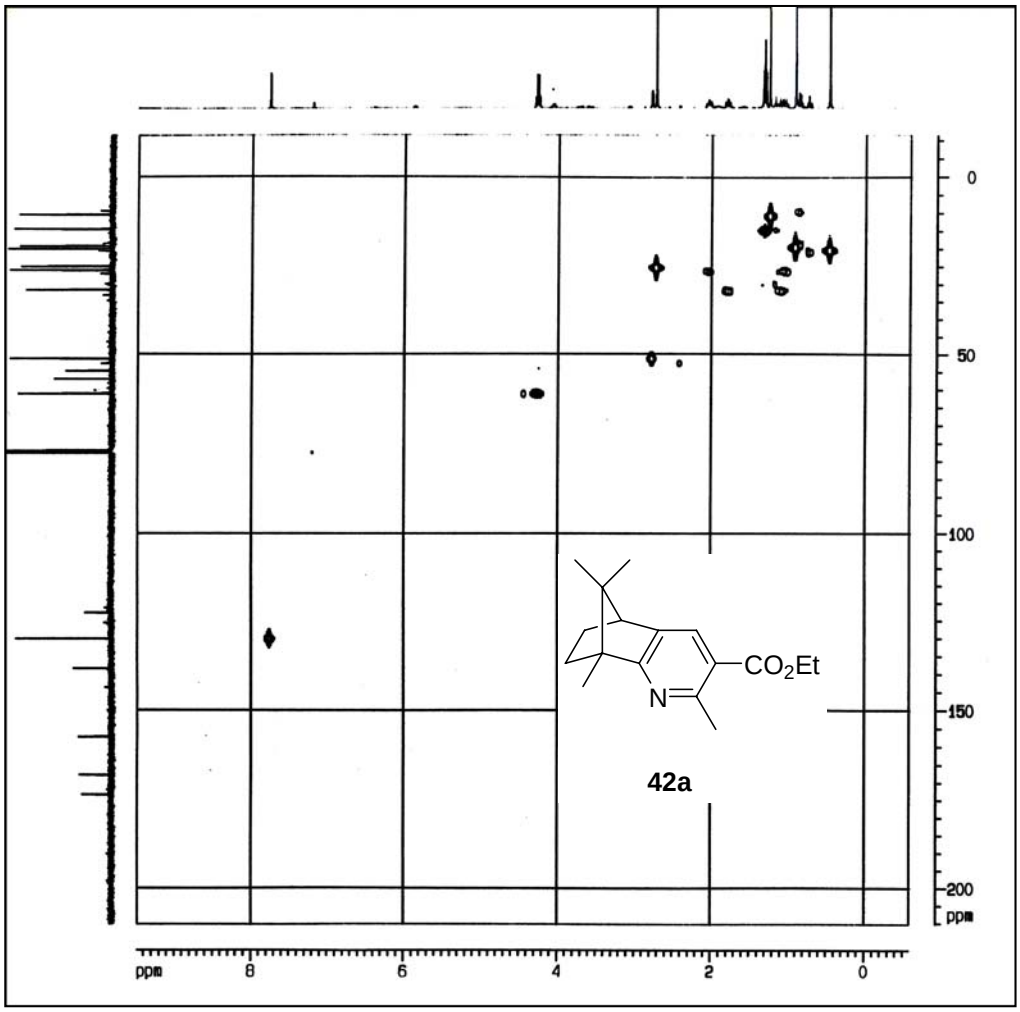


Figure 20: HMQC spectrum of isolated product (**42a**)

HMQC spectrum gives information about interaction of singly bonded H-C in a molecule. HMQC spectrum in Figure 20 showed that the aromatic proton resonating at 7.77 ppm is attached to aromatic carbon at 130.2 ppm. In HMBC spectrum (Figure 21), we observed the interaction of aromatic carbon at 130.2 ppm with bridgehead proton of norbornane moiety. Furthermore, the relation between the carbonyl carbon at 173.5 ppm and aromatic proton at 7.77 ppm

strongly supports the structure of product as **42a**. To be completely sure for the proposed structure, we have taken the mass spectrum (Figure 22) of the product, which was in accordance with the structure we proposed.

HRMS: calcd for $C_{17}H_{24}NO_2$ (M+H): 274.1807. Found $(M+H)^+$: 274.1802.

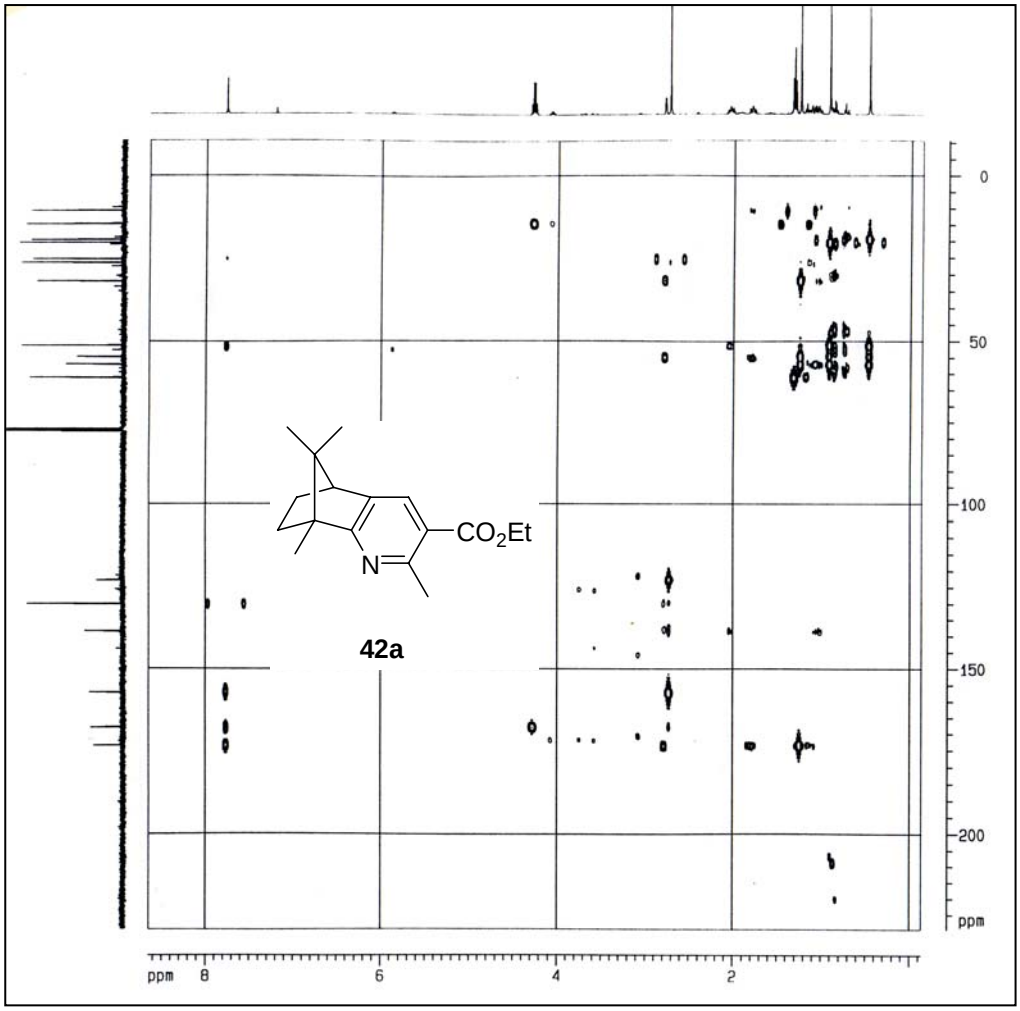


Figure 21: HMBC spectrum of isolated product (**42a**)

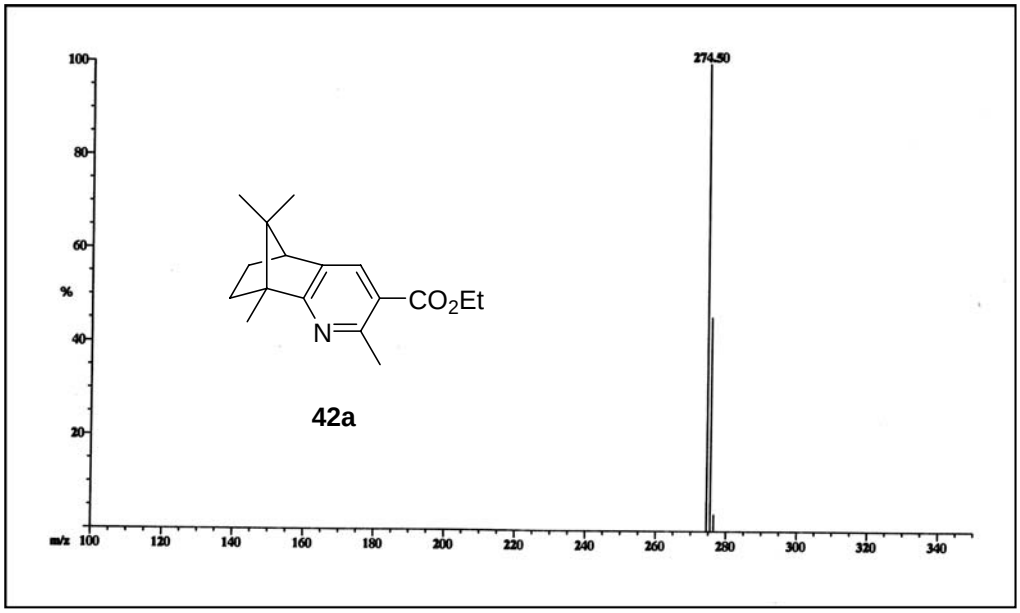


Figure 22: HRMS of isolated product (**42a**)

Optical rotation value of the product **42a** was measured in methanol ($[\alpha]^{20}_{D}$ = +48.2 (c, 0.93, MeOH)). The melting point of pale yellow product was found 71-73^{o}.

2.3.2. Derivatization: Cyclocondensation of (+)-β-Hydroxymethylenecamphor (41) withVarious Enamines (43-48)

As a natural extension of this study, we pursued a complementary investigation aimed at subjecting various enamines **43-48** to this reaction. Selected examples are listed in Table2.

In the synthesis of **43a** (this compound was previously numbered as **12** in the introduction par of this study**)** and **46a**, we isolated the uncyclized intermediates **43c** and **46c** (Figure 23). The isolation of these intermediates was the proof of the first step of the reaction mechanism we proposed in scheme 20.

As it is seen from Scheme 20, the first step is the attack of the lone pair electrons on nitrogen to the carbonyl group on camphor leading to the formation of imines **43c** and **46c**.

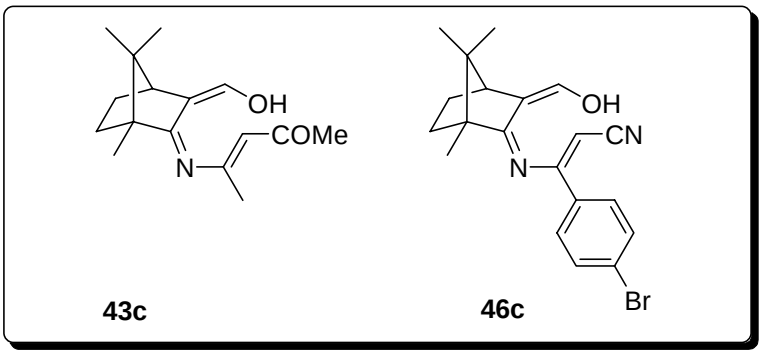
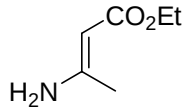
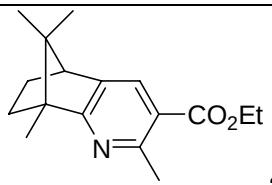
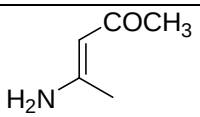
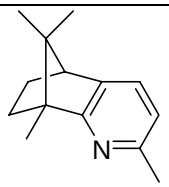
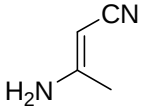
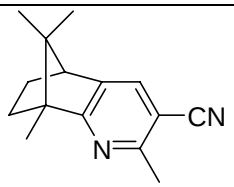
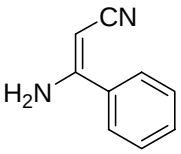
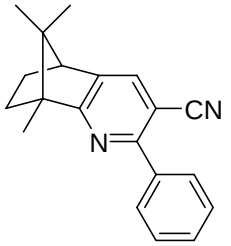
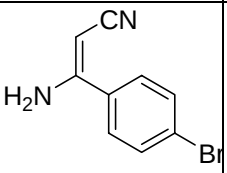
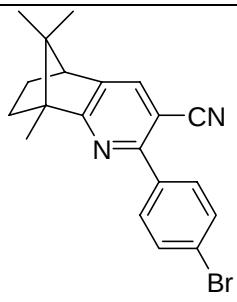
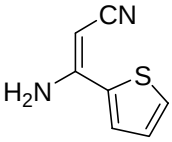
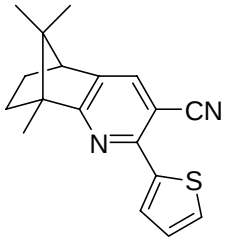
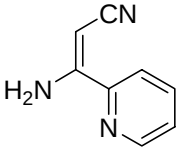
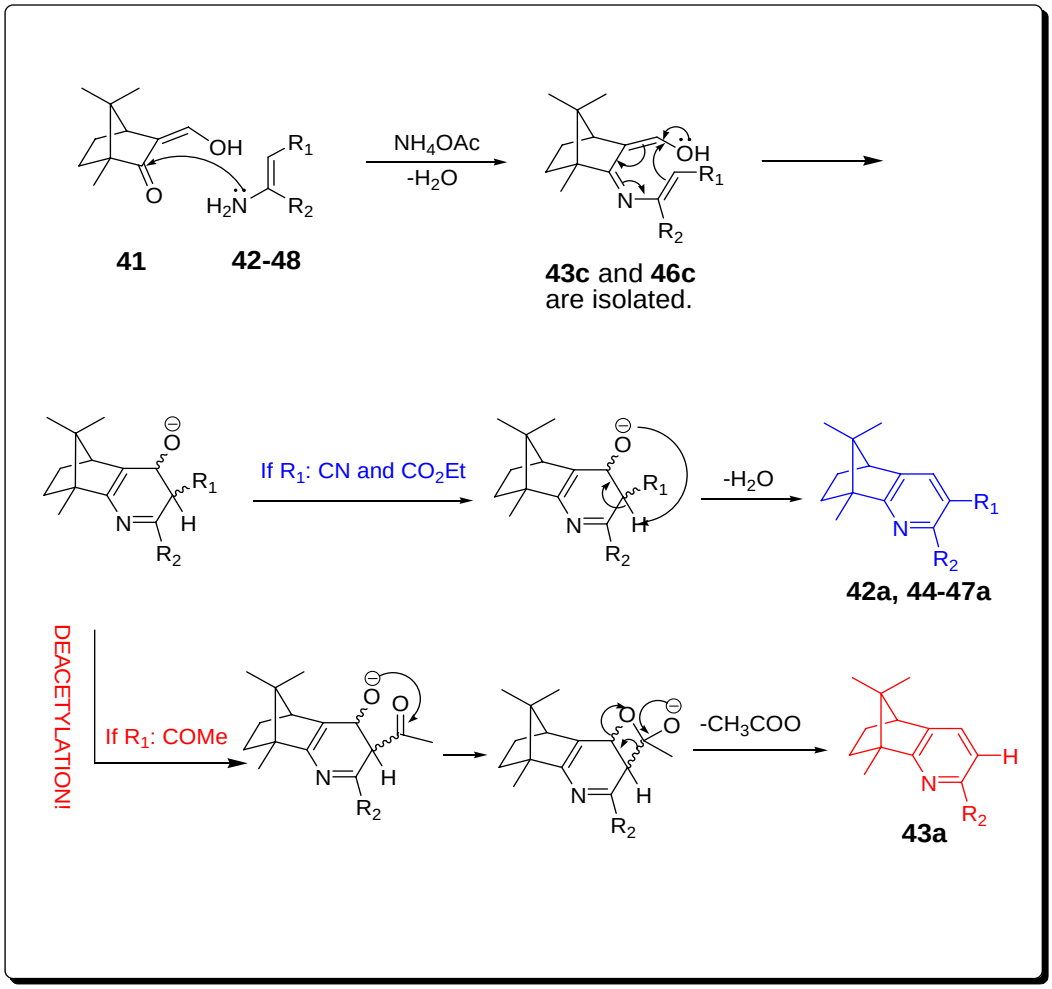


Figure 23: Isolated intermediates **43c** and **46c**.

Table2: Reaction of Enamines **42-48** with (+)-β-Hydroxymethylenecamphor **41**

Entry	Enamine	Product	$[\alpha]^{20}_D$	Yield (%)
1	 **42**	 **42a**	+48.2 (c, 0.93, MeOH)	73
2	 **43**	 **43a**	+25.4 (c, 2.0, Cyclohexane)	71
3	 **44**	 **44a**	+71.6 (c, 0.00141, MeOH)	35

4	 **45**	 **45a**		56
5	 **46**	 **46a**	+22.9 (c, 0.00384, MeOH)	58
6	 **47**	 **47a**	-9.7 (c, 0.00822, MeOH)	80
7	 **48**	Product was not isolated!		



Scheme 20

After the isolation of intermediates **43c** and **46c** we have been sure that the first step of the mechanism must be the imine formation as shown in scheme 20. In the structure elucidation of these intermediates we could not judge whether the isolated intermediates are in 3-hydroxymethylene form or 3-formyl form by looking their NMR spectra. Figure 24 shows ^{1}H-NMR and ^{13}C-NMR of isolated intermediate **43c**. In both ^{1}H-NMR and ^{13}C-NMR spectra of these compounds, lack of aromatic carbons and protons and also the presence of formyl group (doublet at 12.27 ppm, J=12 Hz) in ^{1}H-NMR spectrum were the indication of the isolation of the intermediate product **43c**. The same analysis done for the isolated compound **46c** strenghted our observation that these two compounds stayed as

uncyclised (Appendix). ^{13}C-NMR spectra of both isolated intermediates **43c** and **46c** are in accordance with their structures.

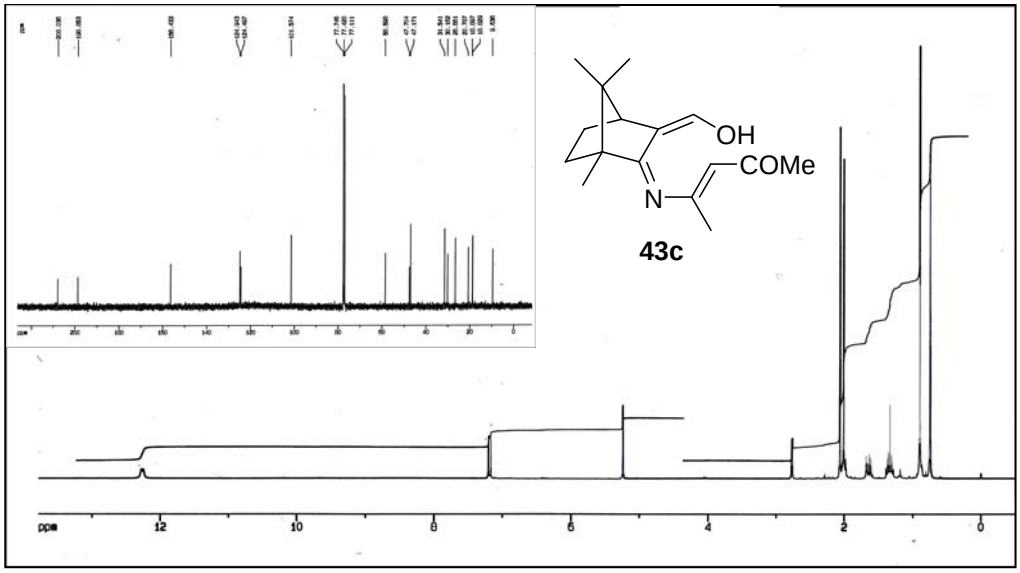


Figure 24: ^{1}H-NMR and ^{13}C-NMR of isolated intermediate **43c**.

In the synthesis of **43a**; cyclocondensation of (+)-β-hydroxymethylenecamphor **41** with fluoral-P **43**; spectroscopic data showed us that the deacetylated product was formed. In the characterization of the product **43a** NMR spectroscopy was helpful (Figure 25 and 26). The mechanistic pathway is explained clearly in scheme 20. Following mechanism was proposed; after the cyclisation occurs, electrons on the oxygen atom attacks to the acetyl group forming a four-memberedcyclic intermediate then openning of that cycle we got deacetyllated product **43a** with the removal of acetate group.

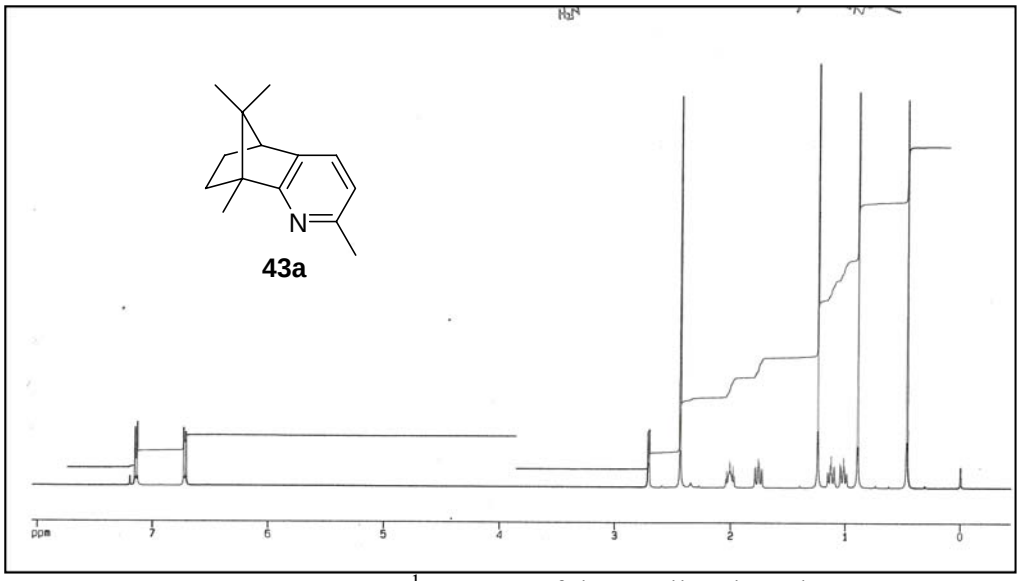


Figure 25: ^{1}H-NMR of deacetyllated product **43a**

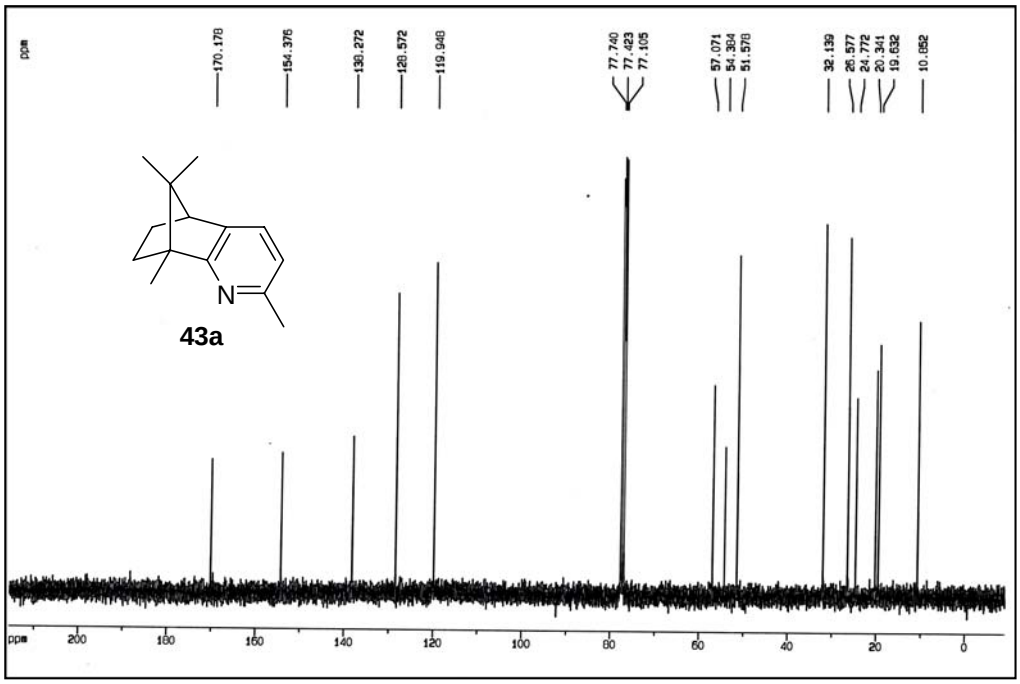


Figure 26: ^{13}C-NMR of deacetyllated product **43a**

The presence of AX system at aromatic region in the ^{1}H-NMR of deacetyllated product **43a** shown in figure 25 gave us the first clue for the unexpected product. A part of the AX system resonates at 7.14 ppm as doublet and X part of AX system resonates at 6.73 ppm as doublet with the coupling constant *J*=7.4 Hz. Then having ^{13}C-NMR of the product indicated in figure 26, we saw 14 carbon peaks and we became sure that the structure of the product as we proposed. This compound was previously synthesized by Gladiali *et al.* in 1986 and they have synthesized compound **43a** with 14% overall chemical yield starting from (+)-camphor **9** in five steps! (Scheme 2). All the results we obtained for characterization of the compound are in consistence with those given in the literature.[17]

As explained in the introduction part of this study, chiral 2-(2-thienyl)pyridines and 2,2'-bipyridines are widely used in asymmetric catalysis, in particular the latter. We achieved the synthesis of chiral camphor-based thienylpyridine **47a** with 80% chemical yield. Despite all attempts to synthesize chiral camphor-based bipyridine **48a**, we could not isolate and characterize the product.

CHAPTER III

CONCLUSION

In conclusion, the reaction of (+)-β-hydroxymethylenecamphor **41** with enamines **42-47** proceeded efficiently to give corresponding six camphor based chiral pyridine derivatives **42-47a** in good yields. Despite all attempts for the synthesis of chiral camphor-based bipyridine **48a**, we could not get the product, instead uncharacterizable compounds. This one-step reaction offers complete regioselectivity and opens up a new class of chiral pyridine synthesis. When compared with the literature synthesis of chiral camphor-based pyridines ours is much more precious since our synthetic method requires less steps and proves to be much more efficient when considering the overall yields. Our methodology is also promising to have various bidentate ligands by choosing the key enamine.

As a furher work, we will test the chiral bidentate thienylpyridine ligand **47a** in asymmetric diethylzinc addition to benzaldeyde. Further studies on the synthesis of new derivatives esspecially chiral bidentate ligands are in progress. Especially, we wish to insert R_2 group having heteroatoms in to the chiral pyridine skeleton. As a future work we plan to insert furan-2-yl, 1H-pyrrol-2-yl, 2-hydroxyphenyl and 2-(diphenylphosphino)phenyl groups to the 2- position of constructed pyridine ring and resultantly test these compounds in asymmetric model reactions as chiral bidentate ligands.

CHAPTER IV

EXPERIMENTAL

Following instruments and materials were used for the purification and characterization of products during the study.

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm from tetramethylsilane. Spin multiplicities are mentioned as: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet). Optical rotation values of products were measured on Krüss Automatic Digital Polarimeter P3002R2. All melting point determinations were performed using Mel-Temp 1002D.

Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV-light and polymolybden phosphoric acid, in ethanol as appropriate. Ethylacetate/hexane mixture systems are used as eluting solvent in TLC and flash column chromatography.

All extracts were dried over anhydrous magnesium sulphate and solutions were concentrated under vacuum by using rotary evaporator.

4.1 Synthesis of (+)-β-hydroxymethylenecamphor (41)

To a stirred solution of Na (1.24 g, 54 mmol) in 20 mL of absolute ether, (8.2 g, 54 mmol) (+)-camphor dissolved in 20 mL of ether is added and the mixture is stirred vigorously in ice bath for 5 min. To this mixture ethyl formate(4.85 mL, 61 mmol) is added dropwise within 30 min. and the following

mixture is left for stirring for 5 h at room temperature. At the work-up stage, 40 mL of water is added dropwise to the mixture and the aqueous layer was separated from organic phase. Then aqueous phase was washed with ether to remove unreacted camphor. Separated aqueous layer was acidified with 30% acetic acid and extracted with 2x50 mL of ether. Finally combined organic phase was removed under reduced pressure to yield (+)-β-hydroxymethylenecamphor in 30% yield as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 9.70 and 9.65 (two s, 1H)
6.70 (s, 1H, methylenic proton)

4.2 Synthesis of enamines having carbonyl moiety

General Procedure:

When 250 mL of concentrated ammonium hydroxide was added to 0.5 moles of β-dicarbonyl, a solid immediately formed in a mildly exothermic reaction. The reaction mixture was allowed to stand for 2 days and then dissolved in chloroform and washed twice with water. The chloroform was dried over $MgSO_4$, filtered, and removed under reduced pressure to give a yellow oily solid. Then the following oily solid was chromatographed on silica gel to give of a pale yellow solid in good yields.

4.2.1 Characterization of ethyl 3-aminocrotonate (42):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.77 and 4.55 (broad s, 2H)
4.45 (s, 1H)

4.03 (q, *J*=7.1 Hz, 2H)
1.83 (s, 3H)
1.18 (t, *J*=7.1 Hz, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 170.2, 159.6, 84.2, 58.5, 22.3, 14.3.

4.2.2 Characterization of (Z)-4-aminopent-3-en-2-one (Fluoral-P) (43):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 9.61 and 5.35 (broad s, 2H)
4.94 (s, 1H)
1.94 (s, 3H)
1.83 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 196.5, 161.3, 95.6, 29.1, 22.1.

4.3 Synthesis of enamines having nitrile moiety:

General Procedure:

To a benzene (40 mL) solution of aliphatic or aryl nitrile (10 mmoles) and acetonitrile (20 mmoles) was added potassium *t*-butoxide (30 mmoles) at room temperature. After being stirred at room temperature for 24 hours, the resulting

suspension was quenched with aqueous sodium bicarbonate (50 mL) and extracted with diethyl ether (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified on column chromatography on silica gel eluting with ethyl acetate/benzene (1:5), followed by recrystallization from ethyl acetate/hexane (1:1) producing high chemical yields.

4.3.1 Characterization of 3-aminobut-2-enenitrile (44):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 4.45 (broad s, 2H)
4.02 (s, 1H)
2.0 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 161.4, 121.2, 65.0, 19.5.

4.3.2 Characterization of 3-amino-3-phenylacrylonitrile (45):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.45-7.33 (m, 5H)
4.76 (broad s, 2H)
4.18 (s, 1H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 161.5, 135.4, 130.9, 129.0 (2C), 126.0 (2C), 119.4, 63.9.

4.3.3 Characterization of 3-amino-3-(4-bromophenyl)acrylonitrile (46):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.51-7.48 (m, 2H)
7.32-7.29 (m, 2H)
4.72 (broad s, 2H)
4.16 (s, 1H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 160.3, 134.3, 132.3 (2C), 127.6 (2C), 125.3, 119.0, 64.6.

4.3.4 Characterization of 3-amino-3-(thiophen-2-yl)acrylonitrile (47):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.35 (d, *J*=4.9 Hz, 1H)
7.27-7.26 (m, 1H)
7.02 and 7.01 (dd, *J*=4.9 Hz, 1H)
4.85 (broad s, 2H)
4.32 (s, 1H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 154.8, 138.0, 128.5 (2C), 126.8, 119.5, 64.0.

4.3.5 Characterization of 3-amino-3-(pyridin-2-yl)acrylonitrile (48):

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 8.56 (d, *J*=4.5 Hz, 1H)
7.73-7.68 (m, 1H)
7.60 (d, *J*=8.0 Hz, 1H)
7.32-7.30 (m, 1H)
5.87 (broad s, 2H)
4.57 (s, 1H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 157.6, 150.0, 149.2, 137.4, 125.5, 120.4, 120.0, 62.2.

4.4 Synthesis of camphor-based chiral pyridines

General Procedure:

To a mixture of (+)-β-hydroxymethylenecamphor (360 mg, 2 mmoles) and enamine (3.4 mmoles) in a sealed tube ammonium acetate (10 mg, 0,13 mmoles) is added and the tube is sealed. Then it was heated for 12 hours in a sand bath at 130 °C. The tube was opened and the crude material was chromotographed on silica gel using ethyl acetate/hexane as the eluting solvent. Organic phase was

removed under reduced pressure to yield optically active camphor-based pyridines in good yields.

4.4.1 Characterization of (*5S,8R*)-(+)-42a:

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.77 (s, 1H)
4.28 (q, *J*=7.0 Hz, 3H)
2.79 (d, *J*=4.0 Hz, 1H)
2.73 (s, 3H)
2.08-2.01 (m, 1H)
1.83-1.77 (m, 1H)
1.32 (t, *J*=7.0 Hz, 3H)
1.25 (s, 3H)
1.16-1.02 (m, 2H)
0.92 (s, 3H)
0.48 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 173.5, 168.0, 157.4, 138.6, 130.2, 122.8, 61.2, 57.2, 54.9, 51.4, 31.9, 26.4, 25.2, 20.3, 19.5, 14.7, 10.6

HRMS calcd for $C_{17}H_{24}NO_2$ (M+H): 274.1807.
Found (M+H) 274.1802.

$[\alpha]^{20}_{D}$ = +48.2 (c, 0.93, MeOH)

4.4.2 Characterization of (*5S,8R*)-(+)-**43a:**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.14 (d, A part of AX system, *J*=7.4 Hz, 1H)
6.73 (d, X part of AX system, *J*=7.4 Hz, 1H)
2.71 (d, *J*=4.0 Hz, 1H)
2.44 (s, 3H)
2.04-1.97 (m, 1H)
1.79-1.73 (m, 1H)
1.24 (s, 3H)
1.16-1.08 (m, 1H)
1.05-0.99 (m, 1H)
0.90 (s, 3H)
0.47 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 170.2, 154.4, 138.3, 128.6, 119.9, 57.1, 54.4, 51.6, 32.1, 26.6, 24.8, 20.3, 19.6, 10.8

HRMS calcd for $C_{14}H_{20}N$ (M+H): 202.1596.
Found (M+H) 202.1607.

$[\alpha]^{20}_{D}$ = +25.4 (c, 2.0, Cyclohexane)

4.4.3 Characterization of uncyclized intermediate 43c:

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 12.28 (d, *J*=11.9 Hz, 1H)
7.20 (d, *J*=12.8 Hz, 1H)
5.24 (s, 1H)
2.77 (d, *J*=3.8 Hz, 1H)
2.06 (s, 3H)
2.01 (s, 3H)
1.68-1.61 (m, 2H)
1.39-1.29 (m, 2H)
0.90 (s, 3H)
0.90 (s, 3H)
0.75 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 208.0, 198.9, 156.4, 124.9, 124.5, 101.6, 58.6, 47.7, 47.2, 31.5, 30.2, 26.7, 20.8, 18.9, 18.8, 9.6.

4.4.4 Characterization of (*5S*,*8R*)-(+)-44a:

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.43 (s, 1H)
2.82 (d, *J*=4.0 Hz, 1H)
2.66 (s, 3H)
2.15-2.04 (m, 1H)
1.87-1.81 (m, 1H)

1.24 (s, 3H)
1.15-1.01 (m, 2H)
0.94 (s, 3H)
0.47 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 174.8, 159.5, 138.8, 131.2, 118.8, 105.5, 57.3, 55.3, 51.3, 31.7, 26.1, 23.9, 20.2, 19.4, 10.5

HRMS calcd for $C_{15}H_{19}N_2$ (M+H): 227.1548.
Found (M+H) 227.1541.

$[\alpha]^{20}_D$ = +71.6 (c, 0.00141, MeOH)

4.4.5 Characterization of (*5S,8R*)-(+)-**45a:**

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.96-7.93 (m, 2H)
7.66 (s, 1H)
7.52-7.43 (m, 3H)
2.96 (d, *J*=4.0 Hz, 1H)
2.24-2.16 (m, 1H)
1.99-1.92 (m, 1H)
1.36 (s, 3H)
1.31-1.16 (m, 2H)
1. 04(s, 3H)
0.60 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 174.6, 158.8, 139.3, 138.0, 132.3, 129.6, 129.1 (2C), 128.5 (2C), 119.2, 103.7, 57.0, 55.1, 51.1, 31.3, 25.8, 20.0, 19.0, 10.1.

4.4.6 Characterization of (*5S*,*8R*)-(+)-46a:

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 7.76 (d, A part of AB system, *J*=8.5 Hz, 2H)
7.59 (s, 1H)
7.56 (d, B part of AB system, *J*=8.5 Hz, 2H)
2.90 (d, *J*=4.0 Hz, 1H)
2.16-2.10 (m, 1H)
1.92-1.86 (m, 1H)
1.28 (s, 3H)
1.22-1.08 (m, 2H)
0.97 (s, 3H)
0.52 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 174.8, 157.5, 139.7, 136.9, 132.2, 131.7 (2C), 130.7 (2C), 124.2, 118.9, 103.6, 57.0, 55.1, 51.1, 31.3, 25.7, 19.9, 19.0, 10.0.

$[\alpha]^{20}_{D}$ = +22.9(c, 0.00384, MeOH)

4.4.7 Characterization of uncyclized intermediate 46c:

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 10.35 (d, *J*=10.8 Hz, 1H)
7.52 (d, *J*=8.3 Hz, 2H)
7.25 (d, *J*=8.3 Hz, 2H)
6.95 (d, *J*=11.0 Hz, H)
4.34 (s, 1H)
2.39 (d, *J*=3.5 Hz, 1H)
2.00-1.93 (m, 1H)
1.66-1.58 (m, 1H)
1.40-1.29 (m, 2H)
0.91 (s, 3H)
0.86 (s, 3H)
0.78 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 210.5, 155.6, 133.7, 132.8 (2C), 129.9, 129.5 (2C), 125.8, 120.9, 118.3, 70.4, 59.3, 49.2, 49.2, 30.4, 28.1, 21.0, 19.0, 9.3.

4.4.8 Characterization of (*5S,8R*)-(+)-47a:

^{1}H-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 8.09 (d, *J*=3.9 Hz, 1H)
7.49 (s, 1H)
7.38 (d, *J*=5.2 Hz, 1H)
7.07-7.04 (m, 1H)
2.83 (d, *J*=4.0 Hz, 1H)
2.12-2.06 (m, 1H)
1.88-1.81 (m, 1H)
1.26 (s, 3H)
1.21-1.15 (m, 1H)
1.10-1.04 (m, 1H)
0.94 (s, 3H)
0.50 (s, 3H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ(in ppm): 174.5, 151.4, 142.9, 139.0, 128.5, 127.7, 119.3, 100.0, 56.7, 55.0, 51.0, 31.3, 29.9, 25.8, 20.0, 18.9, 9.9.

HRMS calcd for $C_{18}H_{19}N_2S$ (M+H): 215.1269.
Found (M+H) 295.1260.

$[\alpha]^{20}_{D}$ = -9.7 (c, 0.00822, MeOH)

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APPENDIX

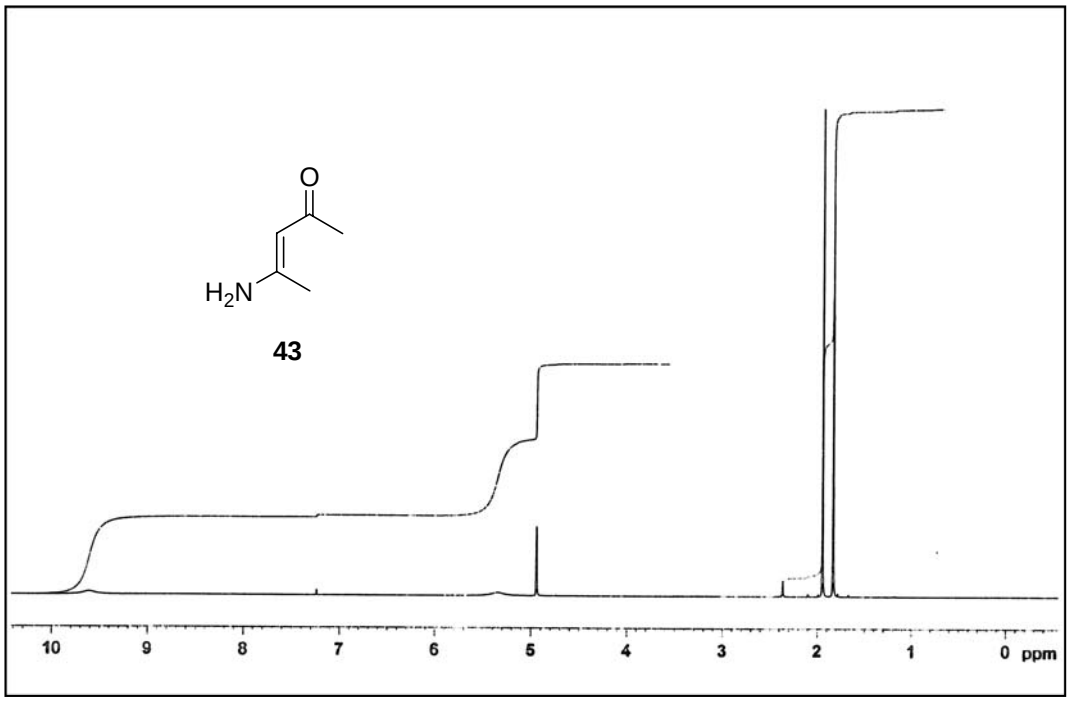

Figure 27: ^{1}H-NMR spectrum of **43**

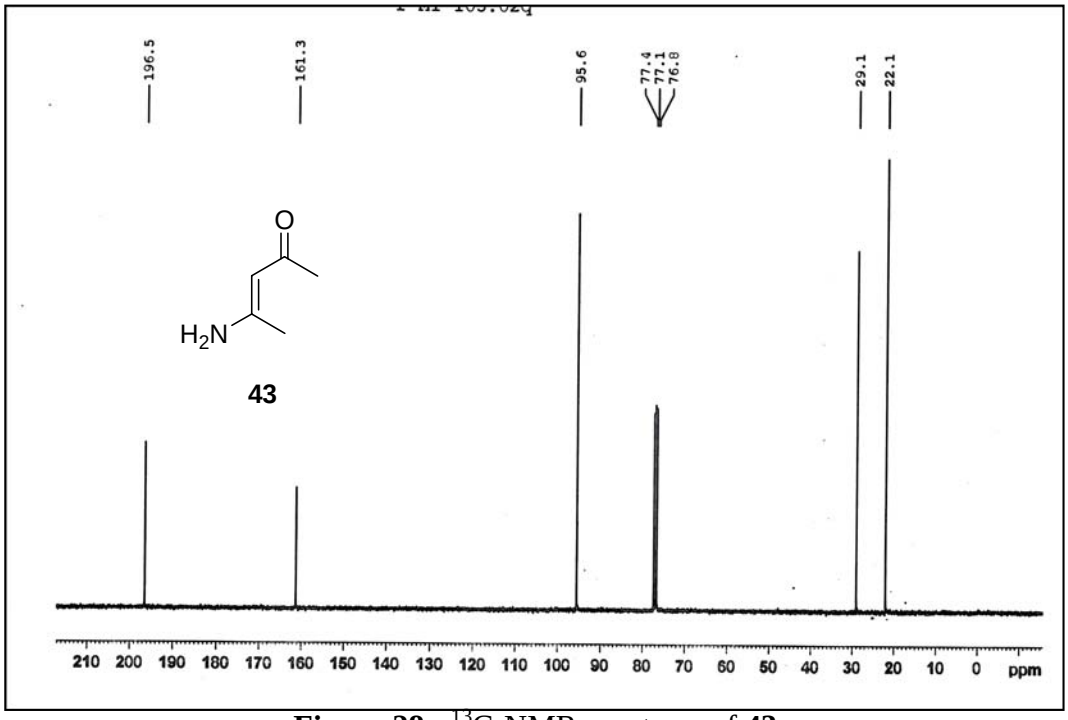

Figure 28: ^{13}C-NMR spectrum of **43**

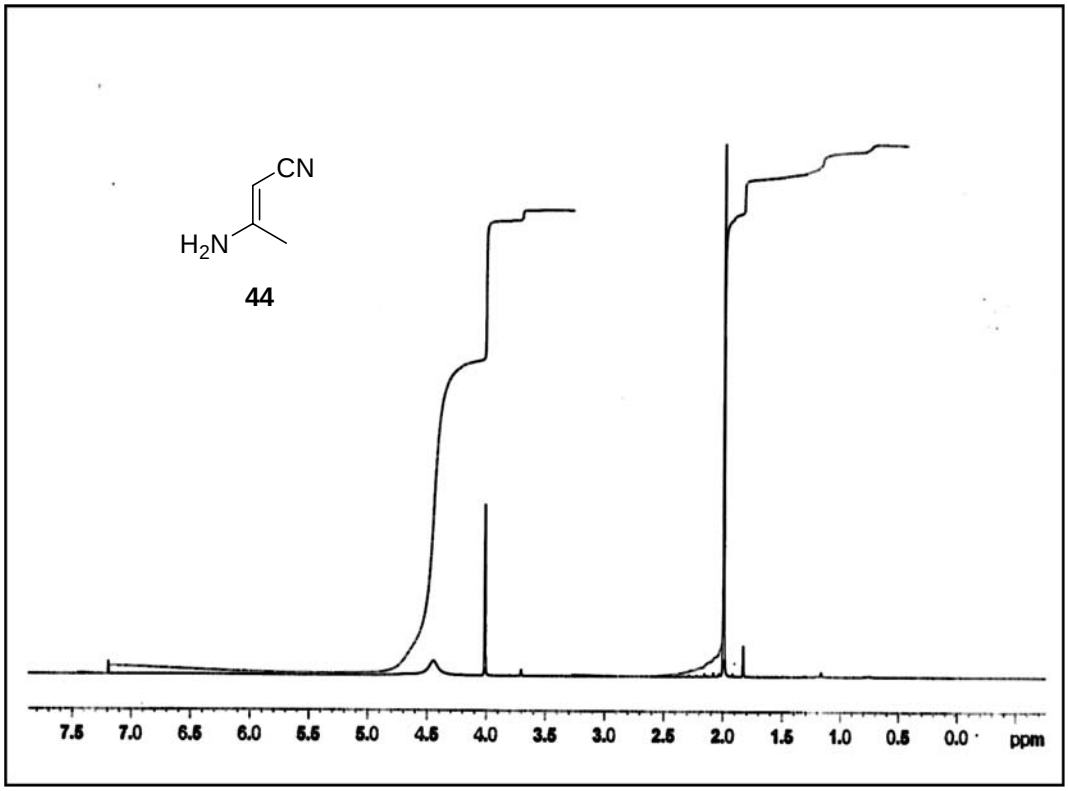

Figure 29: ^{1}H-NMR spectrum of **44**

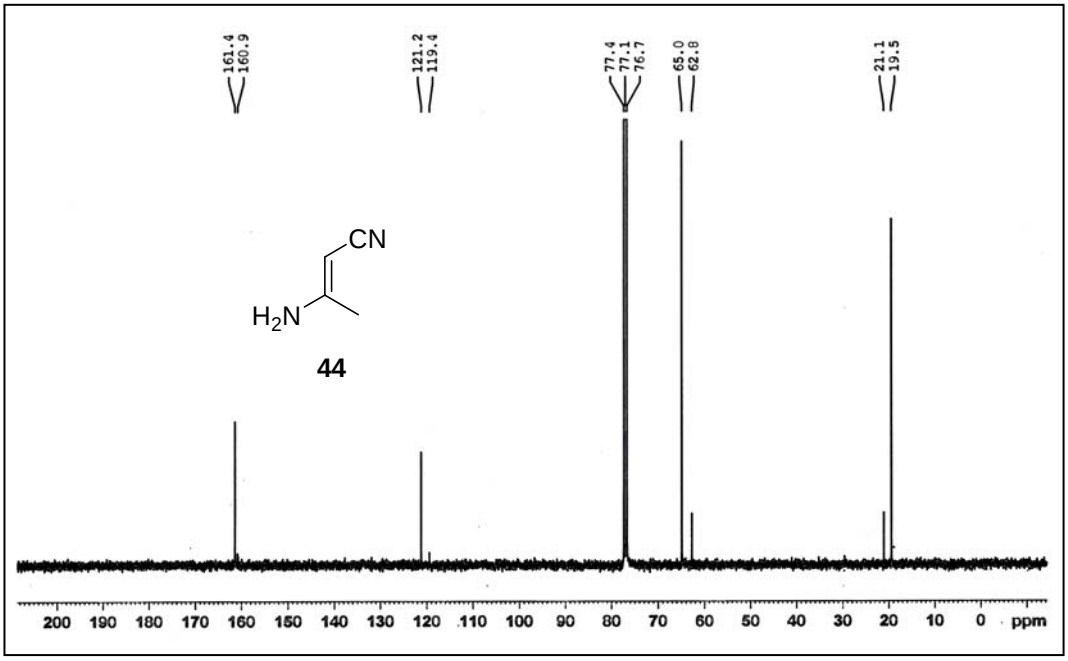

Figure 30: ^{13}C-NMR spectrum of **44**

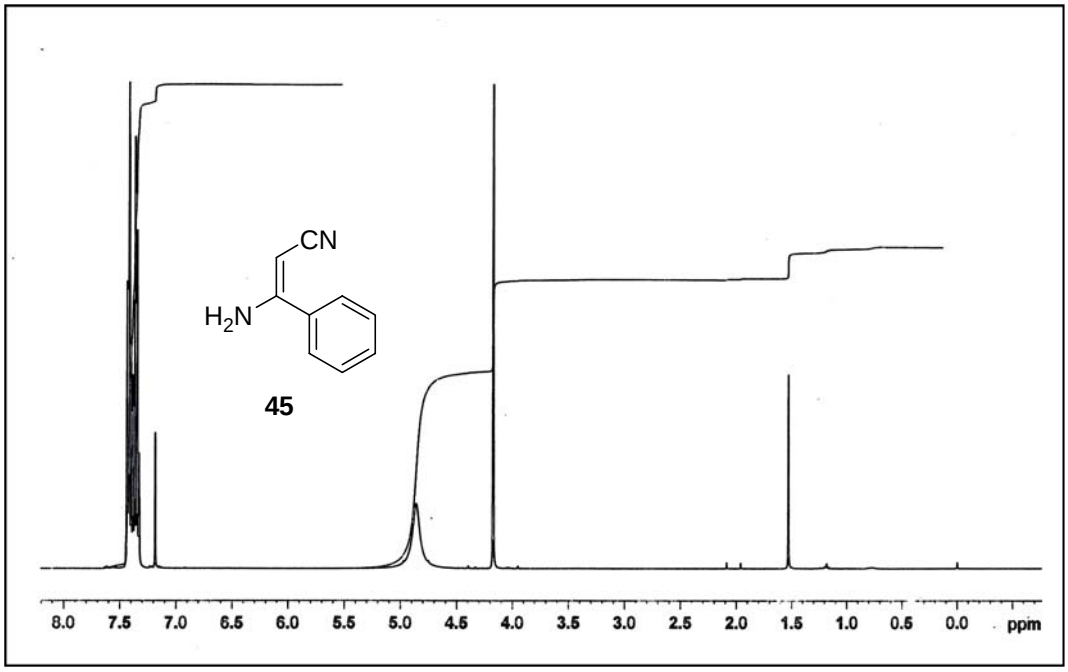

Figure 31: ^{1}H-NMR spectrum of **45**

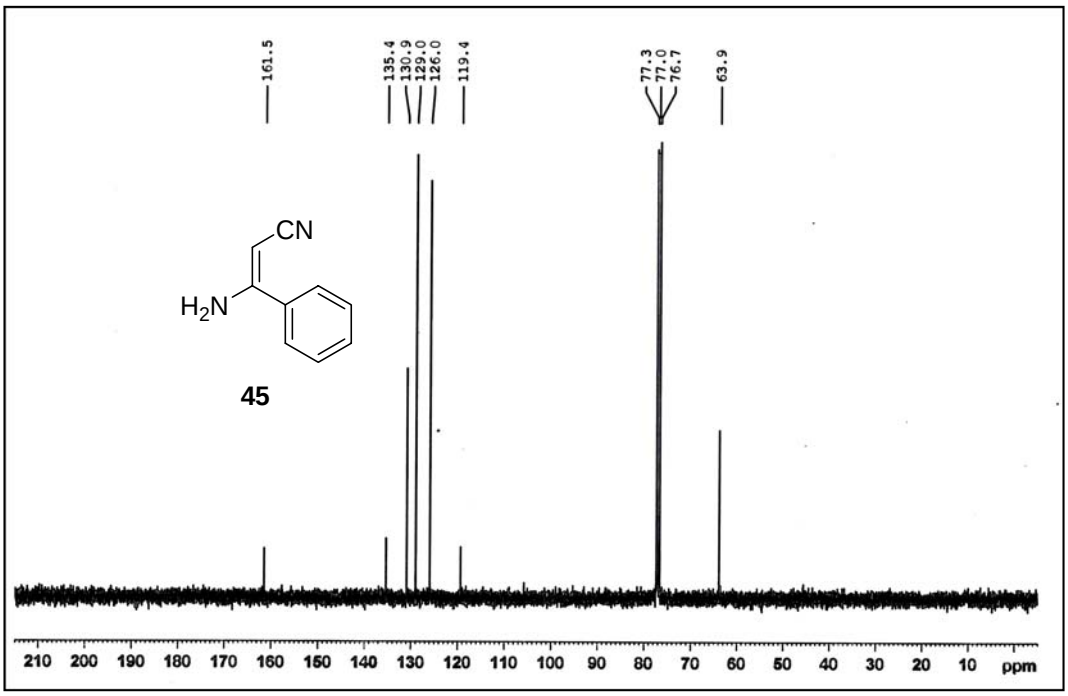

Figure 32: ^{13}C-NMR spectrum of **45**

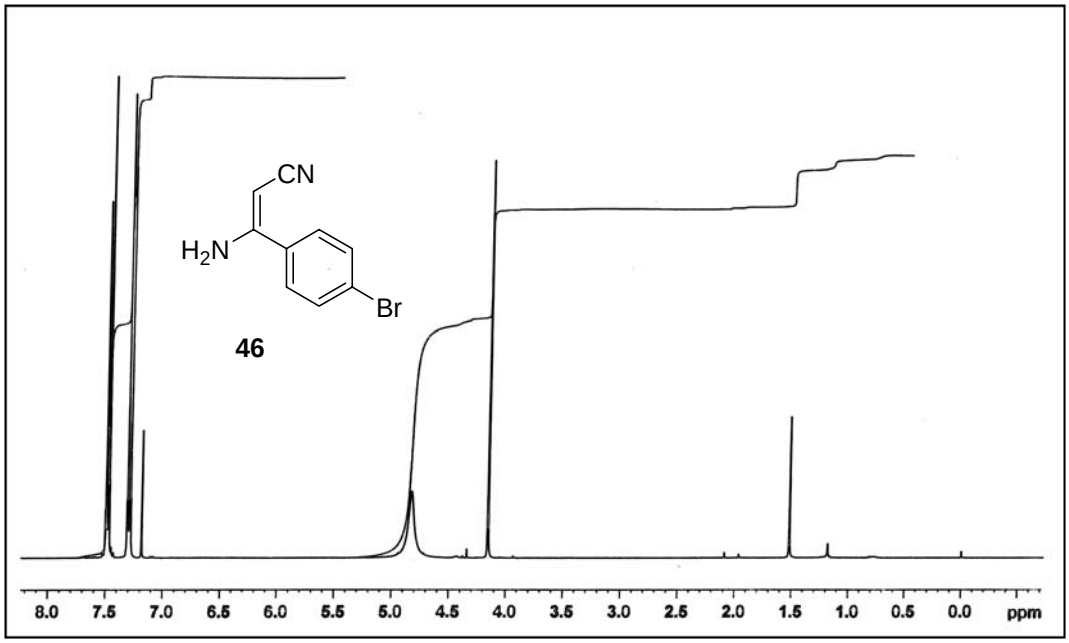

Figure 33: ^{1}H-NMR spectrum of **46**

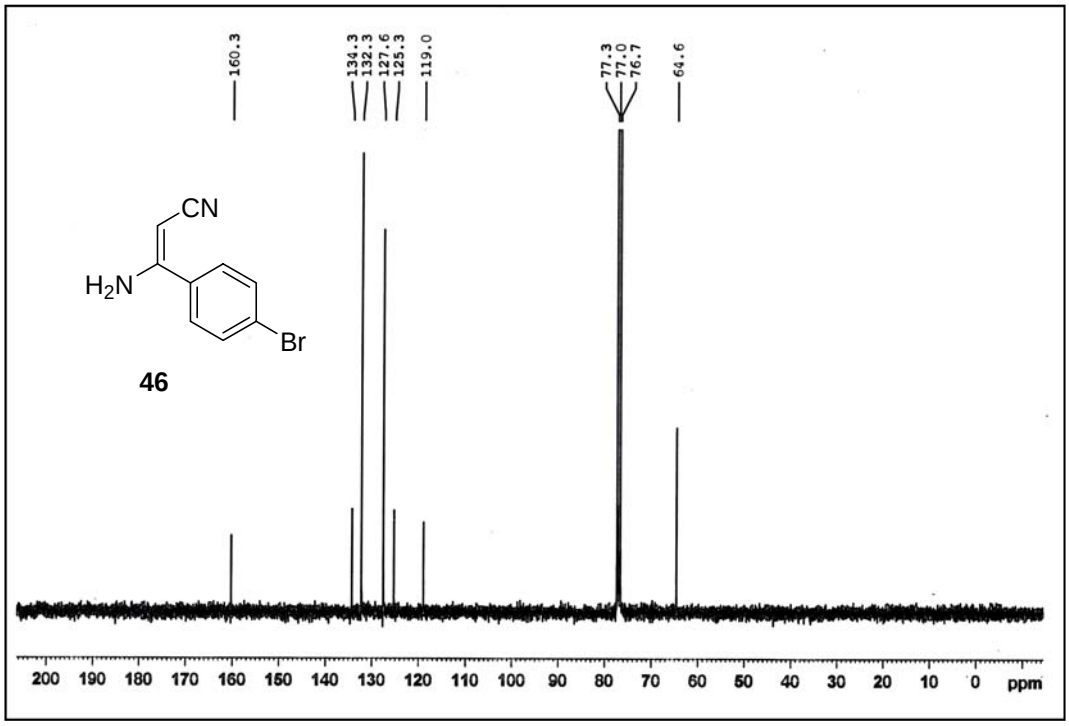

Figure 34: ^{13}C-NMR spectrum of **46**

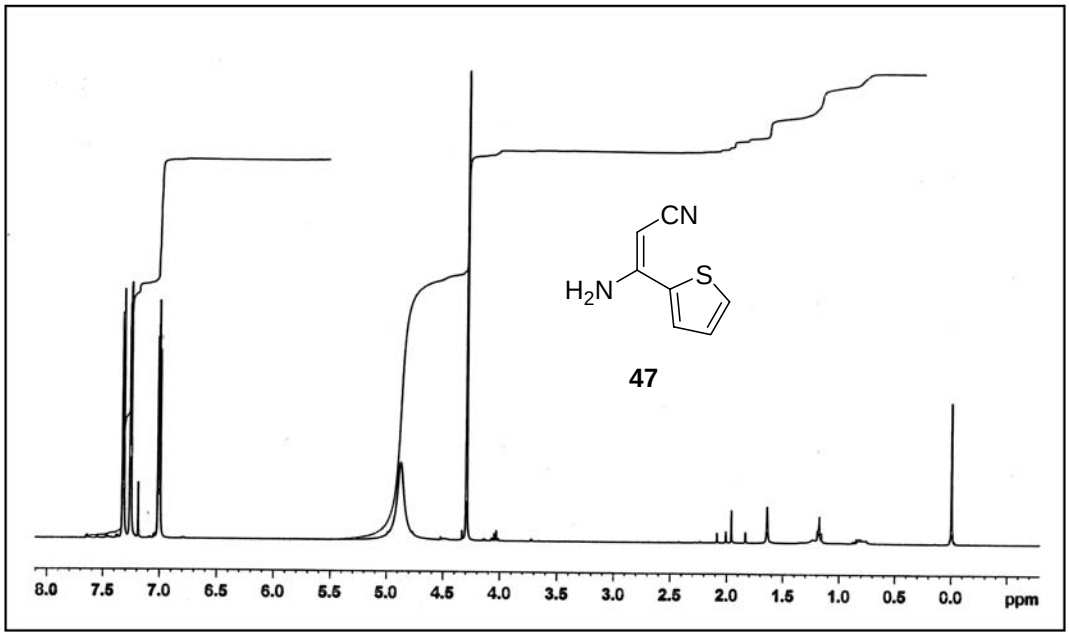

Figure 35: ^{1}H-NMR spectrum of **47**

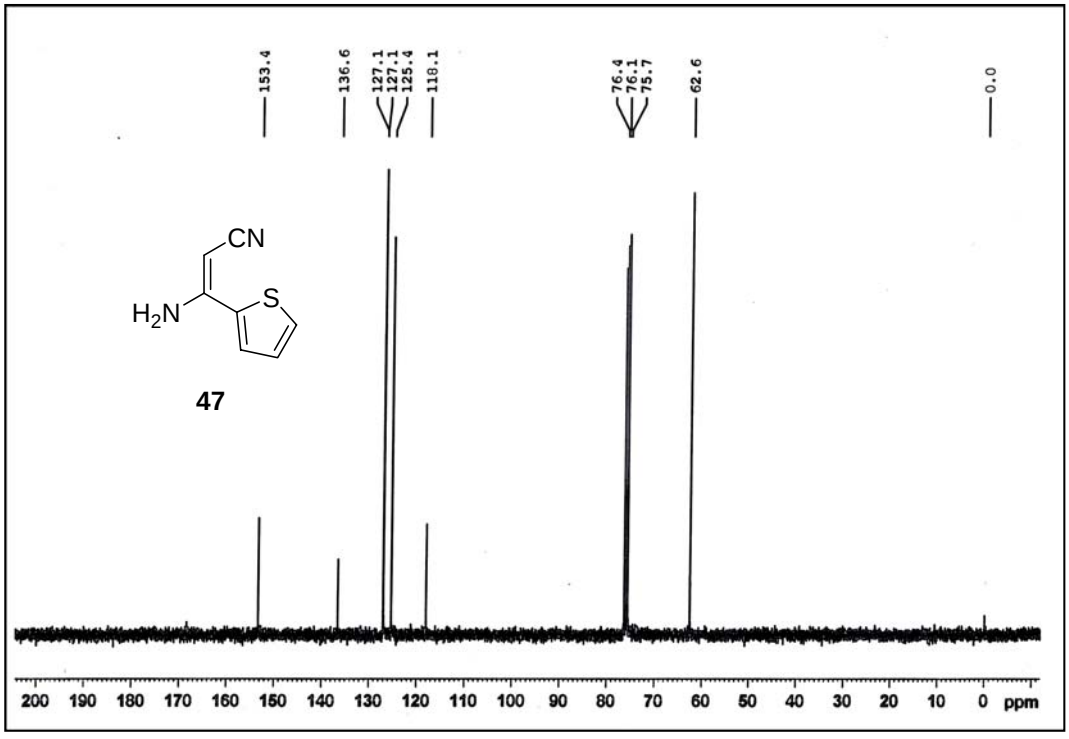

Figure 36: ^{13}C-NMR spectrum of **47**

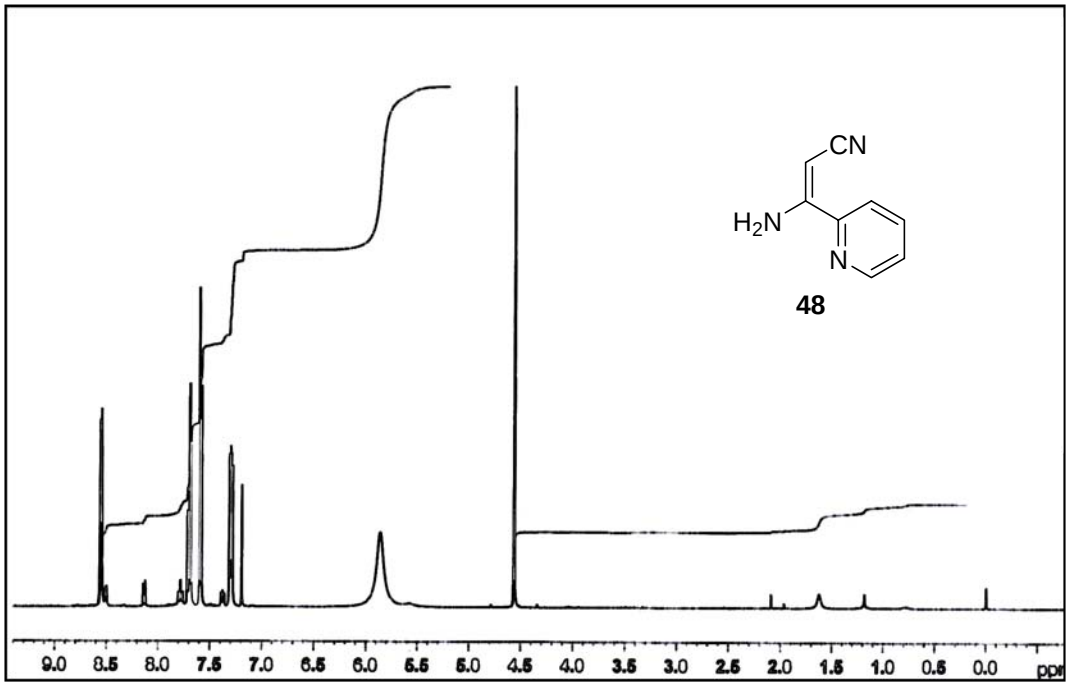

Figure 37: ^{1}H-NMR spectrum of **48**

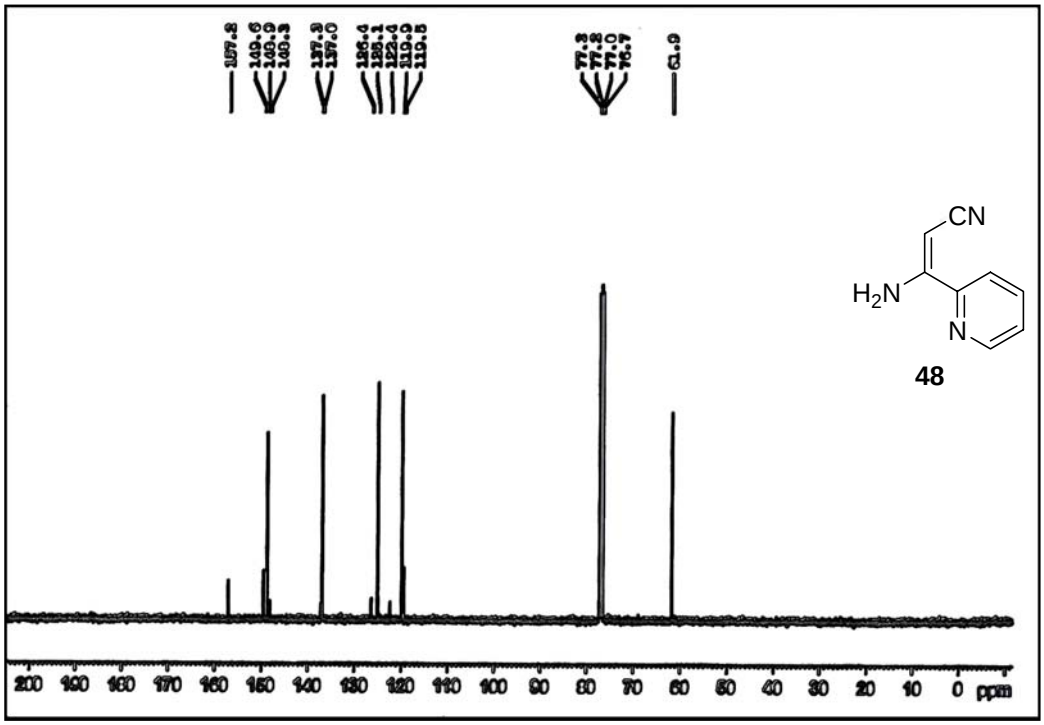

Figure 38: ^{13}C-NMR spectrum of **48**

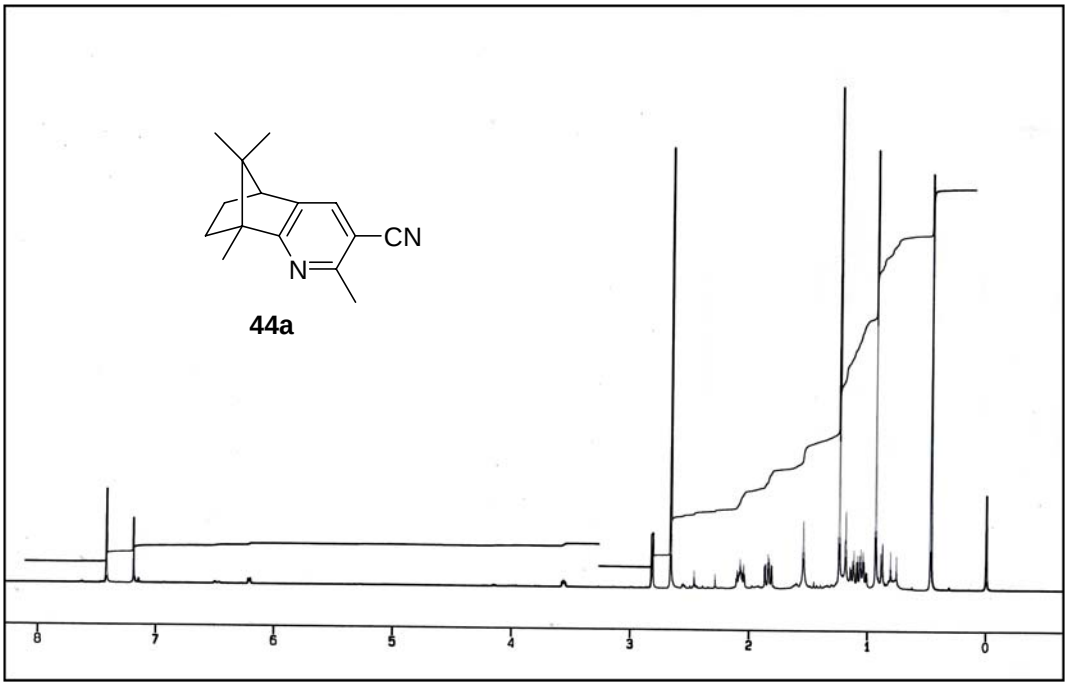

Figure 39: ^{1}H-NMR spectrum of (*5S,8R*)-(+)-**44a**

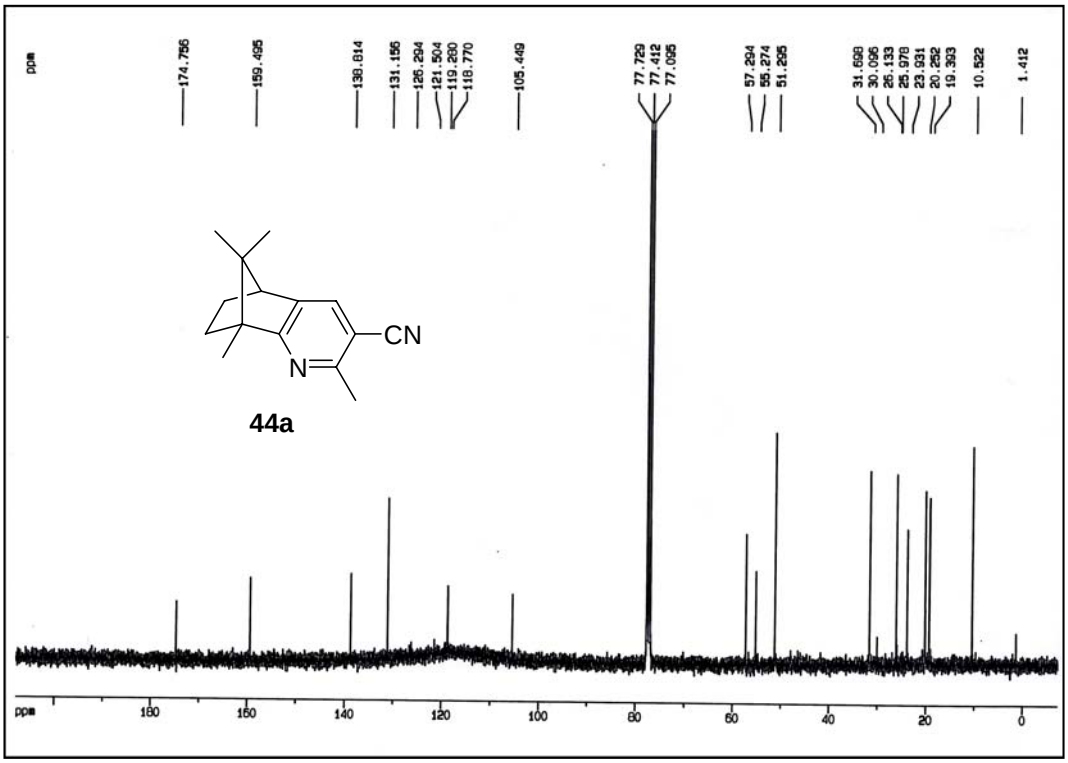

Figure 40: ^{13}C-NMR spectrum of (*5S,8R*)-(+)-**44a**

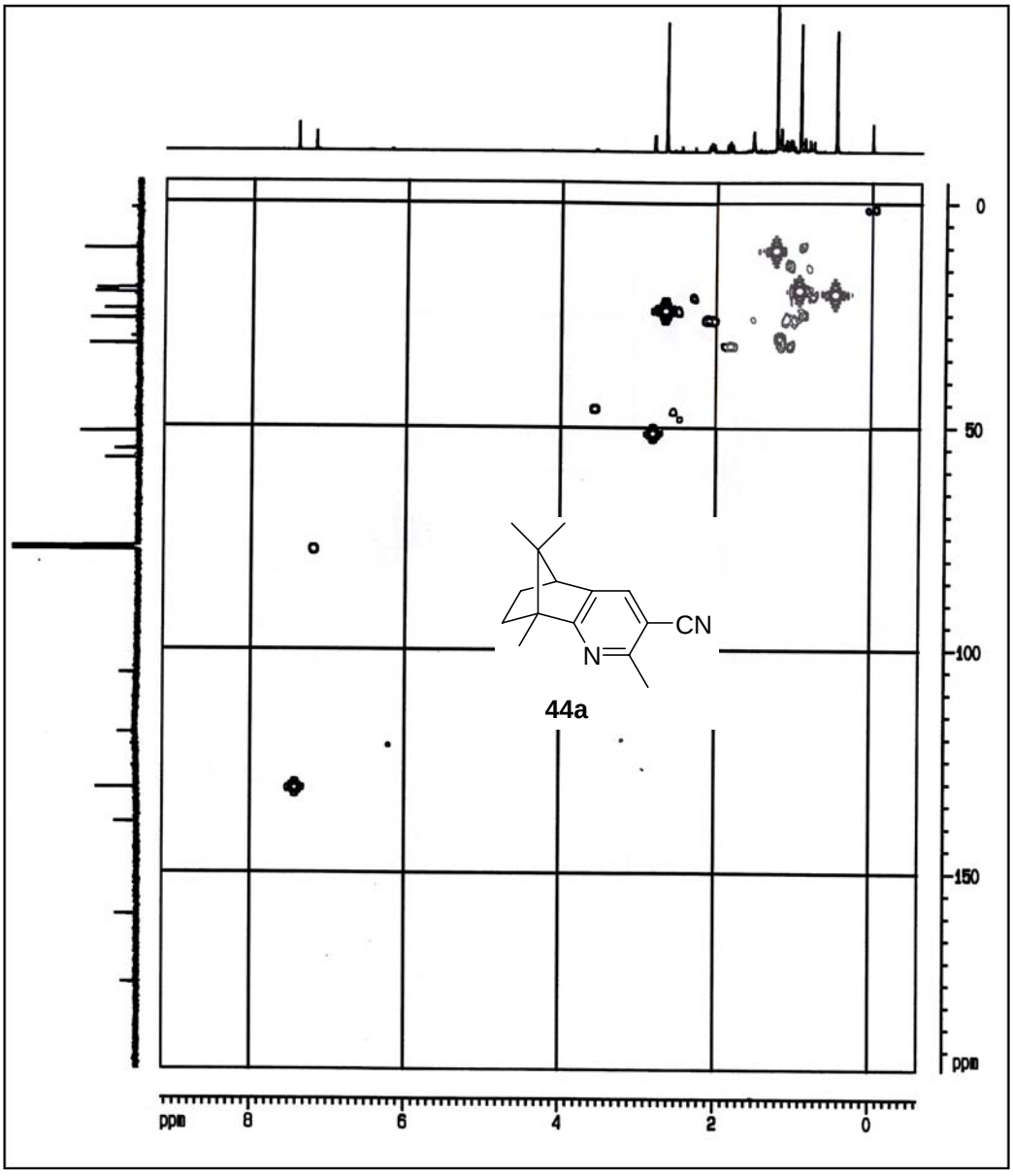

Figure 41: HMQC spectrum of (*5S,8R*)-(+)-**44a**

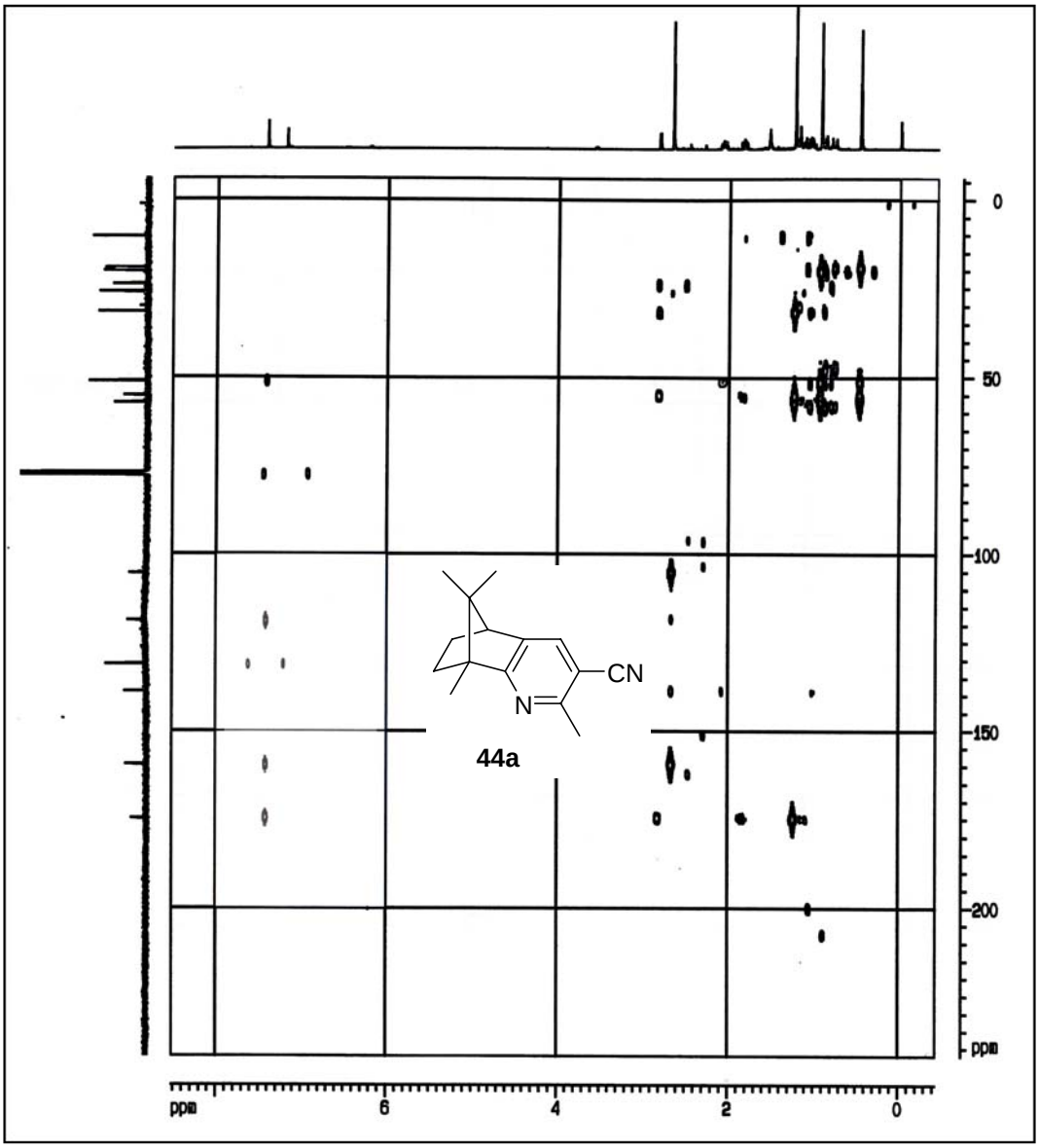

Figure 42: HMBC spectrum of (*5S*,*8R*)-(+)-**44a**

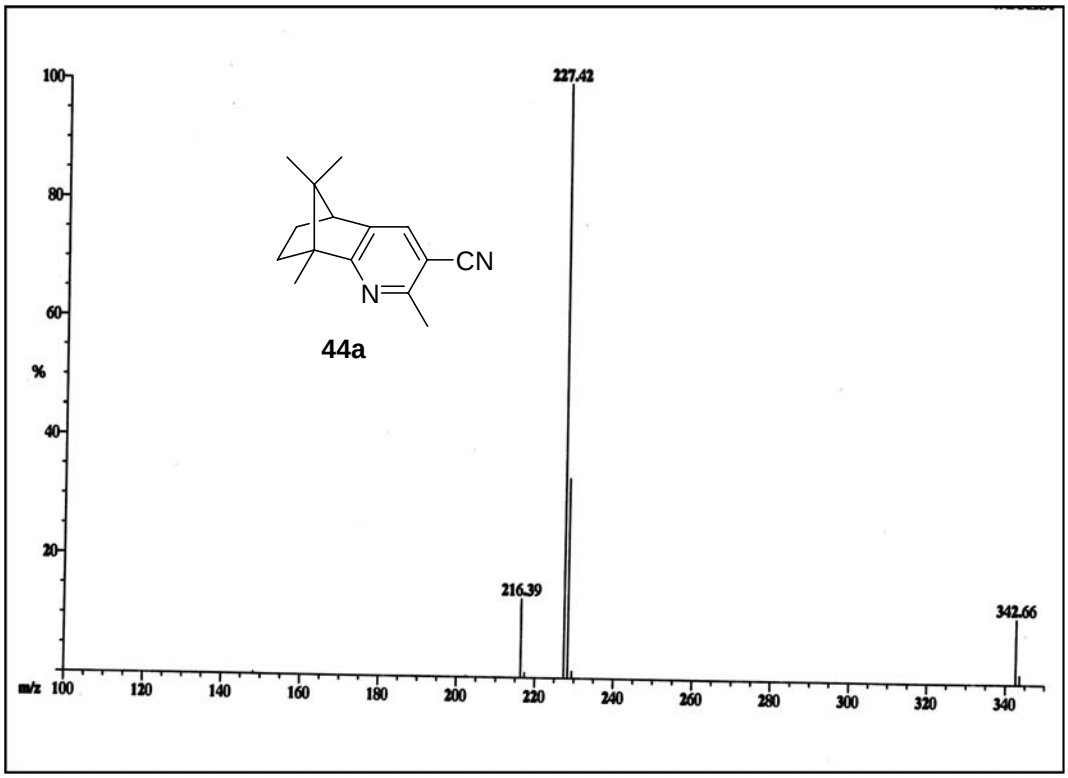

Figure 43: HRMS spectrum of (*5S,8R*)-(+)-**44a**

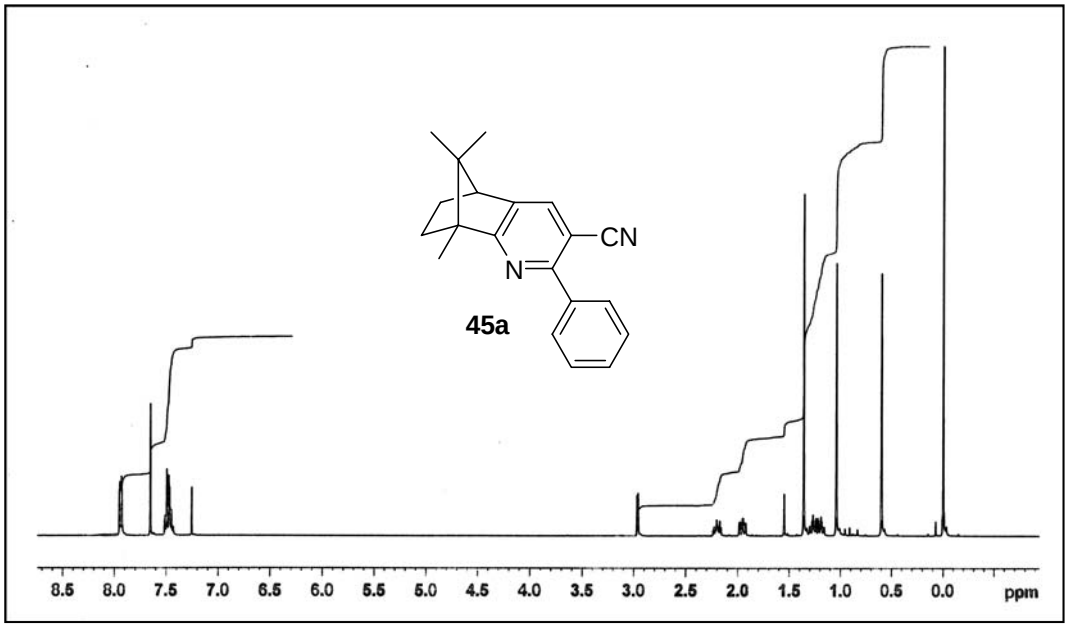

Figure 44: ^{1}H-NMR spectrum of (*5S,8R*)-(+)-**45a**

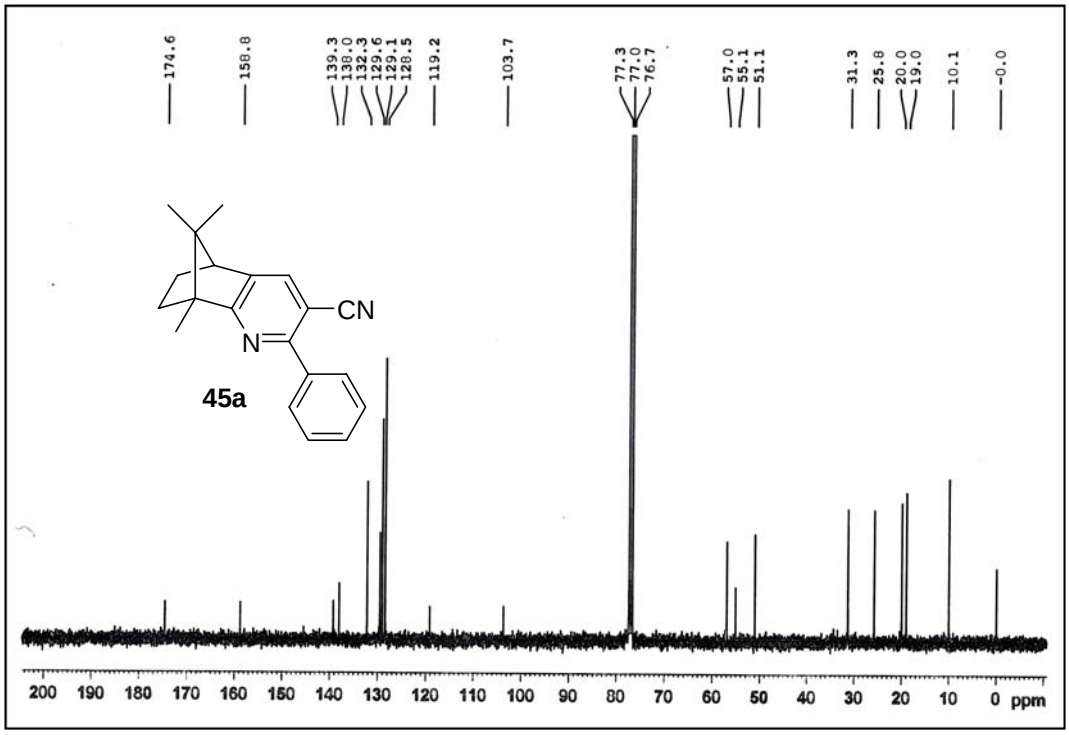

Figure 45: ^{13}C-NMR spectrum of (*5S,8R*)-(+)-**45a**

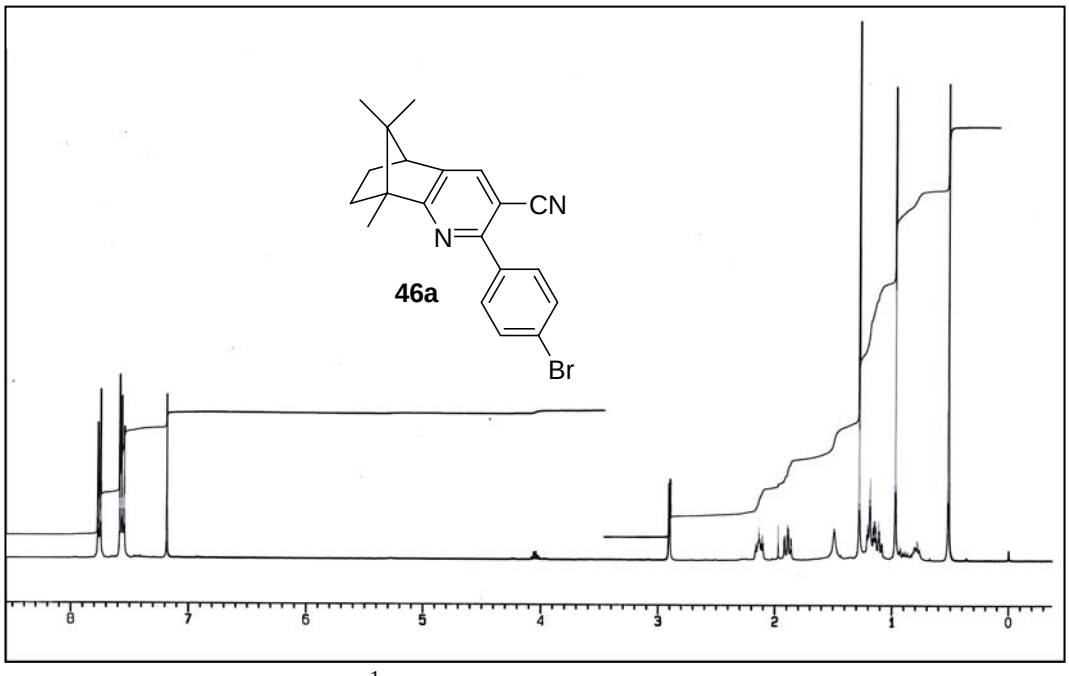

Figure 46: ^{1}H-NMR spectrum of (*5S,8R*)-(+)-**46a**

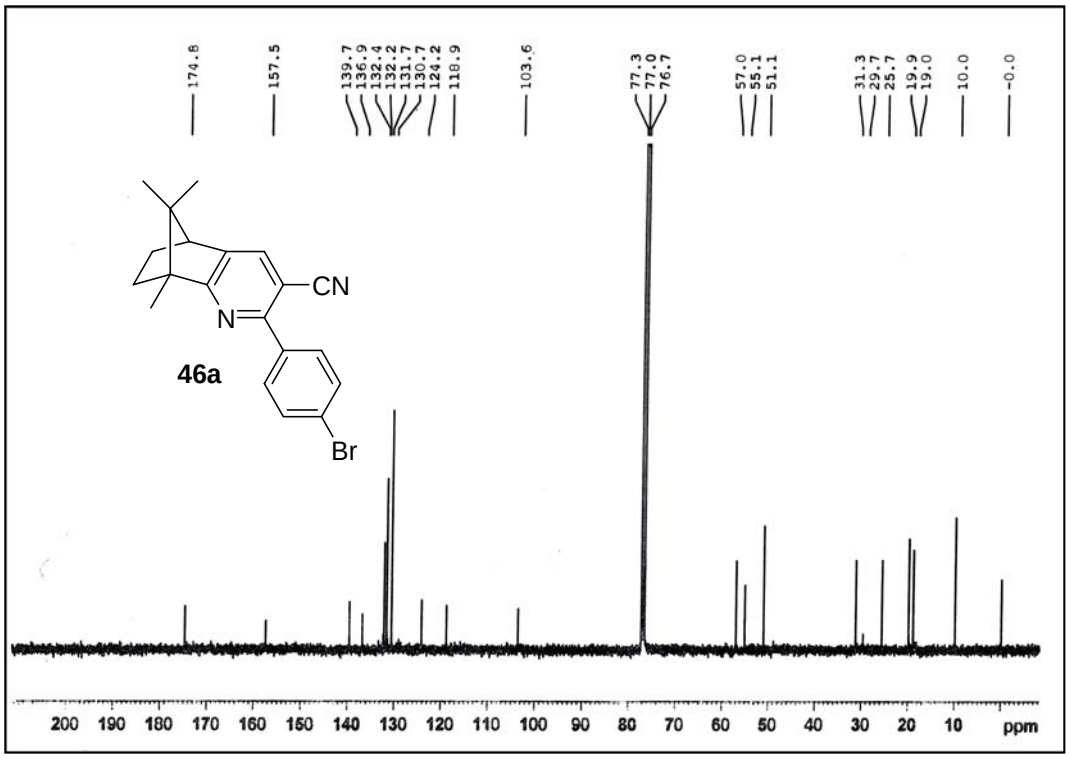

Figure 47: ^{13}C-NMR spectrum of (*5S,8R*)-(+)-**46a**

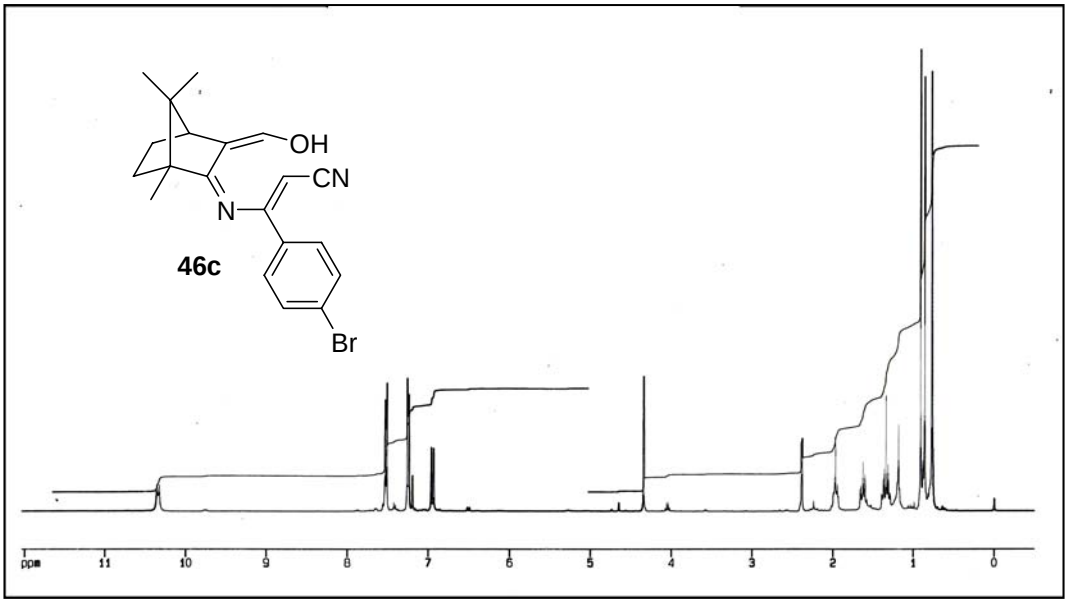

Figure 48: ^{1}H-NMR spectrum of isolated intermediate (*5S,8R*)-(+)-**46c**

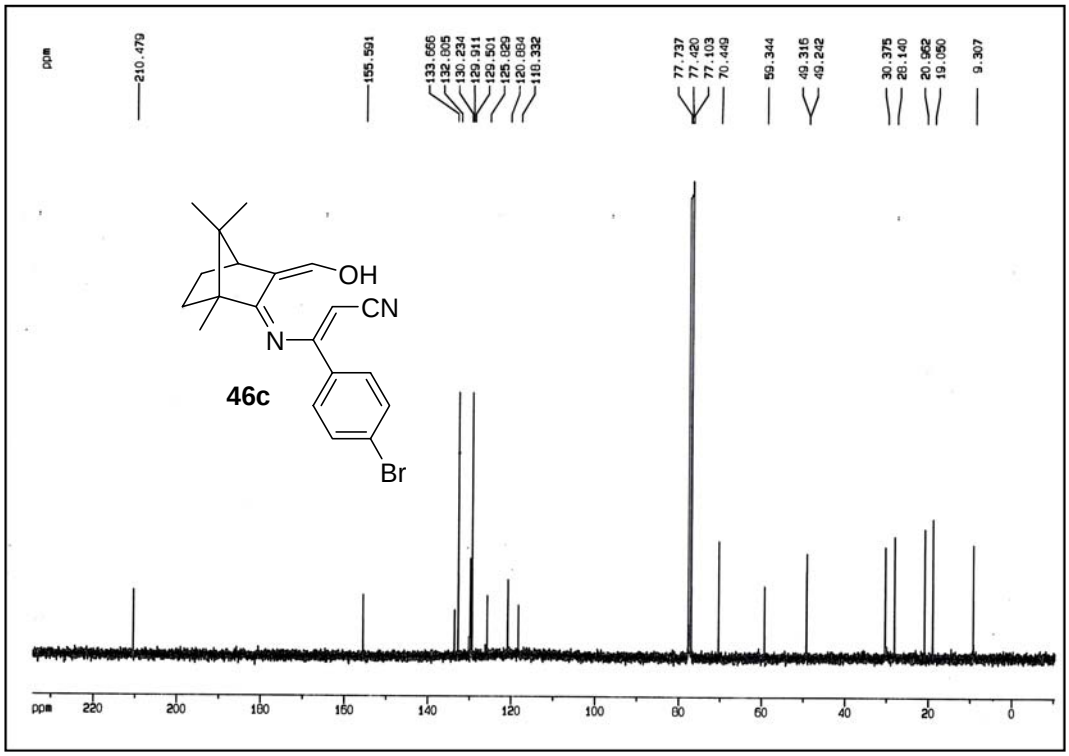

Figure 49: ^{13}C-NMR spectrum of isolated intermediate (*5S,8R*)-(+)-**46c**

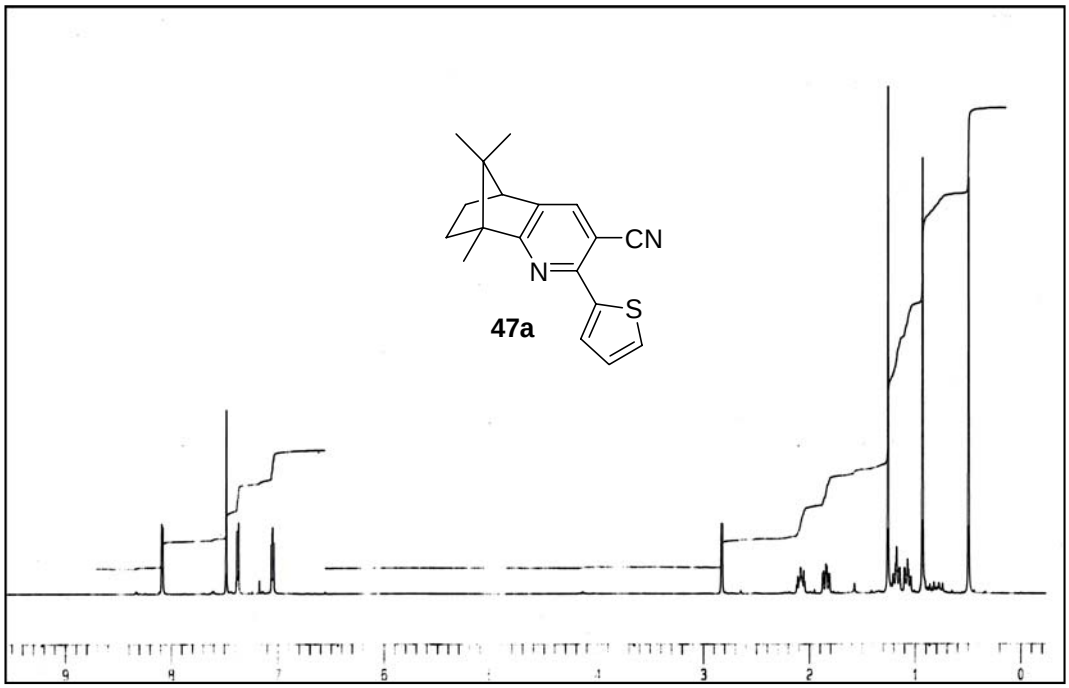

Figure 50: ^{1}H-NMR spectrum of (*5S,8R*)-(+)-**47a**

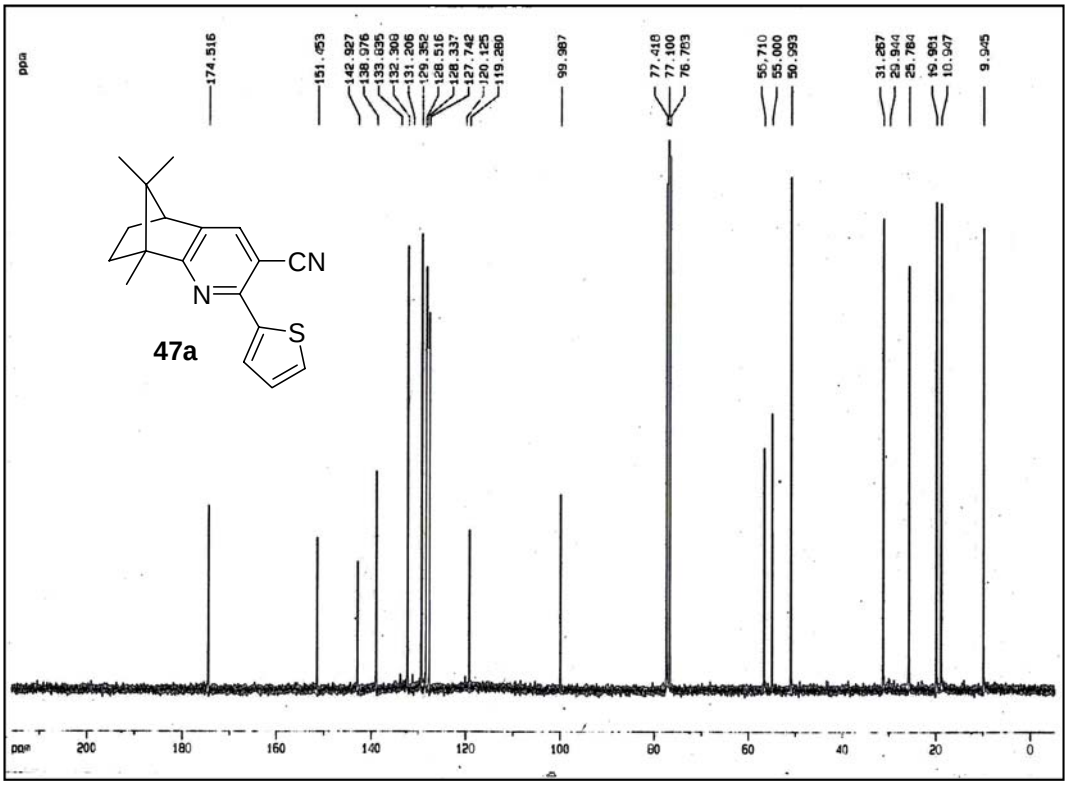

Figure 51: ^{13}C-NMR spectrum of (*5S,8R*)-(+)-**47a**