ENANTIOSELECTIVE SYNTHESIS OF 1-SUBSTITUTED TETRAHYDROISOQUINOLINES

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By

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Abstract

Many organic compounds are chiral and they are useful because of the biological activities associated with them. The biological activities of chiral compounds are often linked to absolute configuration, i.e. a compound and its mirror image can have different biological activities. For example, one enantiomer can be toxic whereas the other enantiomer is non-toxic. Enantioselective synthesis plays a significant role in the synthesis of biologically active compounds. The activity of tetrahydroisoquinolines prompted us to investigate the stereoselective synthesis of selected 1-substituted tetrahydroisoquinolines.

The objectives of this project were to investigate stereoselective synthesis of some 1-substituted tetrahydroisoquinolines and compare different chiral auxiliaries used in the Bischler-Napieralski and Pictet-Spengler reactions and finally to optimize the number of steps needed to prepare the target compounds. The main challenge encountered in the Pictet-Spengler method was the decomposition of the phenylacetaldehyde. The successfully used method was the Bischler-Napieralski reaction because it does not involve the use of a phenylacetaldehyde.

Using the Bischler-Napieralski method, non-stereoselective and stereoselective syntheses of tetrahydroisoquinolines have been achieved. The racemic tetrahydroisoquinolines have been synthesized in a three-step procedure starting from 3,4-dimethoxyphenylethylamine whereas the chiral tetrahydroisoquinolines were synthesized from vanillin in a seven-step reaction procedure. The *R* and *S* enantiomers of α-methylbenzylamine were successfully employed in the synthesis of 1-benzyltetrahydroisoquinolines. However, the *R*-enantiomer of 1,2,3,4-tetrahydro-1-naphthylamine could be used to form a chiral phenylethylamine, while ring closure in a Biscler-Napieralski reaction was not successful under similar reaction conditions.

The diastereoselectivity of the reactions to form the chiral tetrahydroisoquinolines was determined using NMR spectroscopy and was found to be 96% and 90% *de* for the (*R*)- and (*S*)-1-benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline,

respectively. The stereochemistry of the final products was found to be similar to that of the chiral auxiliary starting material for each of the synthesized chiral tetrahydroisoquinolines. Yields for the precursors were good to moderate, especially on the final stages of the synthesis.

Declaration

I, *Vezekile P. Zungu* hereby declare that this research is the outcome of my own investigation and has not already been accepted in substance for any other degree and is not being submitted in candidature for any other degree.

Signed:_____(Vezekile P. Zungu) Date:_____

I hereby confirm that the above statement is true and correct.

Signed:_____ (Prof. Fanie R. van Heerden) Date: _____

(Supervisor)

School of Chemistry and Physics

University of KwaZulu-Natal

Pietermaritzburg

January 2014

Plagiarism

I, *Vezekile P. Zungu*, declare that:

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To my late sister **Thembisile Precious Zungu**

October 1982 – October 2007

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Matthew 19:26 Jesus looked at them and said, "With men this is impossible, but with ***God all things are possible."***

Abbreviations

^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
aq	Aqueous
Ar	Aryl
BBIQ	Bisbenzyltetrahydroisoquinoline
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binapthyl
BuLi	Butyllithium
conc	Concentrated
DCM	Dichloromethane
de	Diastereomeric excess
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazen-2-yl)-4-methylmorpholinium chloride
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour

HRMS	high-resolution mass spectrometry
Hz	Hertz
IBX	*o*-Iodoxybenzoic acid
IR	Infrared
lit	Literature
LRMS	Low-resolution mass spectrometry
m.p.	Melting point
m/z	Mass/charge ratio
Me	Methyl
Me_2SO_4	Dimethyl Sulfate
MeCN	Acetonitrile
MeI	Methyl Iodide
MeOH	Methanol
min	Minutes
Ms	Molecular seives
NMR	Nuclear Magnetic Resonance
NRF	National Research Foundation
^oC	Degrees Celsius
P-gp	P-glycoprotein
Ph	Phenyl
R_f	Retention factor
rt	Room temperature
^{t}Bu	*tert*-Butyl

TFSA	Trifluoromethanesulfonic acid
THIQ	1,2,3,4-Tetrahydroisoquinoline
TLC	Thin-Layer Chromatography
UV	Ultraviolet

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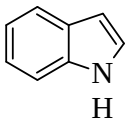
CHAPTER 1

BACKGROUND ON ALKALOIDS AND PROJECT OVERVIEW

1.1 Introduction

Plants synthesize small molecules called alkaloids. The discovery of alkaloids dates back to the early 1800's.[1,2] Alkaloids are subdivided according to the basic skeleton type and they include, amongst others, indole (**1**), quinoline (**2**) and isoquinoline (**3**).[1] Numbering of **3** is shown for nomenclature purposes.



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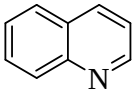

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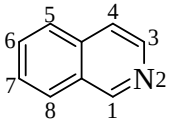

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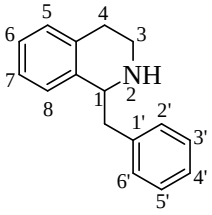
Isoquinoline alkaloids have drawn the attention of synthetic chemists because of their structural diversity and biological activities. Isoquinoline alkaloids that are substituted with a benzyl group in the 1-position are called 1-benzylisoquinolines and are of interest as a result of their antimalarial and antitumour activity. Subclasses of isoquinoline alkaloids include the benzyltetrahydroisoquinolines (**4**), which are represented by morphinanes (**5**), cularines (**6**), protoberberines (**7**) and phthalideisoquinolines (**8**).



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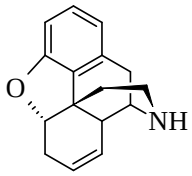

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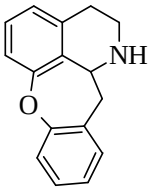

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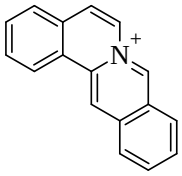

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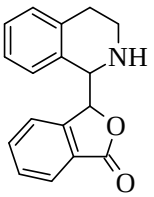

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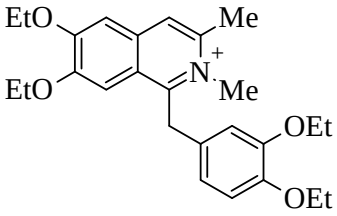
1.2 Biological Activities of Alkaloids

1.2.1 Malaria

Isoquinoline-derived compounds such as **9** inhibit the malaria parasite.[3] As an improvement to existing compounds, tetrahydroquinoline sulfonamides (**10**) have been reported to show strong potency against the malaria parasite at nanomolar concentrations.[4-6]



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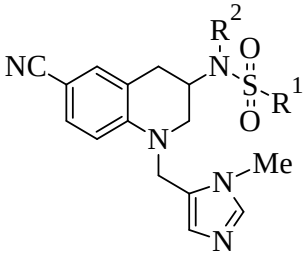

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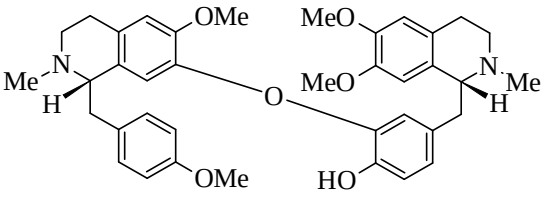
1.2.2 Cancer

Some tetrahydroisoquinolines (THIQ's) occur as dimers and hence they are called bisbenzyltetrahydroisoquinolines (BBIQ's). Neferine (**11**), the major BBIQ isolated from *Nelumbo nucifera* has good anti-cancer activity.[7]



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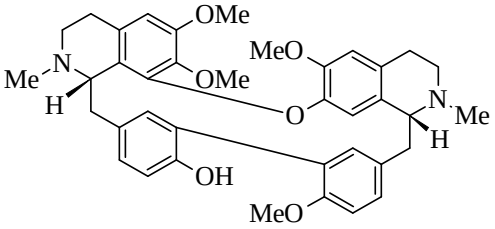

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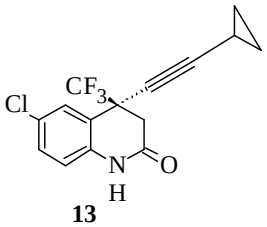
Some of the potent BBIQ's such as funiferine (**12**) are doubly bridged and inhibit the growth of cancerous cells with minor toxicity to a control cell line.[8]

http://www.kew.org/plants-fungi/Nelumbo-nucifera.htm 07/10/2013

Figure 1.1: *Nelumbo nucifera* (Nymphaceae).

1.2.3 HIV/AIDS

Drugs such as the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz (**13**) are used for treating HIV. This treatment is limited by multi-drug resistance (MDR) in the human body. In a recent report, polysubstituted THIQ's (synthesized in a one-pot reaction) with potential pharmaceutical and biological importance are described. For instance, a derivative of a HIV inhibitor, *R*-coclaurine (**14**), 1-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol (**15**) has also a strong potency against HIV with low cytotoxicity.[9]



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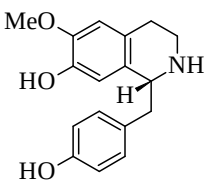

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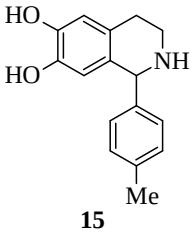

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1.3 Multidrug Resistance

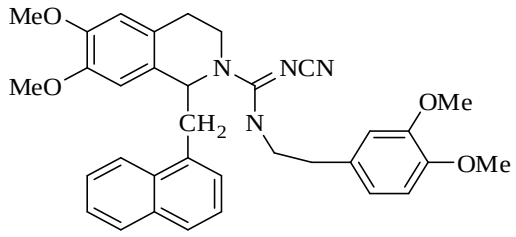
1.3.1 Multidrug Resistance and P-glycoproteins

Multidrug resistance (MDR) is the defense of a group of cells against a large spectrum of drugs with different chemical structures and mechanism of influence on the cell. MDR is a problem in the treatment of patients with cancer and infectious diseases like malaria, tuberculosis and HIV. The main course of MDR is a decrease of drug accumulation which results from a decreased drug influx and an increased drug efflux from cells.[10]

This becomes a problem because most drugs enter the cell by passive diffusion across the cell membrane and hence changes in drug influx may be associated with mutations in the cell membrane structure. The membrane-associated proteins like P-glycoproteins (P-gp) control the drug influx and efflux and they have been found to be overexpressed in tumor cells.[10]

1.4 Tetrahydroisoquinolines as potential MDR Reversers

P-gp mediated MDR is one of the major problems in cancer chemotherapy. P-gp is found in human tissues such as kidneys, liver, intestine and in the blood and the brain barrier.[11] As mentioned before, THIQs show a wide range of biological activities. It has been reported that some THIQ-derived substances have a strong potency for inhibiting P-gp coupled with minor cytotoxicity.[11] For example, B3 (**16**) is a novel and potent MDR reverser, it inhibits P-gp function without producing cardiovascular side effects.[12] Natural BBIQ's such as tetrandrine (**17**) have good MDR reversal activity.[13,14]



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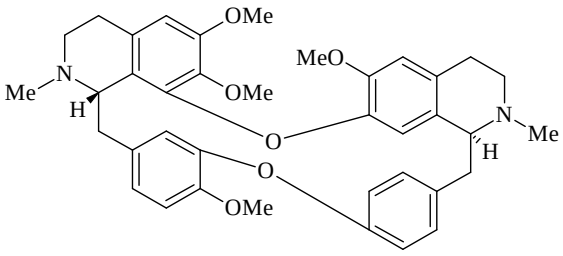

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1.5 Aims and Objectives

Many organic compounds are chiral and they are useful because of the biological activity associated with them. The biological activities of chiral compounds are often linked to the absolute configuration, i.e. a compound and its mirror image can have different activities. Therefore, enantioselective synthesis plays an important role in the synthesis of biologically

active compounds. The activity of THIQ's prompted us to investigate the stereoselective synthesis of selected 1-substituted tetrahydroisoquinolines.

The aims of this project were to:

- Investigate the stereoselective synthesis of 1-substituted tetrahydroisoquinoline derivatives **18** and **19**
- Compare different chiral auxiliaries used in the Bischler-Napieralski and Pictet-Spengler reactions
- Optimize the number of steps to prepare **18** and **19**.

Table 1.1: THIQ's intended for synthesis.

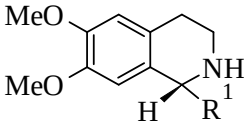	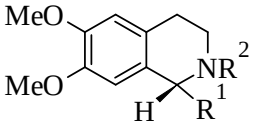
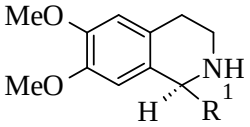	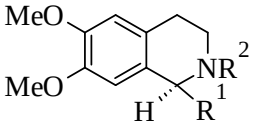
18	**19**

Table 1.2: R-groups employed for synthesis.

R^1	R^2
CH_2Ph	(*R*)-CH(Me)Ph
4-OMePhCH_2	(*S*)-CH(Me)Ph
4-MeOPh	(*R*)-Tetralin
CH_2Me	

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CHAPTER 2

SYNTHETIC APPROACHES TO 1-SUBSTITUTED TETRAHYDROISOQUINOLINES: A LITERATURE REVIEW

2.1 Introduction

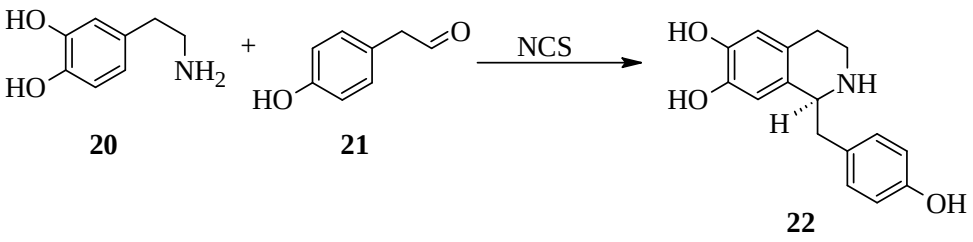
Several approaches for the synthesis of THIQ's have been developed in a number of laboratories over the last five decades. However, the enantioselective synthesis of these compounds remains a challenge. Most naturally occurring 1-substituted THIQ's possess the 1*S* configuration and only a few have been isolated with the 1*R* configuration yet the two enantiomers have different biological activities. The following paragraphs review the synthetic approaches to selected THIQ's. The focus will be on asymmetric synthetic strategies.

2.2 Biosynthesis of Tetrahydroisoquinolines

An understanding of the biosynthetic pathways plays a major role in the synthesis of many natural products since many synthetic pathways mimic biosynthesis. The following paragraph outlines the biosynthesis of norcoclaurine (**22**).

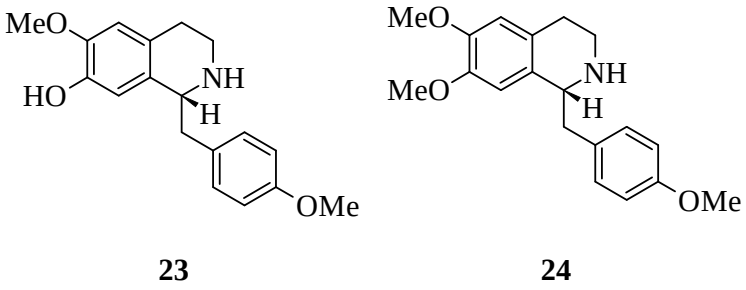
2.2.1 Biosynthesis of (*S*)-Norcoclaurine (22)

The biosynthetic pathway to (*S*)-norcoclaurine (**22**) proceeds by the enzyme-catalyzed condensation of dopamine (**20**) and 4-hydroxyphenylacetaldehyde (4-HPAA) (**21**), (Scheme 2.1).[1,2] These substrates are obtained by decarboxylation and hydroxylation or deamination of tyrosine (**25**).[2]



Scheme 2.1: Biosynthesis of *(S)*-norcoclaurine (**22**).

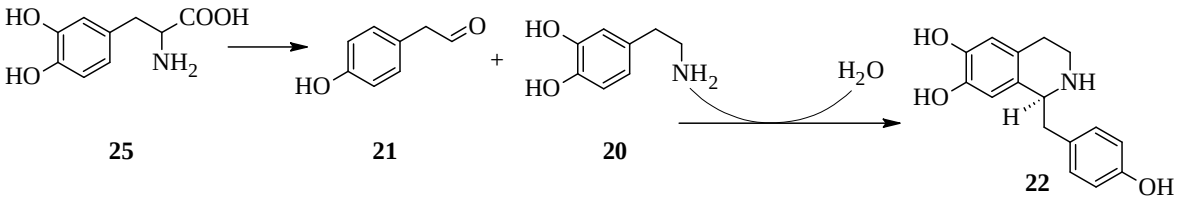
Relate82d 1-tetrahydroisoquinoline alkaloids include (*R*)-4'-*O*-methylcoclaurine (**23**) and (*S*)-*O*,*O*-dimethylcoclaurine (**24**) which were isolated from the leaves of *Annona maricata*.[3]



2.2.2 An Enzymatic Stereoselective Synthesis of (*S*)-Norcoclaurine

This reaction is the stereospecific enzyme-catalyzed Pictet-Spengler condensation of dopamine (**20**) and 4-HPAA (**21**) [obtained from 3,4-dihydroxyphenylalanine (**25**)] to yield the benzylisoquinoline central precursor (*S*)-norcoclaurine (**22**) (Scheme 2.2). This synthetic method is highly efficient and guarantees a very good enantioselectivity. The enzyme (*S*)-norcoclaurine synthase (NCS) has been recently identified[4] and has shown to be an efficient bifunctional catalyst that activates the *p*-hydroxybenzaldehyde (**21**) substrate and drive the Mannich–type condensation with substrate **20** in an enantioselective manner*.[2] The enzyme NCN was isolated from plants such as *Papaver somniferum* (opium poppy) and *Thalictrum flavum* (a common meadow rue).[5]

* In this paper the stereochemistry is indicated incorrectly.



Scheme 1.2: The stereospecific chemoenzymatic synthesis of (*S*)-norcoclaurine (**22**) from tyrosine (**25**) and dopamine (**20**).[2]

2.3 Synthesis of THIQ's

2.3.1 Synthesis of the Isoquinoline Ring

The synthetic approaches towards THIQ's can be classified into 5 different types, depending on where the final bond is formed.[6] The commonly used methods are Type 1 and Type 5 (Fig. 2.1). Type 1 THIQ is synthesised *via* Pictet-Spengler and Bischler-Napieralski reactions.[6] These synthetic methods involve a ring closure between the benzene ring and the carbon atom that forms C-1 of the resulting THIQ. They allow cyclisation reactions and the formation of a stereogenic centre. Type 5 THIQ is synthesised *via* the Pomeranz-Fritstch reaction. Type 2 involves the ring closure between the nitrogen atom and C-1. Type 3 is simply a result of a bond formation between C-3 and the nitrogen atom. The following paragraphs are a brief discussion of the asymmetric synthetic methods.

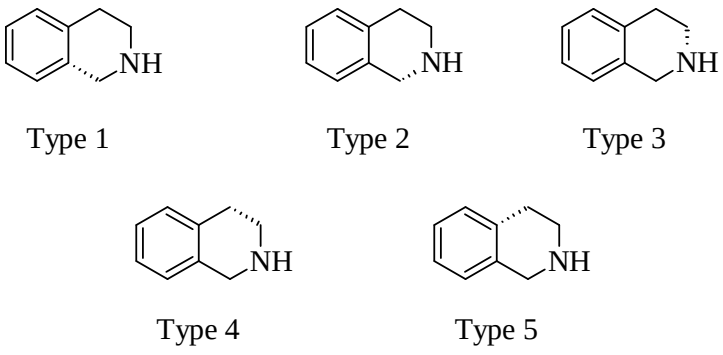


Figure 2.1: Classification of synthetic approaches to THIQ's.

2.4 Methods for the Asymmetric Synthesis of Tetrahydroisoquinolines

THIQ alkaloids are heterocyclic compounds found in many natural and synthetic products. They are well known for their biological activities such as antiarrhythmic, angiotensin-converting enzyme activity, antihypertensive, antitumor,[7] antimicrobial, antiplasmodial, non-competitive inhibition to AMPA receptor and anti-depression activities.[8] They are valuable in synthetic chemistry because they are utilised as synthetic intermediates in a wide range of substances.

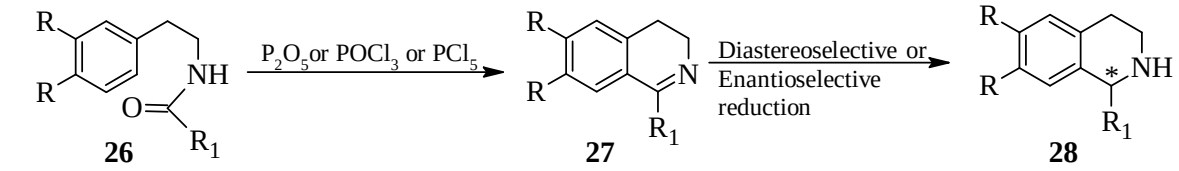
A number of synthetic methods are employed in the asymmetric synthesis of 1-subsituted tetrahydroisoquinolines. These methods include:

- Bischler-Napieralski reaction
- Pictet-Spengler reaction
- Pomeranz-Fritsch reactions
- Metal-catalyzed cyclisation

Asymmetric synthesis is based on the stereo modification of these traditional methods and addresses the absolute configuration of the final product. The following paragraphs discuss these synthetic methodologies in detail.

2.4.1 Bischler-Napieralski Reaction

This reaction was discovered in 1893 by August Bischler and Bernard Napieralski.[9] It makes use of phenylamines and carboxylic acids or acid chlorides as the starting materials to give the acetamide (**26**). Common condensing agents such as phosphorus pentoxide (P_2O_5), phosphorus oxychloride ($POCl_3$) and phosphorus pentachloride (PCl_5) are used to form the 3,4-dihydroisoquinoline **27**, which is then reduced to the corresponding THIQ (**28**) (Scheme 2.3).[10,11] The reduction step determines the stereochemical outcome of the reaction and can be achieved either by diastereoselective or enantioselective methods that will be briefly discussed below.



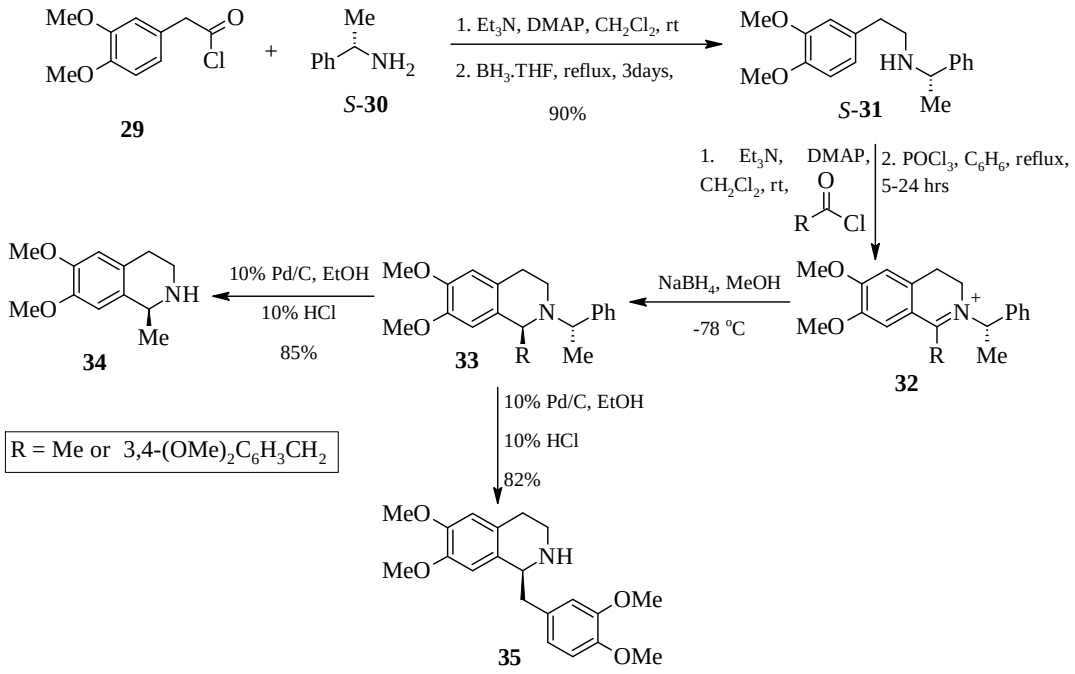
R = OMe, OBn

R_1 = Me, Et, Bn

Scheme 2.2: Representative Bischler-Napieralski reaction.

2.4.1.1 Diastereoselective Bischler-Napieralski Reactions

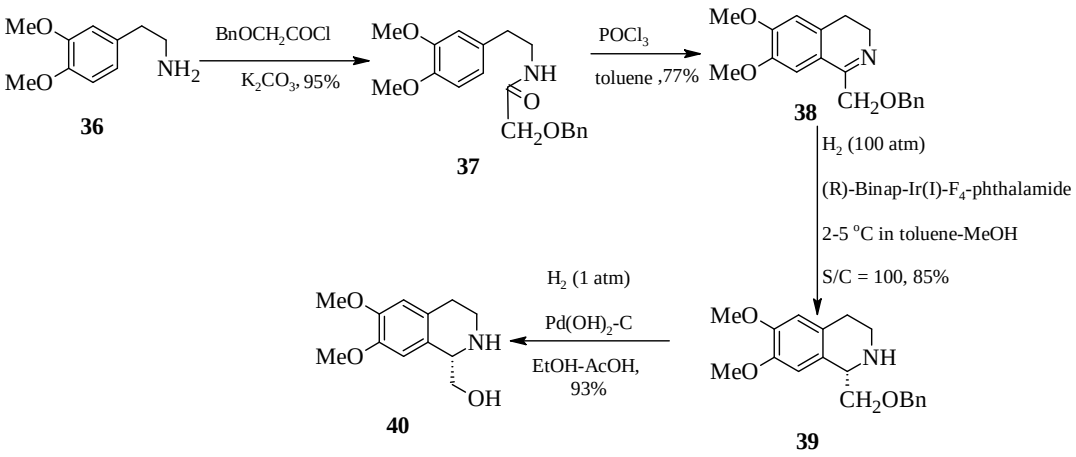
The use of 3,4-dihydroisoquinolinium salts (**32**) have been found to give excellent results in diastereoselective Bischler-Napieralski reactions.[12] (+)-(S)-Salsolidine (**34**) and (*S*)-norlaudanosine (**35**) were prepared in a four-step reaction sequence starting from a condensation reaction of 3,4-dimethoxyphenylacetyl chloride (**29**) and α-methylbenzylamine (**30**) in the THF solution of BH_3 to give **31** in 90% yield (Scheme 2.4).[13] *N*-acylation reaction followed by the Bischler-Napieralski cyclisation afforded the chiral dihydroisoquinolinium salt (**32**) which then afforded the tetrahydroisoquinoline (**33**) upon reduction with $NaBH_4$ in 90-94% diastereoselectivity. Catalytic hydrogenolysis of **33** with H_2-/Pd-C afforded **34** and **35** in 85% and 82% yield, respectively.[12-15]



Scheme 2.3: Diastereoselective synthesis of (+)-(S)-salsolidine (**34**) (*S*)-norlaudanosine (**35**).[13]

2.4.1.2 Enantioselective Bischler-Napieralski Reactions

The Bischler-Napieralski enantioselective synthesis of 1-substituted THIQ's occurs via enantioselective reduction of the resulting prochiral dihydroisoquinoline. This is achieved by the use of a chiral hydride reducing agent or hydrogenation in the presence of a chiral catalyst. Morimoto *et al*.[16] reported the enantioselective synthesis of (*S*)-(+)-calycotomine (**40**) that was accomplished by employing catalytic asymmetric hydrogenation of the dihydroisoquinoline **38** with 0.5 mol % of an iridium (I) complex of (*R*)-BINAP in the presence of 3,4,5,6-tetrafluorophthalimide (Scheme 2.5).

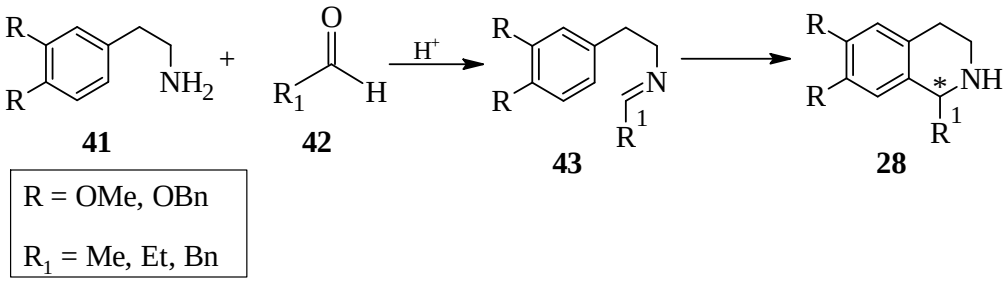


Scheme 2.4: Enantioselective synthesis of (*S*)-(+)-calycotomine (**40**) by Morimoto *et al.*[16]

The amide **37** was prepared from a commercially available 3,4-dimethoxyphenylethylamine (**36**) with benzyloxyacetyl chloride in the presence of potassium carbonate under biphasic conditions in ether and water. Heating of the amide in $POCl_3$ in toluene formed 1-benzyloxymethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**38**), which was transformed to **39** by asymmetric hydrogenation. The final product **40** was obtained in 93% yield, 86% ee via the hydrogenolysis of the *O*-benzyl group in the presence of $Pd(OH)_2$-C.

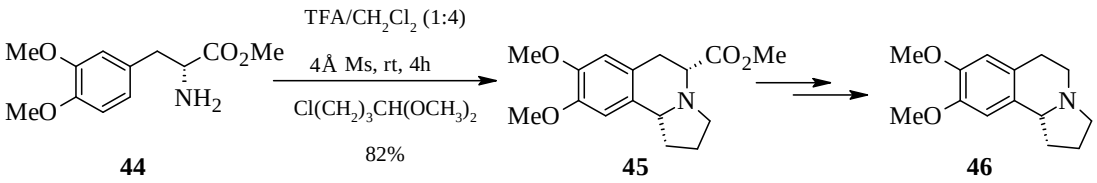
2.4.2 Pictet-Spengler Reaction

This reaction was discovered by Amè Pictet and Theodor Spengler in 1911.[17] It is one of the most important and convenient methods as it forms a stereogenic centre simultaneously with the ring closure. In the syntheses that have been carried out in an asymmetric manner, the chirality transfer occurred from the chiral auxiliary attached to either the *β*-arylethylamine (**41**) or the aldehyde (**42**) component, thus involving a diastereoselective synthesis as shown in Scheme 2.6.[17] The resulting imine (**43**) undergoes Pictet-Spengler cyclisation to give **28**.



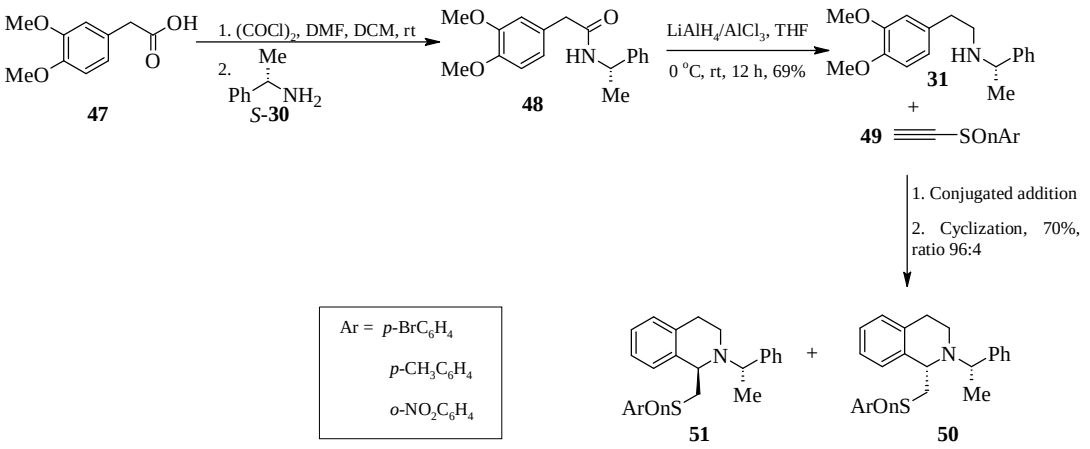
Scheme 2.5: Representative Pictet-Spengler reaction.

The enantiospecific and stereoselective synthesis of (+)-crispine[18] (**46**) was achieved via Pictet-Spengler reaction in 32% yield (Scheme 2.7).[19] This naturally occurring compound was synthesized from commercially available (*R*)-(-)-methyl-2-amino-3-(3,4-dimethoxyphenyl)-propanoate (**44**) and 4-chloro-1,1-dimethoxybutane. Decarboxylation of **45** in a three-step procedure afforded **46** and its antipode was prepared in a similar procedure from a commercially available (*S*)-(+)-amino acid.



Scheme 2.6: Synthesis of (+)-crispine (**46**).[19]

The coupling of the carboxylic acid **47** (Scheme 2.8) with the chiral auxiliaxy amine *S*-**30** afforded the amide **48** that resulted in *S*-**31** upon reduction. The reaction of the intermediate *S*-**31** with chiral actylenic sulfoxide (**49**) was successfully investigated by Yan *et al*.[20] Previous studies have shown that the 3,4-dimethoxyphenylethyl system reacts better with the acetylenic sulfoxides containing a strong electron withdrawing group at the aromatic moiety. Hence one of the aromatic moieties was substituted with the *o*-nitro group and gave excellent diastereoselectivity upon treatment with TFA to provide the mixture of tetrahydroisoquinolines **50** and **51** (96:4 ratio) in 70% yield.

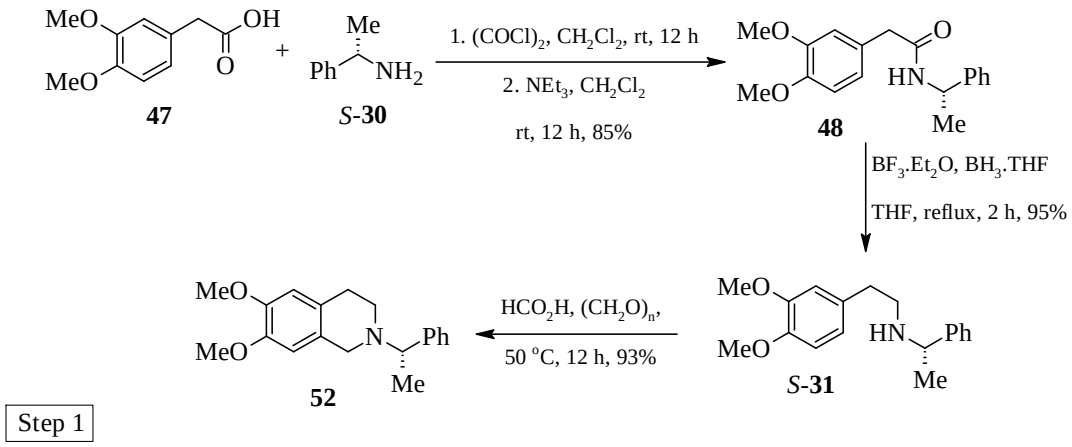


Scheme 2.7: Synthesis of THIQ's **50** and **51** from chiral acetylenic sulfoxides.[20]

2.4.2.1 Electrochemical Synthesis

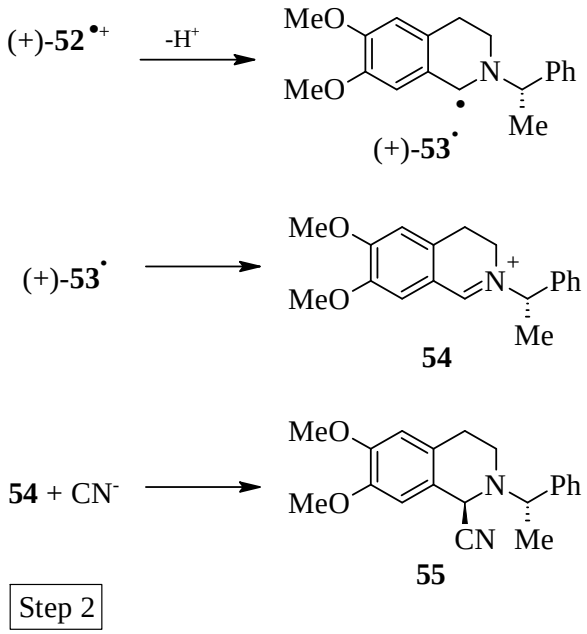
Electrochemistry of natural product has been extensively studied in the later part of the 20th century.[21-23] Pictet-Spengler cyclisation method can be used in conjunction with the electrosynthetic strategies to provide the desired tetrahydroisoquinolines. Louafi *et al.*[24] reported the electrosynthesis of chiral 1-substituted cyanotetrahydroisoquinolines. The key steps in this reaction were the Pictet-Spengler cyclisation to give a THIQ as shown in Scheme 2.9 (step 1) followed by anodic cyanation (step 2) of the resulting THIQ as shown in Scheme 2.10.

The first step of the synthesis was the conversion of the carboxylic acid **47** to the corresponding acid chloride that was condensed with *S*-**30** to afford **48** in 85% yield. Reduction of **48** afforded *S*-**31** in 95% yield which was subjected to Pictet-Spengler cyclization to afford **52** in 93% yield (Scheme 2.9).



Scheme 2.8: Pictet-Spengler cyclisation to form **52**.

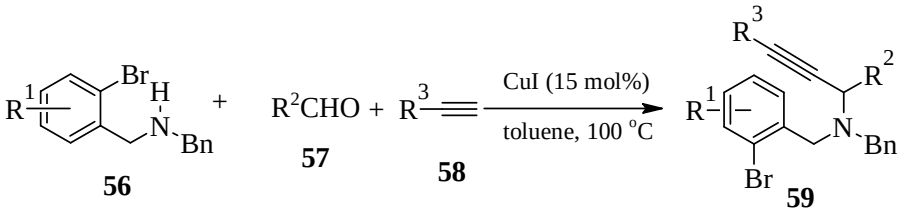
The loss of electron from **52** resulted in the formation of a cationic radical intermediate which further undergone a series of reactions to form **55** (Scheme 2.10). The anodic oxidation of **53** resulted in the formation of an iminium radical **53** which resulted in **54** upon stepwise deprotonation and ionization which afforded **55** when subjected to cyanation with sodium cyanide.



Scheme 2.9: Anodic cyanation of 1-cyanotetrahydroisoquinoline **55**.

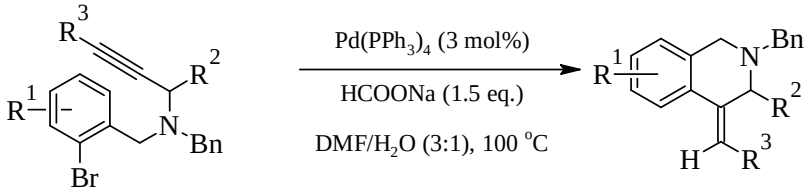
2.4.2.2 Metal-catalysed Reactions

Among various methods used for synthesis of THIQ's, transition metal catalyzed C-C bond formation is considered as one of the modern synthetic strategies.[25-27] Nadakumar *et al.*[8] reported a two-step palladium catalyzed formation of functionalized THIQ's in good yield.[8] The first step (Scheme 2.11) involves a Cu-I catalyzed 3-component coupling reaction of an amine **56**, an aldehyde **57** and a terminal alkyne **58** to give a propargylamine **59**. The second step is a regio- and stereoselective palladium catalyzed 6-*exo-dig* carboxylation of **59** to provide **60**.[8]



56 **57** **58** **59**

Step 1



59 **60**

Step 2

R^1 = H, 4,5-OMe

R^2 = Ph, *iso*-propyl, 4-OMePh

R^3 = Ph, *n*-butyl, 4-OMePh

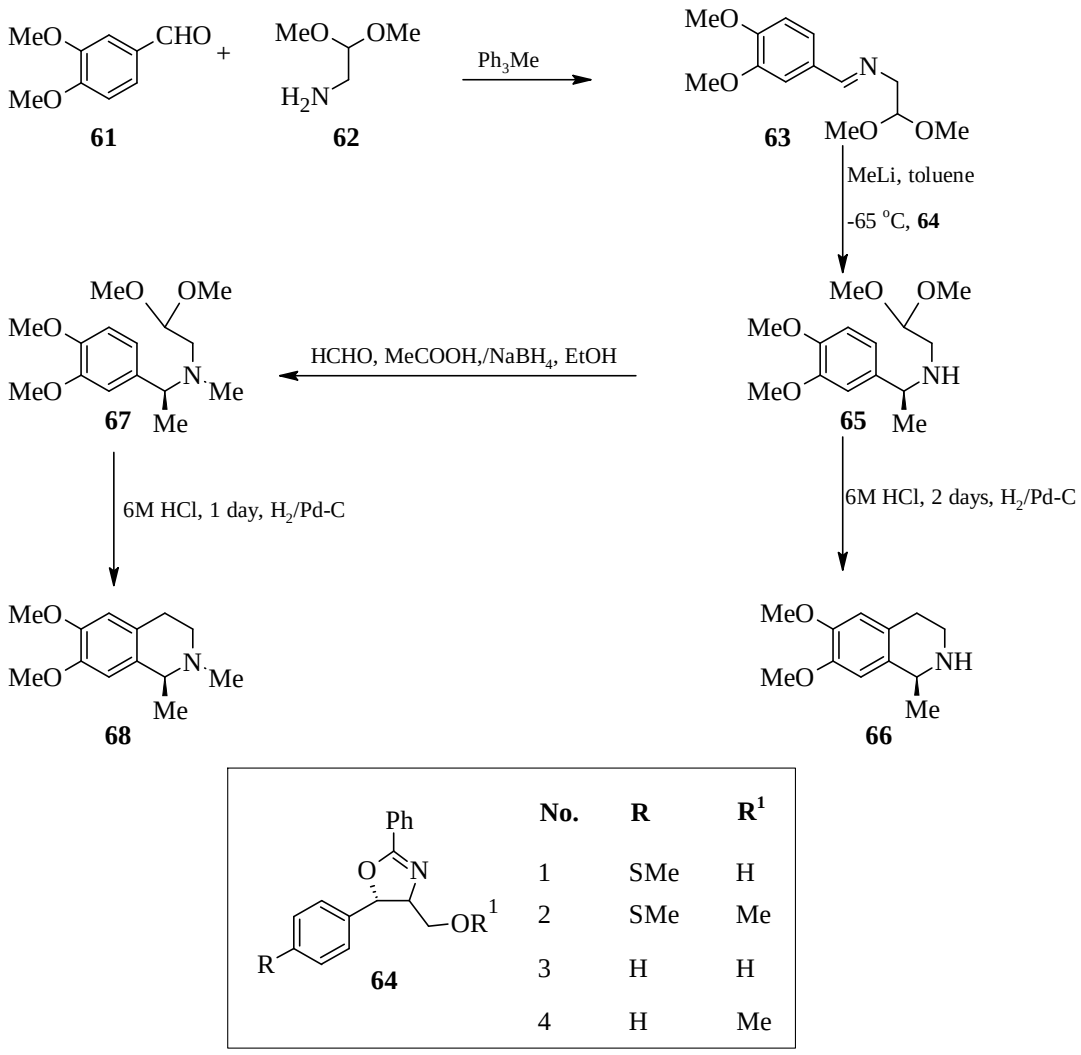
Scheme 2.10: Palladium catalyzed synthesis of **60**.[8]

2.4.3 Pomeranz-Fritsch Reaction

This is a synthetic method for Type 5 THIQ's involving the cyclization reaction of benzylaminoacetal (**65**) under acid-catalyzed conditions. The original Pomeranz-Fritsch reaction method has been improved and modified in many ways.[28,29] The most useful modification was introduced by Bobbit *et al.*[30] in which **62** was reduced *via* catalytic hydrogenation of the imine C=N double bond and by employing Grignard reagents[31] to a benzylaminoacetal intermediate **65** before cyclisation.[30] The latter Pomeranz-Fritsch-Bobbit methodology can either be enantioselective by employing external factors to induce chirality or diastereoselective by introducing chiral auxiliaries.

2.4.3.1 Enantioselective Pomerenz-Fritsch-Bobbit Reaction

Głuszyńska *et al.*[32] reported the enantioselective synthesis of (-)-salsolidine (**66**) and (-)-carnegine (**68**)[33] by employing the Pomerenz-Fritsch-Bobbit methodology (Scheme 2.12). The synthesis started by the condensation of 3,4-dimethoxybenzaldehyde (**61**) with the aminoacetal (**62**) to give **63**. Ligand **64** promote the enantioselective addition of methyllithium to the imine double bond to give **65**. Enantioselectivity in the addition step was achieved by the use of enantiopure oxazolines (**64**). Compounds **66** and **68** were synthesised in 46 and 36% *ee*, respectively.[32]



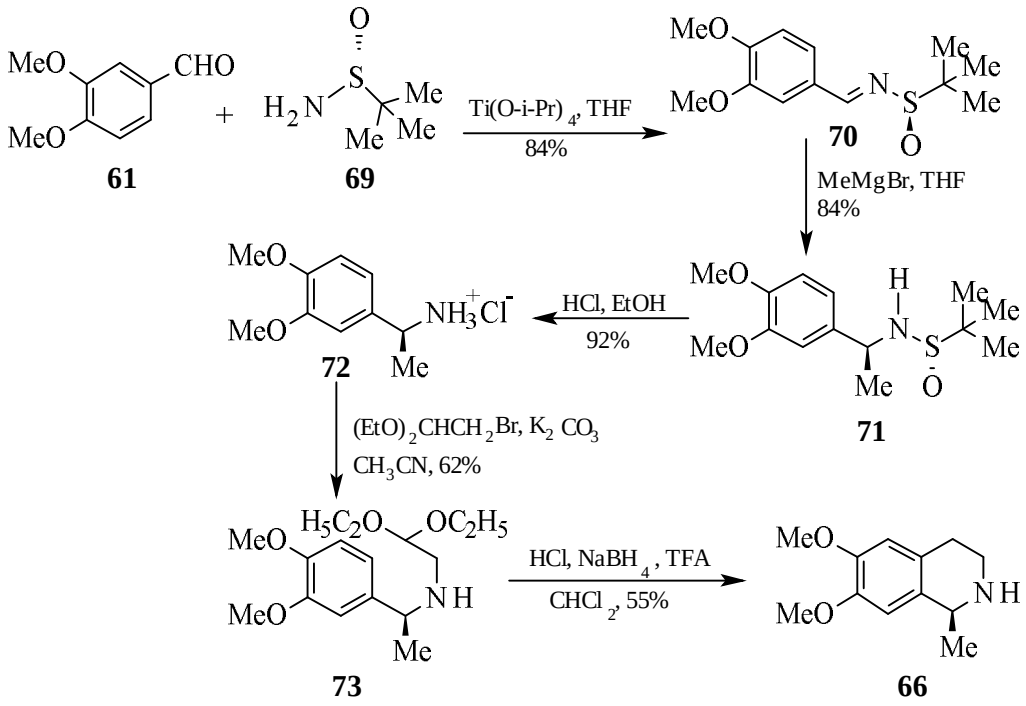
Scheme 2.11: Enantioselective synthesis of (-)-salsolidine (**66**) and (-)-carnegine (**68**).[32]

2.4.3.3 Diastereoselective Pomerenz-Fritsch-Bobbit Reaction

Sulfinimines have been used in the synthesis of natural products and THIQ's because of their good reactivity and stereoselectivity that is due to the electron-withdrawing character of the *N*-sulfinyl moiety.[34]

The enantiomerically pure (*R*)-(*N*)-butanesulfinylimine (**69**) was employed in the diastereoselective synthesis of (-)-salsolidine (**66**) using the Pomeranz-Fritsch-Bobbit methodology (Scheme 2.13).[35] Compound **67** was prepared in a five-step procedure starting from **61** and (*R*)-*tert*-butylsulfinylamide as a chiral auxiliary. The resulting

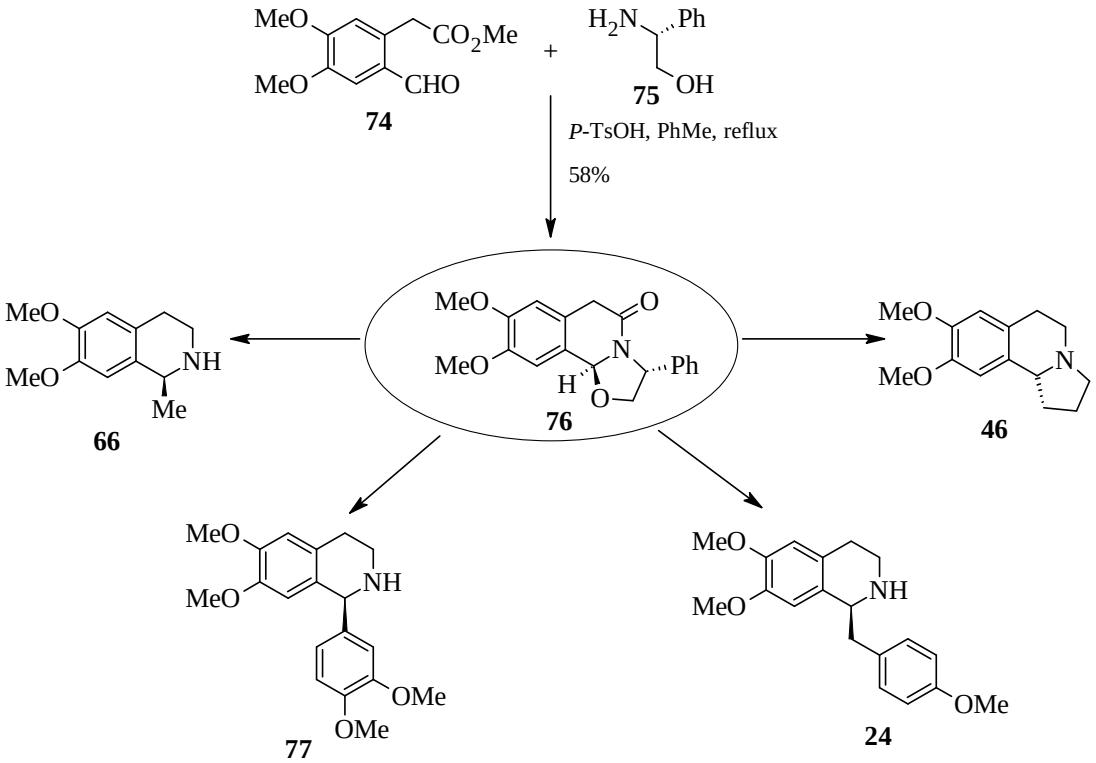
sulfinimine **70** was subjected to methylation with a Grignard reagent to give **71** in 84% yield. The ethanolic solution of **71** was subjected to acid hydrolysis to afford the intermediate **72** that was acetylated to give the aminoacetal (**73**) upon purification. The acetal hydrolysis of **73** afforded **66** in 58% yield, 98% ee.[35]



Scheme 2.12: Diastereoselective synthesis of (-)-salsolidine (**66**) *via* the Pomeranz-Fritsch reaction.[35]

2.4.3 General Approach towards the Synthesis of 1-Substituted THIQ's

A general enantioselective strategy has been reported by Amat *et al* [36] (Scheme 2.14) for 1-substituted THIQ alkaloids. A number of enantiopure 1-substituted THIQ's were synthesized from a tricyclic lactam (**76**) that was obtained by the cyclocondensation of an ester (**74**) with (*R*)-phenylglycinol (**75**). These include (*S*)-(-)-salsolidine (**66**), (-)-crispine (**46**), (-)-norcyptostyline II (**77**) and (-)-*O*,*O*-dimethylcoclaurine (**24**).



Scheme 2.13: THIQ's prepared from tricyclic lactam scaffold (**76**).[36]

2.5 Conclusion

This chapter reviews a variety of methods towards the synthesis of THIQ's starting from the biosynthesis up to the asymmetric synthesis of THIQ's. It has been noted that the asymmetric synthesis of THIQ's has constantly developed over the years. The advantage of the asymmetric synthesis is that it provides both *R* and *S* configurated compounds in good yields whereas the biosynthesis only allows the isolation of small amounts of the compounds and most of them possess the 1*S* configuration. Modification of the traditional methods for the asymmetric synthesis of THIQ's has been a great success in the enantioselective synthesis of these compounds. These methods give good to excellent yields of compounds and also provide the general approach for the synthesis of THIQ's in the stereoselective manner.

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CHAPTER 3

RESULTS AND DISCUSSION

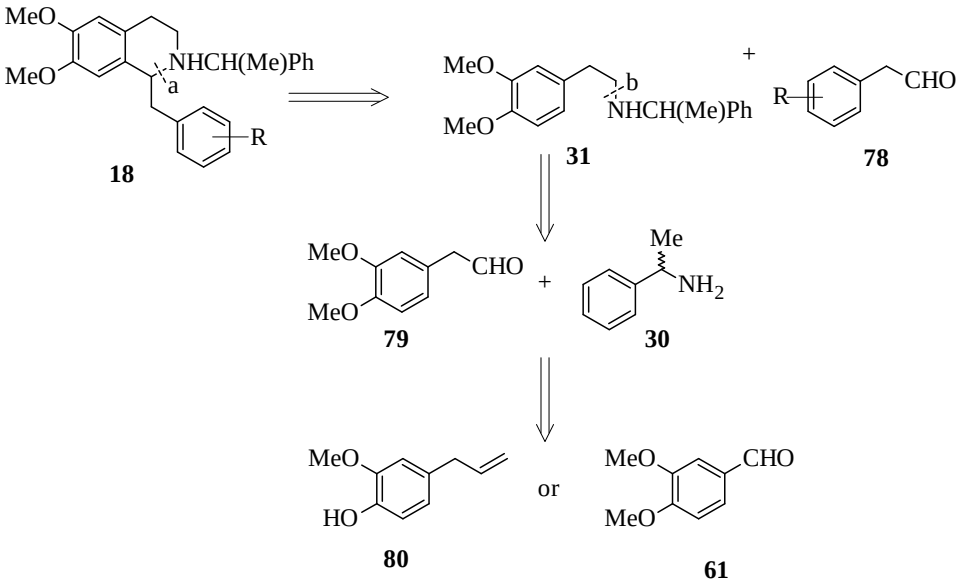
3.1 Introduction

The Pictet-Spengler and Bischler-Napieralski reactions are widely used in the synthesis of THIQ's. The key reagent in both these reactions is a 2-arylethylamine. By attaching a chiral auxiliary to the amine, stereoselective syntheses of THIQ's become feasible. This Chapter discusses the application of the above-mentioned reactions in the preparation of **18** and **19**.

The preparation of the 2-arylethylamine often requires a large number of steps and the first aim was to attempt to minimize the number of steps in the preparation of this intermediate. The second aim was to compare chiral auxiliaries for the synthesis of enantiopure THIQ's. As a first step, a retrosynthetic analysis was performed on **19**, as is explained in the paragraph below.

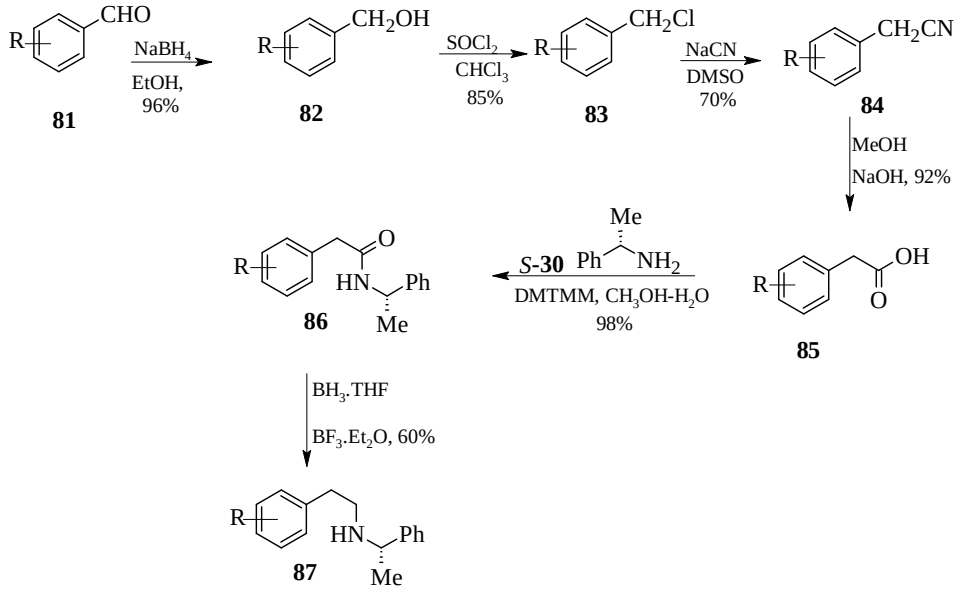
3.2 Retrosynthetic Analysis

For the synthesis of compound **18** (Scheme 3.1), with either the *R* or *S* configuration at C-1, the disconnection at bond *a* leads to β-phenethylamine **31** and phenylacetaldehyde **78**. A second disconnection at *b* affords **79** and the chiral amine **30**. Phenylacetaldehyde **79** can be prepared from eugenol (**80**) by ozonolysis or from 3,4-dimethoxybenzaldehyde (**61**), which is easily prepared from commercially available vanillin. Amine **30** was chosen as the standard chiral auxiliary because it is commercially available as both the *R*- and *S*-enantiomers and the product, *N*-benzylamine, can be easily deprotected by catalytic hydrogenation.



Scheme 3.1: Retrosynthetic analysis of **18**.

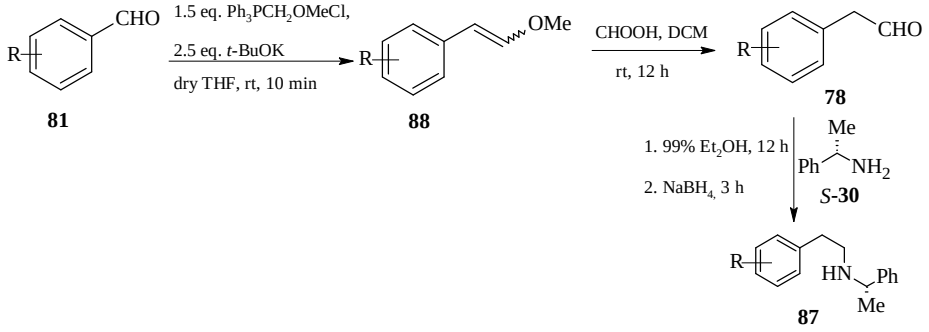
Previous methods used in our research group for the incorporation of the chiral auxiliary amine **30** used long synthetic routes (Scheme 3.2).[1-3] This route to 1-benzyltetrahydroisoquinolines (**19**) was also followed by several other researchers.[3,11] The route consists of six steps which results in a low overall yield although individual steps give good yields.



Scheme 3.2: Incorporation of a chiral auxiliary **30** to the phenylacetic acid intermediate **85**.[1]

The synthesis starts with the conversion of benzaldehyde **81** to the corresponding benzyl alcohol **83** which is further converted to chloride **83** and then to cyanide **84**. Cyanide **84** was then converted to carboxylic acid **85** which was condensed with **30** to form the amide **86**, which was reduced to the amine **87**.

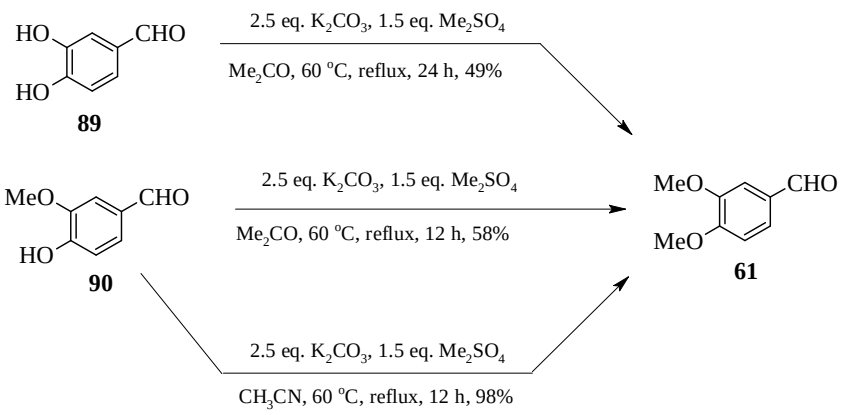
In the synthesis proposed here (Scheme 3.3), the number of steps was reduced to three. The problematic steps are the second and the third steps. Phenylacetaldehydes **78** react readily under acidic or basic conditions to form polymeric products and therefore the hydrolysis of **88** to **78** must be performed under carefully controlled conditions to get a good yield of the product. A one-pot condensation reaction of **78** and **30** to form **87** will eliminate a number of steps. However, this procedure has not been reported for these substrates and the method will have to be developed here.



Scheme 3.3: Proposed synthesis of the chiral amine **87**.

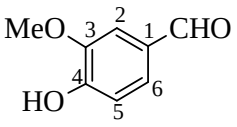
3.3 Preparation of 3,4-Dimethoxybenzaldehyde (61)

This is the first step in the synthesis and the goal was to obtain the highest possible yield. Different reagents and reaction conditions were explored in order to find the method that gives the best yield.



Scheme 3.4: Preparations of 3,4-dimethoxybenzaldehyde (**61**).

The first choice for the starting material was 3,4-dihydroxybenzaldehyde (**89**) that was commercially available, albeit expensive. It was anticipated that the free hydroxyl groups would be easily methylated to give the desired product in a good yield. However, methylation of **89** in anhydrous acetone and K_2CO_3 using dimethyl sulfate (Me_2SO_4) gave the desired product **61** in a low yield (49%) as shown in Scheme 3.4.



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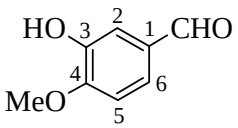
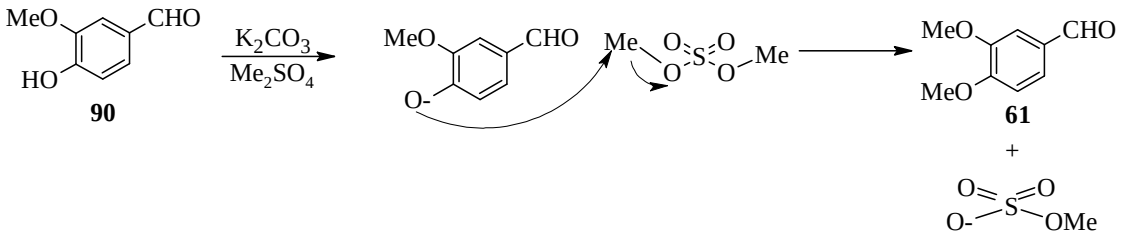


91

The low yield of this reaction was attributed to the formation of the other two by-products (from the TLC) which could be the 3-monomethylated (**90**) and the 4-monomethylated (**91**) products. The low selectivity of this reaction under these reaction conditions prompted us to consider alternative starting materials and vanillin (**90**) was used as starting material for subsequent reactions. By changing the solvent to acetonitrile, a 98% yield of product **61** was obtained. The mechanism for this reaction is illustrated in Scheme 3.5.



Scheme 3.5: The S_N2 reaction between vanillin (**90**) and dimethyl sulfate.

The structure of 3,4-dimethoxybenzaldehyde (**61**) was confirmed by ^{1}H NMR, ^{13}C NMR and 2D NMR. The ^{1}H NMR spectrum displays two sharp singlets for the two methoxy groups resonating at δ_H 3.97 and δ_H 3.99, and three aromatic protons resonating at δ_H 7.00, δ_H 7.41 and δ_H 7.46. The coupling constants of the three aromatic protons show that they form an ABX spin system, one proton at δ_H 7.00 (d, *J* = 8.3 Hz, *ortho* coupling, H-5), proton at δ_H 7.41 (d, *J* = 1.9 Hz, *meta* coupling, H-2) and the proton at δ_H 7.46 (dd, *J* = 8.3 and 1.9 Hz, *ortho* and *meta* coupling, H-6). The aldehyde proton was observed at δ_H 9.86 as a singlet. Assignment of the signals at δ_C 56.0 and 56.2 to the two methoxy groups, δ_C 109.1, 110.5 and 126.8 to C-2, C-5, and C-6, respectively, and δ_C 190.0 to the aldehyde carbon were based on correlations observed in a HSQC experiment.

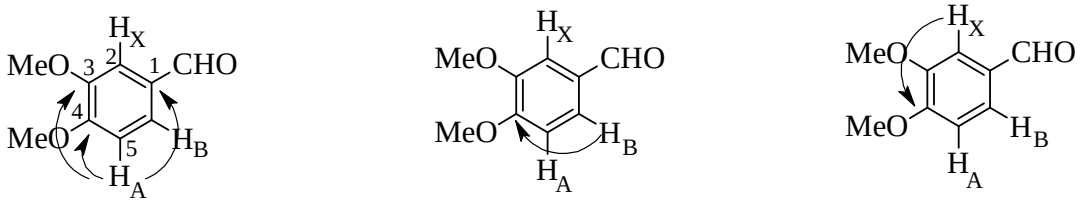


Figure 3.1: HMBC correlations observed for 3,4-dimethoxybenzaldehyde (**61**).

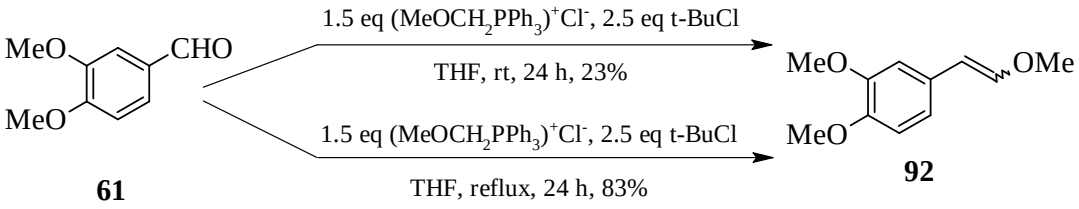
The non-protonated carbons display signals at δ_C 149.7, 154.5 and 130.2. These signals were assigned using an HMBC spectrum as it is able to show signals for protons coupled to carbons that are multiple bonds away. H_A is coupled to both C-3 and C-4 but shows strong correlation with C-3 while on the other hand H_B shows strong correlation with C-4 but not coupled to C-3 (Fig. 3.1). H_X also shows a strong correlation with C-4. The signal at δ_C 149.7 was assigned to C-3 and the signal at δ_C 154.5 was assigned to C-5. The signal at δ_C

130.2 was assigned to C-1. The IR spectrum shows a medium to strong peak at 1732 cm^{-1} which is in accordance with the literature value (1740-1720 cm^{-1}) for the aldehyde C=O bond.[4]

3.4 Preparation of the Phenylacetaldehyde (79)

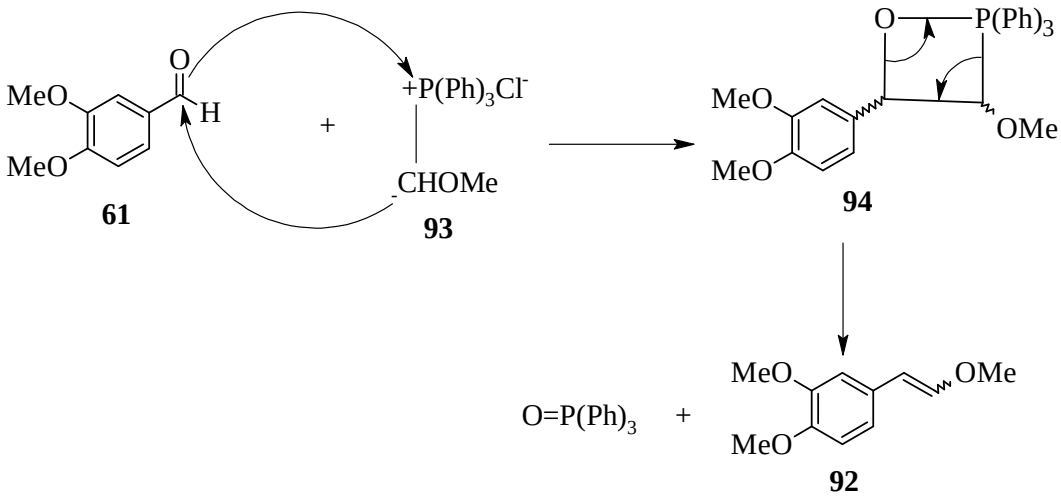
3.4.1 Preparation of 3,4-Dimethoxy-1-(2-methoxyethenyl)benzene (92)

Conversion of 3,4-dimethoxybenzaldehyde (**61**), to the enol ether **92** was attempted as outlined in Scheme 3.6. The first reaction resulted in 23% of the desired product **92** after refluxing the reaction mixture for 24 h. It was observed that the reaction was photosensitive and exothermic, so the synthesis of this intermediate at higher temperatures and in the presence of light was not advisable. Performing the reaction at room temperature for 10 minutes improved the yields to 83%.



Scheme 3.6: Preparation of the enol ether **(92).**

The obtained product **92** gave complex ^{1}H and ^{13}C NMR spectra because it consists of two compounds, *cis*- and *trans*-3,4-dimethoxy-1-(2-methoxyethenyl)benzene (**92**) in equal quantities. The ^{1}H NMR spectrum displayed six methoxy singlets at δ_H 3.67 - 3.88 for the *cis* and *trans*-products. The aldehyde singlet at δ_H 9.77 was no longer observed in the ^{1}H NMR spectrum confirming that the aldehyde was successfully converted to the enol ether **92**. Doublets for the vinylic protons were observed at δ_H 5.17 - 6.06. The mechanism for the Wittig reaction is shown in Scheme 3.7. The IR spectrum of the product shows broad absorptions at 3063, 2924 and 2850 cm^{-1} which agree with the reference[4] values of 3300-2700 cm^{-1} which indicates the presence of the C-H bond. The medium broad signal at 1674 cm^{-1} correlates with the literature values (1680-1600 cm^{-1}) indicating the presence of the C=C bond. The peaks at 1200 cm^{-1} to 1070 cm^{-1} are in accordance with the values listed in literature[12] for C-O bond, 1250-1050 cm^{-1}.



Scheme 3.7: The mechanism of the Wittig reaction to form the enol ether (**92**).

The Wittig reaction was first reported by Wittig and Geissler in 1954.[5] It is the most recognized method for carbonyl olefination. The mechanism of this reaction involves two intermediate species, a di-ionic betaine **93** derived from the phosphonium salt and an oxaphosphetane (the intermediate, **94**) (Scheme 3.7).[6] The reaction of the aldehyde and the phosphonium ylide produces both the *cis* and *trans* oxaphosphetanes (**94**) which undergoes stereospecific syn elimination to provide the corresponding *E*- and *Z*-alkenes (**92**).[6]

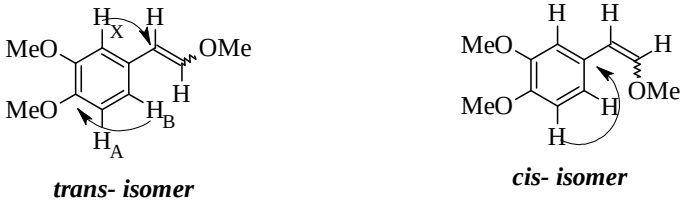


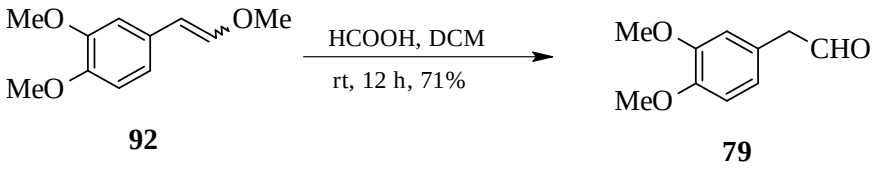
Figure 3.2: HSQC correlations for the *cis* and *trans*- isomers of compound **92**.

The olefinic coupling constants (*J*) in the ^{1}H NMR spectrum show that both the *cis* and the *trans* isomers are present. This is shown by a large *J* value for the olefinic protons that belongs to the *trans* system compared to the smaller *J* values for the *cis* coupled protons.

The HSQC spectrum shows the carbon signals of CH=CHOMe at δ_C 104.8 for the *trans* system and at δ_C 105.6 for the *cis* system. C-4 was assigned to at δ_C 148.6 for *cis* since it shows a strong correlation with H_B of the *cis* system and therefore δ_C 149.0 belongs to the *trans* system.

3.4.2 Hydrolysis of Enol Ether 92

Having successfully prepared the enol ether **92**, the next step involved the synthesis of 3,4-dimethoxyphenylacetaldehyde **79** (Scheme 3.8). The reaction conditions for this reaction are very critical because phenylacetaldehydes are not very stable under both basic and acidic conditions and easily undergo condensation reactions to yield polymeric products. The hydrolysis of the enol ether **92** under mild acidic conditions using 98% HCOOH and DCM afforded the acetaldehyde **79** in 71% yield. The formation of this compound could only be confirmed using ^{1}H NMR shortly after preparation since it is very unstable and could not be kept for longer experiments. The ^{1}H NMR displays a triplet at δ_H 9.77 which integrates for one proton, this confirms the formation of an phenylacetaldehyde **79**.

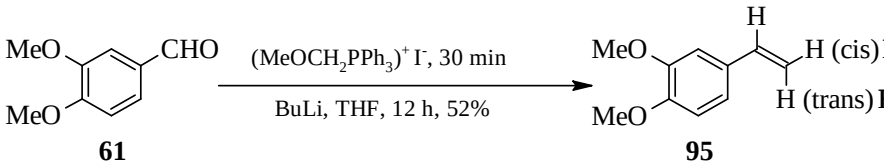


92 **79**

Scheme 3.8: Synthesis of 3,4-dimethoxyphenylacetaldehyde (**79**).

The method for the preparation of the acetaldehyde was changed so that acidic conditions were avoided. The alternative method required the conversion of 3,4-dimethoxybenzaldehyde (**61**) to 3,4-dimethoxyvinylbenzene (**95**) as an intermediate. The 3,4-dimethoxyvinylbenzene (**95**) was converted to the corresponding alcohol (**96**) by hydroboration of the styrene intermediate. The alcohol was then oxidized to the corresponding acetaldehyde by Swern oxidation or the use of *o*-Iodoxybenzoic acid (IBX). In the first attempt at the formation of the acetaldehyde a Swern oxidation was used.

3.4.3 Preparation of 3,4-Dimethoxyvinylbenzene (41)



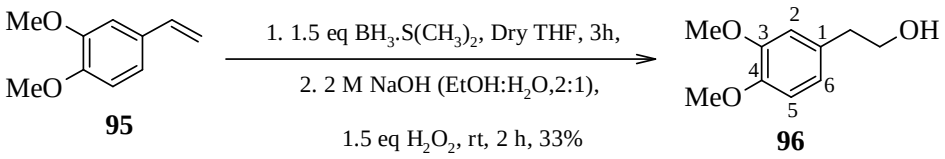
Scheme 3.9: Synthesis of 3,4-dimethoxyvinylbenzene (**95**).

The vinylbenzene (**95**) was prepared from **61** in 52% yield (Scheme 3.9). The product was obtained as light yellow oil. The Wittig reaction was performed using methyltriphenylphosphonium iodide and butyllithium. The structure of **95** was confirmed using ^{1}H NMR, ^{13}C NMR and 2D NMR spectra. The ^{1}H NMR shows three signals for the vinylic protons, the signal at δ_H 5.15 for HC=C$\underline{H}_2$ (*cis*) was a doublet with a coupling constant of 10.9 Hz, the signal at δ_H 5.61 for HC=C$\underline{H}_2$ (*trans*) was also splitted into a doublet and $\underline{H}$C=CH$_2$ was splited into a doublet of doublets at δ_H 6.68 with coupling constants 10.8 and 17.8 Hz. These results are in good agreement with those obtained by Sonopo[2] for the synthesis of a similar compound.

3.4.4 Preparation of 2-(3,4-Dimethoxyphenyl)ethanol (96)

Alcohols have been prepared using a number of methodologies. These methods make use of a variety of metal catalysts and photo-oxidation has also been employed.[7-9] Over-oxidation needs to be avoided in the alcohol-forming reactions since alcohols can be easily oxidized to form the corresponding carboxylic acids.

The alcohol (**96)** was prepared by hydroboration of 3,4-dimethoxyvinylbenzene (**95**) (Scheme 3.10). However, the yield of this reaction was not satisfactory (33%) although a sufficient amount was obtained for the subsequent step. The unsatisfactory yield was due to the fact that the reaction itself was not capable of converting all the starting material and most of the starting material was recovered by chromatographic separation.

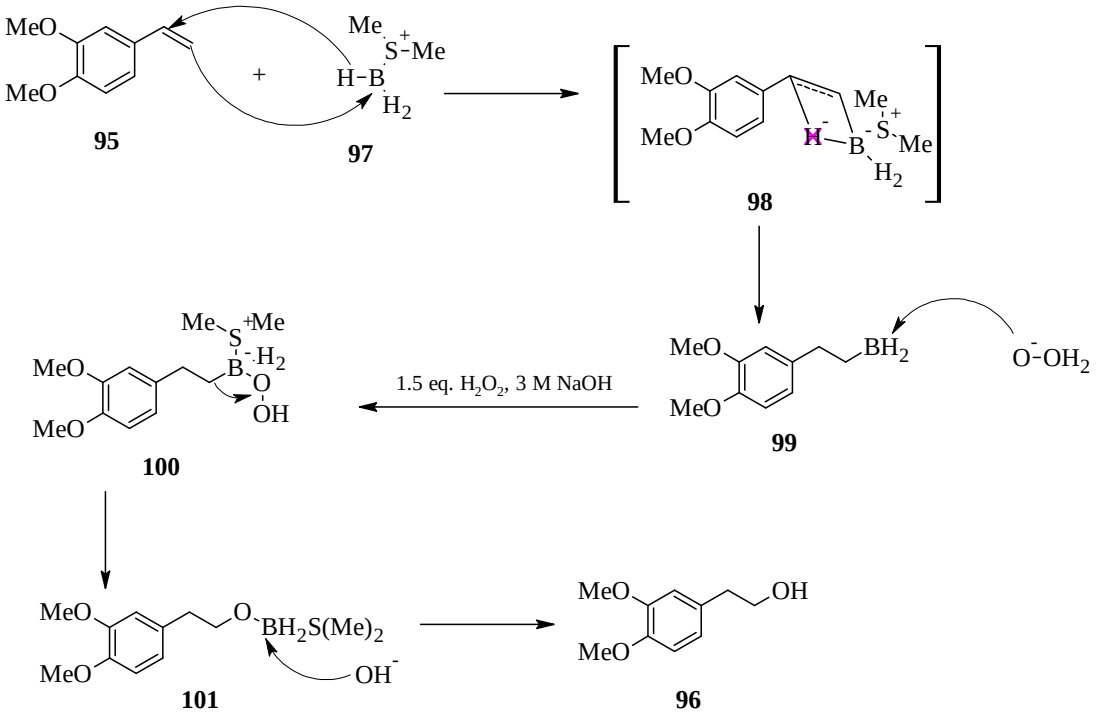


Scheme 3.10: Synthesis of 2-(3,4-dimethoxyphenyl)ethanol (**96**).

The structure of the product was verified by NMR experiments, IR and mass spectrometry. The ^{1}H NMR spectrum show a triplet at δ_H 2.81 for the benzylic methylene group. A triplet at δ_H 3.83 with a coupling constant of 6.4 Hz was assigned to the methylene protons attached to the alcohol and two singlets at δ_H 3.86 and δ_H 3.87 were assigned to the two methoxy groups. The shift of the CH_2 signal reflects the effect of the oxygen atom pulling away the electrons hence deshielding the protons. Other signals were observed in the aromatic region, a broad singlet next to a broadened doublet was observed at δ_H 6.77 integrating for two protons H-2 and H-6 respectively and a doublet was observed at δ_H 6.83 integrating for one proton, H-5.

The carbons were assigned using both 1D NMR and 2D NMR experiments. C-1, C-3 and C-4 were observed at δ_C 131.1, 147.6 and 148.7, respectively. These signals were assigned to quaternary carbons because no correlations to proton signals were observed in the HSQC. The sp^3 carbons resonate at δ_C 38.8 for $\underline{C}H_2CH_2OH$ and at δ_C 55.8 and 56.0 for the two methoxy groups and δ_C 63.8 for $CH_2\underline{C}H_2OH$. The aromatic carbons were assigned at δ_C 116.6 for C-2, δ_C 112.4 for C-5 and δ_C 121.1 for C-6.

Hydroboration was first reported by the Nobel Prize winner, Herbert C. Brown in 1961 as a powerful synthetic tool.[10] This reaction is defined as the addition of a boron hydride to alkenes and alkynes. The addition of borane across a double bond occurs in a concerted manner.[11] The borane adds concertedly and regioselectively to the alkene **95** with the boron atom of the complex **97** bonding to the less substituted carbon of the alkene, giving borane **99** (Scheme 3.11). The more controlled oxidation under inert conditions was required in order to remove boron thus leaving the useful organic fragment.



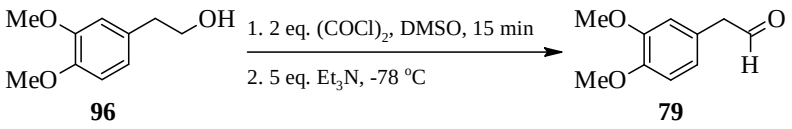
Scheme 3.11: The mechanism for the hydration of (3,4-dimethoxyphenyl)ethene (**95**).

Hydrogen peroxide was used as the oxidizing agent, it replaces the carbon-boron bond in **99** with a carbon-oxygen bond to give **100**. The addition of aqueous NaOH completes the reaction by attacking the intermediate **101** to cleave the B-O-alkyl bond to yield the alcohol **96**.

3.5 Oxidation of the Alcohol

3.5.1 Swern Oxidation

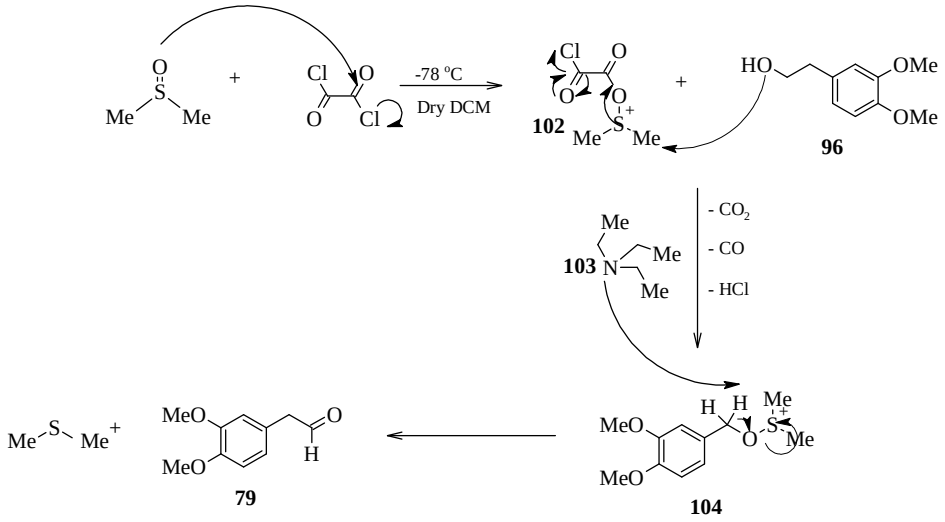
After the successful formation of the alcohol, preparation of the acetaldehyde using the Swern oxidation procedure was attempted (Scheme 3.12). However, a mixture of inseparable products was obtained. This was established by TLC and in the ^{1}H NMR spectrum that was recorded immediately after working up the reaction. The failure of the reaction was attributed to the instability of the phenylacetaldehyde (**79**) under the reaction conditions.



96 **79**

Scheme 3.12: Preparation of the phenylacetaldehyde **79**.

The reaction is initiated by the reaction of dimethyl sulfoxide and oxalyl chloride at -78°C (Scheme 3.13). The resulting intermediate **102** reacts rapidly with the alcohol **96** to form the alkoxysulfonium salt **104**. The nucleophilic attack of triethylamine (**103**) on intermediate **104** results in the formation of the acetaldehyde **79**.[12]

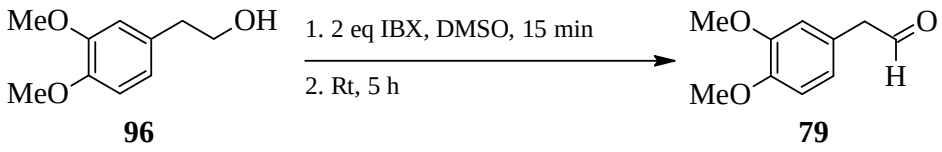


Scheme 3.13: Mechanism for the Swern oxidation.

The Swern oxidation is a well-known method for the preparation of alcohols under mild conditions and is known to work well with sterically hindered alcohols.[13] In our case the lability of the phenylacetaldehyde was a problem. A triplet was observed in ^{1}H NMR spectrum at δ_H 9.77 indicating the presence of the acetaldehyde along with many other signals. The IBX oxidation was also explored since IBX is a versatile reagent and is suitable for mild oxidation of primary alcohols to the corresponding aldehydes.[14]

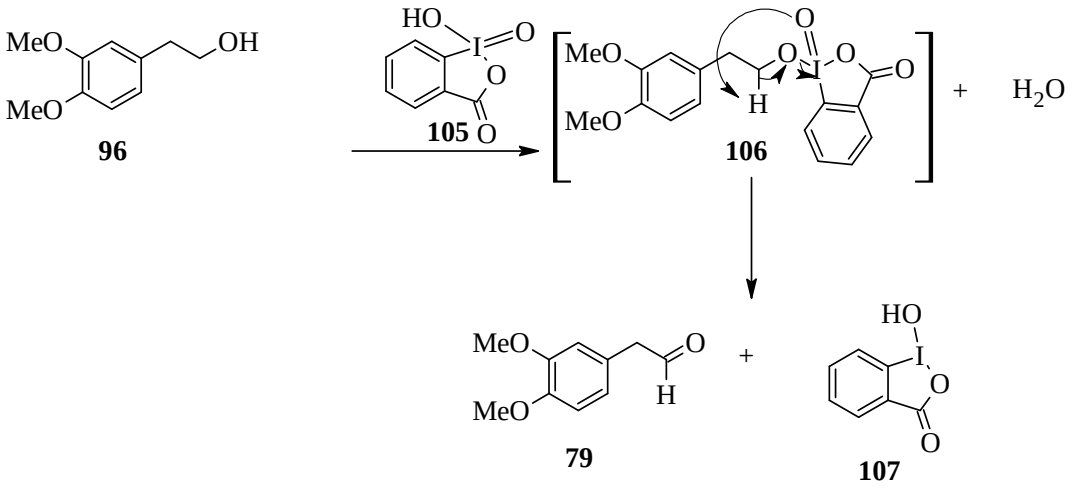
3.5.2 IBX Oxidation

IBX has been extensively employed in the oxidation of alcohols, silyl enol ethers and other organic compounds to their corresponding α,β-unsaturated carbonyl compounds.[14-16] Some of the shortcomings for this reagent are that it is explosive and does not dissolve in most common polar organic solvents. It usually dissolves in highly polar solvents like DMSO which require high temperatures and high vacuum for removal.



Scheme 3.14: IBX oxidation of the alcohol (**96**).

For the synthesis of **79** (Scheme 3.14), IBX was dissolved in DMSO and stirred for 15 minutes at room temperature. DMSO was the solvent of choice since it remarkably reduces the acidity of IBX[17] that could affect the stability of the product, the aldehyde (**79**). A solution of the alcohol in DMSO was added slowly and the reaction was allowed to stir for a further 5 h at room temperature. TLC showed the disappearance of the starting material and the ^{1}H NMR spectrum confirms the presence of the product as the triplet was observed at δ_H 9.77.

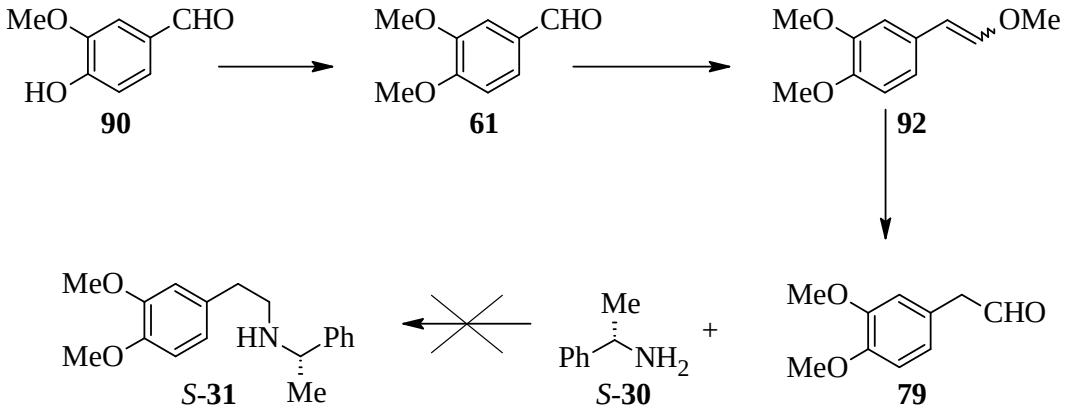


Scheme 3.15: Mechanism for the IBX oxidation of the alcohol 96.

The mechanism for the oxidation of alcohols is explained by Su *et al*.[18] to be a hypervalent twisting mechanism (Scheme 3.15). The first step in the reaction is the ligand exchange reaction where the hydroxyl group of the IBX (**105**) is replaced by the alcohol (**96**) to form the intermediate (**106**) that undergoes a twist and an elimination reaction. The twisting of the intermediate is required to enable the concerted elimination reaction. The elimination step is regarded as the rate-determining step for this reaction that forms the product and furthermore, it yields a very stable byproduct called IBA (**107**).[17,19] Besides the above-mentioned reagents employed for the oxidation of the alcohol, other reagents like ceric ammonium nitrate and manganese dioxide were also used to oxidize the alcohol **79** with no success.

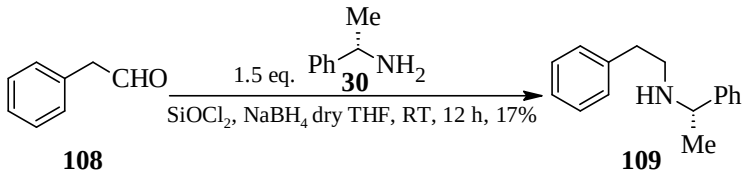
3.6 (*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethylamine (31)

Having prepared the aldehyde (Scheme 3.13), it was condensed with the chiral auxiliary amine (*S*-**30**) in the next step of the proposed synthetic route (Scheme 3.16). Unfortunately, this reaction was not successful despite several attempts. There were always multiple products on the TLC of the crude mixture with one dominant spot for the starting material (*S*-**30**). It was suspected that the phenylacetaldehyde decomposed during the reaction.



Scheme 3.16: Condensation of the phenylacetaldehyde (**79**) and (*S*)-(α)-methylbenzylamine (*S*-**30**).

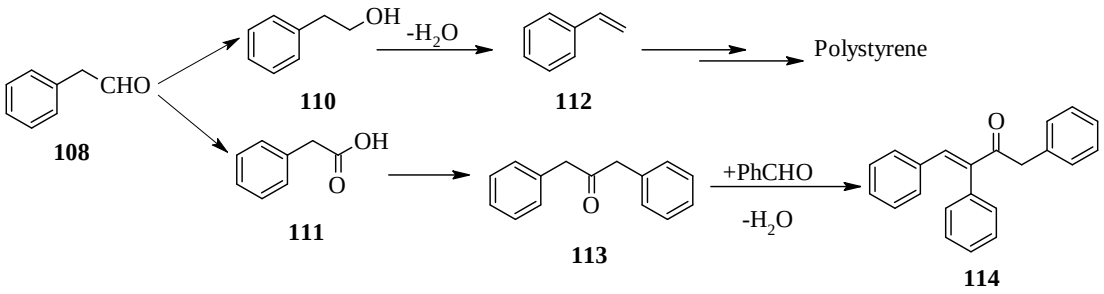
It was decided to perform a model reaction for this reaction which involved the reaction of commercially available and freshly distilled phenylacetaldehyde (**108**) and (*S*)-(α)-methylbenzylamine (*S*-**30**). Several methods for this reaction were attempted to establish suitable reaction conditions. The method that provided better results was the reductive amination of the phenylacetaldehyde using $NaBH_4$-silica chloride.[20] Silica chloride was prepared according to a reported procedure.[21]



Scheme 3.17: Model reaction for the acetaldehyde (**108**) and (*S*)-(α)-methylbenzylamine (*S*-**30**)

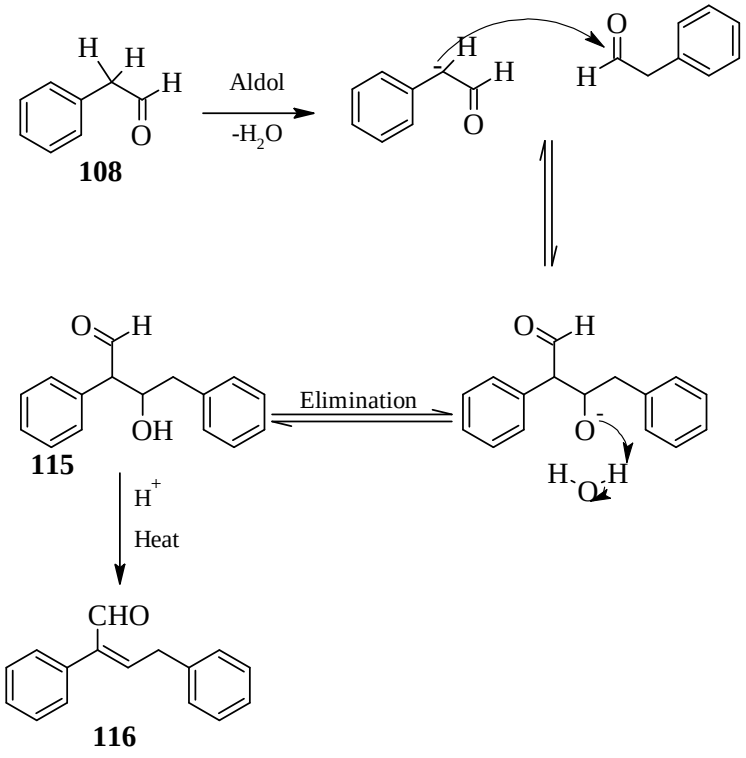
The product (**109**) was obtained in an unsatisfactory yield of 17% (Scheme 3.17). The structure of **109** was confirmed by NMR experiments, IR and MS. The ^{1}H NMR spectrum showed a doublet at δ_H 1.35 for the methyl group, a multiplet at δ_H 2.79 for the four methylene protons, a quartet at δ_H 3.86 for the methine proton and 10 aromatic protons were present as a multiplet at δ_H 7.24-7.42. The MS results found 226.1593 $[M+H]^+$ calculated for $C_{16}H_{20}N$ 226.1596. The optical rotation was measured to be -63.7° at ambient temperature.

The major product in this reaction was the aldol condensation product of the phenylacetaldehyde (**108**). From this result it was clear that the reason for the failure of the earlier attempts for this synthesis were due to the self-condensation reactions that phenylacetaldehydes are prone to undergo. These reactions may be the reason why none of the attempted methods for the synthesis of **31** (Scheme 3.18) provided the expected product. Phenylacetaldehydes are prone to disproportionation and condensation raction in the presence of base and acid, respectively.[22]



Scheme 3.18: Disproportionation pathway of the phenylacetaldehyde (**108**).[1]

In the disproportionation pathway **108** produces the alcohol **110** and phenylacetic acid (**111**). The alcohol formed readily dehydrates to form the styrene (**112**) that polymerizes to form the polystyrene when heated. Phenylacetic acid (**111**) undergoes an aldol condensation reaction to form dibenzyl ketone **113** which reacts further to form **114**.



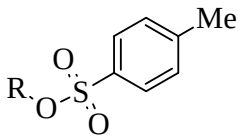
Scheme 3.19: Condensation mechanism of the phenylacetaldehyde (**108**).

In the condensation pathway the first step is the aldol reaction which is accompanied by the elimination reaction to produce the β-hydroxyaldehyde **115**. In the aldol reaction **108** loses a proton from the α-carbon thus producing an enolate ion. The enolate ion then reacts with **108** in the reaction mixture to form the β-hydroxyaldehyde **115** upon protonation of the negatively charged oxygen (Scheme 3.17). Dehydration of the β-hydroxyaldehyde **115** gave the product **116**.[4]

The structure of **116** was elucidated using ^{1}H and COSY NMR spectroscopy. The ^{1}H NMR spectrum shows a doublet at δ_H 3.63 for the CHC<u>H</u>$_2$Ph, a triplet at δ_H 6.80 for the vinylic proton, a multiplet for the ten aromatic protons at δ_H 7.09 – 7.64 as well as the aldehyde singlet at δ_H 9.59. Low resolution mass spectrometry (LRMS) displayed the sodium adduct of the formed product, *m/z* 245.1053 for $C_{18}H_{18}NaO_3$.

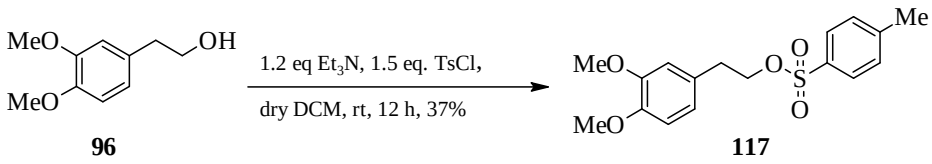
3.6.1 Preparation of 2-(3,4-Dimethoxyphenyl)ethyl 4-methylbenzenesulfonate (55)

After a number of attempts to form **31** from the phenylacetaldehyde **79**, it was decided to explore a different route that allows the formation of the chiral amines by avoiding the use of the phenylacetaldehyde. Tosylation is a well-known method that converts alcohols to tosylates and allows subsequent nucleophilic substitution reactions.[23] The advantage of this method is that it allows the formation of a stable intermediate (alkyl tosylate) with an excellent leaving group.



117

Tosylates (**117**) are better leaving groups than halides and mesylates and their preparation from alcohols avoids skeletal rearrangements and stereochemical ambiguity.[24] This method has been successfully employed in the preparation of various organic compounds without complications. It has been used in the preparation of precursors towards the synthesis of selenium analogues of dopamine,[25] 4-(2-iodoethyl)-1,2-dimethoxybenzene,[26] isosteric analogs of mandipropamid[27] and more.



Scheme 3.20: Preparation of the tosylate (**117**) from the alcohol (**96**).

Compound **117** was prepared in a moderate yield of 37%. This may be attributed to the fact that the both starting materials were not consumed completely at the end of the reaction (Fig. 19). The structure of **117** was confirmed using ^{1}H NMR, ^{13}C NMR, IR and high-resolution MS. In the ^{1}H NMR spectra, a noticeable shift of the CH_2 was observed at δ_H 3.83 in the alcohol **96** to δ_H 4.20 in **117**. Other characteristic signals were observed at δ_H 2.89 (singlet) for the CH_3 protons and δ_H 2.42 (triplet) for the benzylic methylene and seven aromatic protons were observed at the aromatic region from δ_H 6.60 to δ_H 7.67. At δ_H 3.80 and 3.84 there were two singlets representing the protons of the two methoxy groups. at δ_H 4.19 there was a triplet representing the CH_2 group bonded to the tosylate group. In the ESI-TOF mass spectrum using positive ionization, $[M+Na]^+$ was observed at 359.0934 (calculated for $C_{17}H_{20}O_5NaS$ 359.0929).

Figure 3.3: The TLC plate showing the alcohol **96**, the tosylate **117** and tosyl chloride (from the bottom to the top).

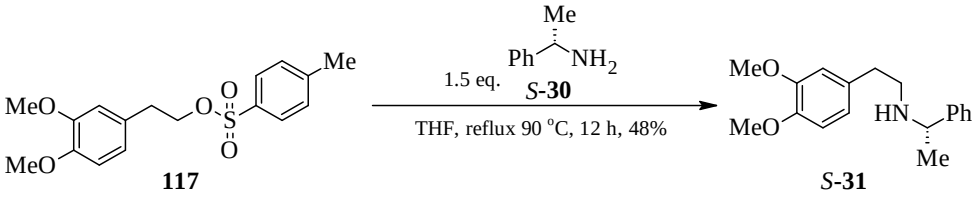
3.7 Synthesis of 1-Substituted Tetrahydroisoquinolines

3.7.1 Preparation of Enantiomerically-pure Tetrahydroisoquinoline Intermediates

Three enantiopure tetrahydroisoquinoline intermediates were successfully prepared in a five-step synthetic route starting from vanillin. This was achieved by introducing chiral auxiliaries on the starting materials. The chiral auxiliaries used were (*S*)-(-)-α-methylbenzylamine (*S*-**30**), (*R*)-(+)-α-methylbenzylamine (*R*-**30**) and (*R*)-1,2,3,4-tetrahydronaphthalene.

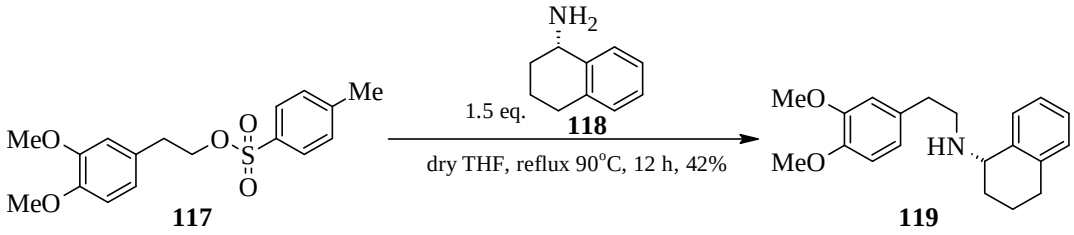
3.7.2 Preparation of (*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethanamine (*S*-31)

Alkylation of amines is often problematic. Unlike alkylation of alcohols where only one product is possible, alkylation of amines can yield a mixture of products – mono-alkylated, dialkylated, trialkylate and tetra-alkylated to form quaternary ammonium salts. If the product is protonated, it becomes soluble in water and is difficult to extract using an organic solvent. To maximize the formation of the monoalkylated amine, it is important to keep the concentration of the alkylating agent (tosylate) low. The amine *S*-**31** was successfully prepared from the tosylate. The tosylate was slowly added to a stirring THF solution of *S*-**30**.



Scheme 3.21: Preparation of the amine (*S*-**31**) to form the tosylate (**117**).

Characteristic proton signals were observed at δ_H 1.36 (doublet) indicative of the methyl group and a multiplet at δ_H 2.75 for the four methylene protons. The ABX spin system was observed in the aromatic region integrating for three protons as well as a 5-proton multiplet for the rest of the aromatic protons. The optical rotation was measured to be +37.05° at 25 °C. Both (*R*) and (*S*) enantiomers were prepared by employing the same procedure in 42% and 45% yields, respectively.



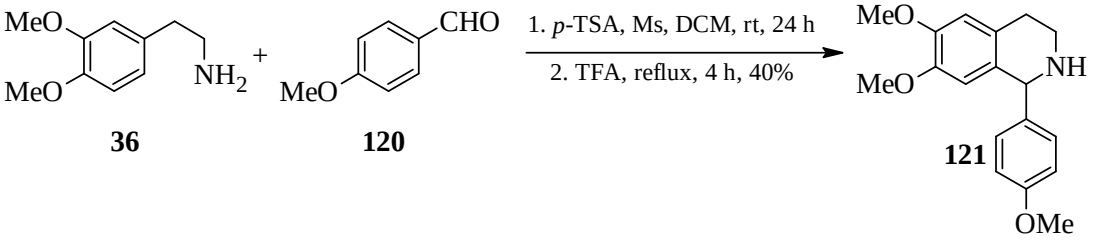
Scheme 3.22: Synthesis of (*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydronaphthalen-1-amine (**119**).

The tetrahydronaphthalene derivative **118** was reacted with **117** by employing the same procedure as in the preparation of *S*-**31**. The ^{1}H NMR spectrum signals were in good agreement with the structure of the product **119** - the four methylene protons at δ_H 1.74 of the cyclohexane ring, a broad singlet at δ_H 2.03 for the proton bonded to the nitrogen atom and the four methylene protons at δ_H 2.91-3.01.

The ^{13}C NMR confirmed the presence of the aromatic quaternary carbons connected to the two methoxy groups at δ_C 147.9 for C-4 and δ_C 149.1 for C-3. The MS spectrum showed a *m/z* of 312.1974 in the positive ionization mode characteristic of the $[M+H]^+$ for this compound.

3.7.3 Model reaction and Attempted Pictet-Spengler Cyclization

After having successfully prepared the benzyltetrahydroisoquinoline intermediate compounds, a model reaction was carried out by using the commercially available homoveratrylamine and *p*-anisaldehyde. Both reagents were freshly distilled before use since they were unreactive before distillation.

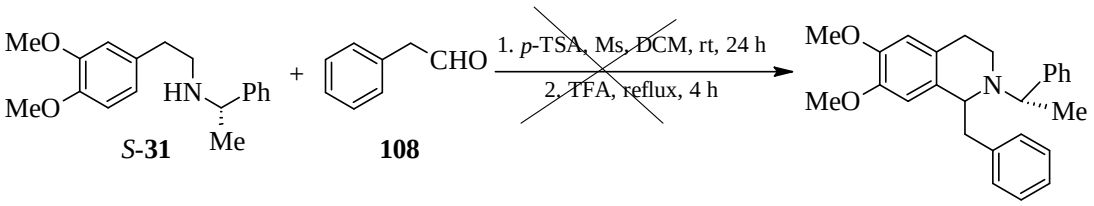


36 120

Scheme 3.23: Model reaction for the synthesis of a THIQ (**121**) via the Pictet-Spengler cyclisation.

The Pictet-Spengler cyclisation for **36** and **120** afforded the product **121** in 40% yield as a yellow oil. The ^{1}H NMR spectrum signal of H-1 was evident at δ_H 3.81 and also the absence of the aldehyde signal proved the occurrence of the reaction. The methylene protons signals were observed over a range, δ_H 2.83 - 3.05. Three methoxy singlets were also observed at δ_H 3.61, 3.75 and 3.85. The quaternary carbon signal for C-4′ appeared more downfield (δ_C 159.6) than the other quaternary carbons, C-6 and C-7 which appeared at δ_C 148.4 and 147.6, respectively. The structure was consistent with the MS and IR data, the former showing *m/z* 300.1605 for $[M+H]^+$ in the positive ionization mode.

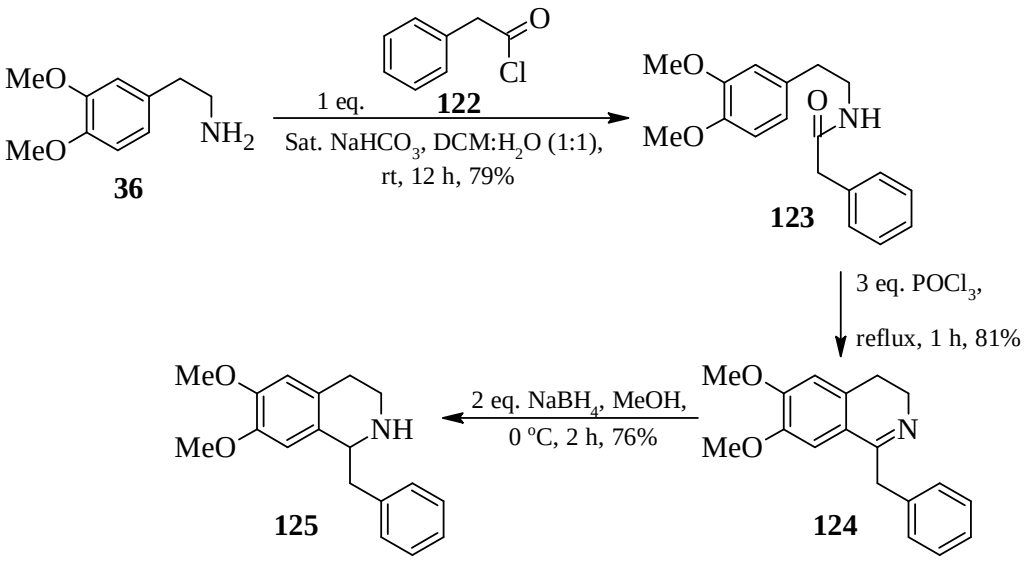
Similar reaction conditions were employed for the synthesis of the chiral tetrahydroisoquinolines but with no luck since the phenylacetaldehyde (**108**) immediately decomposed in the presence of *p*-TSA. Multiple spots were observed on the TLC plate. It was assumed that the phenylacetaldehyde decomposed according to the mechanism explained in Scheme 3.16 and Scheme 3.17. Multiple spots were observed on the TLC plate and the crude ^{1}H NMR spectrum showed unidentified polymeric products.



Scheme 3.24: Attempted synthesis of a chiral THIQ via the Pictet-Spengler cyclisation.

At this stage the alternative method that could be employed in order to synthesize THIQ's was the Bischler-Napieralski cyclisation, even though it adds two more steps in the synthesis. A number of tetrahydroisoquinolines were synthesized by using this method. A model reaction was performed by synthesizing tetrahydroisoquinolines without the chiral auxiliary and enantiopure tetrahydroisoquinolines.

3.7.4 Preparation of 1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (125)

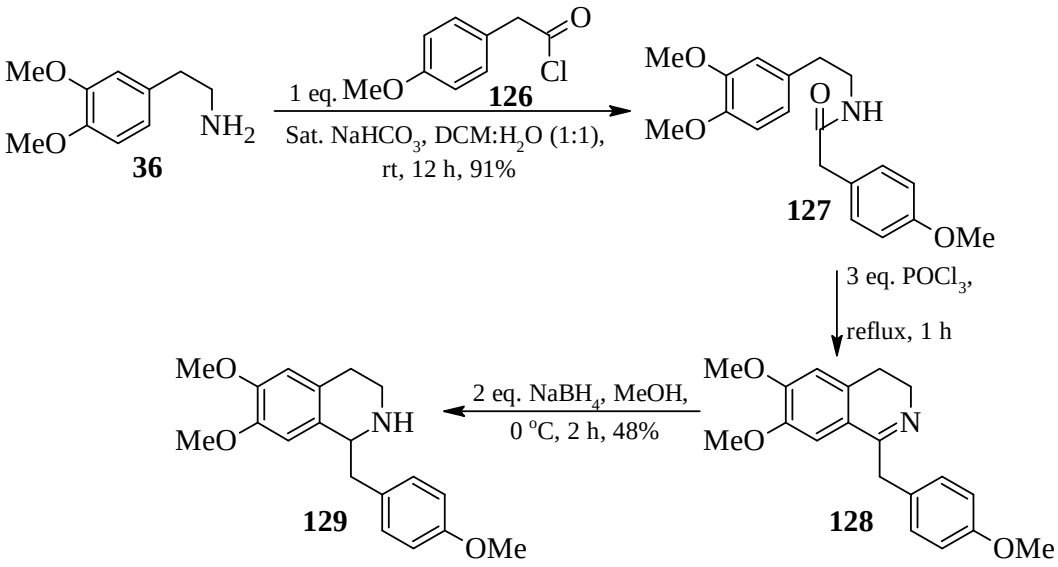


Scheme 3.25: Synthesis of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**125**).

The amine **36** was acylated with **122** to give the amide **123** in 79% yield. The structure of **123** was evident from the ^{1}H NMR spectrum showing a singlet for the benzylic methylene group at δ_H 3.53 and two singlets for the methoxy groups at δ_H 3.82 and δ_H 3.85. The carbonyl signal was not observed in the ^{13}C NMR, which may be attributed to a "keto-enol" equilibrium of the amide. However the IR spectrum showed a carbonyl stretch at 1673 cm^{-1}. The amide was then refluxed in excess $POCl_3$ and gave the dihydroisoquinoline **124** in 81% yield. The dihydroisoquinoline **124** was reduced with $NaBH_4$ at 0 ºC to give the tetrahydroisoquinoline **125** in 76% yield.

The structure of **125** was confirmed by the ^{1}H NMR, ^{13}C NMR, MS and IR spectra. The ^{1}H NMR spectrum showed distinctive signals at δ_H 6.34 and δ_H 6.51 for H-8 and H-5, respectively; the signal for H-6 had disappeared showing that the ring had closed at C-6. The ^{13}C NMR showed the signal for the benzylic carbon at δ_C 42.2 and a signal C-1 at δ_C 56.3. The amine group IR stretch appeared at 3459.6 cm^{-1}.

3.7.5 Preparation of 6,7-Dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (129)

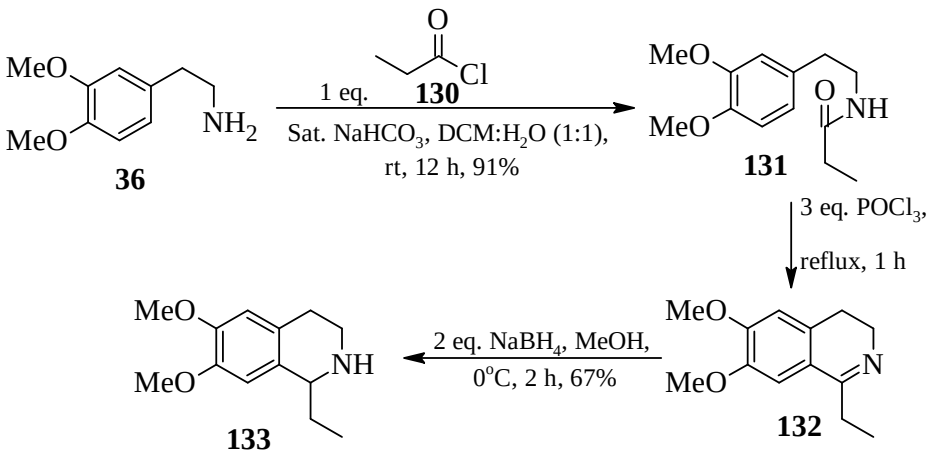


Scheme 3.26: Synthesis of 6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**129**).

The commercially available *p*-methoxyphenylacetic acid was converted to the acid chloride **126** and further used to acylate the amine **36** using the procedure in Scheme 3.25. The THIQ **129** was obtained in 48% yield and the ^{1}H NMR spectrum showed three methoxy singlets at δ_H 3.89, δ_H 3.93 and δ_H 3.94. Comparing to the C-4' signal from that of **125** with that of **129**, a noticeable chemical shift was observed, it shifted from δ_C 129.6 in **121** to δ_C 167.1 in **129** due to the strong electron-withdrawing effect of the methoxy group in the C-4′ position. The MS showed *m/z* of 314.1759.

3.7.6 Preparation of 1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (133)

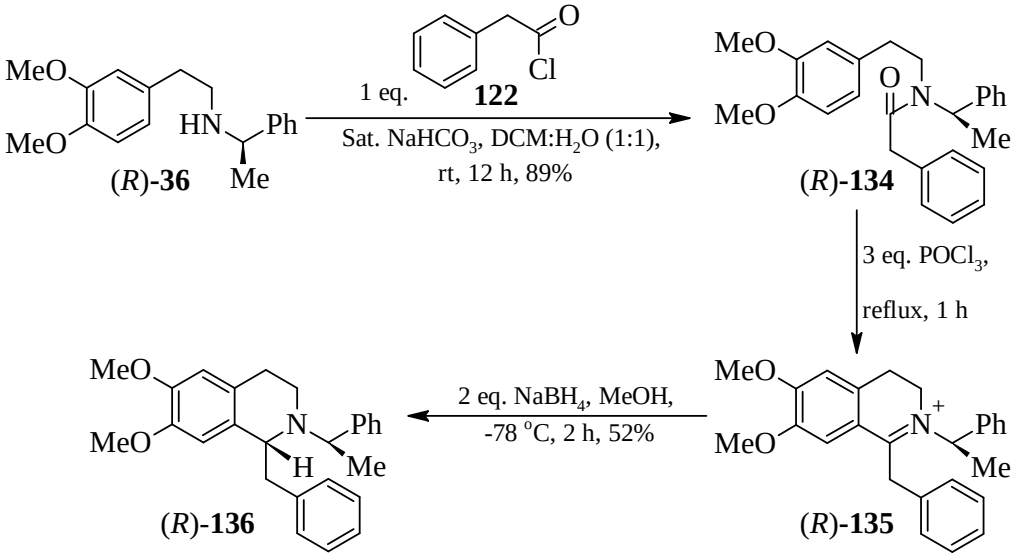
Compound **133** was synthesized in 51% yield (based on the amide, **131**) from 3,4-dimethoxyphenylethylamine (**36**) and propanoyl chloride (**130**). The amide (**131**) was obtained as a yellow solid in 91% yield with a melting point of 125.7 ºC. Bischler-Napieralski cyclisation of **131** followed by reduction of **132** afforded the desired product **133** as a brown oil. In agreement with the structure, a methyl signal was observed at δ_H 1.09, a multiplet for the four methylene protons at δ_H 2.80-3.40 and the two aromatic protons at δ_H 6.59. The MS showed *m/z* 222.1501 and the IR showed the methyl stretch at 2932.4 cm^{-1}.



Scheme 3.27: Synthesis of 1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**133**).

3.7.7 Preparation of (*R*)-1-Benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-136)

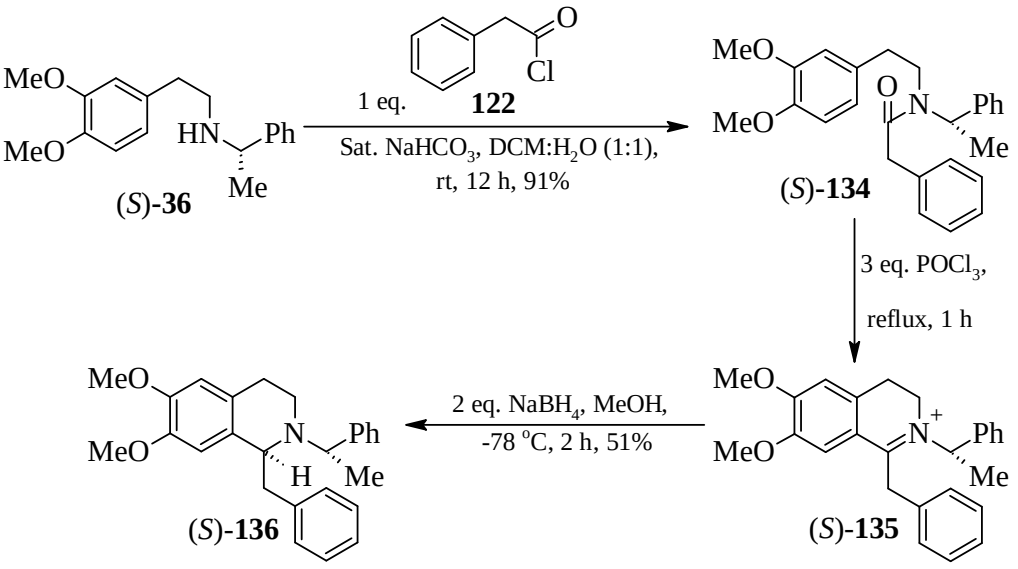
Both the (*R*)- and (*S*)-enantiomers of α-methylbenzylamine (**30**) and (*R*)-(-)-1,2,3,4-tetrahydro-1-naphthylamine were employed in the synthesis of optically pure 1-substituted benzyltetrahydroisoquinolines.



Scheme 3.28: Synthesis of (1*R*)-benzyl-6,7-dimethoxy-*N*-(1*R*-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-**136**).

The amine (*R*-**36**) was acylated with phenylacetyl chloride (**122**) to give the chiral acetamide (*R*-**134**) in 83% yield. Treatment of *R*-**134** with excess $POCl_3$ allowed Bischler-Napieralski cyclisation and gave the dihydroisoquinolinium salt (*R*-**135**) that was used without purification. The hydride reduction of *R*-**135** gave *R*-**136** in 52% yield based on the amide. The product *R*-**136** gave an optical rotation of $[\alpha]_D^{25}$ = +61.6° (1.4, $CHCl_3$). The structure of the product *R*-**136** was in consistent with the NMR and the MS data. The ^{1}H NMR spectrum showed twelve aromatic protons compared to the thirteen aromatic protons found **134**. The signal at δ_C 68.1 was assigned to C-1 and was in good agreement with the previously reported value.[2,3] The MS found *m/z* 388.2285 for $C_{26}H_{30}NO_2$ which is also consistent with the structure of (1*R*)-benzyl-6,7-dimethoxy-*N*-(1*R*-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-**136**).

3.7.8 Preparation of (*S*)-1-Benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*S*-136)



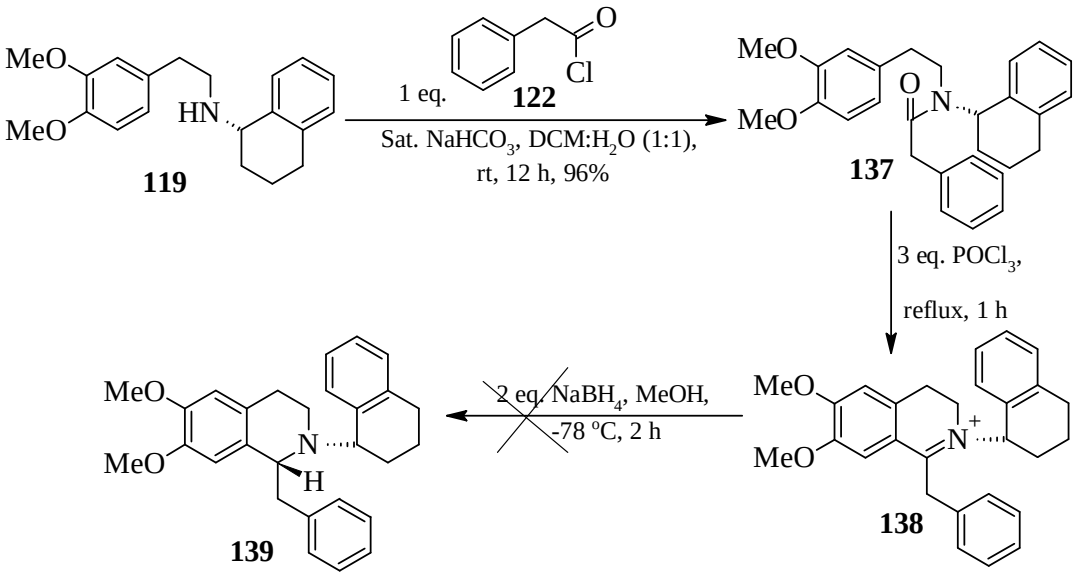
Scheme 3.29: Synthesis (*S*)-1-benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*S*-**136**).

Using the same procedure as in Scheme 3.26, *S*-**136** was synthesized in 51% yield, the spectral data of *R*-**136** and *S*-**136** being in good agreement. The NMR data of the chiral amide *R*-**134** was also in good agreement with that of *S*-**134**. A Bischler-Napieralski

cyclisation of *S*-**134** afforded a single enantiomer *S*-**136** in a moderate yield. The optical rotation of *S*-**136** was in opposite direction to that of *R*-**136** and was measured to be $[\alpha]_D^{25}$ = -83.7° (1.6, $CHCl_3$).

3.7.9 Preparation of 1-Benzyl-6,7-dimethoxy-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2,3,4-tetrahydroisoquinoline (139)

Using the same procedure as in Scheme 3.27, the synthesis of **139** was attempted with no success. Since the amount of the starting material **137** was enough to explore different reaction conditions, various factors that could affect the reaction were changed. The reflux period for the Bischler-Napieralski cyclisation was increase from 1 h to 12 h but there was no change. The NMR showed multiple products with no peaks that were consistent with the structure of **139**.



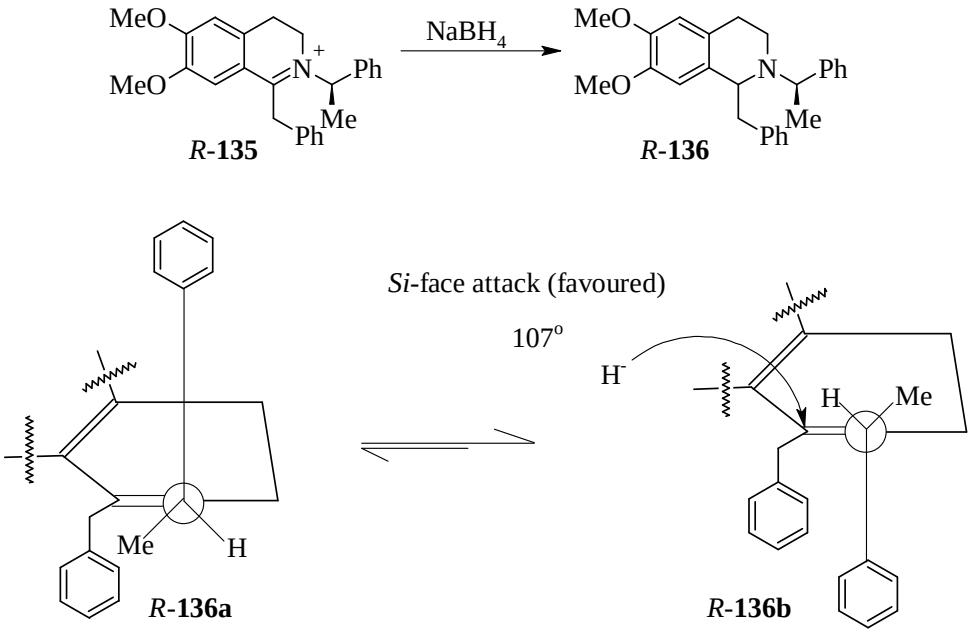
Scheme 3.30: Attempted synthesis of 1-benzyl-6,7-dimethoxy-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2,3,4-tetrahydroisoquinoline (**139**).

3.7.10 Stereochemical Analysis

It has been verified by several researchers that the stereochemical outcome of the product is the Bischler-Napieralski reaction is the same as that of the chiral auxiliary starting material.[28,29] Consequently it was anticipated that the stereochemistry of C-1 in both *R*-

136 and *S*-**136** was going to be *R* and *S*, respectively. The intergrals of the methoxy signals in the ^{1}H NMR data shows one diastereomer for each of the product with 96% and 90% *de* for *R*-**136** and *S*-**136** respectively.

Since the reactivity of the imines is similar to that of carbonyls, the reaction mechanism can be explained by the Burgi's[30] model which explains the reactivity of carbonyls toward nucleophiles. The nucleophilic approach towards the C=N carbon atom pushes the alkyl substituents away thus stretching the C=N distance. The nucleophile approaches along the line that is at an angle of about 107º with the C=N bond.[30]



Scheme 3.31: Mechanism for diastereoselective Bischler-Napieralski reaction.

The stereoselective reduction of the C=N bond of the chiral iminium (**135**) ion is a powerful synthetic tool for the formation of THIQ's with high diastereomeric excess. Scheme 3.30 provides a mechanistic explanation for the diastereoselectivity that occurs in the Bischler-Napieralski reaction. Between *R*-**136a** and *R*-**136b**, the more stable conformation is *R*-**136b** and it allows the nucleophilic attack at the *Si* face therefore resulting in the product with the R-configuration at C-1.

Table 3.1: Summary of THIQ's synthesized.

Compound No.	% Yield
121	40
124	76
129	48
133	67
136	52
140	54

3.8 Conclusion and Recommendations

Stereoselective and non-stereoselective synthesis of THIQ's has been achieved by using the Bischler-Napieralski reaction. Chiral auxiliaries were employed to control the stereochemical outcome of the enantiopure THIQ's. The first attempt using the Pictet-Spengler reaction failed due to the lack of reactivity of the phenylacetaldehyde (**79**). This was not in accordance with the previously reported results in our laboratory. Three different chiral auxiliaries were employed for the synthesis of enantiomerically pure THIQ's. Both (*R*) and (*S*)-(α)-methylbenzylamine gave good results but (*R*)-(-)-1,2,3,4-tetrahydro-1-naphthylamine failed to give a product. This reaction requires further investigation.

The employed synthetic route is straight forward, shorter than the traditional method for the synthesis of THIQ's that has been previously used this research group. It is believed that this method will be of general applicability for the synthesis of similar classes of compounds. Various challenges encountered during the synthesis were overcome by exploring different reaction conditions and it revealed the need for more research that needs to be done based on the reactivity of phenylacetaldehydes.

3.9 References

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CHAPTER 4

EXPERIMENTAL PROCEDURES

4.1 General Experimental Procedure

All reagents were purchased from Aldrich or Merck and used without further purification. Hexanes for chromatographic separation were purified by distillation at 70 °C before use. Anhydrous solvents were obtainable from a Technologies (Newburyport, MA) Pure-Solv. 800 solvent purification system. All reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen using oven-dried glassware.

Analytical thin-layer chromatography (TLC) was performed on aluminium plates covered with silica gel 60 F_{254} (0.25 mm thickness) and precoated with a fluorescent indicator. The developed plates were visualized under UV light (254 nm) and stained with anisaldehyde stain (0.5 mL *p*-anisaldehyde in 85 mL of MeOH containing 4 mL of H_2SO_4 and 10 mL glacial acetic acid) or Drangendorff's reagent [(**Solution A**: bismuth nitrate (0.85 g) was dissolved in a mixture of acetic acid (10.0 mL) and distilled water (40.0 mL). **Solution B**: KI (8.00 g) was dissolved in distilled water (20.0 mL). 5.00 mL of each of the solutions were mixed, acetic acid was added to the solution (20.0 mL) and made up to 100 mL using distilled water)].

Flash chromatography was performed by employing Merck Kielselgel 60 (230-400 mesh) in a glass column with diameter 25 mm or 40 mm with a fritted disc (porosity C). A Chromatotron (model 7924, Harrison Research) was used for centrifugal chromatography. The plates for the Chromatotron (1 mm, 2 mm and 4 mm) were prepared using silica gel 60 PF_{254} (containing gypsum) for preparative chromatography.

All ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded using Bruker DXR-400 and 500 spectrometers at 25 °C. The signal multiplicities were abbreviated as shown below and the chemical shifts were reported relative to the solvent peak as shown in Table 4.1.

Abbreviations used in ^{1}H NMR spectrum signal multiplicities:

s	singlet	t	triplet
brs	broad singlet	q	quartet
d	doublet	m	multiplet
dd	doublet of doublets		

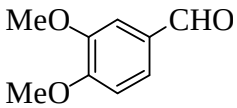
Table 4.1: ^{1}H and ^{13}C NMR solvent Chemical shifts

Solvent	***^{1}H Chemical Shift (δ_H)***	***^{13}C Chemical Shift (δ_C)***
$CDCl_3$	7.26	77.0
DMSO-d_6	2.50	39.5

Infrared spectra were obtained on a Bruker Alpha IR spectrometer and optical rotation was measured using a Bellingham & Stanley Ltd polarimeter (ADP440+) with a cuvette of 1 cm path length. Melting points of recrystallized material were measured using a Reichert electrothermal melting point apparatus. All high-resolution mass spectroscopic (HRMS) data were collected on a TOF Waters LCT Premier mass spectrometer using electrospray ionization in the positive or negative mode with nitrogen as a carrier gas.

4.2 Synthetic Methods

4.2.1 3,4-Dimethoxybenzaldehyde (61)



Method A

A mixture of 3,4-dihydroxybenzaldehyde (**89**) (2.00 g, 14.5 mmol), K_2CO_3, (4.56 mg, 33 mmol) and MeI (2.1 mL, 21.7 mmol) in anhydrous acetone (10 mL) was stirred vigorously at 60 °C under reflux for 24 h. Excess NH_4OH (1 M) was added to the reaction mixture in

order to destroy unreacted Me_2SO_4. The aqueous layer was extracted with EtOAc (2 x 30 mL) and acidified with HCl (30 mL, 1 M). The combined EtOAc layers were washed with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The product was purified by column chromatography (hexanes-EtOAc, 9:1) to give **61** (98.1 mg, 45%) as a yellow oily product.

Method B

A mixture of vanillin (**90**) (200 mg, 1.31 mmol), K_2CO_3, (456 mg, 3.3 mmol) and Me_2SO_4 (0.19 mL, 2.0 mmol) in anhydrous acetone (10 mL) was stirred vigorously at 60 °C under reflux overnight. Excess NH_4OH (1 M) was added to the reaction mixture in order to destroy the unreacted Me_2SO_4. The aqueous layer was extracted with EtOAc (2 x 30 mL), the combined EtOAc layers were washed with water and brine, dried over $MgSO_4$ and concentrated on a rotary evaporator. The product was purified using centrifugal chromatography (hexanes-EtOAc, 9:1) to afford 3,4-dimethoxybenzaldehyde (**61**, 115 mg, 53%) as a yellow oil.

Method C

To a solution of vanillin (**90**) (5.00 g, 32.8 mmol), K_2CO_3 (11.36 g, 82.2 mmol) in dry acetonitrile (40.0 mL), Me_2SO_4 (4.67 mL, 49.3 mmol) was added. The reaction mixture was stirred at 60 °C for 12 h. Excess Me_2SO_4 was destroyed by adding a solution of NH_4OH (1 M) after cooling the reaction mixture to room temperature. The resulting mixture was extracted with Et_2O (3 x 30 mL), washed with brine, dried over $MgSO_4$ and finally concentrated under vacuum. The product was obtained as a yellow oil in (5.08 g, 93%) yield.

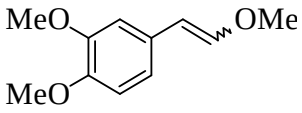
^{1}H NMR ($CDCl_3$): δ_H 3.95 (3H, s, OC<u>H</u>$_3$), 3.97 (3H, s, OC<u>H</u>$_3$), 7.00 (1H, d, *J* = 8.3 Hz, H-5), 7.42 (1H, d, *J* = 1.9 Hz, H-2), 7.46 (1H, dd, *J* = 8.3 Hz, 1.9 Hz, H-6), 9.86 (1H, s, C<u>H</u>O).

^{13}C NMR ($CDCl_3$): δ_C 56.0 (O<u>C</u>H$_3$), 56.2 (O<u>C</u>H$_3$), 109.1 (C-2), 110.4 (C-5), 126.8 (C-6), 130.2 (C-1), 149.7 (C-3), 154.6 (C-4), 191.0 (CHO).

HR-ESI-MS (positive ionization mode), *m/z* found 189.1632 $[M+Na]^+$; calculated for $C_9H_{10}NaO_3$ 189.1639.

IR: ν_{max} (neat)/ cm^{-1} 1240, 1468, 1683.

4.2.2 1,2-Dimethoxy-4-(-2-methoxyvinyl)benzene (92)



A mixture of (methoxymethyl)triphenylphosphonium chloride (4.53 g, 13.2 mmol), *t*-BuOK (1.35 g, 12.0 mmol) in dry THF (15 mL) was stirred at 0 °C for 10 min. 3,4-Dimethoxybenzaldehyde (**61**) (1.00 g, 13.2 mmol) was added and the mixture stirred for 6 h at room temperature. The reaction mixture was diluted with water and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined Et_2O layers were washed with water and brine and dried over a rotary evaporator. Purification by column chromatography (hexanes- EtOAc, 9:1) gave the enol ether **92** as a mixture of the *cis* and *trans* isomers (0.49 g, 42%) as a yellow oil.

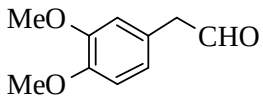
^{1}H NMR ($CDCl_3$): δ_H 3.66 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (6H, s, 2 x OCH_3), 5.16 (1H, d, *J* = 7.1 Hz, C<u>H</u>CHOCH$_3$ *cis*), 5.77 (1H, d, *J* = 12.9 Hz, C<u>H</u>CHOCH$_3$ *trans*); 6.06 (1H, d, *J* = 7.1 Hz *cis*-CHC<u>H</u>OCH$_3$); 6.75 - 6.81 (4H, m, 1H, belongs to *cis* system (H-5), 3H belongs to H-5, H-6 & H-2 belongs to the *trans* system, 6.93 (1H, d, *J* = 12.9 Hz, *trans*-CHC<u>H</u>OCH$_3$), 7.06 (1H, dd, *J* = 8.6 Hz, 1.8 Hz, H-6 *cis*), 7.24 (1H, d, *J* = 1.8 Hz, H-2, *cis*).

^{13}C NMR ($CDCl_3$): δ_C 55.7 (OCH_3), 55.8 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 56.5 (OCH_3), 60.5 (OCH_3), 104.9 (<u>C</u>HCHOCH$_3$ *trans*), 105.5 (<u>C</u>HCHOCH$_3$ *cis*), 108.4 (C-2 *trans*), 111.0 (C-2, C-5), 111.7 (C-2 *cis*), 117.6 (C-6 *cis*), 120.9 (C-6 *trans*), 129.1 (C-1 *cis*), 129.4 (C-1 *trans*), 146.5 5 (CH<u>C</u>HOCH$_3$ *cis*), 147.2 (C-4 *trans*), 147.4 (C-4 *cis*), 147.75 (CH<u>C</u>HOCH$_3$ *trans*), 148.5(C-3 *trans*), 149.1 (C-3 *cis*).

HR-ESI-MS (positive ionization mode), *m/z* found 217.0842 $[M+Na]^+$; calculated for $C_{11}H_{14}NaO_3$ 217.0841.

IR: ν_{max} (neat)/ cm^{-1} 1236, 1462, 1732.

4.2.3 3,4-Dimethoxyphenylacetaldehyde (79)



Method A

To a solution of **92** (100 mg, 0.59 mmol) in dry THF (10 mL), H_2SO_4 (6 M, 0.10 mL) was added in a dropwise manner. The reaction mixture was allowed to stir at room temperature for 1 h. To reaction mixture, saturated aq. $NaHCO_3$ solution (5 mL) was then added dropwise and the organic layer extracted with EtOAc (3 x 10 mL). The combined EtOAc layers were combined, washed with brine and dried over anhydrous $MgSO_4$ and concentrated under vacuum. The product **79** was observed in the ^1H NMR spectrum with a number of impurities.

Method B

To a solution of **92** (100 mg, 0.6 mmol) in dry THF (10 mL), H_2SO_4 (0.1 mL, 6 M) was added in a dropwise manner followed by the addition of a spatula tip of $SiOCl_2$ catalyst. The reaction mixture was allowed to stir at room temperature for 1 h. The reaction was quenched by dropwise addition of -saturated aq. $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with brine and dried over $MgSO_4$. Multiple products were observed on the TLC plate showing decomposition of the phenylacetaldehyde (**79**).

Method C

$FeCl_3.6H_2O$ (0.27 mg, 1 mmol) was stirred in EtOAc-H_2O (1:1) at room temperature for 30 min. TEMPO (100 mg, 0.1 mmol), was added and stirred for 15 min. 2-(3,4-Dimethoxyphenyl)ethanol (**96**) (100 mg, 0.27 mmol) dissolved in EtOAc-H_2O (1:1) was added in a dropwise manner. The reaction mixture was allowed to stir at room temperature for 6 h. The organic layer was extracted using EtOAc, washed with water and brine and then dried over $MgSO_4$ and concentrated under vacuum. In the ^1H NMR spectrum of the crude mixture no product was observed.

Method D

A solution of oxalyl chloride (0.5 mL, 0.5 mmol) at -78 °C, DMSO (0.72 mL) was added in a dropwise manner. The reaction mixture was stirred for 15 min. 2-(3,4-dimethoxyphenyl)ethanol (**96**) (100 mg, 0.5 mmol) in DCM was added slowly over a period of 5 minutes. The stirring was continued for 1 h at -78 °C. Et_3N (0.38 mL, 2.7 mmol) was then added slowly and the reaction mixture was stirred for a further 15 min at -

78 °C. The reaction mixture was allowed to warm to room temperature and the resulting yellow mixture was diluted with water. The organic layer was extracted with DCM (2 x 10 mL) and dried over $MgSO_4$ and concentrated under vacuum at room temperature to avoid decomposition. The crude product **79** was used without further purification in order to avoid decomposition.

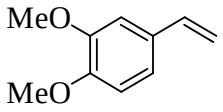
Method E

IBX (**105**) (114 mg, 0.4 mmol) was dissolved in DMSO (3 mL) over 15 min while stirring at room temperature. 2-(3,4-dimethoxyphenyl)ethanol (**96**) (62.0 mg, 0.3 mmol) dissolved in DMSO was added in a dropwise manner at room temperature. The reaction mixture was allowed to stir for a further 5 h at room temperature. The reaction was quenched with water. The organic layer was extracted with EtOAc (3 x 10 mL) dried over $MgSO_4$ and concentrated under vacuum. Purification was carried on silica column chromatography (hexanes-EtOAc, 7:3). Traces of the product **79** were observed in the ^{1}H NMR spectrum.

^{1}H NMR ($CDCl_3$): δ_H 3.62 (2H, d, J = 2.5 Hz C$\underline{H}_2$CHO,), 3.88 (6H, s, 2 x OC$\underline{H}_3$), 6.71 (1H, d, J = 2.1 Hz, H-2); 6.77 (1H, dd, J = 2.1, 8.0 Hz, H-6), 6.87 (1H, d, J = 8.0 Hz, H-5), 9.73 (1H, t, J = 2.4, C$\underline{H}$O).

^{13}C NMR ($CDCl_3$): δ_C 50.1 (CHO$\underline{C}H_2$), 55.9 (O$\underline{C}H_3$), 55.9 (O$\underline{C}H_3$), 111.7 (C-2), 112.7 (C-5), 122.0 (C-6), 124.3 (C-1), 148.5 (C-4), 149.4 (C-3), 199.5 ($\underline{C}$HO).

4.2.4 1,2-Dimethoxy-4-vinylbenzene (95)



n-Butyllithium (2.4 mL, 3.7 mmol) was added at 0 °C to a suspension of methyltriphenylphosphonium iodide (3.00 g, 7.4 mmol) in dry THF (15 mL) and stirred for 20 min followed by dropwise addition of 3,4-dimethoxybenzaldehyde (**61**) (2.00 g, 1.9 mmol) in dry THF over 15 min. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with water and extracted with Et_2O (3 x 30 mL). The combined ether layers were washed with water, brine, dried over $MgSO_4$ and evaporated to dryness under vacuum. Purification by chromatography (hexanes-EtOAc, 9:1) gave **95** (1.04 g, 53% yield) as a pale-yellow oil.

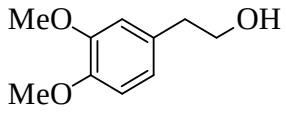
^{1}H NMR ($CDCl_3$): δ_H 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.15 (1H, d, *J* = 10.9 Hz, CHC$\underline{H}_2$, *cis*), 5.61 (1H, *J* = 17.8 Hz, CHC$\underline{H}_2$, *trans*), 6.68 (1H, dd, *J* = 10.8, 17.8 Hz, C$\underline{H}$CH$_2$), 6.82 (1H, d, *J* = 8.2 Hz, H-5), 6.93 (1H, dd, *J* = 2.0, 8.2 Hz, H-6), 6.96 (1H, d, *J* = 2.0 Hz, H-2).

^{13}C NMR ($CDCl_3$): δ_C 55.8 (OCH_3), 55.9 (OCH_3), 108.6 (CH$\underline{C}$H$_2$), 111.1 (C-2), 111.7 (C-5), 119.4 (C-6), 130.8 (C-1), 136.5 ($\underline{C}$HCH$_2$), 149.0 (C-3), 149.1 (C-4).

HR-ESI-MS (positive ionization mode), *m/z* found 165.0915 $[M+H]^+$; calculated for $C_{10}H_{13}O_2$ 165.0916.

IR: ν_{max} (neat)/ cm^{-1}1261, 1462, 1642.

4.2.5 2-(3,4-Dimethoxyphenyl)ethanol (96)



To a solution 3,4-dimethoxyvinylbenzene (**95**) (1.50 g, 9.1 mmol) in dry THF (15 mL), $BH_3.S(CH_3)_2$ (1.30 mL, 1.37 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 6 h then cooled to 0 ºC for 10 min. A cold solution (0 ºC) of NaOH (20 mL, 3 M) was added, followed by H_2O_2 (0.55 mL, 1.8 mmol). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then extracted with Et_2O (3 x 20 mL) and the organic layer was washed with water and brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The resulting crude product was purified by radial chromatography (hexanes-EtOAc, 3:2) to give **96** as a colourless oil (0.55 g, 33%).

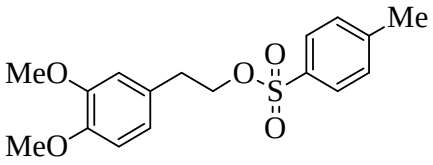
^{1}H NMR ($CDCl_3$): δ_H 2.82 (2H, t, *J* = 6.5 Hz, C$\underline{H}_2$CH$_2$OH), 3.83 – 3.88 (8H, m, 2 x OCH_3, CH$_2$C$\underline{H}_2$OH), 6.77 (2H, m, H-2 & H-6), 6.83 (1H, d, *J* = 8.5 Hz, H-5).

^{13}C NMR ($CDCl_3$): δ_C 38.8 ($\underline{C}$H$_2$CH$_2$OH), 55.9 (CH_3O), 59.9 (CH_3O), 63.8 (CH$_2\underline{C}$H$_2$OH), 111.6 (C-2), 112.4 (C-5), 121.0 (C-6), 131.1 (C-1), 147.9 (C-4), 149.1 (C-3).

HR-ESI-MS (positive ionization mode): *m/z* found 205.0843 $[M+Na]^+$; calculated for $C_{10}H_{14}NaO_3$ 205.2063.

IR: ν_{max} (neat)/ cm^{-1}1232, 1590, 3381.

4.2.6 2-(3,4-Dimethoxyphenyl)ethyl 4-methylbenzenesulfonate (117)



To a solution of 2-(3,4-dimethoxyphenyl)ethanol (**96**) (1.01 g, 5.5 mmol) at 0 ºC in dry DCM (3.00 mL), triethylamine (0.67 mL, 0.7 mmol) was added slowly followed by tosyl chloride (1.57 g, 8.2 mmol). The reaction mixture was stirred at room temperature for 30 min, diluted with DCM and then treated with a saturated aq. $NaHCO_3$ solution. The organic layer was extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under vacuum.[1-3] The crude mixture was purified by column chromatography (hexanes-EtOAc, 3:2) and the product **117** was obtained as a light-yellow oil (0.68 g, 37%).

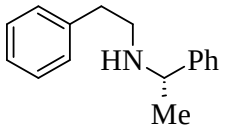
^{1}H NMR ($CDCl_3$): δ_H 2.42 (3H, s, C$\underline{H}_3$-Ph), 2.89 (2H, t, *J* = 7.2 Hz, C$\underline{H}_2$$CH_2O$), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.20 (2H, t, *J* = 7.3 Hz, CH_2C$\underline{H}_2$O), 6.60 (1H, d, *J* = 2.0 Hz, H-2), 6.65 (1H, dd, *J* = 2.0, 8.4 Hz, H-6), 6.74 (1H, d, *J* = 8.1 Hz, H-5), 7.28 (2H, d, *J* = 6.2 Hz, Ph), 7.67 (2H, d, *J* = 8.1 Hz, Ph).

^{13}C NMR ($CDCl_3$): δ_C 21.6 ($\underline{C}H_3$-Ar), 35.0 ($\underline{C}H_2CH_2O$), 55.8 (CH_3O) 55.9 (CH_3O), 70.8 ($CH_2\underline{C}H_2O$), 111.3 (C-2), 112.1 (C-5), 121.0 (C-6), 127.8 (C-Ar),128.7 (C - Ar),129.8 (C-1), 133.0 (C1-Ar), 148.1 (C-4), 148.9 (C-5).

HR-ESI-MS (positive ionization mode), *m/z* found 359.0934 $[M+Na]^+$; calculated for $C_{17}H_{20}NaO_5S$ 359.0929.

IR: ν_{max} (neat)/ cm^{-1}1237, 1464, 2937.

4.2.7 (1*S*)-1-phenyl-*N*-(2-phenylethyl)ethanamine (109)



Method A

Phenylactetaldehyde (**108**) (0.1 mL, 0.8 mmol) in dry THF (10 mL) was refluxed at 60 °C for 10 min followed by the dropwise addition of (*S*)-(α)-methylbenzylamine (*S*-**30**) (0.1 mL, 83 mmol) and the reaction mixture was allowed to stir overnight. Afterwards the reaction mixture was cooled down to 0 ºC and the solution of $NaBH_4$ (126 mg, 3.3 mmol) in methanol was added slowly over 15 min. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc, the organic layer washed with water and brine, dried over $MgSO_4$ and evaporated to dryness. Chromatographic purification (hexanes-EtOAc, 1:1) yielded only the two starting materials.

Method B

To a solution of **108** (100 mg, 0.6 mmol) in dry THF (10 mL), (*S*)-(α)-methylbenzylamine (0.11 mL, 8.3 mmol) was added dropwise. The reaction mixture was allowed to stir overnight and then $Na(CH_3COO)_3BH$ (0.165 g, 0.8mmol) was added to the reaction mixture and then allowed to stir for further 3 h. The mixture was not purified since no major product was observed.

Method C

A spatula tip of silica chloride was added to a stirred mixture of **108** (1.0 mL, 8.32 mmol) and (*S*)-(α)-methylbenzylamine (1.1 mL, 8.32 mmol) in dry THF (10 mL). $NaBH_4$ (1.02 g, 33.3 mmol) dissolved in MeOH (5 mL) was added dropwise at room temperature. The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with aqueous $NaHCO_3$. The mixture was extracted with Et_2O (3 x 15 mL), the organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography (hexanes-EtOAc, 1:1) to yield the product **109** as a yellow oil (0.7 g, 37% yield).

Specific rotation: $[\alpha]_D^{25}$ = -63.7 (c = 1.2, $CHCl_3$).

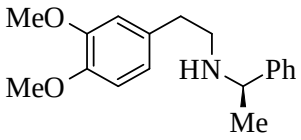
^{1}H NMR ($CDCl_3$): δ_H 1.41 (3H, d, *J* = 6.8 Hz, CHC<u>H</u>$_3$), 2.79-2.90 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$NH), 3.86 (1H, q, *J* = 6.6 Hz, C<u>H</u>CH$_3$), 7.27-7.42 (10H, m, Ph).

^{13}C NMR ($CDCl_3$): δ_C 24.1 (CH3), 36.3 (CH_2CH_2NH), 48.8 (CH_2CH_2NH), 58.1 ((CHCH3), 126.0 – 128.9 (C-Ar), 140.0 (C-Ph), 145.4 (C-1).

HR-ESI-MS (positive ionization mode): *m/z* found 226.1593 $[M+H]^+$; calculated for $C_{16}H_{20}N$ 226.1596.

IR: ν_{max} (neat)/ cm^{-1} 1028, 1182, 2925.

4.2.8 (*R*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethylamine (*R*-31)



Method A

To a solution of 3,4-dimethoxyphenylacetaldehyde (**79**) in dry THF (10 mL), (*R*)-(α)-methylbenzylamine (0.11 mL, 8.3 mmol) was added in a dropwise manner. The reaction mixture was stirred for 3 h, after which saturated aq. $NaHCO_3$ solution was added. The mixture was extracted using EtOAc (3 x 10 mL), the organic layer dried over $MgSO_4$ and concentrated under vacuum. The crude product was subjected to chromatography (hexanes-EtOAc, 3:2) but no major product was isolated.

Method B

To a stirred solution of 3,4-dimethoxyphenylacetic acid (100 mg, 0.4 mmol) in MeOH-H_2O, 10:1 (10 mL) at -15 °C, isobutyl chloroformate (0.05 mL, 0.38 mmol) was added followed by the addition of Et_3N (0.05 mL, 0.4 mmol). The reaction mixture was allowed to stir for 1 h and then (*R*)-(α)-methylbenzylamine was added dropwise (0.07 mL, 0.6 mmol). The reaction mixture was stirred overnight. Multiple products were formed which were then separated by radial chromatography (hexanes-EtOAc, 7:3). No major product was recovered.

Method C

A solution of 2-(3,4-dimethoxyphenyl)ethyl 4-methylbenzenesulfonate (**117**) (1.50 g, 1.49 mmol) in dry THF (15 mL) was added dropwise to a stirring solution of (*R*)-(α)-methylbenzylamine (0.29 mL, 2.2 mmol) in dry THF (1 mL) at room temperature. The reaction mixture was refluxed for 12 h. The crude mixture was purified by column chromatography (DCM-EtOAc, 1:1). The product *R*-**31** was obtained as a yellow oil (61 mg, 48%).

$[\alpha]_D^{25}$ = + 43.2 (1.4, $CHCl_3$).

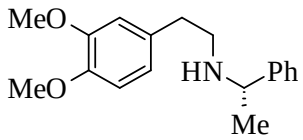
^{1}H NMR ($CDCl_3$): δ_H 1.35 (3H, d, *J* = 6.7 Hz, NHCHC<u>H</u>$_3$Ph), 1.82 (1H, brs, NH) 2.67 – 2.79 (4H, m, PhC<u>H</u>$_2$C<u>H</u>$_2$), 3.75 – 3.80 (1H, m, NHC<u>H</u>CH$_3$Ph), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.67 (1H, d, 1.8 Hz, H-2) , 6.70 (1H, dd, *J* = 1.9; 8.0 Hz, H-6), 6.78 (1H, d, *J* = 8.1-H-5), 7.20 – 7.32 (5H, m, <u>Ph</u>).

^{13}C NMR ($CDCl_3$): δ_C 24.1 (NHCH<u>C</u>H$_3$Ph), 35.8 (R<u>C</u>H$_2$CH$_2$NHR), 48.9 (RCH$_2$<u>C</u>H$_2$NHR), 55.8 (OCH_3), 55.9 (OCH_3), 58.2 (RCH$_2$<u>C</u>H$_2$NHR), 111.4 (C-5), 112.0 (C-2), 120.6 (C-6), 126.6-128.4 (Ar), 132.6 (C_1-Ph), 145.3 (C-3), 147.5 (C-1), 148.9 (C-4).

HR-ESI-MS (positive ionization mode), *m/z* found 308.1633 $[M+Na]^+$; calculated for $C_{18}H_{23}NaNO_2$ 308.1626.

IR: ν_{max} (neat)/ cm^{-1}1028, 1236, 2930.

4.2.9 (*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethylamine (*S*-31)

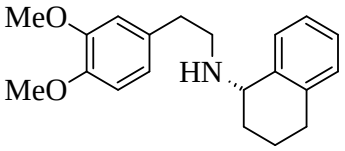


A solution of the tosylate (**117**) (1.35 g, 1.34 mmol) in dry THF (15 mL) was added dropwise to a stirring solution of (*S*)-(α)-methylbenzylamine (*S*-**30**) (0.26 mL, 2.0 mmol) in dry THF (1 mL) at room temperature. The reaction mixture was allowed to reflux at 90 °C for 12 h. The crude mixture was purified by column chromatography (DCM-EtOAc,

1:1). The product *S*-**31** was obtained as a yellow oil (57 mg, 45%). The spectral data was in good agreement with previously synthesized *R*-**31**.

$[\alpha]_D^{25}$ = -37.0 (1.1, $CHCl_3$).

4.2.10 (*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydronaphthalen-1-amine (119)



To a stirring solution of the tosylate (**117**) (64 mg, 0.2 mmol) in dry THF (10 mL) and (*R*)-(-)-1,2,3,4-tetrahydro-1-naphthylamine (0.14 mL, 0.1 mmol) in dry THF (1 mL). The reaction mixture was refluxed at 90 °C overnight and then cooled to room temperature. A saturated aq. $NaHCO_3$ solution (15 mL) was added and the organic layer was extracted with EtOAc (3 x 15 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in a rotary evaporator. The crude mixture was purified in the Centrifugal chromatography (DCM-EtOAc, 1:1). The product **119** was isolated as an orange oil (25 mg, 42%).

$[\alpha]_D^{25}$ = -45.3 (1.1, $CHCl_3$).

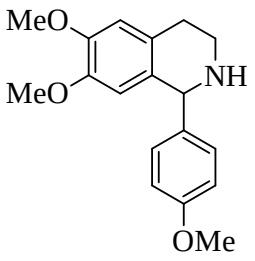
^{1}H NMR ($CDCl_3$): δ_H 1.74 (4H, m, NHCHC$\underline{H}_2$C$\underline{H}_2$), 2.03 (1H, brs, NH), 2.81 (2H, m, C$\underline{H}_2$CH_2NH), 2.91 - 3.01 (4H, m, C$\underline{H}_2$NH & C$\underline{H}_2$Ph), 3.85 (3H, s, OMe), 3.85 (3H, s, OMe), 4.05 (1H, s, NHC$\underline{H}$), 6.73 - 6.80 (3H, m, H-5, H-6 & H-2), 7.06-7.15 (4H, m, Ph).

^{13}C NMR ($CDCl_3$): δ_C 19.3 (C$\underline{H}_2$CH_2Ph), 26.2 (CHC$\underline{H}_2$CH_2), 28.9 (CH_2C$\underline{H}_2$Ph), 29.8 (C$\underline{H}_2$CH_2NH), 55.5 (CHNHC$\underline{H}$CH_2), 56.8 (2 x OCH_3), 111.4 (C-2), 112.2 (C-5), 120.8 (C-6), 126.3 - 138.5 (C-Ar), 147.9 (C-4), 149.1 (C-3).

HR-ESI-MS (positive ionization mode), *m/z* found 312.1974 $[M+H]^+$; calculated for $C_{20}H_{26}NO_2$ 312.1964.

IR: ν_{max} (neat)/ cm^{-1} 1259, 1447, 2924.

4.2.11 6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (121)



To a solution of freshly distilled 2-(3,4-dimethoxyphenyl)ethylamine (**36**) (0.10 mL, 0.60 mmol) in DCM (5 mL) containing a small quantity of *p*-toluenesulfonic acid and 3Å molecular sieves, freshly distilled *p*-anisaldehyde (**120**) (0.07 mL, 0.6 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. The solution was diluted with DCM and filtered, followed by concentration under vacuum. The resulting slurry was then dissolved and refluxed in TFA (3 mL) for 4 h under a nitrogen atmosphere. The resulting solution was then poured into ice and basified with saturated aq. $NaHCO_3$. The organic layer was extracted with DCM, washed with brine and dried under vacuum. The crude mixture was separated using EtOAc-MeOH (5:2) by centrifugal chromatography. The fractions were evaluated on TLC plates stained with Dragendorff's reagent. The product was isolated (55 mg, 40%) as a yellow oil.

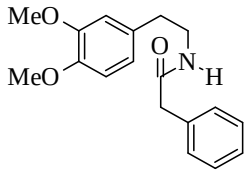
^{1}H NMR ($CDCl_3$): δ_H 3.04 (4H, m, $CH_2C\underline{H_2}NH$), 3.61(3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.81 (1H, d, J = 3.1 Hz, H-1), 3.85 (3H, s, OCH_3), 5.18 (1H, s, H-8), 6.61 (1H, s, H-5), 6.83 (2H, d, J = 8.5 Hz, H-2′ & H-6′), 7.16 (2H, d, J = 8.5 Hz, H-3′ & H-5').

^{13}C NMR ($CDCl_3$): δ_C 30.8 ($\underline{C}H_2CH_2NH$), 40.4 ($CH_2\underline{C}H_2NH$), 55.2 (*p*-OCH_3), 55.8 (2 x OCH_3), 59.6 (C-1), 110.7 (C-8), 116.2 (C-3′ & C-5′), 114.0 (C-2′ & C-6′), 128.9 (C-4a), 126.4 (C8-a), 130.7 (C-3′ or C-5′), 132.3 (C-1′), 147.6 (C-6), 148.4, (C-7), 159.6 (C-4′).

HR-ESI-MS (positive ionization mode), *m/z* found 300.1605 $[M+H]^+$; calculated for $C_{18}H_{22}NO_3$ 300.1600.

IR: ν_{max} (neat)/ cm^{-1} 1123, 1512, 3429.

4.2.12 *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-phenylacetamide (123)



To a solution of freshly distilled 2-(3,4-dimethoxyphenyl)ethylamine (**36**) (0.11 mL, 0.60 mmol) in pyridine (5 mL) or saturated aq. Na_2CO_3 - DCM mixture, (1:1, 6 mL), phenylacetyl chloride (**122**) (0.07 ml, 0.6 mmol) was added and the reaction was stirred at room temperature overnight.[4,5] The organic layer was extracted with DCM (3 x 10 mL) and washed with water and brine. Evaporation of the solvent gave a pale yellow crystalline product, found to be pure *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylacetamide (**123**) (140 mg, 79%).

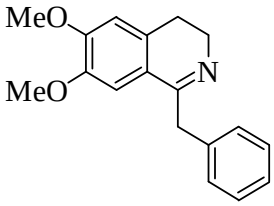
^{1}H NMR ($CDCl_3$): δ_H 2.68 (2H, t, *J* = 7.1 Hz, C$\underline{H_2}$CH_2NH), 3.43 (2H, q, *J* = 7.1Hz, CH_2C$\underline{H_2}$NH), 3.53 (1H, s, C$\underline{H_2}$Ph), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.57 (1H, brs, NH), 6.55 (1H, dd, *J* = 2.0, 8.2 Hz, H-B), 6.60 (1H, d, *J* = 2.0 Hz, H-A), 6.72 (1H, d, *J* = 8.0 Hz, H-X), 7.16 (1H, d, *J* =2.0 Hz, Ph), 7.17 (1H, d, *J* =1.8 Hz, Ph), 7.30 (3H, m, Ph).

^{13}C NMR ($CDCl_3$): δ_C 35.0 ($\underline{C}H_2CH_2NH$), 40.7 ($CH_2\underline{C}H_2NH$), 43.6 (CH_2Ph), 55.8 (OCH_3), 55.9 (OCH_3), 111.4 (C-X), 111.8 (C-A), 120.5 (C-B), 127.5 (C-4′), 129.0 (C5′ & C-3′), 129.4 (C-6′ & C-2′), 131.1 (C-4a), 134.7 (C-1′), 147.7 (C-6), 149.1 (C-7), 207.0 (C=O).

HR-ESI-MS (positive ionization mode), *m/z* found 300.1347 $[M+H]^+$; calculated for $C_{18}H_{22}NO_3$ 300.1342.

IR: ν_{max} (neat)/ cm^{-1} 1231, 1633, 3242.

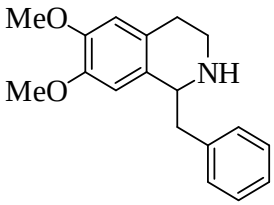
4.2.13 1-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (124)



To a solution of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylacetamide (**123**) (120 mg, 0.52 mmol) in DCM (10 mL) and containing 3Å molecular sieves, excess $POCl_3$ (0.15 mL, 1.6 mmol) was added and the mixture was refluxed for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and then poured into ice. The reaction mixture was extracted with EtOAc, and the combined extracts washed with brine, dried (anhydrous $MgSO_4$) and concentrated under vacuum. The crude mixture (122 mg, 81%) was used without further purification to avoid decomposition.

^{1}H NMR ($CDCl_3$): δ_H 2.86 (2H, t, *J* = 7.8 Hz, C$\underline{H}_2$CH_2NH, 3.78 (3H, s, OCH_3), 3.95 (5H, m, $CH_2C\underline{H}_2NH$, OCH_3), 6.77 (1H, s, H-5), 6.94 (1H, s, H-8), 7.48 (2H, t, *J* = 7.8 Hz, H-3′ & H-5′), 7.61 (1H, t, *J* = 7.5 Hz, H-4′), 8.02 (2H, d, *J* = 7.2 Hz, C-2′ & C-6′)

4.2.14 1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (125)



To a solution of **124** (100 mg, 0.36 mmol) in dry MeOH (5 mL), $NaBH_4$ (27 mg, 0.7 mmol) solution in methanol was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h. A few drops of HCl were added to destroy unreacted $NaBH_4$. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with water and brine then finally dried over $MgSO_4$. The crude mixture was purified by centrifugal chromatography (EtOAc-MeOH, 5:2). The product **125** was obtained as a brown oil (76 mg, in 76%).

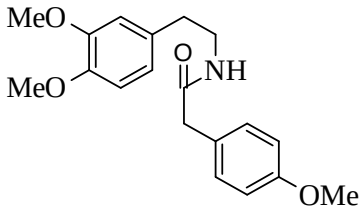
^{1}H NMR ($CDCl_3$): δ_H 2.75 (2H, t, *J* = 5.6 Hz, H-4), 3.23-2.95 (4H, m, H-3, PhC$\underline{H}_2$), 3.62 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.23 (1H, t, *J* = 6.9 Hz, H-1), 4.33 (1H, brs, NH), 6.34 (1H, s, H-8), 6.51 (1H, s, H-5), 7.24-7.15 (5H, m, Ph).

^{13}C NMR ($CDCl_3$): δ_C 39.8 (C-3), 42.2 (CH_2Ph), 55.8 (O$\underline{C}H_3$), 55.8 (O$\underline{C}H_3$), 56.3 (C-1), 109.7 (C-8), 111.7 (C-5), 126.1 – 129.6 (Ph), 138.2 (C-1′), 147.0 (C-6), 147.9 (C-7).

HR-ESI-MS (positive ionization mode), *m/z* found 284.1645 $[M+H]^+$; calculated for $C_{18}H_{22}NO_2$ 284.1651.

IR: ν_{max} (neat)/ cm^{-1} 1512, 1652, 3459.

4.2.15 *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(4-methoxyphenyl)acetamide (127)



4-Methoxyphenylacetic acid (0.27 g, 1.7 mmol) was refluxed in $SOCl_2$ (2 mL, 10 mmol) for 2 h followed by the removal of excess $SOCl_2$ under vacuum. The freshly prepared acid chloride was reacted with 2(3,4-dimethoxyphenyl)ethylamine (0.2 mL, 1.1 mmol) according to the procedure described for (**131**). The product **127** was obtained as a yellow solid (0.32 g, 93%) yield.

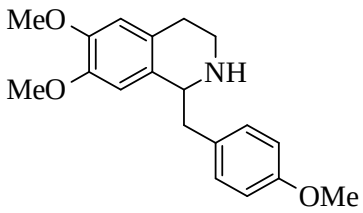
^{1}H NMR ($CDCl_3$): δ_H 2.67 (2H, t, *J* = 7.0 Hz, C$\underline{H_2}$CH_2NH), 3.45 (2H, q, *J* = 7.0 Hz, CH_2C$\underline{H_2}$NH), 3.47 (2H, s, CH_2CO), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.36 (1H, brs, NH), 6.54 (1H, dd, *J* = 2.3, 8.2 Hz, H-6), 6.60 (1H, d, *J* = 1.8 Hz, H-5), 6.72 (1H, d, *J* = 8.0 Hz, H-2), 6.83 (2H, d, *J* = 8.5 Hz, Ph), 7.07 (2H, d, *J* = 8.7 Hz, Ph).

^{13}C NMR ($CDCl_3$): δ_C 35.0 ($\underline{C}H_2CH_2NH$), 40.7 ($\underline{C}H_2CO$), 42.9 ($CH_2\underline{C}H_2NH$), 55.3 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 111.4 (C-2), 111.9 (C-5), 114.5 (2 x C-Ph), 120.6 (C-Ph), 126.7 (C-1), 130.6 (2 x C-Ph), 131.1 (C-6), 147.7 (C-4), 149.1 (C-3), 158.9 (C-Ph), 171.4 (CO).

HR-ESI-MS (positive ionization mode), *m/z* found 352.1518 $[M+Na]^+$; calculated for $C_{19}H_{23}NaNO_4$ 352.1521.

IR: ν_{max} (neat)/ cm^{-1} 1648, 2932, 3314.

4.2.16 6,7-Dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (129)



The title compound was prepared by dissolving **127** (0.2 g, 0.6 mmol) in anhydrous MeCN (10 mL) containing 3Å molecular sieves. Excess $POCl_3$ (0.16 mL, 1.8 mmol) was added and the reaction mixture was stirred for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature followed by the evaporation of MeCN and excess $POCl_3$ in a rotary evaporator. The resulting crude mixture of the dihydroisoquinoline was dissolved in anhydrous MeOH (10 mL), followed by the addition of $NaBH_4$ (68 mg, 1.8 mmol) solution in anhydrous MeOH (5 mL) and stirred for 2 h at room temperature in the presence of 3 Å molecular sieves. The crude mixture was purified on the centrifugal chromatography (EtOAc-MeOH, 5:2). The product **129** was isolated as a brown oil (91 mg, in 48%).

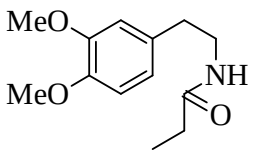
^{1}H NMR ($CDCl_3$): δ_H 2.30 (2H, t, *J* = 7.9 Hz, H-4), 2.75 – 2.80 (1H, m, NH), 3.24 – 3.38 (4H, m, CH_2Ph), 3.89 (4H, m, OCH_3, and H-1), 3.93 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.83 – 6.92 (4H, m, Ph), 7.55 (1H, d, *J* = 2.0 Hz, H-5), 7.70 (1H, dd, *J* = 1.9, 6.4 Hz, H-8).

^{13}C NMR ($CDCl_3$): δ_C 22.7 (C-4), 29.7 (C-3), 31.9 ($\underline{C}H_2Ph$), 52.0 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 (C-1), 110.3 (C-5), 112.1 (C-8), 114.0 (C-3′ & C-4′), 122.7 (C-4b), 123.6 (C-2′ & C-6′), 128.4 (C-4a), 130.0 (C-1′), 148.9 (C-4), 153.1 (C-3), 167.0 (C-4′).

HR-ESI-MS (positive ionization mode), *m/z* found 314.1759 $[M+H]^+$; calculated for $C_{19}H_{24}NO_3$ 314.1756.

IR: ν_{max} (neat)/ cm^{-1} 3465, 1510, 2924.

4.2.17 *N*-[2-(3,4-Dimethoxyphenyl)ethyl]propanamide (131)



2(3,4-Dimethoxyphenyl)ethylamine (**36**) (0.1 mL, 0.6 mmol) and propionyl chloride (0.05 mL, 0.6 mmol) were stirred in saturated Na_2CO_3 - DCM solution, (1:1, 6 mL) at room temperature overnight.[5] The organic layer was extracted with DCM (3 x 10 mL), washed

with water and brine, dried over $MgSO_4$ and the solvent was removed a rotary evaporator. The product **131** was obtained as a yellow oil (120 mg, 91%).

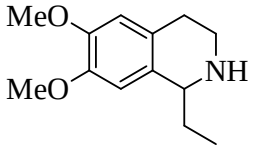
^{1}H NMR ($CDCl_3$): δ_H 1.11 (3H, t, *J* = 8.0 Hz, $CH_2C\underline{H}_3$), 2.14 (2H, q, *J* = 7.6 Hz, $C\underline{H}_2CH_3$), 2.74 (2H, t, *J* = 7.1 Hz, $C\underline{H}_2CH_2NH$), 3.47 (2H, q, *J* = 7.1 Hz, $CH_2C\underline{H}_2NH$), 3.84 (6H, d, *J* = 6.7 Hz, 2 x OCH_3), 5.55 (1H, brs, NH), 6.69 (2H, d, *J* = 6.7 Hz, H-6, H-2), 6.8 (1H, d, 8.8 Hz, H-5).

^{13}C NMR ($CDCl_3$): δ_C 9.9 ($\underline{C}H_3CH_2$), 29.8 ($\underline{C}H_2CH_2NH$), 35.3 (CH_2NH), 40.7 ($CH_3\underline{C}H_2$), 55.9 (OCH_3), 56.0 (OCH_3), 111.3 (C-2), 111.9 (C-5), 120.6 (C-6), 131.4 (C-1), 147.6 (C-4), 147.0 (C-3), 173.7 (CO).

HR-ESI-MS (positive ionization mode), *m/z* found 260.1265 $[M+Na]^+$; calculated for $C_{13}H_{19}NaNO_3$ 260.1263.

IR: ν_{max} (neat)/ cm^{-1} 1637, 2967, 3295.

4.2.18 1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (133)



The title compound was prepared by dissolving compound **131** (85 mg. 0.4 mmol) in anhydrous MeCN (10 mL) containing 3Å molecular sieves. Excess $POCl_3$ (0.11 mL, 1.2 mmol) was added and the reaction mixture was stirred for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature followed by the evaporation of MeCN and excess $POCl_3$. The resulting crude mixture of the dihydroisoquinoline (**132**) was dissolved in anhydrous MeOH (10 mL) in the presence of 3 Å molecular sieves and stirred for 2 h at room temperature. The crude mixture was purified on the centrifugal chromatography (EtOAc-MeOH, 5:2). The product was obtained as an orange oil (57 mg, 67%).

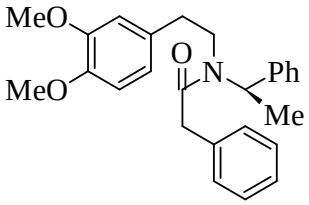
^{1}H NMR ($CDCl_3$): δ_H 1.09 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.25 (1H, m, NH), 1.94 (2H, m, $C\underline{H}_2CH_3$), 2.80 – 3.40 (4H, m, $C\underline{H}_2C\underline{H}_2NH$), 3.85 (6H, 2 x s, 2 x OCH_3), 4.11 (1H, m, H-1), 6.59 (2H, H-5 & H-8).

^{13}C NMR ($CDCl_3$): δ_C10.3 (CH_3), 27.4 ($\underline{C}H_2CH_3$), 28.3 ($\underline{C}H_2CH_2NH$), 40.3 (CH_2NH), 55.9 (C-1), 56.0 (OCH_3), 56.3 (OCH_3), 109.3 (C-5), 111.7 (C-8), 125.7 (C-4b), 127.5 (C-4a), 147.8 (C-6), 148.0 (C-7).

HR-ESI-MS (positive ionization mode), *m/z* found 222.1501 $[M+H]^+$; calculated for $C_{13}H_{20}NO_2$ 222.1494.

IR: ν_{max} (neat)/ cm^{-1} 1121, 2932, 3414.

4.2.19 (*R*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-(1-phenylethylamine)phenylacetamide (*R*-134)



A saturated aq. Na_2CO_3 - DCM mixture, (1:1, 6 mL) of *R*-**36** (230 mg, 0.8 mmol) and phenylacetyl chloride (**122**) (0.8 mL, 0.8 mmol) was stirred at room temperature overnight. After cooling to room temperature, the mixture was extracted with DCM (3 x 10 mL), the combined extracts were washed with water and brine and dried with $MgSO_4$ and evaporated on a rotary evaporator. The product was obtained as a yellow oil (270 mg, 83%) whose NMR spectrum was similar to that of *S*-**134**.

$[\alpha]_D^{25}$ = -41.2 (1.8, $CHCl_3$).

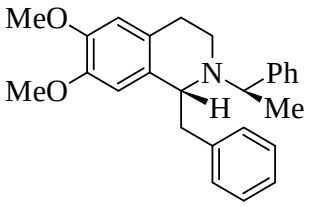
^{1}H NMR ($CDCl_3$): δ_H 1.45 (3H, d, *J* = 7.0 Hz, $CHC\underline{H}_3$), 2.15 (1H, m, $C\underline{H}_2CH_2N$), 2.30 (1H, m, $CH_2C\underline{H}_2N$), 2.56 (1H, m, $C\underline{H}_2CH_2N$), 2.74 (1H, m, $CH_2C\underline{H}_2N$), 3.23 (2H, m, CH_2CO), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (2H, s, CH_2CO), 5.20 (1H, q, *J* = 7.0 Hz, $CHCH_3$), 6.52 (3H, m, H-2, H-5-H-6), 7.38 (13H, m, H-Ar).

^{13}C NMR ($CDCl_3$): δ_C 17.8 ($CHCH_3$), 34.3 (CH_2CH_2N), 36.7 (CH_2CH_2N), 45.5 (CH_2CO), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 ($CHCH_3$), 126.9-129.5 (C-Ar), 147.0 (C-4), 149.0 (C-3), 171.3 (CO).

HR-ESI-MS (positive ionization mode), *m/z* found 426.2030 $[M+Na]^+$; calculated for $C_{26}H_{29}NaNO_3$ 426.2045.

IR: ν_{max} (neat)/ cm^{-1} 1498, 1715, 2972.

4.2.20 1*R*)-1-benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-136)



The title compound was synthesized by dissolving **134** (120 mg, 0.3 mmol) in anhydrous MeCN (10 mL) containing 3Å molecular sieves. Excess $POCl_3$ (0.10 mL, 0.9 mmol) was added and the reaction mixture was stirred for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature followed by the evaporation of MeCN and excess $POCl_3$. The resulting crude mixture of the dihydroisoquinolium salt (*R*-**135**) was dissolved in anhydrous MeOH (10 mL) containing 3 Å molecular sieves and a methanol solution of $NaBH_4$ (34 mg, 0.9 mmol) was then added and stirred for 2 h at room temperature. The crude mixture was purified on the centrifugal chromatography (EtOAc-MeOH, 5:2). It was isolated as a brown oil (60.1 mg, in 52%).

$[\alpha]_D^{25}$ = +61.6 (1.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ_H 1.98 (1H, d, *J* = 7.8 Hz, CH(C<u>H</u>$_3$)Ph), 2.30 - 2.35 (4H, m, CH_2CH_2N), 2.86 (2H, m, C<u>H</u>CH_3), 3.86 (6H, s, OCH_3) 6.66 - 6.68 (2H, m, H-5 and H-8), 1.08 (2H, m, Ph), 7.31 (8H, m, Ph).

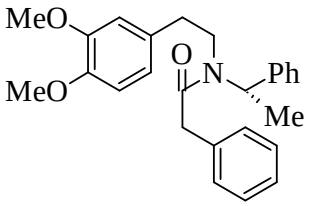
^{13}C NMR ($CDCl_3$): δ_C 22.6 (CH_3), 29.6 (C-4), 32.0 (<u>C</u>H_2Ph), 43.4 (C-3), 55.9 (2 x OCH_3), 68.1 (C-1), 73.5 (<u>C</u>H(CH_3)Ph), 126.4 (C-4), 128.5 (C-8), 129.5 (C-4′), 128.5 (C-3′ & C-5′),

128.6 (C-Ph), 128.8 (C-2′, C-6′, C-4b), 129.5 (C-4a), 138.5 (C-1′ & C1-Ph), 147.1 (C-7), 149.4 (C-6).

HR-ESI-MS (positive ionization mode), *m/z* found 388.2285 $[M+H]^+$; calculated for $C_{26}H_{30}NO_2$ 388.2277.

IR: ν_{max} (neat)/ cm^{-1} 1093, 1592, 2975.

4.2.21(*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-(1-phenylethylamine)-phenylacetam-ide (*S*-134)



A saturated aq. Na_2CO_3 - DCM mixture, (1:1, 6 mL), *S*-**36** (100 mg, 0.4 mmol) and phenylacetyl chloride (0.05 mL, 0.4 mmol) was stirred at room temperature overnight. The solution was extracted with DCM (3 x 10 mL) and washed with water and brine and dried with $MgSO_4$ and concentrated under vacuum. The product *S*-**134** was obtained as a yellow oil (126 mg, 89%) and whose NMR spectra was similar to those of *R*-**134**.

$[\alpha]_D^{25}$ = +43.9 (1.1, $CHCl_3$).

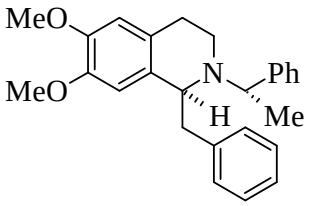
^{1}H NMR ($CDCl_3$): δ_H 1.45 (3H, d, *J* = 7.0 Hz, $CHC\underline{H}_3$), 2.15 (1H, m, $C\underline{H}_2CH_2N$), 2.30 (1H, m, $CH_2C\underline{H}_2N$), 2.56 (1H, m, $C\underline{H}_2CH_2N$), 2.74 (1H, m, $CH_2C\underline{H}_2N$), 3.23 (2H, m, CH_2CO), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (2H, s, CH_2CO), 5.20 (1H, q, *J* = 7.0 Hz, $CHCH_3$), 6.52 (3H, m, H-2, H-5-H-6), 7.38 (13H, m, Ph).

^{13}C NMR ($CDCl_3$): δ_C 17.8 ($CHCH_3$), 34.3 (CH_2CH_2N), 36.7 (CH_2CH_2N), 45.5 (CH_2CO), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 ($CHCH_3$), 126.9-129.5 (C-Ph), 147.0 (C-4), 149.0 (C-3), 171.3 (CO).

HR-ESI-MS (positive ionization mode), *m/z* found 426.2030 $[M+Na]^+$; calculated for $C_{26}H_{29}NaNO_3$ 426.2045.

IR: ν_{max} (neat)/ cm^{-1} 1460, 1684, 1725.

4.2.22 (*S*)-1-Benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*S*-136)



The title compound was synthesized by dissolving (*S*-**134**) (154 mg, 0.4 mmol) in anhydrous MeCN (10 mL) containing 3Å molecular sieves. Excess $POCl_3$ (0.11 mL, 1.2 mmol) was added and the reaction mixture was stirred for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature followed by the evaporation of MeCN and excess $POCl_3$. The resulting crude mixture of the dihydroisoquinolinium salt (*S*-**135**) was dissolved in anhydrous MeOH (10 mL) containing 3 Å molecular sieves, whereupon $NaBH_4$ (45 mg, 1.2 mmol) in MeOH was added and stirred for 2 h at room temperature. The crude mixture was purified by centrifugal chromatography (EtOAc-MeOH, 5:2). The product (*S*-**136**) was isolated as a brown oil (87 mg, in 59%).

$[\alpha]_D^{25}$ = -83.7 (1.6, $CHCl_3$).

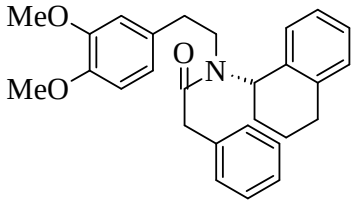
^{1}H NMR ($CDCl_3$): δ_H 1.47 (3H, d, *J* = 7.4 Hz, CHC<u>H</u>$_3$Ph), 1.98 (2H, m, CH_2C<u>H</u>$_2$N), 2.35 (2H, t, *J* = 7.2 Hz, C<u>H</u>$_2$$CH_2$N), 2.77 (2H, m, CH_2Ph), 3.85 (6H, s, 2 x OCH_3), 4.03 (1H, m, C<u>H</u>CH_3Ph), 4.21 (1H, t, *J* = 6.1 Hz, H-1), 6.62 (2H, m, H-5 & H-8), 7.27 – 7.39 (Ph).

^{13}C NMR ($CDCl_3$): δ_C 22.7 (CH<u>C</u>H$_3$Ph), 32.0 (C-4), 41.3 (<u>C</u>H$_2$Ph), 41.9 (C-3), 42.6 (<u>C</u>HCH$_3$Ph), 50.3 (C-1), 55.4 (OCH_3), 55.8 (OCH_3), 111.3 (C-5), 111.5 (C-8), 127.3 (C-4′), 127.5 (C-4″), 128.1 (C-2′ & C-6′), 128.7 (C-3″ & C-5″), 128.7 (C-3′ & C-5′), 129.2 (C-4b, C-2″&C-6″), 130.0 (C-1), 136.3 (C-4a), 138.8 (C-1″), 135.3 (C-1′), 145.7 (C-7), 146.4 (C-6).

HR-ESI-MS (positive ionization mode), *m/z* found 388.2283 $[M+H]^+$; calculated for $C_{26}H_{30}NO_2$ 388.2275.

IR: ν_{max} (neat)/ cm^{-1} 1132, 1232, 1575.

4.2.23 (*S*)-*N*-[2-3,4-Dimethoxyphenyl)-ethyl]-2-phenyl-*N*-(1,2,3,4-tetrahydro-naphthylenylacetamide (137)



A saturated aq. Na_2CO_3 - DCM (1:1, 6 mL) mixture containing the amine **119** (325 mg, 1.0 mmol) and phenylacetyl chloride (**122**) (0.1 mL, 1.0 mmol) was stirred at room temperature overnight. After cooling to room temperature the organic layer was extracted with DCM (3 x 10 mL). The combined extracts were washed successively with water and brine and dried $MgSO_4$ before being concentrated under reduced pressure. The product **137** was obtained as a yellow oil (390 mg, 87%).

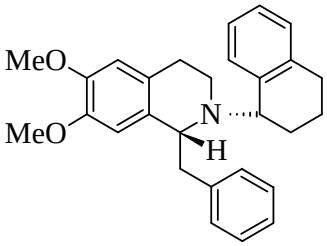
$[\alpha]_D^{25}$ = -73.2 (1.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ_H 2.11 (4H, m, $CHCH_2C\underline{H}_2C\underline{H}_2Ph$), 2.71 – 2.81 (8H, m, $C\underline{H}_2C\underline{H}_2N$, $CHC\underline{H}_2CH_2CH_2Ph$, $C\underline{H}_2Ph$), 3.63 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 4.14 (1H, t, *J* = 6.5 Hz, $C\underline{H}CH_2$), 7.04 (2H, m, H-2 & H-6), 7.18 - 7.20 (7H, H-Ar).

HR-ESI-MS (positive ionization mode), *m/z* found 451.9938 $[M+Na]^+$; calculated for $C_{28}H_{31}NaNO_3$ 451.9920.

IR: ν_{max} (neat)/ cm^{-1} 1217, 1527, 1732.

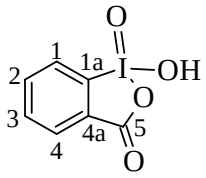
4.2.24 (*S*)-1-Benzyl-6,7-dimethoxy-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2,3,4-tetrahydroisoquinoline (139)



The title compound was synthesized by dissolving **137** (120 mg, 0.3 mmol) in anhydrous MeCN (10 mL) with 3Å molecular sieves. Excess $POCl_3$ (0.08 mL, 0.9 mmol) was added and the reaction mixture was stirred for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature followed by the evaporation of MeCN and excess $POCl_3$. The resulting crude mixture of the dihydroisoquinolinium salt **138** was dissolved in anhydrous MeOH (10 mL), 3 Å molecular sieves were added and the mixture stirred for 2 h at room temperature. The crude mixture could not be purified since there were multiple spots on the TLC.

4.3 Synthesis of Reagents

4.3.1 1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (105)



To a vigorously stirring solution of 2-iodobenzoic acid (1.1 g, 34.5 mmol) in H_2SO_4 (20 mL, 0.73 M) at 0 ºC, $KBrO_3$ (1 g, 4.6 mmol) was added slowly and then allowed to reach room temperature. The reaction mixture was heated to 65 ºC and allowed to stir for further 3 h. The resulting off-white precipitate was filtered via suction filtration and washed with cold water and allowed to dry. The precipitate was recrystallized from methanol. White needle-shaped crystals of the product (**105**) (0.88 g, 91%) were obtained.[6,7]

Mp: 229.4 – 232.1 (Lit[8]: 233 °C).

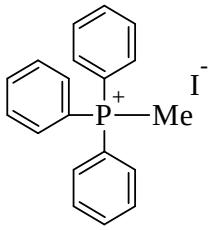
^{1}H NMR (DMSO-d_6): δ_H 7.63 (1H, t, *J* = 7.7 Hz, H-3), 7.78 (1H, t, *J* = 7.4 Hz, H-2), 7.83 (1H, d, *J* = 7.7 Hz, H-4), 7.94 (1H, d, *J* = 7.8 Hz, H-1).

^{13}C NMR ($CDCl_3$): δ_C 121.4 (C-1), 127.2 (C-4), 131.3 (C-4a), 132.0 (C-3), 132.5 (C-2), 135.4 (C-1a), 167.0 (C-5).

HR-ESI-MS (negative ionization mode): *m/z* found 278.9152 $[M+H]^+$; calculated for $C_7H_4IO_4$ 278.9154.

IR: ν_{max} (neat)/ cm^{-1} 1433, 1669, 3089.

4.3.2 Methyltriphenylphosphonium iodide (140)



To a cold (0 °C) solution of triphenylphoshine (10.0 g, 38.0 mmol) in toluene (20 mL), methyl iodide (0.99 mL, 51.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. The solid material was collected by filtration followed by washing with cold toluene. The product was dried in a vacuum oven to give the title compound **140** (9.8 g, 66% yield) as a white powder.

^{31}P NMR (DMSO-d_6): δ_P 23.02.

HR-ESI-MS (positive ionization mode): *m/z* found 278.1153 $[M+H]^+$; calculated for $C_{19}H_{19}P$ 278.1140.

IR: ν_{max} (neat)/ cm^{-1} 1112, 1219, 1439.

4.3.3 Silica chloride (141)

To a well-stirred slurry of silica gel (5 g) in DCM (13.0 mL), $SOCl_2$ (4.3 mL) was added dropwise at room temperature. Vast amounts of SO_2 and HCl gas were evolved as by-products and removed using a delivering tube. The reaction mixture was allowed to stir for 1 h at room temperature whereupon the SiO_2-Cl was collected by gravity filtration as a greyish solid SiO_2-Cl (7.25 g, 96%) which was allowed to dry at room temperature and finally kept in a sealed vial.[9,10]

IR: ν_{max} (neat)/ cm^{-1} 1069, 1219, 2923.

4.4 References

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APPENDIX: COPIES OF NMR SPECTRA

Plate 1: ^{1}H NMR spectrum of (*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1-phenylethylamine (*R*-**31**) in $CDCl_3$

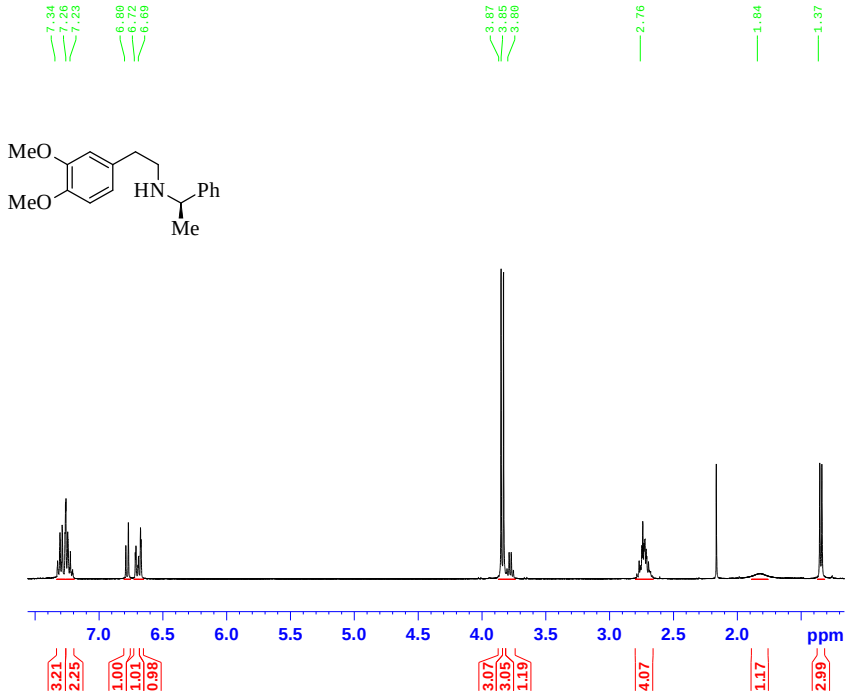

Plate 2: ^{13}C NMR spectrum of (*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1-phenylethylamine (*R*-**31**) in $CDCl_3$

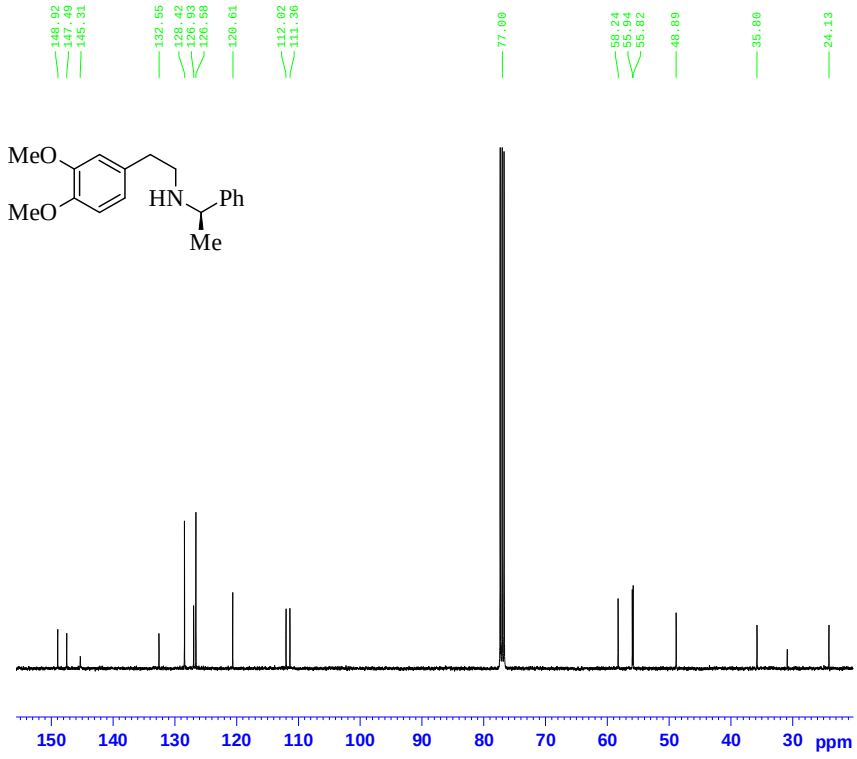

Plate 3:[1]H NMR spectrum of 3,4-dimethoxybenzaldehyde (**61**)in $CDCl_3$

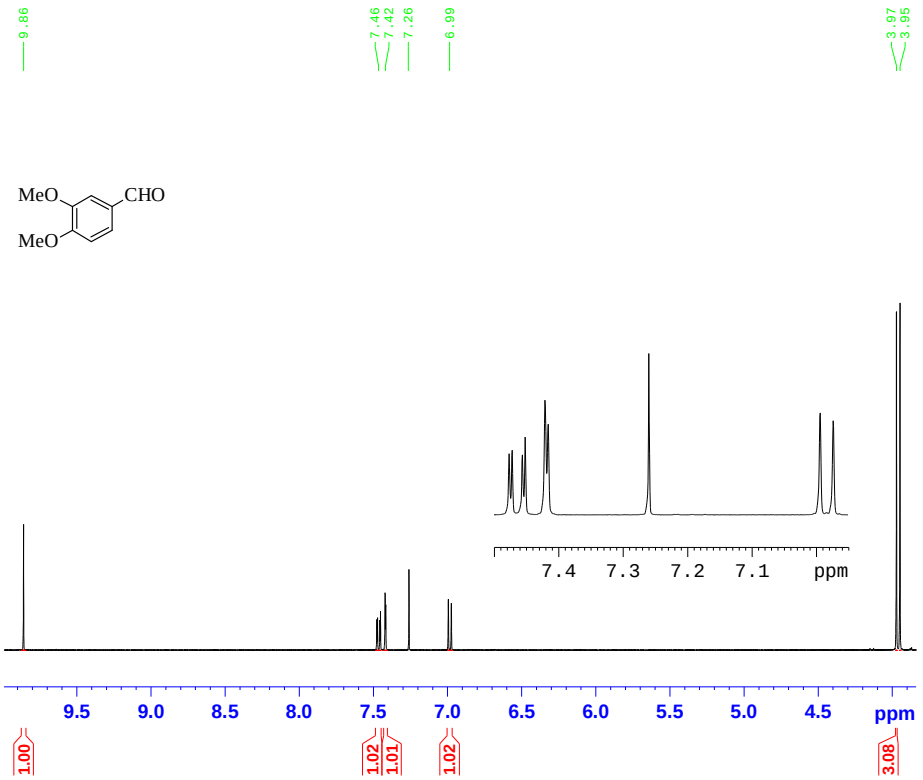

Plate 4: [13]C NMR spectrum of 3,4-dimethoxybenzaldehyde (**61**)in $CDCl_3$

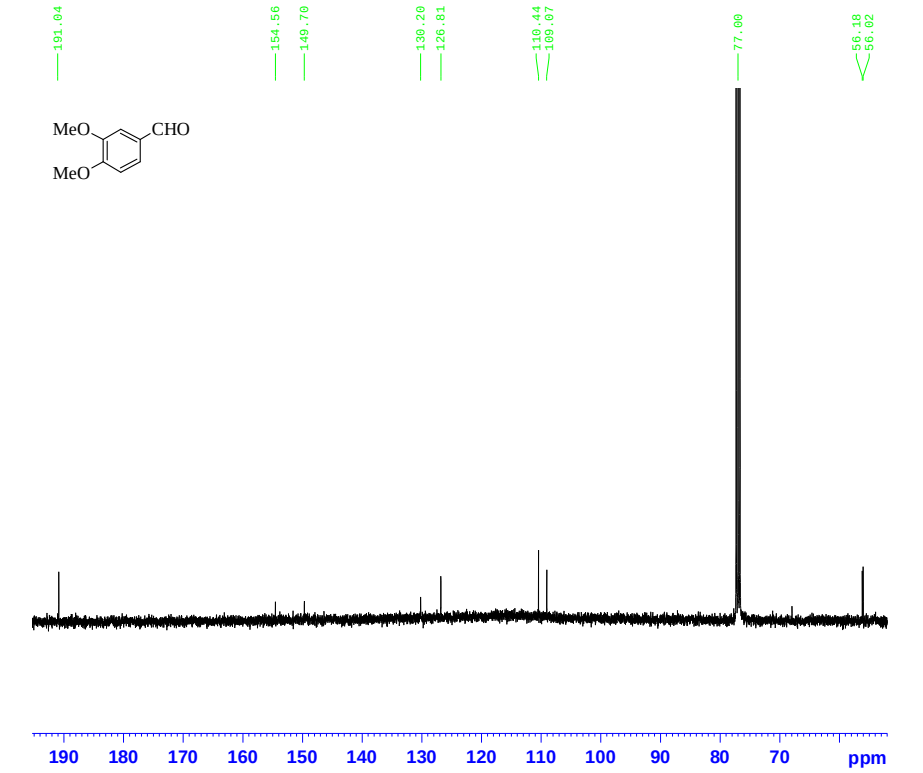

Plate 5: ^{1}H NMR spectrum of 3,4-dimethoxyphenylacetaldehyde (**79**) in $CDCl_3$

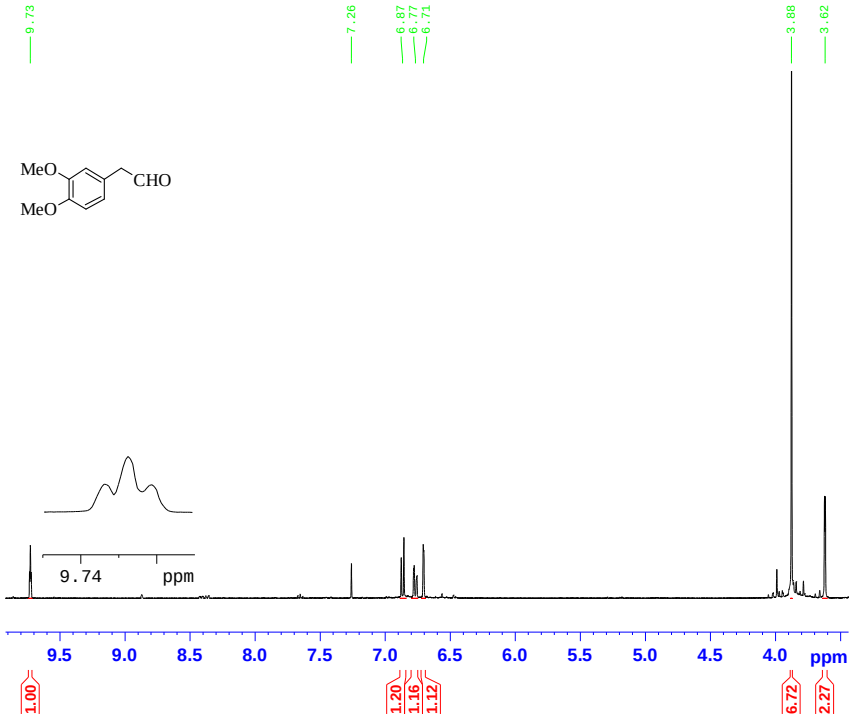

Plate 6: ^{13}C NMR spectrum of 3,4-dimethoxyphenylacetaldehyde (**79**) in $CDCl_3$

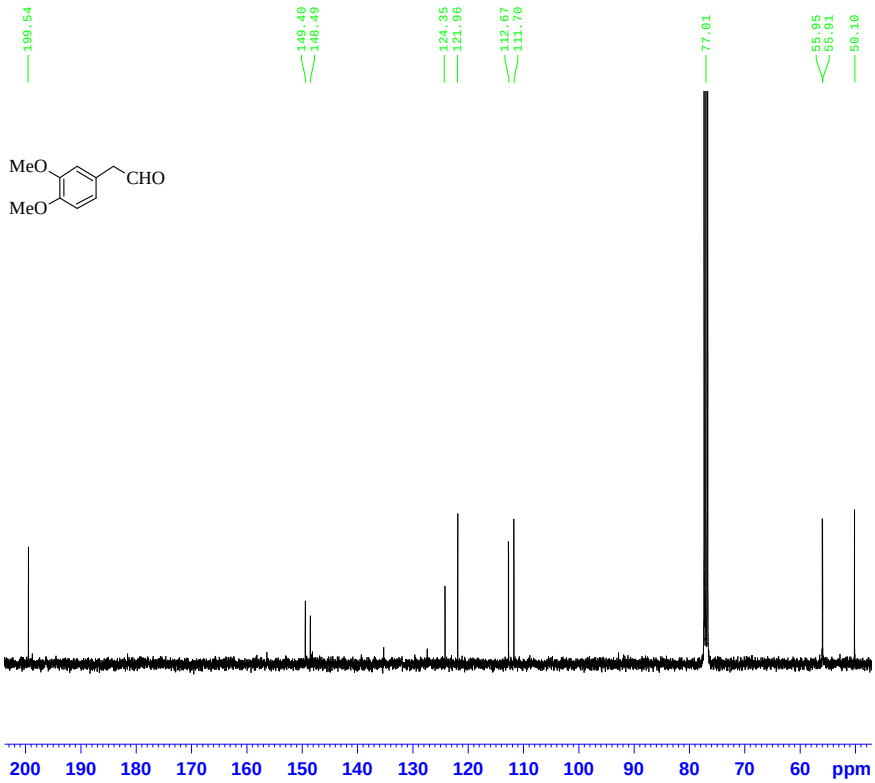

Plate 7: ^{1}H NMR spectrum of 1,2-dimethoxy-4-(-2-methoxyvinyl)benzene (**92**) in $CDCl_3$

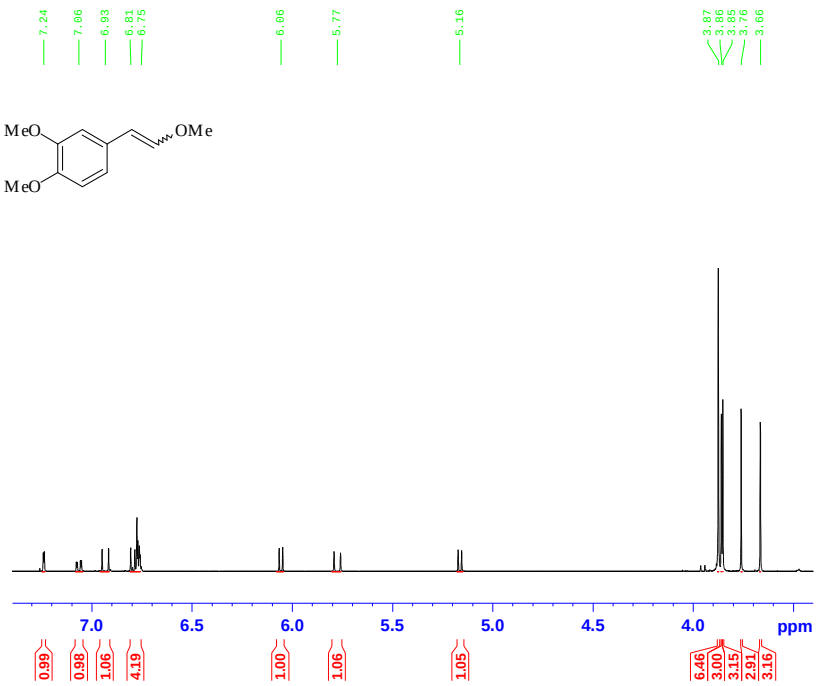

Plate 8: ^{13}C NMR spectrum of 1,2-dimethoxy-4-(-2-methoxyvinyl)benzene(**92**) in $CDCl_3$

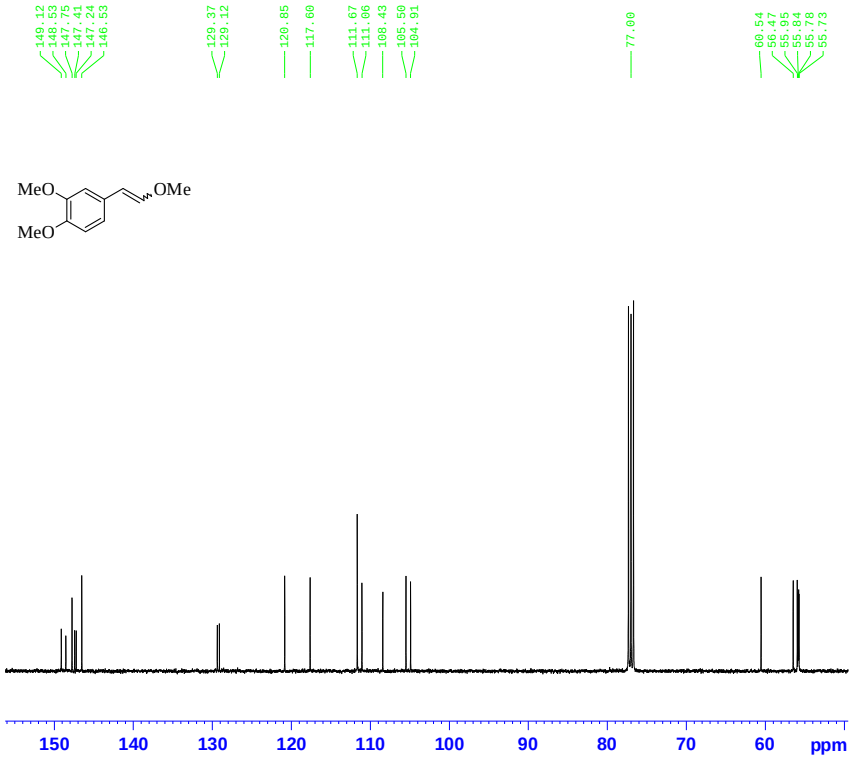

Plate 9: ^{1}H NMR spectrum of 1,2-dimethoxy-4-vinylbenzene (**95**) in $CDCl_3$

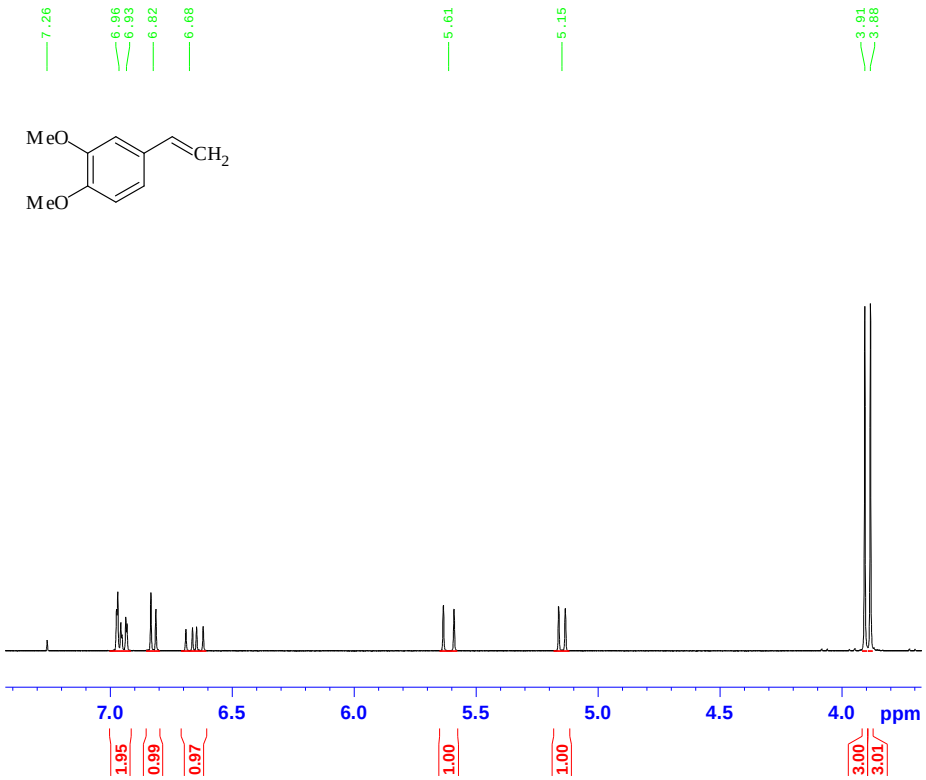

Plate 10: ^{13}C NMR spectrum of 1,2-dimethoxy-4-vinylbenzene (**95**) in $CDCl_3$

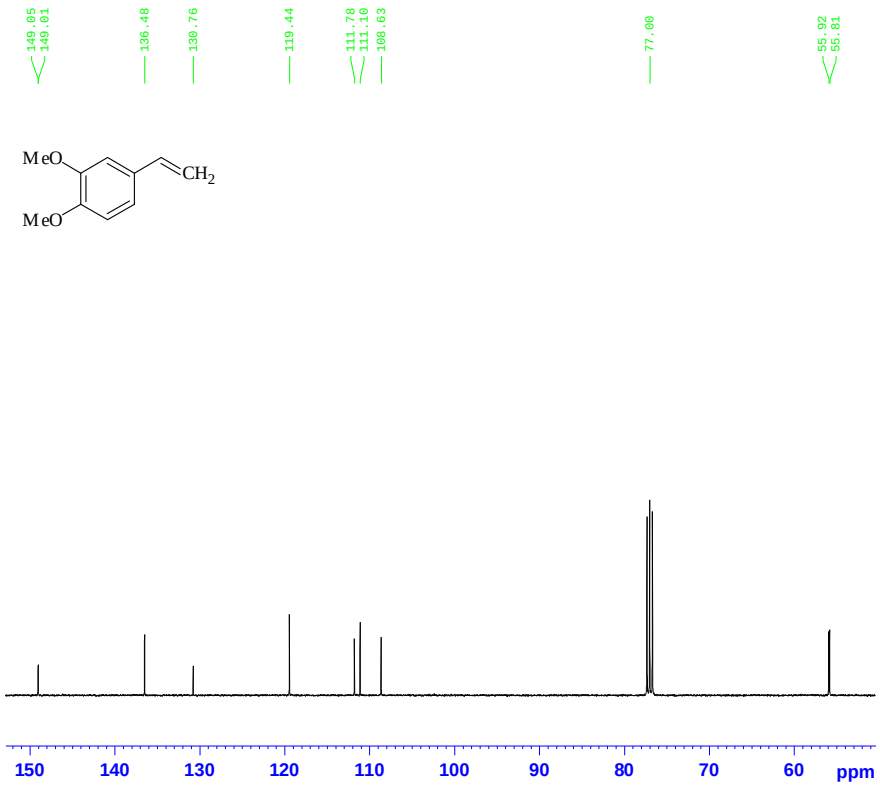

Plate 11: ^{1}H NMR spectrum of 2-(3,4-dimethoxyphenyl)ethanol (**96**) in $CDCl_3$

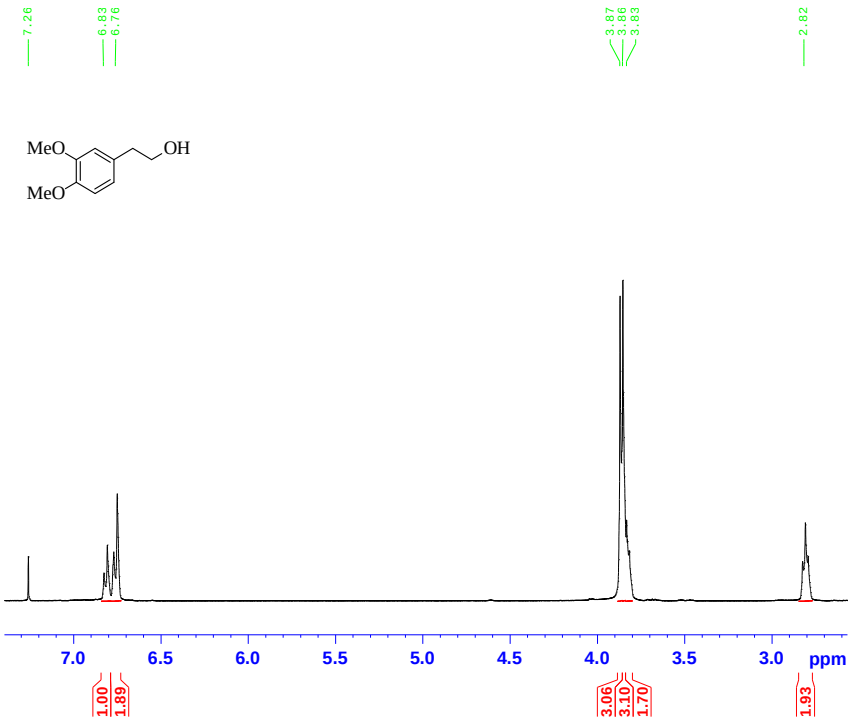

Plate 12: ^{13}C NMR spectrum of 2-(3,4-dimethoxyphenyl)ethanol (**96**) in $CDCl_3$

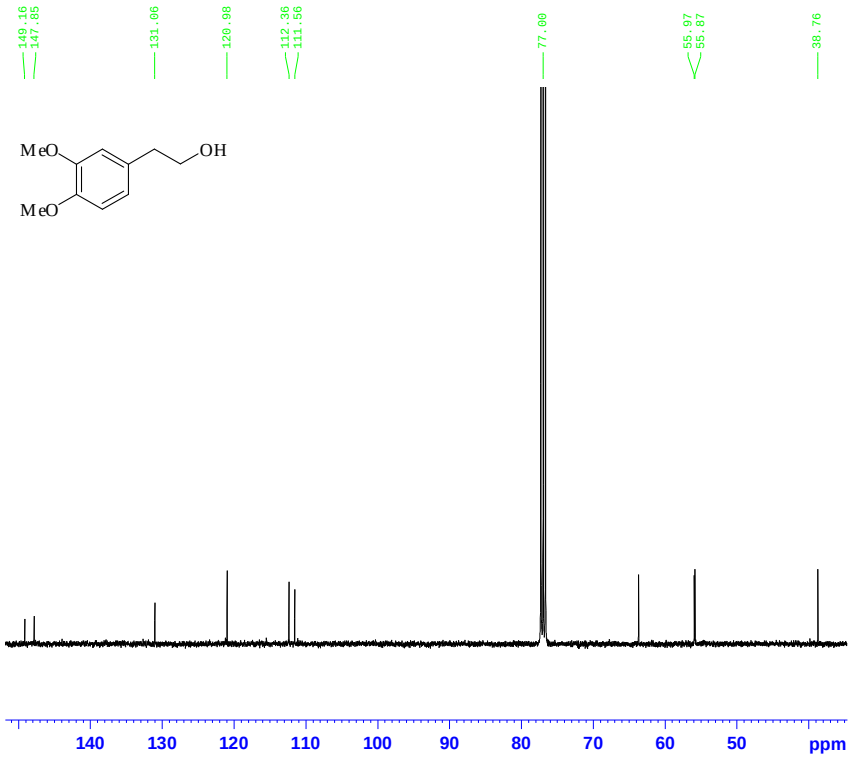

Plate 13: ^{1}H NMR spectrum of IBX (**105**) in DMSO-d_6

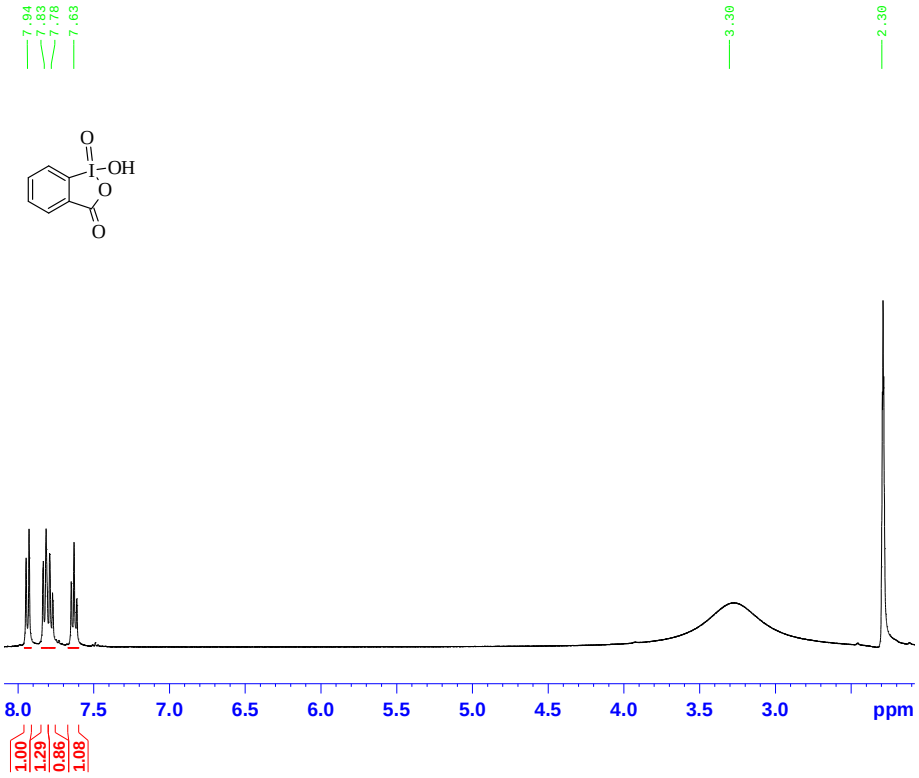

Plate 14: ^{13}C NMR spectrum of IBX (**105**) in DMSO-d_6

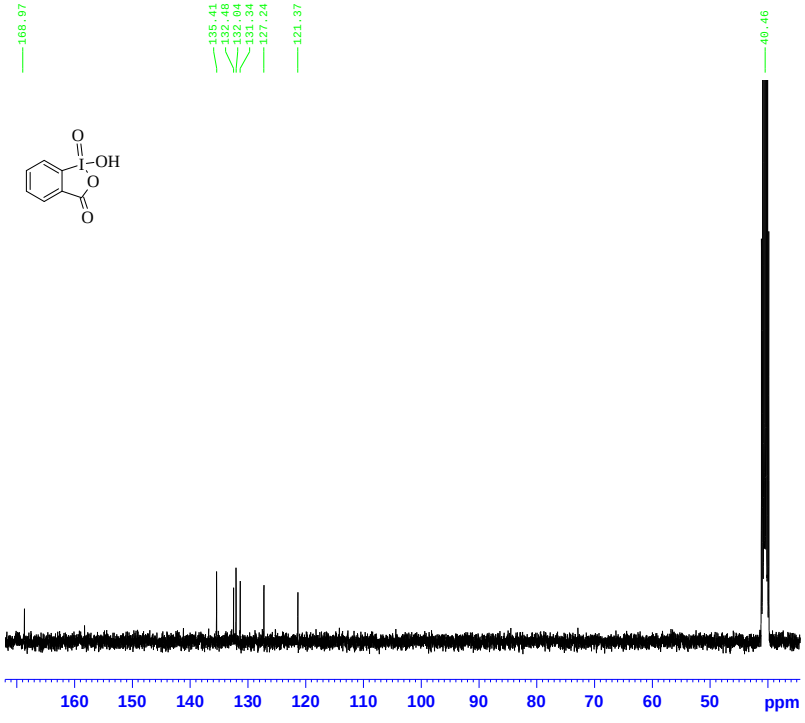

Plate 15: ^{1}H NMR spectrum of (1*S*)-1-phenyl-N-(2-phenylethyl)ethanamine (**109**) in $CDCl_3$

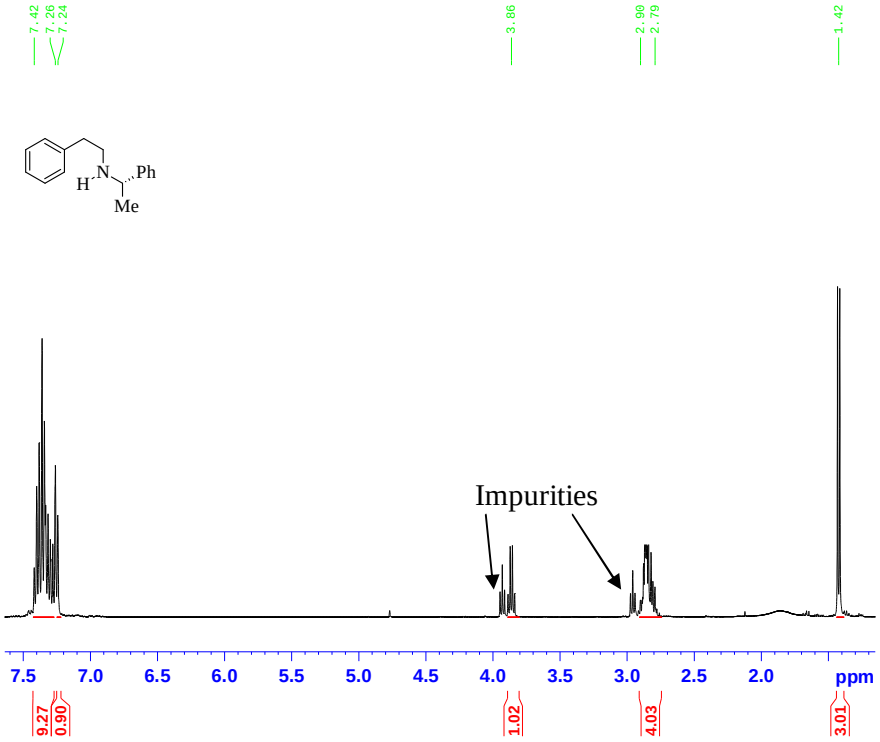

Plate 16: ^{13}C NMR spectrum of (1*S*)-1-phenyl-N-(2-phenylethyl)ethanamine (**109**) in $CDCl_3$

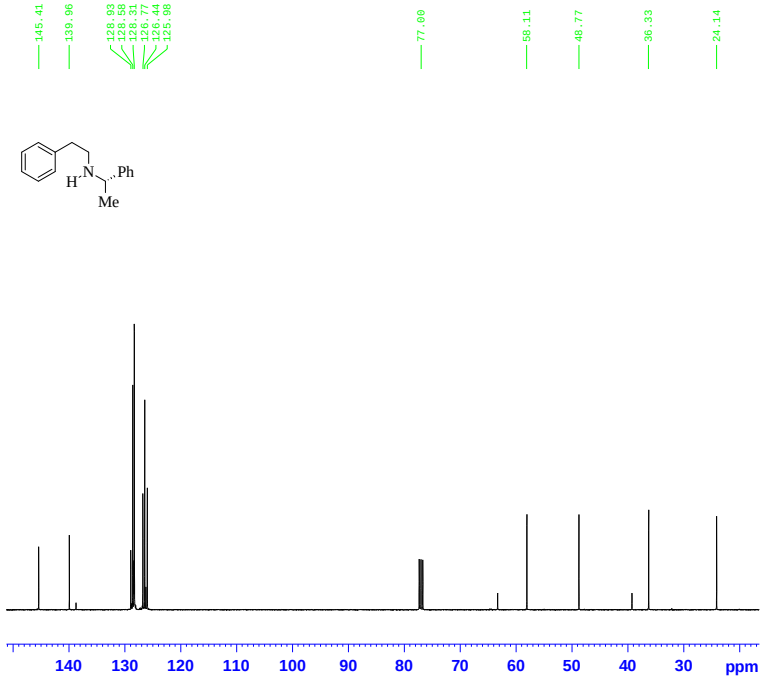

Plate 17: ^{1}H NMR spectrum of the condensation product **116** in $CDCl_3$

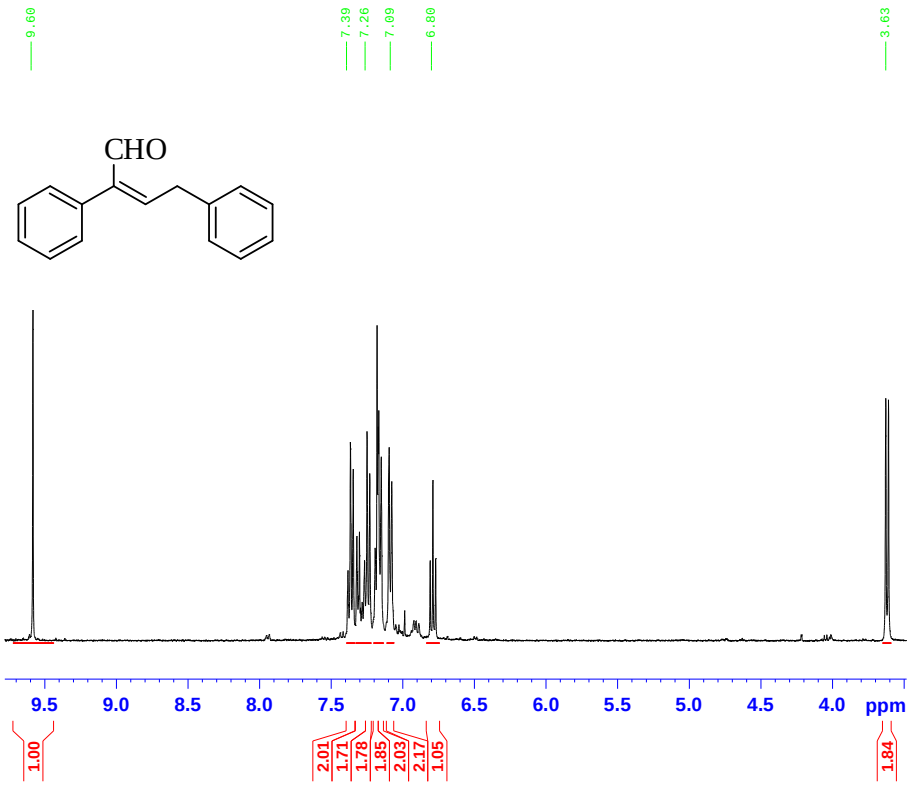

Plate 18: ^{1}H NMR spectrum of 2-(3,4-dimethoxyphenyl)ethyl 4-methylbenzenesulfonate (**117**) in $CDCl_3$

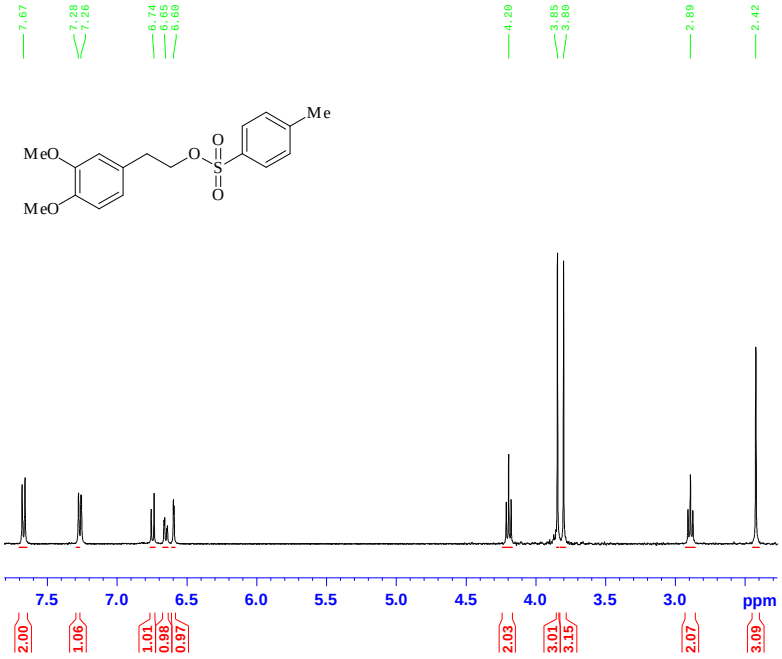

Plate 19: ^{13}C NMR spectrum of 2-(3,4-dimethoxyphenyl)ethyl 4-methylbenzenesulfonate (**117**) in $CDCl_3$

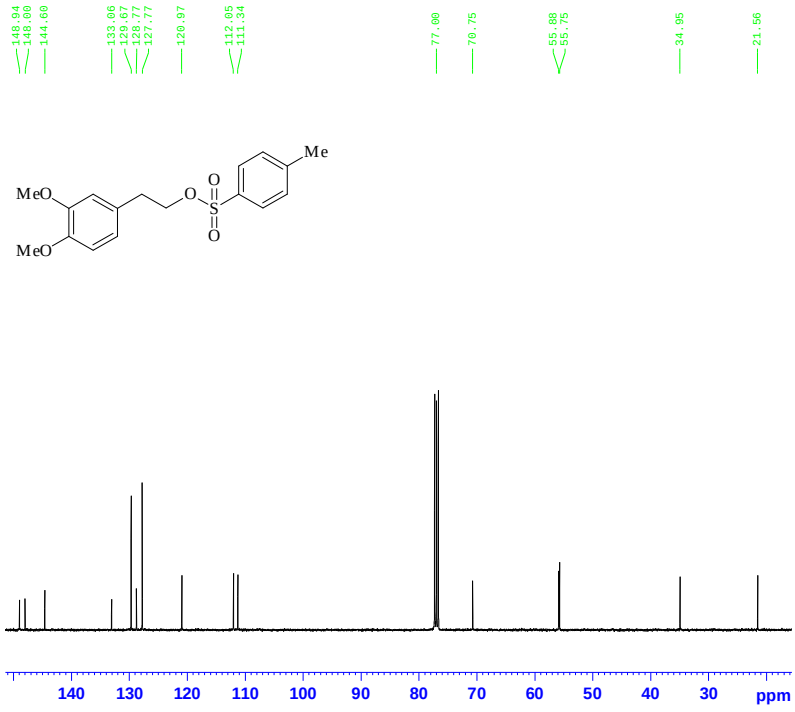

Plate 20: ^{1}H NMR spectrum of (*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydronaphthalen-1-amine (**119**) in $CDCl_3$

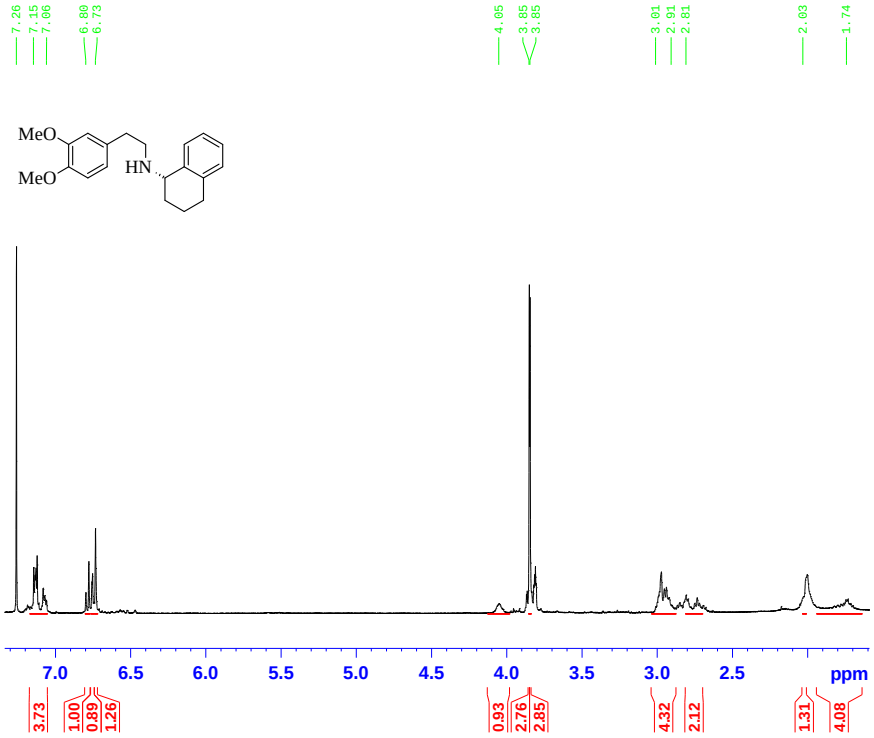

Plate 21: ^{13}C NMR spectrum of (*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydronaphthalen-1-amine (**119**) in $CDCl_3$

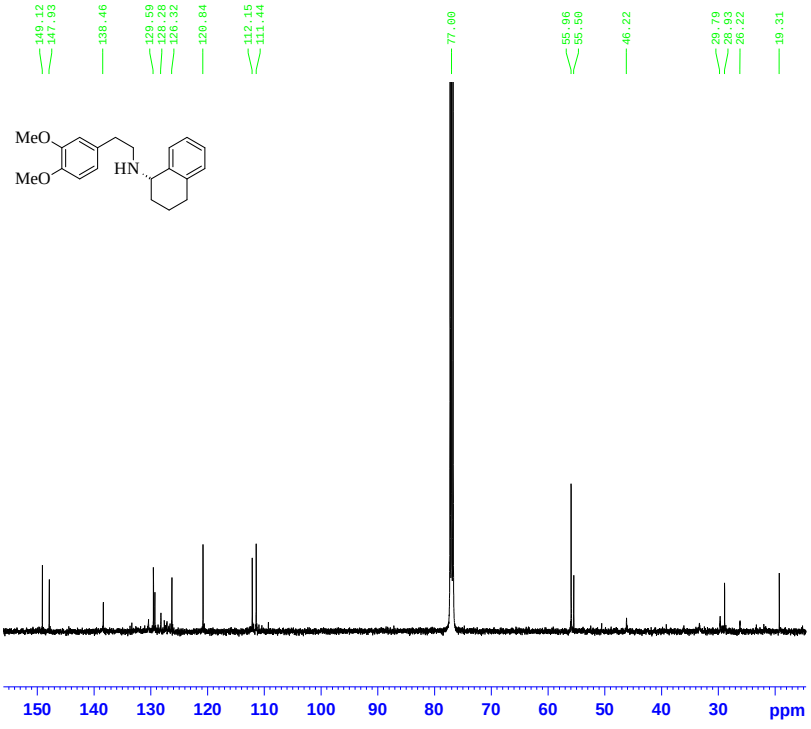

Plate 22: ^{1}H NMR spectrum of 6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**121**) in $CDCl_3$

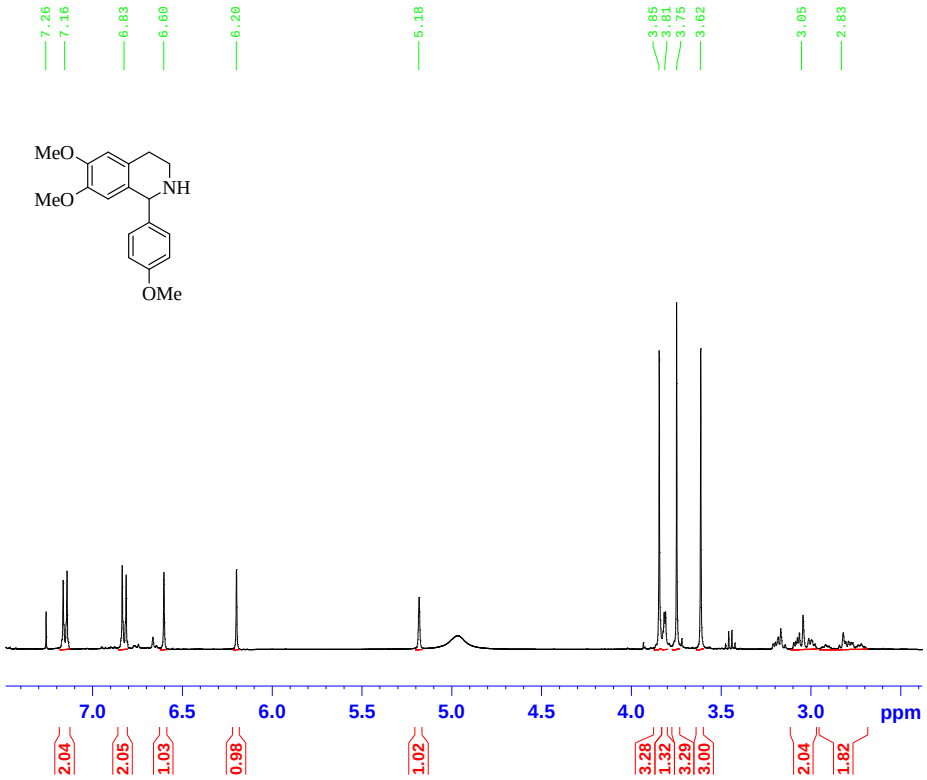

Plate 23: ^{13}C NMR spectrum of 6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**121**) in $CDCl_3$

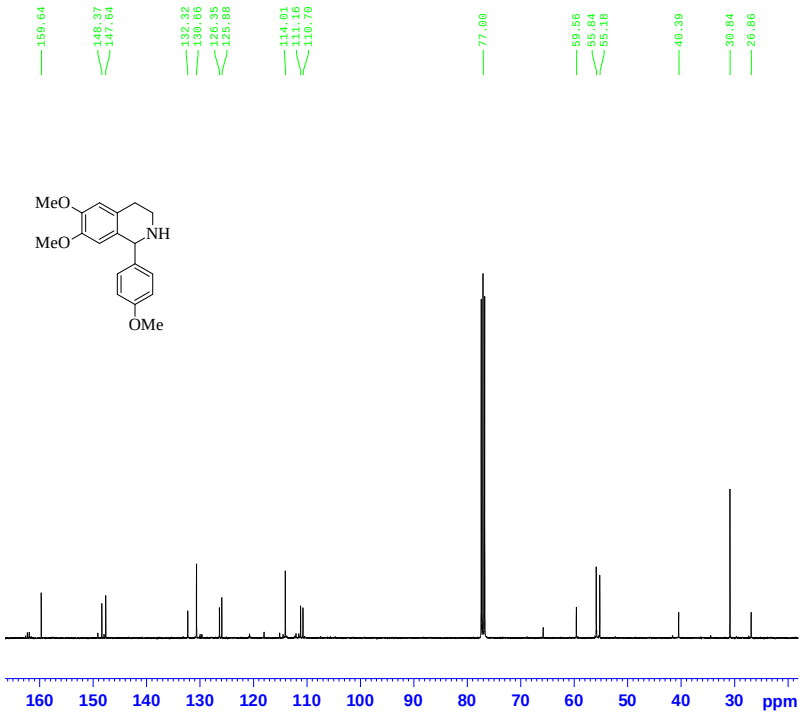

Plate 24: ^{1}H NMR spectrum of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylacetamide (**123**) in $CDCl_3$

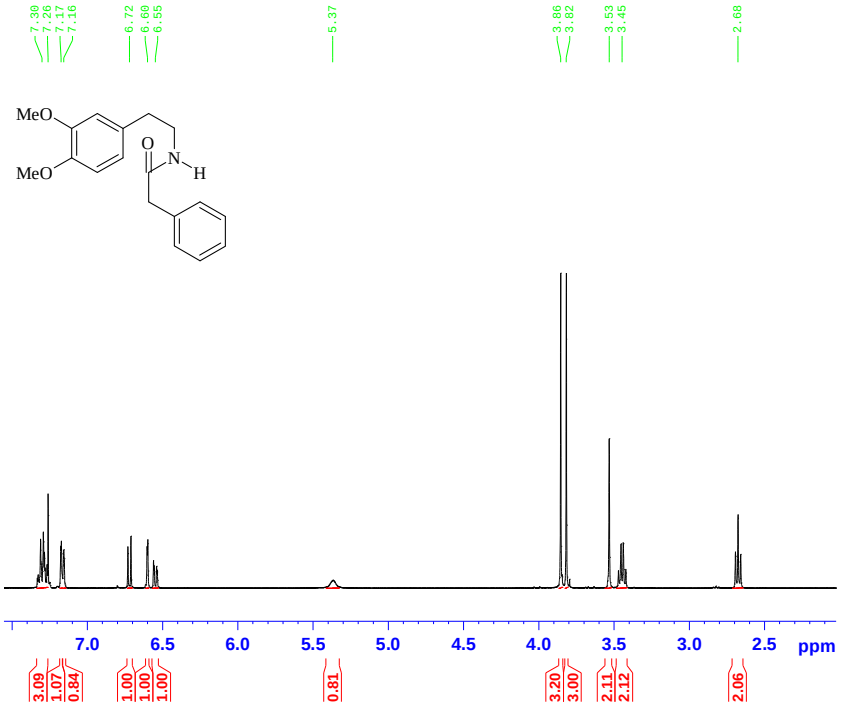

Plate 25: ^{13}C NMR spectrum of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylacetamide (**123**) in $CDCl_3$

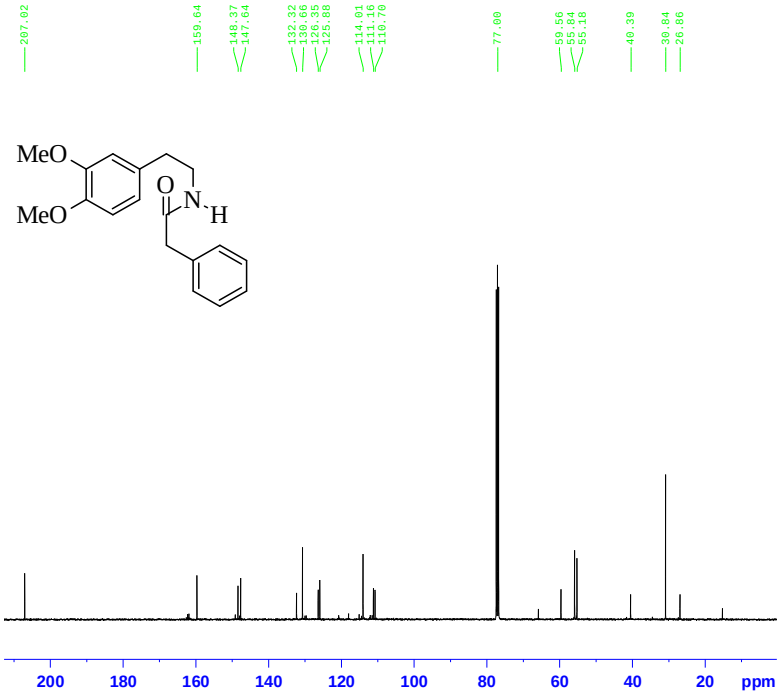

Plate 26: ^{1}H NMR spectrum of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**124**) in $CDCl_3$

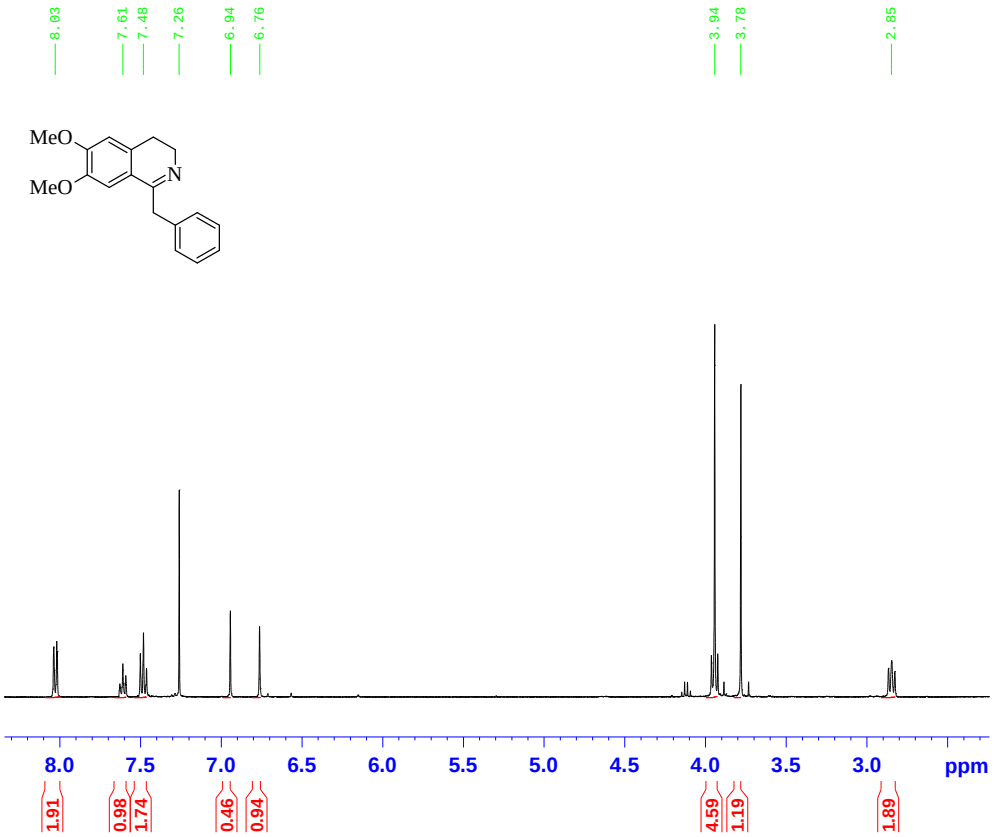

Plate 27: ^{1}H NMR spectrum of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**125**) in $CDCl_3$

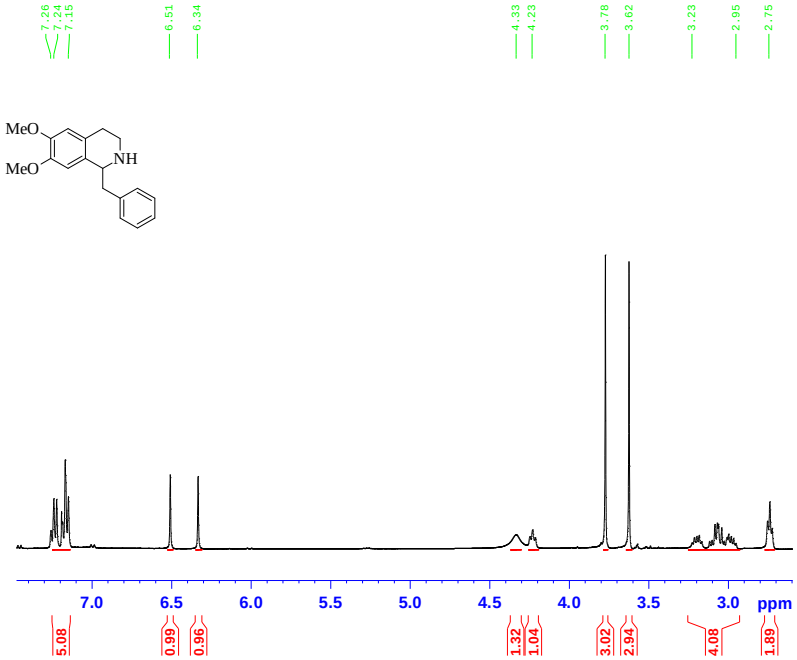

Plate 28: ^{13}C NMR spectrum of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**125**) in $CDCl_3$

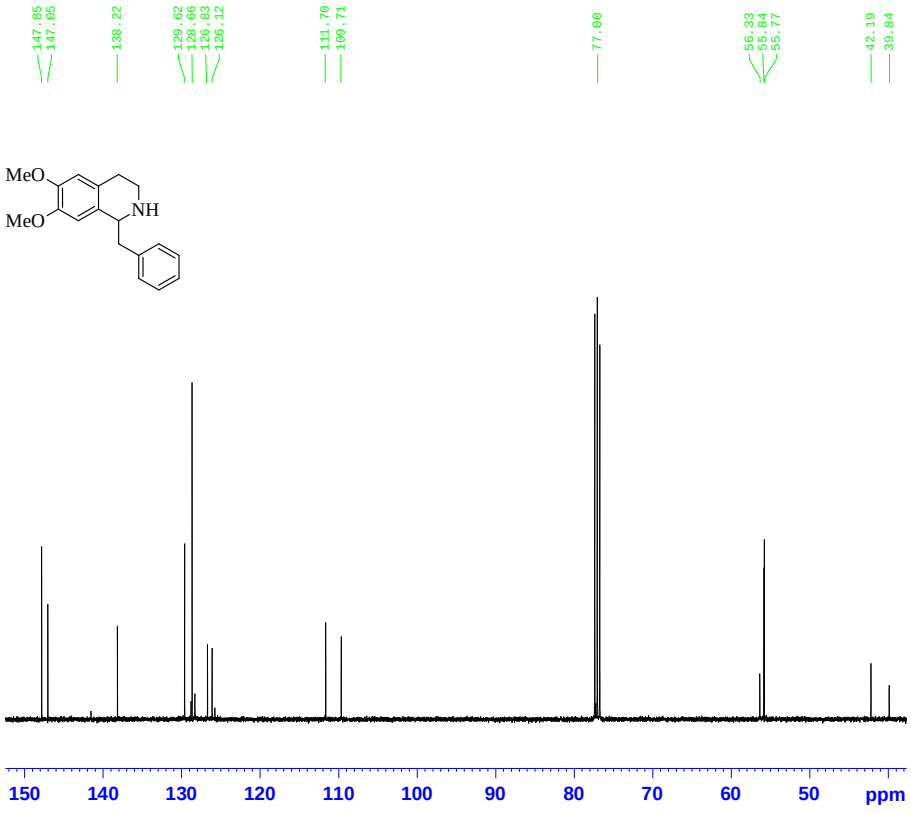

Plate 29: ^{1}H NMR spectrum of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(4-methoxyphenyl)acetamide (**127**) in $CDCl_3$

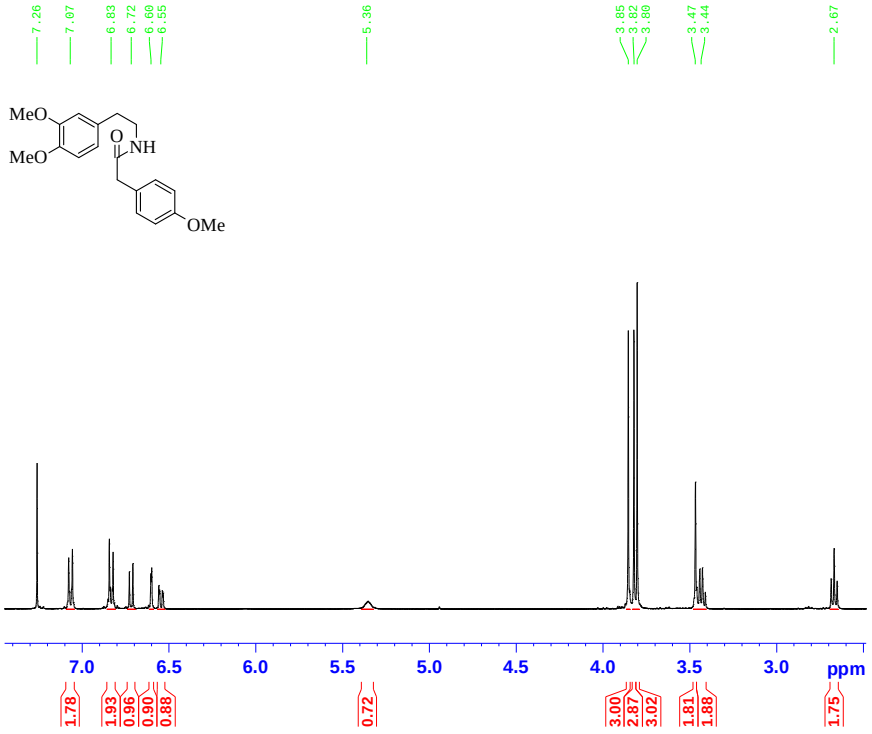

Plate 30: ^{13}C NMR spectrum of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-(4-methoxyphenyl)acetamide (**127**) in $CDCl_3$

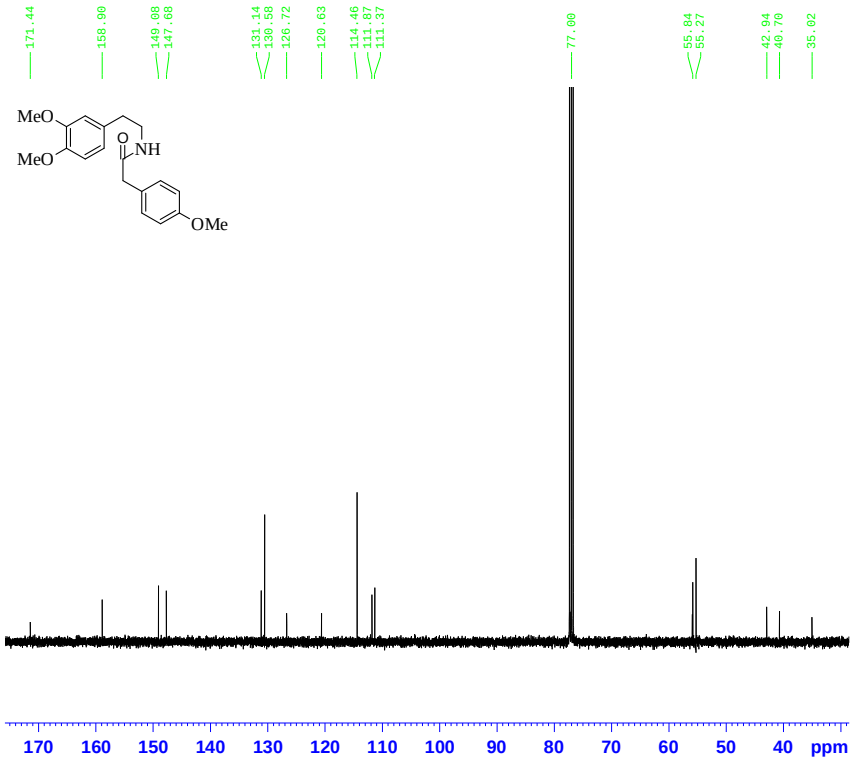

Plate 31: ^{1}H NMR spectrum of 6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**129**) in $CDCl_3$

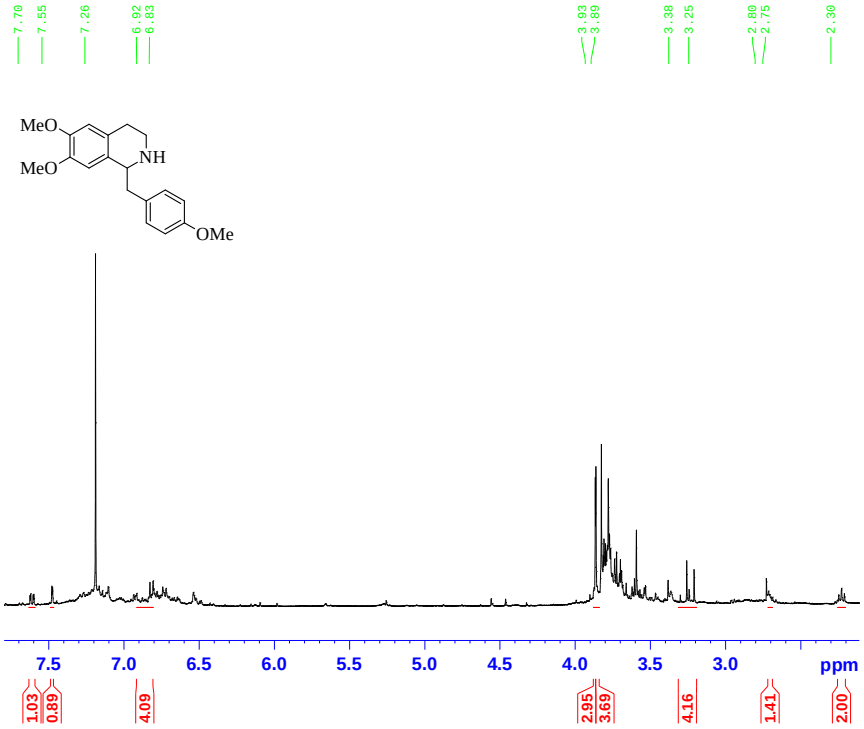

Plate 32: ^{13}C NMR spectrum of 6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**129**) in $CDCl_3$

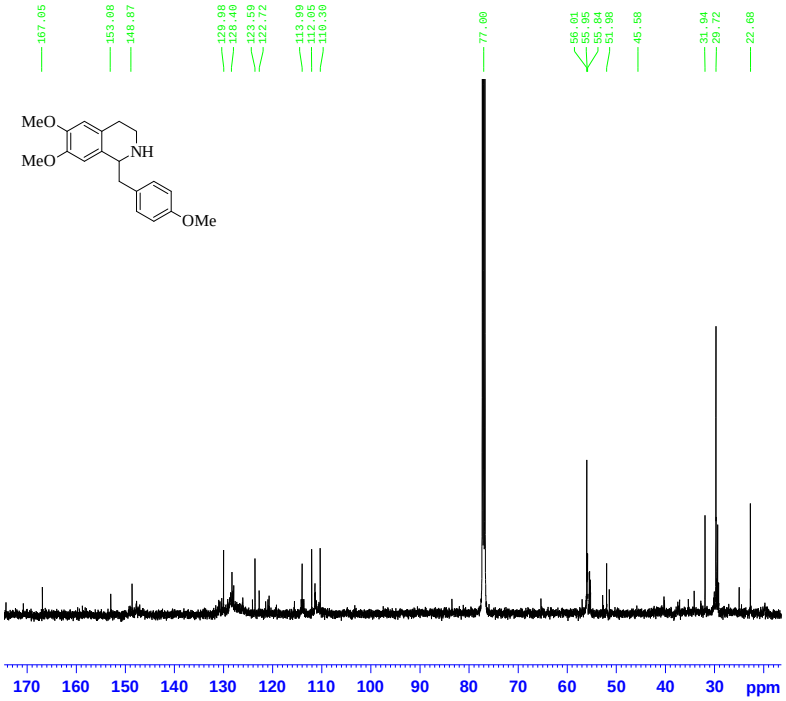

Plate 33: ^{1}H NMR spectrum of *N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (**131**) in $CDCl_3$

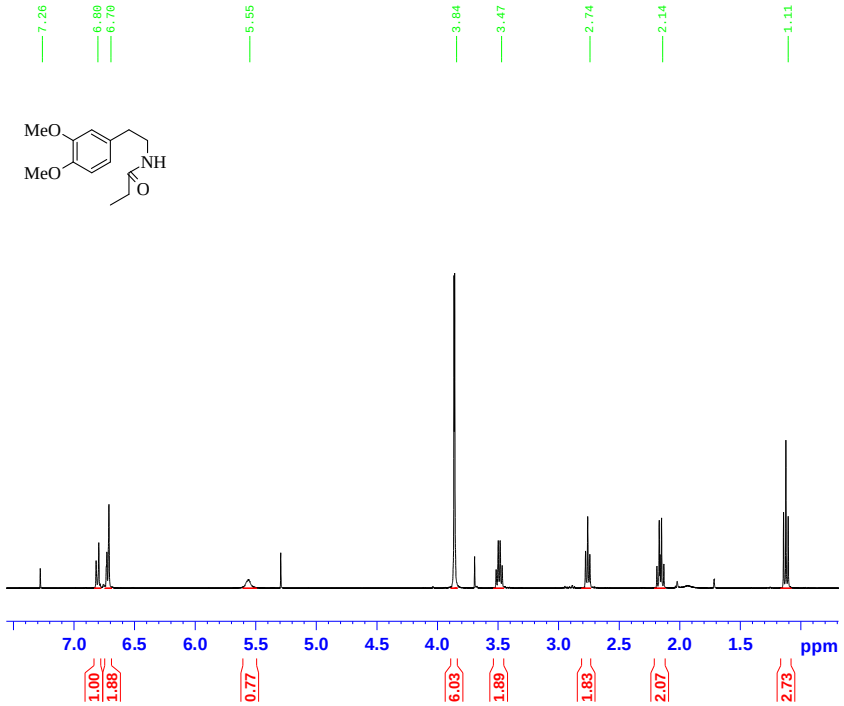

Plate 34: ^{13}C NMR spectrum of *N*-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (**131**) in $CDCl_3$

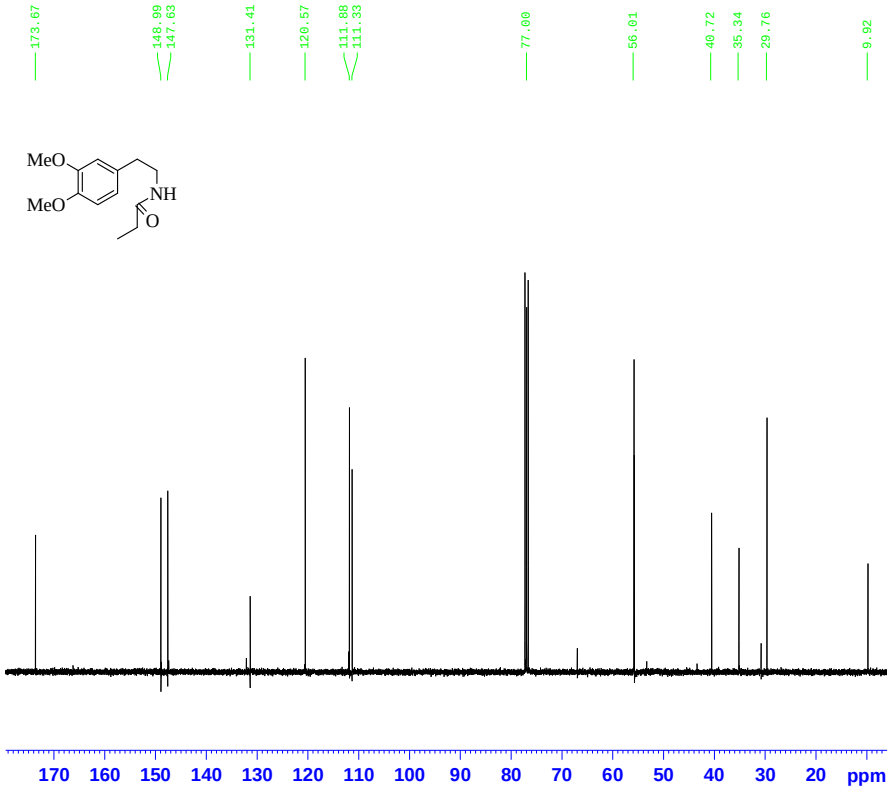

Plate 35: ^{1}H NMR spectrum of 1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**133**) in $CDCl_3$

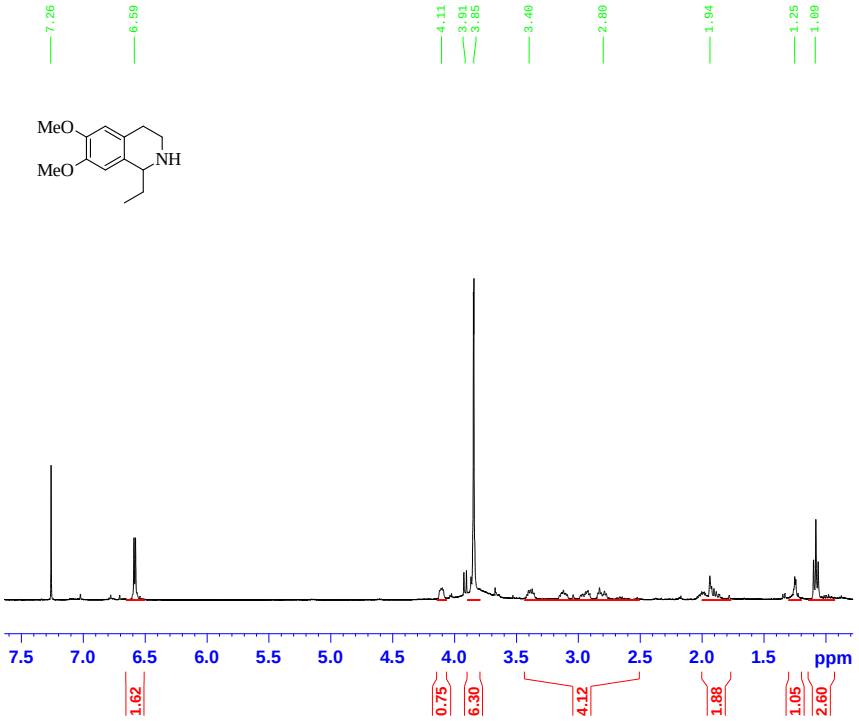

Plate 36: ^{13}C NMR spectrum of 1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**133**) in $CDCl_3$

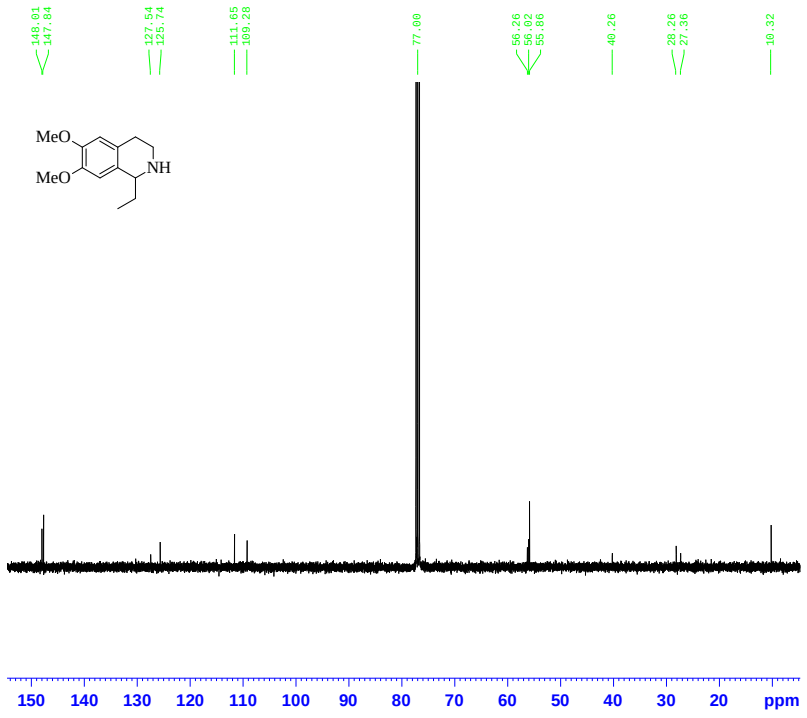

Plate 37: ^{1}H NMR spectrum of 1*R*)-1-benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-**136**) in $CDCl_3$

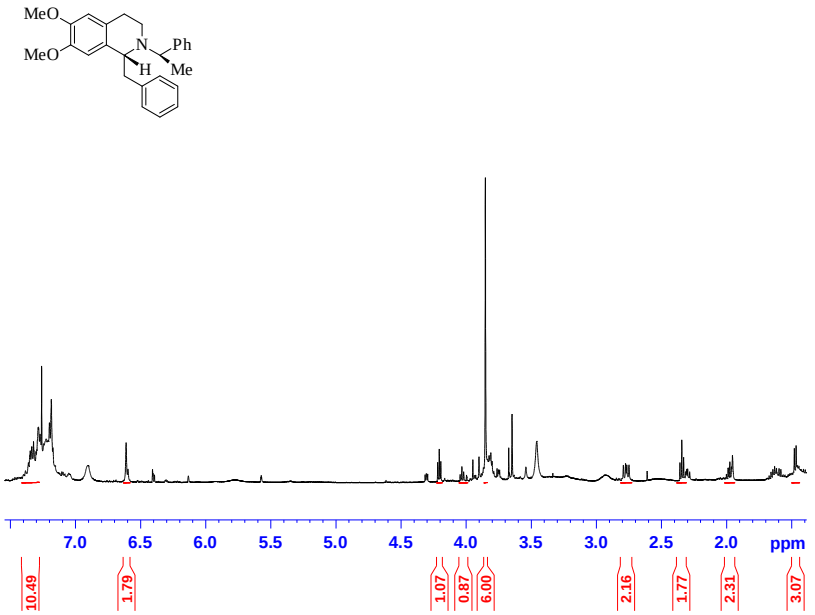

Plate 38: ^{13}C NMR spectrum of 1*R*)-1-benzyl-6,7-dimethoxy-*N*-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-**136**) in $CDCl_3$

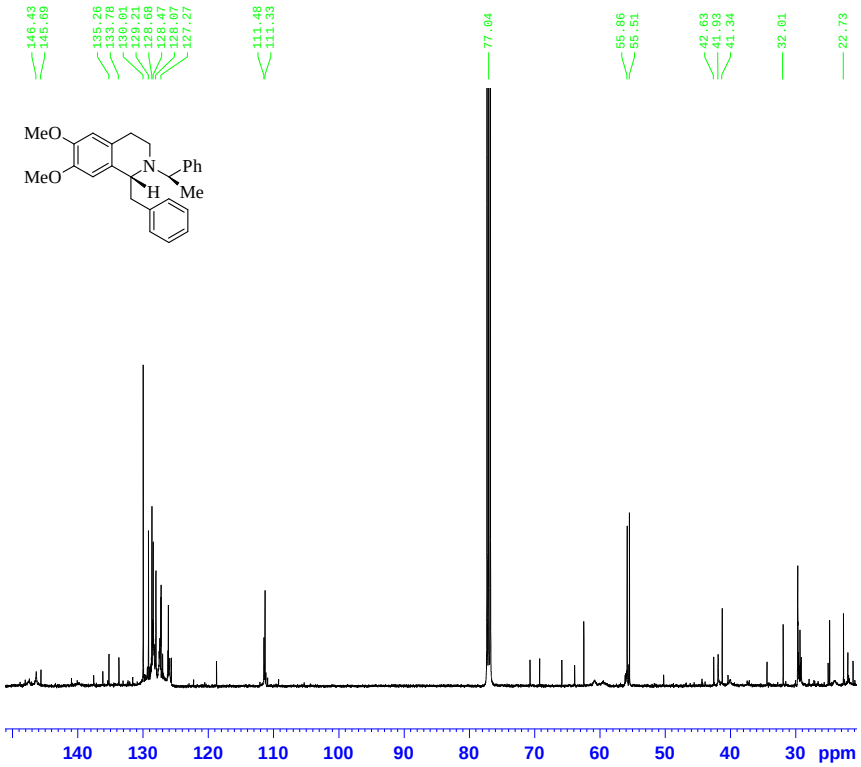

Plate 39: ^{31}P NMR spectrum of methyltriphenylphosphonium iodide (**140**) in DMSO-d_6