SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

BY

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BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **“Synthesis of Biologically Active Compounds”** submitted by Mr. Dushant A. Khobragade was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.

Date:

Subhash P. Chavan

Research Supervisor

DECLARATION

I hereby declare that the thesis entitled **“Synthesis of Biologically Active Compounds”** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr. Subhash P. Chavan. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

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Dedicated

To

My (late) Uncle and Grandmother

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NCL, Pune *Dushant Khobragade*

Contents

Chapter II: Synthetic Studies Towards Other Biologically Active Molecules

General Remarks

1. All the melting points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each section refer to that section only.
3. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ºC.
4. Organic layers were dried over anhydrous sodium sulfate.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualised by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as *m/z*. HRMS were recoreded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

Abbreviations

Ac	Acetyl
ADD	(Azodicarbonyl)dipiperidine
AIBN	2,2-Azobis(isobutyronitrile)
^{t}Am	*tertiary* amyl
Ar	Aryl
Aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane-dimthyl sulfide
Bn	Benzyl
BnBr	Benzyl bromide
Boc	*tertiary* butoxy carbonyl
Bu	Butyl
*s*Bu	*secondary* butyl
*t*Bu	*tertiary*-butyl
CAL	Candida antarctica lipase
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
*m*CPBA	*meta*-chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	Diisopropylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIPT	Diisopropyltartrate

DMAP	4-Dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethy sulfide
DMSO	Dimethyl sulfoxide
dppf	(Bis-diphenylphosphino)ferrocenyl
Et	Ethyl
g	gram(s)
GABA	Gamma-aminobutyric acid
h	hour(s)
IPA	Isopropyl alcohol
IR	Infra red
HMPA	hexamethylphosphoramide
Hz	Hertz
KHMDS	Potassium hexamethyl disilazide
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
LICA	Lithium isopropyl cyclohexylamide
MAD	Methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)
Me	Methyl
min	minute(s)
ml	mililitres
Mp	Melting point
Ms	methanesulfonyl
MVK	Methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methyl morpholine oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorocromate
PDC	Pyridinium dichromate
PEG	Polyethylene glycol

PHMS	Poly(hydromethylysiloxane)
PLE	Pig liver esterase
PMP	*para*-methoxyphenyl
PPA	Polyphosphoric acid
PTAB	Phenyl trimethylammonium tribromide
PTC	Phase transfer catalysis
PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-toluene sulfonic acid
r t	room temperature
TBAB	Tetrabutyl ammonium bromide
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulfate
TBAI	Tetrabutyl ammonium iodide
TBSOTf	*tert*-butyldimethylsilyl triflate
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
Ts	Toluenesulfonyl
Triton-B	Benzyltrimethylammonium hydroxide

Abstract

The thesis entitled "**Synthesis of Biologically Active Compounds**" is divided into two parts-

Chapter-I: deals with total synthesis of antidepressants and is further divided into two sections.

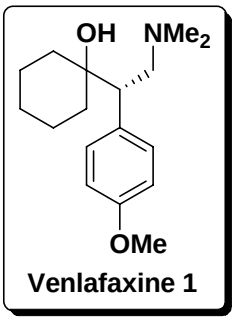
Chapter-II: is further divided into two sections and deals with synthesis of (±)-mesembrine and zafirlukast.

Chapter-I: Total synthesis of antidepressants

Chapter I is divided into two sections and describes total synthesis of (±)-venlafaxine and formal synthesis of (±)-paroxetine.

Section 1: Total Synthesis of (±)-Venlafaxine

This section presents a brief literature review and an account of synthetic endeavor towards (±)-venlafaxine.



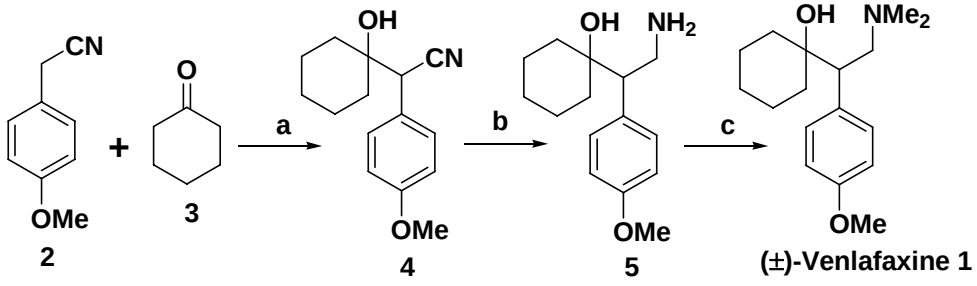
Venlafaxine 1

Venlafaxine **1** is a new generation antidepression drug developed by Wyeth-Ayerst Company at the end of 1993. Its commercial name is Effexor and is also called as Wy-45030.

Literature survey on the synthesis of this important antidepressant revealed that an economically and technically viable process for manufacture of venlafaxine was not available. Earlier patented methods for condensation of *p*-methoxyphenylacetonitrile **2** with cyclohexanone **3** to obtain cyanoalcohol **4** employed hazardous bases, organic solvents under anhydrous and cryogenic conditions to furnish the desired product with

meagre 30% yields. Obviously, this is not a suitable process on industrial scale. Moreover, use of organic solvents makes it undesirable from environment point of view.

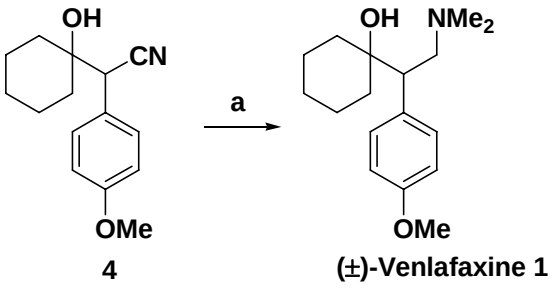
In order to search for an efficient process for condensation a variety of bases were screened. Surprisingly, the simplest and inexpensive bases like NaOH and KOH were found to be far superior to all the other bases examined. The best conditions were found to be 10% aqueous NaOH/KOH under phase transfer conditions.



Scheme 1. *Reagents and conditions:* a) 10% aq. NaOH, cat. $TBAHSO_4$, 0 ^oC, 1 h, (quantitatve yields); b) $LiAlH_4$, $AlCl_3$, THF, 0 ^oC, (99%); c) 35% formalin, HCO_2H, H_2O, Δ, (85%).

Cyanoalcohol **4** was then reduced with $LiAlH_4/AlCl_3$ to give amine **5** in near quantitative yields! Amine **5** was used as such for further reaction. Tilford's modified procedure for *N,N*-dimethylation furnished target molecule **1** in 85% yield (scheme 3).

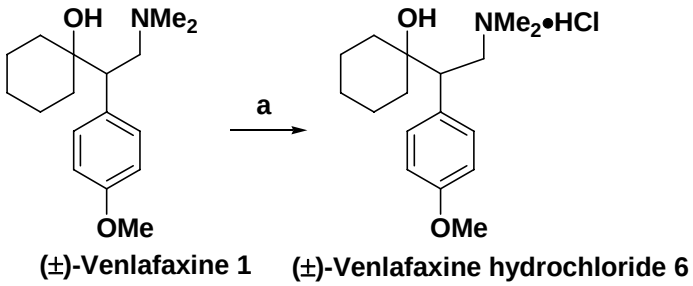
One-pot Synthesis of (±)-Venlafaxine



Scheme 2. *Reagents and conditions:* a) H_2 (280 psi), Raney Ni, 35% formalin, MeOH, 100 ºC, 6 h, 30%.

When cyanoalcohol **4** was subjected to catalytic hydrogenation using Raney nickel, (±)-venlafaxine **1** was obtained in 30% yield and 60% starting material was recovered (scheme 2).

Hydrochloride salt **6** of venlafaxine free base **1** was prepared using isopropyl alcohol saturated with HCl gas and recrystallized from ethyl acetate (scheme 3).

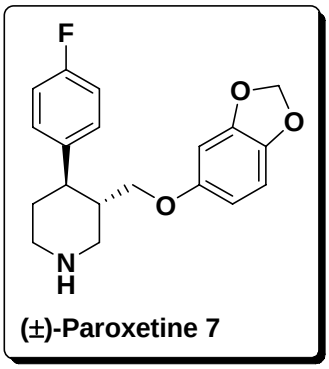


Scheme 3. *Reagents and conditions:* a) HCl/*i*PrOH, EtOAc.

In conclusion, a novel protocol was developed for condensation of arylacetonitriles with cyclic ketones in aqueous medium and was utilized for the synthesis of a commercially important antidepressant drug *viz.* venlafaxine. The process is simple to operate, obviating use of expensive catalysts and hazardous reagents, replacing organic solvents with water as the reaction medium and eliminates the cumbersome purification techniques such as column chromatography, making it eco-friendly.

Section-2: Formal Total Synthesis of (±)-Paroxetine

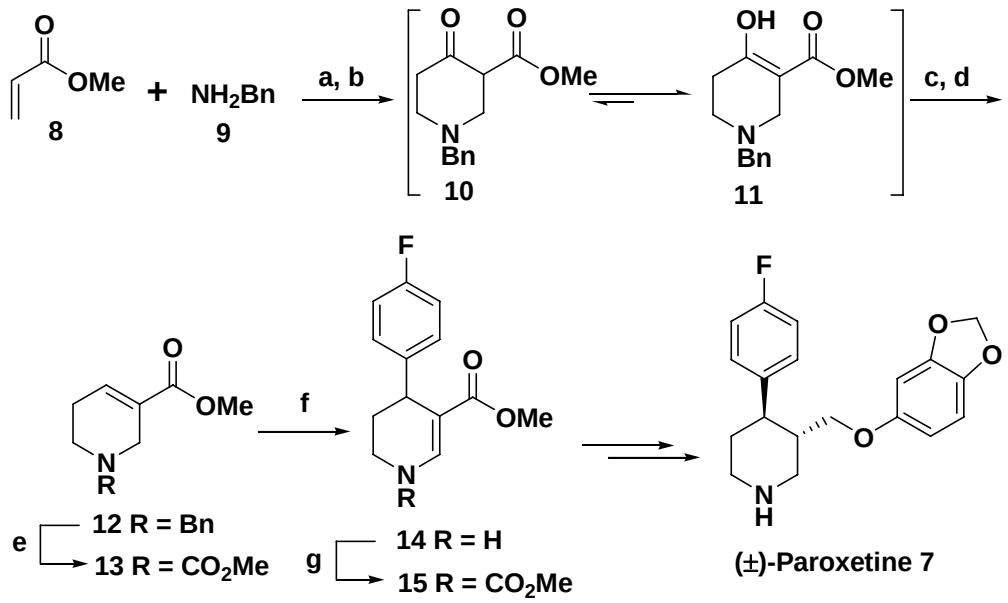
This section details a literature review and a formal total synthesis of (±)-paroxetine.



Paroxetine **7**, also called as Paxil, is an orally administered psychotropic drug. It is a selective serotonin reuptake inhibitor (SSRI) antidepressant, released in 1992 by the pharmaceutical company Glaxo Smith Kline and has since become one of the most prescribed antidepressants in the market due to its efficacy in treating depression as well as a spectrum of anxiety disorders ranging from panic attacks to phobias.

There are several methods by which this vital drug is synthesized, but surprisingly there was not a single route where Heck-coupling was employed during the course of this work. Recently a synthesis appeared describing use of tetrafluoroborate salt as the electrophile. Although the present strategy is similar to that reported in literature, this synthesis utilises commercially available *p*-fluorobromobenzene for the Heck reaction.

Accordingly, methyl acrylate **8** was refluxed with $BnNH_2$ **9** in the presence of Et_3N to give correspondong double Michael adduct, which upon Dieckmann condensation using NaH in refluxing benzene furnished *β*-ketoester, which exists as a mixture of **10** and **11**. Borohydride reduction of the ketoester followed by mesylation of the resultant alcohol and subsequent elimination provided *α,β*-unsaturated ester **12**. Benzyl protection was then exchanged with methyl carbamate to furnish compound **13** and was subjected to Heck coupling under solvent-free conditions. Delightingly, carbamate **13** furnished the corresponding free amine **14**, albiet in moderate yields (scheme 4). Conversion of **14** to paroxetine **7** is reported in the literature. Also, carbamate of **15** was prepared from **14** whose conversion to paroxetine **7** is known.



Scheme 4. *Reagents and conditions:* a) Et_3N, reflux, overnight 90%; b) NaH, PhH, reflux; 82%; c) $NaBH_4$, MeOH, 2 h; d) MsCl, Et_3N, DCM, 0 ^oC to r t, overnight, 75% (for two steps); e) $ClCO_2Me$, $NaHCO_3$, DCM, 80%; f) $pBrC_6H_4F$, $(Ph_3P)_4Pd$, K_2CO_3, Bu_4NBr, 120 ^oC, 2 d, 30%; (g) $ClCO_2Me$, K_2CO_3, DCM, r t, overnight, 85%.

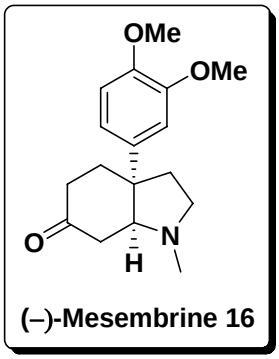
Thus, a formal total synthesis of (±)-paroxetine was accomplished using Heck coupling as the key step.

Chapter-II: Synthetic Studies Towards Other Biologically Active Molecules

Chapter II is divided into two sections and deals with total synthesis of (±)-mesembrine and zafirlukast.

Section-1: Total Synthesis of (±)-Mesembrine

This section presents a brief literature review and a total synthesis of (±)-mesembrine.



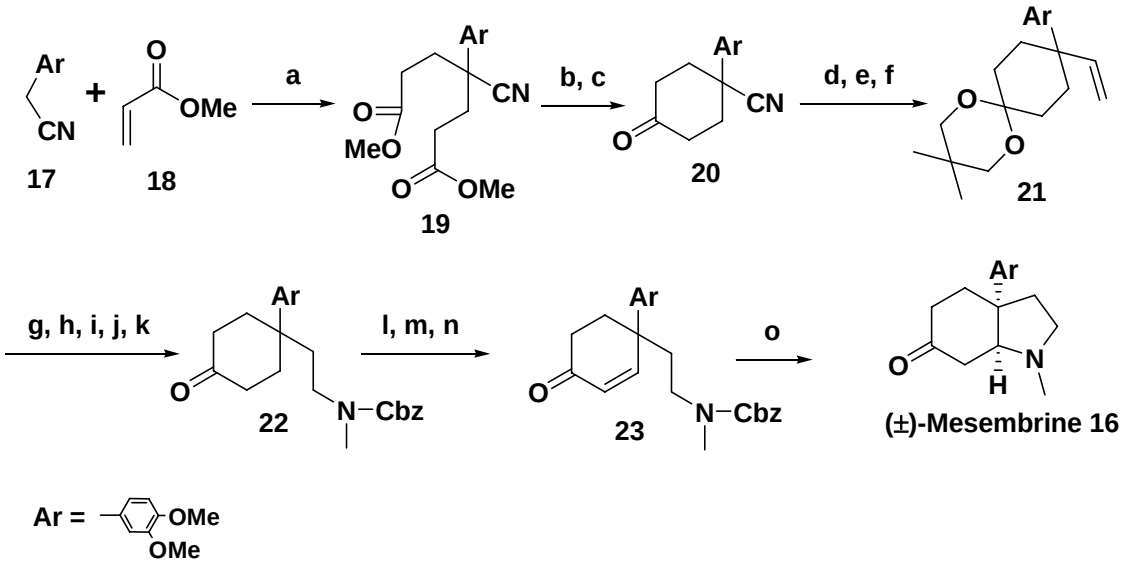
(–)-Mesembrine 16

The Sceletium alkaloid (–)-mesembrine **16** is a naturally occurring serotonin uptake inhibitor. The central challenge in the synthesis of mesembrine and its analogues is the construction of the chiral benzylic quaternary center.

It was decided to explore our recently developed protocol for performing anionic reactions of aryl acetonitriles under aqueous conditions to effect Michael addition for construction of the quaternary center. Quaternary benzylic center embedded in mesembrine and related natural products, provides a test target for the application of such newly developed methodologies.

Michael addition of 3,4-dimethoxyphenylacetonitrile **17** to methyl acrylate **18** using 10% aq. NaOH under PTC conditions afforded double Michael adduct **19** in 75% yield. Alternatively, compound **19** was obtained using catalytic Triton-B in refluxing CH_3CN in quantitative yields! Dieckmann condensation of **19** using NaH in DME furnished β-ketoester, which was demethoxycarbonylated using Krapcho's method to obtain ketone **20**. Ketone **20** was protected as dioxolane with 2,2-dimethyl-1,3-propanediol in refluxing benzene using PPTS as a catalyst.

Nitrile was then reduced with DIBAL in DCM at 0 ^{o}C to obtain aldehyde, which was converted to olefin **21** with methylenetriphenylphosphorane employing Wittig reaction. Olefin **21** was then subjected to hydroboration with BMS complex, followed by alkaline work-up to give alcohol, which was mesylated and the resultant mesylate was further treated with 30% aq. $MeNH_2$ solution in a sealed tube at 100 ^{o}C to yield amine, which was protected as benzyl carbamate. Dioxolane was then hydrolysed by refluxing in an acetone-water mixture (1:1) with a drop of conc. H_2SO_4 to obtain ketone **22**. Silyl enol ether of the resultant ketone **22** was prepared, which was subsequently brominated with NBS to give α-bromoketone, which upon dehydrobromination with LiBr and Li_2CO_3 in hot DMF provided enone **23**. The carbamate was unmasked with $BF_3{\cdot}OEt_2$ in the presence of excess of Me_2S to give the target molecule **16** (scheme 5).



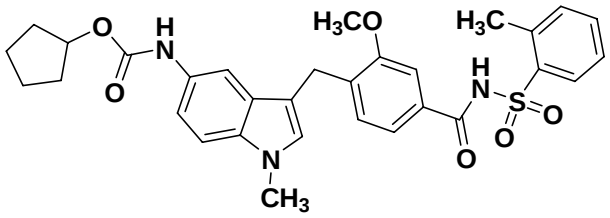
Scheme 5. *Reagents and conditions:* (a) 10% aq. NaOH, $TBAHSO_4$, 0 ^{o}C, 30 min, 76%; (b) NaH, DME, reflux, 3 h, 89%; (c) NaCl, H_2O, DMSO, 140 ^{o}C, 6 h, 87%; (d) $HOCH_2C(CH_3)_2CH_2OH$, PPTS, PhH, reflux, 3 h, 95%; (e) DIBAL, DCM, 0 ^{o}C, 30 min, 100%; (f) $Ph_3P^{+}CH_2I^{-}$, $NaNH_2$, Et_2O:THF (1:1), 0 ^{o}C, 10 min, 82%; (g) BMS, THF, 0 ^{o}C, then 30% aq. H_2O_2, 30% aq. NaOH, 75%; (h) Et_3N, $MeSO_2Cl$, DCM, 0 ^{o}C, 30 min, 100%; (i) 40% aq. $MeNH_2$, THF-H_2O, in sealed tube, 80 ^{o}C, 2 h; (j) $ClCOOCH_2Ph$, K_2CO_3, 0 ^{o}C to r t, 4 h, 88%; (k)) CH_3COCH_3-H_2O, 1-2 drops H_2SO_4, reflux, 24 h, 85%; (l) Et_3N, TMSCl, CH_3CN, reflux, 2 h, 100%; (m) NBS, THF, 0 ^{o}C, 10 min, 100%; (n) Li_2CO_3, LiBr, DMF, 110 ^{o}C, 2 h, 75%; (o) $BF_3.OEt_2$, Me_2S, DCM, 0 ^{o}C- r t, 1 h, 95%.

Thus, a simple and efficient total synthesis of (±)-mesembrine has been achieved in 20% overall yield. Preparation of Michael adduct 19 served as the key step. This approach

involving prochiral cyclohexanone 20 or 22 may serve as an entry to the synthesis of chiral mesembrine.

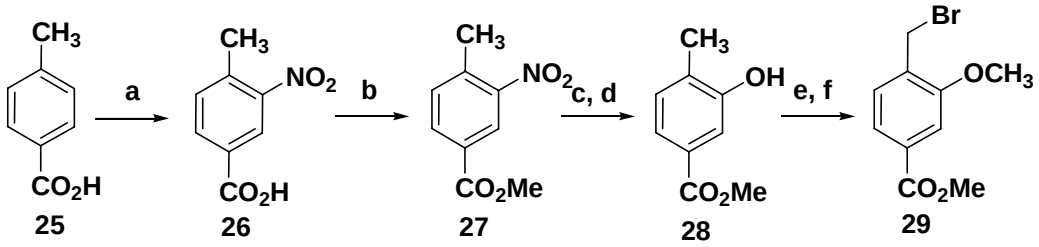
Section-II: Synthetic Studies Towards Zafirlukast

A brief literature review and an account on efforts towards synthesis of zafirlukast is presented.



Zafirlukast 24

Zafirlukast **24**, is a synthetic selective peptide leukotriene receptor antagonist (LTRA), with chemical name 4-(5-cyclopentyloxycarbonylamino-1-methyl-indol-3-ylmethyl-*N*-*o*-tolylsulfonylbenzamide. Zafirlukast is one of a new class of drugs, which acts by blocking the effects of leukotrienes-natural substances, which trigger inflammation, mucous secretion and which cause bronchoconstriction typical of an asthmatic attack. One important factor in the success of the product may be its tablet form, since there are sometimes disadvantages and difficulties associated with the usage of inhalers.

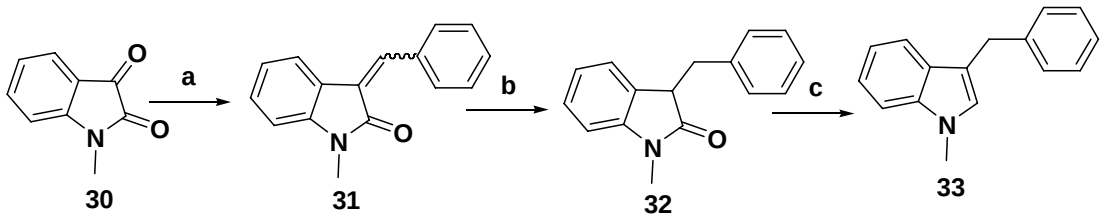


Scheme 6. *Reagents and conditions:* a) fuming HNO_3, conc. H_2SO_4, 0 ^oC, 80%; b) conc. H_2SO_4, MeOH, reflux, 8 h, 85%; c) H_2 (50 psi), Raney Ni, MeOH, r t, 6 h, 96%; d) $NaNO_2$, Urea, 0 ^oC, 44%; e) K_2CO_3, Me_2SO_4, acetone, reflux, 2 h,72%; f) NBS, $(PhCOO)_2$, CCl_4, reflux, 10 h, 96%.

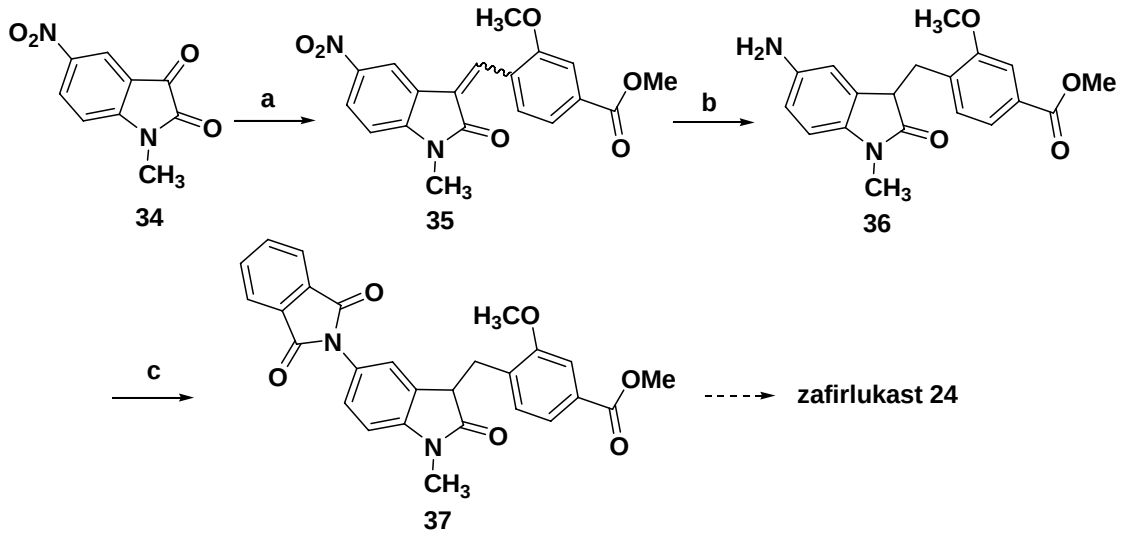
Bromide **29** was prepared as follows. *p*-Toluic acid **25** was nitrated with fuming HNO_3 and conc. H_2SO_4, followed by esterification of the resultant nitro acid with conc. H_2SO_4 in MeOH to give compound **27**. Reduction of the nitro group with Raney nickel

under hydrogen atmosphere, followed by diazotization gave phenol **28** and subsequent methylation of the resultant phenol with MeI, followed by benzylic bromination with NBS, catalysed by benzoyl peroxide gave bromide **29** (scheme 6).

Before directly going for actual synthesis, it was decided to test the efficiency of key step i.e. Wittig reaction as the precious bromide **29** was prepared through a sequence of steps. Accordingly, 1-methylisatin **30** was treated with the ylide generated from the Ph_3P and BnBr to give olefin **31** as a mixture of isomers, which upon catalytic hydrogenation using Raney Ni furnished oxindole **32**. Oxindole **32** was then subjected to reduction with BMS complex to afford indole **33** (scheme 7).



Scheme 7. *Reagents and conditions:* a) $Ph_3P^+CH_2PhBr^-$, NaH, THF, r t, 24 h, 84%; b) H_2, Raney Ni, MeOH, 6 h, 98%; c) BMS, THF, r t, 2 h, 70%.



Scheme 8. *Reagents conditions:* a) $Ph_3P^+CH_2ArBr^-$, NaH, THF, 24 h, 70% b) H_2, Raney Ni, MeOH, 6 h, 94% c) Phthalic anhydride, Et_3N, PhH, reflux, 77%.

With good yield of Wittig reaction on model isatin, it was time to test its efficiency with elaborated bromide **29** and 1-methyl-5-nitroisatin **34**. Thus, to a suspension of **34** in THF was added the ylide generated from Wittig salt of Ph_3P with bromide **29**, to furnish

the expected olefin **35** in 50% yield. Low yields may be attributed to very low solubility of 1-methyl-5-nitroisatin **34** in THF. With proper choice of solvent system yield may be improved. Olefin **35** was then subjected to catalytic hydrogenation using Raney Ni to give oxindole **36** with concomitant reduction of the nitro group. Amine **36** was protected as phthalimide with phthalic anhydride and Et_3N in refluxing benzene to furnish **37** (scheme 8).

Thus, an advanced intermediate **37**, adorned with all requisite fuctionalities for further elaboration, has been synthesized employing Wittig reaction. Due to time constraints, the synthetic plan was not investigated further. However, with judicious choice of reagents and tuning of reaction conditions phthalimide **37** could be taken to target molecule.

Chapter-I: Total Synthesis of Antidepresssants

Section-1: Total Synthesis of (±)-Venlafaxine

1.1.1. Introduction

1.1.1.1. Depression

Depression is one of the most common psychological problems, affecting people of all ages, gender, and background.[1] It is a type of mood disorder, a persistent condition affecting a person's lifestyle, activities and relationships. The cost in human suffering cannot be estimated. Major depression is characterized by various physical and psychological symptoms including profound sadness, loss of interest or pleasure in activities normally enjoyed and other symptoms that impair a person's ability to function. Depression can interfere with normal functioning, and frequently causes problems with work, social and family adjustment. It causes pain and suffering not only to those who have a disorder, but also to those who care about them. Serious depression can destroy family life as well as the life of the depressed person.

1.1.1.2. Types of Depression

1. Major depressive disorder (MDD): It is characterized by a severely depressed mood that persists for longer periods (at least two weeks). It may occur as a single episode or may be recurrent throughout lifespan. Clinically the major depression may be further divided into mild, major and severe. MDD is further subdivided as follows-

Depression with Catatonic Features: Catatonia is characterized by motoric immobility evidenced by catalepsy or stupor. This MDD subtype may also manifest excessive, nonprompted motor activity (akathisia), extreme negativism or mutism, and peculiarities in movement, including stereotypical movements, prominent mannerisms, and prominent grimacing. It is very rarely encountered.

Depression with Melancholic Features: Melancholia is characterized by a loss of pleasure (anhedonia) in most or all activities, a failure of reactivity to pleasurable stimuli, a quality of depressed mood more pronounced than that of grief or loss, a worsening of symptoms in the morning hours, early morning waking, psychomotor retardation, anorexia or excessive guilt.

Depression with Atypical Features: It is characterized by mood reactivity and positivity, significant weight gain or increased appetite, excessive sleep or somnolence, leaden paralysis, or significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection.

Depression with Psychotic Features: These people may be presented with hallucinations or delusions that are either mood-congruent (content coincident with depressive themes) or non-mood-congruent (content not coincident with depressive themes). It is clinically more common to encounter a delusional system as an adjunct to depression than to encounter hallucinations, whether visual or auditory.

2. Dysthymia: Is a long-term, mild depression that lasts for a minimum of two years. Those with Dysthymia are vulnerable to co-occurring episodes of Major Depression. This disorder often begins in adolescence and crosses the lifespan. People who are diagnosed with major depressive episodes and dysthymic disorder are diagnosed with double depression. Dysthymic disorder develops first and then one or more major depressive episodes happen later.

3. Bipolar I Disorder: Is an episodic illness in which moods may cycle between mania and depression. It is also called as "Manic Depression".

4. Bipolar II Disorder: Is an episodic illness that is defined primarily by depression but evidences episodes of hypomania.

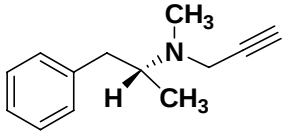
5. Postpartum Depression: Or Post-Natal Depression is clinical depression that occurs within two years of childbirth. Due to physical, mental and emotional exhaustion combined with sleep-deprivation; motherhood can "set women up" so to speak for clinical depression.

1.1.2. Antidepressants

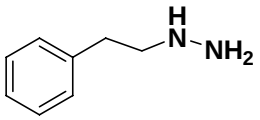
1.1.2.1. Clssification of Antidepressants

According to their chemical structures and mode of action antidepressant drugs are classified[3,4,5] as follows-

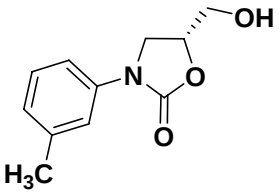
1. Monoamine Oxidase Inhibitors: MAOIs act by inhibiting the activity of monoamine oxidase preventing the breakdown of monoamine neurotransmitters thereby increasing the available stores. There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, adrenaline and noradrenaline. MAO-B preferentially deaminates phenylethylamine and trace amines. Dopamine is equally deaminated by both types. Examples of MAOIs are selegiline **1**, phenelzine **2**, toloxatone **3**, iproniazid **4** etc.



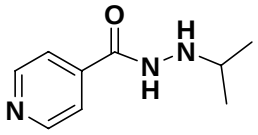
Selegiline 1



Phenelzine 2



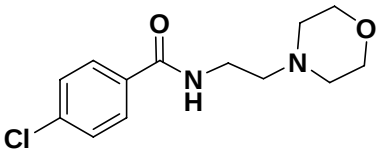
Toloxatone 3



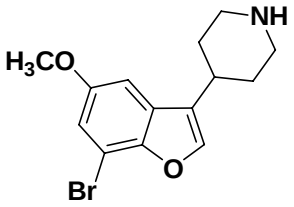
Iproniazid 4

2. Reversible Inhibitors of Monoamine Oxidase A: The early MAOIs inhibited monoamine oxidase irreversibly. When they react with monoamine oxidase, they permanently deactivate it, and the enzyme cannot function until it has been replaced by the body, which can take about two weeks. A few newer MAOIs are reversible, meaning that they can inhibit the enzyme for a time, but eventually detach, allowing the enzyme to function once more. They are referred to as RIMAs. Examples include moclobemide **5**, brofaromine **6** etc.

Total Synthesis of (±)-Venlafaxine

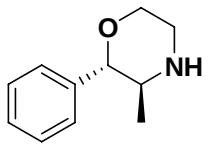


Moclobemide 5

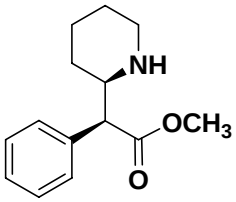


Brofaromine 6

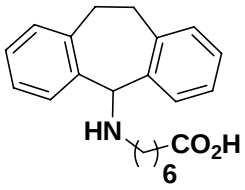
3. Dopamine Reuptake Inhibotor: Inhibit the reuptake of extracellular dopamine back into the presynaptic cell by blocking the cell membrane-standing dopamine transporter. This usually results in an elevated extracellular dopamine level. DARIs bind at the transporter molecule and form a non-covalent complex with it. As far as the DARI-molecule is large enough (which is normally the case), it suppresses the binding of other substances that are transporter substrates – as endogenous compounds (like dopamine) and drugs (e.g. amphetamine). A very special kind of pseudo-DARIs have been developed that bind covalently at the transporter, permanently block the binding of larger drugs like cocaine, but allow small molecules like dopamine to pass through. Drugs falling under this category are phenmetrazine **7**, methylphenidate **8**, amineptine **9**, vanoxerine **10** etc.



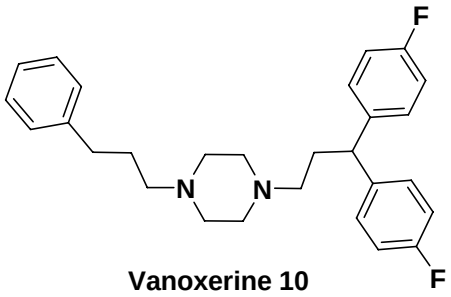
Phenmetrazine 7



Methylphenidate 8



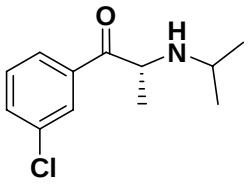
Amineptine 9



Vanoxerine 10

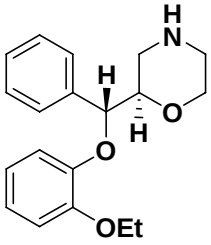
4. Norepinephrine-Dopamine Reuptake Inhibitors: As the name suggests, this class of antidepressants inhibits reuptake of both the norepinephrine and dopamine e. g. bupropion **11**.

Total Synthesis of (±)-Venlafaxine

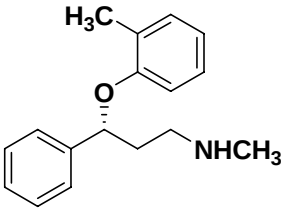


Bupropion 11

5. Norepinephrine Reuptake Inhibitors (NARIs): These elevate the extracellular level of the neurotransmitter norepinephrine in the central nervous system by inhibiting its reuptake from the synaptic cleft into the presynaptic neuronal terminal *via* the norepinephrine transporter. Virtually, they do not act at other monoamine transporters. Examples of NARIs include reboxetine **12**, atomoxetine **13** etc.

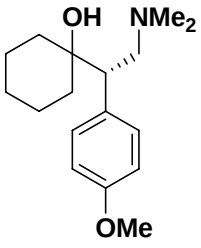


Reboxetine 12

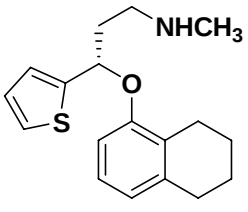


Atomoxetine 13

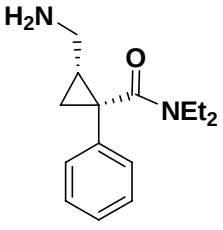
6. Serotonin-Norepinephrine Reuptake Inhibitors: Are a class of antidepressants used in the treatment of clinical depression and other affective disorders. They act upon two neurotransmitters in the brain that are known to play an important part in mood, namely, serotonin and norepinephrine. Candidates of this category are venlafaxine **14**, duloxetine **15**, milnacipran **16** etc.



Venlafaxine 14



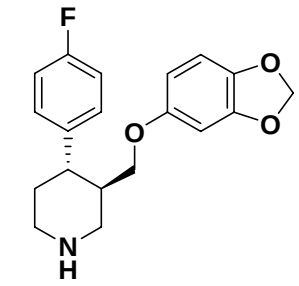
Duloxetine 15



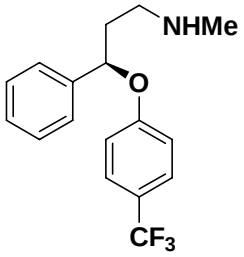
Milnacipran 16

7. Selective Serotonin Reuptake Inhibitors: This class of antidepressants is used for treating depression, anxiety disorders and some personality disorders. These drugs prevent reuptake of a neurotransmitter called serotonin or 5-hydroxytryptamine, thereby increasing

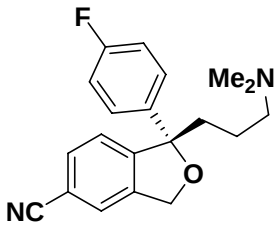
the extracellular level of serotonin into the presynaptic cell. A low level of serotonin is responsible for depression. They are selective in that they do not have inhibitory action upon other monoamine transporters. As compared to other classes this is more prefered as they have lesser side effects and drug interactions. Examples are paroxetine **17**, fluoxetine **18**, citalopram **19**, sertraline **20** etc.



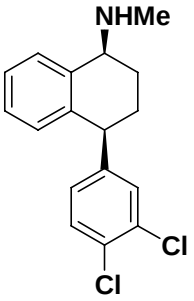
Paroxetine 17



Fluoxetine 18

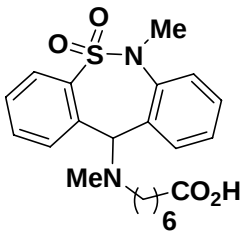


Citalopram 19



Sertraline 20

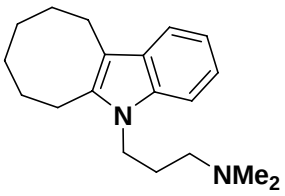
8. Selective Serotonin Reuptake Enhancers: Is a group of antidepressants, which enhances the reuptake of serotonin instead of blocking it. Examples of selective serotonin reuptake enhancer (SSRE) include tianeptine **21** etc.



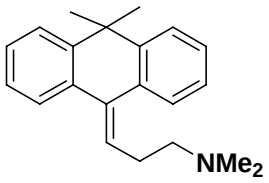
Tianeptine 21

9. Tricyclic Antidepressants: Tricylic antidepressants (TCAs) work by inhibiting the re-uptake of the neurotransmitters norepinephrine, dopamine, or serotonin by nerve cells. Tricyclics may also possess an affinity for muscarinic and histamine H1 receptors to varying degrees. This class of antidepressants is plagued by lack of pharmacological

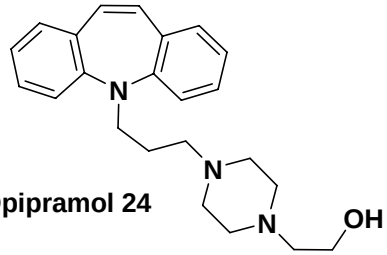
specificity, adverse side effects, delayed onset of action and potential for fatal overdose. Examples include iprindole **22**, melitracen **23**, opipramol **24**, doxepin **25** etc.



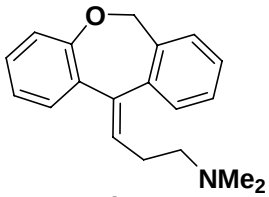
Iprindole 22



Melitracen 23

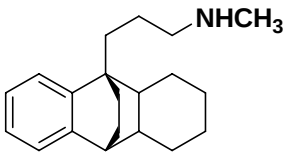


Opipramol 24

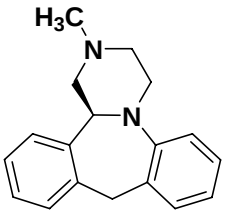


Doxepin 25

10. Tetracyclic Antidepressants: Like TCAs, this class also causes many side effects. Generally these drugs are used when other types of drugs are ineffective. Candidates of this class are maprotiline **26**, mianserin **27** etc.



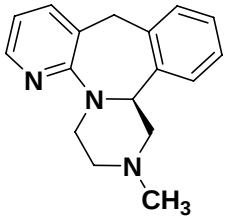
Maprotiline 26



Mianserin 27

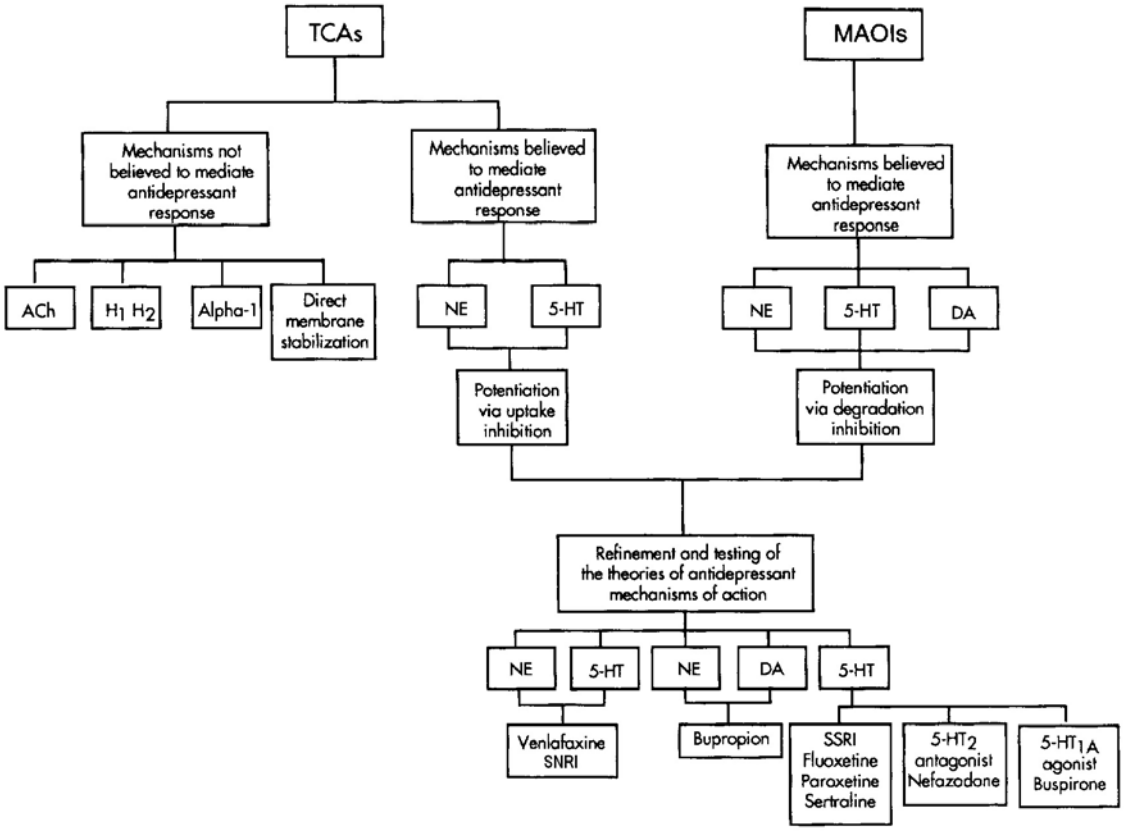
11. Noradrenergic and Specific Serotonergic Antidepressants: These are a relatively new class of antidepressants. As per name, they are thought to act by noradrenergic autoreceptor and heteroreceptor antagonism combined with specific serotonergic antagonism. This results in increases in both noradrenergic and specific serotonergic transmission. NaSSAs have fewer side effects than tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) while being equally effective. Examples of this class include mirtazapine **28** etc.

Total Synthesis of (±)-Venlafaxine



Mirtazapine 28

<u>Classification of antidepressants according to neurotransmitter activity.</u>



1.1.2.3. General mechanism of action of antidepressants

There are many neurotransmitters[6,7] in the brain e.g. serotonin or 5-hydroxy tryptamine (5HT), dopamine, noradrenaline (NA) or norepinephrine (NE), acetylcholine (ACh), glutamate and GABA. These compouds are sometimes referred to as biogenic monoamines. If some of these transmitters get out of balance e.g. you have too much or too little of a particular transmitter, some mental disorder will be observed. This is explained by the so-called "monoamine hypothesis". Serotonin (5-HT) and noradrenaline (NA) in the brain are involved with control of sleep/wake, emotions, mood, arousal, emotion, drive, temperature regulation, feeding etc. If a person has reduced levels of serotonin and noradrenaline in the part of the brain that controls above said factors, the person is said to be suffering from depression. There are many theories about how depression occurs but present day clinical pharmacology treats depression on the basis of monoamine hypothesis.

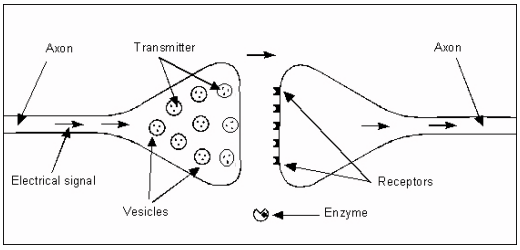


Figure 1. A synapse

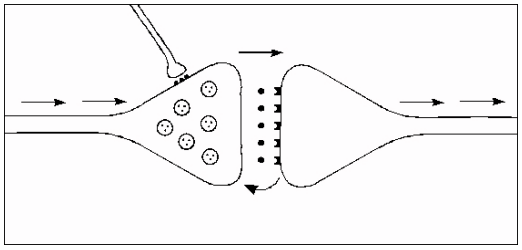


Figure 2. Normal nerve activity

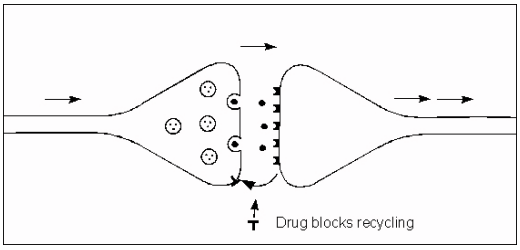


Figure 3. Reduced nerve activity

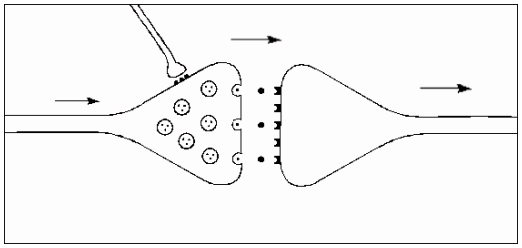


Figure 4. Reduced nerve activity but with recycling blocked, and increased passage of messages

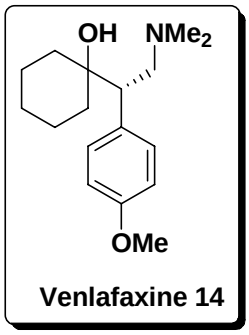
In normal condition electrical impulse (e. g. tighten the muscle etc.) is sent from the brain cell down one of the nerve fibres/neurons towards the end. When this message or impulse arrives at the end of the nerve fibre, a chemical (known as "transmitter") is released from the nerve end which travels across the gap between the first nerve fibre and the next, receiving one. When the transmitter hits the receptor on the side, the receptor changes shape. This causes changes inside the nerve ending which sets off an electrical message in that nerve fibre on to the next brain/nerve cell. This sequence then carries on until the effect occurs (e. g. the muscle moves etc.). The transmitter is either broken down

by enzymes (e. g. monoamine oxidase etc.) and removed or taken back up again into the nerve ending (i. e. recycled) - a process known as re-uptake. The nerve fibre and synapse is then ready for next message.

If the levels of serotonin or noradrenaline are reduced, it will lower the activity and produce the symptoms of depression. Then increasing the levels of serotonin or noradrenaline should help to reduce the symptoms. One way of doing this is to block the reuptake (recycling) of transmitters. This is just what these antidepressants do. They block the reuptake of serotonin and noradrenaline, so the next time an impulse comes along, there is more transmitter, a stronger message is passed, and activity in that part of the brain is increased i. e. symptoms of depression vanish.

1.1.3. Venlafaxine

1.1.3.1. Introduction



Venlafaxine 14

Introduction of SSRIs proved to be a major advancement in the pharmacotherapy of depression, both from a practical and theoretical basis. Venlafaxine **14** is a new generation antidepressant drug[3,6-8] developed by Wyeth-Ayerst Company in 1993. It is marketed in the racemic form under different trade names. Recently, generic version of venlafaxine has been approved by USFDA. Venlafaxine is a phenylethylamine compound, which exhibits a unique pharmacological profile with antidepression properties. It inhibits reuptake of biogenic amine like serotonin and norepinephrine,[9,10] hence called as Serotonin Norepinephrine Reuptake Inhibitor (SNRI). Although venlafaxine is sold as a racemate, (–)-venlafaxine is a more potent inhibitor of norepinephrine synaptosomal uptake while (+)-venlafaxine is more selective in serotonin uptake. It is different from other antidepressants in that it has no or little activity on a variety of neuroreceptors[3] (e. g. α or β-adrenergic receptors, muscarinic receptors, cholinergic receptors, histaminic receptors etc.). Like TCAs it has no activity at the fast sodium channels of cardiac cells, therefore devoid of cardiotoxicity. It does not inhibit MAO activity. It is unique among antidepressants in that it downregulates β-receptors after a single dose and causes rapid onset of clinical antidepressant activity. It inhibits dopamie reuptake at high dosage. The absence of other significant sites of pharmacological action gives it wide therapeutic window. Coadministration of two drugs, which inhibit individually either srotonin or norepinephrine uptake has been shown to shorten the treatment time. Likewise, combination of two drugs inhibiting both serotonin and norepinephrine uptake appears to produce a more rapid onset of clinical antidepressant activity than either mechanism alone.

1.1.3.2. Polymorphism

Polymorphism is the property of a substance to exist in two or more crystalline phases that have different arrangements and/or conformations of molecules in the solid state.[11] Racemic venlafaxine hydrochloride is highly polymorphic existing in five different polymorphic forms.[12,13] The five polymorphs of venlafaxine hydrochloride are classified according to their main melting endotherm in differential scanning calorimetry (DSC): form 1 (210-212 °C), form 2 (208-210 °C), form 3 (202-204 °C, phase from melting), form 4 (219-220 °C, hydrate/alcohol solvate), and form 5 (216-218 °C, phase from sublimation).

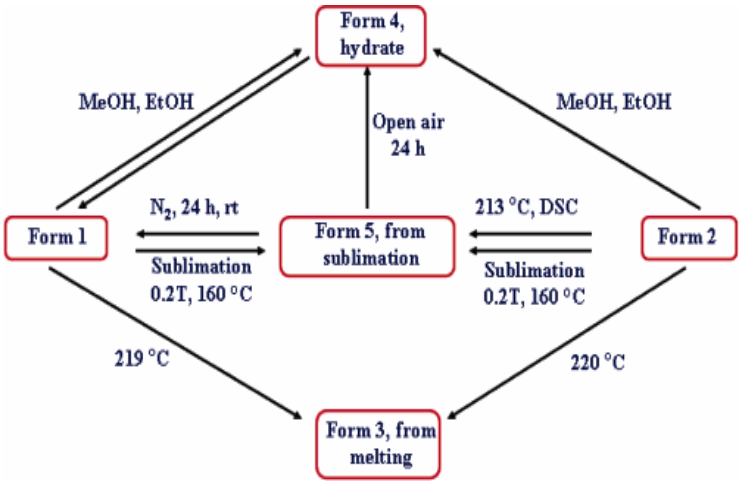


Figure 5. Phase transformations in venlafaxine hydrochloride polymorphs 1-5

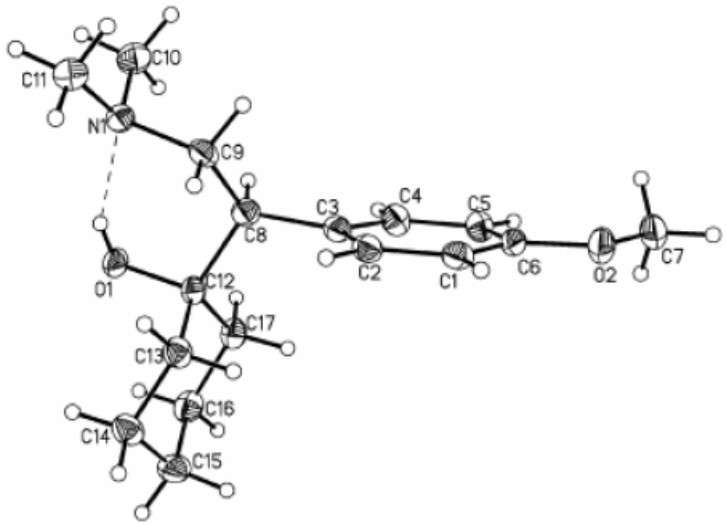


Figure 6. ORTEP diagram of venlafaxine free base to show the intramolecular O-H…N (1.77 Å, 145.8°) hydrogen bond. Thermal ellipsoids are drawn at 50% probability level.

Total Synthesis of (±)-Venlafaxine

Like its hydrochloride salt, venlafaxine free base does not exhibit polymorphism. It has monoclinic space group *P*21/*c*. The intramolecular O-H…N interaction ties up the molecule in a single conformation.

1.1.3.3. Pharmacology

A. Clinical profile

Rapid onset of action is one of the criteria for a perfect antidepressant. Venlafaxine is shown to be superior to placebo in a variety of trials.[14-17] In contrast to SSRIs, venlafaxine has an ascending dose-response curve. This is consistent with a second mechanism of action (i.e. inhibition of norepinephrine), which becomes clinically relevant. At 225 mg/day the magnitude of antidepression effect is 50% higher than that seen with SSRIs. A response rate for 375 mg/day is five times that of placebo after one week of treatment. Like a number of antidepressants, venlafaxine is metabolised to a pharmacologically active metabolite *o*-desmethylvenlafaxine (ODV).[18] ODV has longer plasma half-life (10 hours) than venlafaxine (4 hours), which probably prolongs its duration of action. Venlafaxine and ODV have no MAO inhibitory activity. It is available in extended-release as well as immediate-release dosings. Extended-release dosing simplifies dosing, single dose a day is sufficient.[19]

B. Safety and Tolerance

Like SSRIs, venlafaxine does not have significant effects on the sodium fast channels, which gives it a wide therapeutic window. Treatment for acute overdoses does not require specific or unusual intervention beyond general nursing care and observation. Overdosing is frequently accompanied by nausea and vomitting, which further limits its toxicity. The most common adverse side effects are nausea, dizziness and somnolence. Like SSRIs, venlafaxine may cause sexual dysfunction after a prolonged treatment. At higher doses common side effects observed are hypertension, sweating and tremor.

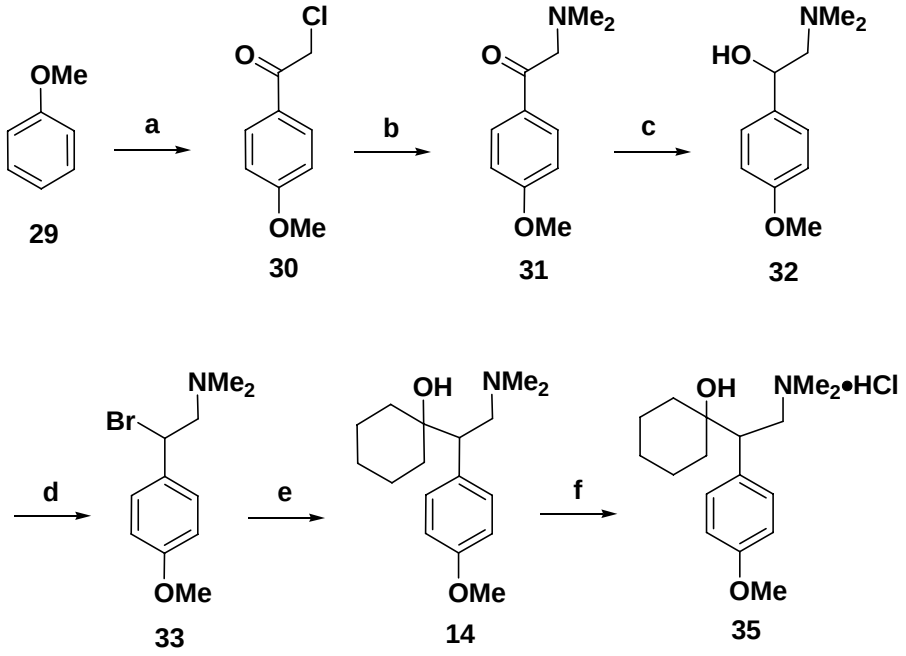
C. Cost effectiveness

Venlafaxine, offering potential pharmacological benefits including early onset of action, dose flexibility, broad range of activity, improved tolerance and efficacy proves a cost-effective drug. An earlier response can be particularly beneficial in more severely depressed patients.[20]

1.1.4. Literature Survey

A brief literature survey of total syntheses of venlafaxine and its sila-analogs is presented.

Jinpei[21] (*J. China Pharm. Univ*. **1999**, *30*, 249)



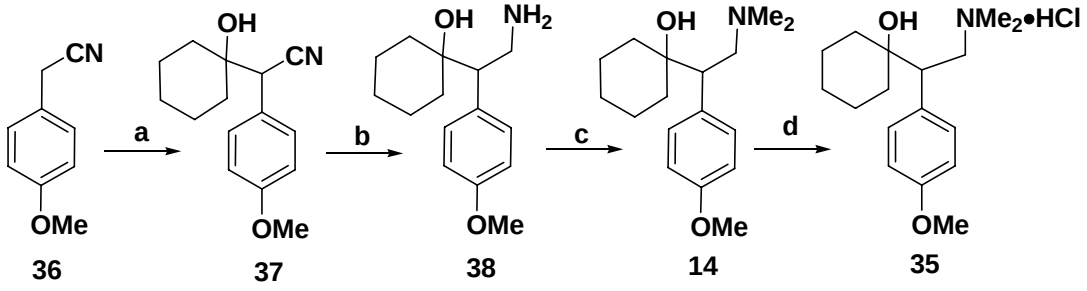
Scheme 1. *Reagents and conditions:* a) $ClCO_2CH_2Cl$, $AlCl_3$, PhH, reflux, 4 h, 70%; b) 33% aq. Me_2NH, EtOH, r t, 15 h; c) KBH_4, EtOH, r t, 8 h, 64%; d) PBr_3, $CHCl_3$, 0 ^oC then reflux, 15 h, 53%; e) Mg, THF, reflux, then 0 ^oC , cyclohexanone **34** then reflux, 1 h; f) conc. HCl, 47% (for 2steps).

Friedel-Craft acylation of anisole **29** with chloroacetyl chloride provided chloride **30**, which upon treatment with Me_2NH afforded amidoketone **31**. Reduction of compound **31** with KBH_4 gave aminoalcohol **32**, which was further converted into the corresponding bromide **33** using PBr_3. Grignard reaction of bromide **33** with cyclohexanone **34** gave venlafaxine **14**. Its hydrochloride salt **35** was prepared using conc. HCl (scheme 1).

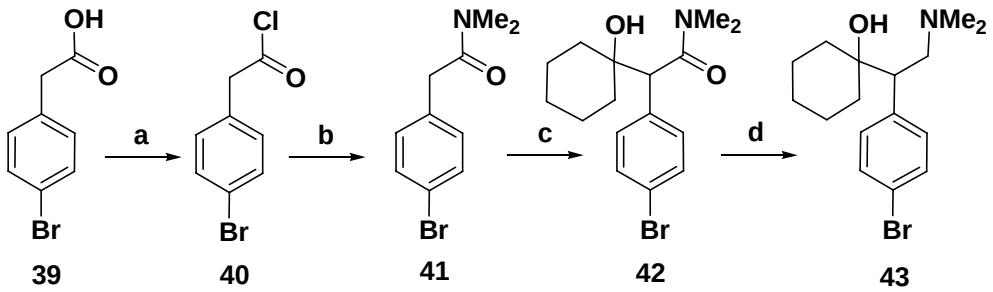
Yardley[22,23] (*J. Med. Chem.* **1986**, *33*, 2899-2905; US Patent No. 4, 535, 186, **1985**)

p-Methoxyphenylacetonitrile **36** was condensed with cyclohexanone **34** using LDA at –78 ^oC to obtain cyanoalcohol **37**. Compound **37** was then subjected to hydrogenation with 5% Rh/Al_2O_3 in NH_3/EtOH system to afford aminoalcohol **38**. *N,N*-Dimethylation of the primary amine **38** was effected with modified Eschweiler-Clarke reaction to afford

venlafaxine **14**. Hydrochloride salt of venlafaxine, **35** was prepared using 20% HCl in IPA (scheme 2).



Scheme 2. *Reagents and conditions:* a) LDA, THF, –78 ^{o}C then cyclohexanone **34**, 2 h, 83%; b) H_2, 5% Rh/Al_2O_3, NH_3-EtOH (2:8), 57%; c) HCHO, HCO_2H, H_2O reflux, overnight; d) HCl (20% in *i*PrOH) 80% (for 2 steps).

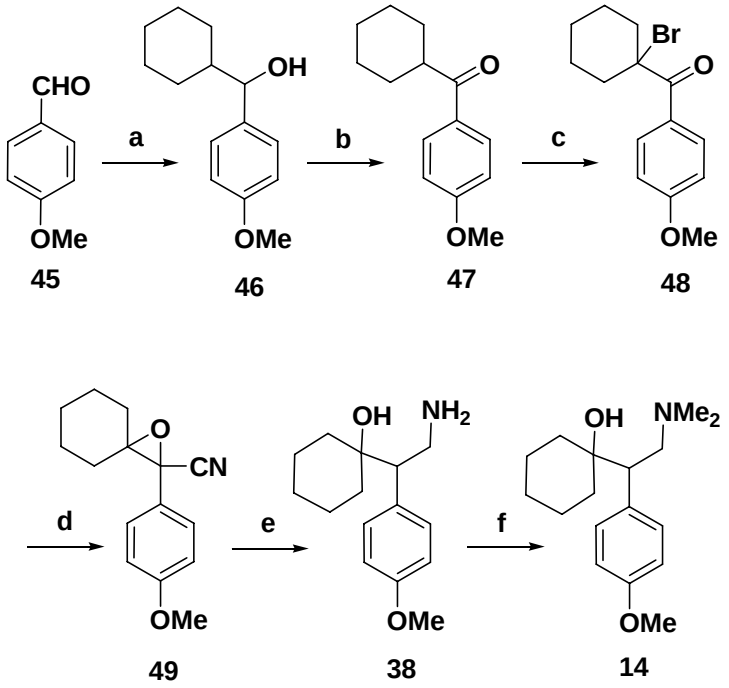


Scheme 3. *Reagents and conditions:* a) $(COCl)_2$, DMF, DCM, r t, 4 h; b) Me_2NH, DCM, r t, overnight, 97% (2 steps); c) LDA, THF, –78 ^{o}C, then cyclohexanone **34**, 50 min, 44%; d) $LiAlH_4$, conc. H_2SO_4, THF, 0 ^{o}C, 1 h, 40%.

In these cases formation of tetrahydroisoquinolines by the reaction of the activated ring position with the electropholic iminium intermediates of Eschweiler-Clarke reaction occurred. Also, traces of oxazines were detected in these reactions. This problem was circumvented in a modified route (scheme 3), where *p*-bromophenylacetic acid **39** was converted into its chloride **40** using $(COCl)_2$ in the presence of DMF. Acid chloride **40** was treated with Me_2NH to give corresponding acetamide **41**. Condensation of acetamide **41** with cyclohexanone **34** at –78 ^{o}C using LDA furnished amidoalcohol **42**, which was reduced using AlH_3 to yield venlafaxine analog **43**. A small library of several derivatives have been prepared by these methods.

Total Synthesis of (±)-Venlafaxine

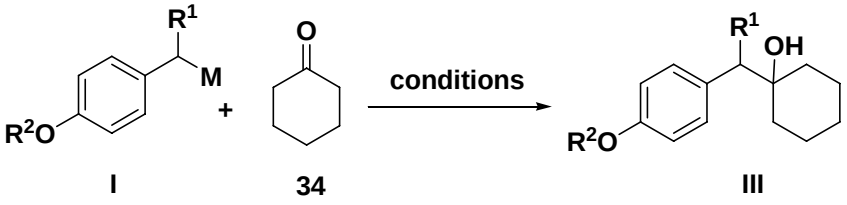
Rathod[24] (EP 1249447, **2001**)



Scheme 4. *Reagents and conditions:* a) cyclohexyl magnesium bromide **44**, THF, 10 ^{o}C to r t, 6 h, 80%; b) CrO_3, H_2O, r t, 3 h, 76%; c) PTAB, THF, reflux, 3 h, 82%; d) NaCN, MeOH, r t, 2 h, 64%; e) H_2, Raney Ni, NH_3-EtOH, 500 kPa, r t, 7 h, 78%; f) HCHO, HCO_2H, H_2O, reflux, 6 h, 75%.

Rathod *et. al.* patented a procedure for synthesis of venlafaxine **14** involving Grignard reaction of cyclohexyl magnesium bromide **44** with *p*-anisaldehyde **45** to yield carbinol **46**. Oxidation of the carbinol with CrO_3 furnished corresponding ketone **47**, which upon α-bromination with PTAB gave α-bromoketone **48**. Spiroepoxide **49** was obtained by treatment of bromoketone **48** with NaCN. Catalytic hydrogenation of spiroepoxide **49** with Raney nickel afforded aminoalcohol **38**, which was converted into venlafaxine **14** by a known method (scheme 4).

Shepherd[25] (GB 2 227 743, **1990**)

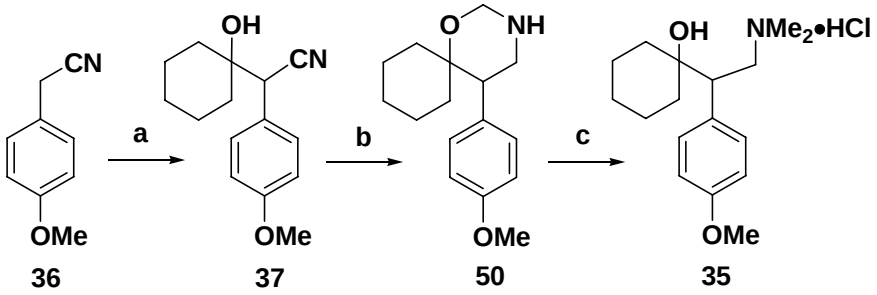


Scheme 5. Condensation of **I** with cyclohexanone **34**

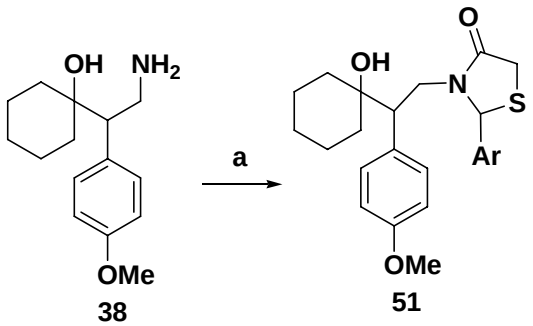
Total Synthesis of (±)-Venlafaxine

Shepherd patented a method, where compound **I** (R^1 = CN, $CONMe_2$, $CSNMe_2$; R^2= H, Me or a protecting group and M = Li, Na, K, MgX) was condensed with cyclohexanone **34** using different bases or the corresponding Grignard (**I**, M = MgX) reagent to obtain compound **III** (R^1 = CN, $CONMe_2$, $CSNMe_2$; R^2 = H, Me or a suitable protecting group). Compound **III** was converted to venlafaxine **14** (R^2 = Me, R^1 = CH_2NMe_2) by reducing **III** with a suitable reducing agent (for R^1 = CN, hydrogenation followed by *N,N*-dimethylation; AlH_3 for $CONMe_2$, Raney nickel for $CSNMe_2$ etc.). Compound **III** has also been converted to *O*-desmethylvenlafaxine, a potent antidepressant drug, by unmasking the protection/reduction in proper sequence (e.g. hydrogenation using Raney nickel when R^1 = $CSNMe_2$ and R^2 = Bn etc.). Obvious disadvantages of the method are use of the strong and hazardous bases like LDA, BuLi, Grignard reagents, necessity of cryogenic conditions, use of anhydrous organic solvents accompanied by low yields in the first step, which are unsuitable from industrial point of view.

Rangappa[26a] (*Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279-3281)



Scheme 5. *Reagents and conditions:* a) cyclohexanone **34**, NaOH, Bu_4NBr, H_2O-MeOH, r t, 15 h, 96%; b) Raney Ni, H_2 (10 atm), anhydrous NH_3-MeOH, 35-40 ^oC, then formalin, 25-30 ^oC, 3 h, 83%; c) HCO_2H, HCHO, reflux, 25-30 h, then HCl in *i*PrOH (pH = 2), 85%.



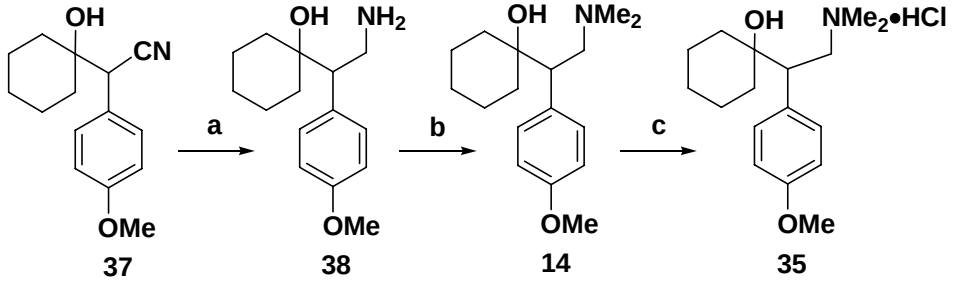
Scheme 6. *Reagents and conditions:* a) ArCHO, $HSCH_2COOH$, DCC, THF or MW.

Total Synthesis of (±)-Venlafaxine

Soon after the grant of US patent[34,37] filed by us, Rangappa *et. al.* published their work, which involved condensation of *p*-methoxyphenylacetonitrile **36** with cyclohexanone **34**, using NaOH in MeOH-H_2O (1:1) medium. Catalytic hydrogenation of cyanoalcohol **37** with Raney nickel followed by reaction with formalin gave oxazine **50**, which was further subjected to Eschweiler-Clarke conditions to obtain venlafaxine free base **14**. Treatment of **14** with *i*PrOH/HCl gave its hydrochloride salt **35**.

Use of MeOH in the first step is undesirable from ecology point of view. Besides, it takes longer time for condensation. Recently, they have also prepared several analogues[26b] of venlafaxine which, exhibited antimicrobial activity.

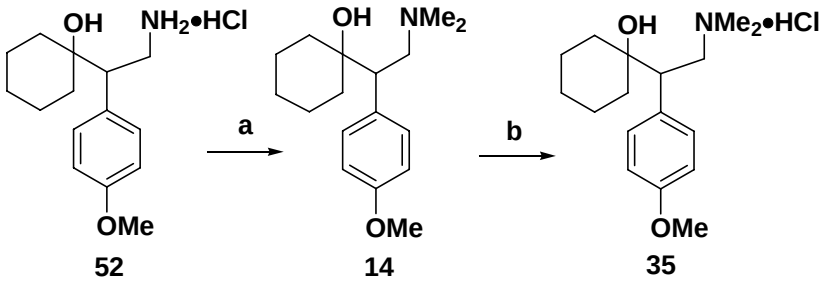
Saigal[27] (US 7,026,513, **2006**)



Scheme 7. *Reagents and conditions:* a) H_2 (35 psi), Raney Ni, aq. NH_3-MeOH, r t, 90%; b) HCO_2H, HCHO, H_2O, reflux; 16 h; c) HCl / *i*PrOH.

A slightly modified method was patented by Saigal *et. al.* from Nicolas Piramal India Limited, where catalytic hydrogenation of cyanoalcohol **37**, using Raney nickel was carried out in aqueous NH_3-EtOH system (scheme 7).

Dolitzky[28] (US 6,924,393, **2005**)



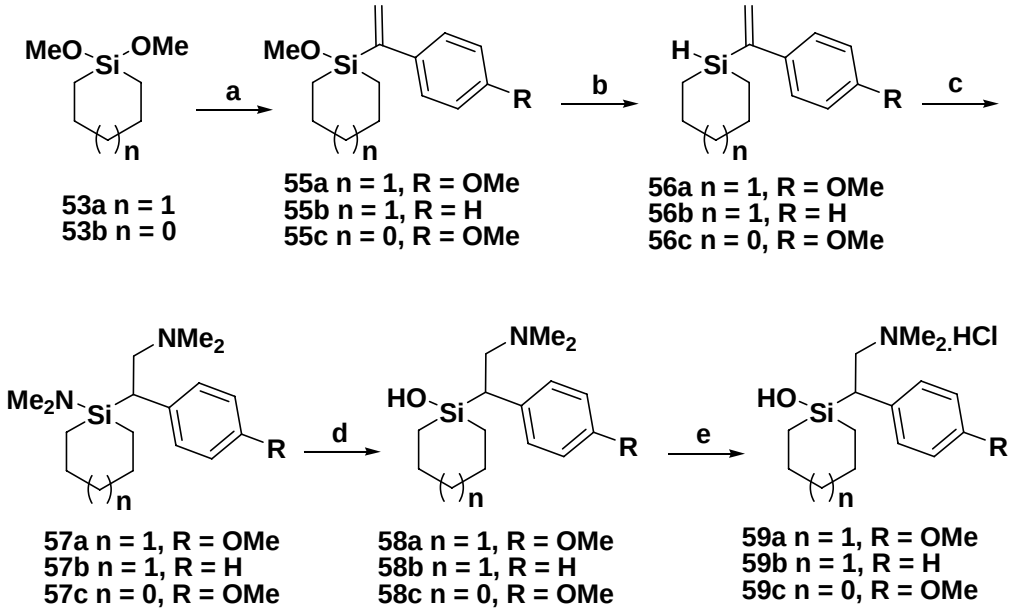
Scheme 8. *Reagents and conditions:* a) HCO_2H, HCHO, reflux, 21 h; c) HCl gas, acetone or *i*PrOH.

Total Synthesis of (±)-Venlafaxine

An another modified process for the preparation of venlafaxine hydrochloride **35** was patented by Dolitzky *et. al.*, which employed amine hydrochloride **52** instead of the free amine **38** (scheme 8). Synthesis of different polymorphs of venlafaxine hydrochloride has also been disclosed in the patent.

Sila-venlafaxines

Tacke[29,30] (*J. Organometallic Chemistry* **2006**, *691*, 3589-3595; *Organometallics* **2006**, *25*, 1188-1198)

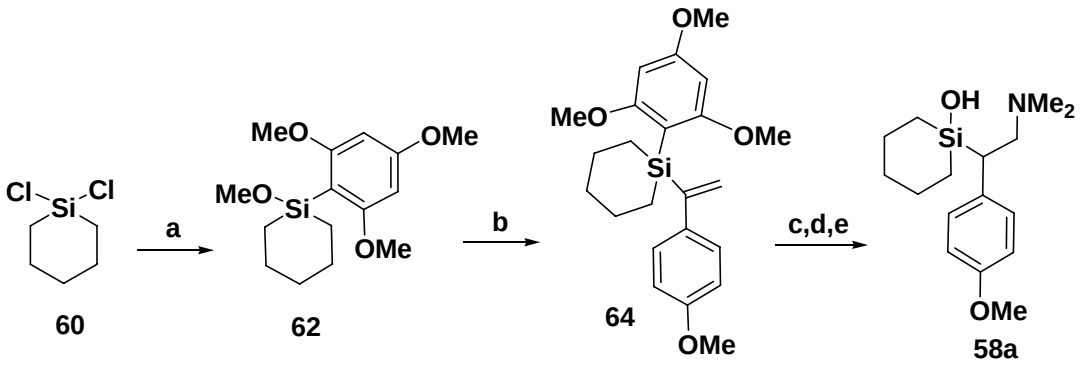


Scheme 9. *Reagents and conditions:* a) 1-arylvinylmagnesium bromide **54**, TMEDA, hexane, –78 ºC, 59%; b) $LiAlH_4$, 83%; c) $LiNMe_2$, Me_2NH, 40%; d) H_3O^+, 91%; e) $Et_2O{\cdot}HCl$, 93%.

Silavenlafaxine **59a**, desmethoxy sila-venlafaxine **59b** and its five membered analog **59c** and their hydrochloride salts have been prepared by Tacke *et. al.* from the 1,1-dimethoxy-1-silacyclohexane **53a** (and cyclopentane **53b**). Reaction of **53a** (or **53b**) with (1-arylvinyl) magnesium bromide **54** (R = H or OMe) gave 1-methoxy-1-(arylylviny)-1-silacyclohexane **55a** and **55b** (cyclopentane **55c**), which upon treatment with $LiAlH_4$ afforded 1-(arylviny)-1-silacyclohexane **56a** and **56b** (cyclopentane **56c**). Compound **56** was then reacted with $LiNMe_2$ in the presence of Me_2NH to furnish 1-(dimethylamino)-1-(2-dimethyalmino)-1-aryl-1-silacyclohexane **57a** and **57b** (cyclopentane **57c**). Hydrolysis of compound **57** yielded silavenlafaxine **58a** and desmethoxy-sila-venlafaxine **58b** and five

membered analog of silavenlafaxine **58c**. Their hydrochloride salts **59a, 59b** and **59c** were prepared by treatment with ethereal HCl (scheme 9).

Tacke[31,32] (*Organometallics* **2004**, *23*, 4987-4994; *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2555-2558)



Scheme 10. *Reagents and conditions:* a) i. 2,4,6-trimethoxyphenyllithium **61**, TMEDA, hexane; ii. MeOH, 66%; b) (1-(4-methoxyphenyl)vinyl)lithium **63**, TMEDA, hexane, –78 ^{o}C, 47%; c) 2 M HCl in Et_2O; d) $LiNMe_2$, Me_2NH, THF, 40%; e) KOAc, AcOH (pH = 5), 86%.

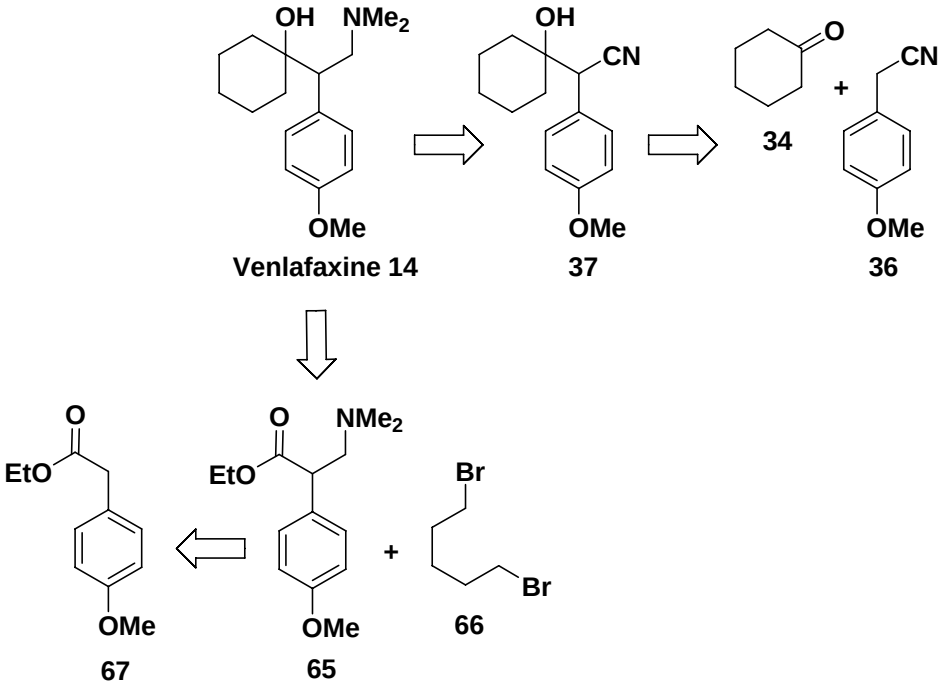
Treatment of 1,1-dichloro-1-silacyclohexane **60** with one equivalent 2,4,6-trimethoxyphenylbutyllithium **61** followed by methanolysis afforded 1-methoxy-1-(2,4,6-trimethoxyphenyl)-1-silacyclohexane **62**. Compound **62** was further reacted with 1-(4-methoxyphenyl)vinyllithium **63** to obtain 1-[1-(4-methoxyphenyl)vinyl]-1-(2,4,6-trimethoxyphenyl)-1-silacyclohexane **64**, which upon treatment with ethereal HCl yielded 1-chloro-1[1-(4methoxyphenyl)vinyl]-1-silacyclohexane, chlorine was replaced with NMe_2 using $LiNMe_2$ in the presence of Me_2NH, followed by hydrolysis gave racemic silavenlafaxine **58a**. Racemic silavenlafaxine was resolved with CSA and then converted into its HCl salt (scheme 10). Apart from norepineprine reuptake inhibition, ***R*-58a** showed anti-emetic properties.

1.1.5. Present Work

Synthesis of venlafaxine **14** was undertaken due to its immense commercial significance, unique antidepressant activity, exclusive special structure and a morphological effect.

1.1.5.1. Retrosynthesis

As depicted in scheme 11, retrosynthetic analysis reveals that target molecule **14** could be obtained from the corresponding cyanoalcohol **37**, which in turn could be derived from *p*-methoxyphenylacetonitrile **36** and cyclohexanone **34**. In synthetic sequence *p*-methoxyphenylacetonitrile **36** could be condensed with cyclohexanone **34** using a suitable base to obtain cyanoalcohol **37**, which could be reduced with a suitable reducing agent followed by *N,N*-dimethylation by some known literature method. Alternatively, target molecule **14** could also be obtained from from aminoester **65** and 1,5-dibromopentane **66** by Grignard approach. Aminoester **65** could be obtained from ethyl 2-(4-methoxyphenyl) acetate **67**.



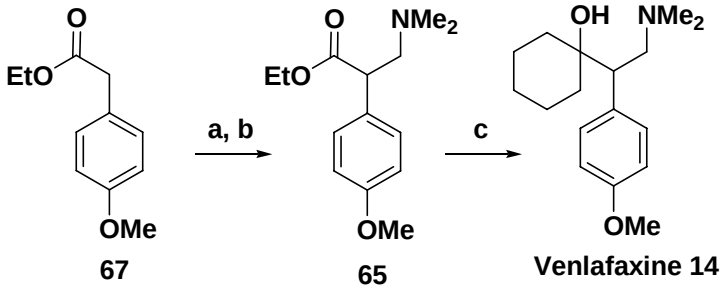
Scheme 11. Retrosynthetic analysis of venlafaxine **14**

1.1.5.2. Results and discussion

Patented literature methods[23-25] were not suitable from industrial point of view as they involved expensive, hazardous reagents, toxic chemicals, anhydrous organic solvents, cryogenic conditions etc. Some routes were a bit lengthy. Although, a method is known in literature, which involved condensation of *p*-methoxyphenylacetonitrile **36** with cyclohexanone **34**, use of strong bases like BuLi[22] and LDA,[25] cryogenic conditions and anhydrous solvents makes it undesirable from industrial point of view. Also, they suffer from low yields under these conditions. So, development of a more efficient, cost-effective, ecologically and technically viable protocol was apt.

Total synthesis of (±)-venlafaxine by Grignard approach

As depicted in retrosynthetic analysis, target molecule **14** could be obtained from aminoester **65** and 1,5-dibromopentane **66**. Grignard reaction of 1,5-dibromopentane **66** with aminoester **65** would give target molecule **14**. Compound **65** was prepared[33] by heating a mixture of ethyl 2-(4-methoxyphenyl)acetate **67**, $(HCHO)_n$ and K_2CO_3 in PhMe at 85 ^oC in the presence of TBAI. It was further treated with Me_2NH in THF at room temperature in the presence of catalytic amount of $FeCl_3$ to furnish aminoester **65** in 79% yield in 45 minutes (scheme 12). In the absence of catalyst, it took 48 hours for completion of the reaction.



Scheme 12. *Reagents and conditions:* a) $(HCHO)_n$, K_2CO_3, TBAI, PhMe, 80 ^oC, 3.5 h; b) Me_2NH, r t, 45 min, 58% (two steps); c) $BrMg(CH_2)_5MgBr$, THF, 0 ^oC then reflux, 3.5 h , 50%.

IR spectrum of compound **65** showed an absorption at 1727 cm^{-1} revealing the presence of ester function. ^1H NMR spectrum of compound **65** showed two doublets at δ 7.23 and 6.83 revealing presence of four aromatic protons. A quartet at δ 4.14 corresponded to $OC\mathit{H}_2CH_3$. A sharp singlet appeared at δ 3.78 corresponding to O*Me*. A

doublet of doublet at δ 3.73 was assigned to benzylic proton proximal to ester function. Two doublets of doublet that appeared at δ 3.01 and 2.42 revealed two C*H*$_2$NMe$_2$ protons. The singlet at δ 2.27 belonged to N-*Me*$_2$. The triplet at δ 1.22 corresponded to three OCH$_2$C*H*$_3$ protons. ^{13}C NMR spectrum of compund **65** showed a signal at δ 172.4 characteristic of ester function. Six aromatic carbons appeared at δ 158.6, 129.4, 128.5, 113.7. A signal at δ 62.7 was ascribed to *C*H$_2$-NMe$_2$, while O*C*H$_2$CH$_3$ carbon appeared at δ 59.8. The carbon of methyl ether appeared at δ 54.5. The benzylic carbon was found to appear at δ 49.3. The signal at δ 45.2 was attributed to N*Me*$_2$ and the signal at δ 13.8 was assigned to OCH$_2$*C*H$_3$. Further, the molecular weight of compound **65** was confirmed by MS spectrum, showing a signal at 251 indicating M$^+$.

Next, aminoester **65** was reacted with Grignard reagent prepared from 1,5-dibromopentane **66** in THF to afford venlafaxine **14** free base in 50% yield (scheme 11).

IR spectrum of venlafaxine **14** showed an absorption at 3164 cm^{-1} indicating the presence of *OH* group. ^{1}H NMR spectrum of venlafaxine **14** showed two doublets at δ 7.03 and 6.79 revealing four aromatic protons. A singlet at δ 3.79 indicated presence of O*Me*, a triplet at δ 3.28 revealed benzylic proton and two doublets at δ 2.93 and 2.28 were assigned to C*H*$_2$NMe$_2$. The singlet at δ 2.33 corresponded to N*Me*$_2$, and the multiplets at δ 1.23-1.27 and 0.83-1.00 corresponded to the remaining cyclohexyl protons. ^{13}C NMR spectrum of venlafaxine **14** showed four signals at δ 157.7, 132.0, 129.4, 112.7 revealing aromatic carbons. Quaternary carbon proximal to OH appeared at δ 73.4. Signal at δ 60.7 corresponded to *C*H$_2$NMe$_2$. The signal at δ 54.3 was attributed to O*C*H$_3$. The signal at δ 51.2 revealed benzylic carbon. The signal at δ 44.8 revealed N-*Me*$_2$ carbons and the signals at δ 37.5, 30.7, 25.5, 21.0, 20.7 correspond to cyclohexyl ring carbons. Molecular formula C$_{17}$H$_{27}$NO$_2$ of venlafaxine was further confirmed by MS spectrum showing a signal at 277 indicating M$^+$.

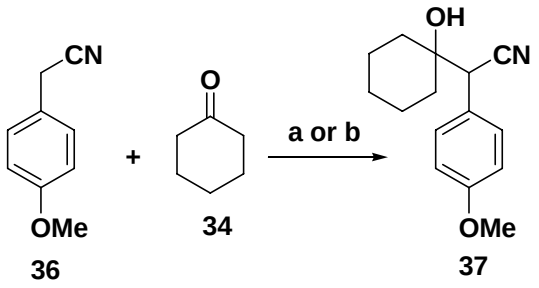
<u>Green synthesis of (±)-venlafaxine</u>

Though the above synthesis is short and efficient, Grignard reaction employing Mg and organic solvents makes it unsuitable for industrial scale.

Hence an alternative scheme was looked at, which employs commercially available and inexpensive *p*-methoxyphenylacetonitrile **36** and cyclohexanone **34**. First, it was decided to see whether efficiency of the method reported in the literature could be improved. Accordingly, *p*-methoxyphenylacetonitrile **36** was condensed with

cyclohexanone **34** according to the literature procedures using BuLi, LDA etc. but these efforts to improve yields were fruitless.

Condensation of *p*-methoxyphenylacetonitrile 36 with cyclohexanone 34

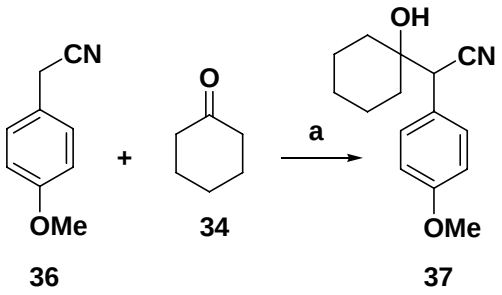


Scheme 13. *Reagents and conditions:* a) BuLi or LDA, or THF or Hexane, –78 °C; b) ROM/ROH or THF, (Where, M = Na, K; R = Me, Et, *i*Pr, *t*Bu), low yields, dehydrated byproduct formed.

Since condensation of *p*-methoxyphenylacetonitrile **36** with cyclohexanone **34** according to the literature methods using BuLi or LDA gave poor yields (scheme 13), in order to look for an efficient way for condensation, a variety of bases like $NaNH_2$, NaH, metal alkoxides (ROM where, R = Me, Et, *i*Pr, *t*Bu etc. and M = Na, K etc.), NaOH, KOH was studied. With metal alkoxides, reaction was incomplete at low temperatures. At room temperature, the cyanoalcohol formed undergoes dehydration. Also, use of $NaNH_2$ and NaH did not improve the situation. Different reaction conditions were studied but without success. Sometimes, these bases formed some undesired side products.

Finally, attention was diverted to much milder and inexpensive bases like NaOH and KOH. Surprisingly, these bases proved to be the most suitable and efficient of all the tried bases. Use of one equivalent powdered NaOH or KOH at 0 ºC gave cyanoalcohol **37** in 83% yield within an hour when a mixture of *p*-methoxyphenylacetonitrile **36** and powdered NaOH or KOH was stirred for 30 minutes and then cyclohexanone **34** was added dropwise at 0-10 ºC. Catalytic amount of powdered NaOH or KOH at 0 ºC in the presence of phase transfer catalyst for a short period of time provided the required condensed product **37** in 85% yield. 50% aqueous NaOH or KOH solution under phase transfer catalysis at 0-10 ºC also gave cyanoalcohol **37** in about 85% yield. Finally, it was observed that 10% aqueous NaOH or KOH under phase transfer catalysis at 0-10 ºC for 1 hour (scheme 14) were the most suitable conditions giving the cyanoalcohol **37** in almost quantitative yields![34] Condensation of *p*-methoxyphenylacetonitrile **36** with cyclohexanone **34** was also effected with PEG (MW-6000) at room temperature in 73% yields. Longer

reaction times or catalyst loading did not affect the yields. Results of this study are listed in table 2.



Scheme 14. *Reagents and conditions:* a) 10% aq. NaOH or KOH, cat. $TBAHSO_4$, 0-10 ºC, 1 h, quantitative yields.

IR spectrum of compound **37** showed an absorption at 3492, 3406 cm^{-1} for hydroxyl group and at 2241 cm^{-1} suggesting the presence of CN. ^1H NMR spectrum of compound **37** showed two doublets at δ 7.26 and 6.89 corresponding to four aromatic protons. The signal at δ 3.81 corresponded to O*Me*. The signal at δ 3.71 corresponded to benzylic proton. The multiplet at δ 1.51-1.75 corresponded to ten protons of the cyclohexane region and a broad singlet at δ 1.17 for 1H was due to the hydroxy group. ^{13}C spectrum of compound **37** showed four signals at δ 159.6, 130.6, 123.6, 114.0 corresponding to aromatic ring carbons and a signal at δ 119.8 revealed the presence of *C*N. The signal at δ 72.6 was assigned to the quaternary carbon proximal to the OH group. The signal at δ 55.2 revealed the presence of O*C*H_3. The signal at δ 49.2 corresponded to the benzylic carbon, and three signals at δ 34.8, 25.1, 21.4 corresponded to the cyclohexyl ring carbons. Further, its molecular formula was confirmed by MS spectrum showing signal at 225 corresponding to M^+.

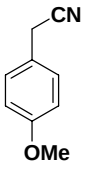
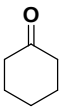
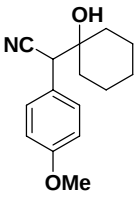
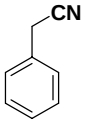
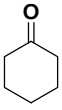
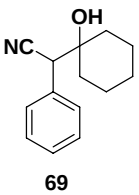
Table 2. Condensation of *p*-methoxyphenylacetonitrile 36 with cyclohexanone 34 using various bases

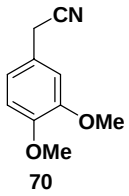
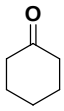
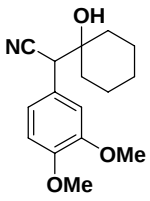
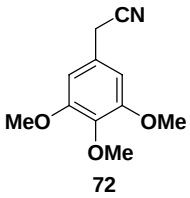
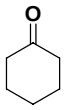
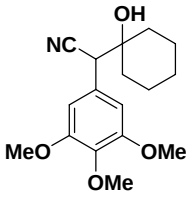
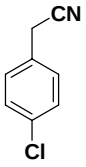
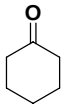
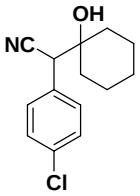
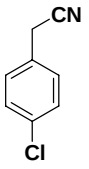
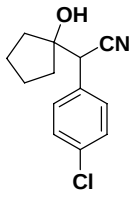
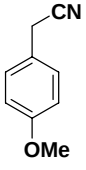
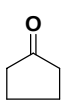
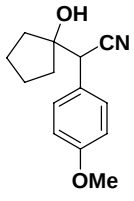
Entry	Base (solvent)	Catalyst	Temp.	Time	Yield
1.	BuLi/LDA (THF)	---	–78 ºC	30 min	30%
2.	ROM (ROH/THF)	---	–78 ºC	30 min	Incomplete reaction
3.	$NaNH_2$ (THF)	---	–50 ºC	45 min	Poor yields
4.	NaH (THF)	---	0 ºC	60 min	45%

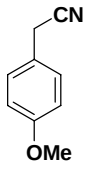
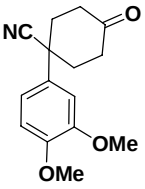
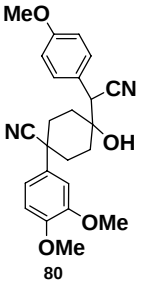
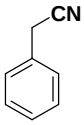
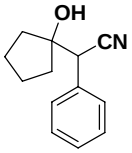
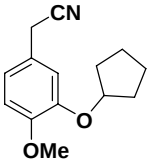
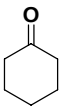
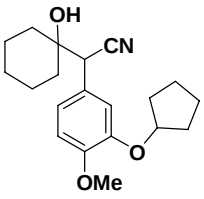
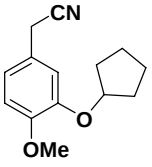
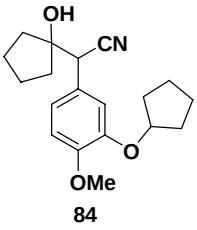
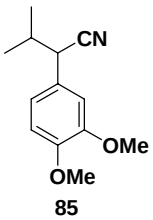
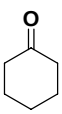
5.	Powdered equimolar NaOH/KOH	$TBAHSO_4$	0-10 ºC	60 min	83%
6.	Powdered catalytic NaOH/KOH	$TBAHSO_4$	0-10 ºC	60 min	85%
7.	50% aq. catalytic NaOH/KOH	$TBAHSO_4$	0-10 ºC	60 min	85%
8.	10% aq. catalytic NaOH/KOH	$TBAHSO_4$	0-10 ºC	60 min	quantitative
9.	Powdered catalytic NaOH/KOH	PEG	R T	60 min	73%

Having successfully demonstrated a novel and mild method for condensation, it was decided to explore the strength and weakness of this method. Generality of the protocol[35] was established by condensing various arylacetonitriles with ketones. Results of this study are listed in table 3.

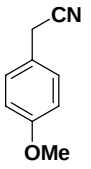
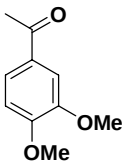
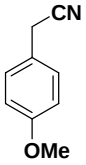
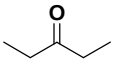
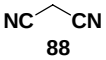
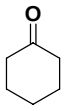
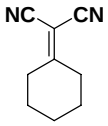
Table 3. Condensation of arylacetonitriles with ketones

Entry	Nitrile	Ketone	Product	PTC[a]	Time	Yield
1.	 **36**	 **34**	 **37**	$TBAHSO_4$	1 h	97
2.	 **68**	 **34**	 **69**	$TBAHSO_4$	1 h	87

3.	 70	 34	 71	$TBAHSO_4$	1 h	95
4.	 72	 34	 73	$TBAHSO_4$	1 h	90[b]
5.	 74	 34	 75	$TBAHSO_4$	45 min	87
6.	 74	 76	 77	$TBAHSO_4$	45 min	73[c]
7.	 36	 76	 78	TBAI[d]	1 h	83

8.	 36	 79	 80	$TBAHSO_4$	45 min	56[e]
9.	 68	 76	 81	TBAI[d]	1 h	96
10.	 82	 34	 83	TBAI[d]	2 h	66
11.	 82	 76	 84	$TBAHSO_4$	2 h	96
12.	 85	 34	N R[f]	$TBAHSO_4$	O N	---

Total Synthesis of (±)-Venlafaxine

13.	 **36**	 **86**	N R	$TBAHSO_4$	O N[g]	---
14.	 **36**	 **87**	N R	$TBAHSO_4$	O N	---
15.	 **88**	 **34**	 **89**	$TBAHSO_4$	30 min	77

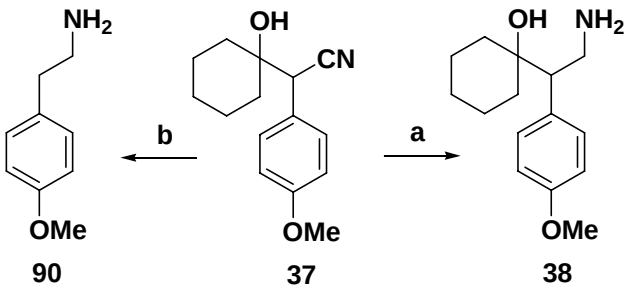
a. PTC = Phase transfer catalyst
b. Powdered nitrile was used
c. About 10% dehydrated product was obtained
d. TBAI = Tetrabutyl ammonium iodide
e. Powdered ketone was used
f. No reaction was observed even at room temperaure
g. ON = overnight

From this study it was observed that arylacetonitriles could be readily condensed with cyclic ketones only. Sterically demanding nitriles (e.g. **85**) failed to give the condensed product. Cyclohexanols (e.g. **37**, **69**, **71**, **73**, **75**, **80**, **83**) formed were stable enough under reaction conditions and should be freed from the base thoroughly after work-up, otherwise they have propensity to undergo retro-condensation. Once isolated, they are quite stable and can be stored for infinite time at room temperature. Corresponding cyclopentanols (e.g. **77**, **78**, **81**, **84**) were found to be rather unstable and showed a tendency to undergo spontaneous dehydration during reaction itself, if continued for longer times even at 0 ºC and upon storage for longer times even in refrigerator. Malononitrile **88**

was readily condensed with cyclohexanone **34** to give the dehydrated product **89** as the only product under reaction conditions.

Reduction of cyanoalcohol 37

Reduction of the cyanoalcohol **37** to aminoalcohol **38** was tried using different reducing agents. $NaBH_4$ alone or in combination with $AlCl_3$ [36] or I_2 [37] was not able to bring about reduction and only starting material was recovered.



Scheme 15. *Reagents and conditions:* a) H_2 (280 psi), Raney Ni, MeOH, 100 ºC, 6 h, 30%; b) H_2 (280 psi), Raney Ni, NH_3-MeOH (20%), 100 ºC, 6 h, 30%.

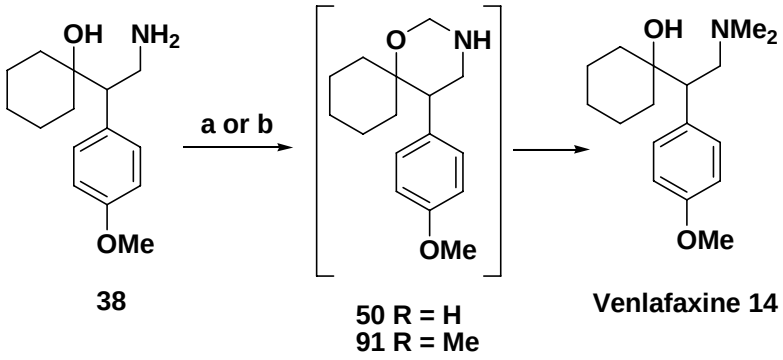
Hydrogenation of **37** using HCO_2NH_4 in the presence of Pd-C was not satisfactory. Catalytic hydrogenation with 5% Rh/Al_2O_3 gave a mixture of products. Reduction of **37** with $NH_2NH_2{\cdot}H_2O$ using Raney nickel gave aminoalcohol **38** in 60% yield. Catalytic hydrogenation of **37** using Raney nickel at 280 psi and 100 ºC in 20% NH_3 in MeOH gave only undesired amine **90** as a major product alongwith starting material **37**. When the reduction was carried out under neutral conditions in MeOH, under identical conditions 30-40% required amine **38**, and 50-60% starting material **37** was recovered back (scheme 15). Thus, novel conditions were developed, where usage of expensive catalyst was avoided and the reaction could be performed employing inexpensive catalyst.

Alternativley, while cyanoalcohol **37** was reduced with $LiAlH_4$ in THF at 10-15 ºC to obtain aminoalcohol **38** in 92% yields, $LiAlH_4$-$AlCl_3$ reduction gave almost quantitative yields!

IR spectrum of aminoalcohol **38** showed absorptions at 3362, 3294 cm^{-1} characteristic of OH and the NH_2 functionality. ^1H NMR spectrum of aminoalcohol **38** showed two doublets at δ 7.15 and 6.80, corresponding to four aromatic protons. The signal at δ 3.78 was assigned to O*Me*.

Total Synthesis of (±)-Venlafaxine

<u>*N,N*-dimethylation of aminoalcohol 38: completion of total synthesis</u>



Scheme 16. *Reagents and conditions:* a) 35% HCHO, 88% HCO_2H, MW, 5 min, poor yields; b) 35% HCHO, 88% HCO_2H, H_2O, reflux, overnight, 85%.

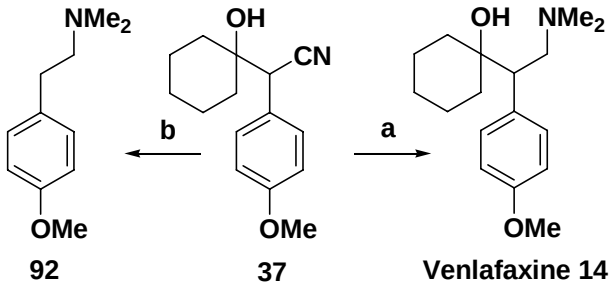
Finally, the *N,N*-dimethylation was accomplished *via* a modified Eschweiler-Clarke's procedure using 35% HCHO, 88% HCO_2H employing a large excess of water as illustrated by Tilford *et. al*. in 85% yields.[38] *N,N*-Dimethylation of aminoalcohol **38** was also carried out with microwave irradiation. When the reaction mixture was heated in a microwave oven at 100 ^oC for 2 minutes, a faster moving spot appeared on TLC along with venlafaxine **14**. The faster moving spot disappeared when reaction was continued for 2 more minutes, which is probably the the oxazine[22,23,26a] intermediate **50** (R = H) **or 91** (R = Me)**,** which was not isolated (scheme 16). The unoptimized yields were poor under microwave conditions and the method needs further investigation.

<u>One-pot synthesis of (±)-venlafaxine</u>[39]

Later, it was discovered that when catalytic hydrogenation of compound **37** was carried out using Raney nickel in the presence of formalin (35% aq. HCHO), venlafaxine **14** was obtained in 30% yield with 60% of the recovered starting material (scheme 17).

The venlafaxine free base **14** formed under these conditions can be separated simply by acid-base treatment and the starting material can be recycled. This makes the process attractive from industrial point of view. Sometimes, up to 74% venlafaxine **14** was obtained, but the results were not reproducible. Similarly, it was observed that when the reaction was carried out in 20% NH_3-MeOH system, cyanoalcohol **37** underwent retro-condensation and the resultant *p*-methoxyphenylacetonitrile was reduced to amine **90**,

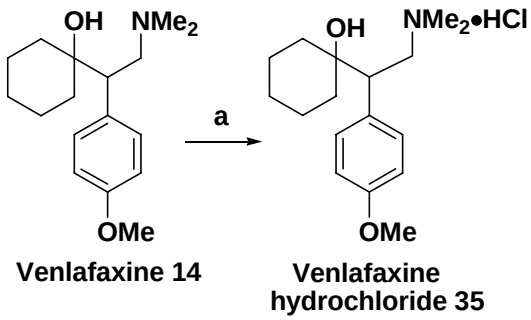
which underwent subsequent *N,N*-dimethylation to give amine **92** with the recovered starting material (scheme 17).



Scheme 17. *Reagents and conditions:* a) H_2 (280 psi), Raney Ni, 35% HCHO, MeOH, 100 ºC, 6 h, 30%; b) H_2 (280 psi), Raney Ni, 35% HCHO, NH_3-MeOH (20%), 100 ºC, 6 h, 30%.

Preparation of (±)-venlafaxine hydrochloride 35

Hydrochloride salt of the free venlafaxine base, **35** was prepared by dropwise addition of *i*PrOH saturated with HCl gas to a solution of venlafaxine free base in ethyl acetate (scheme 18). It was further crystallized from ethyl acetate.



Scheme 18. *Reagents and conditions:* a) 20% HCl (gaseous) in *i*PrOH, 92%.

IR spectrum of venlafaxine hydrochloride **35** showed absorptions at 3323, 3192 cm^{-1} indicating the presence of -*OH*. ^{1}H NMR spectrum of compound **35** showed a broad signal at δ 11.41 indicating H^+. Four protons in the aromatic region appeared at δ 7.13 and 6.83 as two doublets. A doublet that appeared at δ 4.07 was assigned to benzylic proton. A sharp singlet at δ 3.78 indicated the presence of O*Me*. N*Me*$_2$ protons appeared as two doublets at δ 2.82 and 2.63. Multiplets appearing at δ 3.11-3.35, 1.47-1.70, 0.84-1.29 corresponded to remaining 13 protons. ^{13}C NMR spectrum of compound **35** exhibited four signals at δ 158.7, 131.1, 130.1, 113.9 corresponding to six aromatic carbons. The signal at

δ 73.4 indicated the presence of quaternary carbon proximal to OH. The signal at δ 59.9 revealed CH_2NMe_2. The signal at δ 55.0 corresponded to OCH_3. The signal at δ 52.3 indicated benzylic carbon, while signals at δ 44.9 and 42.5 were due to the N-CH_3 carbons. Signals at δ 36.4, 31.2, 25.2, 21.4 and 21.0 corresponded to cyclohexyl ring carbons. MS spectrum of compound **35** showed signal at 277 corresponding to M-HCl.

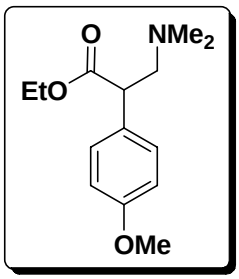
1.1.5.3. Conclusion

Key step of the synthesis i.e. condensation of *p*-methoxyphenylacetonitrile **36** with cyclohexanone **34** was achieved emplyoing mild and inexpensive bases like NaOH, KOH under phase transfer conditions in quantitative yields in aqueous medium! The step is highly efficient and simple to operate, does not require further purification of the intermediate cyanoalcohol. Another salient feature of the process is that the product is simply filtered off from the reaction mixture and dried in air. The intermediate formed is of very high purity and was used as such for further reaction. The protocol is generalized for many substituted acetonitriles and ketones. Again, novel conditions were developed where the usage of expensive catalyst like Rh/Al_2O_3 was avoided and the inexpensive and commercially available catalyst *viz.* Raney nickel was employed. Further, catalytic hydrogenation of the intermediate cyanoalcohol followed by subsequent *N,N*-dimethylation could be performed in one pot to obtain venlafaxine free base.

Thus, a highly efficient, practical, industrially, technically, ecologically viable and cost-effective process for multigram synthesis of venlafaxine has been developed obviating the use of hazardous and expensive reagents and chemicals. To the best of our knowlede this is the best synthesis of venlafaxine as of today! The process has been patented in different patent offices including India and US.

1.1.6. Experimental

Ethyl 3-(dimethylamino)-2-(4-methoxyphenyl)propanoate (65)



A mixture of ethyl *p*-methoxyphenylacetate **67** (4 g, 20.62 mmol), paraformaldehyde (1.05 g, 35.0 mmol) and TBAI (0.381 g, 1.03 mmol) was heated in PhMe (16 ml) at 80-85 ºC for 3.5 hours. The reaction mixture was allowed to cool. Then, a solution of Me_2NH in THF was added to the reaction mixture at 0 ºC in the presence of catalytic $FeCl_3$ (0.160 g, 0.001 mol) and stirred for 45 minutes. After completion of the reaction, 100 ml water was added to the reaction mixture and aqueous layer was acidified with conc. HCl (pH = 2). Aqueous layer was washed with DCM (3x 50 ml) and made alkaline (pH = 8) using 5% NaOH solution, extracted with DCM (3x 50 ml), washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatographic purification over silca gel (0.5% MeOH in $CHCl_3$) furnished aminoester **65** as a thick colourless oil (3.08 g).

When the reaction was carried out without catalyst, it took 48 hours for completetion.

Molecular formula : $C_{14}H_{21}NO_3$

Yield : 58%

IR ($CHCl_3$) : 3498, 3356, 3018, 2978, 1727, 1611, 1513, 1249, 1216, 1178, 758 cm^{-1}

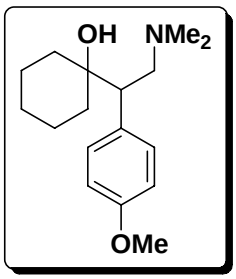
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.23 (d, *J*= 8.79 Hz, 2H), 6.83 (d, *J*= 8.79 Hz, 2H), 4.14 (m, 2H), 3.78 (s, 3H), 3.73 (dd, *J*= 5.37 Hz and 10.26 Hz, 1H), 3.01 (dd, *J*= 9.77 Hz, 12.21 Hz, 1H), 2.42 (dd, *J*= 5.37 Hz and 12.21 Hz, 1H), 2.27 (s, 6H), 1.22 (t, *J*= 7.33 Hz)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 172.4, 158.6, 129.4, 128.5, 113.7, 62.7, 59.8, 54.5, 49.3, 45.2, 13.8

MS (EI) *m/z* : 251 (M^+), 206, 162, 148, 133, 119, 101, 91, 77, 65, 58

Total Synthesis of (±)-Venlafaxine

Venlafaxine (14)



To a suspension of Mg (0.114 g, 4.75 mmol) in THF (2 ml) a solution of dibromopentane **66** (0.536 g, 2.33 mmol) in THF (2 ml) was added drop-wise at 0-5 ºC. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. Again, the reaction mixture was cooled to 0-5 ºC and a solution of amino ester **39** (0.45 g, 1.79 mmol) in THF (5 ml) was added to it drop-wise. After the addition, the reaction mixture was first allowed to come to room temperature within 0.5 hour and then refluxed for 3.5 hours. The reaction mixture was allowed to cool and 50% aq. NaOH solution was added to the reaction mixture (pH = 12), extracted with ethyl acetate (50 ml x 2), washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% MeOH in $CHCl_3$) to furnish venlafaxine **14** as a colourless solid (0.25 g).

Molecular formula : $C_{17}H_{27}NO_2$

Yield : 50%

Mp : 74-76 ºC

IR ($CHCl_3$) : 3164, 2982, 2938, 2860, 2832, 2782, 1610, 1512, 1465, 1445, 1277, 1246, 1217, 1180, 1039, 755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.03 (d, *J*= 8.79 Hz, 2H), 6.79 (d, *J*= 8.79 Hz, 2H), 3.79 (s, 3H), 3.28 (t, *J*= 12.20 Hz, 1H), 2.93 (dd, *J*= 2.93 Hz and 12.20 Hz, 1H), 2.33 (s, 6H), 2.28 (dd, *J*= 3.42 Hz and 12.70 Hz, 1H), 1.23-1.27 (m, 8H), 0.83-1.00 (m, 2H)

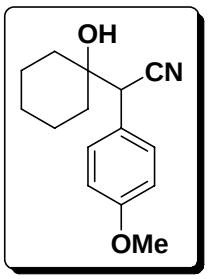
^{13}C NMR (50 MHz, $CDCl_3$) : δ 157.7 (C), 132.0 (C), 129.4 (CH), 112.7 (CH), 73.4 (C), 60.7 (CH_2), 54.3 (CH_3), 51.2 (CH), 44.8 (CH_3), 37.5 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 21.0 (CH_2), 20.7 (CH_2).

MS (EI) *m/z* : 277 (M^+), 258, 219, 179, 162, 134, 119, 99, 91, 81

Analysis : Calculated for C-73.61, H-9.81, N-5.05; found; C-73.49, H-9.55, N-4.82

Total Synthesis of (±)-Venlafaxine

2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl) acetonitrile (37)



A mixture of *p*-methoxyphenylacetonitrile **36** (100 g, 0.68 mol), 10% aqueous NaOH solution (100 ml, 0.25 mol) and $TBAHSO_4$ (5 g, 0.014 mol) was stirred at room temperature for 30 minutes. A dark red colour appeared. To this was added cyclohexanone **34** (67 g, 0.680 mol) in small portions at 0 ºC, with vigorous stirring, in such a way that temperature should not rise above 10 ºC. A white solid was formed within 30 minutes to one hour. The solid was crushed and the reaction mixture was further stirred vigorously at room temperature for one more hour. The solid was filtered, washed with water till neutral to pH paper and air-dried. Crystallization from ethyl acetate-petroleum ether (500:350, v/v) gave a bright white solid (161.66 g).

Molecular formula : $C_{15}H_{19}NO_2$

Yield : 97%

Mp : 126-7 ºC

IR (Nujol) : 3492, 3406, 2924, 2855, 2241, 1614, 1456, 1377, 1254, 982, 833, 789 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.26 (d, *J*= 8.61 Hz, 2H), 6.89 (d, *J*= 8.61 Hz, 2H), 3.81(s, 3H), 3.71 (s, 1H), 1.51-1.75 (m, 10H), 1.17 (bs, 1H)

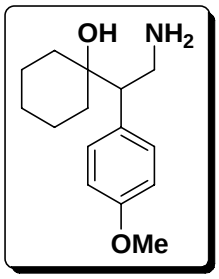
^{13}C NMR (50 MHz, $CDCl_3$) : δ 159.6 (C), 130.6 (C), 123.6 (CH), 119.8 (CN), 114.0 (CH), 72.6 (C), 55.2 (CH_3), 49.2 (CH), 34.8 (CH_2), 25.1 (CH_2), 21.4 (CH_2).

MS (EI) *m/z* : 245 (M^+), 147, 132, 116, 99, 91, 81, 65, 55.

Analysis : Calculated for C-73.44, H-7.81, N-5.71 found C-73.24, H-7.52, N-5.32

Total Synthesis of (±)-Venlafaxine

1-(2-Amino-1-(4-methoxyphenyl)ethyl) cyclohexanol (38)



To a mechanically stirred solution of $AlCl_3$ (103.60 g, 0.779 mol) in THF (900 ml), at 0 ºC, $LiAlH_4$ (59.80 g, 1.575 mol) was added cautiously, in portions. Temperature was maintained below 10 ºC. A solution of cyanoalcohol **37** (130.0 g, 0.530 mol) in THF (500 ml) was added drop-wise over a period of 1.5 hours. The reaction mixture was then brought to room temperature and stirred for 30 minutes. The reaction mixture was again cooled in an ice-salt bath. The reaction was quenched with ethyl acetate (60 ml) maintaining the temperature below 10 ºC. The reaction mixture was then transferred to a beaker, cooled externally in an ice-salt bath and treated very cautiously with 25% aq. NaOH solution (360 ml) with mechanical stirring. (After addition of about 50 ml 25% aq. NaOH solution, a hard solid was formed, cooling was removed and the contents were stirred manually during the addition of remaining NaOH solution). The solid was loosened at room temperature, which was further stirred for 1 hour. A bright white solid appeared. The solid was filtered off, washed thoroughly with ethyl acetate. The filtrate was concentrated *in vacuo* and combined with the above washings, washed with brine, dried over anhydrous Na_2SO_4, filtered and ethyl acetate removed under reduced pressure to obtain aminoalcohol **38** as a thick yellow oil (129.4 g).

Molecular formula : $C_{15}H_{23}NO_2$

Yield : 98%

IR (Neat) : 3362, 3294, 2931, 2855, 1601, 1584, 1509, 1455, 1295, 1178, 1034, 968, 832, cm^{-1}

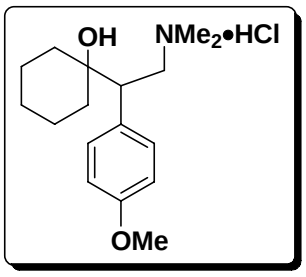
^{1}HNMR (200 MHz, $CDCl_3$) : δ 7.15 (d, *J*= 8.59 Hz, 2H), 6.80 (d, *J*= 8.59 Hz, 2H), 3.78 (s, 3H), 3.11-3.32 (m, 2H), 2.66 (t, *J*= 6.57 Hz, 4H), 1.42-1.75 (m, 7H), 1.00-1.30 (m, 3H)

<u>*N,N*-Dimethylation of aminoalcohol (38)</u>

A mixture of aminoalcohol **37** (132 g, 0.53 mol), 35% formalin (120 ml, 1.26 mol), 88% formic acid (312 ml, 7.3 mol) and water (1350 ml, 75 mol) was refluxed for 24 hours. The reaction mixture was allowed to cool and extracted with ethyl acetate (3x 500 ml). The aqueous layer was made alkaline with 40% aq. NaOH solution saturated with NaCl and extracted with ethyl acetate (4x 500 ml). The combined organic extracts were washed with

chilled water (2x 300 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford venlafaxine **14** as a thick colourless liquid, which solidified upon standing (121.88 g, 83% yield).

1-(2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl) cyclohexanol hydrocloride (35)



Venlafaxine **14** (92.4 g) was dissolved in ethyl acetate (450 ml) at 50-55 ºC, filtered hot then cooled to 10-15 ºC and pH was adjusted to <2 with addition of isopropyl alcohol saturated with HCl gas and allowed to stand for 15 minutes. The white solid was filtered off, washed with EtOAc (75 ml), and then with petroleum ether (150 ml). The crystalline salt was dissolved in MeOH (160 ml) at 50-55 ºC and filtered when hot. The hydrochloride salt **35** was precipitated by adding ethyl acetate drop-wise, at room temperature. After 4 hours the solid was filtered and washed with ethyl acetate (100 ml). The solid (98.3 g) was allowed to dry in air (6-8 hours).

Molecular formula **:** $C_{17}H_{28}ClNO_2$

Yield **:** 94%

Mp : 219-220 ºC

IR (Nujol) : 3323, 3192, 3045, 2922, 2853, 2586, 2522, 2466, 1612, 1512, 1464, 1443, 1242, 1178, 1038, 970, 829, 817, 770, 735 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 11.41 (bs, 1H), 7.13 (d, *J*= 8.71 Hz, 2H), 6.83 (d, *J* = 8.71 Hz, 2H), 4.07 (d, *J*= 12.89 Hz, 1H), 3.78 (s, 3H), 3.11-3.35 (m, 3H), 2.82 (d, *J*= 4.93 Hz, 3H), 2.63 (d, *J*= 4.93 Hz, 3H), 1.47-1.70 (m, 7H), 0.84-1.29 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 158.7 (C), 131.1 (C), 130.1 (CH), 113.9 (CH), 73.4 (C), 59.9 (CH_2), 55.0 (CH_3), 52.3 (CH), 44.9 (CH_3), 42.5 (CH_3), 36.4 (CH_2), 31.2 (CH_2), 25.2 (CH_2), 21.4 (CH_2), 21.0 (CH_2)

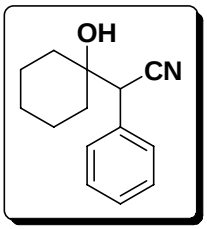
MS (EI) *m/z* **:** 277 (M-HCl), 275, 259, 214, 120

Total Synthesis of (±)-Venlafaxine

<u>One-pot preparation of (±)-venlafaxine</u>

Cycloalkanol **37** (5 g, 0.02 mol) was subjected to hydrogenation (200 psi) using Raney nickel (0.75 g) in an autoclave reactor in MeOH (100 ml) in the presence of formalin (35% solution 25 ml) at 60 ºC for 6 hours. The reaction mixture was allowed to cool and filtered. The catalyst was thoroughly washed with MeOH. The combined filtrate was concentrated under reduced pressure to afford an oily residue, which was then dissolved in ethyl acetate and washed with 10% aq. HCl. The aqueous layer was washed with ethyl acetate, basified using 10% aq. NaOH solution saturated with NaCl, and extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish a bright white solid (1.69g, 30%). The first ethyl acetate fraction after washing with water, brine, drying over anhydrous Na_2SO_4, filtered and concentration under reduced pressure returned unreacted **37** (3 g, 60%).

2-(1-Hydroxycyclohexyl)-2-phenyl acetonitrile (69)



Molecular formula : $C_{14}H_{17}NO$

Yield : 87%

Mp : 101-2 ºC

IR ($CHCl_3$) : 3450, 3019, 2937, 2859, 2242, 1602, 1494, 1455, 1216, 1151, 1080, 980, 758, 668 cm^{-1}

^{1}H MNR (200 MHz, $CDCl_3$) : δ 7.36 (s, 5H), 3.79 (s, 1H), 1.53-1.76 (m, 10H), 1.17 (bs, 1H)

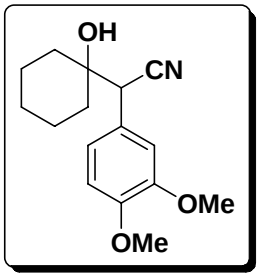
^{13}C NMR (50 MHz, $CDCl_3$) : δ 131.7, 129.4, 128.4, 128.2, 119.6, 72.6, 49.0, 34.8, 34.6, 25.0, 21.3

MS (EI) m/z : 215 (M^+), 177, 149, 130, 122, 99, 89, 81, 79, 67, 61, 55

Analysis : Calculated for $C_{14}H_{17}NO$; C-78.10, H-7.96, N-6.51 found C-78.32, H-8.06, N-6.38

Total Synthesis of (±)-Venlafaxine

2-(3,4-Dimethoxyphenyl)-2-(1-hydroxycyclohexyl) acetonitrile (71)



Molecular formula : $C_{16}H_{21}NO_3$

Yield : 95%

Mp : 134-5 ºC

IR ($CHCl_3$) : 3415, 3019, 2936, 2857, 2249, 1600, 1514, 1453, 1253, 1026, 757 cm^{-1}

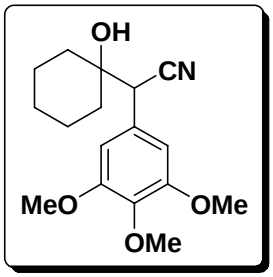
^{1}H MNR (200 MHz, $CDCl_3$) : δ 6.81 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.70 (s, 1H), 1.89 (s, 1H), 1.49-1.55 (m, 9H), 1.15 (bs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 148.9, 148.6, 123.9, 127.8, 119.7, 112.3, 110.7, 72.5, 55.7, 49.4, 34.8, 34.7, 25.0, 21.3

MS (EI) *m/z* : 275 (M^+), 257, 242, 224, 189, 177, 162, 131, 99, 90, 81, 69, 63

Analysis : Calculated for $C_{16}H_{21}NO_3$; C-69.79, H-7.69, N-5.09 found C-70.15, H-7.49, N-5.15

2-(1-Hydroxycyclohexyl)-2-(3,4,5-trimethoxyphenyl) acetonitrile (73)



Molecular formula : $C_{17}H_{23}NO_4$

Yield : 90%

Mp : 156-8 ºC

IR ($CHCl_3$) : 3473, 2943, 2854, 2239, 1596, 1511, 1466, 1424, 1331, 1247, 1152, 985, 863, 710, 680, 668, cm^{-1}

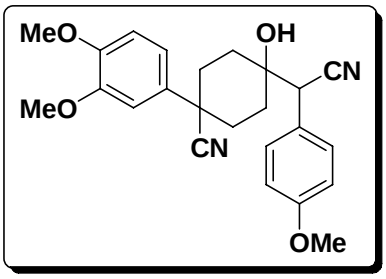
^{1}H MNR (200 MHz, $CDCl_3$) : δ 6.53 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.67 (s, 1H), 1.77 (bs, 2H), 1.55-1.66 (m, 8H), 1.19 (bs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 153.2, 138.2, 127.1, 119.4, 116.8, 72.7, 60.7, 56.2, 50.3, 35.1, 34.9, 25.2, 21.6

Analysis : Calculated for $C_{17}H_{23}NO_4$; C-66.86, H-7.59, N-4.59 found C-66.69, H-7.37, N-4.24

Total Synthesis of (±)-Venlafaxine

4-(Cyano(4-methoxyphenyl)methyl)-1-(3,4-dimethoxyphenyl)-4-hydroxycyclohexanecarbonitrile (80)



Molecular formula : $C_{24}H_{26}N_2O_4$

Yield : 56%

Mp : 148-152 ºC

IR (Nujol) : 3406, 2925, 2855, 2240, 1611, 1516, 1462, 1377, 1250, 1026, 838, 768 cm^{-1}

^{1}H MNR (200 MHz, $CDCl_3$): δ 7.30 (d, *J*= 8.72 Hz, 2H), 6.82-6.97(m, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.81 (s, 1H), 1.93-2.27 (m, 6H), 1.72 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 149.1, 148.8, 132.5, 130.5, 122.8, 121.9, 119.0, 117.5, 114.4, 111.2, 109.0, 71.0, 56.0, 55.9, 55.3, 49.4, 43.2, 33.2, 32.4, 32.3, 32.2

Analysis : Calculated for $C_{24}H_{26}N_2O_4$; C-70.92, H-6.45, N-6.89 found C-70.59, N-6.39, H-6.65

Spectra

1.1.6 References

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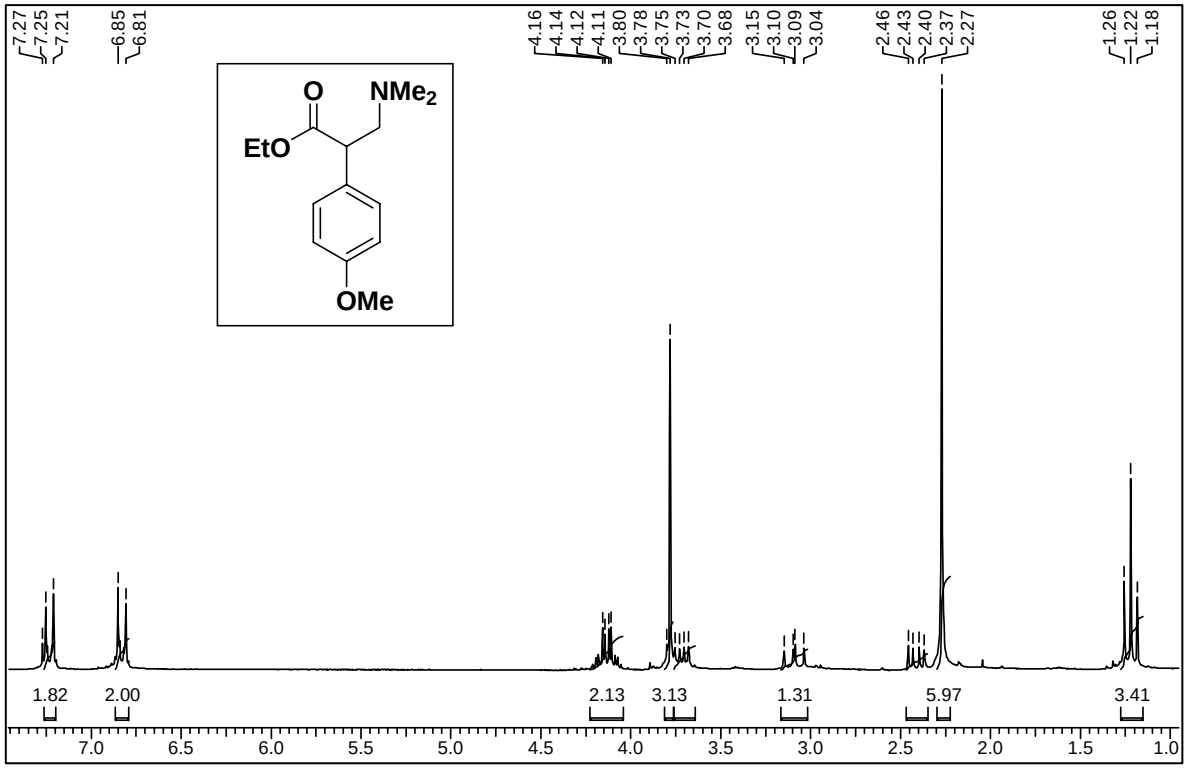
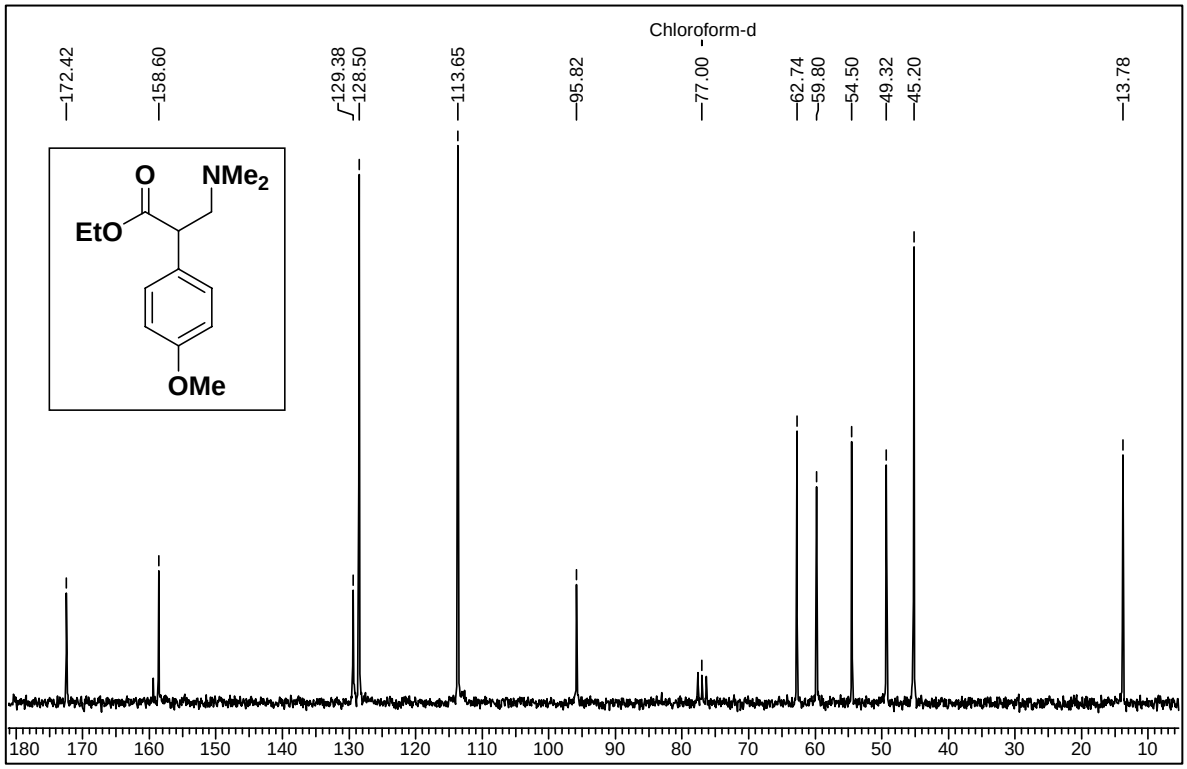
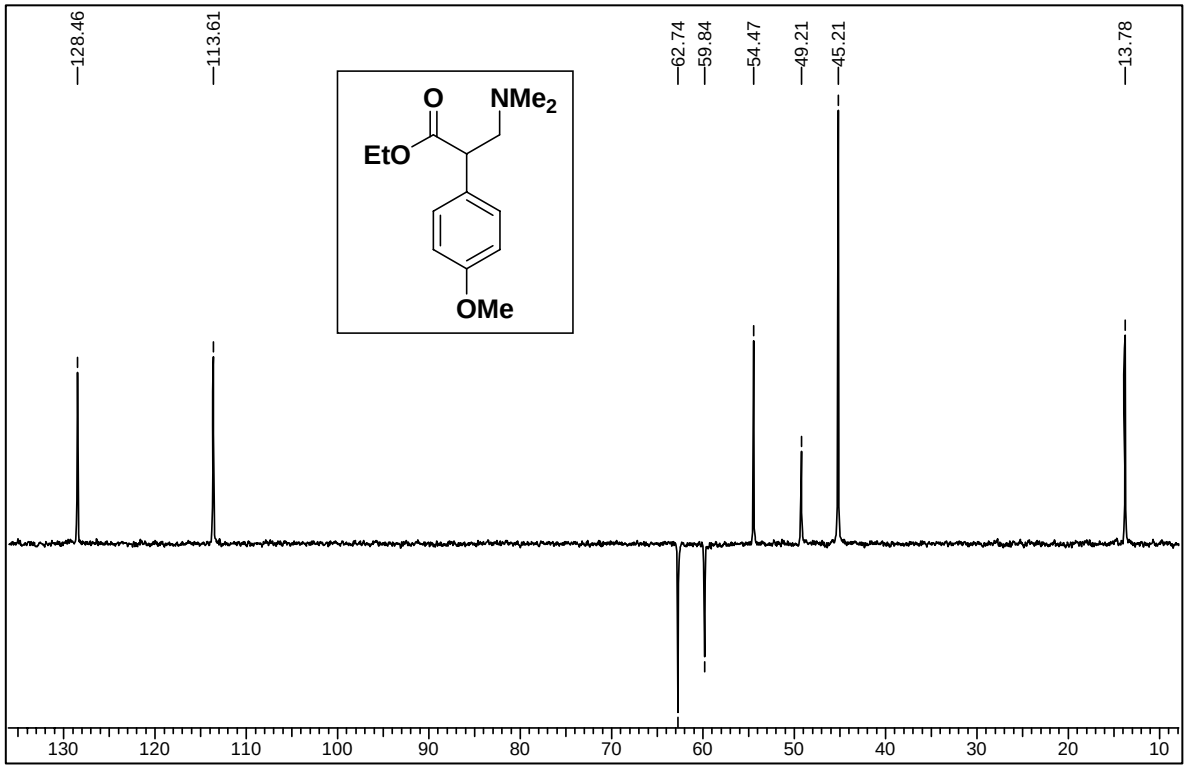


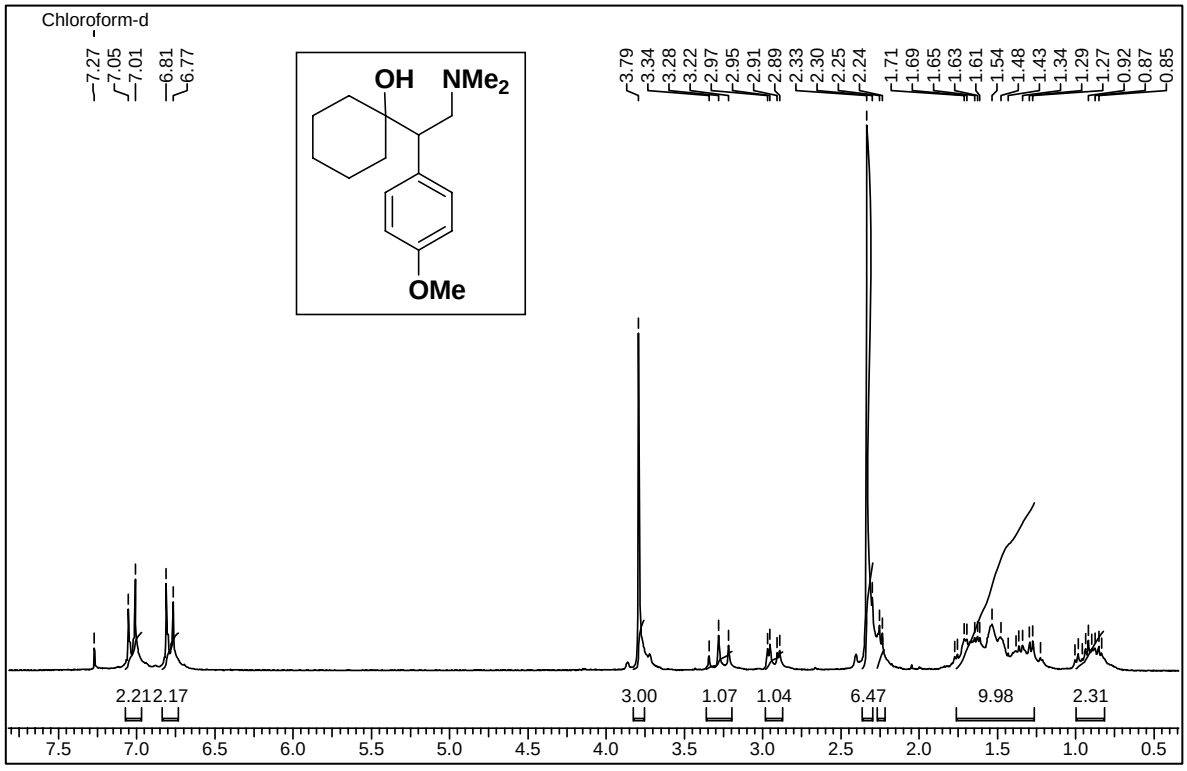
^{1}H NMR Spectrum of Compound 65 (200 MHz, $CDCl_3$)



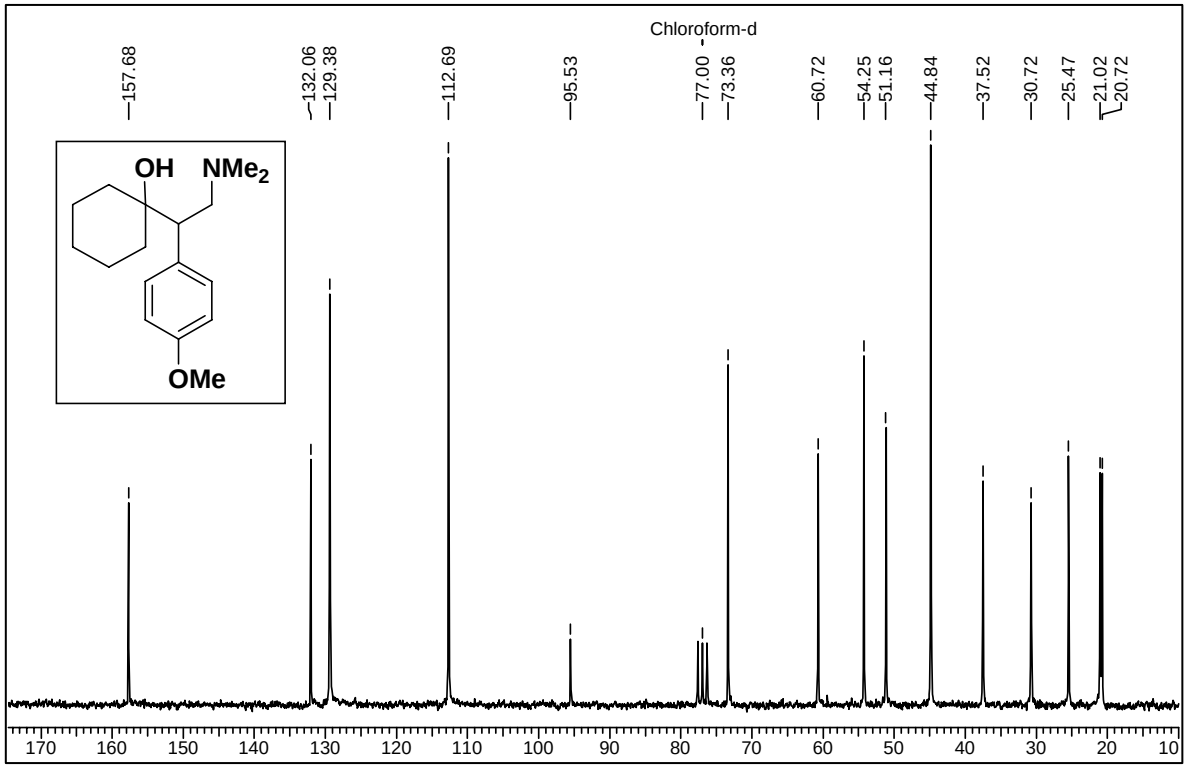
^{13}C NMR Spectrum of Compound 65 (50 MHz, $CDCl_3$ + CCl_4)



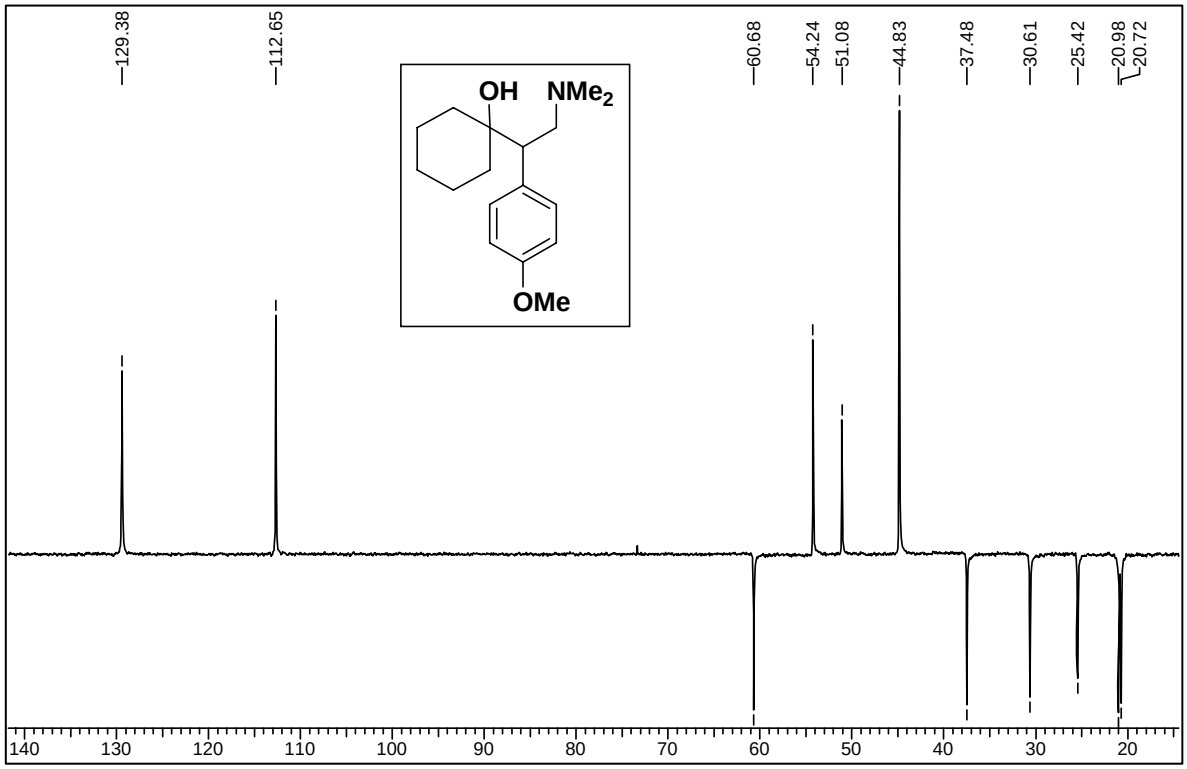
DEPT NMR Spectrum of Compound 65 (50 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR Spectrum of Venlafaxine 14 (200 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Venlafaxine 14 (50 MHz, $CDCl_3$ + CCl_4)



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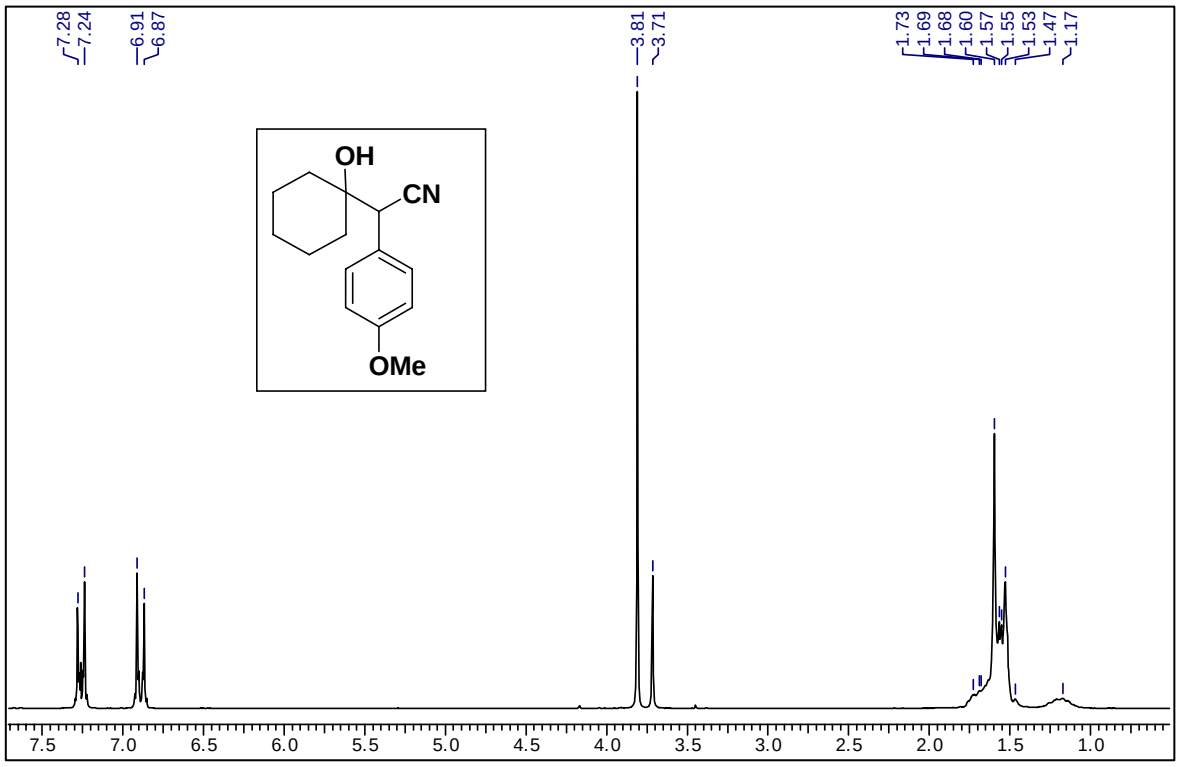

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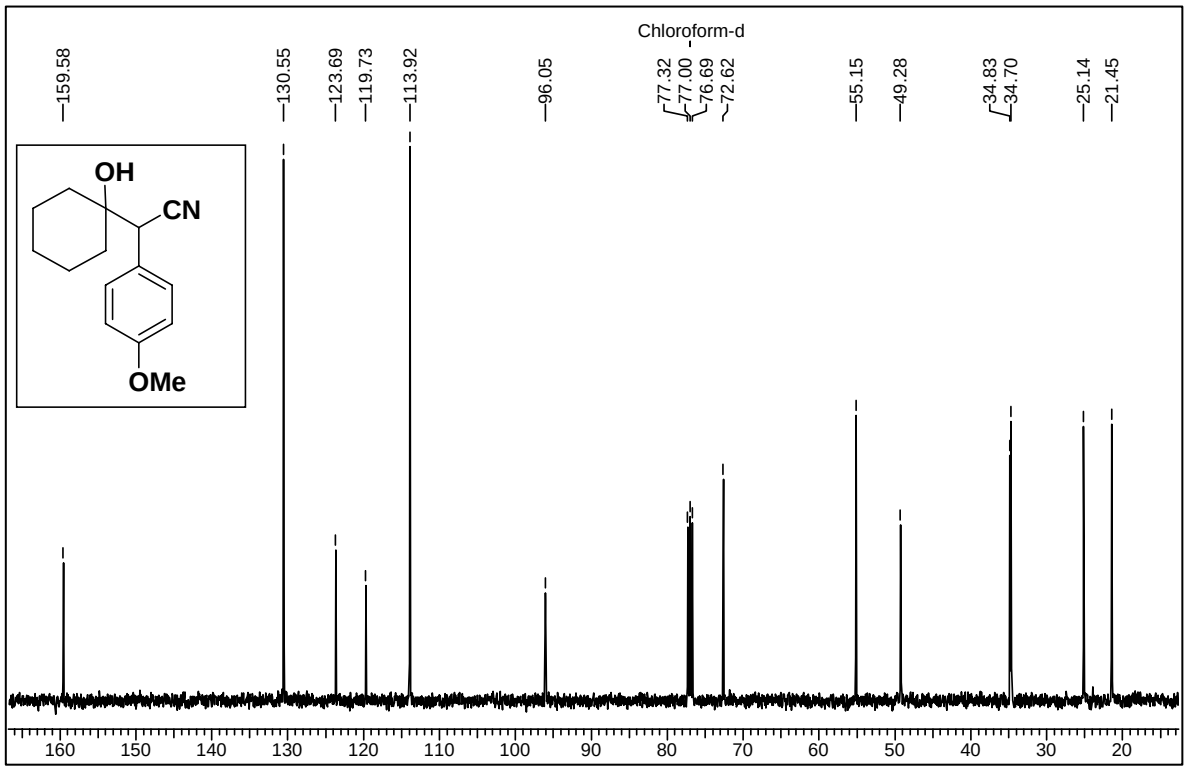
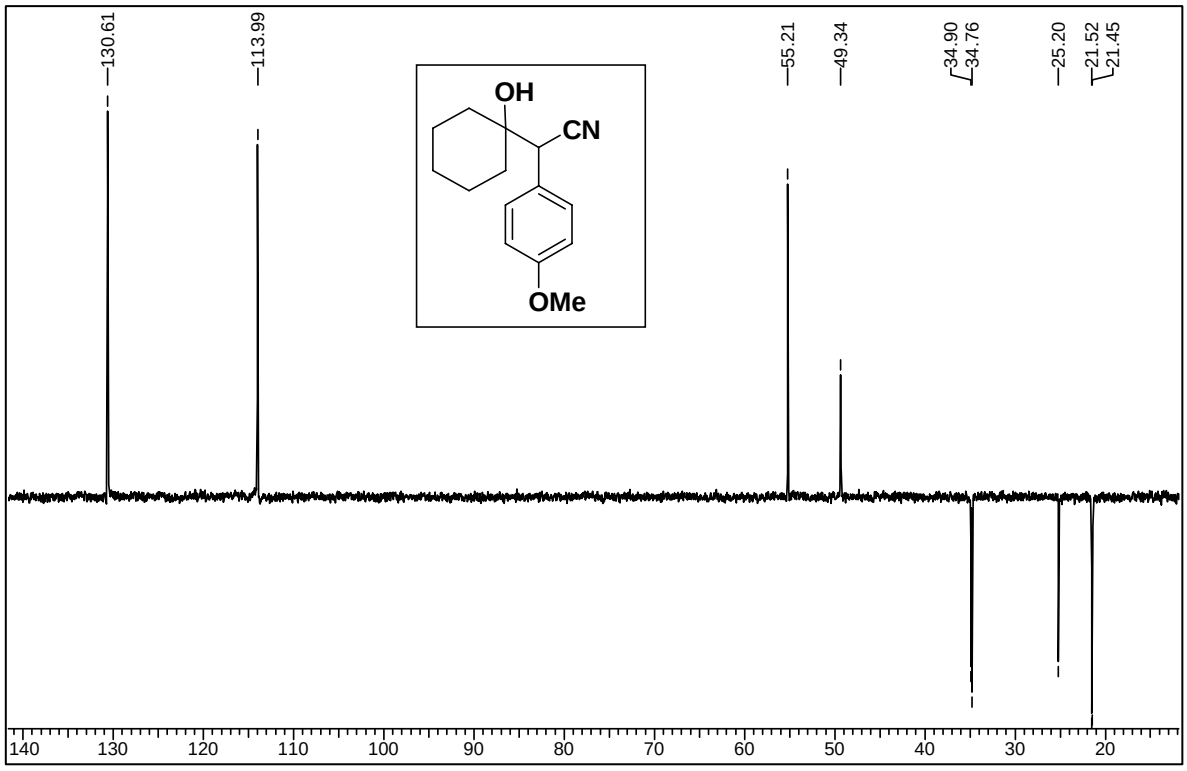
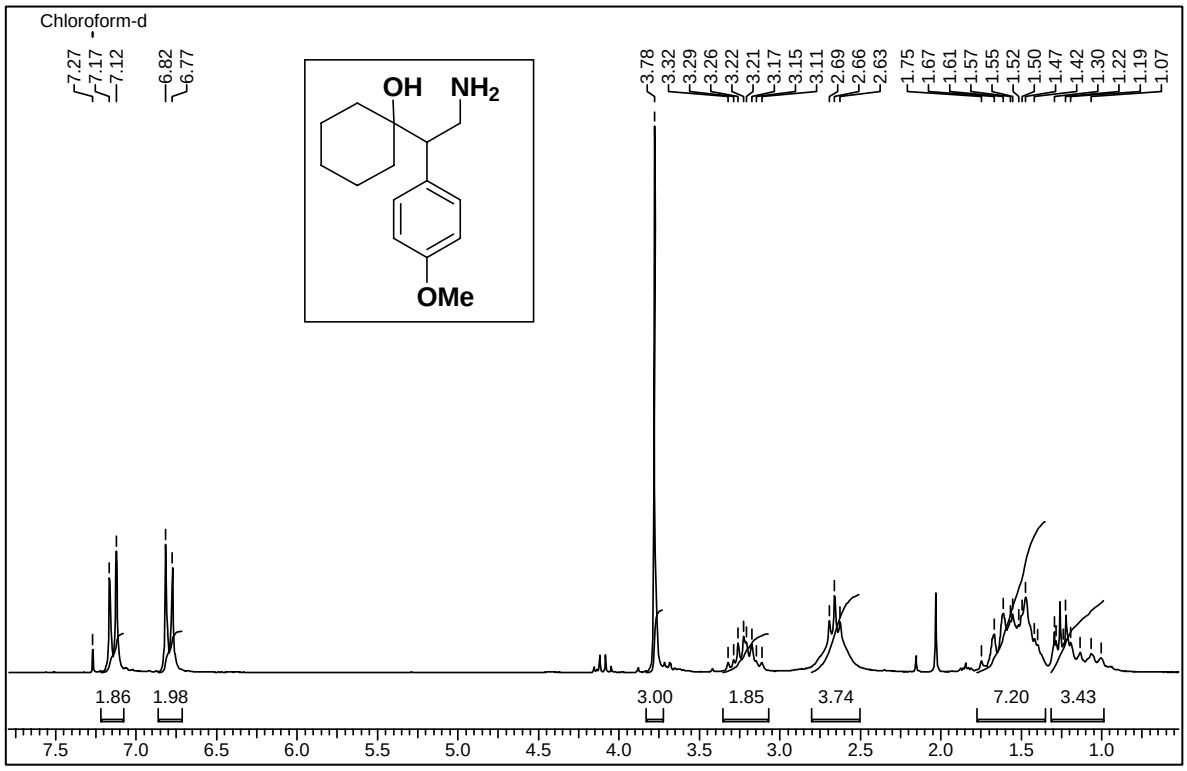


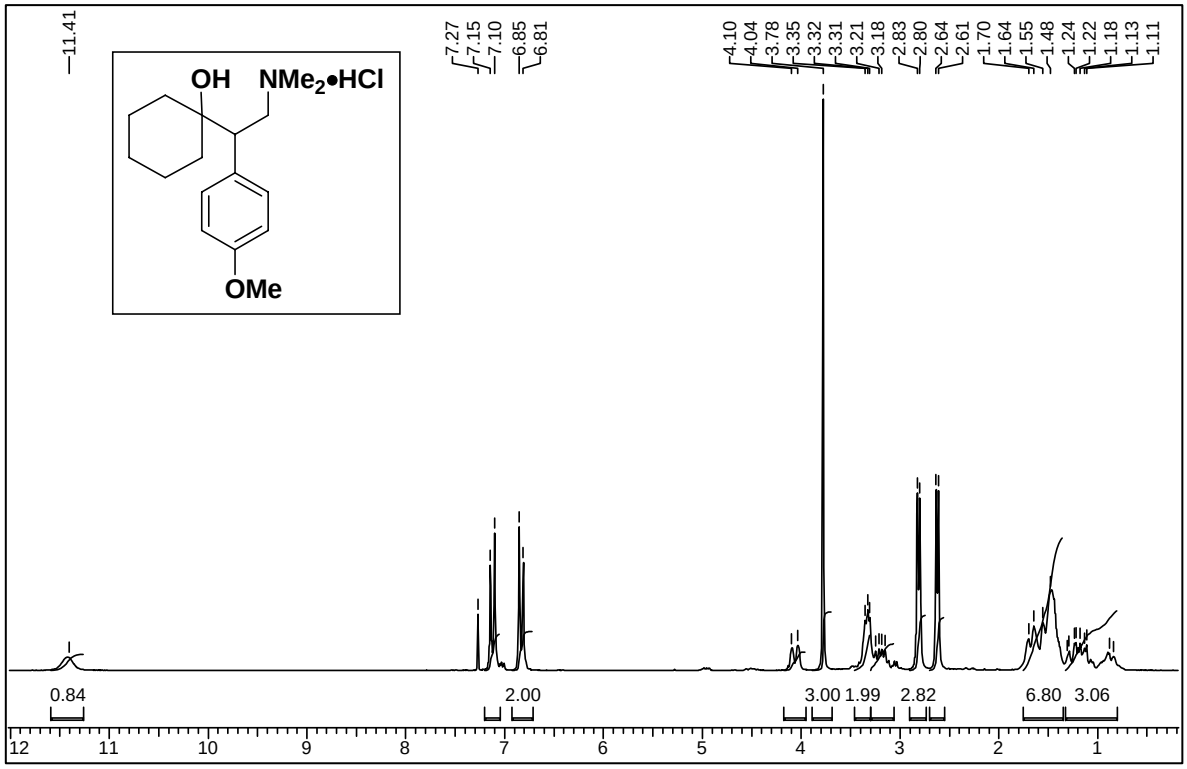
^{13}C NMR Spectrum of Compound 37 (200 MHz, $CDCl_3$ + CCl_4)



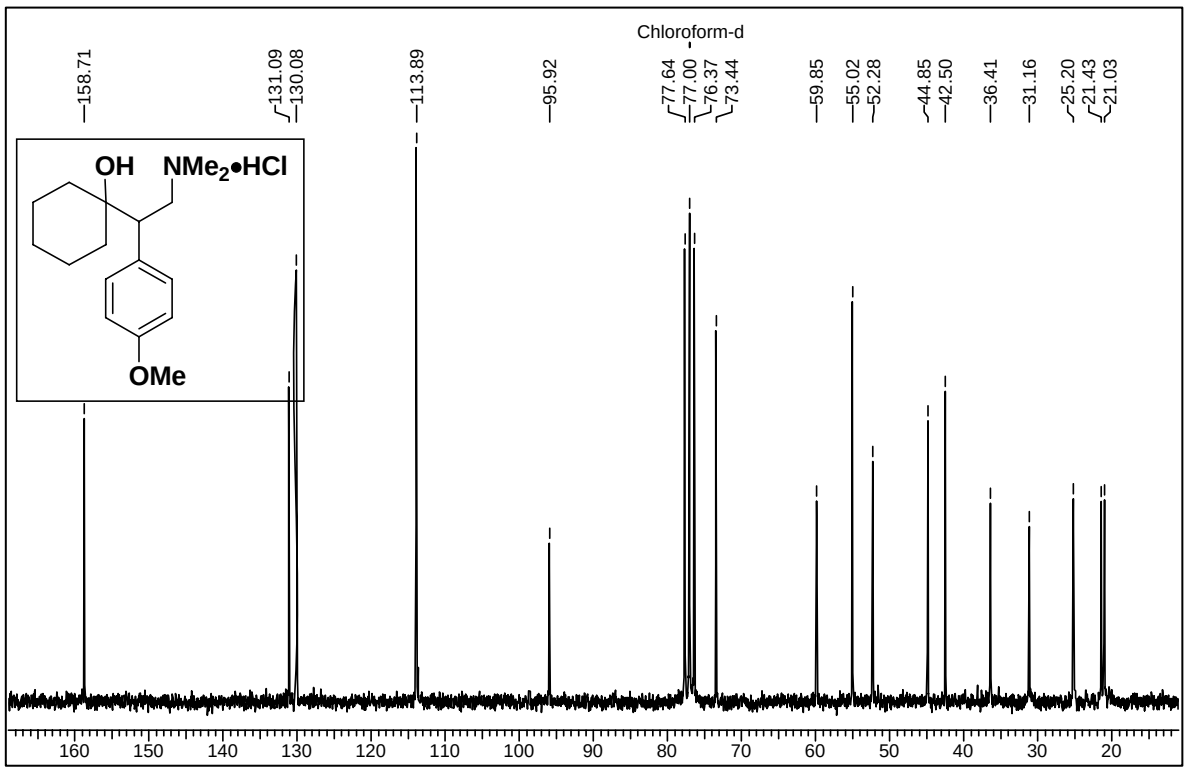
DEPT NMR Spectrum of Compound 37 (50 MHz, $CDCl_3$ + CCl_4)



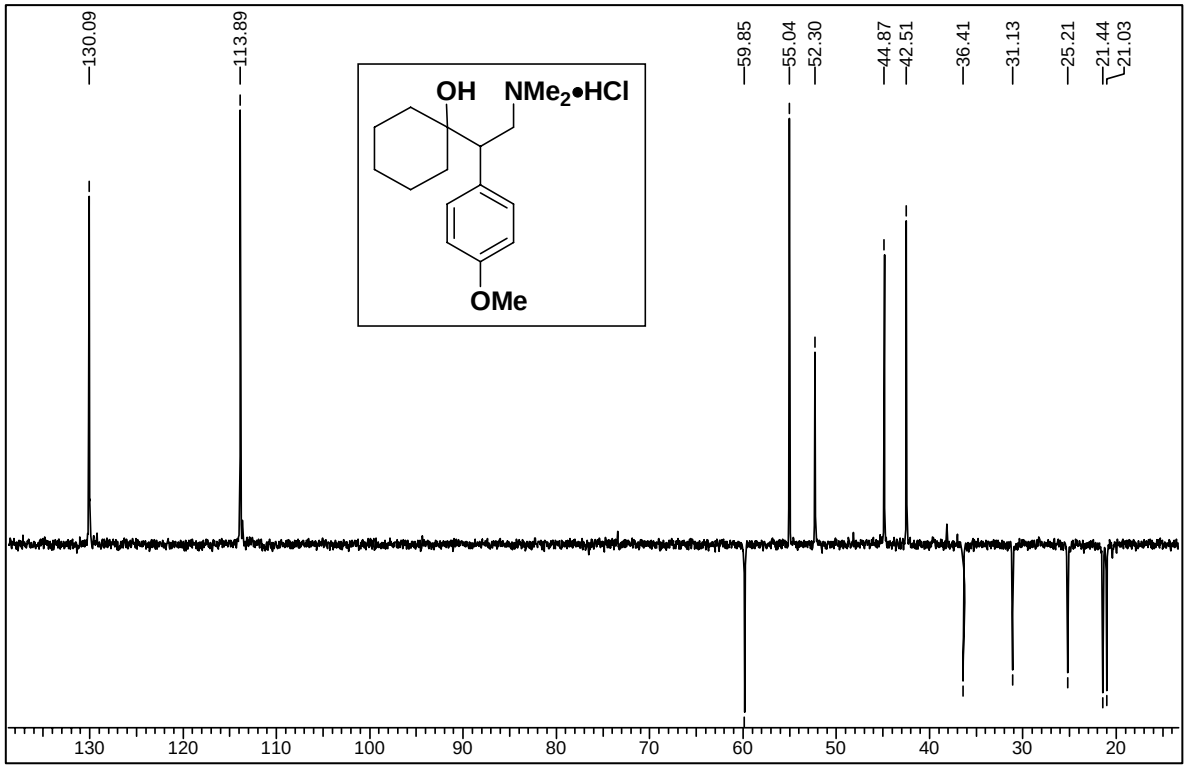
^{1}H NMR Spectrum of Compound 38 (50 MHz, $CDCl_3$)



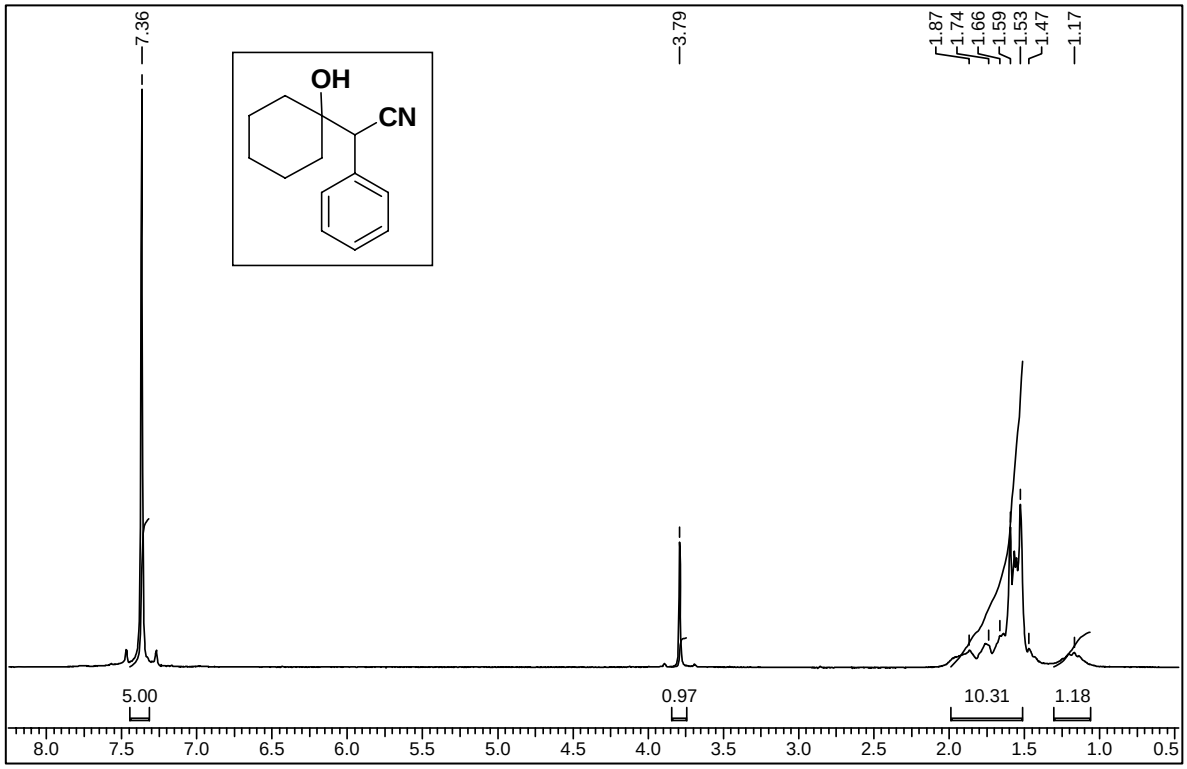
^{1}H NMR Spectrum of Compound 35 (50 MHz, $CDCl_3$)



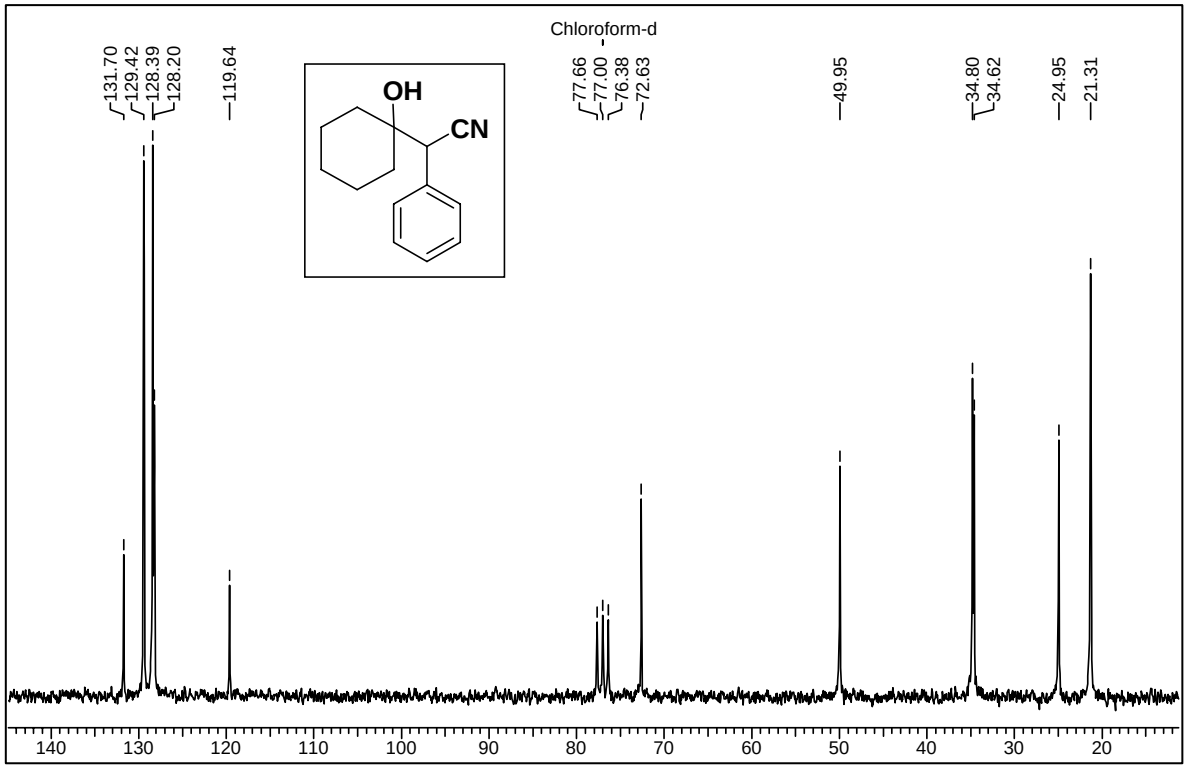
^{13}C NMR Spectrum of Compound 35 (50 MHz, $CDCl_3$ + CCl_4)



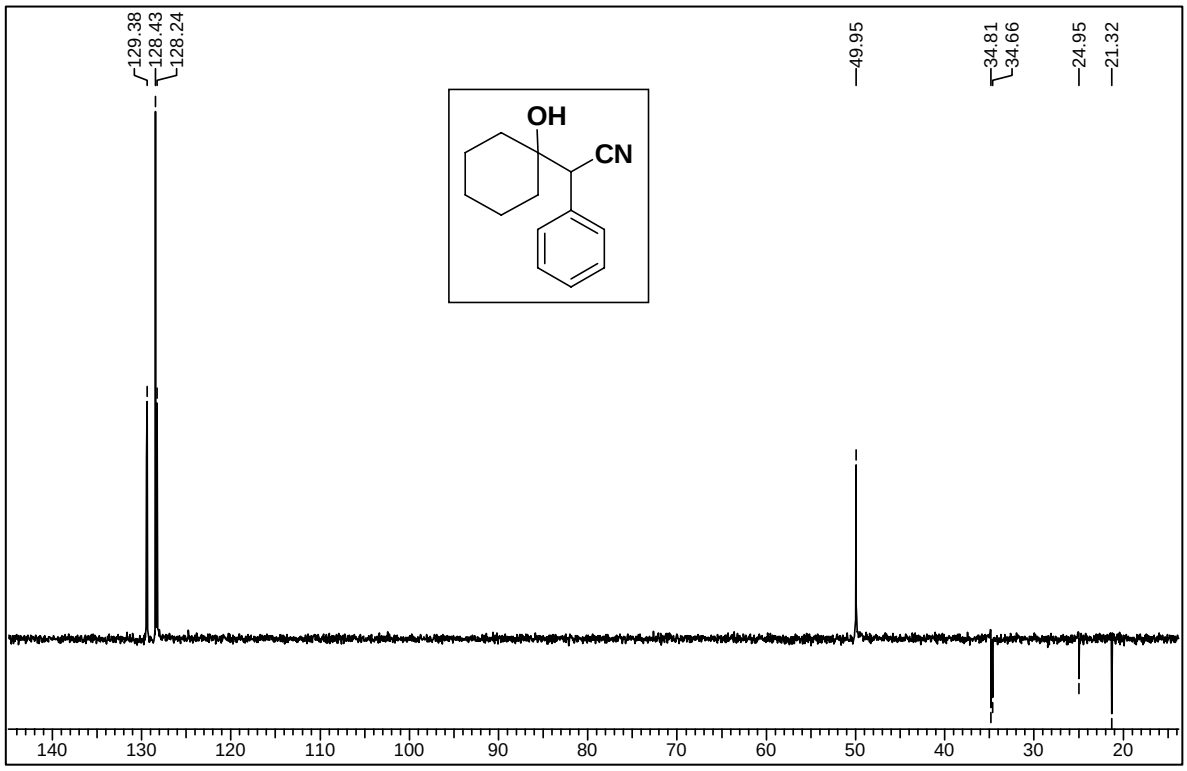
DEPT NMR Spectrum of Compound 35 (50 MHz, $CDCl_3$ + CCl_4)



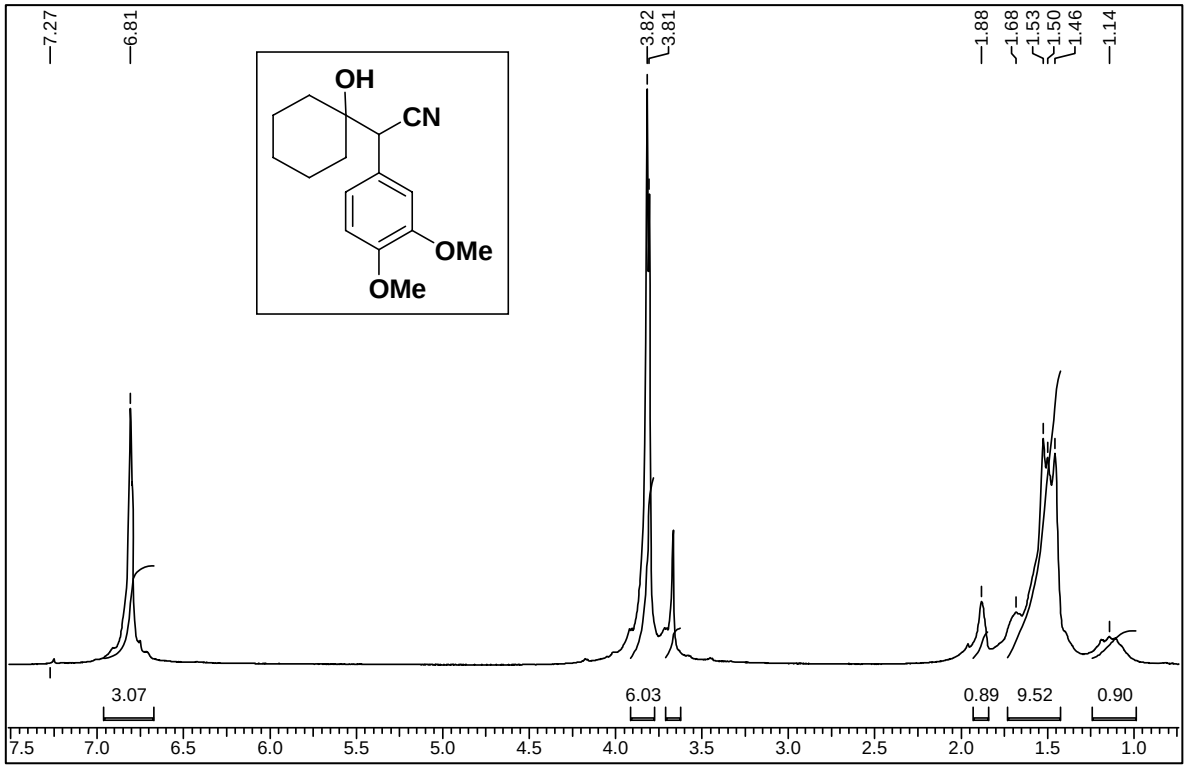
^{1}H NMR Spectrum of Compound 69 (50 MHz, $CDCl_3$)



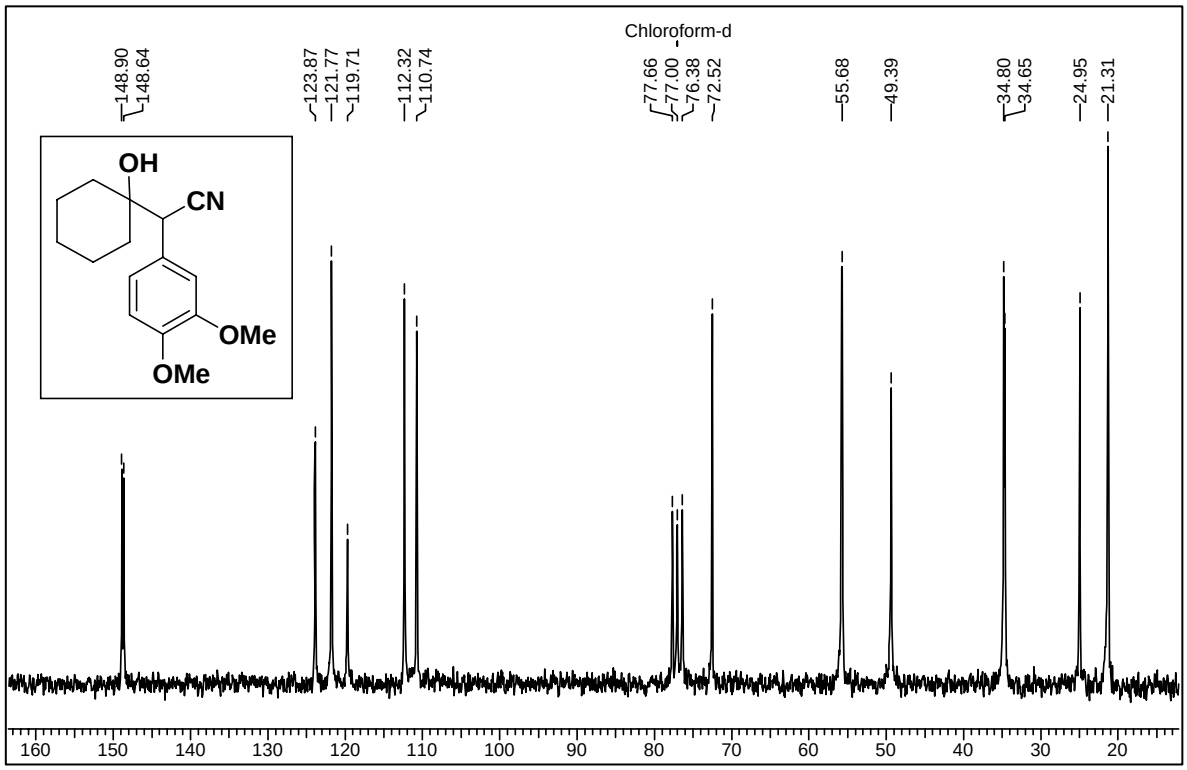
^{13}C NMR Spectrum of Compound 69 (50 MHz, $CDCl_3$)



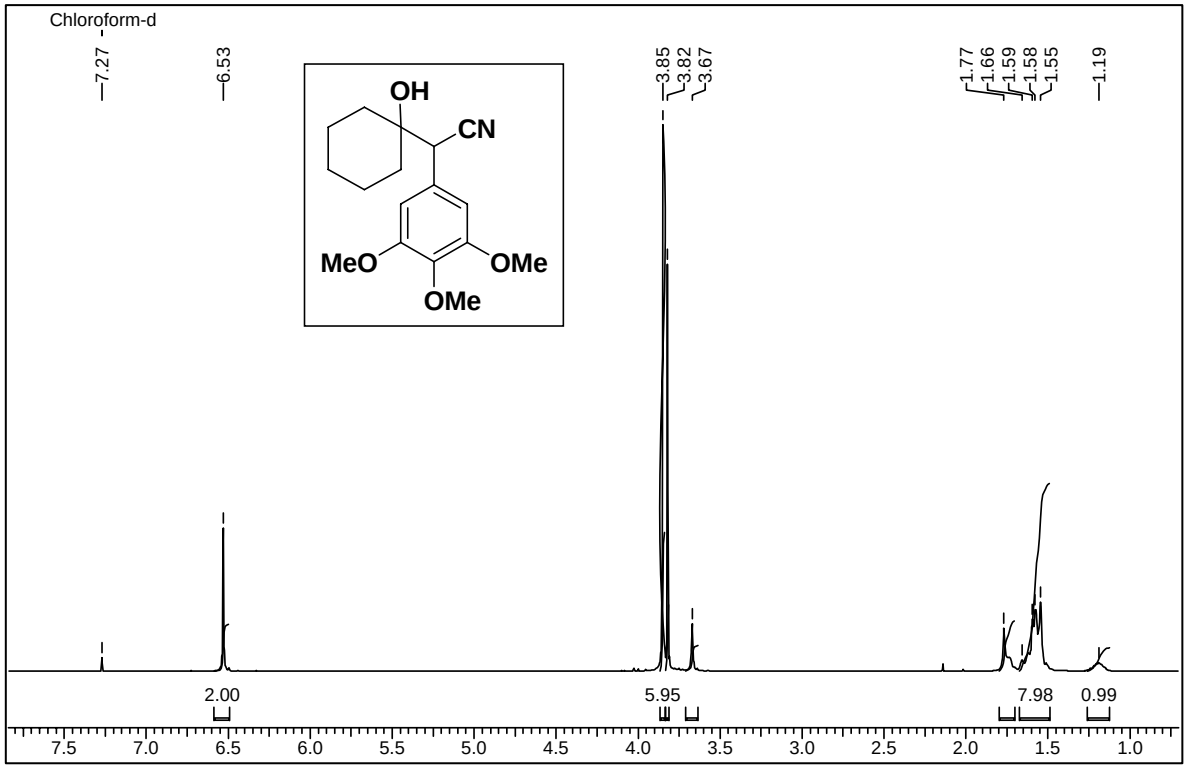
DEPT NMR Spectrum of Compound 69 (50 MHz, $CDCl_3$ + CCl_4)



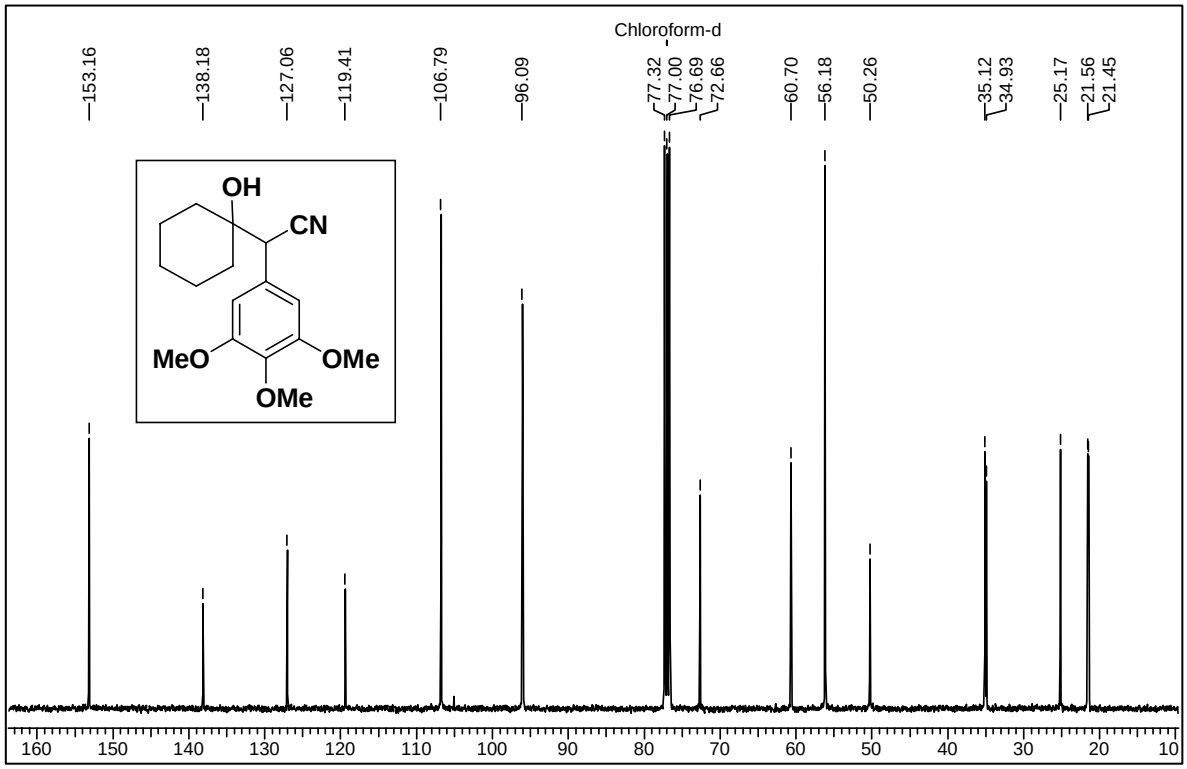
^{1}H NMR Spectrum of Compound 71 (50 MHz, $CDCl_3$)



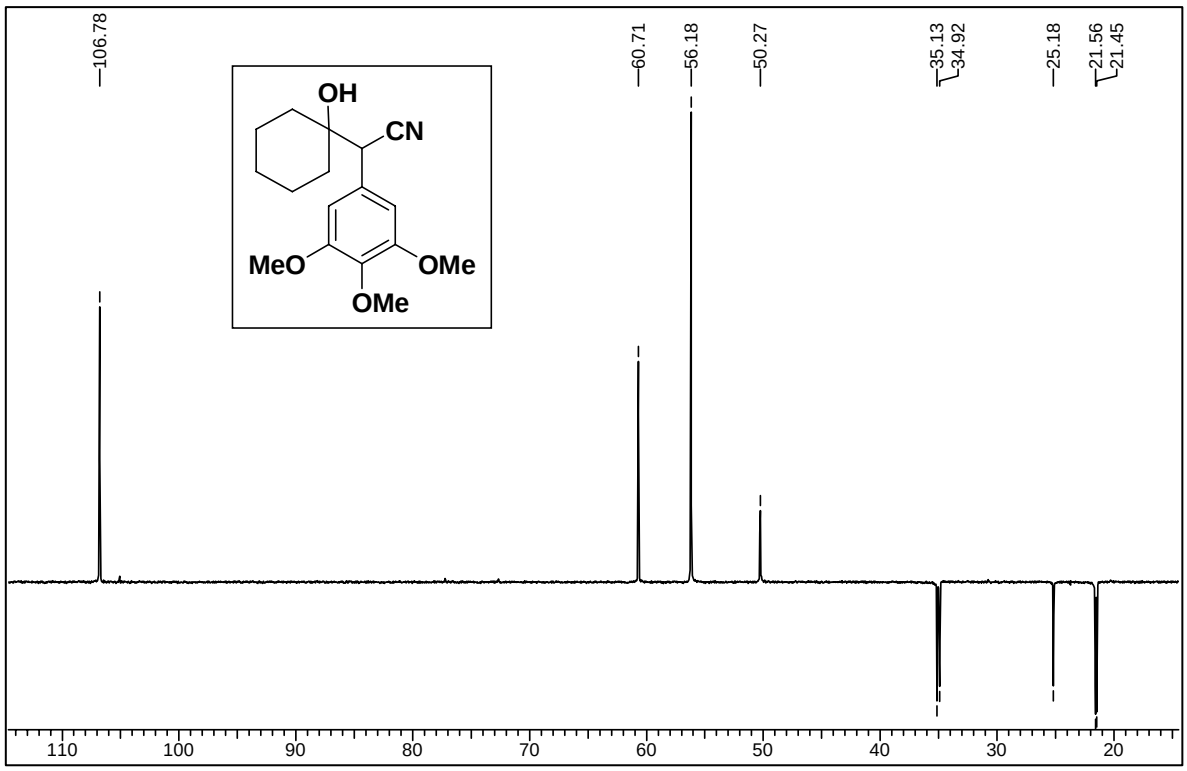
^{13}C NMR Spectrum of Compound 71 (50 MHz, $CDCl_3$)



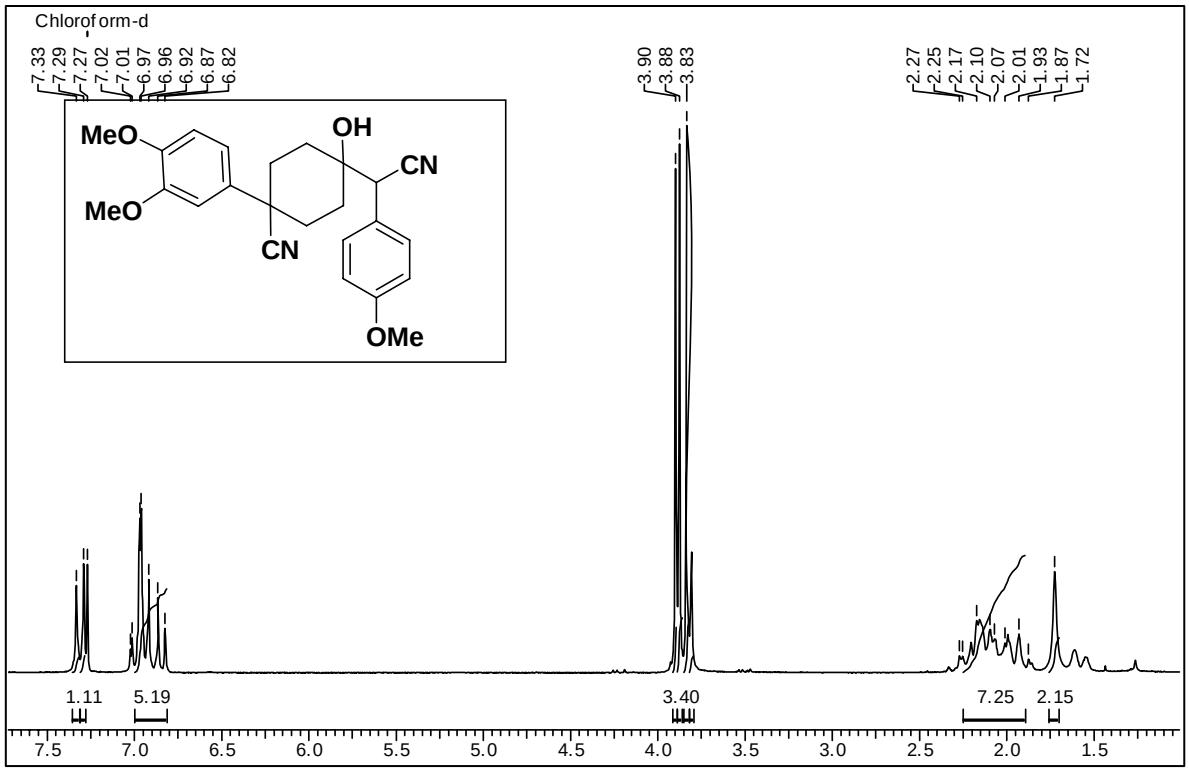
^{1}H NMR Spectrum of Compound 73 (500 MHz, $CDCl_3$)



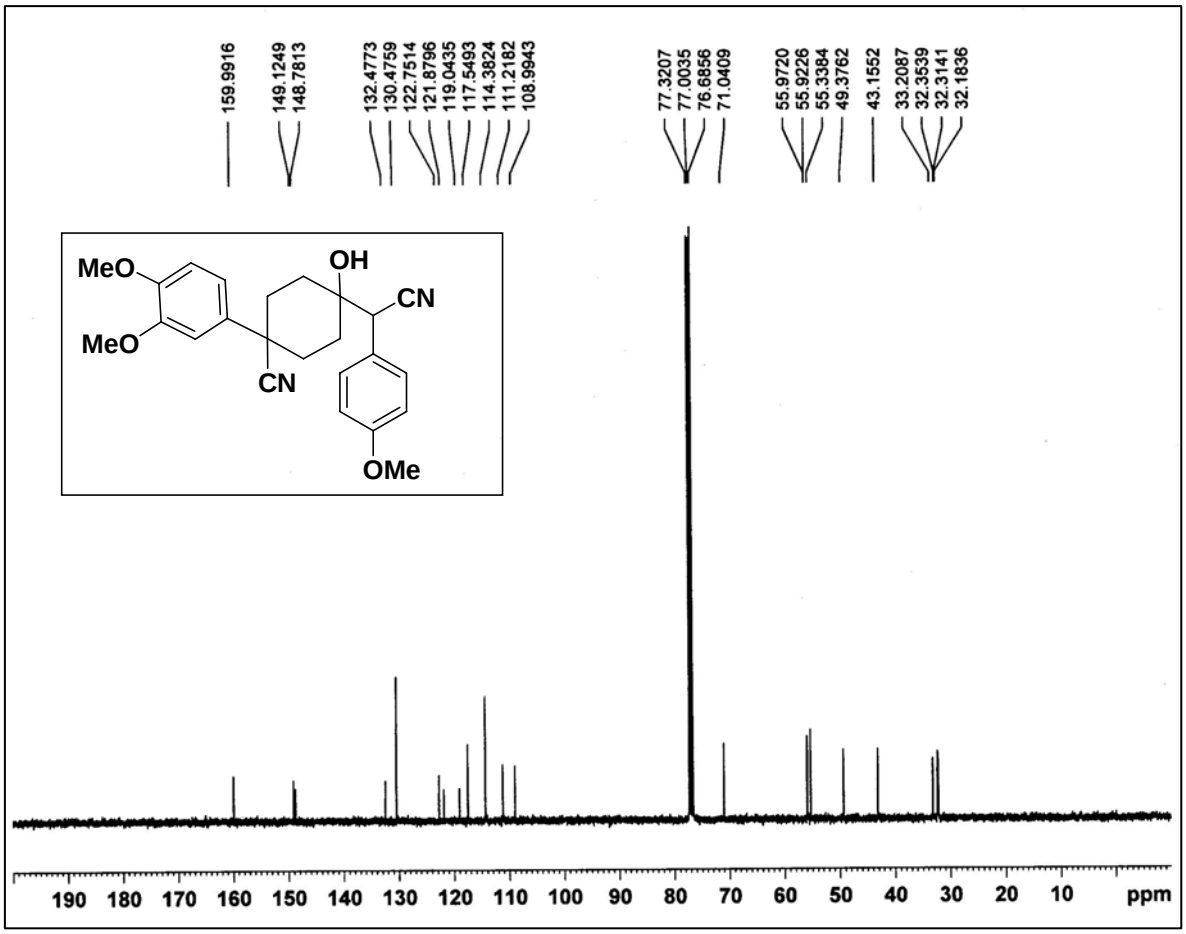
^{13}C NMR Spectrum of Compound 73 (125 MHz, $CDCl_3$ + CCl_4)



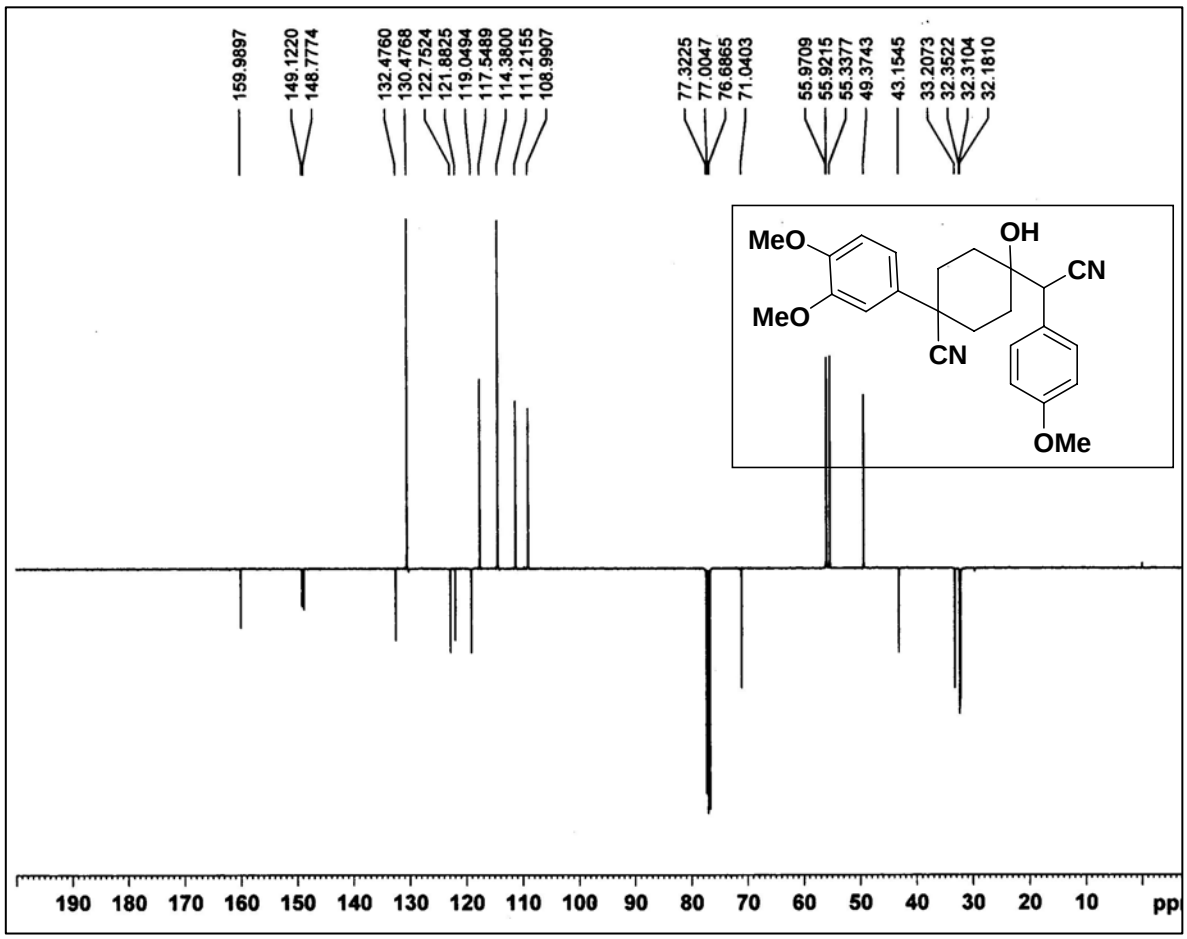
DEPT NMR Spectrum of Compound 73 (125 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR Spectrum of Compound 80 (200 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound 80 (100 MHz, $CDCl_3$)



DEPT NMR Spectrum of Compound 80 (100 MHz, $CDCl_3$)

Section-2: Formal Total Synthesis of (±)-Paroxetine

1.2.1. Introduction

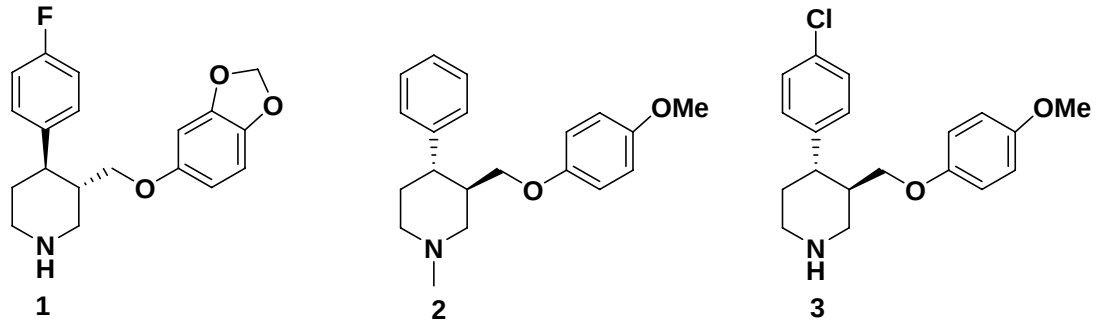


Figure 1. Antidepressants (–)-paroxetine **1**, (+)-femoxetine **2**, and peptidomimetic inhibitor Roche-1 **3**.

3-Substituted-4-arylpiperidines[1] exhibit a wide range of biological activity e. g. (–)-paroxetine **1**, and (+)-femoxetine **2**, marketed under different trade names, are selective serotonin reuptake inhibitors,[2] used in the treatment of depression, obsessive compulsive disorder, and panic, marketed under different trade names. The piperidine Roche-1 **3**, is nonpeptide peptidomimetic type III inhibitor of renin.[3] Paroxetine is an orally administered psychotropic drug chemically known as (–)-*trans*-4*R*-(*p*-fluorophenyl)-3*S*-(3',4'-methylenedioxyphenoxy)methyl) piperidine hydrochloride hemihydrate. It has become one of the most prescribed antidepressants due to its efficacy in treating depression as well as a spectrum of anxiety disorders ranging from panic attacks to phobias, since its release in 1992 by the pharmaceutical company Glaxo Smith Kline.

1.2.2. Polymorphism

Two crystal forms of paroxetine hydrochloride hemihydrate (form-I) and IPA crystal solvate crystals (form-II) are reported by Itaya *et. al.*[4]

1.2.3. Clinical Profile

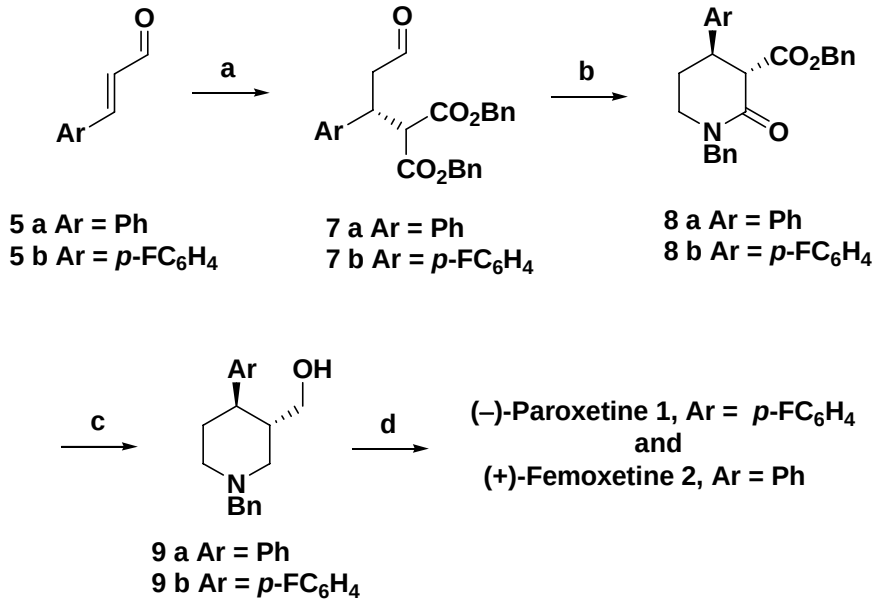
It differs from other antidepressants in having some muscarinic binding property. It is well absorbed and has a high degree of plasma protein binding.[5] It is well tolerated and has lower toxicity. Side effects are drowsiness, sweating and sexual dysfunction.[6] It may cause movement abnormalities or distonia. Usual dose is 20 mg/d but can be increased to 60 mg/d if necessary. It exhibits common discontinuation reactions as observed with other SSRIs and venlafaxine.

1.2.4. Literature Review

Literature survey revealed that several methods have been devised to prepare 4-arylpiperidine motif.[7-14] Syntheses of paroxetine can be categorized as: (a) cyclization of chiral linear compounds,[7] (b) expansion of chiral five-membered rings,[8] (c) asymmetric nucleophilic addition to *α,β*-unsaturated *δ*-lactams or piperidine derivatives,[9] (d) desymmetrization of *meso*-glutalimides,[10] (e) exploitation of pyridines,[11] (f) kinetic resolution of intermediate esters,[12] (g) optical resolution of piperidine derivatives,[4,13] and (h) miscellaneous.[14]

(a) Cyclization of chiral linear compounds

Jørgensen[7a] (*Angew. Chem. Int. Ed.* **2006**, *45*, 4305 –4309)

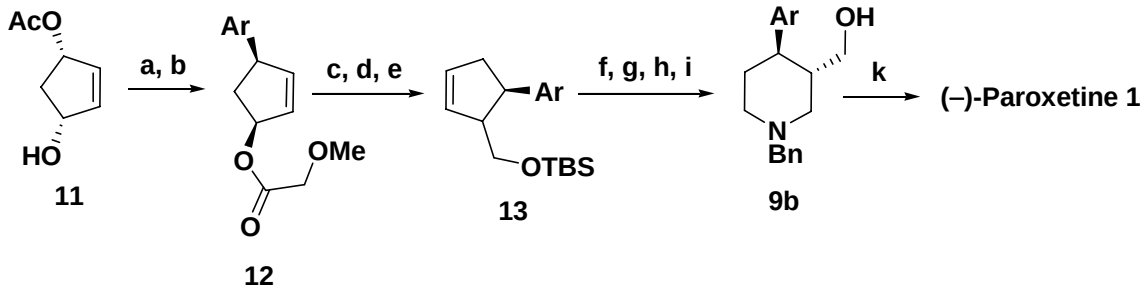


Scheme 1. *Reagents and conditions:* a) (*S*)-2-[bis(3,5-bis(trifluoromethyl) phenyl(trimethylsilyloxyl) methyl] pyrrolidine (10 mol %), EtOH, 0 ºC, 96 h, 72%, 86% ee; b) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70%; c) $LiAlH_4$, THF, Δ, 85%; d) ref. 7d-h, 9a, 10a,b, 13a,b, 14b for paroxetine **1** and ref. 7h, 10a,b for femoxetine **2**.

Jorgensen *et. al.* reported formal total synthesis of (–)-paroxetine **1** and (+)-femoxetine **2** employing first enantioselective organocatalytic conjugate addition of malonates to *α,β*-unsaturated aldehydes. The organocatalytic 1,4-addition of dibenzylmalonate **4** to cinnamaldehyde **5** using the L-proline derivative (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (*S*)-**6** as the catalyst

afforded Michael adduct **7a** in 80% yield 91% ee and **7b** in 72% and 86% ee. Compound **7** was converted into lactam **8** in a tandem process comprising three steps: imine formation, reduction, and lactamization, in 70% overall yield with an excellent diastereomeric ratio of 13:1 referring to the *trans* lactam. Lactam **8** was reduced with $LiAlH_4$ to give **9** in 85% yield as one diastereomer, which follwed by etherification with sesamol **10**, hydrogenolysis of the benzyl protection furnished (–)-paroxetine **1**, as reported in the literature.[5d-h, 8a,b, 11a,b, 12b] The two-step asymmetric synthesis of **8a** and **8b** leads to (+)-femoxetine **2** and (–)-paroxetine **1** in overall seven and six steps respectively (scheme 1).

Kobayashi[7b] (*Tetrahedron Lett.* **2004**, *45*, 8065–8068)

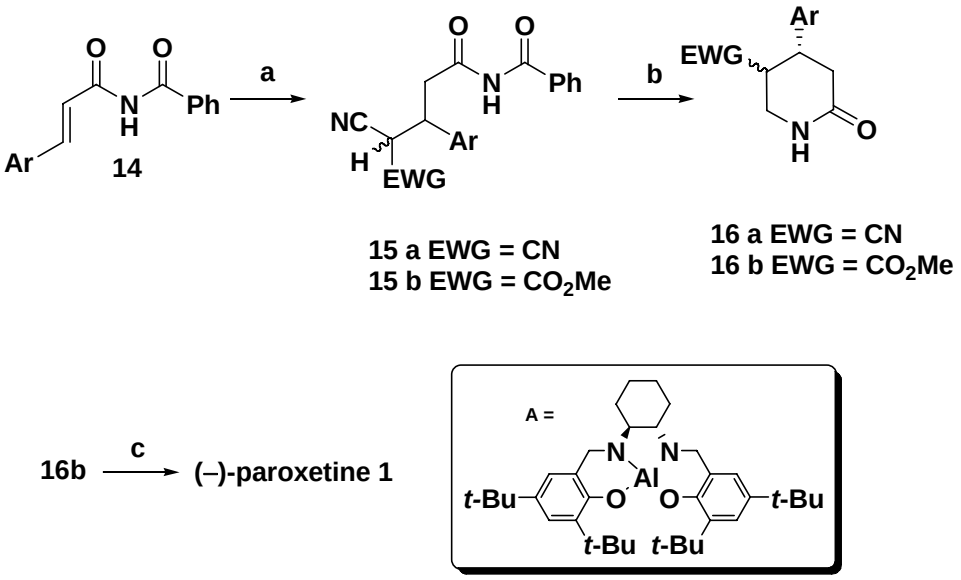


Scheme 2. *Reagents and conditions:* a) *p*-FC_6H_4MgCl, CuI, THF; b) $MeOCH_2CO_2H$, DIAD, PPh_3, –78 ºC, 63%; c) (*i*PrO)$Me_2SiCH_2Cu{\cdot}MgICl$, THF, 2 h; d) H_2O_2, KF, $KHCO_3$, 60-65 ºC; e) TBSCl, imidazole, 58%; f) O_3, –70 ºC, then, Me_2S; g) $NaBH_4$, 0 ºC; h) I_2, imidazole, PPh_3; i) $BnNH_2$, dioxane, 115 ºC, 47% (for 4 steps); j) Bu_4NF, 76%; k) ref. 7d-h, 9a,b, 13a,b, 14b.

Kobayashi *et. al.* reported syntheses of paroxetine **1** and femoxetine **2** based on regio- and stereoselective allylation of cyclopentenyl esters. Thus, reaction of monoacetate **11** with *p*-FC_6H_4MgCl (3 equiv.) in the presence of CuI (30 mol %) followed by Mitsunobu inversion with $MeOCH_2CO_2H$ afforded **12** in 63% yield from **11**. Reaction of **12** with (*i*-PrO)$Me_2SiCH_2Cu{\cdot}MgICl$ furnished **13** after Tamao oxidation and subsequent TBS protection. Compound **13** was efficiently transformed into piperidine **9b** utilizing established protocol (scheme 2). Similarly, compound **9b** can be elaborated to (–)-paroxetine **1** by known chemistry.

Formal Total Synthesis of (±)-Paroxetine

Jacobsen[7c] (*J. Am. Chem. Soc.* **2003**, *125*, 11204–11205)



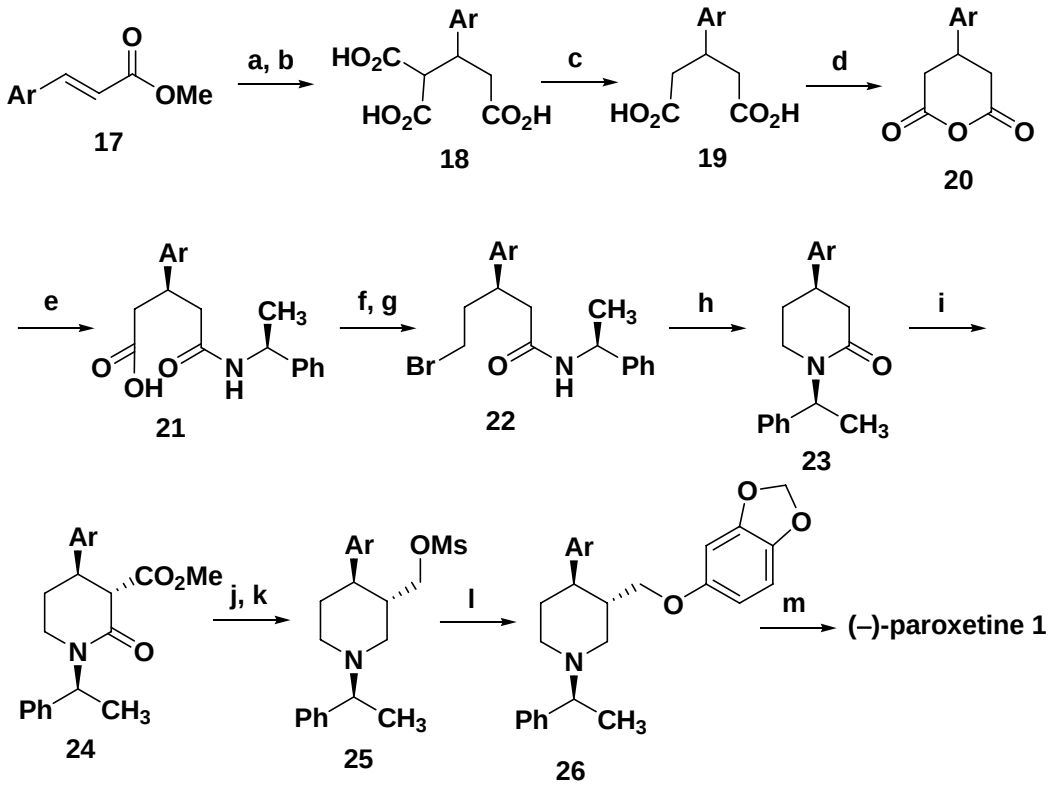
Scheme 3. *Reagents and conditions:* a) **A**, $CNCH_2CN$ or $CNCH_2CO_2Me$, *t*BuOH, cyclohexane, 23 ºC; b) reduction; c) ref. 11b.

Jacobson and Taylor demonstrated application of their methodology for the preparation of enantiomerically enriched piperidines, as exemplified by an expedient asymmetric catalytic synthesis of (–)-paroxetine **1**. Thus, (–)-paroxetine **1** was prepared from **14** through the intermediacy of **15** and **16** in six steps in 47% overall yield, following a synthesis developed at Sumigo Fine Chemicals (scheme 3).[11b]

Wang[7d] (*Tetrahedron: Asymmetry* **2001**, *12*, 419–426)

Wang *et. al.* reported a convenient and practical method for the preparation of chiral 4-aryl-2-piperidinone from 3-arylglutaric anhydride and (*S*)-methylbenzylamine, which was exploited in the synthesis of (–)-paroxetine **1** (scheme 4). Diacid **19** was prepared from 4-fluorocinnamic acid methyl ester **17** in three steps (Michael addition to ester **17**, hydrolysis of triester **18**, and decarboxylation of the resultant acid).[7,8] Prochiral 3-substituted glutaric anhydride **20** was then obtained by dehydration of the commercially available diacid **20** in acetyl chloride.

Formal Total Synthesis of (±)-Paroxetine

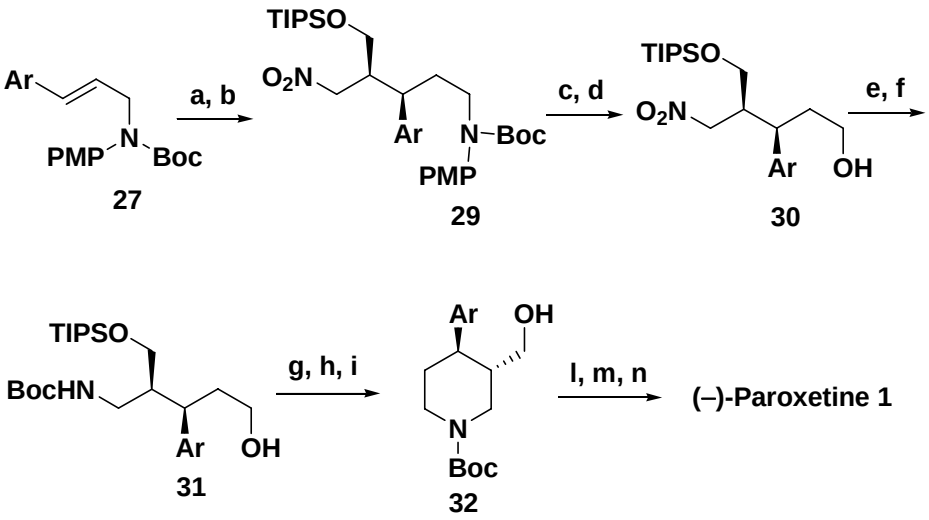


Scheme 4. *Reagents and conditions:* a) NaOMe, $CH_2(CO_2Me)$, MeOH, reflux, 20 h, 70%; b) 1 N NaOH, reflux, 20 h; c) conc. HCl, reflux, 20 h, 70% (two steps); d) CH_3COCl, reflux, 20 h, 90%; e) (*S*)-methylbenzylamine, Et_3N, PhMe, −78 °C, 10 h, r t, 10 h, 70%; f) Et_3N, $ClCO_2iBu$, THF, −78 to 0 °C, 20 h, then $NaBH_4$, H_2O, 0-25 °C, 20 h, 86%; g) PBr_3, conc. HBr, 0-25 °C, 4 days, 70%; h) NaH, THF, reflux, 20 h, 85%; i) LDA, THF, –78 ºC, $ClCO_2Me$, 4 h, 78%, 99% de; j) $LiAlH_4$, THF, reflux, 72 h, 65%; k) MsCl, DCM, r t, 20 h; l) i. sesamol, Na, PrOH, reflux, 36 h; ii. HCl, 64%; (m) H_2, Pd-C, MeOH, 68%.

Desymmetrisation of *meso*-3-substituted glutaric anhydride **20** with (*S*)-methylbenzylamine (99% *ee*) was effected in PhMe at −78 °C, according to the procedure described by Karanewsky.[10] In the amidation of 3-arylglutaric anhydride **20**, mixture of hemiamides **21a** and **21b** was obtained in 98% yield, former being the major isomer. The carboxyl group of hemiamide **21a** was converted into the bromide **22** through the intermediacy of alcohol in satisfactory yield by reduction of the corresponding mixed anhydride with $NaBH_4$, bromination of the resultant alcohol with PBr_3 and HBr then gave bromide **22** in moderate yields. Treatment of bromide **22** with sodium hydride suspended in refluxing THF afforded chiral 2-piperidinone **23** in 85% yield and >99% de after recrystallisation. C-3 acylation of 2-piperidinone **23** with $ClCO_2Me$ using LDA gave *trans*-3,4-disubstituted 2-piperidinone **24**. Reduction of 2-piperidinone **24** with $LiAlH_4$ provided 3-hydroxymethyl piperidine, which was converted into mesylate **25**. Treatment of mesylate **25** with sesamol **10** in the presence of NaOPr, provided aryl ether **26**. Ether **26** was treated

with HCl, and the resultant hydrochloride salt was purified by recrystallisation. The chiral auxiliary was removed by hydrogenolysis to provide (–)-paroxetine **1** as its hydrochloride salt.

Beak[7e,f] (*J. Am. Chem. Soc.* **2001**, *123*, 1004–1005; *J. Am. Chem. Soc*. **2002**, *124*, 11689–11698)

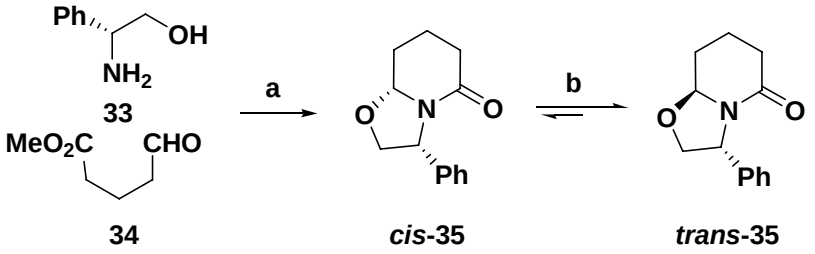


Scheme 5. *Reagents and conditions:* a) BuLi, (–)-sparteine, PhMe, –78 ºC; b) (*E*)-triisopropyl(3-nitroallyloxy) silane, 83%, >99:1 dr; c) HCl, $CHCl_3$; d) $NaBH_4$; e) Pd/C, HCO_2NH_4; f) $(Boc)_2O$, 95%; g) MsCl, Et_3N; h) KO*t*Bu, THF; i) TBAF, 83%; j) MsCl, Et_3N; k) sesamol, NaH, DMF; l) TFA, 72%, >97:3 dr.

Beak *et. al.* reported synthesis of (–)-paroxetine **1** by employing their methodology involving (–)-sparteine-mediated lithiation and conjugate addition of *N*-Boc-*N*-(*p*-methoxyphenyl)-allylamines to *α,β*-unsaturated nitro compounds. Thus, treatment of **27** with BuLi in the presence of (–)-sparteine in PhMe at –78 ºC followed by conjugate addition to nitroalkene **28** provided the desired carbamate (*S,S*)-**29** in 83% yield as a single diastereomer (Scheme 5). Hydrolysis and reduction of the resultant aldehyde provided nitro alcohol (*R,S*)-**30** in 88% yield. Reduction of the nitro group by transfer hydrogenation and subsequent Boc protection afforded (*R,S*)-**31** in 95% yield. Cyclization mediated by mesylate of the alcohol followed by unmasking the remaining alcohol protection afforded (*S,R*)-**32** in 83% yield. Mesylation of **32** followed by displacement of the mesyl with sesamol and subsequent Boc deprotection provided (–)-paroxetine **1** in 72% yield and >97:3 ee (11 steps, 41% from **27**). This protocol was also applied to the synthesis of (+)-femoxetine **2**.

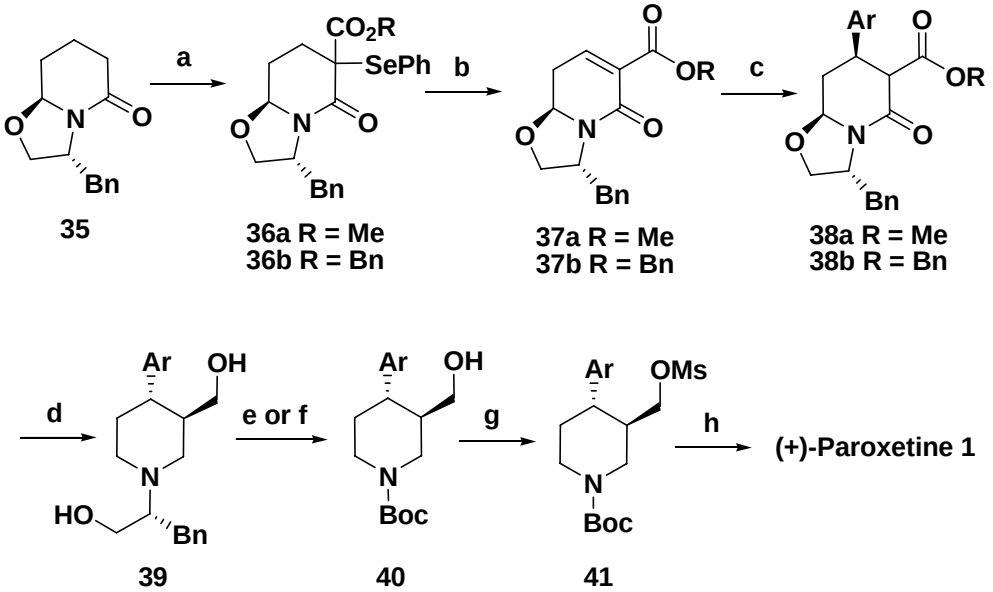
Formal Total Synthesis of (±)-Paroxetine

Bosch[7g] (*J. Org. Chem.* **2000**, *65*, 3074–3084)



Scheme 6. *Reagents and conditions:* a) PhMe, reflux, 36 h, 86% (*cis/trans*, 85:15); b) TFA, DCM, 25 ºC, quantitative, (*cis/trans*, 14:86).

An enantiodivergent synthesis of (+)- and (–)-paroxetine **1** and (+)-femoxetine **2** was reported by Bosch *et. al.* starting from enatiomerically pure *cis*-**35** and *trans*-**35** lactams. Lactams *cis*-**35** and *trans*-**35** were obtained by azeotropic removal of water from a solution of (*R*)-phenylglycinol **33** and methyl 5-oxopentanoate **34** (scheme 6) in PhMe, as a 85:15 mixture, respectively in 86% overall yield. The mixture was separated by column chromatography. Similarly, when a solution of lactam *cis*-**35** and TFA in DCM was stirred for 64 hours at 25 °C, a 14:86 mixture of *cis*-**35** and *trans*-**35** was recovered quantitatively!

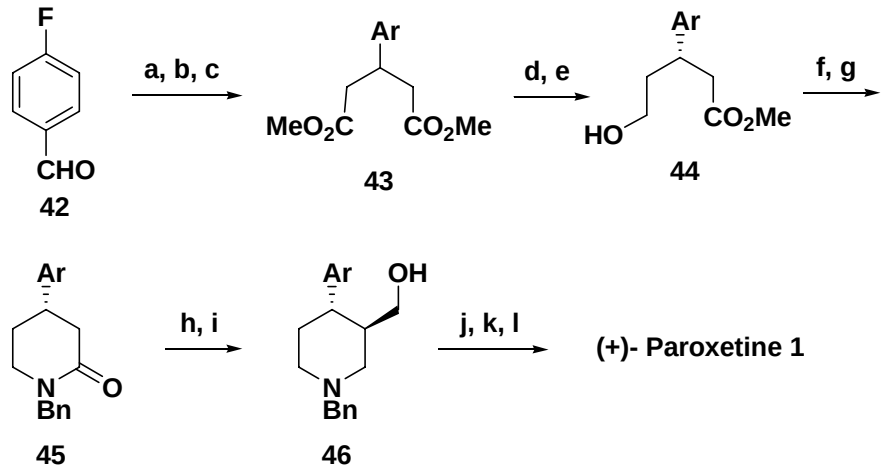


Scheme 7. *Reagents and conditions:* a) LHMDS, $ClCO_2R$, –78 ºC, THF, then PhSeBr; 85% for **29a** 77% for **29b**; b) O_3, –78 ºC to 25 ºC, DCM; c) (*p*-FC_6H_4)CuCNLi, –78 ºC, THF, 80% for **31a** and 70% for **31b**; d) $LiAlH_4$, $AlCl_3$, THF, –78 ºC, H_2, $Pd(OH)_2$, MeOH, 74%; e) H_2, $(Boc)_2O$, $Pd(OH)_2$, EtOAc, 73%; f) MsCl, pyridine, 10 ºC; g) sesamol, NaOMe, MeOH, reflux; h) TFA, DCM, 57% (for 2 steps).

Formal Total Synthesis of (±)-Paroxetine

Treatment of *trans*-**35** with LHMDS (2.2 equiv.), $ClCO_2Me$ or $ClCO_2Bn$ (1.0 equiv.), respectively, and PhSeBr (1.4 equiv.), followed by ozonolysis of the resultant selenides (*trans*-**36a** and *trans*-**36b**) under neutral conditions (Scheme 7) furnished lactams *trans*-**37a** and *trans*-**37b**. Conjugate addition of *p*-$FC_6H_4CuCNLi$ to *trans*-**37a** and *trans*-**37b** provided lactams *trans*-**38a** and *trans*-**38b** in 70% and 75% respectively. Lactams **38a** and **38b** were treated with alane ($LiAlH_4/AlCl_3$), which caused the cleavage of C-O bond of the oxazolidine ring and simultaneous reduction of the ester and amide carbonyl group to give the alcohol **39** (Scheme 6). Alcohol **39** was deprotected and the free amine was protected as its Boc derivative **40.** Alcohol **40** was converted into mesylate **41** and the mesyl group was further replaced with sesamol using NaH. Subsequent Boc deprotection furnished (–)-paroxetine **1**.

Yu[7h] (*Tetrahedron Lett.* **2000**, *41*, 5647–5651)



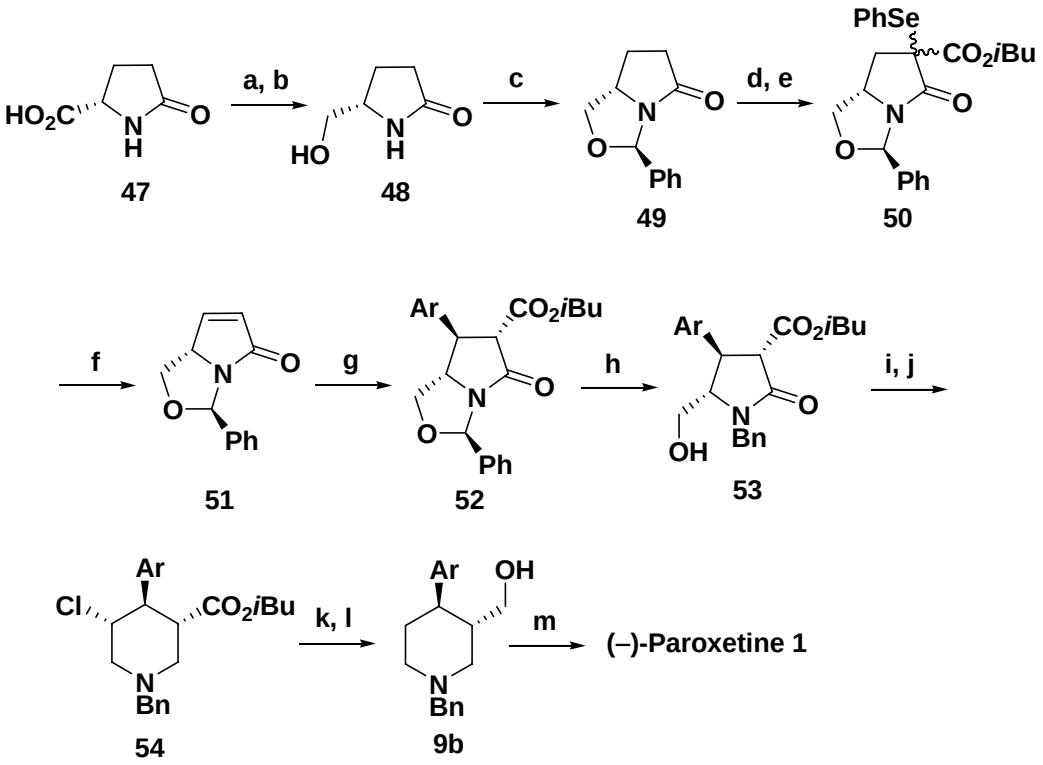
Scheme 8. *Reagents and conditions:* a) CH_3COCH_2COOEt, b) NaOH, Δ; c) MeOH, H^+, 75%; d) PLE (pH = 7), 10% aq. acetone, 95%; e) BMS, THF, 94%; f) MsCl, Et_3N; g) $BnNH_2$, Et_3N, PhMe, 82%, >99% ee; h) NaH, $(MeO)_2CO$, Δ, 88%; i) $LiAlH_4$, 71% or BH_3·THF, 92%; j) MsCl, Et_3N, PhMe; k) sesamol, NaH, DMF, 60 ºC, 80%; l) H_2 (70 psi), 5% Pd/C, IPA-AcOH, 93%.

Yu *et. al.* reported an enzyme hydrolysis mediated asymmetric synthesis of (–)-paroxetine **1** (scheme 8). Synthesis commenced with preparation of bis ester **43** in 75% yield by reaction of *p*-fluorobenzaldehyde **42** with ethyl acetoacetate using NaOH, followed by esterification. Hydrolysis of **43** with PLE consistently afforded optically active acid ester, in 86% yield and 95% ee, which was reduced with BMS to obtain alcohol **44** in 94% yield. Alcohol **44** was mesylated, which on treatment with benzylamine provided

lactam **45** in 82% yield and >99% ee. Lactam **45** upon acylation and subsequent reduction with either $LiAlH_4$ (71% yield) or BH_3·THF in refluxing THF (92% yield) gave aminoalcohol **46**. Etherification with sesamol in DMF (80% yield) followed by hydrogenolysis of the benzyl group using 5% Pd/C in IPA-AcOH (93% yield) completed the synthesis of (+)-paroxetine **1**.

(b) Expansion of chiral five-membered rings

Cossy[8a,b] (*Eur. J. Org. Chem.* **2002**, 3543–3551; *Tetrahedron Lett.* **2001**, *42*, 5705–5707)



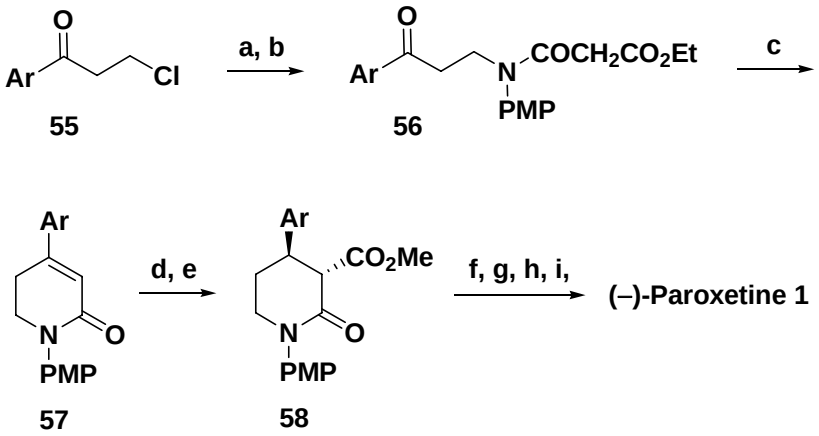
Scheme 9. *Reagents and conditions:* a) $SOCl_2$, MeOH, 0 ºC to r t; b) $NaBH_4$, EtOH, 0 ºC to r t, 80%; c) PhCHO, cat. PTSA, PhMe, reflux, 69%; d) LHMDS, THF, –78 ºC, then $ClCO_2iBu$; e) PhSeCl, –78 ºC; f) H_2O_2, DCM, 0 ºC, 99%; g) $(p\text{-}FC_6H_4)_2CuLi$, THF, –78 ºC, 97%, 98% de; h) BF_3·OEt_2, Et_3SiH; i) MsCl, EDC, 0 ºC to r t; j) Et_3N, reflux, 84%; k) Bu_3SnH, AIBN, PhMe, reflux; l) $LiAlH_4$, THF, 0 ºC to r t, 100%; m) ref. 7d-h, 9a,b, 13a,b, 14b.

An elegant formal synthesis of (–)-paroxetine **1** employing enantioselective ring enlargement of a trisubstituted prolinol was reported by Cossy *et. al*. After treatment of L-pyroglutamic acid **47** with $SOCl_2$ in MeOH (88% yield), the resultant methyl ester was reduced with $NaBH_4$ in EtOH at 0 °C to room temperature in 90% yield and the amidoalcohol **48** was protected with benzaldehyde in the presence of a catalytic amount of PTSA. Optically pure bicyclic compound **49** was isolated in 69% yield. *α,β*-Unsaturated

lactam **51** was prepared through conventional steps i. e. treatment of **45** with LHMDS and quenching with $ClCO_2iBu$ followed by PhSeCl and then oxidative elimination of the selenide **50** with H_2O_2. Conjugate addition of $(p\text{-}FC_6H_4)_2CuCNLi$ to **51** was achieved at –78 °C in THF to give compound **52** in 70% yield with >98% diastereomeric excess. Treatment of compound **52** with $BF_3{\cdot}OEt_2$ and Et_3SiH furnished amino alcohol **53**. When **53** was treated with MsCl (1.1 equiv) at 0 °C in EDC for 50 min and then heated under reflux for 36 hours in the presence of Et_3N (3.1 equiv), the expected trisubstituted 5-chloropiperidine **54** was isolated in 84% yield as a single diastereomer. Treatment of chloropiperidine **54** with Bu_3SnH in the presence of AIBN in refluxing PhMe replaced chlorine with hydride, the ester was reduced with $LiAlH_4$ in THF, which furnished the expected known piperidine **9b** in quantitative yields (Scheme 9).

(c) Asymmetric nucleophilic addition to *α,β*-unsaturated *δ*-lactams or piperidine derivatives

Buchwald[9a] (*J. Am. Chem. Soc.* **2003**, *125*, 11253–11258)

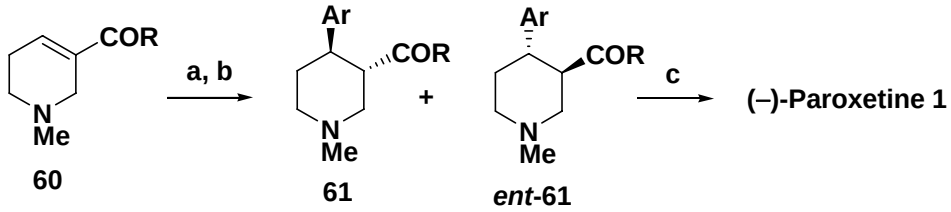


Scheme 10. *Reagents and conditions:* a) $PMPNH_2$, Et_3N, THF, reflux, 75%; b) $ClCOCH_2CO_2Et$, Na_2CO_3, DCM; c) NaOEt, EtOH, reflux, 74%; d) PMHS, *t*AmOH, (*S*)-*p*-tol-BINAP, $CuCl_2$, NaO*t*Bu, C_6H_5F, air, 23 °C 90%, 90% ee; e) NaH, MeOH, $(MeO)_2CO$, PhMe, reflux, 86%; f) $BH_3{\cdot}THF$, reflux, 97%; g) CAN, $CH_3CN\text{-}H_2O$ (3:1); h) $(Boc)_2O$, NaOH, PhMe, H_2O, 75% (two steps); i) i. Cs_2CO_3, xylene, 130 °C; ii. TFA, DCM, 52% (two steps).

Buchwald *et. al.* elegantly applied their catalytic enantioselective conjugate reduction methodology to the synthesis of (–)-paroxetine **1** as depicted in scheme 10. Thus, a mixture of *p*-anisidine, 4-fluoro-3-chloropropiophenone **55** and Et_3N was refluxed in THF to afford amine in 77% yield, which after amidation gave compound **56**. Refluxing a

solution of compound **56** in the presence of NaOMe in EtOH afforded lactam **57**. Catalytic enantioselective reduction of lactam with excess of PMHS and *t*AmOH afforded **58** in 90% yield and 90% ee using 0.5 mol % (*R*)-*p*-tolBINAP. Compound **58** was converted to **59** in two steps (81% overall yield). Further PMP group was replaced with Boc, alcohol was converted into ether using tosylate of sesamol, which followed by Boc deprotection furnished (–)-paroxetine **1**.

Keshava Murthy[9b] (*Tetrahedron Lett.* **2003**, *44*, 5355–5358)



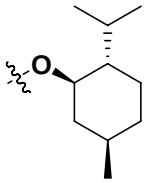
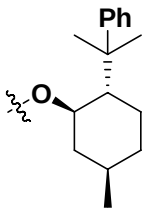
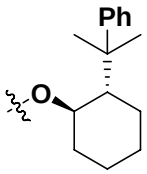
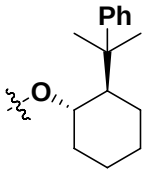
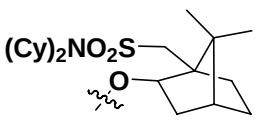
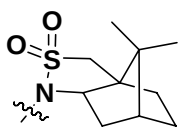
Scheme 11. *Reagents and conditions:* a) *p*-FC_6H_4MgBr; b) KO*t*Bu; c) ref. 15.

Keshava Murthy *et. al.* reported a highly stereoselective method for the preparation of a key synthetic precursor of paroxetine by asymmetric conjugate addition (scheme 11). The menthol-based Michael acceptors **61** (Table 1, entries 1–4) were prepared in near-quantitative yields by a modification of the procedure described by Meth-Cohn *via* transesterification of arecoline (**60**, R = OMe) in PhMe using the requisite menthol or menthol-derived auxiliary (1.0 equiv.) together with KO*t*Bu (0.05 equiv.). For the isoborneol-based auxiliary (entry 5), it was necessary to transesterify 10-dicyclohexylsulfamoylisoborneol with methylnicotinate (BuLi, THF) followed by quaternization (iodomethane) and reduction ($NaBH_4$). The camphorsultam-based auxiliary (entry 6) was obtained using the procedure described by Ho and Mathre.

A diethyl ether solution of *p*-fluorophenylmagnesium bromide was added to the Michael acceptor **66** in PhMe at 0-10 °C. Thermodynamically more stable C-3, C-4- *trans* isomer was obtained by treatment of the Michael adducts **61** with catalytic KO*t*Bu in PhMe, which can be further elaborated to (–)-paroxetine **1** by known literature methods.[15]

Formal Total Synthesis of (±)-Paroxetine

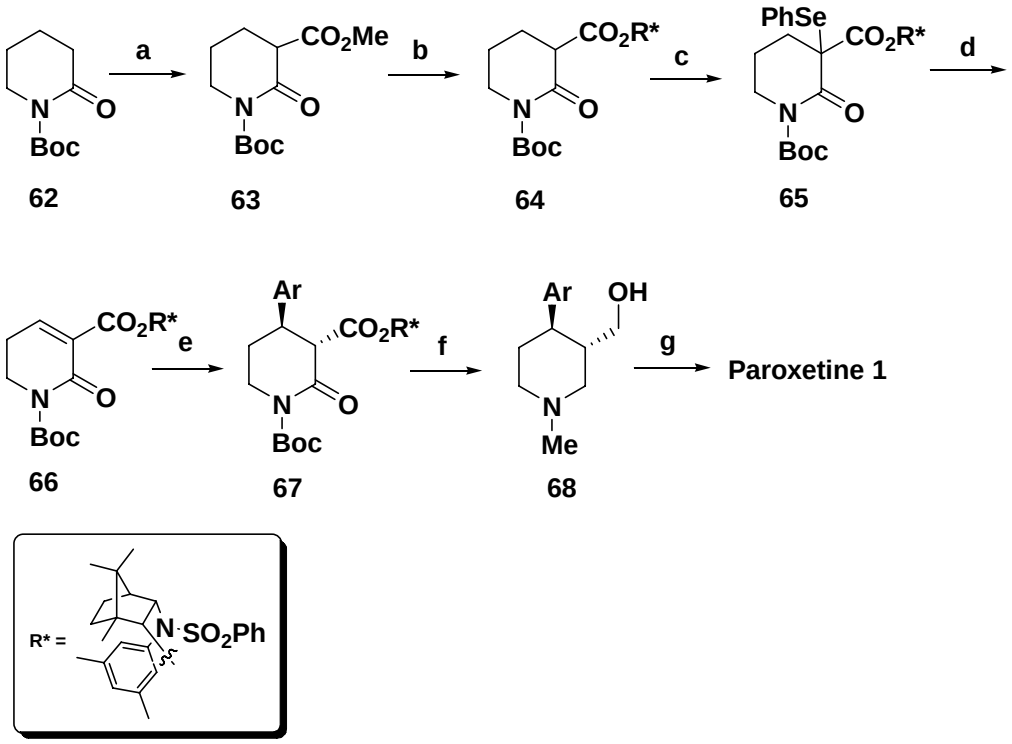
Table 1. Ratio of **61**:***ent*-61** for various auxiliaries.

Entry	R	61	*Ent*-61	Yield (%)
1.		1.0	1.0	75
2.		3.7	1.0	76*
3.		4.0	1.0	86*
4.		1.0	4.0	86*
5.		2.7	1.0	67
6.		>9.8	<0.2	75

*Yield assessed by NMR

Formal Total Synthesis of (±)-Paroxetine

Cossy[9c,d] (*New J. Chem.* **2003**, *27*, 475–482; *Tetrahedron Lett.* **2001**, *42*, 7805–7807)

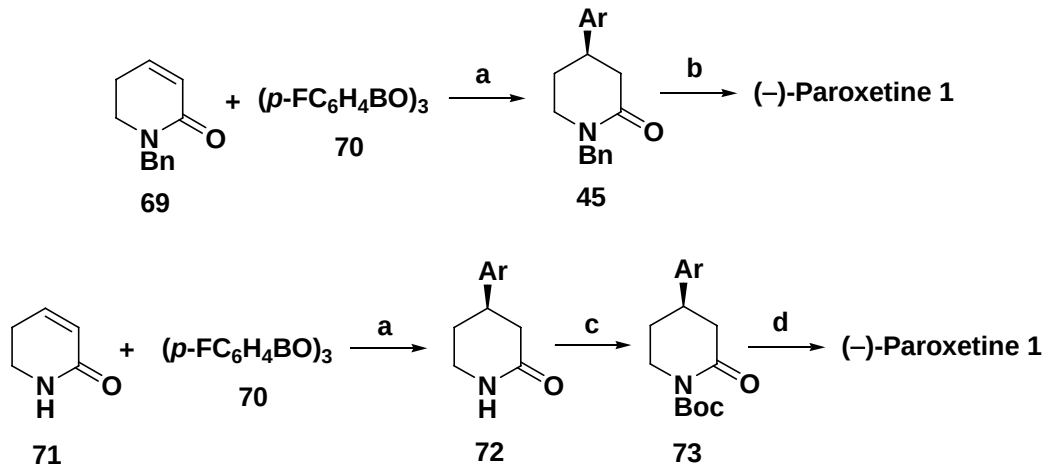


Scheme 12. *Reagents and conditions:* a) LHMDS, THF, –78 ºC to r t, $ClCO_2Me$, 93%; b) R*OH, DMAP, powdered MS (4 Å), PhMe, reflux, 50%; c) NaH, sonication, THF, r t, PhSeCl, HMPA, 68%; d) H_2O_2 (excess), DCM, 0 ºC, 100%; e) Ar_2CuLi, THF, –78 ºC, 80%; f) $LiAlH_4$, THF, 0 ºC to r t, then reflux, 85%; g) ref. 11b.

A short formal synthesis of paroxetine **1** employing diastereoselective cuprate addition to a chiral racemic olefinic amido ester was reported by Cossy *et. al.* Treatment of *N*-Boc δ-valerolactam **62** with LHMDS in THF at −78 °C followed by the addition of $ClCO_2Me$ afforded the corresponding methyl amidocarboxylate **63** in 93% yield. Asymmetric amido ester **64** was readily obtained by transesterification of **63** with the chiral racemic auxiliary R*OH in refluxing PhMe mediated by DMAP, as a mixture of diastereomers in 50% yield in 65:35 ratio. Phenylselenation of the mixture of **64** gave selenide **65** as a 75:25 mixture of diastereomers**,** which were oxidized with H_2O_2 in DCM at 0 °C to furnish lactam **66** in quantitative yields. Addition of $(p\text{-}FC_6H_4)_2CuLi$ to lactam **66** in THF at –78 °C provided compound **67** in 80% yield (Scheme 12). Cleavage of the chiral auxiliary in compound **67** was accomplished by reduction with $LiAlH_4$ in THF to give a known amino alcohol **68** in 85% yield.

Formal Total Synthesis of (±)-Paroxetine

Hayashi[9e] (*J. Org. Chem.* **2001**, *66*, 6852–6856)



Scheme 13. *Reagents and conditions:* a) Rh/(*R*)-BINAP (30 mol%), dioxane, 40 ºC, 12 h, 63%; b) ref. 5h; c) $(Boc)_2O$, DMAP, CH_3CN; d) ref. 7h.

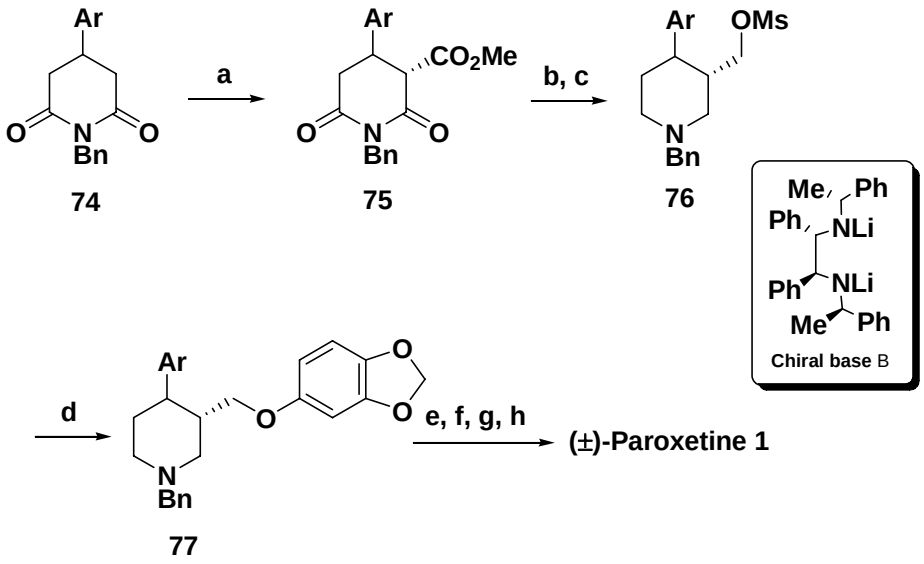
Hayashi *et. al.* described the first example of an excellent catalytic asymmetric synthesis of *p*-fluorophenyl-2-piperidinones, which is realized by the rhodium catalyzed asymmetric 1,4-addition of arylboron reagents to 5,6-dihydro-2(1*H*)-pyridinones. Thus, the reaction of *N*-benzyl-5,6-dihydro-2(1*H*)-pyridinone **69** with *p*-fluorophenylboroxine **70** and water in the presence of Rh/(*R*)-binap catalyst in dioxane at 40 °C for 12 hours gave (*R*)-**45** in 63% yield and 97% ee (scheme 13). Similarly, reaction of 5,6-dihydro-2(1*H*)-pyridinone **71** with *p*-fluorophenylboroxine **70** gave arylation product (*R*)-**72** of around 98% ee in high yields. Compound **72** was converted into its Boc derivative **73**, a known intermediate[7h] reported in the synthesis of paroxetine **1**.

(d) Desymmetrization of *meso*-glutalimides

Simpkins[10a,b] (*Tetrahedron* **2003**, *59*, 9213–9230; *Synlett* **2002**, 2074–2076)

Simpkins *et. al.* applied the chiral base desymmetrisation of imides to the synthesis of the antidepressant (–)-paroxetine **1** (scheme 14). Deprotonation of imide **74** with a chiral base **B** at –78 ºC in THF, followed by quenching with $CNCO_2Me$ afforded imide **75**. reduction of imide **75** with $LiAlH_4$ in refluxing THF gave alcohol with concomitant reduction of both imide carbonyls, which was mesylated to obtain **76**. Mesylate **76** was transformed into the (–)-paroxetine **1** through a sequence of usual steps through the intermediacy of ether **77**.

Formal Total Synthesis of (±)-Paroxetine



Scheme 14. *Reagents and conditions:* a) Chiral base **B** , THF, –78 ºC, then MeO_2CCN, 71%, 97% ee; b) $LiAlH_4$, THF, reflux, overnight, 90%; c) MsCl, pyridine, 72%; d) sesamol, NaOMe, MeOH, reflux, overnight, 55%; e) $CH_3CHClOCOCl$, 0 ºC to r t; f) reflux, 3 h; g) MeOH, reflux, 2 h; h) NaOH, 54%.

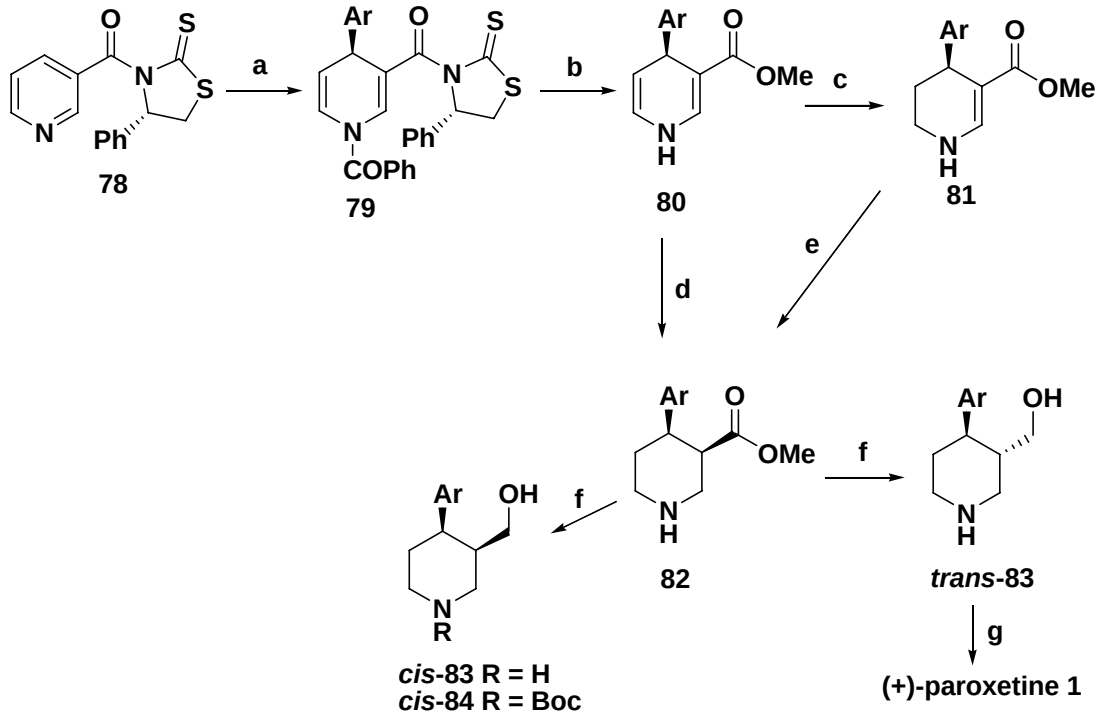
(e) Exploitation of pyridines

Yamada[11a] (*Tetrahedron Lett.* **2005**, *46*, 8673-8676)

Yamada and Jahan reported an elegant formal total synthesis of (–)-paroxetine **1** and (+)-femoxetine **2** by using chiral 1,4-dihydropyridines as key intermediates. Addition of a cuprate generated from *p*-FC_6H_4Li and $CuBr{\cdot}SMe_2$ to a pyridinium salt bearing a chiral auxiliary produced from **78** with $ClCO_2Me$ gave 1,4-adduct **79** in 69% yield with 95% de. Removal of the chiral auxiliary was accomplished by treatment with NaOMe in DCM to yield ester **80** (Scheme 15). Hydrogenation of dihydropyridine **80** in the presence of PtO_2 in EtOH proceeded regioselectively to give tetrahydropyridine **81**. When the reduction was allowed to continue for six days, simultaneous reduction of both double bonds in dihydropyridine **80** proceeded and provided a 4:1 mixture of *cis*- and *trans*-piperidines **82**. On the other hand, further reduction of the remaining double bond in **81** was accomplished by use of DCM-AcOH (4:1) as a mixed solvent to afford a 15:1 mixture of *cis*- and *trans*- piperidines **82**.

Isomerization of *cis*-piperidine **82** into *trans*-piperidine **82** was achieved in quantitative yield by treatment with NaOMe at 50 ºC in PhMe. Reduction of ester **82** provided alcohol **83**, which is the reported precursor of (–)-paroxetine **1**. Similar reduction of *cis*-piperidine **82** afforded *cis*-alcohol **83**, which was converted to *N*-Boc derivative **84**.

Formal Total Synthesis of (±)-Paroxetine



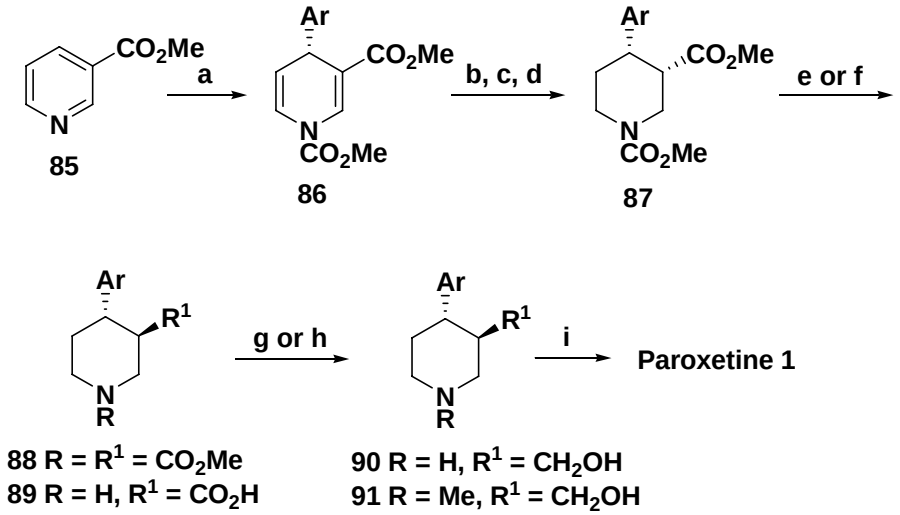
Scheme 15. *Reagents and conditions:* a) ClCOR, (p-$FC_6H_4F)_2CuLi{\cdot}LiBr$, –70 ºC, 78%, >99% de; b) 28% NaOMe, MeOH, DCM, r t, 3 h, 71%; c) H_2 (1 atm), PtO_2 (10 Wt %), EtOH, 27 h, 91%; d) H_2 (1 atm), PtO_2 (20 Wt %), EtOH, 6 d, 91%; e) H_2 (1 atm), PtO_2 (10 Wt %), DCM-AcOH, 32 h; f) $LiAlH_4$, THF, 4.5 h, 82%; g) ref. 12e, 13b.

A formal synthesis of (+)-femoxetine **2** was also accomplished according to a procedure similar to the formal synthesis of (–)-paroxetine **1**. This method can provide all the stereoisomers of a 3,4-disubstituted piperidine.

Liu[11b] (*Heterocycles* **1999**, *51*, 2439-2444)

Liu *et. al.* reported a synthesis of an intermediate for paroxetine starting from pyridine. Addition of p-FC_6H_4MgBr to the solution of CuCl, 1,10-phenanthroline and the *N*-acyl pyridinium salt obtained by treatment of methyl nicotinate **85** with methyl chloroformate afforded the *p*-fluorophenyl-1,4-dihydropyridine **86** in 50% yield. Hydrogenation of dihydropyridine under hydrogen atmosphere (50-60 psi) in a warm solution of MeOH-THF (1:1) provided tetrahydropyridine. The unaffected double bond in tetrahydropyridine was then reduced with Mg in MeOH to obtain a *cis*/*trans* mixture of piperidine **87**. The *cis* isomer was converted into the *trans* isomer by treatment with 1 N KOH solution in MeOH. The *trans* piperidine ester **87** was then hydrolysed with aq. KOH

solution and *N*-protected *trans* piperidine carboxylic acid **88** was obtained in 70% yield. The carbamate **88** was then hydrolyzed to *trans*-arylnipetonic acid **89**, which was reduced with $NaBH_4$ *via* its anhydride to obtain **90** or *trans* ester **87** was reduced to *N*-methylpiperidine carbinol **91** with $LiAlH_4$. Both the intermediates has been converted into (±)-paroxetine **1** (scheme 16).



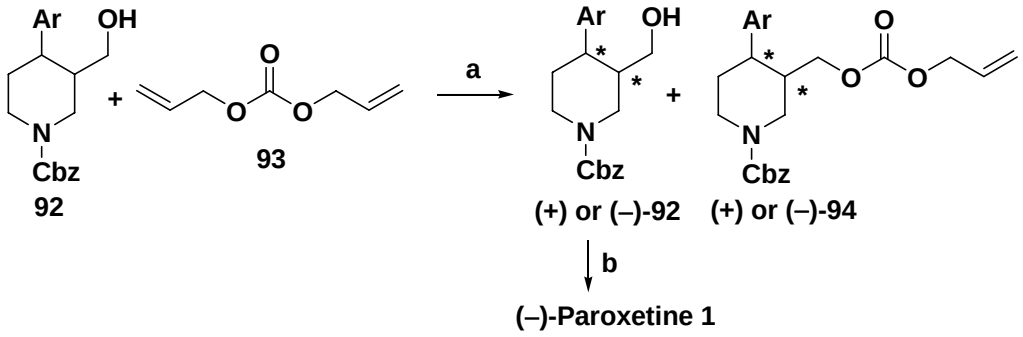
Scheme 16. *Reagents and conditions:* a) $ClCO_2Me$, CuCl, 1,10-phenanthronine, *p*-fluorophenylmagnesium bromide, THF, 0-15 ºC, 16 h, 50%; b) H_2, (50-60 psi), 10% Pd-C, MeOH-THF (1:1), 50 ºC, 24 h, 99%; c) Mg powder, MeOH, 0 ºC, 2 h then r t, 24 h; d) 1 N KOH in MeOH, reflux, 30-40 min; e) 2 N aq. KOH, MeOH, r t, 16-24 h, 70%; f) 2 N aq. KOH, MeOH, reflux, 16-24 h, 68%; g) Et_3N, $ClCO_2iBu$, THF, –50 to –20 ºC, 2 h, then $NaBH_4$, water, 0 ºC, 2 h, 88%; h) $LiAlH_4$, THF, reflux, 72 h, 80%; i) ref. 12e, 13b.

(f) Kinetic resolution of intermediate esters

Gotor[12a,b,c] (*Tetrahedron: Asymmetry* **2003**, *14*, 1725–1731; *J. Org. Chem.* **2003**, *68*, 3333–3336; *J. Org. Chem.* **2001**, *66*, 8947–8953)

Gotor *et. al.* reported an enzymatic resolution of *trans*-*N*-benzyloxycarbonyl-4-(4-fluorophenyl)-3-hydroxymethyl piperidine **92**, a chiral intermediate in the synthesis of (−)-paroxetine **1**, by alkoxycarbonylation with diallylcarbonate **93** using *Candida antarctica* lipase B (CAL-B) with high enantioselectivity (95% ee) using various organic solvents. Transformation of alcohol **92** into paroxetine is known in the literature (scheme 17).[16]

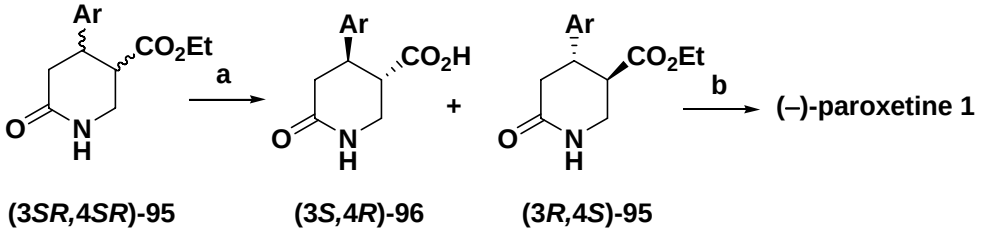
Formal Total Synthesis of (±)-Paroxetine



Scheme 17. *Reagents and conditions:* a) CAL-B, organic solvent; b) ref. 16.

Palomo[12d,e] (*Tetrahedron: Asymmetry* **2002**, *13*, 2653–2659; *Tetrahedron: Asymmetry* **2002**, *13*, 2375–2381)

Palomo *et. al.* resolved (±)-*trans*-4-(*p*-fluorophenyl)-6-*oxo*-piperidin-3-ethyl carboxylate (3*SR,*4*SR*)-**95** enzymatically using CAL-B into (3*R,*4*S*)-**96** carboxylic acid and (3*S,*4*R*)-**95** (scheme 18), an intermediate for the synthesis of (–)-paroxetine **1**.[15]



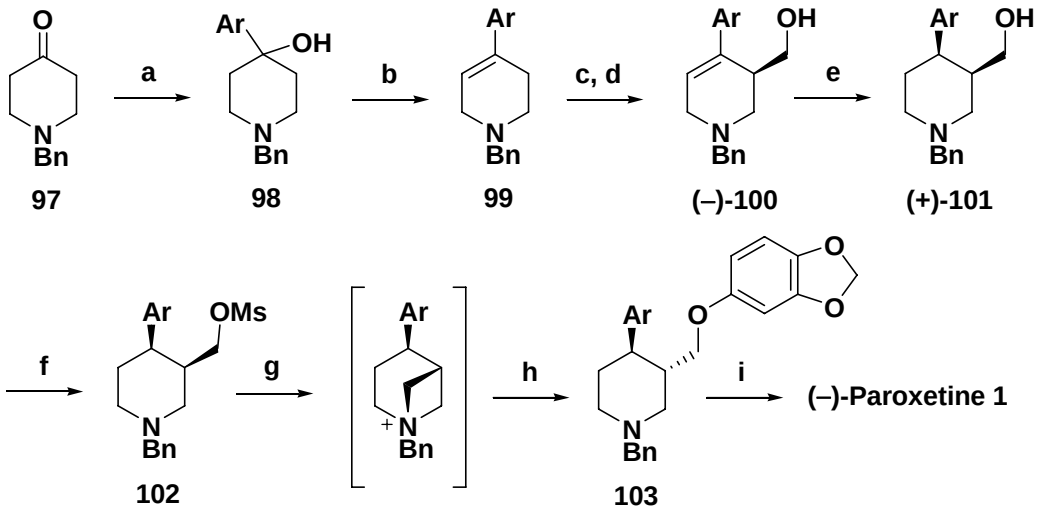
Scheme 18. *Reagents and conditions:* a) CAL-A, H_2O; b) ref. 15.

(g) Optical resolution of piperidine derivatives

Nemes[13] (*Eur. J. Org. Chem.* **2004**, 3336–3339)

Nemes's simple, practical and effective strategy for the stereoselective synthesis of (–)-paroxetine **1** is depicted in Scheme 19. Grignard reaction of *p*-FC_6H_6MgBr with 1-benzyl-4-piperidone **97** afforded alcohol **98**. *N*-benzyl-tetrahydropyridine derivative **99** was isolated as *p*-toluenesulfonate in 73% yield, after dehydration of **98** with PTSA. Prins reaction of **99** furnished racemic tetrahydropyridine-3-methanol *rac*-**100** in 59% yield. Resolution of the *rac*-**100** provided (–)-**100** in 41% yield. Stereoselective reduction of (–)-**100** on Pd/C catalyst, with the retention of the *N*-benzyl protective group, led to *cis*-piperidine-3-methanol (3*R*,4*R*)-**101**. Final enantiomeric purity was ensured by repeated

crystallization as the L-dibenzoyltartrate salt in 78% yield. The *cis*-amino alcohol methanesulfonate derivative **102** was then obtained in 97% yield with MsCl. Reaction of **102** with sesamol in xylene in the presence of NaOH resulted in the formation of *trans*-*N*-benzylparoxetine **103**. Hydrogenolysis of **103** then completed the synthesis of (–)-paroxetine **1** in 90% yield.



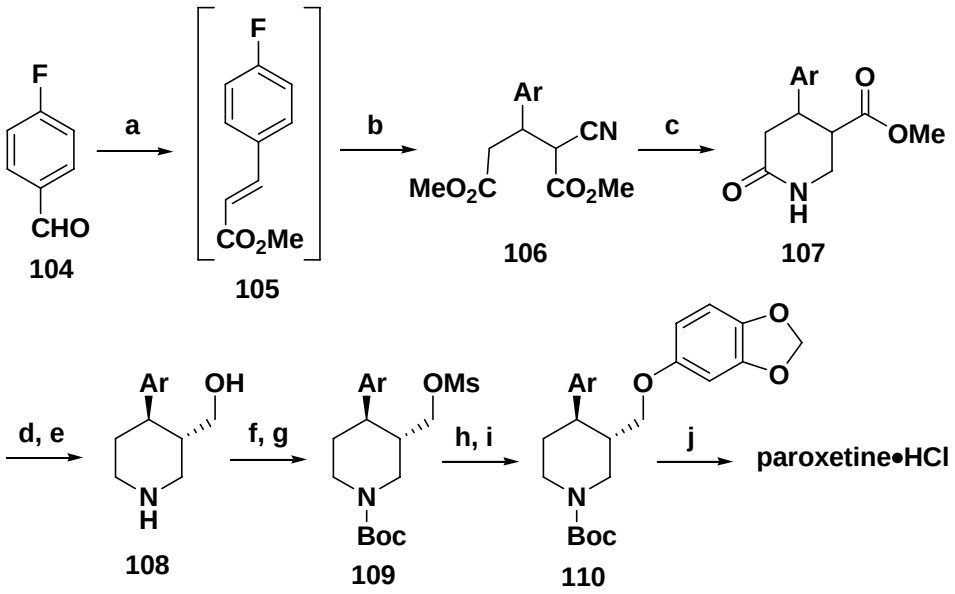
Scheme 19. *Reagents and conditions:* a) *p*-FC_6H_4MgBr, THF/PhMe; b) PTSA, ClC_6H_5, reflux; (c) CH_2O, HCl, H_2SO_4, H_2O, 80 °C; d) (–)-dibenzoyltartaric acid/acetone; e) (i) H_2, Pd/C, AcOH, HCl, H_2O, 40 °C; (ii) NaOH, H_2O; (iii) (–)-dibenzoyltartaric acid, acetone; (f) MsCl, Et_3N, DCM; (g) NaOH, H_2O, xylene, *s*BuOH, 140 °C; (h) H_2, Pd/C, *i*PrOH, 40 °C, 5 x 10^5 Pa.

Itaya[4] (*Chem. Pharm. Bull.* **2000**, *48*, 529–536)

Itaya *et. al.* reported a convenient synthesis of paroxetine hydrochloride from *p*-fluorobenzaldehyde **104** involving optical resolution. Methyl *p*-fluorophenyl cinnamate **105** was prepared from *p*-fluorobenzaldehyde **104** and MeOAc in the presence of NaOMe. Methyl cyanoacetate was subsequently added to the reaction mixture to afford dimethyl 2-cyano-3-(*p*-fluorophenyl) glutarate **106** in 79% yield.

Compound **106** was hydrogenated using Ra-Co to give (±)-*cis,trans*-4-(p-fluorophenyl)-5-methoxycarbonylpiperidine-2-one **107** in 90% yield, which was further treated with NaOMe to give *trans*-**107** isomer. Compound **107** was reduced with $LiAlH_4$ to give (3*SR*,4*SR*)-*trans*-4-(*p*-fluorophenyl)-3-hydroxymethylpiperidine **108** in 83% (from **106**). The racemic alcohol was optically resolved using L-*o*-chlorotartranilic acid to give salt of (3*S*,4*R*)-*trans*-4-(*p*-fluorophenyl)-3-hydroxymethyl piperidine **108**. The amino alcohol **108** was protected as its Boc derivative in PhMe/H_2O and the free alcohol was

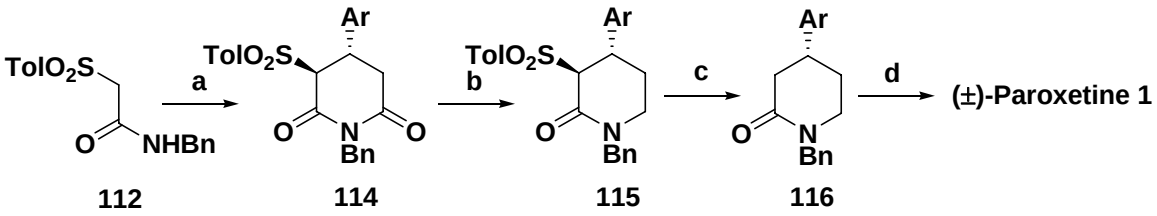
mesylated to obtain **109**, which was subsequently reacted with sesamol to give *N*-Boc paroxetine **110**. Compound **110** was dissolved in IPA and HCl was introduced to the solution to obtain paroxetine hydrochloride IPA solvate crystals **111** (scheme 20).



Scheme 20. *Reagents and conditions:* a) MeOAc, NaOMe, b) $CNCH_2CO_2Me$, 79%; c) H_2, Ra-Co, 90%; d) NaOMe; e) $LiAlH_4$; f) L-*o*-chlorotartranilic acid; g) $(Boc)_2O$; h) MsCl; i) NaOMe, sesamol; j) HCl/IPA.

(h) Miscellaneous

Chang[14a] (*Tetrahedron* **2003**, *59*, 9383-9387)

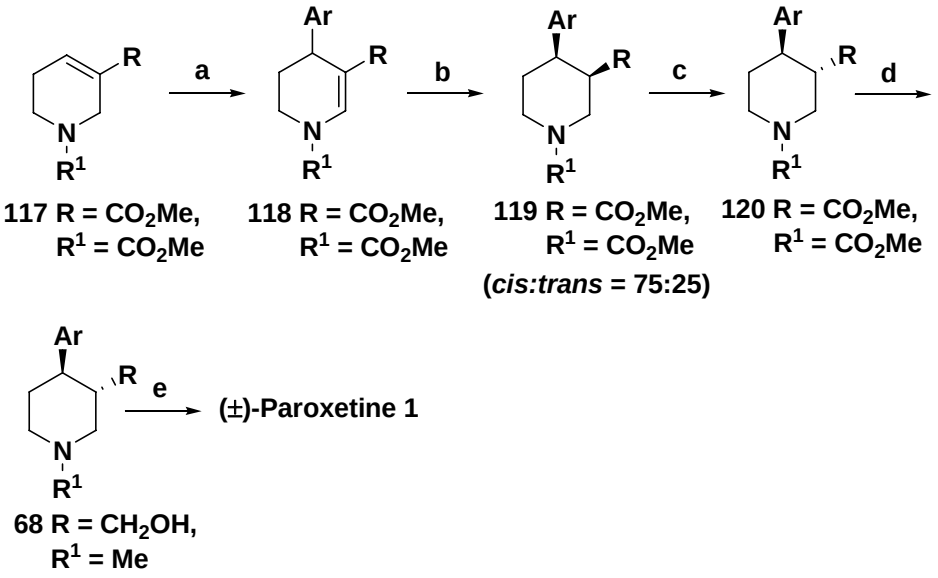


Scheme 21. *Reagents and conditions:* a) NaH, (*E*)-ethyl-3-(*p*-fluorophenyl) acrylate **113**, THF, 75%; b) $LiAlH_4$, Et_3N, THF, reflux, 3 h, 76%; c) Na-Hg, MeOH, 90%; d) ref. 7h.

Chang *et. al.* reported a formal synthesis of (±)-paroxetine **1** employing their methodology for the preparation of 4- or 5-substituted 3-sulfonyl-*δ*-lactams *via* regioselective reduction of *N*-alkyl-3-sulfonyl glutarimides. Michael addition of compound **112** to (*E*)-ethyl-3-(*p*-fluorophenyl) acrylate **113** provided *N*-benzyl-3-sulfonyl glutarimide **114** (scheme 21). Compound **114** was reduced with $LiAlH_4$ in refluxing THF in the

presence of Et_3N to give the corresponding *δ*-lactam **115** in 76% yield. Reductive desulfonylation of **115** with sodium amalgam in MeOH solution furnished **116** in 90% yield, whose conversion into (±)-paroxetine **1** is reported.

Correia[14b] (*Org. Lett.* **2006**, *8*, 1657-1660)

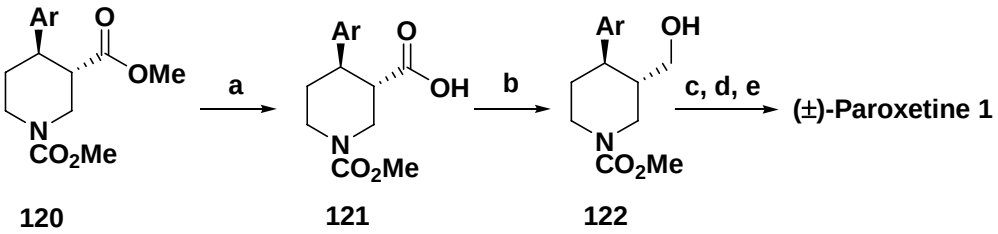


Scheme 22. *Reagents and conditions:* a) *p*-fluorobenzenetetrafluoroborate, $Pd(OAc)_2$, (10 mol%), AcOH-H_2O, r t, 4 h, 74%; b) Mg/MeOH, ultrasound, 24 h, 100%; c) MeONa, MeOH, reflux; d) $LiAlH_4$, THF, reflux, 56%.

Correia and Jahan reported the first synthesis of (±)-paroxetine **1** employing Heck-chemistry for formation of bond between piperidine nucleus and aromatic ring. Heck arylation of olefin **117** with *p*-fluorobenzenetetrafluoroborate using $Pd(OAc)_2$, (10 mol%) in AcOH-H_2O system afforded compound **118** in 74% yield. Ester **118** was efficiently reduced with Mg in MeOH to give a diastereomeric mixture of *cis*- and *trans*-4-(4-fluorophenyl)-piperidine-1,3-dicarboxylic acid dimethyl esters **119** in quantitative yields in a ratio of 75:25. Equilibration to the thermodynamically more stable *trans* isomer **120** was accomplished by refluxing the stereoisomeric mixture with NaOMe in MeOH (68% yield). Reduction of **120** with $LiAlH_4$ gave a known intermediate **68** in 80% yield (Scheme 22).

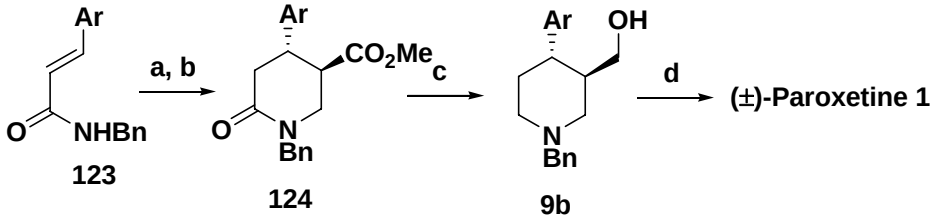
An alternative synthesis of (±)-paroxetine **1** has also been reported by Correia and Jahan The *cis-trans* mixture of 4-(*p*-fluorophenyl)-piperidine-1,3-dicarboxylic acid dimethyl esters **119** was equilibrated to the *trans* isomer **120** using 1 M KOH in methanol under reflux for 40 min. In the sequence, the solvent was evaporated and the mixture was

hydrolyzed using aq. 2 M KOH at room temperature for 12 h, furnishing the expected carboxylic acid **121** in 64% yield. Reduction of **121** with BMS gave the primary alcohol **122** in 82% yield. Alcohol **122** was then converted into mesylate, and the mesyl group was replaced with sesamol. Basic hydrolysis of the carbamate with methanolic KOH under reflux gave (±)-paroxetine **1** in 73% yield (scheme 23).



Scheme 23. *Reagents and conditions:* a) 2 M aq. KOH, r t, 12 h, 64%; b) BMS, THF, 0 ºC to r t, 16 h, 82%; c) MsCl, Et_3N, DCM, r t, 45 min; d) sesamol, NaH, DMF, reflux, 3 h, then, r t, 12 h, 56%; e) KOH, MeOH, reflux, 6 d, 73%.

Ihara[14c] (*J. Org. Chem.* **2005**, *70*, 3957-3962)



Scheme 24. *Reagents and conditions:* a) TBSOTf, NEt_3, *t*BuOH, EDC, r t; b) NaOMe, MeOH-PhMe, reflux (58% for 2 steps); c) $LiAlH_4$, THF, reflux, quantitative; d) ref. 7h.

Ihara *et. al.* demonstrated application of their intermolecular aza-double Michael methodology leading to functionalized piperidin-2-ones for the synthesis of paroxetine and two other alkaloids. The sequence employed to prepare paroxetine **1**, as outlined in Scheme 24, started with reaction of the unsaturated amide **123** with methyl acrylate in the presence of TBSOTf, Et_3N, and *t*BuOH in DCE to provide a mixture of *trans*- and *cis*-3,4-disubstituted piperidinones **124**, which was treated with NaOMe to afford *trans*-**124** in 58% overall yield (for 2 steps). Reduction of *trans*-**124** with $LiAlH_4$ quantitatively furnished the known pipereidinol **9b**, whose transformation into paroxetine **1** has been reported in the literature.

1.2.5. Present Work

Due to their unique biological properties, the piperidines have long been target molecules in organic synthesis. Most of the reported syntheses of paroxetine **1** suffer from low efficiency and/or lenghthy sequence. Therefore, interest of the pharmaceutical industry in the manufacture of this drug requires the development of new synthetic methods amenable to large scale preparation.

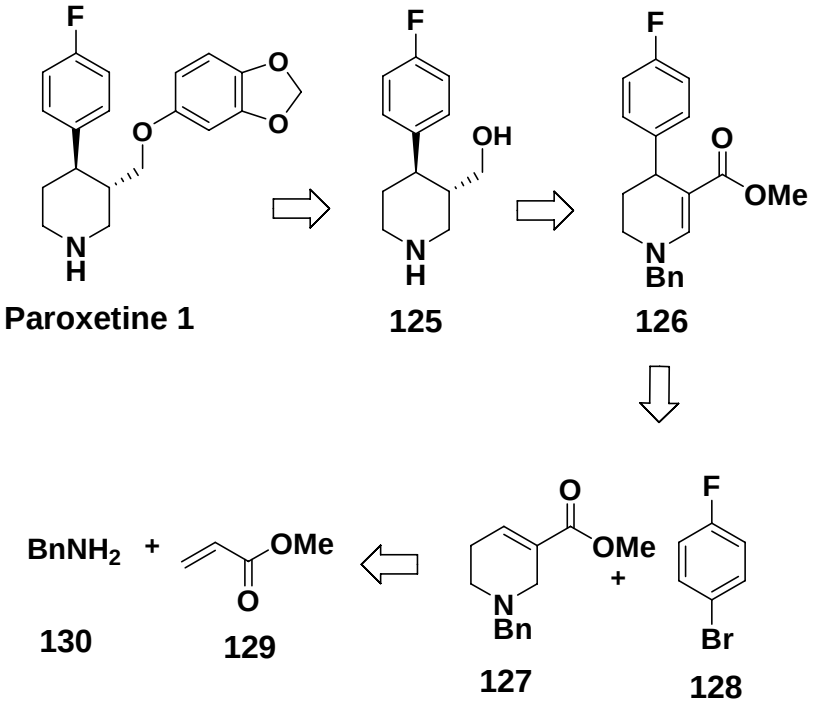
In connection with an ongoing programme on the synthesis of biologically active compounds, especially antidepressant compounds, we have recently developed a technically and economically viable protocol[17] for the synthesis of antidepressant drug venlafaxine (section 1). Our interest in development of practical routes for such molecules, prompted us to undertake synthesis of another highly active antidepressant drug paroxetine **1**.

Among the palladium-catalyzed C-C couplings, Heck reaction holds a prominent position due to its exceptional versatility, thus allowing ingenious applications in the total synthesis of complex organic structures. Although organic synthesis is enormously benefited by Heck chemistry,[18-22] surprisingly, when the synthesis of paroxetine was undertaken not a single approach was reported until very recently.[14b] During the course of synthetic endeavor of paroxetine, Heck protocol was reported to construct 4-arylpiperidine system forging a bond between C-4 of piperidine nucleus and aryl moiety. Reluctance to such approach may be attributable to the resistance of such complex acrylates to undergo arylation resulting in low conversions or yields of the desired Heck-adducts, posing a serious drawback. Accompanying decomposition or polymerization or side reactions under the harsh reaction conditions generally employed for such substrates could be other possible factors. We investigated our synthetic plan employing traditional, commercially available halide *viz. p*-fluorobromobenzene as the coupling partner as compared to the *p*-fluorobenzenediazonium tetrafluoroborate salt recently reported in the literature.

1.2.5.1. Retrosynthetic analysis

Retrosynthetic analysis revealed that the target molecule **1** could be obtained from amino alcohol **125**, which in turn could be derived from aminoester **126**, which could be presumably built from the olefin **127** and *p*-fluorobromobenzene **128** employing Heck

reaction. Olefin **127** could be conveniently prepared from the commercially available materials *viz.* methyl acrylate **129** and $BnNH_2$ **130** (scheme 25).



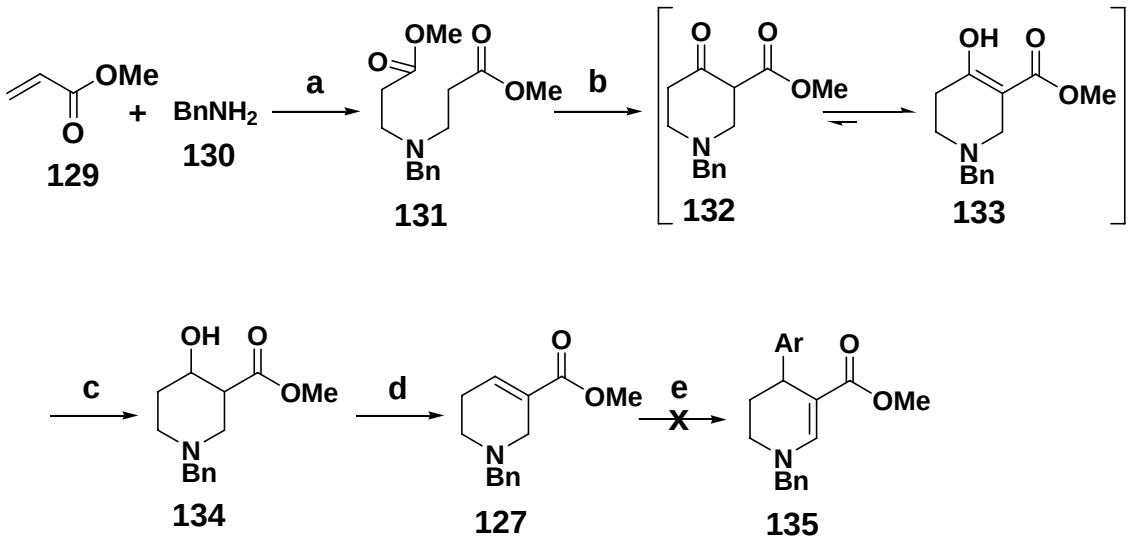
Scheme 25. Retrosynthetic analysis.

1.2.5.2. Results and discussion

Olefin **127** was obtained from methyl acrylate **129** and benzylamine **130** as follows. A neat mixture of methyl acrylate **129** and $BnNH_2$ **130** was refluxed in the presence of Et_3N to furnish double Michael adduct **131** in 90% yield (scheme 26).[23]

IR spectrum of compound **131** showed an absorption at 1733 cm^{-1} characteristic of ester function. ^1H NMR spectrum compound **131** showed a multiplet at δ 7.25-7.34 revealing aromatic protons (5H). The singlet at δ 3.68 revealed six protons corresponding to two ester methoxy groups (6H). The singlet at δ 3.63 suggested presence of the benzylic protons. Two triplets at δ 2.84 and 2.50 corresponded to the remaining 8 protons. ^{13}C NMR spectrum of compound **131** showed signal at δ 172.3 characteristic of ester function. The signals at δ 138.7, 128.5, 128.0, 126.9 revealed the aromatic carbons. Benzylic carbon appeared at δ 58.2. Signal at δ 51.1 indicated methoxy methyl carbon. Remaining four carbons appeared at δ 49.01, 32.4. Further, mass spectrum of compound **131** showed a signal at 279 revealing M^+ confirming its molecular formula.

Formal Total Synthesis of (±)-Paroxetine



Scheme 25. *Reagents and conditions:* a) Et_3N, reflux, overnight, 90%; b) NaH, PhH, reflux, 3 h, 82%; c) $NaBH_4$, MeOH, 0 ºC to r t, 2 h; d) MsCl, Et_3N, DCM, 0 ºC to r t, overnight, 75% (for two steps); e) $Pd(OAc)_2$ or $Pd(Ph_3P)_4$, K_2CO_3, Bu_4NBr, 120 ºC, 2 d.

Compound **131** was further subjected to Dieckmann condensation using NaH in refluxing benzene to give ketoester **132** in 82% yield, which existed as a mixture of tautomers **132** and **133**.[23,24]

IR spectrum of the tautomers (**132** and **133**) showed an absorption at 3368 cm^{-1} corresponding to enolic OH and absorptions at 1748 and 1718 cm^{-1} characteristic of *β*-ketoester. ^{1}H NMR spectrum of β-ketoester **132** (and **133**) revealed a broad singlet at δ 11.96 characteristic of intramolecularly hydrogen bonded enolic proton. The multiplet at δ 7.29-7.37 revealed presence of five aromatic protons. The singlet at δ 3.77 revealed methoxy protons (3H). The singlet at δ 3.67 was attributed to benzylic protons (2H). The remaining protons appeared at δ 3.21, 2.93, 2.65, 2.44. ^{13}C NMR spectrum of compound **132** revealed a signal at δ 203.2, characteristic of carbonyl carbon. Ester carbonyl carbon appeared at δ 171.1. Aromatic and two olefinic carbons appeared at δ 170.3, 168.9, 137.9, 137.6, 128.8, 128.6, 128.24, 128.20, 127.3, 127.1 and 96.4. The benzylic carbon appeared at δ 62.0. The signal at δ 61.5 was attributed to C-2. The signals at δ 56.3 and 54.9 were assigned to methoxy carbons. Other carbons appeared at δ 53.0, 51.9, 51.1, 49.8, 48.6, 40.5, 29.3. Mass spectral analysis revealed a signal at 247 (M^+) confirming the assigned structure.

Formal Total Synthesis of (±)-Paroxetine

Ketoester **132** was reduced with $NaBH_4$ in MeOH at 0 ºC and the resultant alcohol **134** was mesylated in DCM, which underwent concomitant elimination to afford the desired olefin **127** in 75% yield (scheme 25).

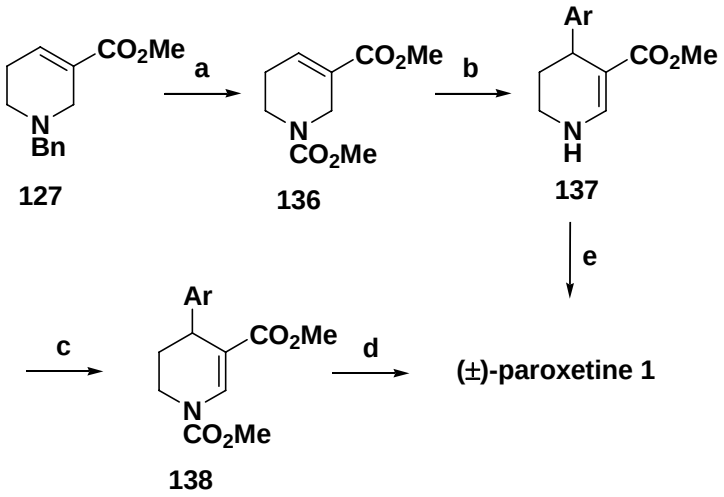
IR spectrum of compound **127** revealed absorption at 1714 cm^{-1} characteristic of α,β-unsaturated ester. ^1H NMR spectrum of olefin **127** showed a multiplet at δ 7.34-7.40 in the aromatic region (5H). Multiplet at δ 7.04-7.07 was ascribed to olefinic proton. The singlet at δ 3.76 was due to methoxy protons. Benzylic protons appeared at δ 3.71 while the remaining protons resonated at δ 3.29, 2.59, 2.33-2.43. ^{13}C NMR spectrum showed a signal at δ 166.3 characteristic of α,β-unsaturated ester function. Aromatic and olefinic carbon appeared at δ 138.0, 137.8, 129.1, 128.9, 128.3, 127.2. The signal at δ 62.3 revealed benzylic carbon. Remaining three carbons (CH_2) appeared at δ 51.5, 48.2, 26.4. Molecular formula $C_{14}H_{17}NO_2$ was further confirmed by its MS spectrum, which showed a signal at 233 correponding to M^+.

Feasibility of the Heck reaction was tested under various conditions. Arylation of the olefin **127** to *p*-fluorophenyl piperidine **135** using $Pd(OAc)_2$ was not successful in various solvents like DMF, MeOH or CH_3CN in the presence or absence of TBAB using various bases like Et_3N, K_2CO_3, Na_2CO_3, $NaHCO_3$ etc. Even $Pd(Ph_3P)_4$ was not able to bring about arylation under aforementioned reaction conditions. Also, subjection of the olefin **127** as per procedure reported by Correia *et. al.*[3a] employing traditional commercially available electrophile *p*-fluorobromobenzene did not furnish expected Heck adduct **135** (scheme 25).

Benzyl protection of the acrylate was then exchanged with methyl carbamate with $ClCO_2Me$ using K_2CO_3 in DCM at room temperature to obtain compound **136** in 80% yield.

IR spectrum of compound **136** showed a broad absorption at 1704 cm^{-1} due to carbamate and ester merging together. ^1H NMR spectrum of carbamate **136** exhibited a multiplet at δ 7.05-7.09 corresponding to olefinic proton. The downfield appearance of this signal indicated that its position is β to the electron withdrawing group i.e., ester function. Benzylic protons appeared at δ 4.16 as a doublet. Two singlets at δ 3.76 and 3.73 revealed carbamate and ester methoxy groups. Remaining four protons appeared at δ 3.53 as a triplet and a multiplet at δ 2.28-2.38. ^{13}C NMR spectrum showed signals at δ 165.1 and 155.6 corresponding to ester and carbamate carbonyls. The olefinic carbons appeared at δ 137.5 and 128.0. The ester and carbamate methoxy carbons resonated at δ 52.4 and 51.4. The

three signals that appeared at δ 42.4, 39.2, 25.1 were assigned to CH_2. MS spectrum of compound **136** showed a signal at 199 corresponding to M^+ further confirming its molecular formula.



Scheme 26. *Reagents and conditions:* (a) $ClCO_2Me$, $NaHCO_3$, DCM, r t, 24 h, 80%; (b) **128**, $Pd(Ph_3P)_4$, K_2CO_3, Bu_4NBr, 120 ºC, 2d, 45%; (c) $ClCO_2Me$, K_2CO_3, DCM, r t, overnight, 85%; d) ref 11b, 12e, 14b; e) ref 11a.

Having obtained the carbamate **136**, it was subjected to Heck reaction. Delightfully, carbamate **136** underwent arylation smoothly under solvent free conditions in TBAB melt and this was accompanied by concomitant unmasking of the carbamate protection to furnish free amine **137**, albeit in moderate yields (scheme 26).

IR spectrum of compound **137** showed an absorption at 3467 cm^{-1} revealing the presence of amine function and the absorption at 1682 cm^{-1} characteristic of *α,β*-unsaturated ester. ^1H NMR spectrum of **137** showed signal at δ 7.72 corresponding to olefinic proton. Four aromatic protons appeared as two multiplets at δ 7.11-7.15 and 6.93-6.97. The broad singlet at δ 4.76 was attributed to benzylic protons. The methoxy protons resonated at δ 3.58. The signals at δ 3.99 (d, 1H), 3.10-3.14 (m, 1H), 2.93 (dt, 1H), 1.93-2.00 (m, 1H), 1.79 (dd, 1H) matched well with the remaining protons. ^{13}C NMR spectrum of compound **137** showed a signal at δ 168.6 revealing ester function. The aromatic carbons appeared at δ 161.3 corresponding to carbon proximal to F. *ortho* carbons appeared at δ 114.7. Signal at δ 129.0 corresponded to *meta* carbons. Quaternary aromatic carbon was observed at δ 142.0. Signals at δ 143.9 and 95.9 corresponded to olefinic carbons. Methoxy carbon appeared at δ 50.5. The benzylic carbon appeared at δ 35.5 and the two CH_2

appeared at δ 36.0 and 28.9. Further assigned structure was confirmed by Mass spectral analysis and single crystal X-ray diffraction pattern.

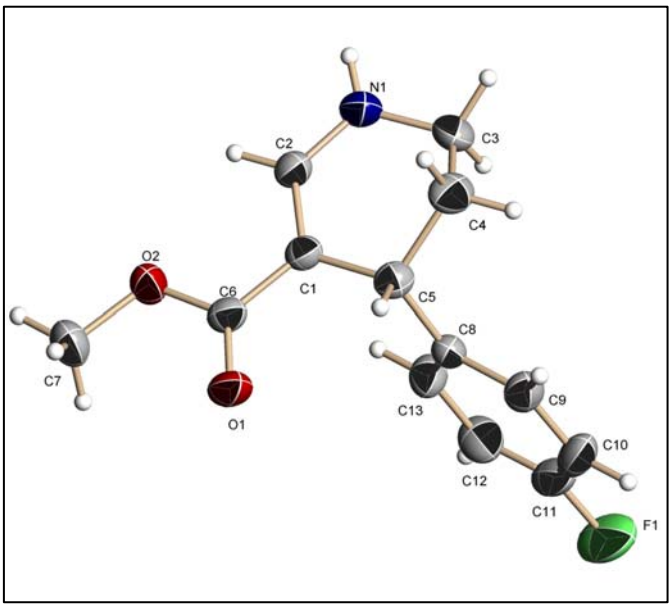


Figure 2. ORTEP representation of compound **137**.

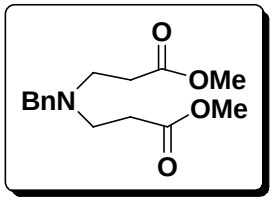
Transformation of amine **137** into paroxetine is known in the literature.[11a] Also, carbamate derivative of amine **137**, **138** was prepared, which is a known intermediate in the synthesis of paroxetine.[11b,12e,14b] Thus, formal total synthesis of (±)-paroxetine **1** was accomplished in overall six steps.

1.2.5.3. Conclusion

Formal total synthesis of (±)-paroxetine has been accomplished employing Heck reaction utilising traditional commercially available *p*-fluorobromobenzene as compared to *p*-fluorobenzenediazonium tetrafluoroborate salt employed in literature synthesis with comparable 20% overall yield in six steps, under solvent free conditions.

1.2.9. Experimental

Dimethyl 3,3′-(benzylazanediyl) dipropanoate (131)



A neat mixture of methyl acrylate **129** (63 ml, 0.70 mol) and $BnNH_2$ **130** (25 g, 0.23 mol) was refluxed in the presence of Et_3N (65 ml, 0.46 mol) overnight. Excess methyl acrylate was distilled off, the residue was taken in EtOAc and washed with water, brine, dried over anhydrous Na_2SO_4 and filtered. Solvent removed under reduced pressure. The resultant oil was chromatographed over silica gel using EtOAc-pet ether to furnish Michael adduct **131** as a yellow oil (58.67 g).

Molecular formula : $C_{15}H_{21}NO_4$

Yield : 90%

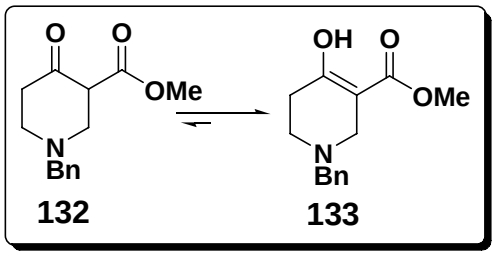
IR ($CHCl_3$) : 3022, 2953, 2835, 1733, 1495, 1454, 1438, 1356, 1333, 1216, 1176, 1129, 1045, 846, 757, 699, 668 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.25-7.34 (m, 5H), 3.68 (s, 6H), 3.63 (s, 2H), 2.84 (t, *J*= 7.07 Hz, 4H), 2.50 (t, *J*= 7.07 Hz, 4H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 172.3, 138.7, 128.5, 128.0, 126.9, 58.2, 51.1, 49.01, 32.4

MS (EI) *m/z* : 302 (M+Na), 280 (M+1), 266, 206, 194.

Methyl 1-benzyl-4-oxopiperidine-3-carboxylate (132) and methyl 1-benzyl-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate (133)



To a suspension of NaH (5.38 g, 0.13 mol) in benzene, a solution of Michael adduct **131** (25 g, 0.09 mol) in PhH was added drop-wise and refluxed for 3 hours. The reaction mixture was allowed to cool and quenched with saturated NH_4Cl solution, extracted with ethyl acetate, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatographic separation over silica gel (EtOAc- pet ether) afforded ketoester, as a pale yellow oil (18.15 g), which exists as a mixture of tautomers **132** and **133**.

Formal Total Synthesis of (±)-Paroxetine

Molecular formula : $C_{14}H_{17}NO_3$

Yield : 82%

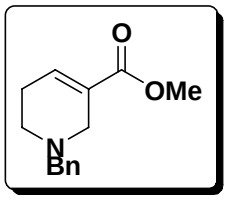
IR ($CHCl_3$) : 3368, 3020, 1748, 1718, 1667, 1623, 1445, 1366, 1308, 1237, 1216, 1121, 1061, 756, 700, 669 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 11.96 (bs, 0.61H), 7.29-7.37 (m, 5H), 3.77 (s, 3H), 3.67 (s, 2H), 3.21 (s, 1.58H), 2.27-3.14 (m, 1.30H), 2.65 (q, *J*= 5.68 Hz, 2H), 2.44 (t, *J*= 5.68 Hz, 1.62H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 171.1, 170.3, 168.9, 137.9, 137.6, 128.8, 128.6, 128.24, 128.20, 127.3, 127.1, 96.4, 62.0, 61.5, 56.3, 54.9, 53.0, 51.9, 51.1, 49.8, 48.6, 40.5, 29.3

MS (EI) *m/z* : 248 (M+1), 246, 218, 216, 214, 194.

Methyl 1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate (127)



To a solution of *β*-ketoester **132** (12.6 g, 0.05 mol) in MeOH, $NaBH_4$ (0.97 g, 0.03 mol) was added in portions at 0 ºC. The reaction mixture was stirred at room temperature for 2 hours. MeOH was removed on rotavapor, water was added to it and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a faint yellow syrup. To the solution of this syrup in DCM, Et_3N (10.65 ml, 0.08 mol) was added and cooled to 0 ºC, MsCl (4.35 ml, 0.05 mol) was added drop-wise *via* syringe at 0 ºC. The reaction mixture was allowed to warm gradually and left overnight. It was observed that the mesylate was formed smoothly and subsequently underwent elimination under reaction conditions to afford the desired olefin. The reaction mixture was washed with water, brine and dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated under reduced pressure and the resultant residue was chromatographed over silica gel to furnish olefin **127** as a pale yellow syrup (8.84 g).

Molecular formula : $C_{14}H_{17}NO_2$

Yield : 75% (for 2 steps)

IR ($CHCl_3$) : 3025, 2922, 2809, 1714, 1658, 1438, 1365, 1268, 1217, 1126, 1055, 1045, 970, 755, 721, 699, 667 cm^{-1}

Formal Total Synthesis of (±)-Paroxetine

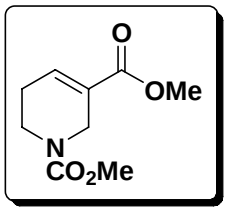
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.34-7.40 (m, 5H), 7.04-7.07 (m, 1H), 3.76 (s, 3H), 3.71 (s, 2H), 3.29 (q, *J*= 2.78, 2H), 2.59 (t, *J*=5.68 Hz, 2H), 2.33-2.43 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 138.0, 137.8, 129.1, 128.9, 128.3, 127.2, 62.3, 51.5, 48.2, 26.4

MS (EI) *m/z* **:** 233 (M^+), 218, 203, 199

Analysis **:** Calculated for $C_{14}H_{17}NO_2$**;** C-72.70, H-7.41, N-6.06 found C-72.55, H-7.32, N-5.98

Dimethyl 5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (136)



To a mixture of olefin **127** (2.5 g, 0.011 mol) and $NaHCO_3$ (0.455 g, 0.005 mol) in DCM, $ClCO_2Me$ (1.534 g, 0.016 mol) was added drop-wise at 0 ºC and stirred at room temperature for 24 hours. The reaction mixture was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatographic separation (SiO_2) using EtOAc-pet ether gave a faint yellow syrup (1.83 g).

Molecular formula **:** $C_9H_{13}NO_4$

Yield **:** 85%

IR ($CHCl_3$) **:** 3020, 2955, 2926, 1704, 1656, 1627, 1449, 1412, 1343, 1289, 1238, 1217, 1191, 1123, 1092, 1052, 756, 668 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.05-7.09 (m, 1H), 4.16 (d, *J*= 2.27 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.53 (t, *J*= 5.69 Hz, 2H), 2.28-2.38 (m, 2H)

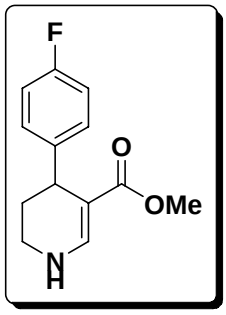
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 155.6, 137.5, 52.4, 51.4, 42.4, 39.2, 25.1

MS (EI) *m/z* **:** 221 (M+Na), 199 (M^+), 197, 181, 179, 157, 137, 151,129, 123

Analysis **:** Calculated for $C_9H_{13}NO_4$; C-54.26, H-6.58, N-7.03 found C-54.02, H-6.35, N-6.78

Formal Total Synthesis of (±)-Paroxetine

Methyl 4-(4-fluorophenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (137)



A mixture of olefin **135** (1 g, 5.024 mmol), *p*-fluorobromobezene **128** (1.76 g, 10.05 mmol), $Pd(Ph_3P)_4$ (0.58 g, 10 mol%), K_2CO_3 (1.386 g, 10.05 mmol) and TBAB (2.33 g, 10.05 mmol) was heated at 120 ºC under argon atmosphere for 2 days. The reaction mixture was allowed to cool, water was added to it and extracted with EtOAc, washed with brine, dried (anhydrous Na_2SO_4), filtered and the solvent was evaporated *in vacuo*. Column chromatographic purification (SiO_2) using EtOAc-pet ether furnished amine **137** as a colourless solid (0.531 g).

Molecular formula : $C_{13}H_{14}FNO_2$

Yield : 45%

Mp : 156-8 ºC

IR ($CHCl_3$) : 3467, 3019, 1682, 1626, 1506, 1438, 1353, 1314, 1284, 1216, 1108, 1070, 930, 757, 669 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.72 (d, *J*= 6.27 Hz, 1H), 7.11-7.15 (m, 2H), 6.93-6.97 (m, 2H), 4.76 (bs, 1H), 3.99 (d, *J*= 4.76 Hz, 1H), 3.58 (s, 3H), 3.10-3.14 (m, 1H), 2.93 (dt, *J*= 3.26 Hz and 13.05 Hz, 1H), 1.93-2.00 (m, 1H), 1.79 (dd, *J*= 2.26 Hz and 13.05 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C), 161.3, 143.9 (CH), 142.0 (C), 129.0 (C-*meta*), 114.7 (C- *ortho*), 95.9 (C), 50.5 (CH_3), 36.0 (CH_2), 35.5 (CH), 28.9 (CH_2)

MS (EI) *m/z* : 235 (M^+), 221, 201, 199, 195, 187, 157, 130, 102.

Analysis : calculated for $C_{13}H_{14}FNO_2$; C-66.37, H-6.00, F-8.08, N-5.95 found C-66.25, H-5.82, F-7.88, N-9.45

Crystal data of compound 137 : Empirical formula- $C_{13}H_{14}FNO_2$; Formula weight- 235.25; Temperature- 297(2) K; Wavelength- 0.71073 Å; Crystal system, space group- Orthorhombic, Pbca; Unit cell dimensions- a = 9.173(2) Å α= 90º., b = 13.436(3) Å β = 90º., c = 19.662(4) Å γ = 90º.; Volume- 2423.3(9) $Å^3$; Z, Calculated density- 8, 1.290 Mg/m^3; Absorption coefficient- 0.097 mm^{-1}; F(000)- 992; Crystal size- 0.53 x 0.44 x 0.30 mm; Theta range for data collection- 2.88 to 25.00º; Limiting indices- -10<=h<=10, -

15<=k<=15, -23<=l<=21; Reflections collected/unique- 11343/2129 [R(int) = 0.0203]; Completeness to theta = 25.00º- 100.0%; Absorption correction- Semi-empirical from equivalents; Max. and min. transmission- 0.9714 and 0.9503; Refinement method- Full-matrix least-squares on F^2; Data/restraints/parameters- 2129/0/155; Goodness-of-fit on F^2- 1.133; Final R indices [I>2sigma(I)]- R1 = 0.0475, wR2 = 0.1227; R indices (all data)- R1 = 0.0556, wR2 = 0.1273; Largest diff. peak and hole- 0.167 and -0.132 e. $Å^{-3}$.

Bond lengths [Å] and angles [º] for compound 137.

F(1)-C(11)	1.356(3)
O(1)-C(6)	1.222(2)
O(2)-C(6)	1.342(2)
O(2)-C(7)	1.440(3)
N(1)-C(2)	1.332(3)
N(1)-C(3)	1.443(3)
N(1)-H(1)	0.8600
C(1)-C(2)	1.359(3)
C(1)-C(6)	1.440(3)
C(1)-C(5)	1.505(3)
C(2)-H(2)	0.9300
C(3)-C(4)	1.508(3)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-C(5)	1.541(3)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-C(8)	1.526(3)
C(5)-H(5)	0.9800
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(8)-C(13)	1.372(3)
C(8)-C(9)	1.380(3)
C(9)-C(10)	1.385(3)
C(9)-H(9)	0.9300
C(10)-C(11)	1.364(4)
C(10)-H(10)	0.9300
C(11)-C(12)	1.352(4)
C(12)-C(13)	1.386(3)
C(12)-H(12)	0.9300
C(13)-H(13)	0.9300
C(6)-O(2)-C(7)	116.56(17)
C(2)-N(1)-C(3)	119.90(18)
C(2)-N(1)-H(1)	120.1
C(3)-N(1)-H(1)	120.1
C(2)-C(1)-C(6)	120.84(19)

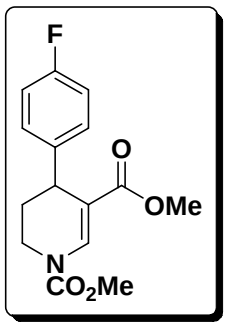
C(2)-C(1)-C(5)	120.45(18)
C(6)-C(1)-C(5)	118.52(16)
N(1)-C(2)-C(1)	124.3(2)
N(1)-C(2)-H(2)	117.9
C(1)-C(2)-H(2)	117.9
N(1)-C(3)-C(4)	109.8(2)
N(1)-C(3)-H(3A)	109.7
C(4)-C(3)-H(3A)	109.7
N(1)-C(3)-H(3B)	109.7
C(4)-C(3)-H(3B)	109.7
H(3A)-C(3)-H(3B)	108.2
C(3)-C(4)-C(5)	110.81(18)
C(3)-C(4)-H(4A)	109.5
C(5)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
C(5)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.1
C(1)-C(5)-C(8)	115.26(16)
C(1)-C(5)-C(4)	108.97(16)
C(8)-C(5)-C(4)	111.27(17)
C(1)-C(5)-H(5)	107.0
C(8)-C(5)-H(5)	107.0
C(4)-C(5)-H(5)	107.0
O(1)-C(6)-O(2)	120.95(19)
O(1)-C(6)-C(1)	124.4(2)
O(2)-C(6)-C(1)	114.64(16)
O(2)-C(7)-H(7A)	109.5
O(2)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
O(2)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(13)-C(8)-C(9)	117.9(2)
C(13)-C(8)-C(5)	123.12(18)
C(9)-C(8)-C(5)	118.94(19)
C(8)-C(9)-C(10)	121.5(2)
C(8)-C(9)-H(9)	119.3
C(10)-C(9)-H(9)	119.3
C(11)-C(10)-C(9)	118.1(2)
C(11)-C(10)-H(10)	120.9
C(9)-C(10)-H(10)	120.9
C(12)-C(11)-F(1)	119.6(3)
C(12)-C(11)-C(10)	122.5(2)
F(1)-C(11)-C(10)	117.9(3)
C(11)-C(12)-C(13)	118.5(3)
C(11)-C(12)-H(12)	120.8
C(13)-C(12)-H(12)	120.8
C(8)-C(13)-C(12)	121.5(2)
C(8)-C(13)-H(13)	119.2
C(12)-C(13)-H(13)	119.2

Torsion angles [º] for compound 137.

C(3)-N(1)-C(2)-C(1)	3.0(3)
C(6)-C(1)-C(2)-N(1)	-179.44(19)
C(5)-C(1)-C(2)-N(1)	5.7(3)
C(2)-N(1)-C(3)-C(4)	-34.9(3)
N(1)-C(3)-C(4)-C(5)	57.7(2)
C(2)-C(1)-C(5)-C(8)	-107.8(2)
C(6)-C(1)-C(5)-C(8)	77.2(2)
C(2)-C(1)-C(5)-C(4)	18.1(3)
C(6)-C(1)-C(5)-C(4)	-156.89(18)
C(3)-C(4)-C(5)-C(1)	-48.8(2)
C(3)-C(4)-C(5)-C(8)	79.4(2)
C(7)-O(2)-C(6)-O(1)	-0.5(3)
C(7)-O(2)-C(6)-C(1)	-179.05(19)
C(2)-C(1)-C(6)-O(1)	-175.3(2)
C(5)-C(1)-C(6)-O(1)	-0.3(3)
C(2)-C(1)-C(6)-O(2)	3.2(3)
C(5)-C(1)-C(6)-O(2)	178.22(17)
C(1)-C(5)-C(8)-C(13)	12.6(3)
C(4)-C(5)-C(8)-C(13)	-112.1(2)
C(1)-C(5)-C(8)-C(9)	-168.91(17)
C(4)-C(5)-C(8)-C(9)	66.4(2)
C(13)-C(8)-C(9)-C(10)	-0.2(3)
C(5)-C(8)-C(9)-C(10)	-178.79(19)
C(8)-C(9)-C(10)-C(11)	0.0(3)
C(9)-C(10)-C(11)-C(12)	0.0(4)
C(9)-C(10)-C(11)-F(1)	179.21(19)
F(1)-C(11)-C(12)-C(13)	-179.0(2)
C(10)-C(11)-C(12)-C(13)	0.2(4)
C(9)-C(8)-C(13)-C(12)	0.4(3)
C(5)-C(8)-C(13)-C(12)	178.9(2)
C(11)-C(12)-C(13)-C(8)	-0.4(4)

Formal Total Synthesis of (±)-Paroxetine

Dimethyl 4-(4-fluorophenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (138)



To a mixture of amine **137** (0.300 g, 1.28 mmol) and K_2CO_3 (0.352 g, 2.55 mmol) in DCM, $ClCO_2Me$ (0.145 g, 1.54 mmol) was added drop-wise at room temperature and stirred overnight. The reaction mixture was then washed with water, brine, dried over anhydrous Na_2SO_4, filtered and the DCM was evaporated *in vacuo*. The residue was chromatographed over silica gel using ethyl acetate-pet ether (2:8) to furnish a colourless oil (0.318 g).

Molecular formula : $C_{15}H_{16}FNO_4$

Yield : 85%

IR : 3109, 2998, 1728, 1633, 1597, 1439, 1244, 1172, 768 cm^{-1}

^{1}H NMR(200 MHz, $CDCl_3$) : δ 8.28 (bs, 1H), 7.06 (dd, *J*= 5.78 Hz and 8.79 Hz, 2H), 6.93 (t, *J*= 8.79 Hz, 2H), 3.97 (bs, 2H), 3.83 (s, 3H), 3.62 (s, 3H), 2.97 (t, *J*= 12.55 Hz, 1H), 1.84-2.03, (m, 2H)

^{13}C NMR(100 MHz, $CDCl_3$) : δ 166.9, 162.7 (C*ipso*), 160.3 (C*ipso*), 153.2 (C), 139.4 (C), 136.5 (CH), 128.9 (*meta*CH), 128.8 (*meta*CH), 115.2 (*ortho*CH), 115.0 (*ortho*CH), 108.9 (C), 53.6 (CH_3), 51.2 (CH_3), 37.8 (CH_2), 35.5 (CH), 29.0 (CH_2)

MS (EI) *m/z* : 316 (M+Na)

Spectra

1.2.5. References

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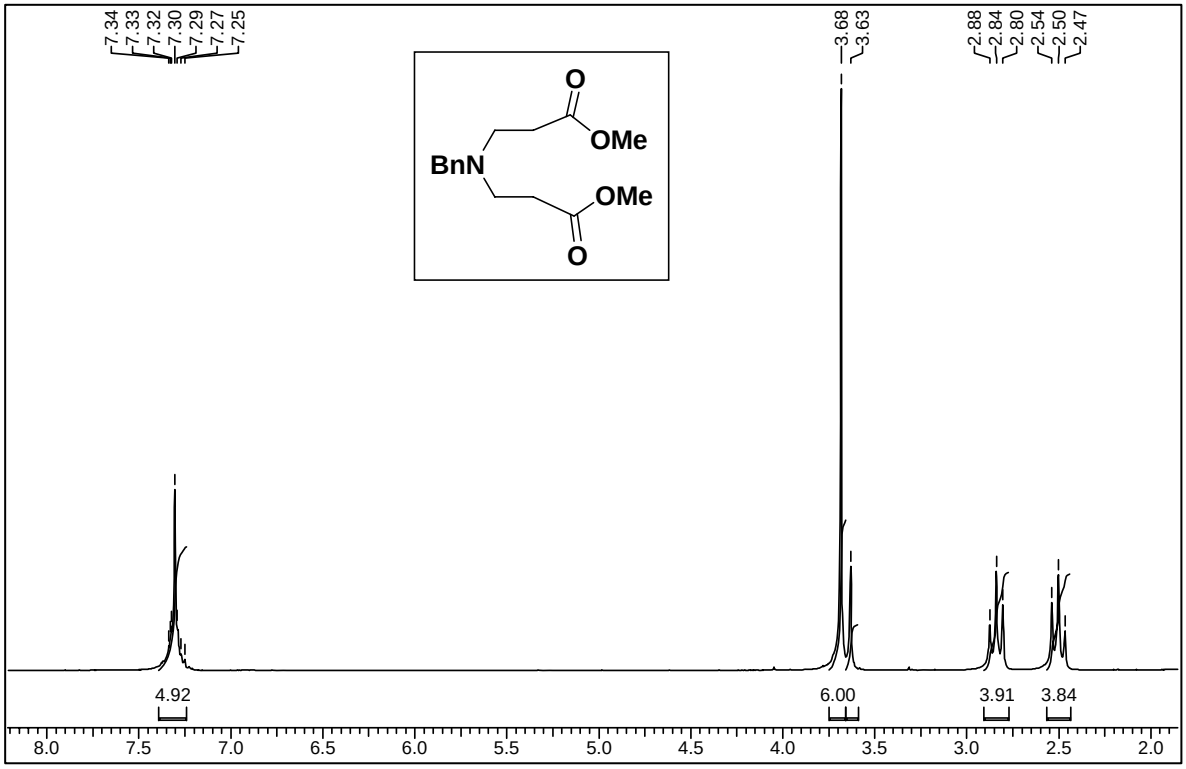
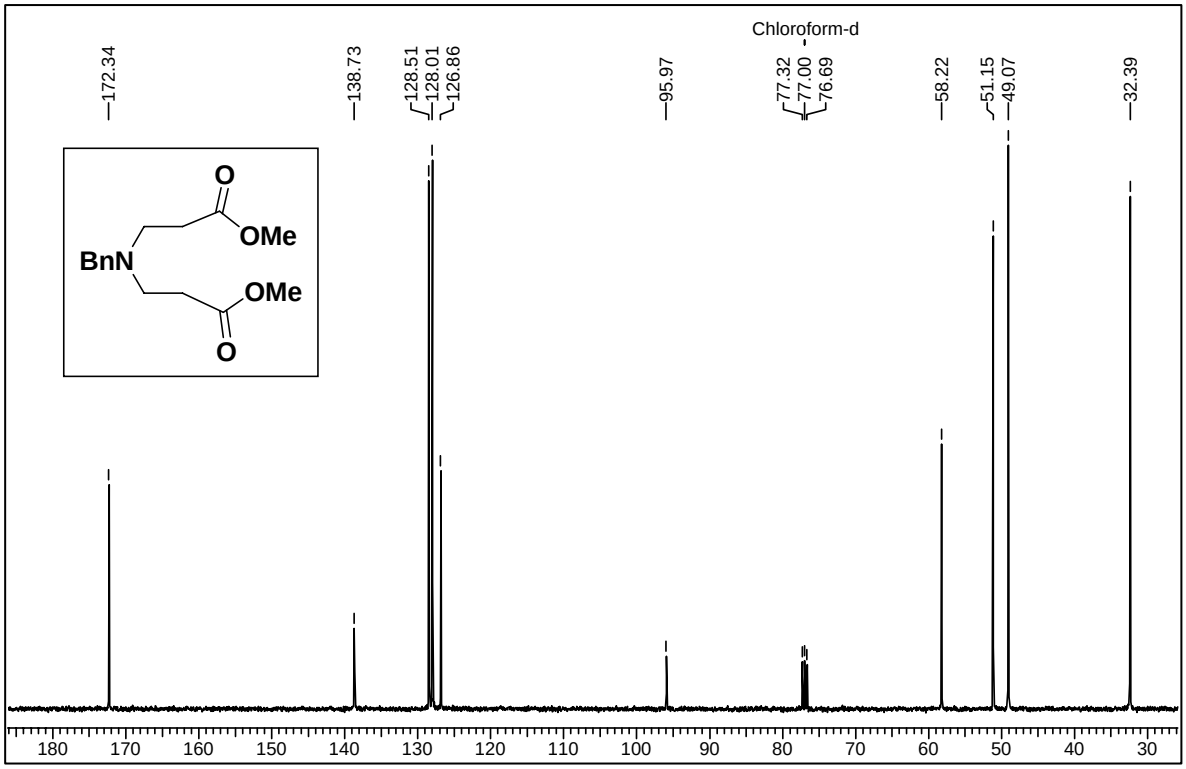
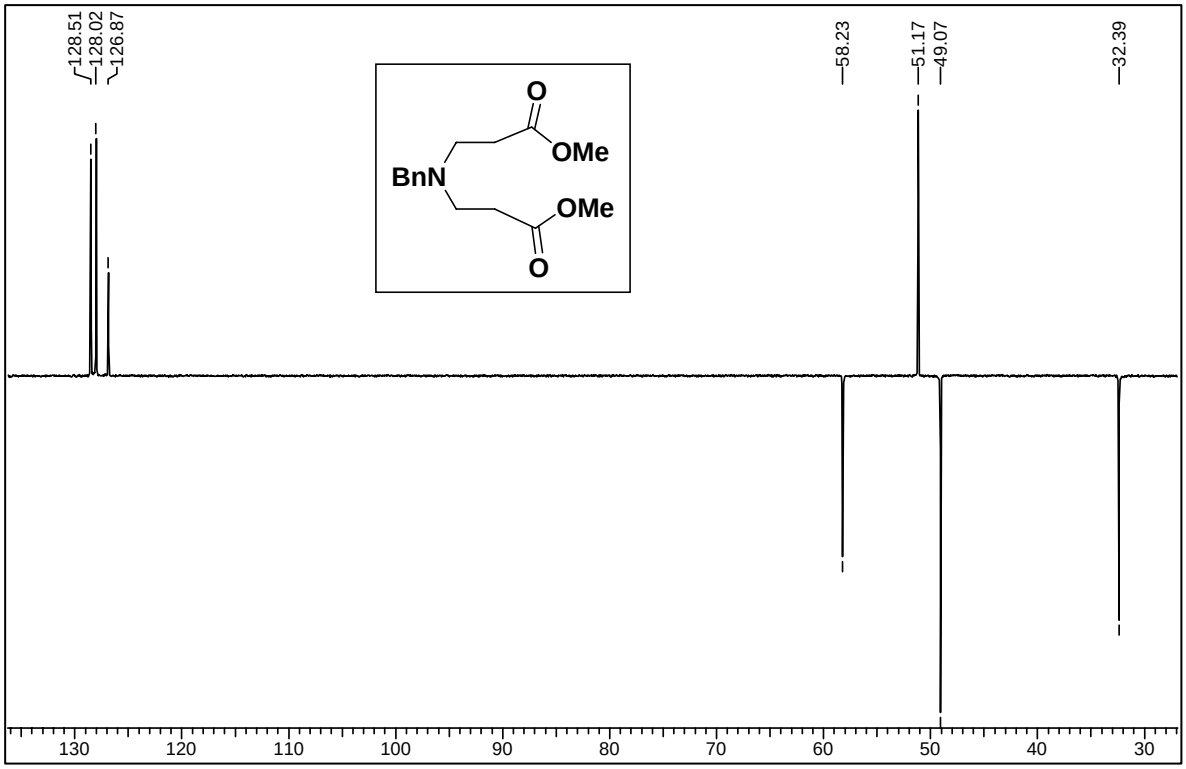


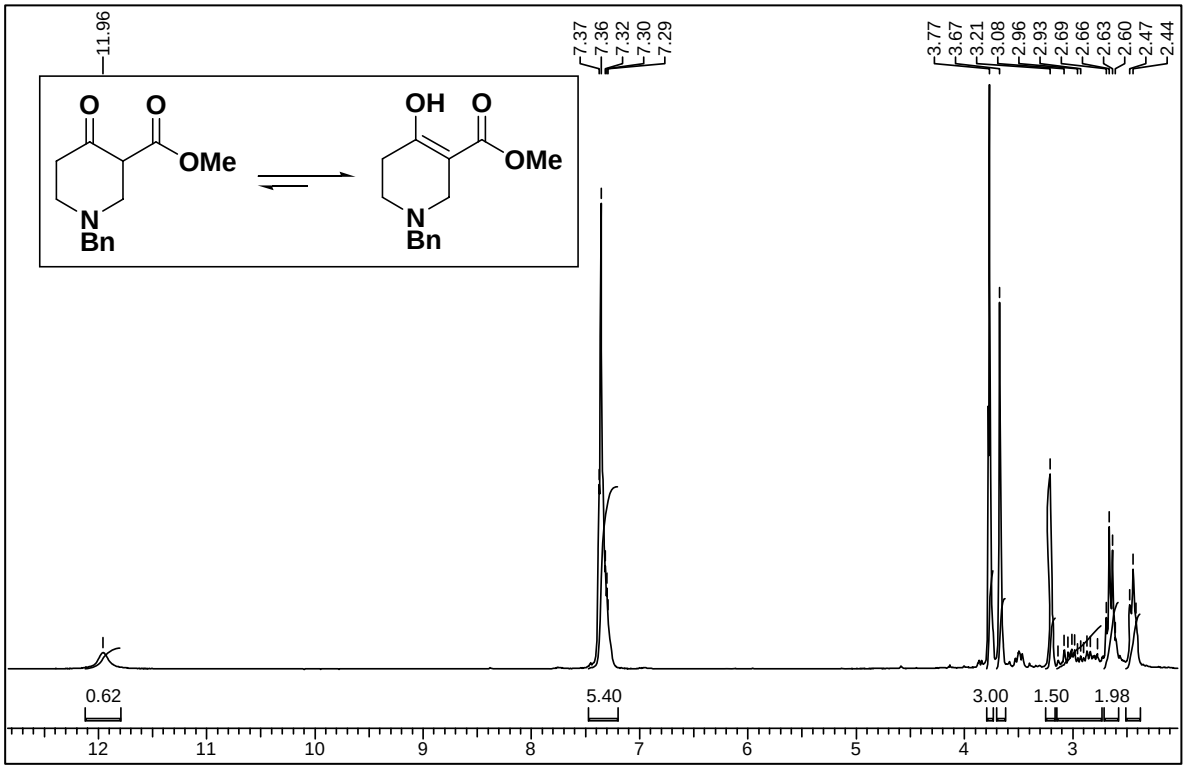
^{1}H NMR Spectrum of Compound 131 (200 MHz, $CDCl_3$)



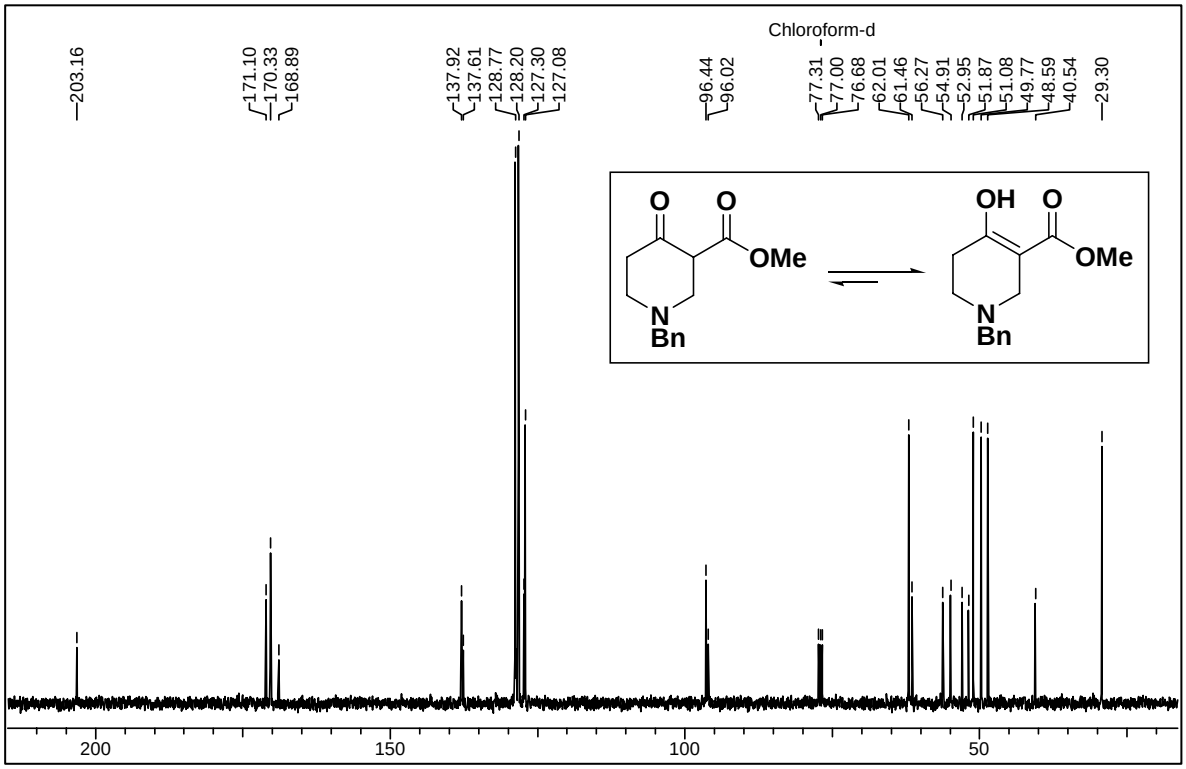
^{13}C NMR Spectrum of Compound 131 (100 MHz, $CDCl_3$ + CCl_4)



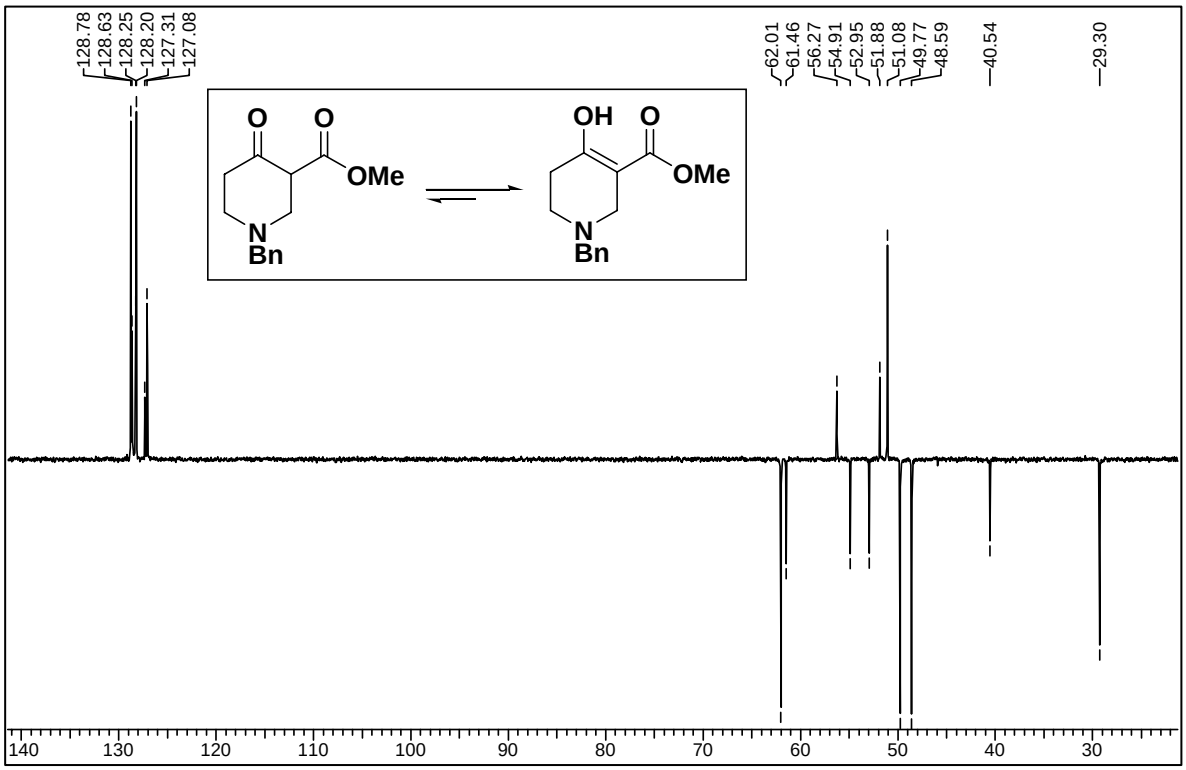
DEPT NMR Spectrum of Compound 131 (100 MHz, $CDCl_3$ + CCl_4)



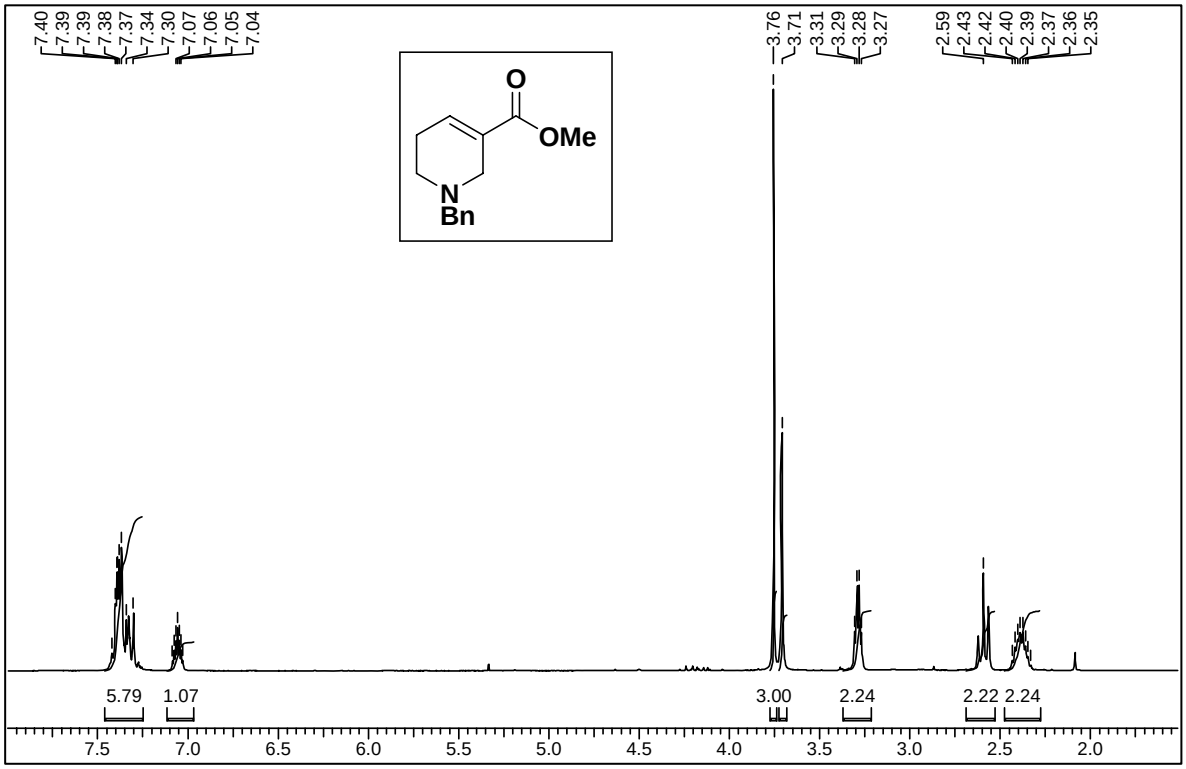
^{1}H NMR Spectrum of Compound 132 + 133 (200 MHz, $CDCl_3$)



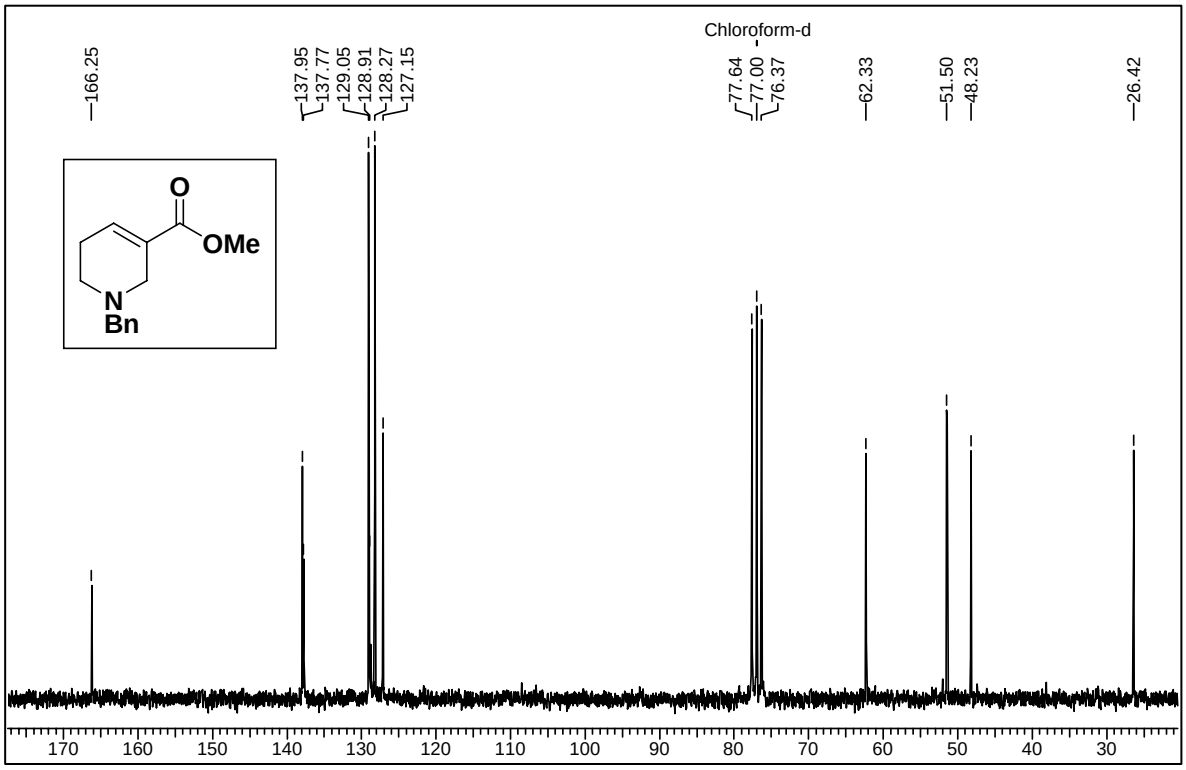
^{13}C NMR Spectrum of Compound 132 + 133 (100 MHz, $CDCl_3$ + CCl_4)



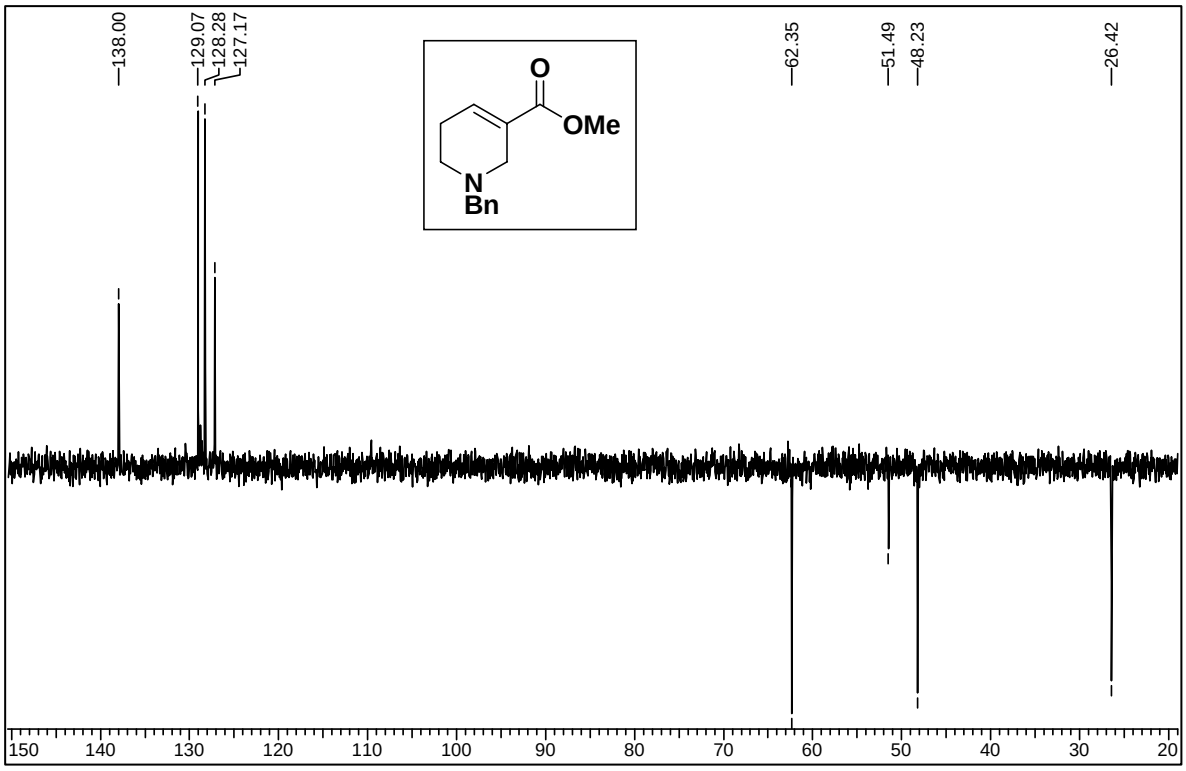
DEPT NMR Spectrum of Compound 132 + 133 (100 MHz, $CDCl_3$ + CCl_4)



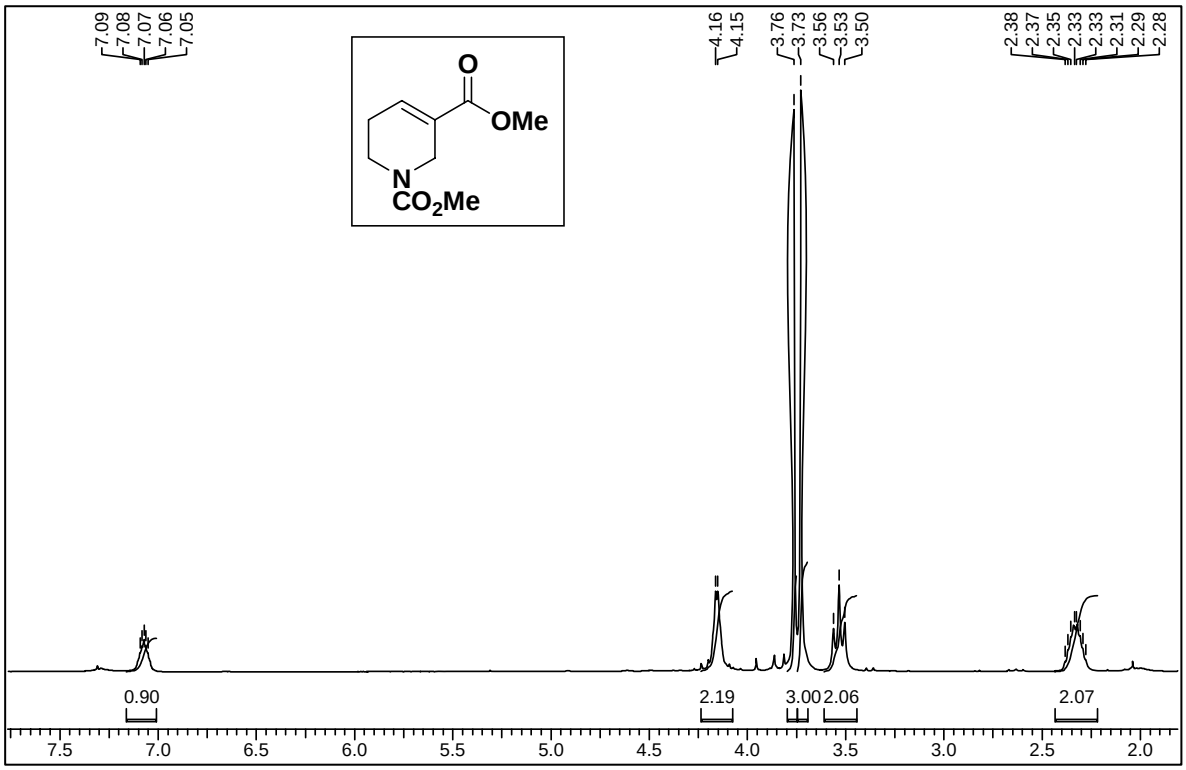
^{1}H NMR Spectrum of Compound 134 (200 MHz, $CDCl_3$)



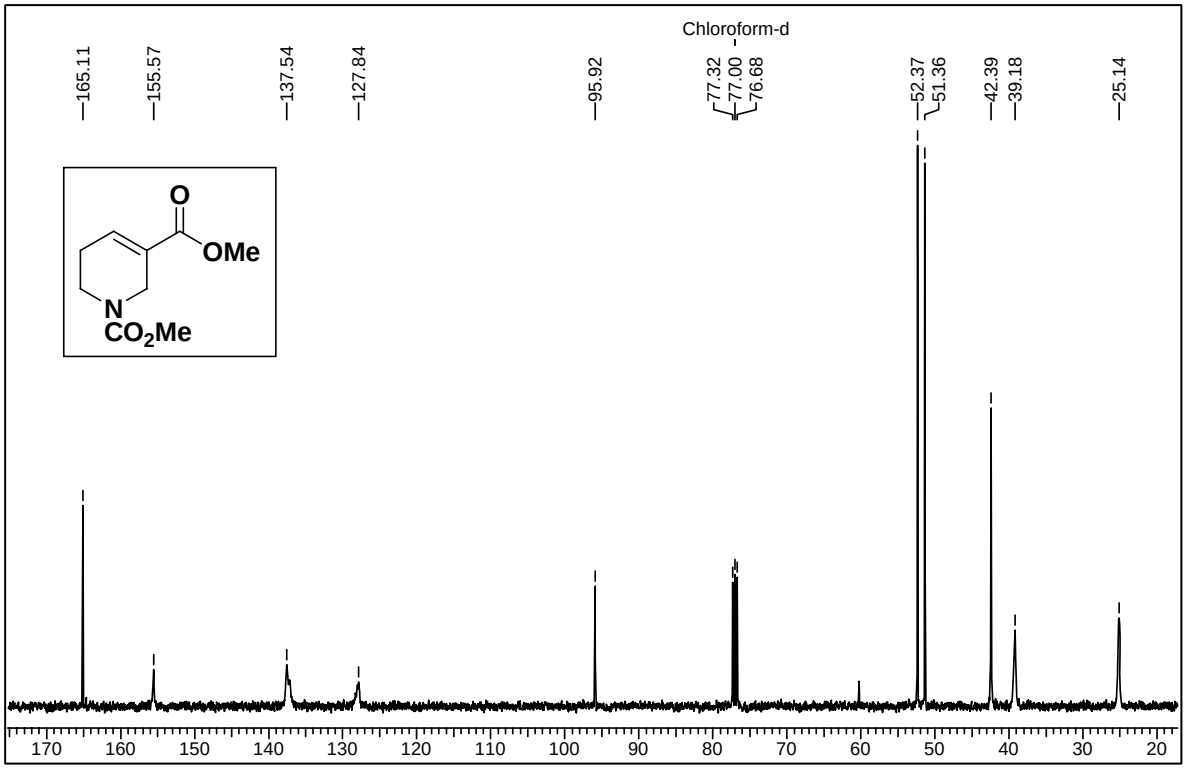
^{13}C NMR Spectrum of Compound 134 (100 MHz, $CDCl_3$)



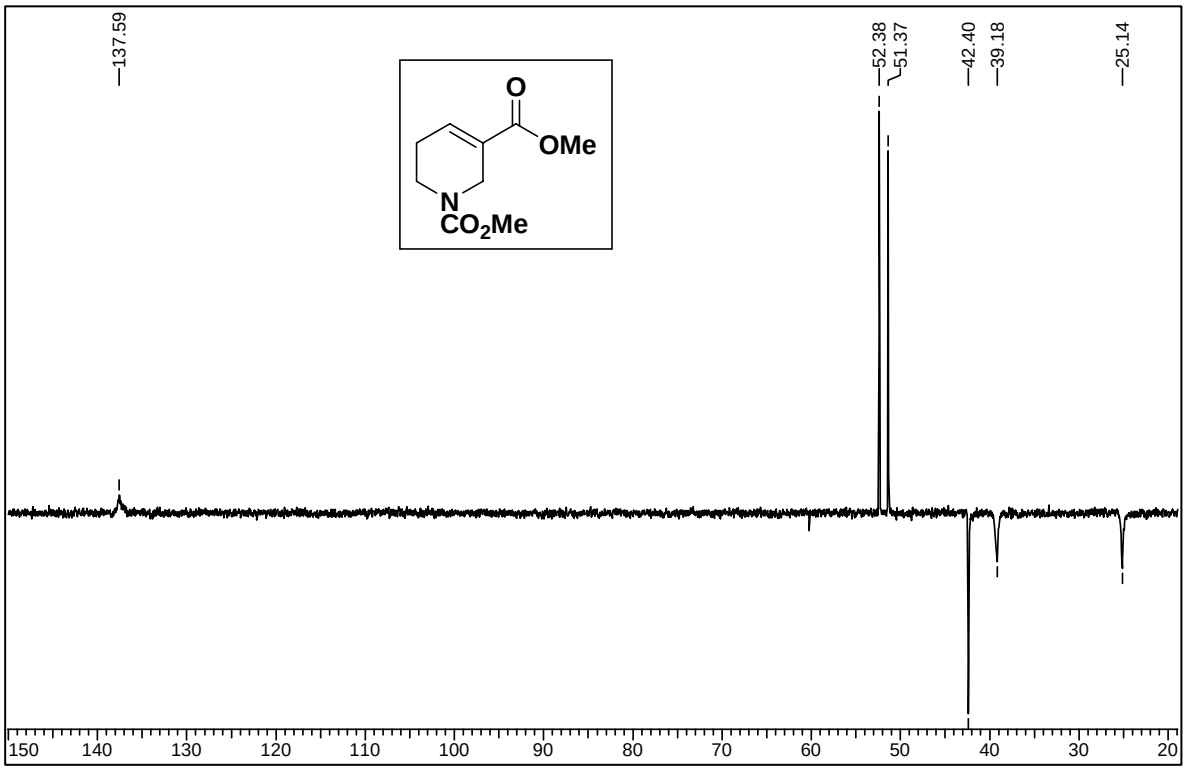
DEPT NMR Spectrum of Compound 134 (100 MHz, $CDCl_3$ + CCl_4)



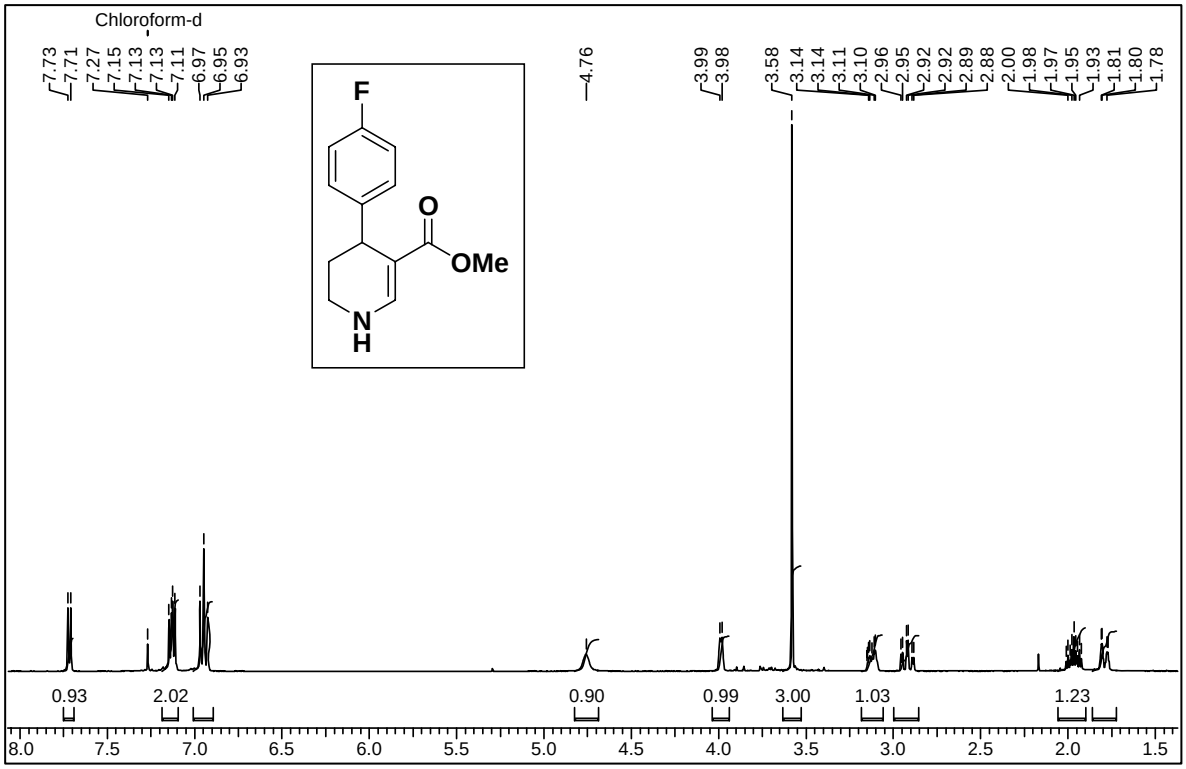
^{1}H NMR Spectrum of Compound 136 (200 MHz, $CDCl_3$)



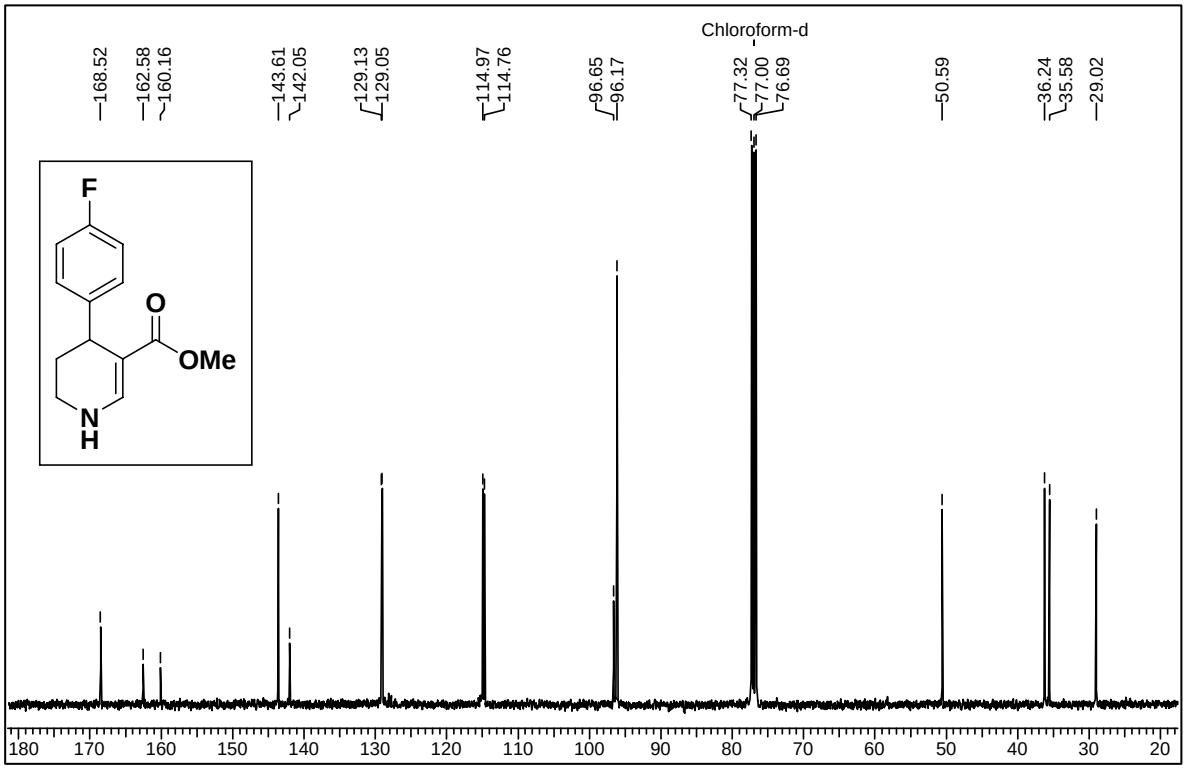
^{13}C NMR Spectrum of Compound 136 (100 MHz, $CDCl_3$ + CCl_4)



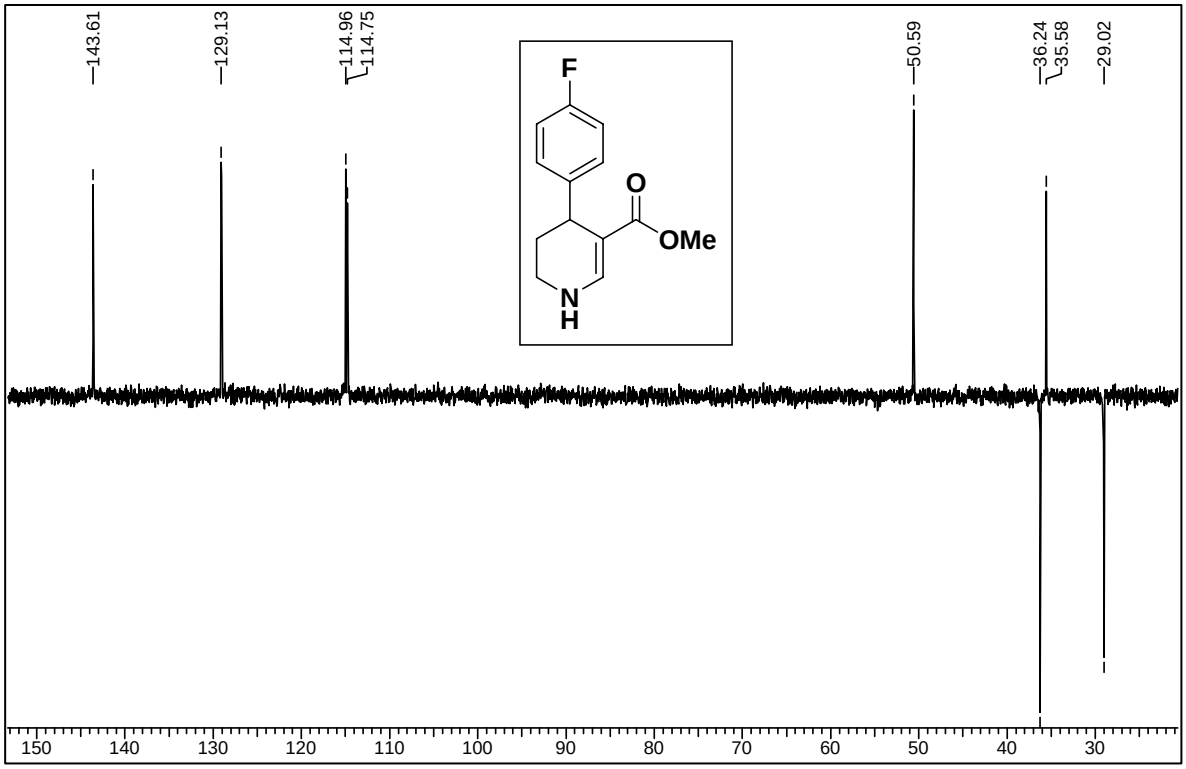
DEPT NMR Spectrum of Compound 136 (100 MHz, $CDCl_3$ + CCl_4)



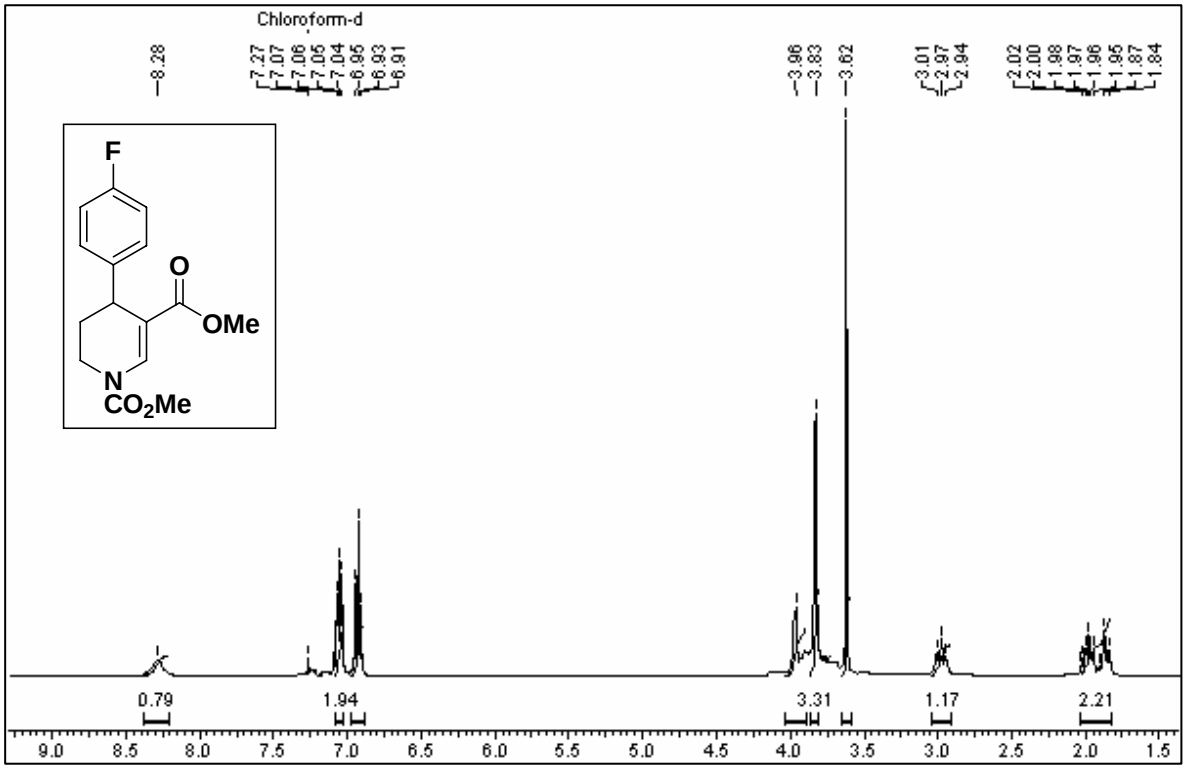
^{1}H NMR Spectrum of Compound 137 (200 MHz, $CDCl_3$)



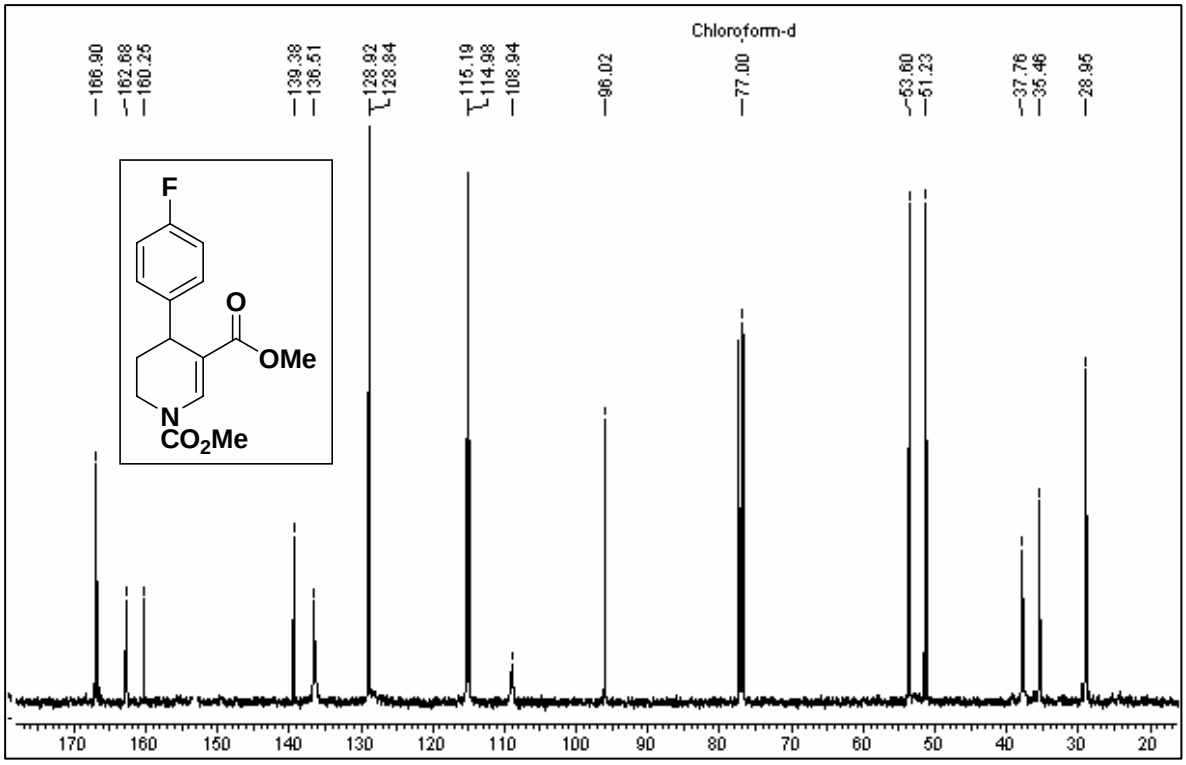
^{13}C NMR Spectrum of Compound 137 (100 MHz, $CDCl_3$ + CCl_4)



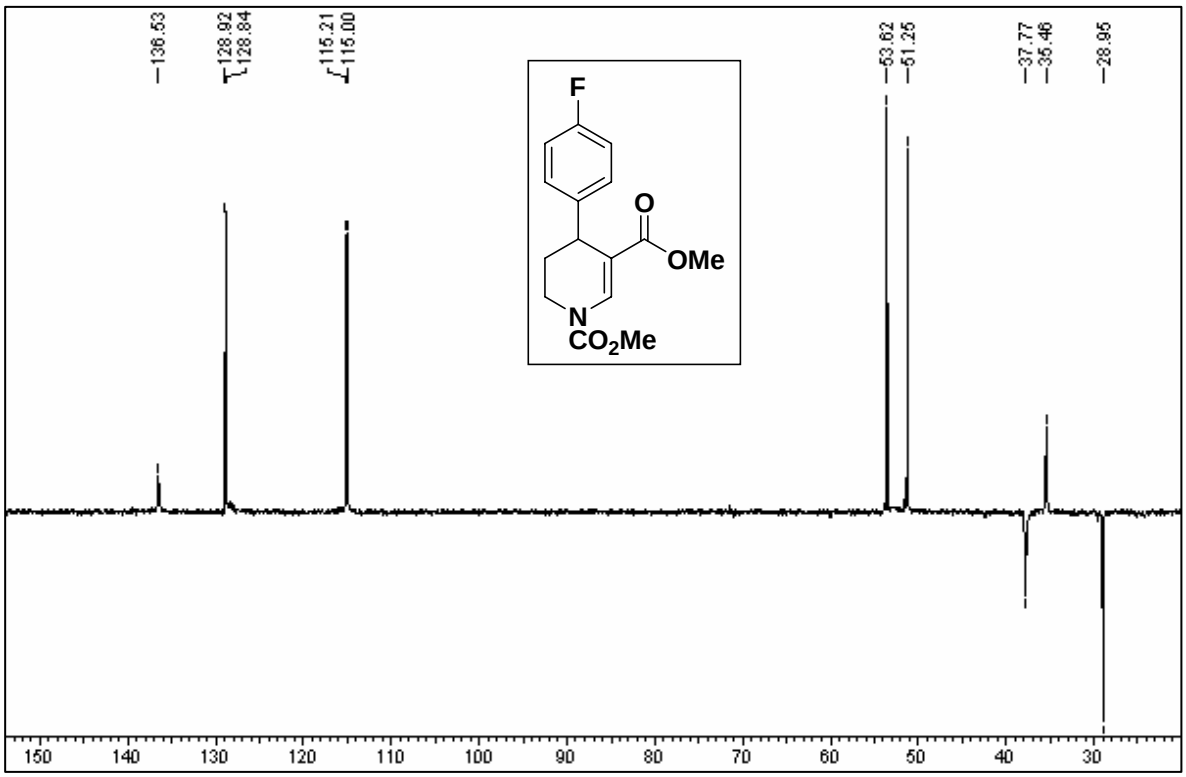
DEPT NMR Spectrum of Compound 137 (100 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR Spectrum of Compound 137 (200 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound 138 (100 MHz, $CDCl_3$ + CCl_4)



DEPT NMR Spectrum of Compound 138 (100 MHz, $CDCl_3$ + CCl_4)

Chapter-II: Synthetic Studies Towards Other Biologically Active Molecules

Section-1: Total Synthesis of (±)-Mesembrine

2.1.1. Introduction

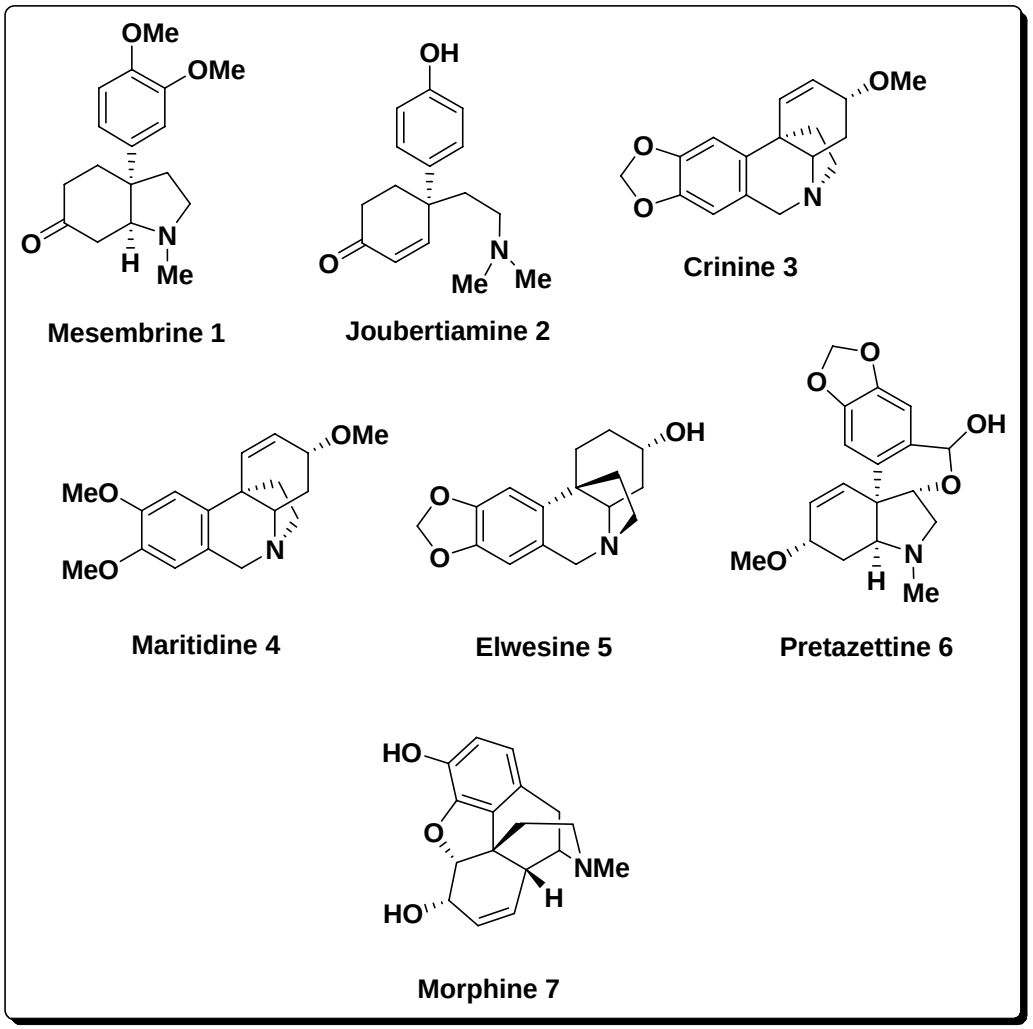


Figure 1. Mesembrine **1** and related members of the family.

Interest in the constituents of certain Sceletium species of the family Aizoaceae, e. g., mesembrine **1**, joubertiamine **2**, dates back to 1896 when the alkaloids were detected in the drug-preparation *Channa.*[1] (–)-Mesembrine **1**, chemically being *N*-methyl-3a-(3',4'-dimethoxyphenyl)-6-oxo-*cis*-octahydroindole, is a naturally occurring serotonin uptake inhibitor.[2] Its structure was elucidated by Popelak and coworkers in 1960.[3] Due to their biologically significant activities and intriguing structural relationship with the more complex *Amaryllidaceae* alkaloids like crinine **3**, maritidine **4**, elwesine **5**, pretazettine **6,** morphine **7** etc., possessing a highly congested quaternary center, these alkaloids have been attracting considerable attention of organic chemists over the years.[4]

2.1.2. Biosynthesis

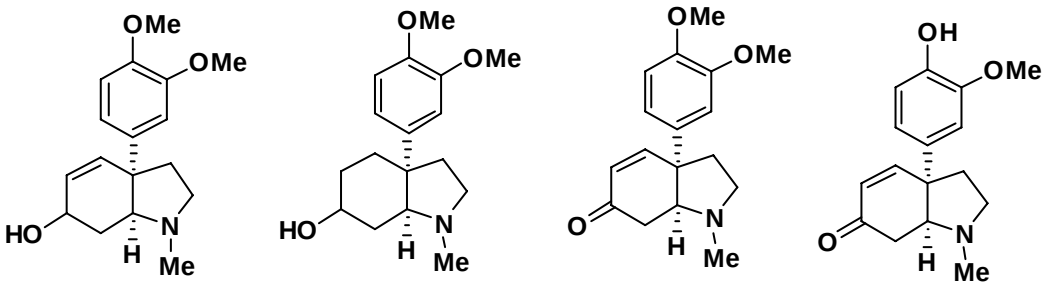
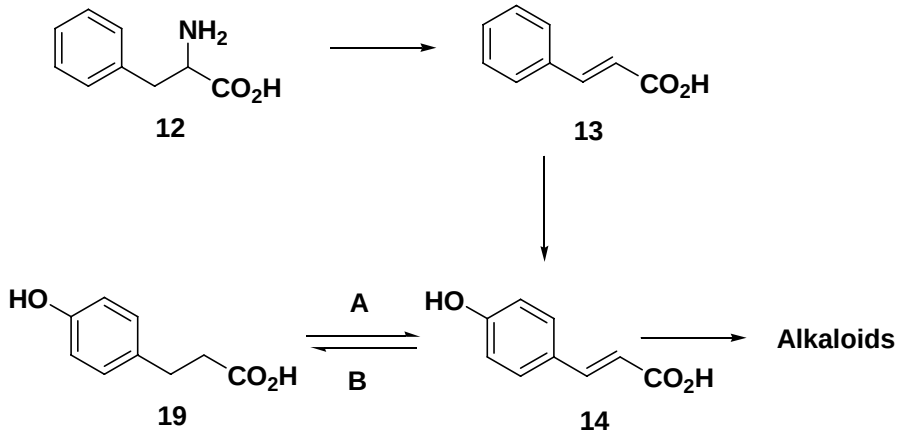


Figure 2. Some other Sceletium alkaloids.

Jeffs *et. al.* established that phloretic acid and sceletenone are intermediates in the biosynthesis of mesembrine and related octahydroindole alkaloids.[5] They administered the labeled compounds including phenylalanine **12**, cinnamic acid **13**, 4'-hydroxycinnamic acid **14** to *Sceletium strictum* and their incorporation into mesembrenol **8**, the major alkaloid are recorded. Experimental evidence suggested that 3'-aromatic oxygen function of mesembrine **1**, is introduced at a late stage of biosynthesis. This was conferred from the fact that incorporation of labeled 3',4'-dihydroxycinnamic acid [5'-^{3}H] **15** and ferulic acid [5'-^{3}H] **16** was very low. Feeding experiments with tritium labeled 4'-hydroxycinnamaldehyde [3',5'-$^{3}H_2$] **17**, 4'-hydroxycinnamyl alcohol [3',5'-$^{3}H_2$] **18**, 4'-hydroxydihydrocinnamic acid [3',5'-$^{3}H_2$] (phloretic acid) **19**, 4'-hydroxydihydrocinnamyl alcohol [3',5'-$^{3}H_2$] **20** showed that phloretic acid **19** is a good precursor. Incorporation of radiolabel from **18** into mesembrenol **8** was limited to the aromatic ring. Relatively high incorporation of **19** usually not regarded as a common intermediate can be explained by assuming the existence of a pathway in which **19** is converted to 4'-hydroxycinnamic acid **14** as shown in scheme 1.

Intact incorporation of doubly labeled ferulic acid **16** into sceletenone **11** and mesembrenol **8** was confirmed by ^{14}C data (0.15% incorporation of ^{3}H:^{14}C = 6.26:1, 46% ^{3}H retention and 0.1% incorporation ^{3}C:^{14}C = 12.6:1, 93%, ^{3}H retention, respectively). The loss of 54% tritium label in phenolic base may be accounted for by the potential lability of tritium adjacent to a phenolic hydroxy group under the conditions used in the isolation of the alkaloids.

Total Synthesis of (±)-Mesembrine



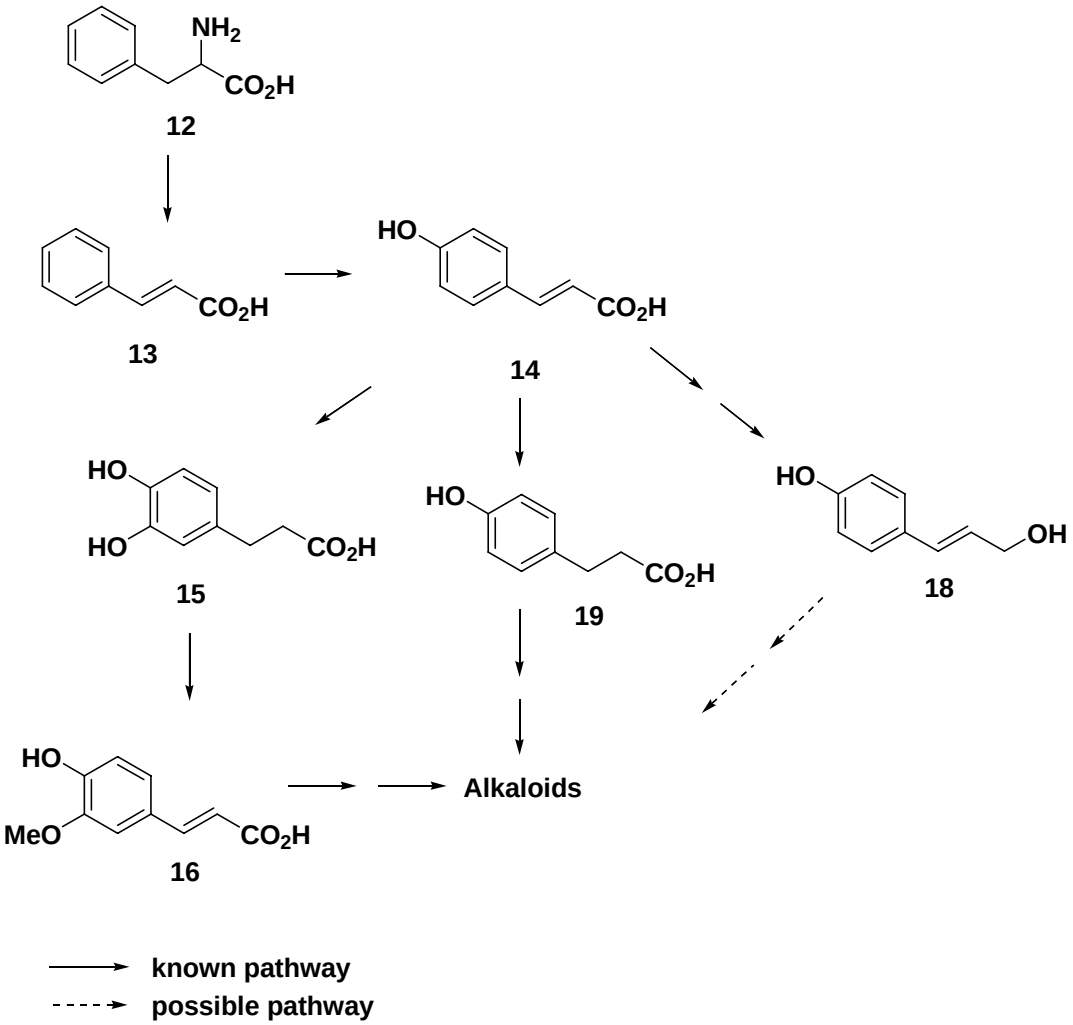
Scheme 1. Phloretic acid as a precursor to Sceletium alkaloids.

The role of ferulic acid **16** in the biosynthetic pathway was monitored by a trapping experiment involving the feeding of phloretic acid [3',5'-$^{3}H_2$] **19** in the presence of excess of inactive ferulic acid **16**. When radiolabeled **19** was administered to *Sceletium strictum* plant alone, a 2.26% incorporation of label in mesembrenol **8** in the presence of 6 molar excess of **16** incorporation of label was lowered to 0.92% and accompanied by a 0.32% incorporation of **19** is lowered in the trapping experiment but is still at a relatively high level demonstrating its direct incorporation into the alkaloids. Incorporation of various precursors was consistent with the existence of a metabolic grid as represented in scheme 2.

Role of sceletenone

Sceletenone [3',5'-$^{3}H_2$] **11** was administered to *Sceletium strictum* and after 12 days mesembrenol **8**, isolated after rigorous purification retained a level of radioactivity corresponding to 2% incorporation. This indicated that sceletenone **11** is an intermediate in the biosynthesis of 3',4'-dioxyaryl alkaloids of the mesembrine family and 3'-aromatic oxygen was introduced at a late stage after the formation of octahydroindole ring.

Further, when mesembrenone-[5'-^{3}H] and mesembrenone-[4'-*o*-methyl-^{3}H] **10** were fed to *S. strictum*, 1.1% incorporation of *o*-methyl labeled mesembrenone into mesembrenol and incorporation of mesembrenone [5'-^{3}H] into mesembrine **1** and mesembrenol **8** suggested that biosynthesis of the mesembrine alkaloids involved sequential reduction of the cyclohexenone chromophore.



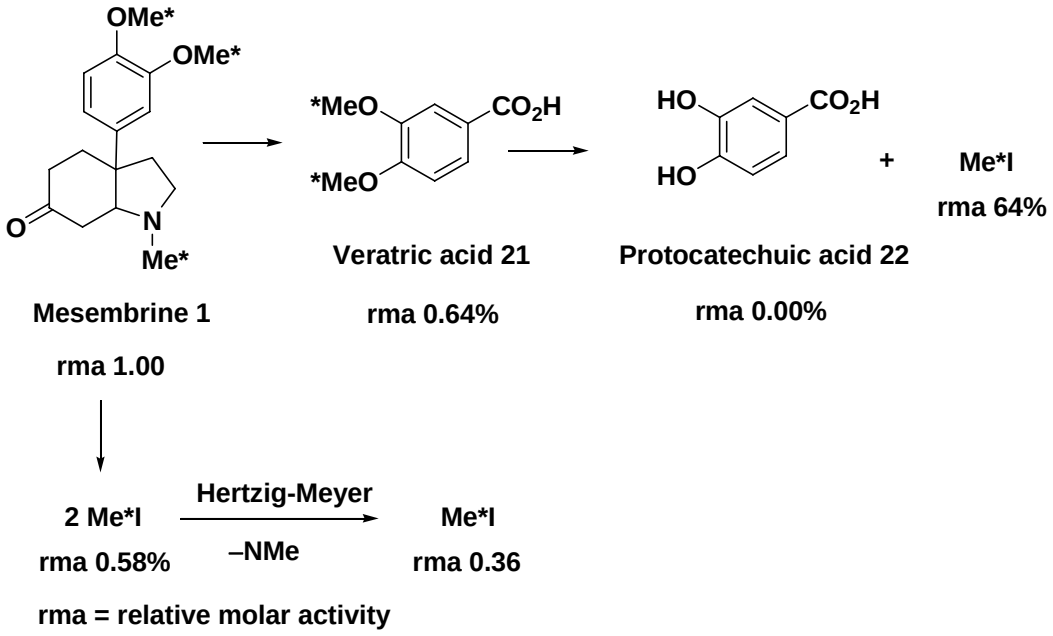
Scheme 2. Established and possible metabolic pathways.

Feeding of mesembrenone-[5'-^{3}H] **10** and sceletenone-[5'-^{3}H] **11** to the young 3-month old plants resulted in spectacularly high incorporation into mesembrenol. The result provided firm evidence for the formation of the non-phenolic alkaloids from the phenolic alkaloids. Also, since sceletenone **11** isolated from the feeding of mesembrenone-[5'-^{3}H] **10** to *Sceletum strictum* was not radioactive, *o*-demethylation did not appear to be an important biosynthetic process in the formation of phenolic alkaloids in this plant.

In an independent experiment Herbert and Kattah[6] isolated radioactive mesembrine **1** from radiolabeled methionine feeding experiment (^{14}C-methyl labeled) showed that all of the radioactivity was associated with methyl groups (Zeisel-Hertzig-Meyer). Each methyl is equally labeled since the ratio of activity for the two methoxy groups to the *N*-methyl is very close to 2:1. This was further confirmed independently by separate experiments where, vigorous oxidation of methionine-derived mesembrine to veratric acid **21** was found

to contain 64% of the original activity present in the alkaloid corresponding to the two methoxy groups. This was in turn confirmed by its conversion to inactive protocatechuic acid **22** and radiolabeled methyl iodide.

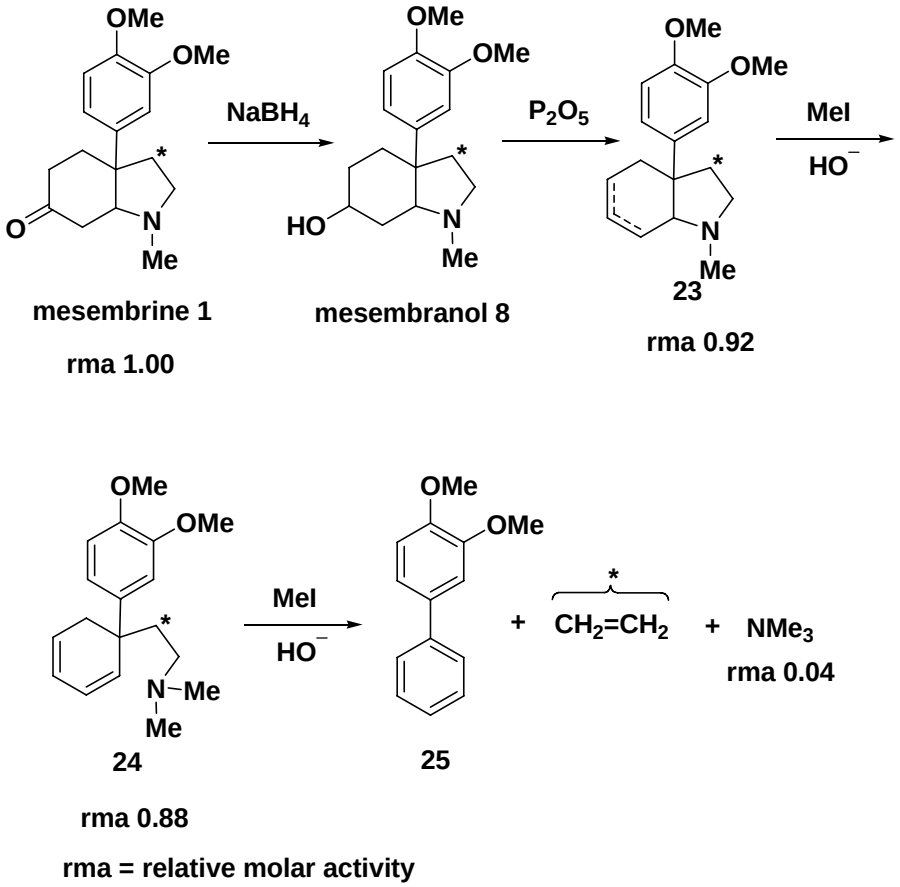
Feeding experiments with phenylalanine **12**, in which the site of the ^{14}C was located at C-2, C-3 or uniformly on the carbons of the aromatic ring, only the ring labeled amino acid resulted in any significant incorporation of radiolabel into the alkaloid fraction. Feeding with both [*2*-^{14}C] and [*3*-^{14}C]tyrosines resulted in a significant incorporation of the label into the alkaloid fraction. From these observations, it was concluded that phenylalanine **12** is not converted to tyrosine in the biosynthesis of this alkaloid and each of these amino acids follows separate metabolic routes. Vigorous oxidation of mesembrine derived from DL-[*ring*-^{14}C]phenylalanine afforded veratric acid **21**, which was shown to contain all of the radioactivity present in the original alkaloid. Therefore, it was deduced that aromatic ring of the alkaloid is derived from aromatic nucleus of the amino acid.



Scheme 3. Determination of source of aromatic ring of mesembrine from nucleic acid.

That the entire side chain of the amino acid was lost in the conversion of phenylalanine **12** to mesembrine **1** was evident from the lack of incorporation of label from the feeding experiments with DL-[*2*-^{14}C]phenylalanine and DL-[*3*-^{14}C]phenylalanine. When labeled mesembrine derived from [3-^{14}C]tyrosine was converted to **24** and subjected to Hofmann degradation, 3,4-dimethoxybiphenyl **25** and Et_3N (trapped as tetramethylammonium iodide) produced from the reaction were virtually inactive. These

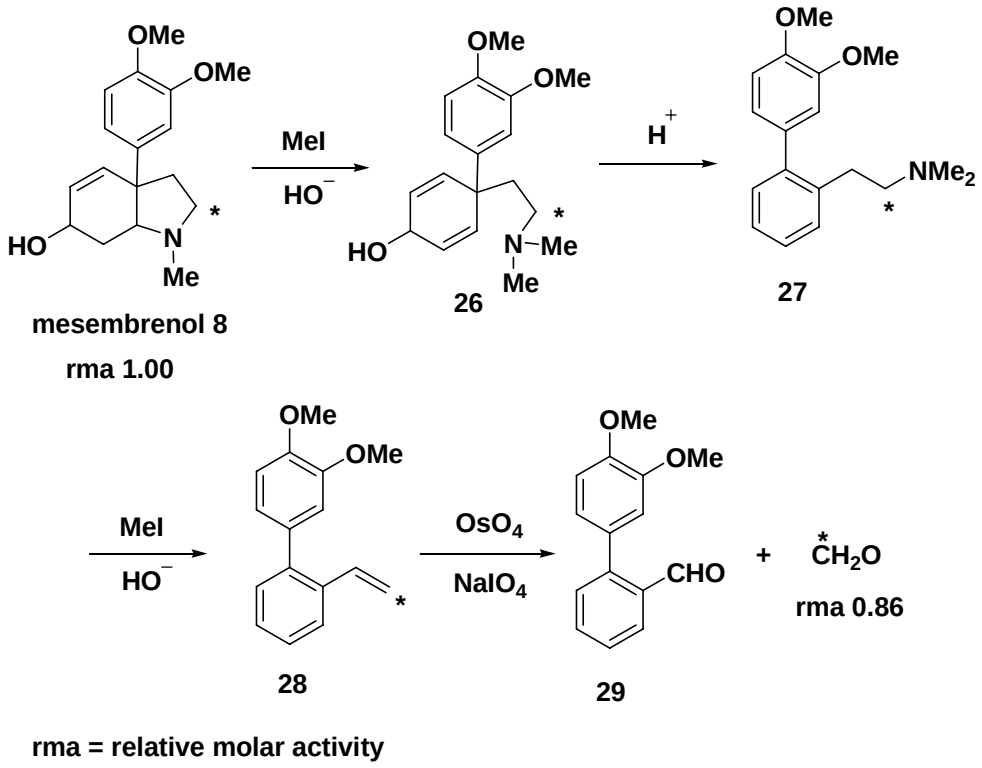
results indicated that the label is contained on the ethylene produced in this reaction and restricts the sites of label in the mesembrine to the C-2 and C-3 carbons of the ethamine bridge (scheme 4 and 5).



Scheme 4. Fate of C-3 carbon in the amino acid metabolism and formation of octahydroindole system.

The Hofmann degradation of mesembrenol **8**, the major alkaloid in *S. strictum* afforded the dienol, which without isolation was smoothly rearranged in 1 N hydrochloric acid to the biphenyl system **27.** The structure of **27** was confirmed by its chemical synthesis. A second Hofmann degradation on **27** afforded styrene **28**, which on cleavage with OsO_4, $NaIO_4$ in aq. dioxane gave a quantitative yields of formaldehyde, which was isolated as its dimedone adduct. When a sample of mesembrenol derived from a feeding experiment with [*2*-^{14}C]tyrosine was degraded in this manner the radioactive label was shown to be located to greater than 86% on the C-2 carbon atom, which indicated that tyrosine is incorporated intact into the octahydroindole skeleton of these alkaloids (scheme 4 and 5).

Total Synthesis of (±)-Mesembrine



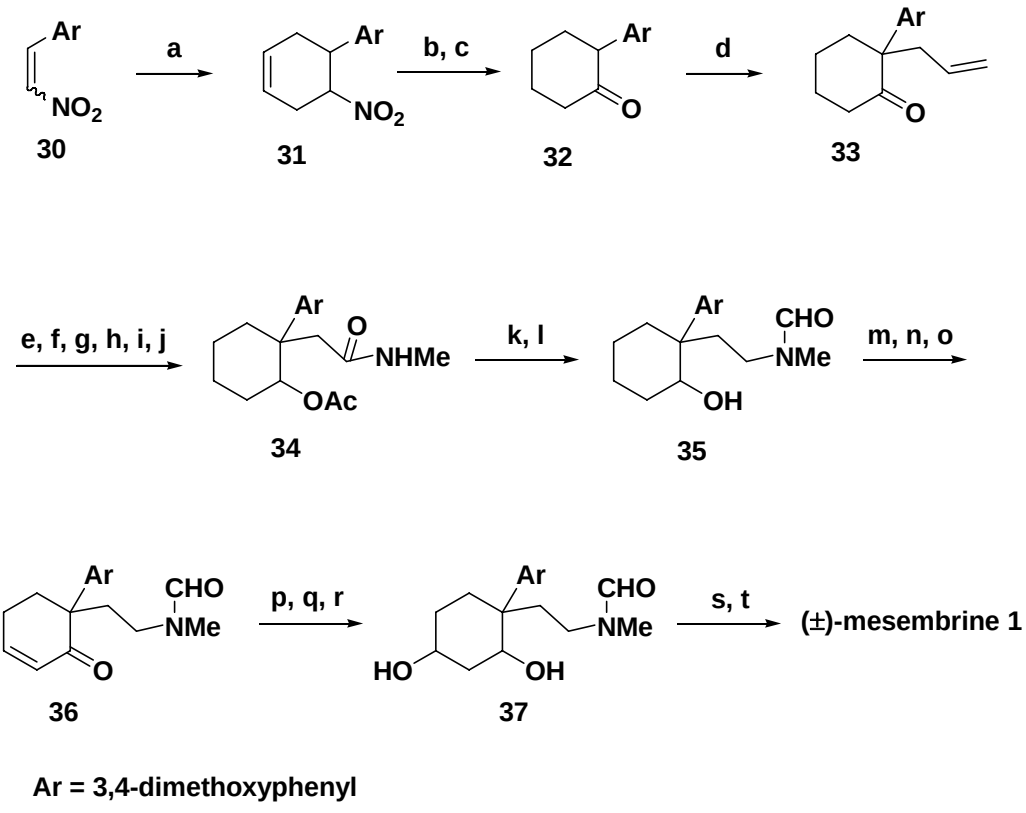
Scheme 5. Fate of C-2 carbon in the amino acid metabolism and formation of octahydroindole system

Thus, biosynthetic studies concluded that aromatic ring of phenylalanine provided the aromatic C_6 unit present as the 3,4-dimethoxyphenyl ring and C_6C_2N unit is derived from tyrosine, which constitutes the octahydroindole moiety. The carbons of the *O*- and *N*-methyl groups are provided by the *S* methyl of methionine, presumably *via* the agency of the ubiquitous biological transmethylating agent *S*-adenosylmethionine.

2.1.3. Literature Review

Present section details the reported syntheses of mesembrine **1**.

Roudriguez[7a,b] (*Tetrahedron Lett.* **1965**, 4847-4851; *Tetrahedron*, **1968**, *24*, 6583-6589)

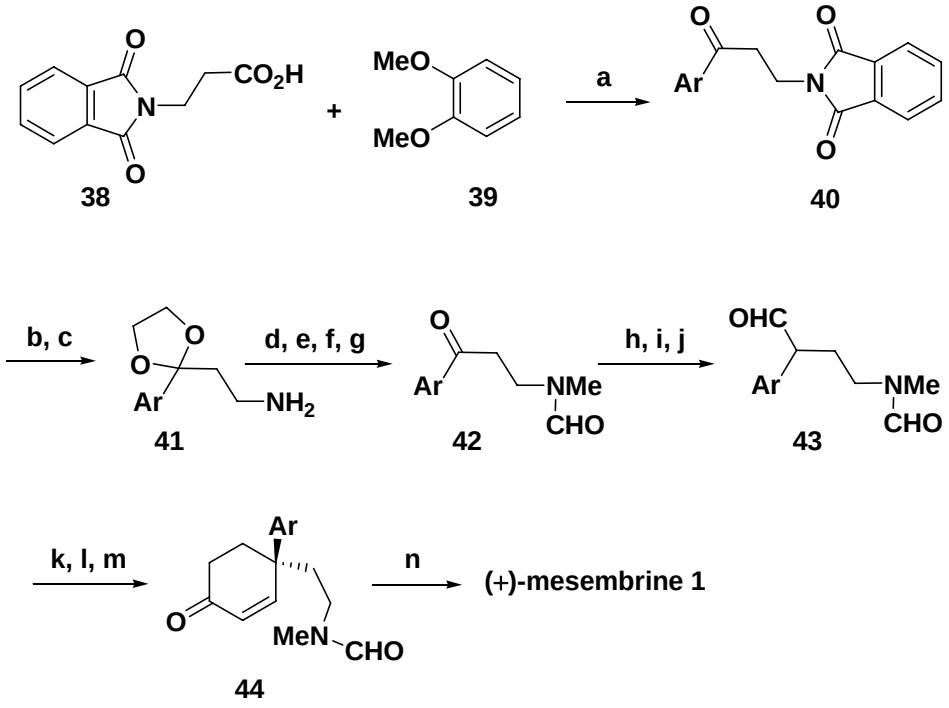


Scheme 6. *Reagents and conditions:* a) butadiene, 76%; b) Nef reaction, 70%; c) H_2, 5% Pd/C; d) NaH, allyl bromide, 80%; e) $LiAlH_4$, 90%; f) Ac_2O, pyridine, 92%; g) OsO_4, $NaIO_4$, 80%; h) Ag_2O, 93%; i) $(COCl)_2$; j) $MeNH_2$; k) $LiAlH_4$, 90%; l) HCO_2Ac, 92%; m) H_2CrO_4, 80%; n) PTAB, 90%; o) $CaCO_3$, DMF, reflux, 85%; p) Clorox oxidation, quantitative; q) $Cr(OAc)_2$, 40%; r) $NaBH_4$, quantitative; s) Pt/O_2, EtOAc, 3 d; t) H_3O^+, 50%.

Roudriguez and Shamma reported a total synthesis of (±)-mesembrine **1** using nitrostyrene and butadiene as the starting materials employing Diels-Alder reaction. Nitrostyrene **30** was condensed with butadiene to furnish the nitrocyclohexene **31**. Ketone **32** was obtained by Nef reaction on **31** followed by preferential catalytic reduction (scheme 6). Compound **32** was alkylated with ally1 bromide to yield olefin **33**. Reduction of **33** with $LiAlH_4$, followed by acetylation afforded the acetate, which with OsO_4-$NaIO_4$ oxidation and further oxidation of the resultant aldehyde with silver oxide, followed by amidation

gave compound **34**. $LiAlH_4$ reduction of **34** gave the amino alcohol, which upon *N*-formylation gave compound **35**. Compound **35** was oxidized to give ketone, which upon bromination followed by dehydrobromination, produced enone **36**. Enone **36** was epoxidized with Clorox and subsequent reduction of the epoxide using chromous acetate, followed by reduction with $NaBH_4$, afforded diol **37**. Preferential oxidation with Pt/air, followed by acid catalyzed dehydration, finally yielded (±)-mesembrine **1**.

Yamada[8] (*Tetrahedron Lett.* **1971**, 1133-1136)

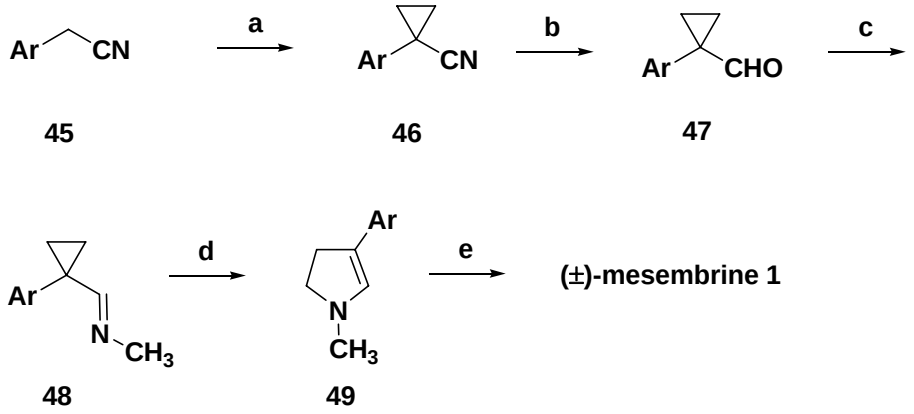


Scheme 7. *Reagents and conditions:* a) PPA, 59%; b) $HOCH_2CH_2OH$, PTSA; c) N_2H_4, 82%; d) HCO_2Ac; e) $LiAlH_4$, 82%; f) HCO_2Ac; g) PTSA, acetone, 70%; h) $ClCH_2CO_2Me$, KO*t*Bu; i) NaOH; j) AcOH, Δ, 90%; k) L-proline pyrrolidide; l) MVK; m) AcOH, H_2O, pyrrolidine, 38%; n) 10% HCl-EtOH, 78%.

Yamada and Otani reported the first chiral synthesis of (+)-mesembrine **1** employing L-proline derivative (scheme 7). *β*-phthaloylaminopropionic acid **38** was condensed with veratrole **39** to furnish phthaloylamino ketone **40**. Ketone **40** was ketalized with ethylene glycol followed by treatment with hydrazine hydrate to give an amine **41**. Formylation of **41**, followed by reduction of the formamide with $LiA1H_4$ gave a secondary amine, which was formylated again and the ketal was hydrolyzed to give ketone 4**2**. Conversion of ketone **42** to aldehyde **43** was accomplished with modified Darzens method. Aldehyde **43** was treated with methyl vinyl ketone in the presence of L-proline pyrrolidide

and the Michael adduct upon annulation gave cyclohexenone **44** in 38% yield. Treatment of **44** with 10% ethanolic HCl furnished (+)-mesembrine **1**.

Stevens[1] (*J. Org. Chem.* **1975**, *40*, 3495-3498)



Scheme 8. *Reagents and conditions:* a) LDA, EDC, THF, –78 ºC, 86%; b) DIBAL; c) $MeNH_2$; d) NH_4I; e) MVK, HCl.

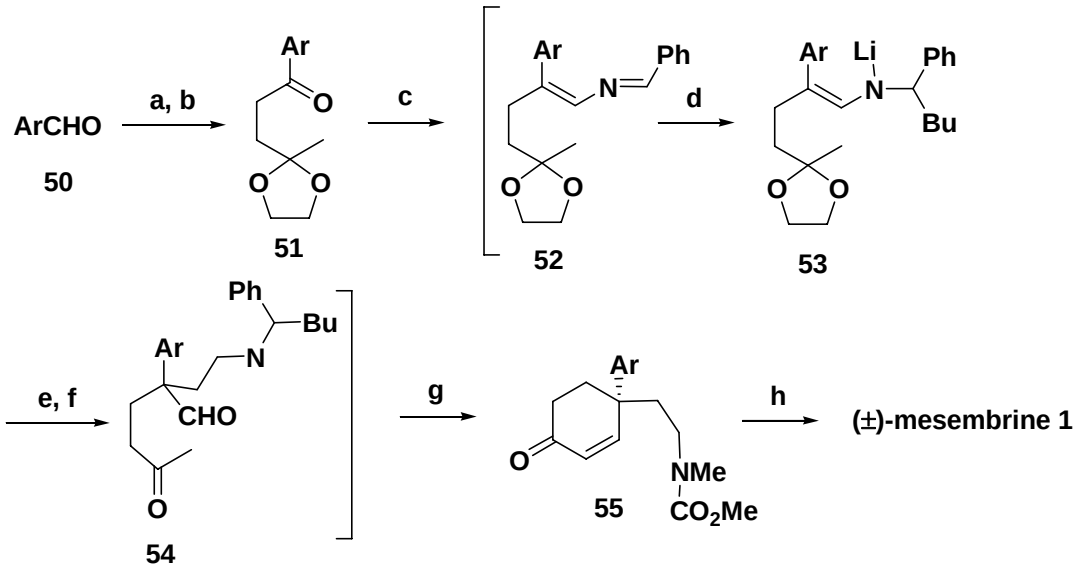
Stevens *et. al.* reported an efficient total synthesis of (±)-mesembrine **1** employing acid-promoted rearrangement of cyclopropylimine to 2-pyrroline, followed by acid-catalyzed annulation of this intermediate with methyl vinyl ketone. Cyclopropanation of 3,4-dimethoxyphenyl acetonitrile **45** was effected with EDC using LDA to obtain nitrile **46**. Reduction of **46** to the corresponding aldehyde **47** employing DIBAL and subsequent imine formation proceeded smoothly to afford cyclopropylimine **48**, which upon ammonium iodide induced rearrangement furnished the required 2-pyrroline **49.** HCl-catalyzed annulation of **49** with methyl vinyl ketone provided (±)-mesembrine **1** (scheme 8).

Tahk and Keely[9] reported a similar synthesis of (±)-mesembrine **1** employing pyrroline **49**.

Martin[10] (*J. Org. Chem.* **1979**, *44*, 3391-3396)

Martin *et. al.* reported a facile total synthesis (±)-mesembrine **1**, employing a general strategy for the construction of quaternary carbon atoms *via* geminal alkylation of monoprotected 1,4-dione as the key step. Requisite monoprotected 1,4-dione **51** was conveniently prepared in 75% overall yield by addition of the Grignard reagent derived

from 2-methyl-2-(2-bromoethyl)-1,3-dioxolane to veratraldehyde **50**, followed by Jones oxidation (scheme 9).



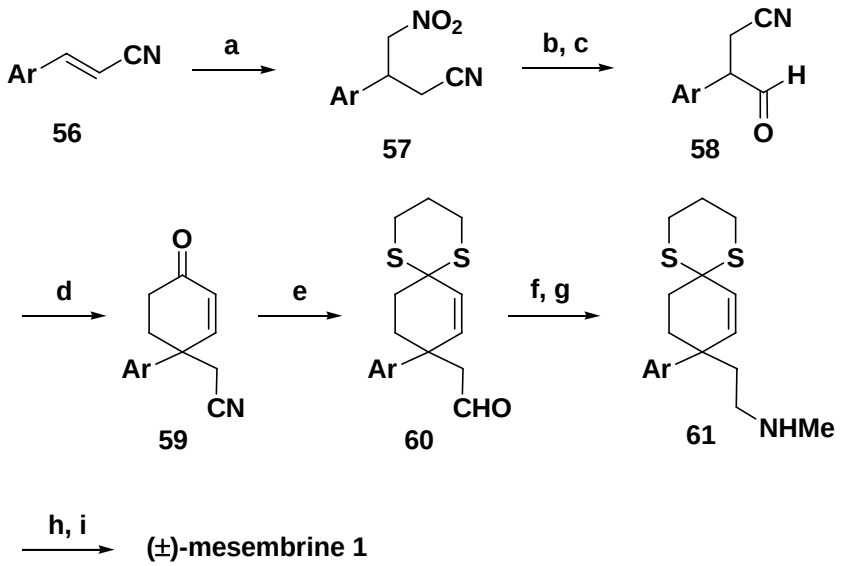
Scheme 9. *Reagents and conditions:* a) $BrMg(CH_2)_2C(OCH_2CH_2O)CH_3$, THF; b) $HCrO_4^-$, 75%; c) $PhCH{=}NCHLiP(O)(OEt)_2$, THF, –78 ºC to r t, reflux; d) BuLi, –78 ºC; e) $Br(CH_2)_2NMeCO_2Me$, –78 ºC to 25 ºC; f) H_3O^+; g) KOH, H_2O, MeOH, 25 ºC, 65%; h) KOH, H_2O, EtOH, Δ, 82%.

Olefination of **51** with diethyl *N*-benzylideneaminolithiomethyl phosphonate afforded 2-azadiene **52**, which cleanly underwent regioselective 1,2-addition of BuLi generating the metallo enamine **53** *in situ*, which upon alkylation with *N*-(2-bromomethyl)-*N*-methylcarbamate followed by acidic work up furnished *δ*-ketoaldehyde **54**. Subsequent treatment of δ-ketoaldehyde **54** with aq. KOH-MeOH resulted in facile annulation to give the key intermediate 4,4-disubstituted cyclohexenone **55** in 65% overall yield. Hydroxide-induced *N*-decarbomethoxylation of **55**, followed by ensuing spontaneous cyclization of the intermediate furnished (±)-mesembrine **1** in 82% yield.

Sanchez[11] (*Chem. Lett.* **1981**, 891-894)

Sanchez and Tabbals reported a total synthesis of (±)-mesembrine **1**, employing cinnamonitrile as the starting material. Conjugate addition of CH_3NO_2 to cinnamonitrile **56** using Triton-B in CH_3CN or KF/18-crown-6 furnished nitro compound **57**. Compound **57** was subjected to modified Nef reaction, followed by acid hydrolysis of the acetal intermediate to obtain cyanoaldehyde **58** in 73% yield (scheme 10).

Total Synthesis of (±)-Mesembrine



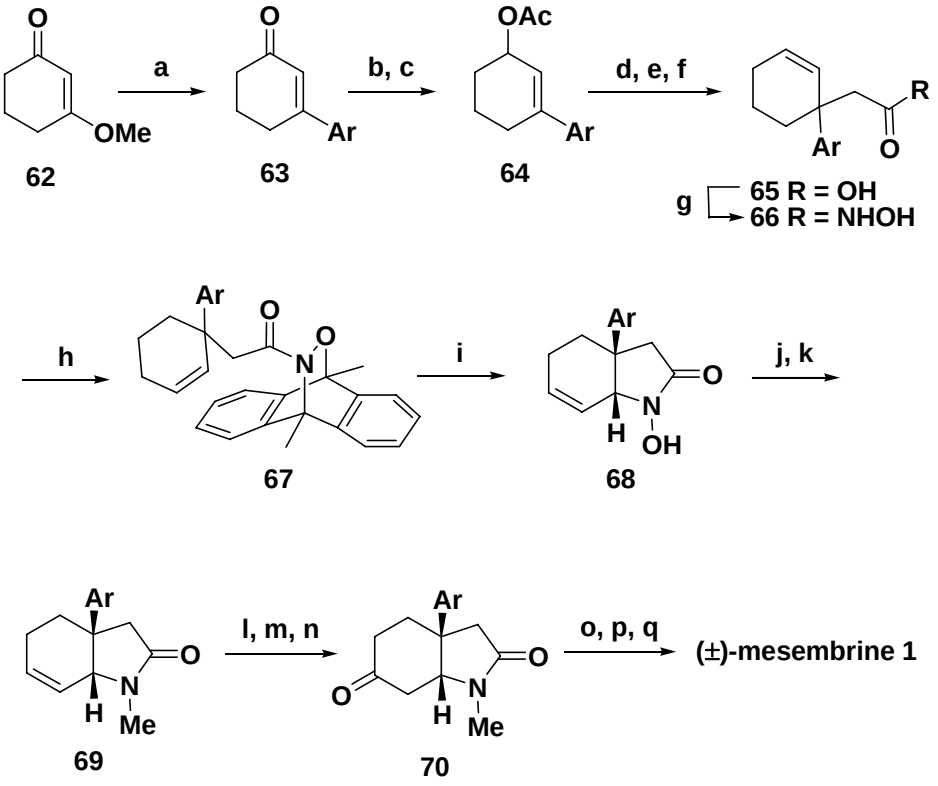
Scheme 10. *Reagents and conditions:* a) CH_3NO_2, KF, 18-crown-6 or CH_3NO_2, Triton-B, 70-90%; b) i) NaOMe, MeOH; ii) H_2SO_4, MeOH; c) HCl-H_2O, 73%; d) i. MVK, DBN, ii. Pyridine-AcOH, 48%; e) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, 73%; f) DIBAL, PhMe; g) $MeNH_2{\cdot}HCl$, $NaCNBH_3$; h) NCS, $AgNO_3$; i) Amberlyst-15, PhH, 35% (3 steps).

Requisite 4,4-substituted cyclohexenone **59** was constructed by DBN catalysed Michael addition of methyl vinyl ketone, followed by Robinson annulation in 48% overall yield. The enone carbonyl was protected with 1,3-propanedithiol in the presence of $BF_3{\cdot}OEt_2$ and the resultant nitrile was reduced with DIBAL in PhMe to furnish aldehyde **60**. Aldehyde **60** was then treated with $MeNH_2{\cdot}HCl$, followed by $NaCNBH_3$ in *t*BuOH to afford amine **61**. Thioacetal was deprotected using NCS in the presence of $AgNO_3$ and further treated with Amberlyst-15 in warm benzene to furnish (±)-mesembrine **1**.

Keck[12] (*J. Org. Chem.* **1982**, *47*, 1302-1309)

A total synthesis of (±)-mesembrine **1** has been described by Keck and Webb employing intramolecular ene cyclization of an acylnitroso olefin, giving cyclic hydroxamic acid, "ene product". Lithioveratrole was condensed with 3-methoxy-2-cyclohexen-l-one **62**, followed by acid work-up afforded enone **63**. $NaBH_4$ reduction, followed by exposure of the resultant alcohol to acetic anhydride in pyridine gave acetate **64** in 67% yield. Claisen rearrangement of **64** using Ireland method furnished crystalline **65** (scheme 11). Hydroxamic acid **66** was obtained in 78% yield by Jones and Hurd method from acid **65.** Oxidation of **66** in the presence of 9,10-dimethylanthracene gave Diels-Alder adduct **67** in 83% yield.

Total Synthesis of (±)-Mesembrine

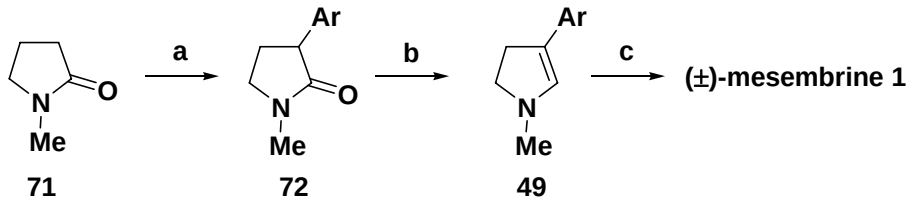


Scheme 11. *Reagents and conditions:* a) Lithioveratrole, Et_2O, H_3O^+, 72%; b) $NaBH_4$, EtOH, –20 ºC to r t, 89%; c) Ac_2O, pyridine, 76%; d) LICA, THF, HMPA, –78 ºC; e) TBSCl, THF, reflux; 71%; f) $SOCl_2$, PhH, DMF, reflux; g) $NH_2OH{\cdot}HCl$, Na_2CO_3, Et_2O-H_2O, 0 ºC, 78%; h) $n$$Pr_4NIO_4$, $CHCl_3$, DMF, 9,10-DMA, 83%; i) PhMe, reflux, 100%; j) $TiCl_3$, H_2O, MeOH, Na_2CO_3, 78%; k) NaH, MeI, THF, 90%; l) NBS, DME-H_2O, 0 ºC, 88%; m) Bu_3SnH, AIBN, PhMe, reflux, 90%; n) PCC, DCM, 0 ºC, 85%; o) $HOCH_2CH_2OH$, PTSA, PhH, reflux; p) $LiAlH_4$, THF, reflux; q) H_3O^+, 75% (for 3 steps).

This adduct was decomposed in refluxing PhMe to afford "ene product" **68** in quantitative yields. This cyclic hydroxamic acid was converted to the corresponding lactam by $TiC1_3$ reduction according to the procedure of Miller and Mattingly, which was *N*-methylated with MeI using oil-free NaH in dry THF to yield **69**. Lactam **69** reacted smoothly with 1 equiv. of NBS in aq. DME to give bromohydrin, which upon replacement of bromine with tin hydride gave lactam alcohol, which upon further oxidation with PCC in DCM at 0 ºC gave keto lactam **70**. Protection of **70** with ethylene glycol in refluxing benzene containing a trace of PTSA gave ketal and the lactam was then reduced with $LiAlH_4$ in THF and the crude amino ketal, thus obtained was treated with dil. HC1 to furnish (±)-mesembrine **1**.

Total Synthesis of (±)-Mesembrine

Pinnick[13] (*Tetrahedron Lett.* **1983**, *24*, 4785-4788)

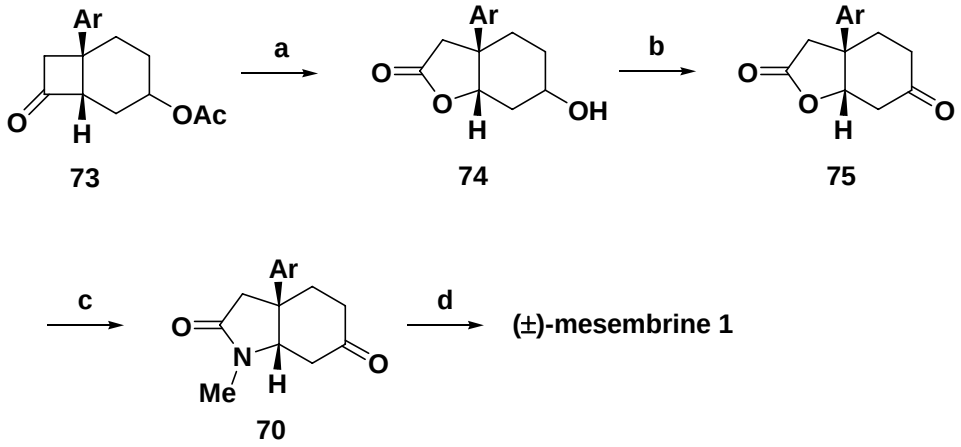


Scheme 12. *Reagents and conditions:* a) Lithium *N*-cyclohexyl-*N*-isopropylamide, bromoveratrole, THF, 30-40%; b) DIBAL, THF; c) MVK, 58-64% (from **72**).

Pinnick and Kochhar *et. al.* reported a short and efficient synthesis of (±)-mesembrine **1** from 1-methyl-2-pyrrolidone **71**. 1-Methylpyrrolidone **71** was arylated with bromoveratrole and the resultant 3-aryl-2-pyrrolidone **72** was reduced with DIBAL to furnish the 2-pyrroline **49**. 2-Pyrroline **49** was treated with methyl vinyl ketone to give (±)-mesembrine **1** in 58-64% overall yield from **72** (scheme 12).

A similar synthesis of (±)-mesembrine **1** was reported by Kim and Curphey[14] starting from 1-methyl-3-pyrrolidone by addition of aryllithium followed by dehydration to obtain 2-pyrroline **49**.

Jeffs[15] (*J. Org. Chem.* **1983**, *48*, 3861-3863)



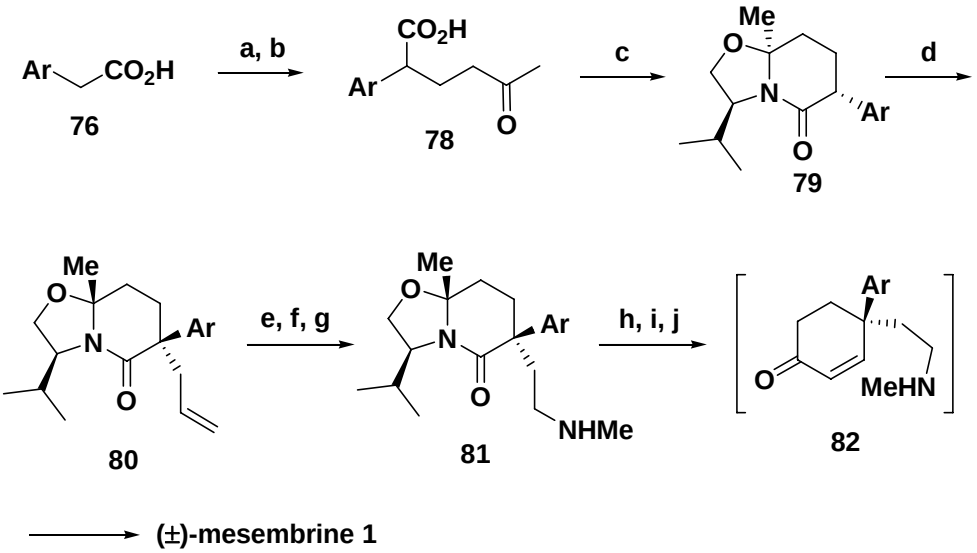
Scheme 13. *Reagents and conditions:* a) 30% H_2O_2, NaOH, 100%; b) PCC, 88%; c) $MeNH_2$, EtOH; d) ref. 12.

Jeffs *et. al.* reported a short and efficient formal synthesis of (±)-mesembrine **1**, employing a substituted cyclobutanone. Cyclobutanone **73** on Bayer-Villiger oxidation with 30% alkaline H_2O_2 afforded hydroxy lactone **74** in quantitative yields (scheme 13).

Total Synthesis of (±)-Mesembrine

Oxidation of **74** with PCC gave keto lactone **75** in 86% yield. Refluxing keto-lactone **75** in ethanolic $MeNH_2$ for 12 hours furnished the *cis* octahydroindolone **70**, is a known intermediate[12] reported in the synthesis of (±)-mesembrine **1**.

Meyers[16] (*J. Am. Chem. Soc.* **1985**, *107*, 7776-7778)

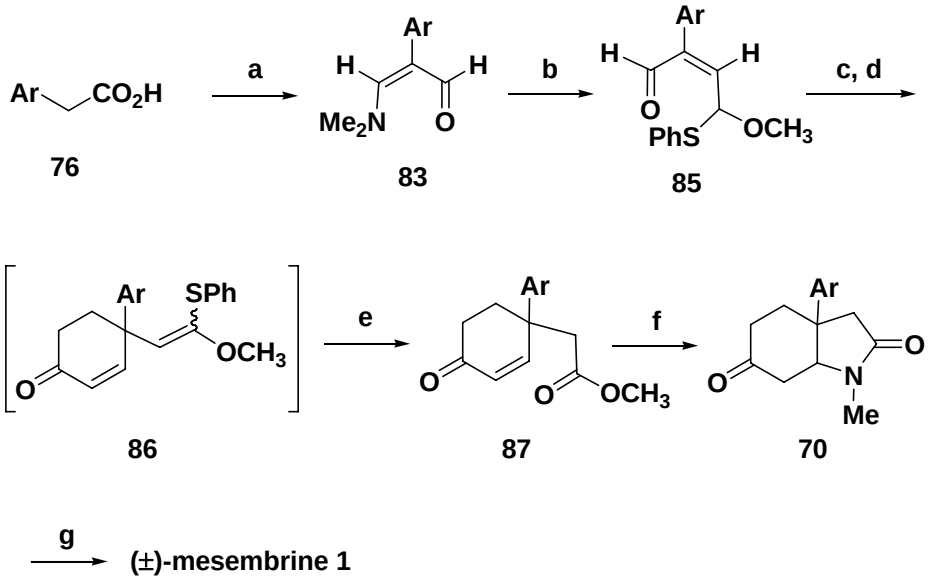


Scheme 14. *Reagents and conditions:* a) BuLi, THF, then **77**; b) PPTS, EtOH, 60 ºC, 85%; c) (*S*)-valinol, PhMe, reflux, 16 h, 90%; d) *s*BuLi, allyl bromide, THF, 71%; e) OsO_4, $NaIO_4$, Et_2O-H_2O, r t, 6 h; f) $MeNH_2$; g) $NaCNBH_3$; h) $LiAl(OEt)_3H$, DME-PhMe, –20 ºC; i) $Bu_4NH_2PO_4$, EtOH, Δ; j) 4 N NaOH, r t, 60%.

Keto-acid **78** was prepared from the dilithio salt of (3,4-dimethoxyphenyl)acetic acid **76** and 2-methyl-2-(2-iodoethy1)-1,3-dioxolane **77** using BuLi in THF, followed by hydrolysis of the acetal with PPTS in EtOH at 60 ºC (scheme 14). Treatment of **78** with (*S*)-valinol in PhMe under reflux for 16 hours produced bicyclic lactam **79** as a mixture of diastereomers. The diastereomeric mixture was metalated with *s*BuLi in THF at –20 ºC and treated with allyl bromide to give compound **80** in 90% yield with high diastereoselectivity. The allyl group was transformed into the aminoethyl group in 72% yield, by Lemieux oxidation and the resultant aldehyde was immediately subjected to reductive amination to furnish secondary amine **81**. Reduction of **81** with $LiAl(OEt)_3H$ afforded the tricyclic product, which was heated with an ethanolic solution of $Bu_4NH_2PO_4$ to furnish the keto aldehyde, which upon further treatment with 4 N NaOH at room temperature spontaneously underwent cyclization to furnish (+)-mesembrine **1** *via* **82**.

Total Synthesis of (±)-Mesembrine

Livinghouse[17] (*J. Org. Chem.* **1986**, *51*, 1629-1631)



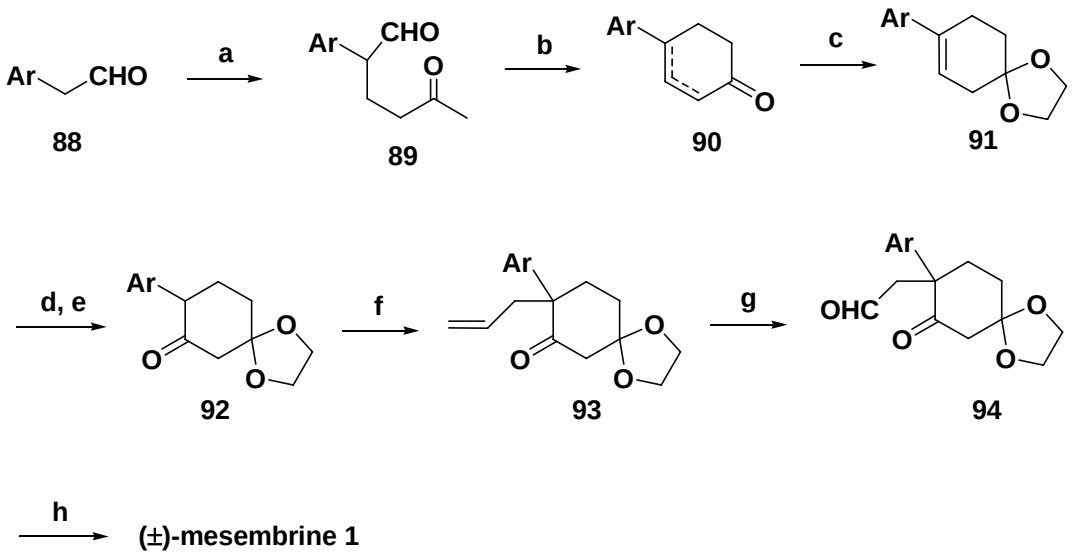
Scheme 15. *Reagents and conditions:* a) DMF, $POCl_3$; b) [methoxy(phenylthio)-methyl]lithium **84**; 10% aq. H_2SO_4, 63%; c) MVK, DBN; d) 0.3 N NaOEt in EtOH; e) PTSA, THF-H_2O, reflux, 24 h, 91% (3 steps); f) $MeNH_2$, THF, 80 ºC then THF-H_2O, 71%; g) ref. 12.

Livinghouse and Hackett reported an efficient formal synthesis of (±)-mesembrine **1** *via* a *p*-(methoxy(pheny1thio)methylidene) enolate Robinson annulation sequence. Starting material **83** was prepared by the exhaustive formylation of 3,4-dimethoxyphenylacetic acid **76** with $POC1_3$ in DMF. Exposure of **83** to [methoxy(phenylthio)-methyl]lithium **84**, followed by hydrolysis of the resultant adduct with 10% aq. H_2SO_4 provided the enal **85** in 63% yield. Sequential treatment of a THF solution of **85** with methyl vinyl ketone in the presence of DBN followed by 0.3 N ethanolic NaOEt furnished the cyclohexenones **86** as a mixture of *E/Z* isomers in 10:1 ratio (scheme 15).

The mixture of cyclohexenones **86** was subjected to PTSAcatalyzed hydrolysis to provide the corresponding methyl ester **87**. Exposure of **87** to $MeNH_2$, followed by imine hydrolysis afforded keto-lactam **70** in 71 % yield, whose conversion into (±)-mesembrine **1** is reported in the literature.[12]

Total Synthesis of (±)-Mesembrine

Hoshino[18] (*Chem. Pharm. Bull.* **1987**, *35*, 2734-3743)



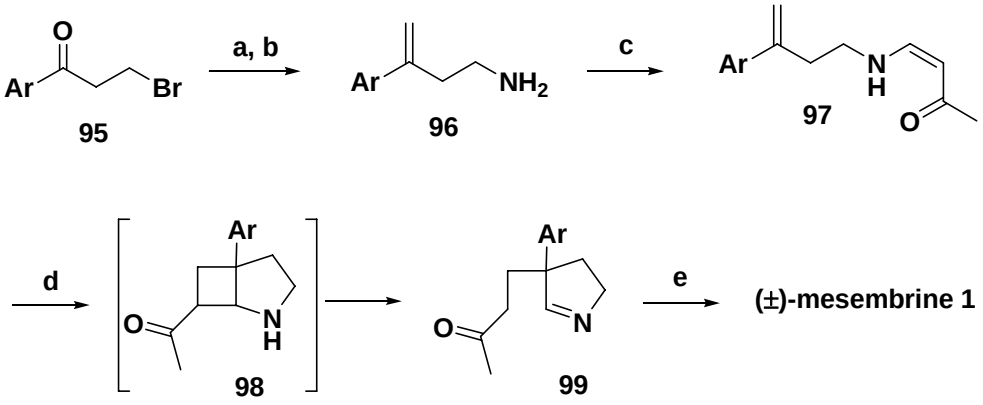
Scheme 16. *Reagents and conditions:* a) MVK, pyrrolidine, K_2CO_3, then 10% HCl; b) AcOH, reflux; c) $HOCH_2CH_2OH$, PTSA, PhH; d) *m*CPBA, Et_2O; e) $LiClO_4$, Bu_3PO, PhH; f) 50% NaOH, allyl bromide, 18-crown-6, 25 ºC, 30 min; g) OsO_4, $NaIO_4$, 62%; h) $MeNH_2$·HCl, $NaCNBH_3$, then H_3O^+.

Condensation of homoveratraldehyde **88** with methyl vinyl ketone *via* pyrrolidine enamine in the presence of K_2CO_3 in THF at room temperature and subsequent hydrolysis with 10% HCl furnished ketoaldehyde **89**. Refluxing **89** with AcOH gave cyclized product **90**, ketalization of which afforded cyclohexene **91** in 46% yield. Epoxidation of **91** with *m*CPBA in ether gave an epoxide in 91% yield, which upon rearrangement in the presence of $LiClO_4$ and Bu_3PO in boiling benzene gave cyclohexanone **92** in moderate to good yields. Alternatively, compound **92** was obtained in 80% yield by hydroboration-oxidation, followed by oxidation with Collin's reagent. Alkylation of **92** with allyl bromide gave olefin **93** at 25 ºC in 70% yield within 30 minutes. Oxidation of **93** with OsO_4-$NaIO_4$ gave an aldehyde **94** in 62% yield, which upon reductive amination with $MeNH_2$·HCl and $NaCNBH_3$, followed by acid treatment afforded (±)-mesembrine **1** in 15% yield (scheme 16).

Winkler[19] (*J. Am. Chem. Soc.* **1988**, *110*, 4831-4832)

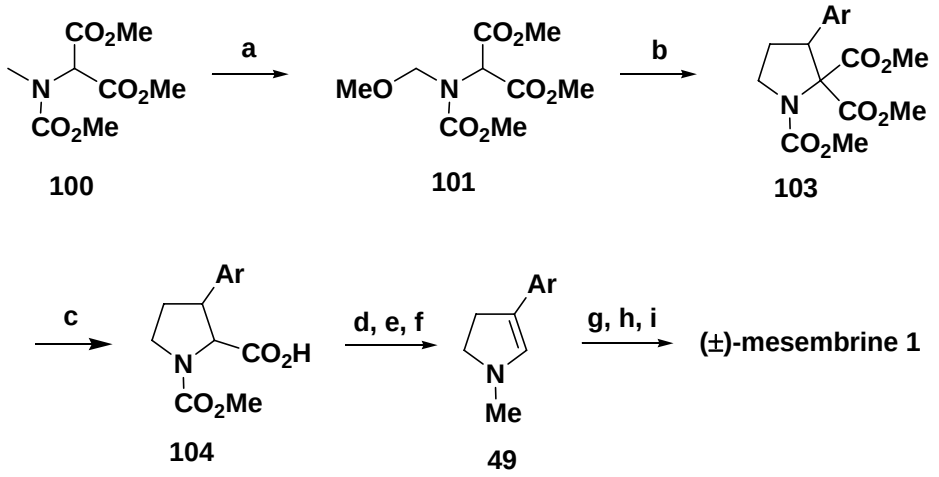
An efficient and elegant synthesis of (±)-mesembrine **1** was reported by Winkler *et. al.* utilizing the vinylogous amide photocycloaddition-retro-Mannich-Mannich sequence. Treatment of Tebbe reagent with compound **95**, obtained from reaction of veratrole with 3-bromopropionyl chloride, led to the formation of styryl bromide, which upon treatment

with ammonia furnished amine **96** in 89% yield (scheme 17). Condensation of **96** with 4-chloro-3-buten-2-one provided compound **97** in 77% yield. Irradiation of **97** furnished photocycloaddition-retro-Mannich product **99** *via* **98**. Methylation of **99** with trimethyloxonium tetrafluoroborate followed by treatment with DMAP in reluxing CH_3CN produced (±)-mesembrine **1** in 84% yield.



Scheme 17. *Reagents and conditions:* a) Tebbe reagent; b) NH_3, 89%; c) 4-chloro-3-buten-2-one, 77%; d) *hv*, 74%; e) trimethyloxonium tetrafluoroborate, DMAP, CH_3CN, reflux, 84%.

Shono[20] (*Chem. Lett.* **1989**, 1963-1969)



Scheme 18. *Reagents and conditions:* a) –2 e, MeOH-AcOH, 77%; b) 3,4-dimethoxy-4'-vinylbenzene **102**, $TiCl_4$, Et_3N, DCM, 87%; c) NaOH, DMF, Δ, 94% (overall); d) –2 e, THF-H_2O; e) PTSA, DCM, 48% (2 steps); f) $LiAlH_4$, THF; g) HCl gas; h) MVK, CH_3CN; i) H_3O^+, 63% (3 steps).

Shono *et. al.* reported an elegant synthesis of (±)-mesembrine **1** exploiting α,α,*N*-tris(methoxycarbonyl)-β-arylpyrrolidine obtained by Lewis acid treatment of dimethyl *N*-

methoxycarbonyl-*N*-methoxymethylaminomalonate with aryl olefin. Starting compound **101** was prepared in 77% yield by anodic oxidation of dimehtyl *N*-methoxycarbonyl-*N*-methylaminomalonate **100** in MeOH containing AcOH (scheme 18). A solution of **101** and Et_3N in DCM was added dropwise into a refluxing solution of 3,4-dimethoxy-4'-vinylbenzene **102** and $TiCl_4$ in DCM and further refluxed for 1 hour after addition to give compound **103** in 87% yield. Hydrolysis of **103** and subsequent decarboxylation gave acid **104** in 94% yield. Anodic oxidation of **104** in THF-H_2O solvent, followed by acid treatment gave an enecarbamate, which in turn was reduced with $LiAlH_4$ to give 2-pyrroline **49**, which was condensed with methyl vinyl ketone to afford (±)-mesembrine **1** in 63% yield.

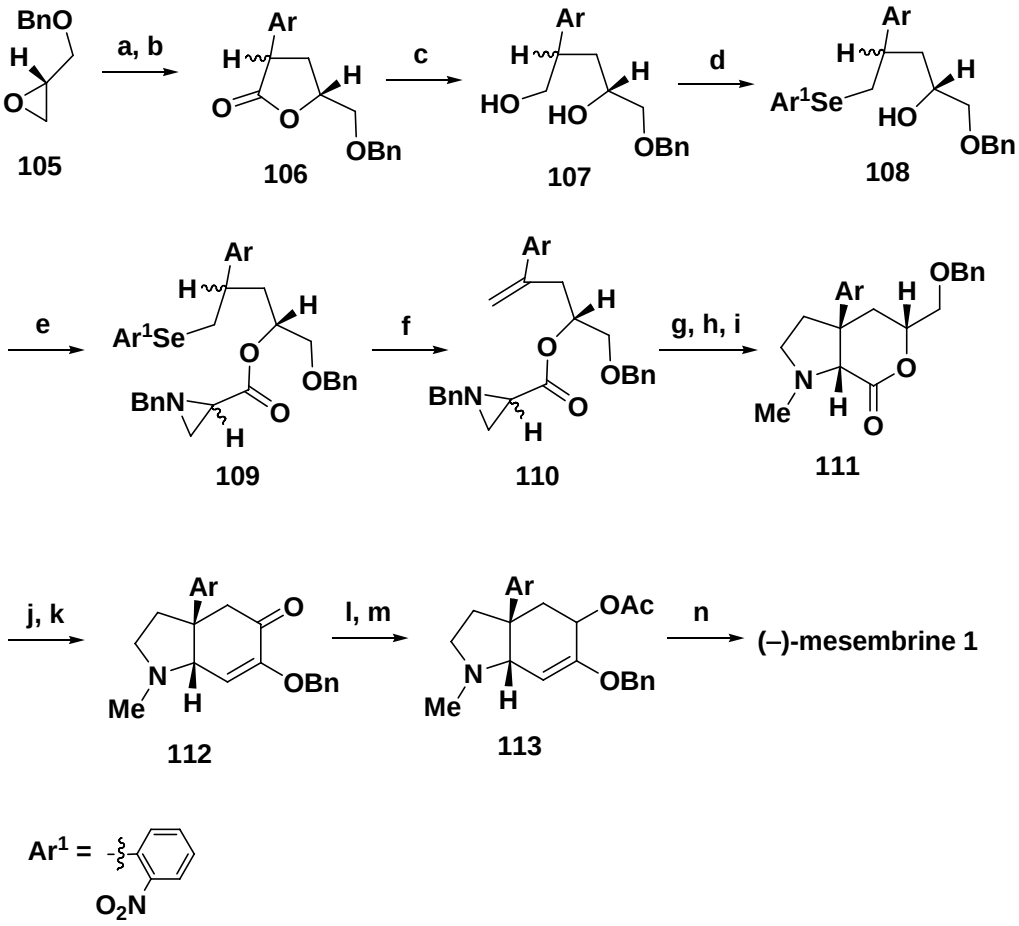
Takano[21a,b,c] (*Chem. Lett.* **1990**, 1239-1242; *Tetrahedron Lett.* **1981**, *22*, 4479-4482; *Chem. Lett.* **1981**, 1385-1386)

Takano *et. al.* reported an enantiospecific synthesis of (–)-mesembrine **1** employing intramolecular 1,3-dipolar cycloaddition using (*S*)-*O*-benzylglycidol **105** as starting material. Accordingly, 3,4-dimethoxyphenyl acetonitrile **45** was condensed with (*S*)-*O*-benzylglycidol **105** using LDA as a base to furnish cyanoalcohol, which upon basic hydrolysis gave lactone **106** in 64% overall yield as a mixture of diastereoisomers (scheme 19). $LiAlH_4$ reduction of lactone **106** yielded diol **107** in 97% yield.

Primary hydroxy group of **108** was replaced using Grieco protocol to give selenide **108** in 94% yield. Aziridine ester **110** was formed in 93% yield by treatment of the secondary alcohol **108** with 2,3-dibromopropionyl chloride in the presence of Et_3N followed by reaction with $BnNH_2$ in the same pot. Compound **109** upon exposure to 30% H_2O_2 furnished olefin **110** quantitatively, which upon heating at 250 ºC in degased xylene in a sealed tube furnished the pyrrolidine lactone **111** in 85% yield as a single isomer.

Catalytic hydrogenation of **111** with $Pd(OH)_2$ furnished free secondary amine in 88% yield without affecting *o*-benzyl ether, which upon treatment with 37% formalin, followed by $NaBH_4$ brought about spontaneous *N*-methylation and reduction of the lactone to furnish aminodiol. Subsequent Swern oxidation of the aminodiol followed by intramolecular aldolization of the resultant keto-aldehyde furnished enone **112** in 75% overall yield. Reduction of **112** under Luche conditions yielded allylic alcohol as a mixture of isomers, which was converted into acetate **113**. Treatment of acetate **113** with Li in

liquid NH_3 resulted in concurrent debenzylation and reductive elimination to furnish (–)-mesembrine **1**.

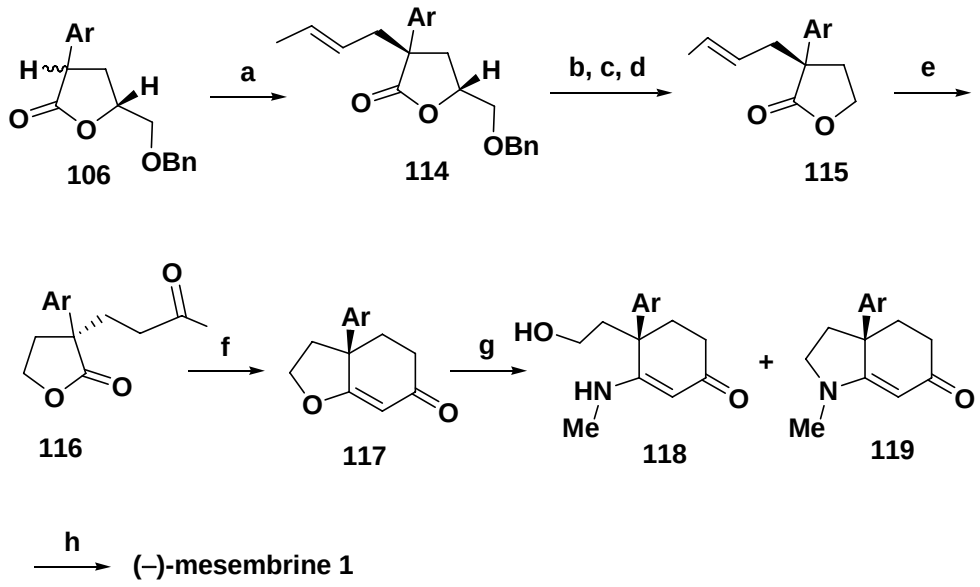


Scheme 19. *Reagents and conditions:* a) LDA, 3,4-dimethoxyphenylacetonitrile **45**, THF, –78 ºC to r t; b) 10% KOH-EtOH, reflux, overnight, then 10% HCl-EtOH, r t, 64% overall; c) $LiAlH_4$, THF, 0 ºC, 40 min, 97%; d) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, r t, 1 h, 94%; e) 2,3-dibromopropionyl chloride, Et_3N, DCM, –10 ºC, 30 min then $BnNH_2$, r t, 5 h, 93%; f) 30% H_2O_2, DCM, 0 ºC to r t, 9 h, 100%; g) xylene, 250 ºC, (sealed tube), 20 min, 85%; h) H_2, 20% $Pd(OH)_2$-C, MeOH, r t, 8 h, 88%; i) 37% formalin, MeOH, 0 ºC, 1 h then, $NaBH_4$, 0 ºC to r t, 75%; j) $(COCl)_2$, DMSO, DCM, –78 ºC, 1.5 h, then Et_3N, –71 ºC to r t; k) 0.5 N NaOH, EtOH, r t, 11 h, 75%; l) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 ºC, 1.5 h, m) Ac_2O, Et_3N, DMAP, DCM, 0 ºC to r t, 9 h, 76%; n) Li, liquid NH_3, –33 ºC, 10 min, 26%.

An another modified synthesis was reported from lactone **106**. Alkylation of **106** with crotyl bromide using LDA gave the α,α-disubstituted lactone **114**, which upon acid catalyzed debenzylation afforded the primary alcohol, which on sequential saponification, periodate cleavage and reduction gave lactone **115**, in 75 % overall yield (scheme 20).

Total Synthesis of (±)-Mesembrine

Palladium catalyzed oxidation of **115** led to a regioselective carbonylation to give methyl ketone **116**. Base induced intramolecular cyclization of the keto lactone **116** yielded bicyclic enone **117** in 66 % yield. Treatment of enone **117** with aq. $MeNH_2$ gave the monocyclic vinylogous amide **118** in 41% yield accompanied by 7% yield of bicyclic compound **119**. Conversion of **118** into **119** was eventually accomplished in 85 % yield using an equimolar amount of DEAD and Ph_3P. Reduction of **119** with Li metal in liquid NH_3 furnished (–)-mesembrine **l**.

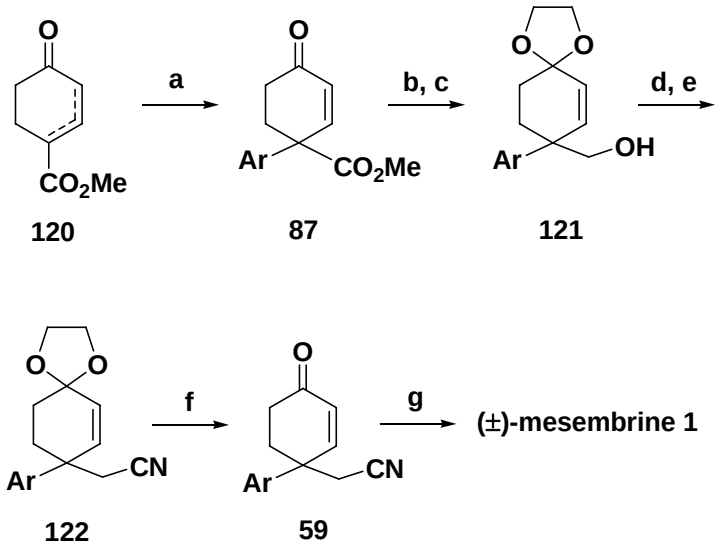


Scheme 20. *Reagents and conditions:* a) LDA, crotyl bromide, THF, –78 ºC; b) conc. HCl, EtOH, reflux, 3 h; c) 20% KOH in MeOH, CO_2 gas, then $NaIO_4$; d) $NaBH_4$, H_3O^+; e) $PdCl_2$, CuCl, wet DMF, O_2, 1 week; f) KO*t*Bu, THF, reflux, overnight; g) 40% $MeNH_2$, sealed tube, 180 ºC, 1 h; h) Li / NH_3.

Pinhey[22] (*J. Chem. Soc. Perkin Trans 1*, **1991**, 1053-1057)

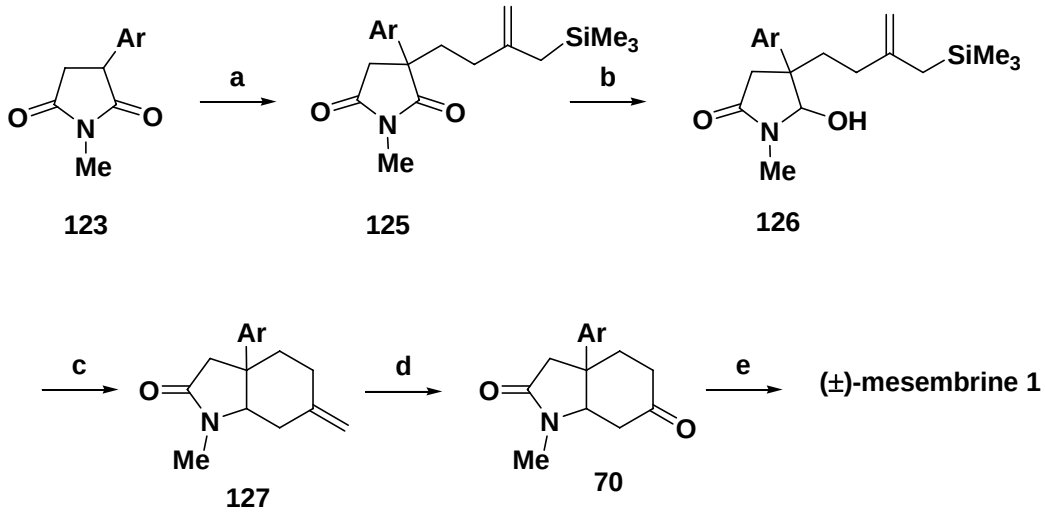
A formal synthesis of (±)-mesembrine **1** have been reported by Pinhey and Parkinson employing 3,4-dimethoxyphenyllead triacetate as electrophilic arylating agent to generate the quaternary benzylic center. Arylation of the mixture of vinylogous *β*-keto esters **120** with excess 3,4-dimethoxyphenyllead triacetate gave intermediate **87** in almost quantitative yields. The ketone function was protected as its ethylene ketal, ester was then reduced with $LiAlH_4$ to yield alcohol **121**. Alcohol **121** was readily converted to nitrile **122** with tetrabutylammonium cyanide in HMPA at 80 ºC in high overall yield *via* corresponding tosylate (scheme 21). Hydrolysis of the ketal furnished enone **59**, whose transformation into (±)-mesembrine **1** is known in the literature.[11]

Total Synthesis of (±)-Mesembrine



Scheme 21. *Reagents and conditions:* a) 3,4-dimethoxyphenyllead triacetate, pyridine, $CHCl_3$, 0 ºC, 15 min, then 55 ºC, 48 h, 57%; b) $HOCH_2CH_2OH$, PTSA, PhMe, reflux, 18 h, 92%; c) $LiAlH_4$, Et_2O, r t, 3 h, 84%; d) PTSA, pyridine, r t, 48 h, 79%; e) Bu_4NCN, HMPA, 80 ºC, 30 h, 76%; f) HCl, THF, r t, 94%; g) ref. 11.

Remuson[23a,b] (*Heterocycles*, **1992**, *34*, 37-49; *Tetrahedron Lett.* **1985**, *26*, 4083-4086)

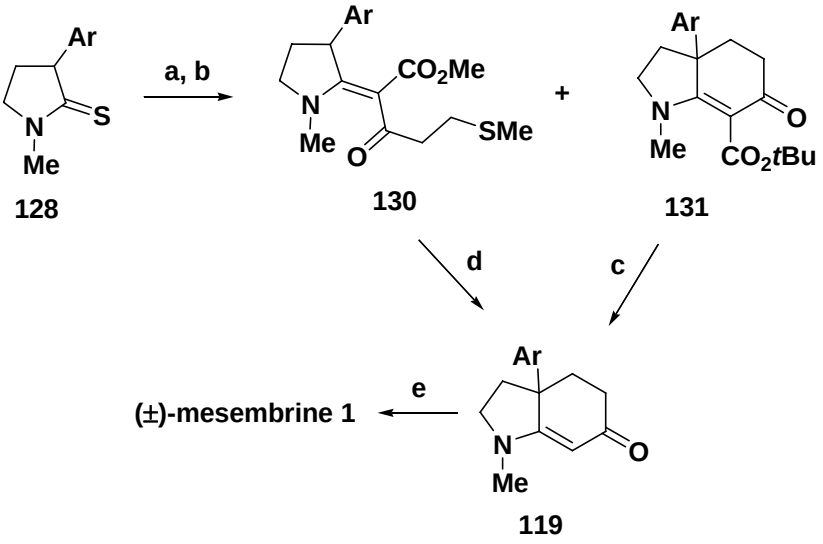


Scheme 22. *Reagents and conditions:* a) NaH, 3-[(trimethylsilyl)methyl]but-3-enyl-4-methyl benzenesulfonate **124**, DME, 0 ºC, 60%; b) $NaBH_4$, EtOH, 1,2 drops 2 N HCl, 24 h, 67%; c) MsCl, Et_3N, DCM, –20 ºC to r t, overnight, 80%; d) O_3, DMS, –78 ºC, 95%; e) $HOCH_2CH_2OH$, PTSA, PhH, reflux, then $LiAlH_4$, THF, reflux, then H_3O^+, 75% (for 3 steps).

Remuson *et. al.* reported a formal synthesis of (±)-mesembrine **1**, employing intramolecular cyclization of allyl silyl substituted *N*-acyliminium ion. 3-Arylimide **123** was alkylated with 3-[(trimethylsilyl)methyl]but-3-enyl-4-methylbenzenesulfonate **124**

using NaH in DME to furnish imide **125** in 60% yield (scheme 22). Compound **125** was reduced with $NaBH_4$ in EtOH with addition of 1,2 drops of 2 N HCl to furnish the hindered amido alcohol **126** as a mixture of diastereoisomers in 67% yield in accordance with the literature precedence. The amido alcohol **126** was converted into the acyliminium ion under basic condition (MsCl, Et_3N, DCM, –20 ºC), which stereoselectively underwent concomitant cyclization to furnish compound **127**. Ozonolysis of compound **127** furnished keto-lactam **70**, whose transformation into (±)-mesembrine **1** is reported in the literature. Similar syntheses were reported by Speckamp *et. al.*[23c,d] and Rajagopalan[23e] starting from imide **123** and **125** respectively.

Michael[24] (*Tetrahedron Lett.* **1992**, *33*, 6023-6024)



Scheme 23. *Reagents and conditions:* a) MeI, DCM; b) *t*-butyl 3-oxopent-4-enoate **129**, Et_3N, DCM, r t, 56% for **130** and 17% for **131**; c) TFA, 71%; d) TFA, ultrasound, 82%; e) ref. 21b.

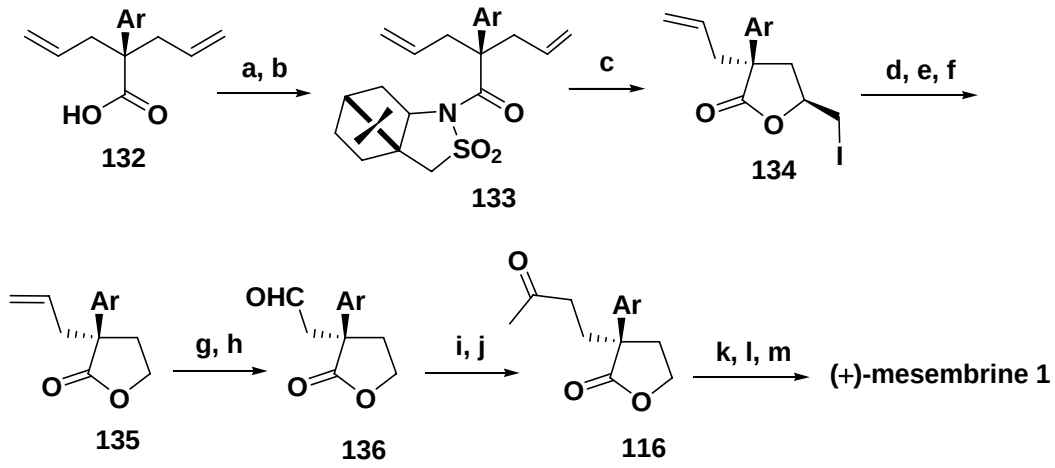
Michael *et. al.* reported a formal synthesis of (±)-mesembrine **1**, employing condensation of 3-aryl Δ^1-pyrrolinium salts with *t*butyl 3-oxopent-4-enoate, followed by TFA treatment (scheme 23). Alkylation of thiolactam **128** with MeI, followed by reaction of the resultant 2-methylthio-Δ^1-pyrrolinium iodide with *t*-butyl 3-oxopent-4-enoate **129** gave compound **131** in 56% yield, resulting from the expected Knoevenagel-like condensation, followed by interception of the enone by the liberated methanethiolate anion and hexahydroindolone and compound **131** in 17% obtained from conjugate addition of the competitively formed enamine to **129**, followed by condensation. Both **130** and **131** yielded Δ^7-mesembrenone **119** after treatment with TFA (71% from 4, 82% from 5).

Total Synthesis of (±)-Mesembrine

Reduction of Δ^7-mesembrenone **119** to (±)-mesembrine **1** using Li in liquid NH_3 is documented in the literature.[21b]

Shibuya[25] (*Tetrahedron Lett.* **1992**, *33*, 6999-7002)

An enantioselctive synthesis of (+)-mesembrine **1** was reported by Shibuya *et. al.*, employing halolactonization of bis-*γ,δ*-unsaturated carboxylic imides derived from a camphorsultam for the formation of quaternary carbons in a highly diastereoselective fashion. Symmetrical diene-carboxylic acid **132**, prepared from ethyl 3,4-dimethoxyphenyl acetate through sequential diallylation and saponification, was condensed with a sultam derived from D-camphorsulfonic acid, under the methods reported by Oppolzer, to give *N*-acylsultam **133** in 65% yield (scheme 24).



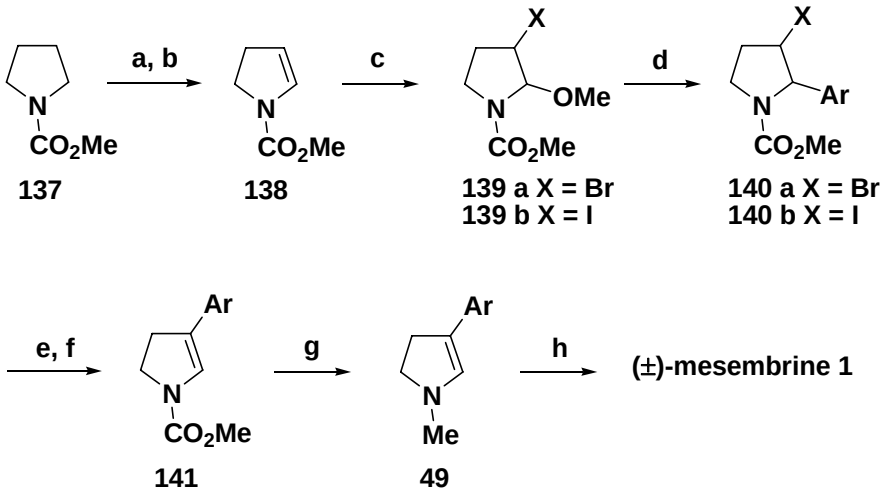
Scheme 24. *Reagents and conditions:* a) $SOCl_2$; b) Sultam; c) I (collidine)$_2ClO_4$, DCM, MeOH, H_2O, –50 ºC; d) 10% NaOH, then CO_2; e) $NaIO_4$; f) $NaBH_4$; g) O_3, DCM, pyridine, –78 ºC; h) Me_2S; i) $MeCH{=}PPh_3$, THF; j) $PdCl_2$, CuCl, O_2, wet DMF; k) KO*t*Bu, THF, reflux, overnight; l) 40% $MeNH_2$, sealed tube, 180 ºC, 1 h; m) Li / NH_3.

Treatment of **133** with iodonium di-sym-collidine perchlorate gave a diastereoisomeric mixture of **134**, in 83% yield. Treatment of **134** with aq. KOH (20%) followed by acid work-up and sequential saponification, periodate cleavage and reduction in the same flask gave lactone **135** in 80% yield. Ozonolysis of **135** gave aldehyde **136** in 70% yield. Wittig reaction of **136** with $MeCH{=}PPh_3$ in THF, followed by palladium catalyzed oxidation gave the requisite methyl ketone **116**. Ketone **116** was transformed into (±)-mesembrine **1** according to the literature procedure i. e. treatment with KO*t*Bu,

followed by treatment with 40% aq. $MeNH_2$ in a sealed tube followed by Li/NH_3 reduction.

Matsumura[26] (*Tetrahedron*, **1993**, *49*, 8503-8512)

Matsumura *et. al.* reported an elegant total synthesis of (±)-mesembrine **1**, exploiting anodic oxidation protocol for introduction of aryl groups at position *β* to the nitrogen atom of cyclic amines involving 1,2-migration of aryl group. Pyrrolidine **137** upon anodic oxidation gave compound **138**. Anodic *α*-methoxylation of cyclic amine **138** gave pyrrolidine **139**. *α*-Methoxy group in compound **139** was replaced with an aryl group (3,4-dimethoxyphenyl) to obtain compound **140**, which upon subsequent silver ion-promoted migration of the *α*-aryl group to the *β*-position gave pyrroline **141**. Reduction of compound **141** furnished pyrroline **49**, which upon treatment with methyl vinyl ketone furnished (±)-mesembrine **1** (scheme 25).



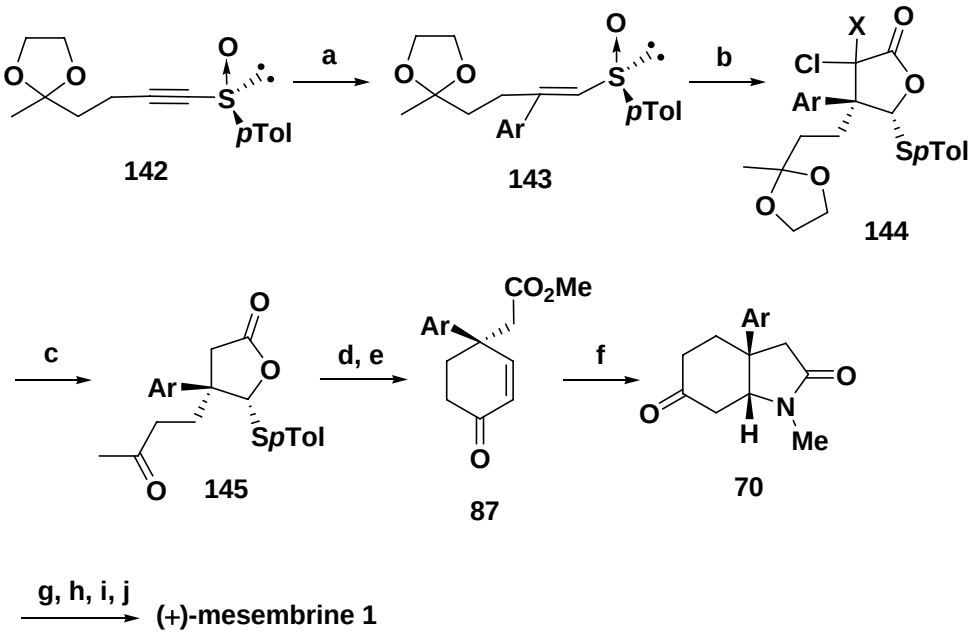
Scheme 25. *Reagents and conditions:* a) –e / MeOH; b) H^+, Δ, 76%; c) X^+, MeOH, 66% for X = Br, 93% for X = I; d) veratrole, H^+, 83% for X = Br, 90% for X = I; e) Ag^+, MeOH, 66% for X = Br, 72% for X = I; f) H^+ or Δ; g) $LiAlH_4$, 67%; h) MVK, 93%.

Kosugi[27] (*Tetrahedron:Asymmetry*, **1993**, *4*, 1409-1412)

Kosugi *et. al.* employed an elegant way of transfer of chirality by cycloaddition of enantiomerically pure *β,β*-disubstituted vinyl sulfoxides with dichloroketene to give *β,β*-disubstituted γ-lactones for the synthesis of (+)-mesembrine **1**, *via* 4,4-disubstituted cyclohexenones. Synthesis commenced with conjugate addition of aryl cuprate to the acetylenic sulfoxide **142** to give vinylic sulfoxide **143** in 73% yield. A THF solution of

trichloroacetyl chloride was slowly added to a THF solution of **143** containing freshly prepared Zn-Cu at 0 ºC to furnish the mixture of monochloro and dichloro lactones **144**.

Kosugi[27] (*Tetrahedron:Asymmetry*, **1993**, *4*, 1409-1412)

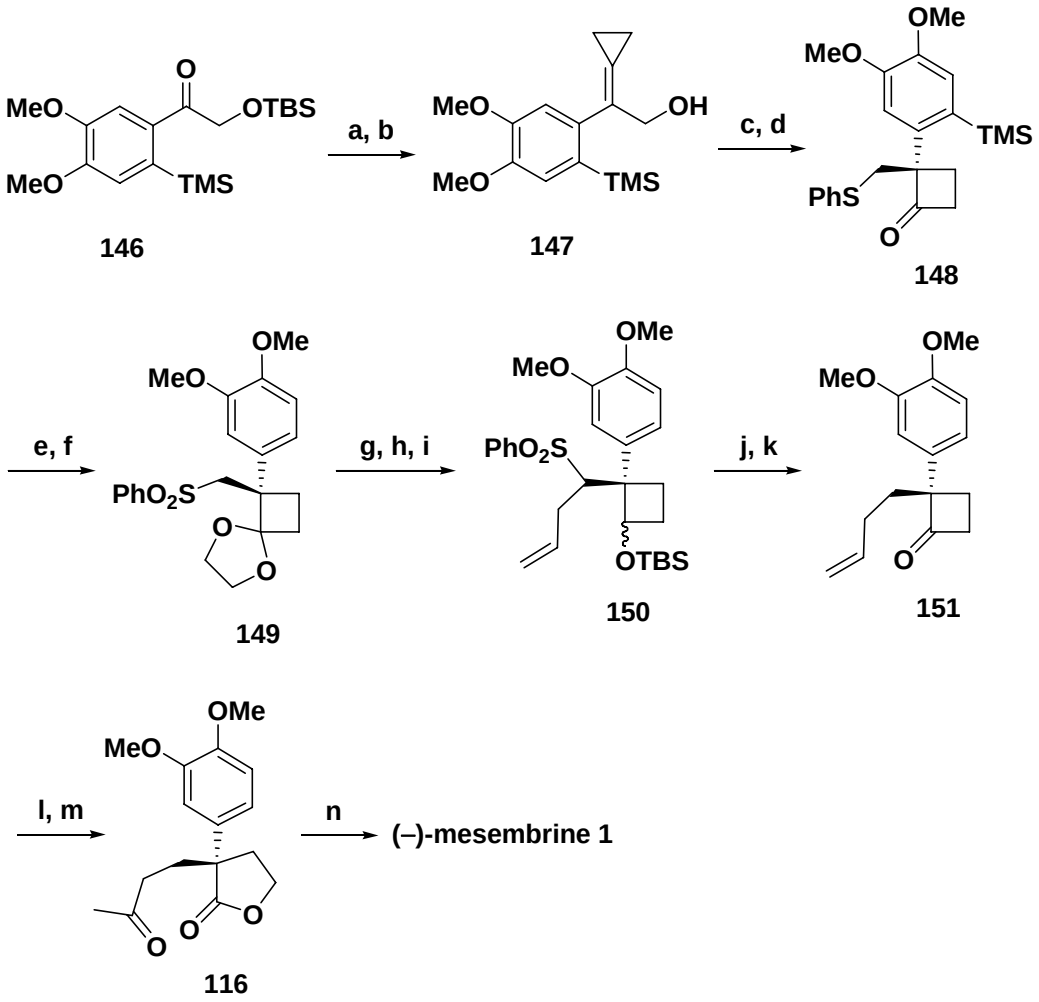


Scheme 26. *Reagents and conditions:* a) ArCu, THF, 73%; b) Cl_3CCOCl, Zn-Cu, THF, 0 ºC; c) Zn-AcOH, 0 ºC, and then, AcOH, H_2O, 60 ºC, 2 h, 47% (2 steps); d) K_2CO_3, MeOH; e) CH_2N_2, 65%; f) $MeNH_2$, THF; g) 2-ethyl-2-methyl-1,3-dioxolane, PTSA; h) $LiAlH_4$, THF; i) H_3O^+; j) NH_4OH, 79% (3 steps).

This mixture was subjected to dechlorination with Zn in AcOH, which with concomitant deacetalizatin gave lactone **145** in 47% overall yield. Intramolecular aldol-type condensation using K_2CO_3 in MeOH furnished the enone carboxylic acid, which upon esterification with CH_2N_2 gave ester **87** in 65% overall yield. Heating the ester with $MeNH_2$ in THF yielded lactam **70** in 83% yield. Protection of the carbonyl group, reduction of the amide functionality with $LiAlH_4$, followed by deprotection gave (+)-mesembrine **1** (scheme 26).

Fukumoto[28] (*J. Org. Chem.* **1995**, *60*, 6785-6790, *Tetrahedron Lett.* **1994**, *35*, 6499-6502)

Fukumoto *et. al.* reported a concise and highly enantioselective formal synthesis of (–)-mesembrine **1**, exploiting substituent effect by a trimethylsilyl group on enantioselectivity of the tandem Katsuki-Sharpless asymmetric epoxidation and enantiospecific ring expansion strategy for the enantioselective construction of benzylic quaternary carbon center (scheme 27).



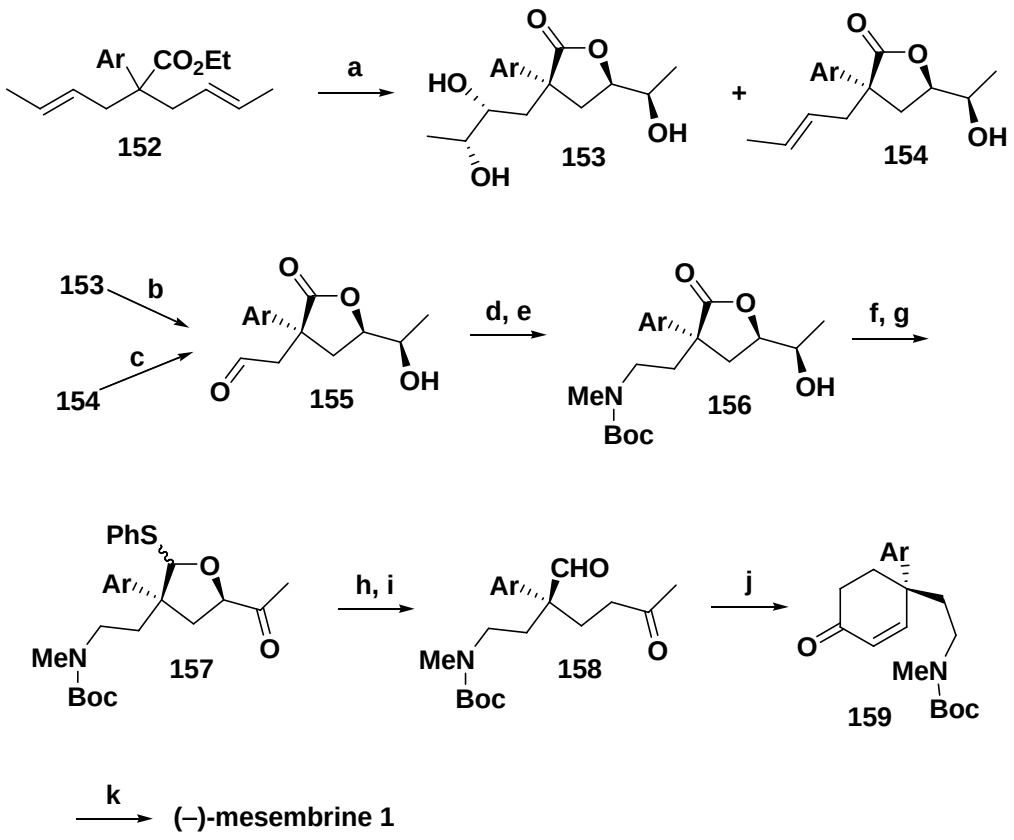
Scheme 27. *Reagents and conditions:* a) cyclopropyltriphenylphosphonium bromide, NaH, THF, 65 ºC, 3 h; b) Bu_4NF, THF, r t, 3 h; c) L-(+)-DIPT, *t*BuOOH, Ti(O*i*Pr)$_4$, 4 Å molecular sieves, DCM, –40 ºC, 48 h; d) PhSSPh, Bu_3P, THF, reflux, 1 h; e) $HOCH_2H_2OH$, PTSA, PhH, reflux, 4.5 h; f) *m*CPBA, $NaHCO_3$, DCM-H_2O, r t, 1.5 h; g) BuLi, allyl bromide, THF, r t, 5 h; h) PTSA, acetone-H_2O, reflux, 12 h then $NaBH_4$, MeOH**,** r t, 30 min; i) TBSOTf, Et_3N, DCM, r t, 10 min; j) Na-Hg, Na_2HPO_4, MeOH, r t, 12 h then Bu_4NF, THF, r t, 3 h; k) DMSO, $(COCl)_2$, DCM, –78 ºC, 10 min, then Et_3N, 0 ºC, 5 min; l) TESOTf, 2,6-lutidine, DCM, r t, 10 min, O_3, DCM, –78 ºC, 20 min, then $NaBH_4$, 10% HCl, r t, 10 min; m) O_2, $PdC1_2$, CuCl, DMF-H_2O, r t, 48 h; n) ref. 21b, 25.

Accordingly, ketone **146** was converted into cyclopropylidene ether in 54% yield by Wittig reaction with cyclopropylidenetriphenylphosphorane, which upon desilylation with Bu_4NF furnished alcohol **147** in 84% yield. Tandem asymmetric epoxidation and 1,2-rearrangement of **147** was carried out with *t*-butyl hydroperoxide in the presence of diisopropyl L-(+)-tartarate [(+)-DIPT], titanium tetraisopropoxide [Ti(O*i*Pr)$_4$] and 4 Å molecular sieves to give cyclobutanone in 65% yield with 92% ee, which was converted into sulfide **150** in 91% yield. In the absence of TMS group, ee was only moderate (63%).

Total Synthesis of (±)-Mesembrine

Sulfide **148** was then subjected to standard acetalization conditions, followed by oxidation of the sulfide with *m*CPBA to give sulfone **149** in 88% yield. Optically pure sulfone **149** was alkylated with allyl bromide, the acetal was hydrolysed and the resultant ketone was reduced with $NaBH_4$ and subsequent silylation with TBSOTf using Et_3N gave silyl ether **150** (100%). Desulfonylation with Na-Hg, followed by deprotection of silyl ether with Bu_4NF afforded alcohol, which was oxidized under Swern conditions to furnish ketone **151** in 82% yield. Successive treatment of ketone **151** with TESOTf in the presence of 2,6-lutidine and ozone, followed by $NaBH_4$ reduction and treatment with 10% HCl gave olefinic lactone, which upon subjection to Wacker oxidation furnished ketone **116** (100%), which has been previously transformed into (–)-mesembrine **1** in three steps.[21b, 25]

Ogasawara[29] (*Heterocycles*, **1996**, *42*, 135-139)



Scheme 28. *Reagents and conditions:* a) AD-mix-β, $K_4Fe(CN)_6$; b) $Pb(OAc)_4$, PhH, r t; c) O_3, DCM, –78 ºC; d) BnNHMe, $NaBH_3CN$, MS, 4 Å; e) H_2, $Pd(OH)_2$, $(Boc)_2O$, AcOEt-EtOH, 93%; f) DIBAL, DCM, –78 ºC; g) PhSH, $BF_3{\cdot}OEt_2$, DCM, –78 ºC to r t, 54%; h) Swern oxidation, 100%; i) Bu_3SnH, AIBN, PhH, reflux; j) 10% KOH-MeOH, r t, 77%; k) HCl-EtOH, reflux, 87%.

Total Synthesis of (±)-Mesembrine

Ogasawara and Yoshimitsu reported a total synthesis of (–)-mesembrine **1**, employing *meso* desymmetrization of the olefin ester **152** by enantioselective Sharpless AD reaction and radical initiated reaction. Synthesis commenced with treatment of σ–symmetric ester **152** with AD-mix-β containing $K_4Fe(CN)_6$ in the presence of methanesulfonamide at 0 ºC for 140 hours to give a mixture of diastereomeric pairs of lactone **153** and ene-lactone **154** in 54% and 30% yield respectively. With two equiv. of AD-mix-β only lactone **153** was obtained in 89% yield (scheme 28).

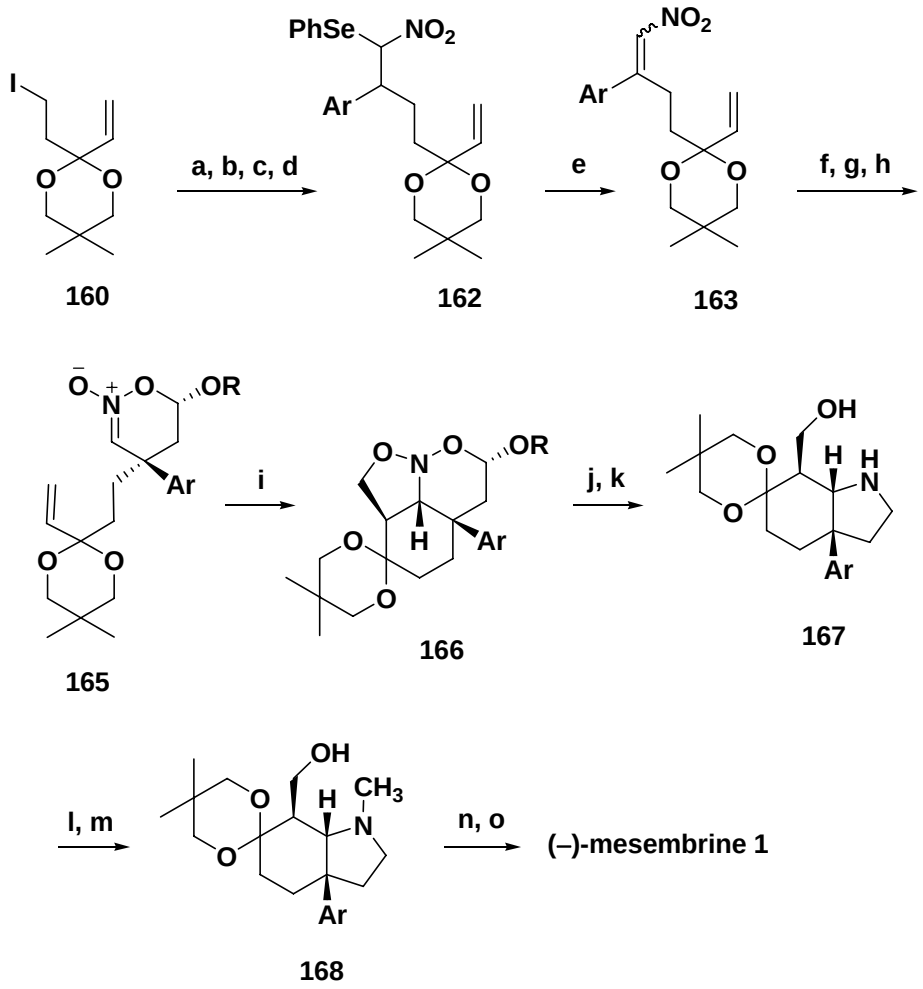
Lactone **153** was treated with a little excess of $Pb(OAc)_4$ in benzene to give aldehyde **155**, followed by reductive amination of **155** with BnNHMe in the presence of $(Boc)_2O$ furnished carbamate **156**. Similarly, when ene-lactone **154** was subjected to ozonolysis same aldehyde was obtained, which was transformed into carbamate **156**. Lactone **156** was reduced to lactol, which was converted into the hemithioketal **157**, which upon sequential reduction, thioketalization and oxidation yielded keto hemithioacetal. Treatment of the keto hemithioacetal with Bu_3SnH in refluxing benzene in the presence of AIBN furnished desired keto aldehyde **158**, which upon annulation with KOH gave the cyclohexenone **159**. Exposure of cyclohexenone **159** to dil. HCl effected concurrent removal of the carbamate group with concurrent intramolecular Michael addition to furnish (–)-mesembrine **1** in excellent yield.

Denmark[30] (*J. Org. Chem.* **1997**, *62*, 1675-1686)

Denmark and Marcin reported a total synthesis of (–)-mesembrine **1** employing asymmetric construction of quaternary carbon center by tandem [4+2]/[3+2] cycloaddition of a nitroalkene. Treatment of iodide **160** with activated zinc, followed by transmetalation with copper cyanide in the presence of LiCl provided the intermediate organocopper species. Conjugate addition of this organocopper reagent to (*E*)-2-(3,4-dimethoxyphenyl)-1-nitroethene **161**, after trapping with PhSeBr, furnished nitro selenide **162**. Oxidation of **162**, followed by elimination with H_2O_2 gave desired nitroalkene **163** in 72% overall yield as a 1.0:1.5 (*E*/*Z*) mixture. The mixture was isomerized to 23:1 (*E*/*Z*) ratio with MAD.

E/*Z*-nitroalkene mixture **163** was treated with 1 equiv. of MAD and was allowed to stir for 5 min and then (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol vinyl ether (–)-**164** was introduced. After 1 hour, an additional equiv. of MAD was slowly added to drive the reaction to completion. This protocol reproducibly provided the desired [4+2]-cycloadduct **165** in 82-86% yield with 25-29/1 diastereoselectivity (scheme 29).

Total Synthesis of (±)-Mesembrine



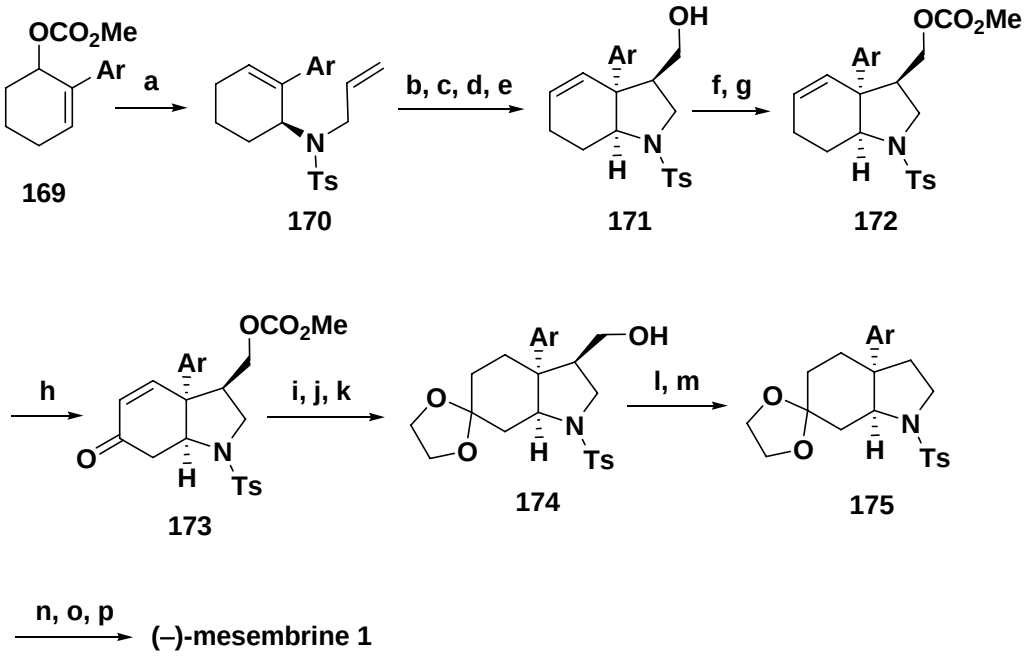
Scheme 29. *Reagents and conditions:* a) Zn dust, b) CuCN·2LiCl; c) (*E*)-2-(3,4-dimethoxyphenyl)-1-nitroethene **161**; d) PhSeBr; e) H_2O_2, H_2O-THF, 72% (2 steps); f) MAD, PhMe, –10 ºC; g) MAD, 5 min; h) (–)-**164**, 1 h; i) MAD, (1 equiv.), PhMe, –10 ºC; j) PhH, reflux, 2 h, 79% (2 steps); k) H_2, Raney Ni, MeOH, 36 h, 74%; l) CH_2O/H_2O, MeOH; m) H_2, Raney Ni, MeOH, 81% (overall); n) (1,1'-(azodicarbonyl)dipiperidine, *t*BuOMgBr, THF, r t, 2 h, 80%; o) TFA, r t, 28 h, then 30% NaOH, reflux, 2.5 h, 60%.

Tandem intramolecular [3+2]-dipolar cycloaddition of nitronate **165** in refluxing benzene afforded tricyclic nitroso acetal **166**, as a 30/1 mixture of diastereomers, in 79% overall yield. Catalytic hydrogenation of **166** using W2 Raney Ni furnished amine **167** in 74% yield. Reaction of the amino alcohol **167** with formaldehyde produced an intermediate that was subsequently hydrogenated over Raney-nickel to afford the *N*-methyl amino alcohol **168** in 81% yield. PCC oxidation of amino alcohol **168** by Mukaiyama method (1,1′-(azodicarbonyl)dipiperidine (ADD) and *t*butoxymagnesium bromide) furnished enal in 80% yield, which upon treatment with 60% TFA, for 28 hours at room temperature,

provided presumed enolic α-keto aldehyde, which upon treatment with 30% NaOH cleaved the alkoxymethylene group to afford target molecule **1**.

Mori[31] (*J. Org. Chem.* **1997**, *62*, 3263-3270)

Mori *et. al.* reported total synthesis of (–)-mesembrine **1** *via* palladium-catalyzed enantioselective allylic substitution and zirconium-promoted cyclization (scheme 30). A solution of allyl carbonate **169** and *N*-tosylallylamine in THF was warmed in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2.8 mol %) and dppb (5.6 mol %) as a ligand at 50 °C for 13 hours, to obtain tosylamide **170** in 80% yield and 86% ee.

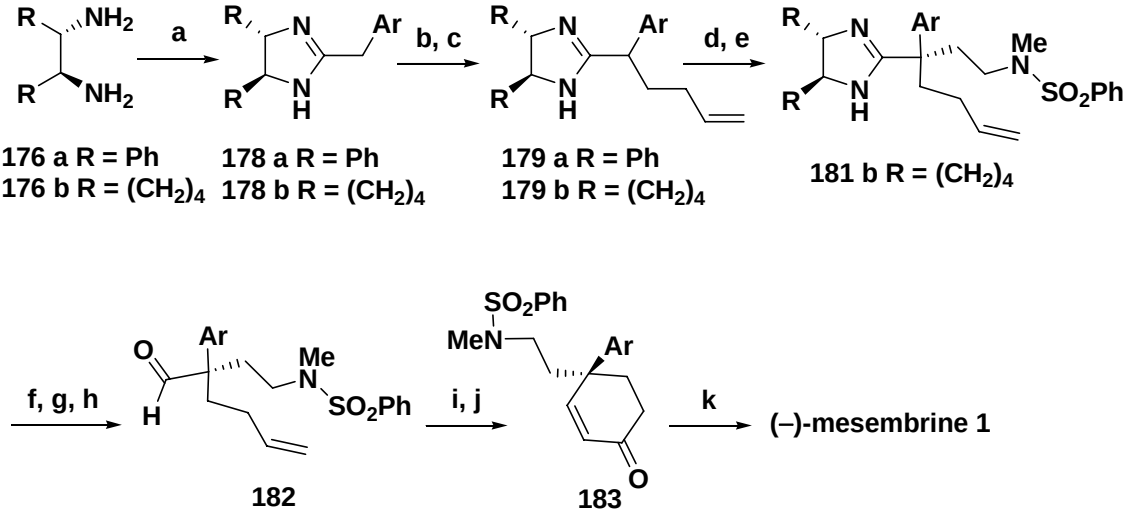


Scheme 30. *Reagents and conditions:* a) $Pd_2dba_3{\cdot}CHCl_3$, (*S*)-BINAPO, *N*-tosylallylamine, THF, r t, 19 h, 86% yield, 86% ee; b) Cp_2ZrBu_2; c) MeMgBr; d) O_2; e) H_3O^+; f) Bu_4NF; g) $ClCO_2Me$, 91%; h) CrO_3, 3,5-dimethylpyrazole, 65%; i) H_2, Pd/C; j) $(TMSOCH_2)_2$, TMSOTf; k) K_2CO_3, MeOH, 75%; l) Dess-Martin periodinane; m) $RhCl(PPh_3)_3$, n) Na-naphthalenide, THF, –78 ºC ; o) BuLi, MeI, THF, 1 h; p) 10% aq. HCl, r t, 18 h, 35%.

To a THF solution of Cp_2ZrBu_2 was added a THF solution of **170** at –78 ºC and the solution was stirred at room temperature for 4 hours, which upon hydrolysis provided hexahydroindole derivative **171**. Free alcohol **171** was converted into its carbonate **172**. Allylic oxidation of **172** with CrO_3 gave enone **173**. Enone **173** was reduced with Pd/C and the resultant ketone was acetalized, followed by carbonate deprotection to furnish free alcohol **174**. Alcohol **174** was oxidized with Dess-Martin periodinane and subsequently

deformylated with $RhCl(PPh_3)_3$ to give acetal **175**. Detosylation with sodium naphthalenide, methylation of the free amine followed by hydrolysis of the acetal gave (–)-mesembrine **1**.

Langlois[32] (*Tetrahedron Lett.* **1998**, *39*, 8979-8982)



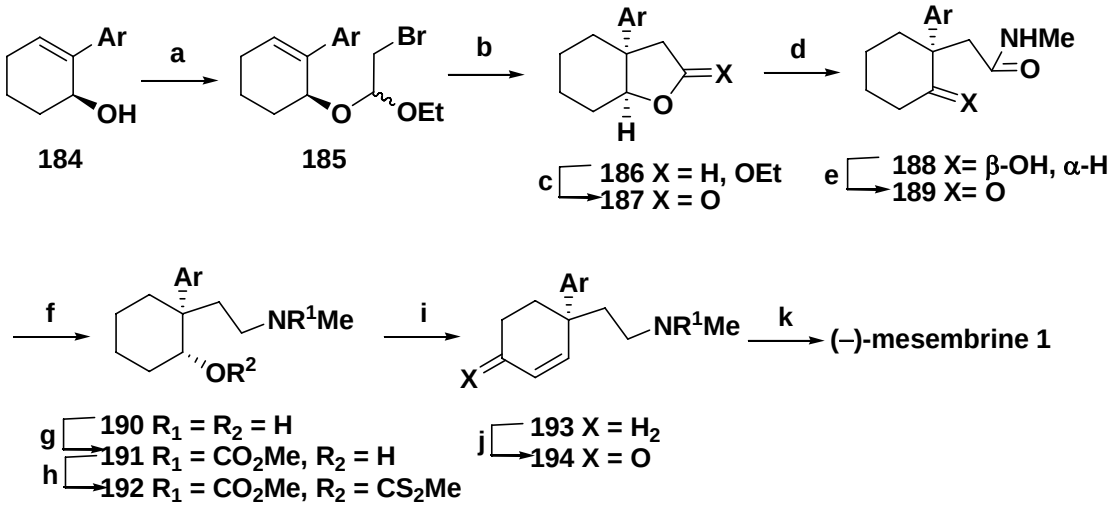
Scheme 31. *Reagents and conditions:* a) **177**, Et_3N, DCM, r t, 24 h, 85-86%; b) BuLi, THF, –25 °C; c) 4-bromobutene, –5 to –10 °C, 93-94%; d) BuLi, THF, –25 °C, 15 min; e) 2-(*N*-methylphenylsulfonamido)ethyl trifluoromethane sulfonate **180**, –78 °C, 12 h, 58-70%; f) MeI, BaO, $EtNO_2$, 130 °C, 6 h; g) $NaBH_4$, EtOH, 0-5 °C, 30 min; h) 0.5 N HCl, 0-5 °C, 30 min, 77% (3 steps); i) $PdCl_2$, CuCl, H_2O-DMF, O_2, 45 °C, 24 h, 69%; j) KOH, dioxane, 100 °C, 18 h, 88%; k) Li/NH_3, THF, *t*BuOH, –78 °C, 30 min, 74%.

Langlois *et. al.* reported a concise synthesis of (–)-mesembrine **1** employing stereoselective alkylation of dianion derived from *C2* symmetric imidazolines allowing efficient formation of quaternary benzylic center. Compounds **178a** and **178b** were obtained by condensing hydrochloride salt of ethyl 2-(3,4-dimethoxyphenyl)acetimidate **177** with either (*S,S*)-l,2-diamino-l,2-diphenylethane **176a** and (*S,S*)-1,2-diaminocyclohexane **176b**. Regioselective alkylation of dianions derived from imidazoline derivatives **178a** and **178b**, using two equiv. of BuLi at –25 °C, with 1.1 equiv. of 4-bromobutene at –5 °C to –10°C afforded imidazolines **179a** and **179b** in high yields.

Again, alkylation of the dianion of **179a** and **179b**, with triflate derivative **180** using BuLi furnished quaternary substituted imidazolines **181a** and **181b** in acceptable yields and in diastereomeric excess of 75% and more than 95% respectively. Imidazoline **181b** was *N*-permethylated using an excess of MeI under pressure in a sealed tube and the resultant

imidazolinium derivative was in turn reduced with $NaBH_4$ and the resultant aminal was then converted to the desired aldehyde **182** in good overall yield using 0.5 N HCI. Terminal olefin in **182** was subsequently converted to the corresponding methyl ketone **183** under Wacker's conditions. The synthesis was completed by an intramolecular aldol reaction, followed by cleavage of the phenylsulphonyl protection group under Birch conditions to afford (–)-mesembrine **1** (scheme 31).

Ogasawara[33] (*Tetrahedron Lett.* **1998**, *39*, 7747-7750)

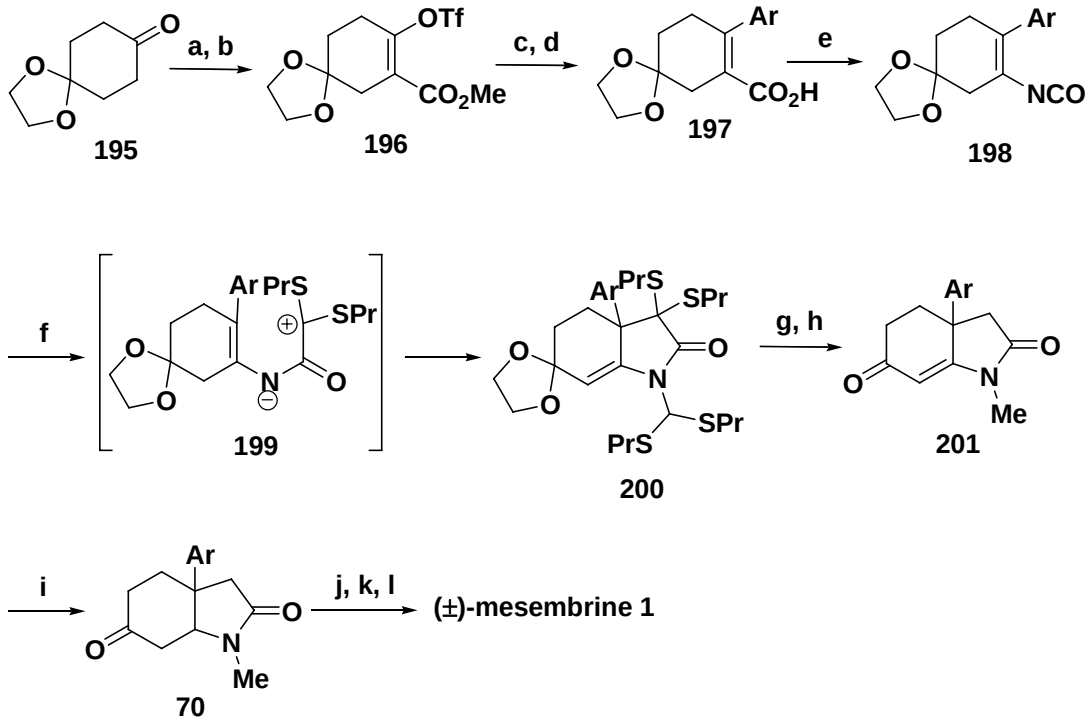


Scheme 32. *Reagents and conditions:* a) ethyl vinyl ether, NBS, Et_2O, 0 °C to r t, 24 h, 98%; b) Bu_3SnCI (cat.), AIBN (cat.), $NaBH_4$, *t*BuOH, reflux, 6 h (87%); c) *m*CPBA, $BF_3{\cdot}OEt_2$ (cat.), DCM, r t, 1 h, 93%; d) $Me_2NH{\cdot}HCI$, Me_3Al, THF, reflux, 8 h, 98%; e) Swern oxidation, 80%; f) $LiAIH_4$ THF, reflux, 2 d; g) $ClCO_2Me$, Et_3N, DCM, r t, 75%; h) CS_2, NaH, MeI, THF, r t, 6 h, 91%; i) *o*-dichlorobenzene, reflux, 18 h, 82%; j) CrO_3-3,5-dimethylpyrazole, DCM, –15 °C, 2 h, 73%; k) 10% KOH, EtOH, reflux, 24 h, 35%.

Enantiomerically pure allylic alcohol **184** was treated with ethyl vinyl ether in the presence of NBS to give bromo-acetal **185**. Treatment of **185** with $NaBH_4$ in the presence of a catalytic amount of Bu_3SnCl and AIBN gave cyclized product **186** through a radical intermediate, which on reaction with *m*CPBA in the presence of $BF_3{\cdot}OEt_2$, afforded γ-lactone **187**. To introduce the cyclohexene double bond, **187** was first converted to keto-amide **189**, *via* **188**. Reduction of **189** with $LiAlH_4$ afforded single amino-alcohol **190**, which was transformed into cyclohexene **193**, through intermediacy of **191** and **192**. Allylic oxidation of **193** gave cyclohexenone **194**, which was decarbamoylated to give (–)-mesembrine **1** by concurrent cyclization (Scheme 32).

Total Synthesis of (±)-Mesembrine

Rigby[34] (*Org. Lett.* **2000**, *2*, 1673-1675)



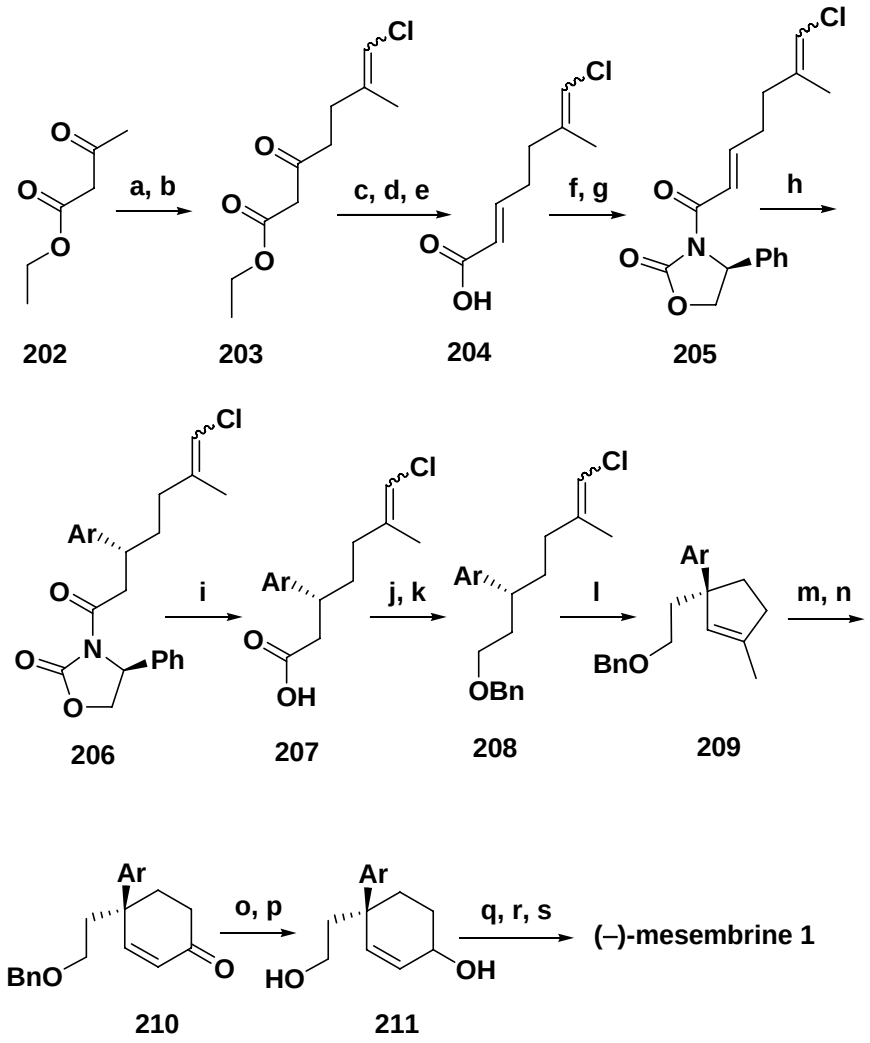
Scheme 33. *Reagents and conditions:* a) NaH, $(MeO)_2CO$, b) NaH, Tf_2O, 87%; c) tributyl(3,4-dimethoxyphenyl)stannane, d) LiOH, MeOH, 81%; e) $(PhO)_2P(O)N_3$, Et_3N, PhH, 80%; f) 2,2-dimethyl-5,5-bis(propylthio)-2,5-dihydro-1,3,4-oxadiazoline, PhH, reflux, 66%; g) Raney Ni, EtOH; h) H_3O^+, 100%; i) SmI_2-HMPA, *t*BuOH, THF, 70%; j) $HOCH_2CH_2OH$, H^+; k) $LiAlH_4$, THF; l) H_3O^+, 75%.

Rigby and Dong reported a synthesis of (±)-mesembrine **1** by a sequence featuring [4 + 1] cycloaddition of bis-(alkylthio) carbene with a functionalized vinyl isocyanate. Synthesis commenced with commercially available monoprotected dione **195**, which was transformed in four steps *via* vinyl triflate **196** to the key *β*-aryl-*α,β*-unsaturated acid **197** in 71% overall yield (Scheme 33). Exposure of **197** to DPPA/TEA, followed by attempted purification of the resultant acyl azide on silica gel gave the rearranged vinyl isocyanate **198**, which was immediately heated in refluxing benzene in the presence of excess 2,2-dimethyl-5,5-bis(propylthio)-2,5-dihydro-1,3,4-oxadiazoline to afford the crucial 2:1 adduct **200** through intermediate **199**.

Raney nickel mediated reductive cleavage of all four carbon-sulfur bonds in compound **200** delivered the requisite enamide **201** after acetal hydrolysis. Reduction of the remaining enamide alkene to the *cis*-fused aryloctahydroindole system **70** was achieved by employing SmI_2-based reduction protocol. This followed by a routine series of

operations i.e. protection of the ketone, reduction of the amide and hydrolysis of the acetal afforded (±)-mesembrine **1**.

Taber[35] (*J. Org. Chem.* **2001**, *66*, 143-147)



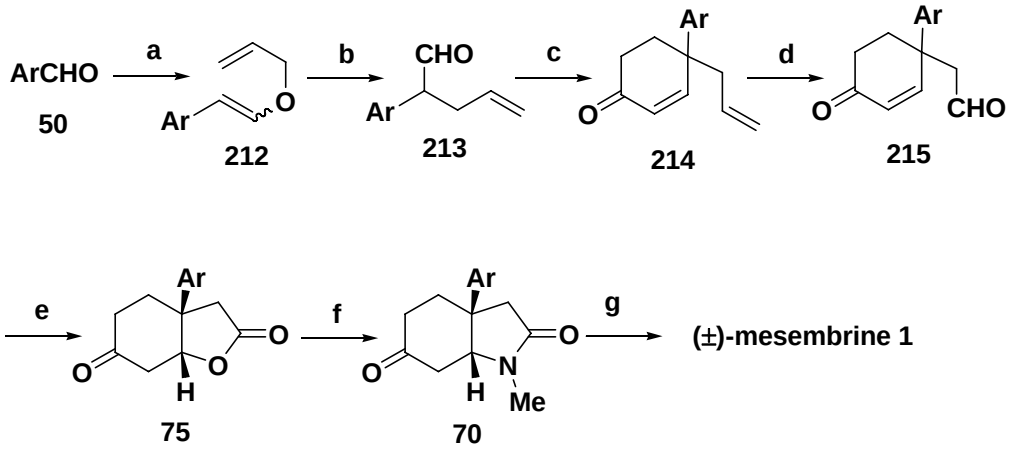
Scheme 34. *Reagents and conditions:* a) NaH, THF, BuLi; b) 3-bromo-1-chloro-2-methylpropene, 73%; c) $NaBH_4$, EtOH, 80%; d) MsCl, Et_3N, DCM, 87%; e) LiOH, 1,4-dioxane-H_2O, 64%; f) Me_3COCl, Et_3N, THF; g) lithium (*S*)-(+)-4-phenyl-2-oxazolidinone, 68%; h) (3,4-dimethoxyphenyl) magnesium iodide, CuBr·Me_2S, THF, DMS, 94%; i) H_2O_2, LiOH-H_2O; j) $LiAlH_4$, THF, Δ, 89%; k) NaH, DMF, BnCl, 84%; l) KHMDS, Et_2O, 85%; m) O_3, Ph_3P; n) PTSA, PhH, reflux, Dean-Stark, 83%; o) $LiAlH_4$, THF, 87%; p) Na/NH_3, THF, –78 °C; 86%; q) MsCl, Et_3N, Et_2O, 84%; r) $MeNH_2$, H_2O-THF; s) MnO_2, DCM, 68%.

Taber and Neubert described a total synthesis of (–)-mesembrine **1**, employing diastereoselective conjugate addition and subsequent intramolecular alkylidene C-H insertion (scheme 34). Alkylation of the dianion of acetoacetate **202** with 3-bromo-1-chloro-2-methylpropene was effecetd to give ketoester **203** in good yield. Reduction of the

ketone **203** and mesylation of the resultant alcohol was accompanied by concomitant elimination to give (*E*)-α,β-unsaturated ester, which upon hydrolysis with LiOH afforded acid **204**. Next, the chiral auxiliary was introduced by the reaction of lithium (*S*)-(+)-4-phenyl-2-oxazolidinone with the mixed anhydride of **204** derived from pivalic acid to obtain **205**.

Conjugate addition of arylmagnesium iodide to acyl oxazolidinone **205** proceeded with high stereoselectivity to funish **206**. Hydrolysis of the oxazolidinone amide **206** then gave acid **207**. Acid **207** was subjected to $LiAlH_4$ reduction and the resultant alcohol was converted into its benzyl ether **208**. Benzyl ether **208** cyclized smoothly to give cyclopentene **209** with retention of absolute configuration. Ozonolysis of **209** gave the intermediate keto aldehyde, which upon cyclization with KOH in MeOH, involving intramolecular aldol reaction and subsequent dehydration gave cyclohexenone **210**, under acid catalysis. The cyclohexenone **210** was reduced ($LiAlH_4$) to the secondary alcohol, and subsequent debenzylation gave diol **211**. The primary alcohol was then selectively converted to mesylate, which following amination, oxidation, and cyclization then gave (–)-mesembrine **1**.

Kulkarni[36] (*Tetrahedron Lett.* **2002**, *43*, 2297-2298)



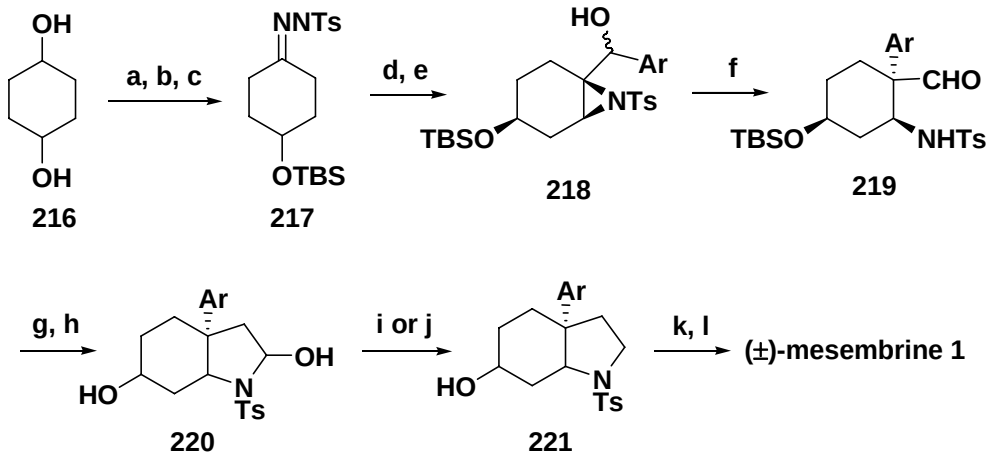
Scheme 35. *Reagents and conditions*: a) CH_2:$CHCH_2OCH_2P^+Ph_3Cl^-$, KO*t*Bu, THF, 0 °C, 1 h, 93%; b) xylene reflux, 7 h, 98%; c) MVK, ethanolic KOH (cat.), ether, 0 ºC to r t, 24 h, 85%; d) OsO_4 (cat.), $NaIO_4$, 5 h, 60%; e) CrO_3, H_2SO_4, acetone, 4 h, 60%; f) $MeNH_2$ excess, MeOH, 80 °C, 12 h in sealed tube, quantitative; g) i. 2-ethyl-2-methyl-1,3-dioxolane, PTSA, reflux, 2 h, ii. $LiAlH_4$ excess, THF-Et_2O, reflux, 23 h, iii. 10% aq. HCl, r t, 2 days, 72%.

Total Synthesis of (±)-Mesembrine

Kulkarni *et. al.* reported a short and efficient synthesis of (±)-mesembrine **1** employing tandem Wittig olefination-Claisen rearrangement. Reaction of veratraldehyde **50** with allyloxymethylenetriphenylphosphonium chloride using KO*t*Bu as the base furnished the *E*/*Z*-mixture of allyl vinyl ether **212** in good yield, which smoothly underwent Claisen rearrangement in refluxing xylene to furnish 2-aryl-4-pentenal **213** in quantitative yields. Compound **213** on treatment with methyl vinyl ketone and a catalytic amount of ethanolic KOH underwent tandem Michael addition–intramolecular aldol condensation to give allyl cyclohexenone **214** in 85% yield.

Aldehyde **215** was obtained in 60% yield by treatment of **214** with a catalytic amount of OsO_4 and 1.5 equiv. of $NaIO_4$. Jone's oxidation of **215** furnished lactone **75**. Treatment of lactone **75** with excess $MeNH_2$ gave the lactam **70**. The lactam was then subjected to ketal exchange with 2-ethyl-2-methyl-1,3-dioxolane. The excess dioxolane was removed under vacuum and the crude lactam was reduced with $LiAlH_4$. Acid hydrolysis of the crude ketal amine so obtained gave (±)-mesembrine **1** (scheme 35).

Tu[37] (*Org. Lett.* **2003**, *5*, 2319-2321)



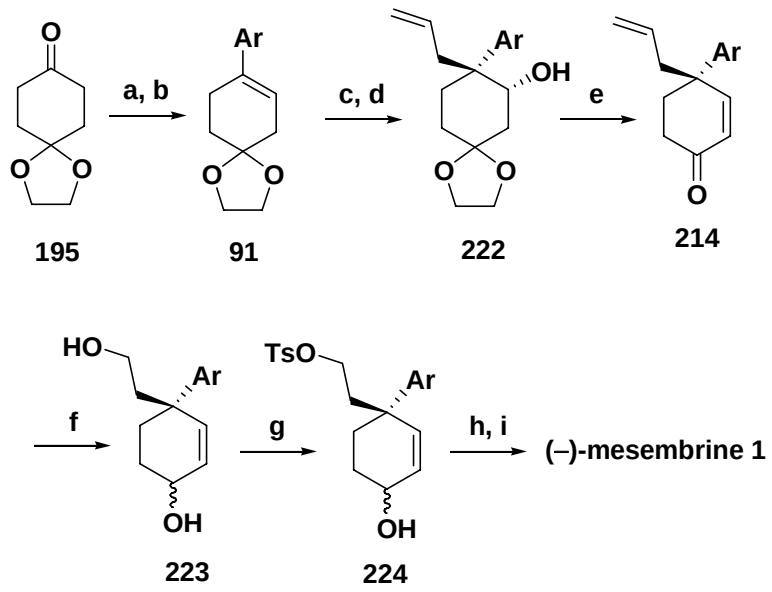
Scheme 36. *Reagents and conditions:* a) TBSCl, Im; b) PCC, DCM; c) $TsNHNH_2$, THF, 60% (3 steps); d) BuLi then veratraldehyde; e) TsNClNa, PTAB; f) $ZnBr_2$, DCM, 98%; g) $MeOCH{=}PPh_3$; h) $HClO_4$, 85% (2 steps); i) Red-Al, *o*-xylene, reflux, 6 h, 50%; j) i. $NaBH_3CN$, $TiCl_4$, DCM, –78 ºC; ii. Na-naphthalenide, DME,–78 ºC, 93% (2 steps); k) $NaCNBH_3$, $ZnCl_2$, formalin; l) PDC, DCM, 90%.

A short and general approach to (±)-mesembrine **1** has been developed employing stereocontrolled $ZnBr_2$-catalyzed rearrangement of 2,3-aziridino alcohol (scheme 36). Synthesis commenced with transformation of the commercially available cyclohexane-1,4-diol **216** to hydrazone **217** in three steps in 60% overall yield. Shapiro coupling of **217** with

3,4-dimethoxybenzaldehyde followed by aziridination afforded aziridino alcohol **218** as a mixture of isomers (2:1) in 26% overall yield. Subjection of **218** to catalytic amounts of $ZnBr_2$, in DCM at room temperature for 1 hour furnished **219** in a single diastereoisomeric form, which was then converted into **220** in 85% overall yield.

Reduction of **223** with Red-Al resulted in amino alcohol **221**. Alternatively, **221** was obtained in excellent yields when **220** was treated with $NaBH_3CN$ and $TiCl_4$ in DCM at –78 °C followed by removal of the tosyl group using sodium naphthalenide. After *N*-methylation of **221**, followed by oxidation using PDC, **221** ultimately was converted into (±)-mesembrine **1**.

Taber[38] (*J. Org. Chem.* **2005,** *70***,** 7711-7714**)**

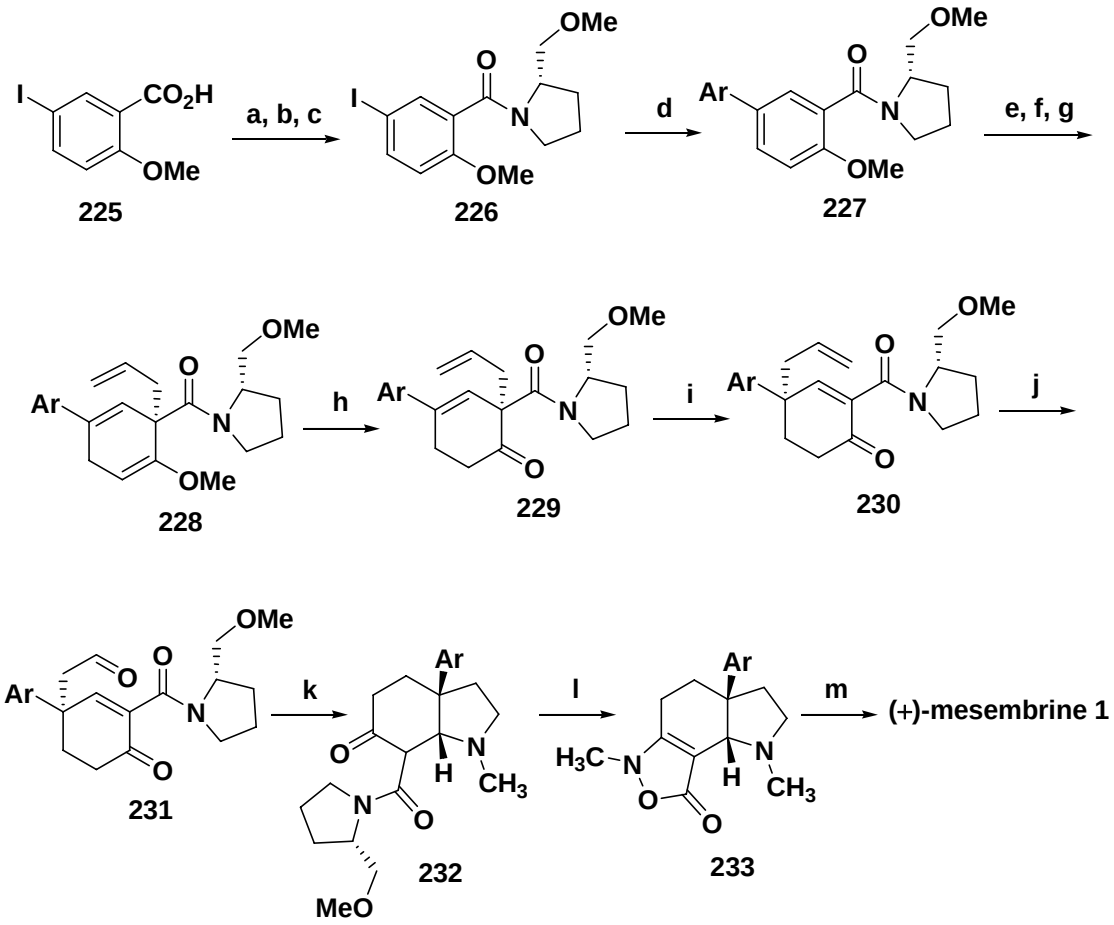


Scheme 37. *Reagents and conditions:* a) 3,4-(dimethoxyphenyl)magnesium bromide, THF, 0-20 °C, overnight; b) $HOCH_2CH_2OH$, PTSA (cat.), PhH, reflux, 64%; c) Shi's catalyst, DME-CH_3CN-H_2O, 0 °C, 4 h; d) allylmagnesium chloride, THF, 0-20 °C, overnight, 73%; e) 10% aq. HCl, THF, reflux, 1 h, 92%; f) O_3, MeOH, –78 °C; $CeCl_3 \cdot 7H_2O$, $NaBH_4$, 0 °C, 73%; g) TsCl, Et_3N, DCM, 20 °C, overnight, 90%; h) 40% aq. CH_3NH_2, THF, 65 °C, 1 h; i) MnO_2, DCM, 20 °C, 3 h, 61%.

Taber and He reported a short synthesis of (–)-mesembrine **1** employing enantioselective construction of quaternary stereogenic centre. Treatment of 3,4-(dimethoxyphenyl) magnesium bromide with cyclohexanone **198** gave the known alkene **91** after dehydration using PTSA in the presence of excess ethylene glycol. Shi expoxidation of **91** followed by ring opening of the resultant crude epoxide by allylmagnesium chloride furnished the enantiomerically enriched secondary alcohol **223** in

96% ee. Exposure of **222** to 10% aqueous HCl in THF gave the enone **214**. Selective ozonolysis of the terminal double bond in **214** followed by treatment of the resultant ozonide *in situ* with $NaBH_4$ in the presence of $CeCl_3$ furnished diol **223** as a 4:1 mixture of diastereomers. The primary hydroxyl group in diol **223** was selectively converted into the corresponding tosylate **224**, which on heating with 40% aq. $MeNH_2$, followed by oxidation using activated MnO_2 gave (–)-mesembrine **1** (scheme 37).

Malachowski[39] (*Org. Lett.* **2006**, *8*, 4007-4010)



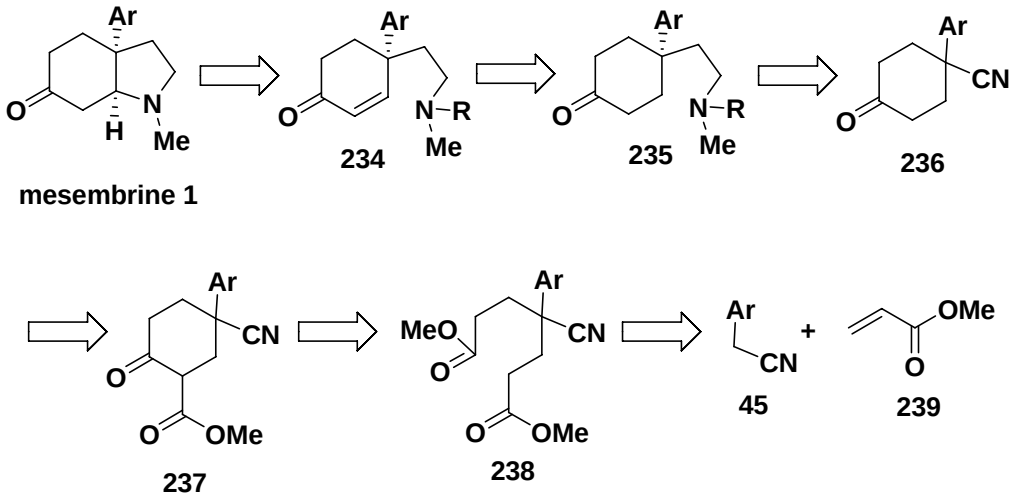
Scheme 38. *Reagents and conditions:* a) $SOCl_2$, b) L-prolinol; c) MeI, NaH; d) $Pd(OAc)_2$, PPh_3, K_2CO_3, Ar-$B(OH)_2$, BuOH, H_2O, 96%; e) Li, NH_3, *t*BuOH, –78 ºC; f) 1,3-pentadiene; g) allyl bromide, 70% (for 3 steps), de >99:1; h) 6 N HCl, MeOH, 95%; i) 1,2-DCB, Δ, 80%; j) O_3, DMS; k) $MeNH_2$, $NaCNBH_3$, 63% for 2 steps; l) MeNHOH, EtOH, Δ, 60%; m) $Mo(CO)_6$, CH_3CN, H_2O, Δ, 75% (for 2 steps).

Malachowski *et. al.* demonstrated a total synthesis of mesembrine **1**, employing a sequence of three reactions: enantioselective Birch reduction-allylation, enol ether hydrolysis, and Cope rearrangement resulting in the stereoselective generation of chiral quaternary center on a 2-cyclohexen-1-one ring. Synthesis commenced with conversion of

acid **225** into acid chloride and coupling with (L)-prolinol as the chiral auxiliary, followed by methylation of the alcohol to obtain the *o*-anisic acid derivative **226** in 75% yield (scheme 38). Cross-coupling of **226** with 3,4-dimethoxyphenylboronic acid furnished biaryl derivative **227**. Birch reduction of **227** followed by Cope rearrangement provided compound **228** with excellent chemoselectivity. Hydrolysis of compound **228** with 6 N HCl gave cyclohexen-2-one **229** that susequently rearranged to **230**. Ozonolysis of the terminal alkene afforded aldehyde **231**, which was immediately subjected to reductive amination. Resultant secondary amine spontaneously underwent conjugate addition to afford **232**. Cleavage of the chiral auxiliary with *N*-methylhydroxylamine afforded **233**, which was reduced, hydrolyzed, and decarboxylated in one step with $Mo(CO)_6$ to afford (+)-mesembrine **1**.

2.1.4. Present Work

2.1.4.1. Retrosynthetic analysis



Ar = 3,4-dimethoxyphenyl,
R = protecting group

Scheme 39. Retrosynthetic analysis.

Retrosynthetic analysis (scheme 39) revealed that target molecule **1** could be obtained from enone **234**, which in turn could be prepared from ketone **235**. Elaboration of nitrile **236,** employing a suitable sequence would give compound **235**. Ketone **236** in turn could be obtained from *β*-ketoester **237**. Demethoxycarbonylation of *β*-ketoester **237** would give 4,4-disubstituted ketone **236**. *β*-ketoester **237** in turn could be obtained by double Michael addition of methyl acrylate **239** to 3,4-dimethoxyphenylacetonitrile **45**, followed by Dieckmann condensation of the resultant double Michael adduct **238**.

2.1.4.2. Results and discussion

In connection with an ongoing programme on the synthesis of biologically active compounds, we have recently developed a technically and economically viable protocol[40] for the synthesis of antidepressant drug venlafaxine. In order to establish generality of the protocol it was decided to employ this protocol for the construction of quaternary carbon center, a formidable challenge posed by such molecules as mesembrine **1** and related members of this family of alkaloids.

Total Synthesis of (±)-Mesembrine

Accordingly, Michael addition of 3,4-dimethoxyphenyl acetonitrile **45** to methyl acrylate **239** using 10% aq. NaOH or KOH at 0 ºC, under phase transfer conditions gave double Michael adduct **238** in 75% yield within 1 hour.[40] Alternatively, compound **238** was obtained quantitatively using Triton-B as a catalyst, in refluxing CH_3CN (scheme 40).

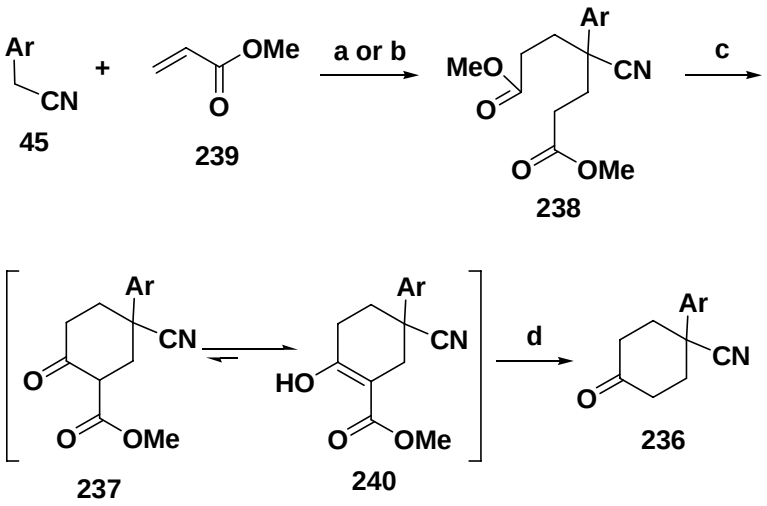
IR spectrum of compound **238** showed a strong absorption at 1736 cm^{-1} characteristic of ester carbonyl and an absorption at 2232 cm^{-1} characteristic of nitrile. ^1H NMR spectrum of compound **238** showed a multiplet at δ 6.94-6.80 corresponding to three aromatic protons. The six ester methoxy protons appeared at δ 3.58, and the other two methoxy protons appeared at δ 3.87 and 3.84. The multiplet at δ 2.04-2.48 accounted for the remaining eight protons. ^{13}C NMR spectrum of compound **238** showed signal at δ 172.2 correponding to ester function. The six aromatic carbons appeared at δ 149.5, 148.9, 128.3, 120.9, 111.4, 108.8. A signal at δ 118.3 indicated nitrile carbon. The methoxy carbons appeared at δ 55.8 and 51.6. The signal at δ 46.4 revealed the quaternary carbon and the remaining four carbons appeared at δ 35.7 and 29.9. Molecular formula of compound **238** was further confirmed by its MS spectrum, which showed a signal at 350 corresponding to M+1.

Michael adduct **238** was subjected to Dieckmann condensation using NaH in DME under reflux for 3 hours to give *β*-ketoester in 89% yield, which exists as a mixture of keto-enol tautomers **237** and **240**.

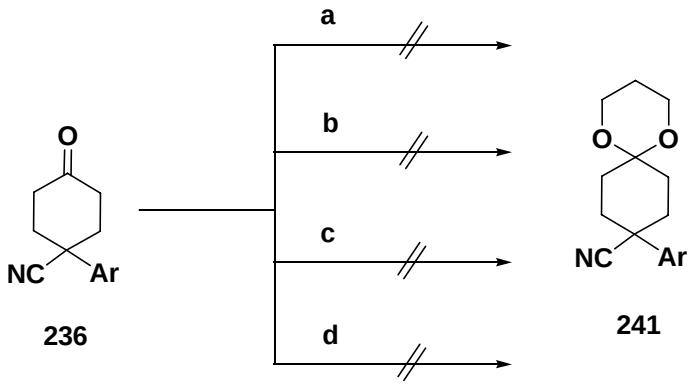
IR spectrum of tautomers **237** and **240** showed a broad absorption at 3365 cm^{-1} and 1665 cm^{-1} characteristic of *β*-ketoester and an absorption at 2236 cm^{-1} corresponding to nitrile group. ^1H NMR spectrum of *β*-ketoester showed a broad singlet at δ 12.20 characteristic of enol proton. The three aromatic protons appeared at δ 6.95 and 6.84 as multiplet and doublet respectively. The signals at δ 3.89, 3.84 and 3.75 revealed nine methoxy protons. Multiplets at δ 2.49-3.00 and 2.13-2.24 revealed seven protons. ^{13}C NMR spectrum of β-ketoester showed two signals at δ 171.5 and 170.5 corresponding to ester function, which may be attributed to mixture of tautomers. Signals at δ 149.2, 148.8, 131.6, 121.7, 111.2, 109.1 revealed six aromatic protons. A signal at δ 117.4 corresponded to nitrile carbon. The methoxy protons appeared at δ 55.8, and 51.5. Mass spectral analysis of compound **237** and **240** showed signals at 318 and 317 corresponding to M+1 and M^+ respectively, further confirming its molecular formula.

The mixture of tautomers **237** and **240** was subjected to demethoxycarbonylation in wet DMSO at 140 ºC for 6 hours using Krapcho's method[41] to obtain ketone **236** in 87%

yield (scheme 40). Use of THF as a solvent for Dieckmann condensation gave low yields (about 40%).



Scheme 40: *Reagents and conditions:* a) 10% aq. NaOH, $TBAHSO_4$, 0 ºC, 1 h, 75%; b) Triton-B (cat.), CH_3CN, reflux, overnight, (quantitative); c) NaH, DME, reflux, 3 h, 89%; d) NaCl, DMSO, H_2O, 140 ºC, 6 h, 87%;



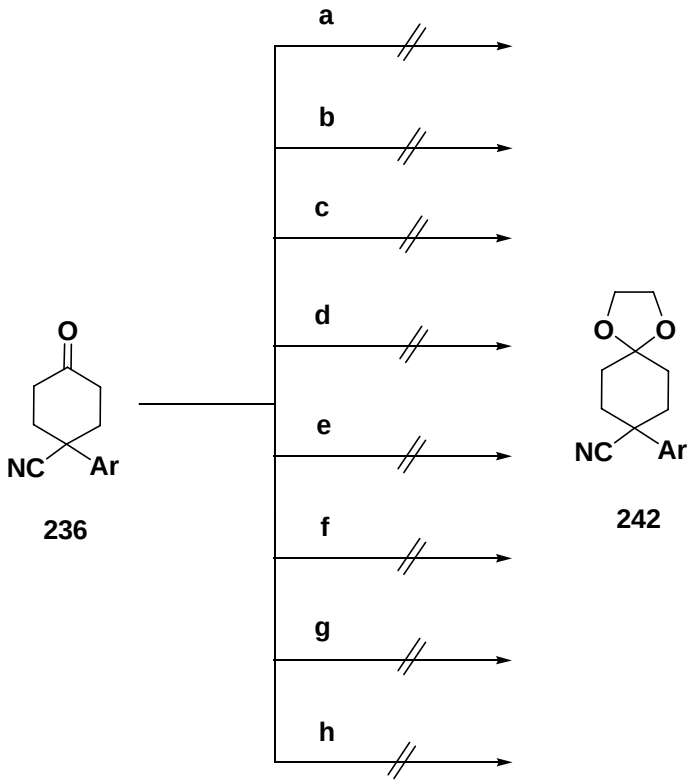
Scheme 41. *Reagents and conditions:* a) 1,3-propanediol, PTSA, PhH, reflux, b) 1,3-propanediol, PPTS, PhH, reflux; c) 1,3-propanediol, $(COOH)_2$, PhH, reflux; d) 1,3-propanediol, CSA, PhH, reflux.

Absorptions at 2241 cm^{-1} and 1710 cm^{-1} in the IR spectrum of compound **236** confirmed the presence of nitrile and ketone function. ^1H NMR spectrum of compound **236** showed signals at δ 6.99 and 6.86 revealing three aromatic protons. Methoxy protons appeared as two singlets at δ 3.92 and 3.89. ^{13}C NMR spectrum of compound **236** showed signal at δ 206.4 revealing carbonyl function. The aromatic protons were revealed by signals at δ 149.0, 148.8, 130.7, 121.0, 111.0, 108.7. The signal at δ 117.2 suggested presence of nitrile function. The methoxy carbons appeared as a singlet at δ 55.6. Quaternary carbon appeared at δ 42.2. The remaining four carbons appeared at δ 38.2 and

36.6. Appearance of signals at 260 and 259 in the MS spectrum of compound **236** corresponding to M+1 and M^+ further confirmed its molecular formula.

Surprisingly, protection of the ketone **236** with 1,3-propanediol[42] in the presence of either PTSA, PPTS, CSA or $(COOH)_2$ as a catalyst was not successful (scheme 41).

Also, replacing 1,3-propanediol with ethylene glycol or transdioxolation with 2-ethyl-2-methyl-1,3-dioxolane[42] did not give the expected 1,3-dioxolane **242** (scheme 42).

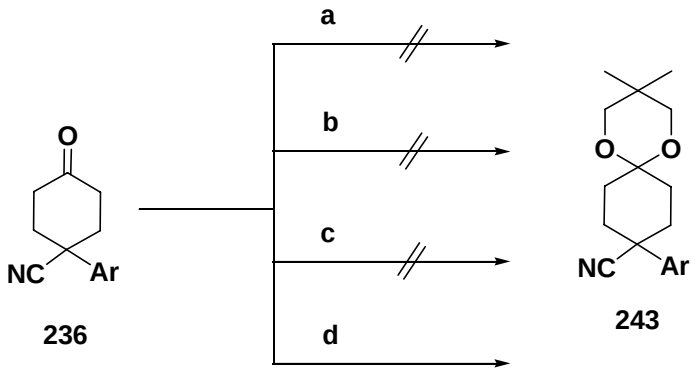


Scheme 42: *Reagents and conditions:* a) $HOCH_2CH_2OH$, PTSA, PhH, reflux, b) $HOCH_2CH_2OH$, PPTS, PhH, reflux; c) $HOCH_2CH_2OH$, $(COOH)_2$, PhH, reflux; d) $HOCH_2CH_2OH$, CSA, PhH, reflux; e) 2-ethyl-2-methyl-1,3-dioxolane, PTSA, PhH, reflux, f) 2-ethyl-2-methyl-1,3-dioxolane, PPTS, PhH, reflux, g) 2-ethyl-2-methyl-1,3-dioxolane, $(COOH)_2$, PhH, reflux, h) 2-ethyl-2-methyl-1,3-dioxolane, CSA, PhH, reflux,

Even 2,2-dimethyl-1,3-propanediol didn't give the desired compound either using PTSA, CSA or oxalic acid. Eventually, acetal **243** was obtained with 2,2-dimethyl-1,3-propandiol using PPTS as a catalyst, in refluxing benzene over Dean-Stark apparatus (scheme 43).

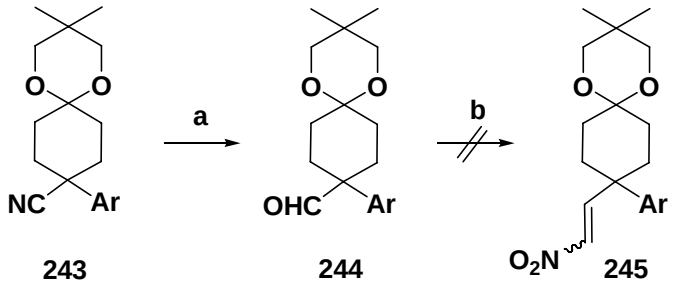
Disappearance of absorption at 1710 cm^{-1} in the IR spectrum of compound **243** indicated formation of acetal. An absorption at 2237 cm^{-1} indicated the presence of nitrile function. Appearance of singlet at δ 0.99 corresponding to methyl protons and a doublet at δ 3.53 corresponding to C*H*$_2$s proximal to oxygens of acetal in ^{1}H NMR spectrum of

compound **243** indicated formation of acetal. Disappearance of the signal at δ 206.4 corresponding to carbonyl carbon and appearance of signal at δ 95.7 revealing acetal quaternary center proximal to the oxygen atoms and a signal at δ 22.4 indicating the acetal methyls in the ^{13}C NMR spectrum of compound **243** also suggested formation of the acetal. Molecular formula of the acetal was further confirmed by MS spectrum, which showed signals at 346 and 345 corresponding to M+1 and M^+ respectively.



Scheme 43: *Reagents and conditions:* a) 2,2-dimethyl-1,3-propanediol, PTSA, PhH, reflux; b) 2,2-dimethyl-1,3-propanediol, CSA, PhH, reflux; c) 2,2-dimethyl-1,3-propanediol, $(COOH)_2$, PhH, reflux; d) 2,2-dimethyl-1,3-propanediol, PPTS, PhH, reflux, 7 h, 95%.

Nitrile **243** was then reduced with DIBAL in DCM at 0 ºC to obtain aldehyde **244** in quantitative yields (scheme 44).



Scheme 44: *Reagents and conditions:* a) DIBAL, DCM, 0 ºC, 1 h, quantitative; b) CH_3NO_2, NaH or KO*t*Bu, THF.

Appearance of absorptions at 1713 cm^{-1} and 2712 cm^{-1} and disappearance of absorption at 2237 cm^{-1} in the IR spectrum of compound **244** indicated conversion of nitrile into aldehyde. ^1H NMR spectrum of compound **244** showed a sharp singlet at δ 9.29 revealing aldehyde function. ^{13}C NMR spectrum of compound **244** showed appearance of signal at δ 200.6 characteristic of aldehyde carbonyl. Further, appearance of signal at 348

in the MS spectrum of compound **244** corresponding to M^+ confirmed its molecular formula.

Attempts to homologate the aldehyde **244** by nitroaldol reaction with CH_3NO_2 were not successful (scheme 44). Then another course was taken to homologate aldehyde **244**, where it was olefinated employing Wittig reaction with methylene triphenylphosphorane to obtain compound **246** in 82% yield using $NaNH_2$ as a base in THF.

Disappearance of strong absorption at 1713 cm^{-1} and 2712 cm^{-1} in the IR spectrum of compound **246** indicated formation of the olefin. ^1H NMR spectrum of compound **246** showed a doublet of doublet at δ 5.81 and two doublets at δ 5.09 and 4.92 suggesting the formation of olefin. Disappearance of signal at δ 200.6 and appearance of signals at δ 112.7 and 146.2 in ^{13}C NMR spectrum of compound **246** corroborated with the above observation. Further, appearance of signals in the MS spectrum of compound **246** at 347 and 346 revealing M+1 and M^+ confirmed its molecular formula.

Further olefin **246** was subjected to hydroboration with BMS complex, followed by alkaline work up (30% aq. NaOH and 30% aq. H_2O_2) to obtain alcohol **247** in 75% yield (scheme 45).

IR spectrum of compound **247** exhibited a broad signal at 3462 cm^{-1} characteristic of hydroxy function. Absence of any signals in the olefinic region and appearance of a signal at δ 3.29 revealing –C*H*$_2$OH function in the ^1H NMR spectrum of compound **247** indicated conversion of olefin into the terminal alcohol. ^{13}C NMR spectrum of compound **247** also showed absence of the olefinic carbons and showed a signal at δ 59.0 indicative of –*C*H$_2$OH function. Molecular formula of alcohol **247** was further confirmed by its MS spectrum showing a signal at 364 revealing M^+.

Subsequently, alcohol **247** was converted into mesylate **248** (scheme 45) with MsCl using Et_3N in DCM at 0 ºC in quantitative yields!

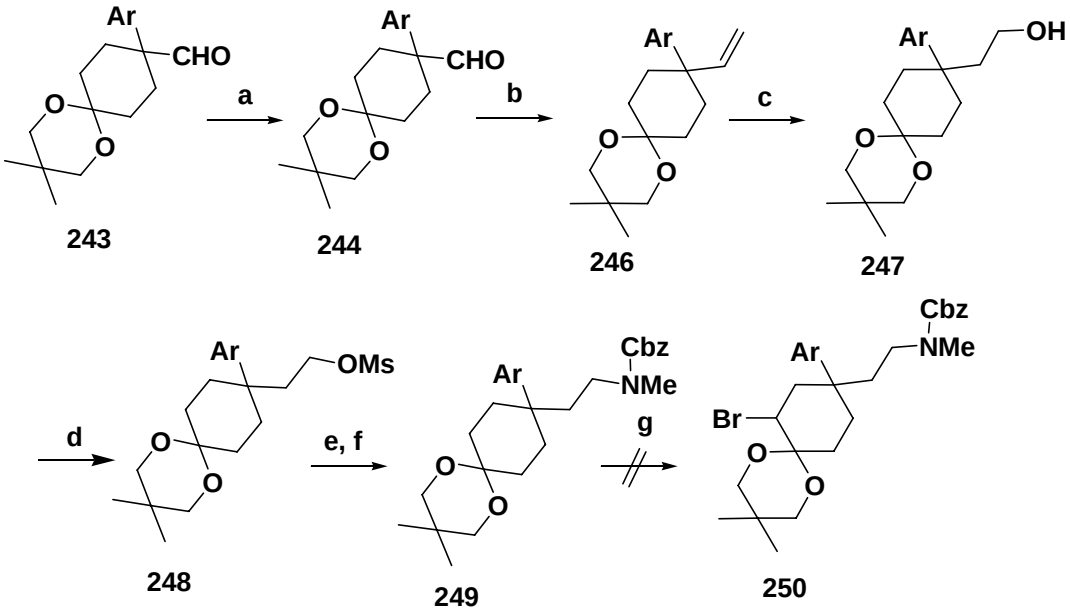
IR spectrum of compound **248** showed absence of an absorption at 3462 cm^{-1}. ^1H NMR spectrum of compound **248** showed an additional signal at δ 2.25 indicating -SO_2*Me*. ^{13}C NMR spectrum of compound **248** showed a signal at δ 36.1 indicative of -SO_2*Me*.

Mesylate **248** was treated with 30% aq. $MeNH_2$ solution in a sealed tube at 100 ºC and the resultant free amine was protected with $ClCO_2Bn$ to obtain benzyl carbamate **249** using K_2CO_3 as a base in THF-H_2O in 88% overall yield (scheme 45).

IR spectrum of compound **249** showed strong absorption at 1694 cm^{-1} characteristic of the carbamate function. ^1H NMR spectrum of compound **249** showed appearance of two

singlets at δ 7.36 and 7.33, corresponding to the carbamate phenyl ring. The splitting of signal may be due to mixture of rotamers. The singlets at δ 5.11 and 5.06 corresponded to the benzylic protons of the carbamate function. Molecular structure of carbamate **249** was further confirmed by its mass spectrum, which showed appearance of the signals at 512 and 511 corresponding to the M+1 and M^+ respectively.

Subjection of the acetal **249** to α-bromination[43] with Br_2 in the presence of $AlCl_3$ in MeOH or THF didn't give required *α*-bromoacetal **250** (scheme 45).



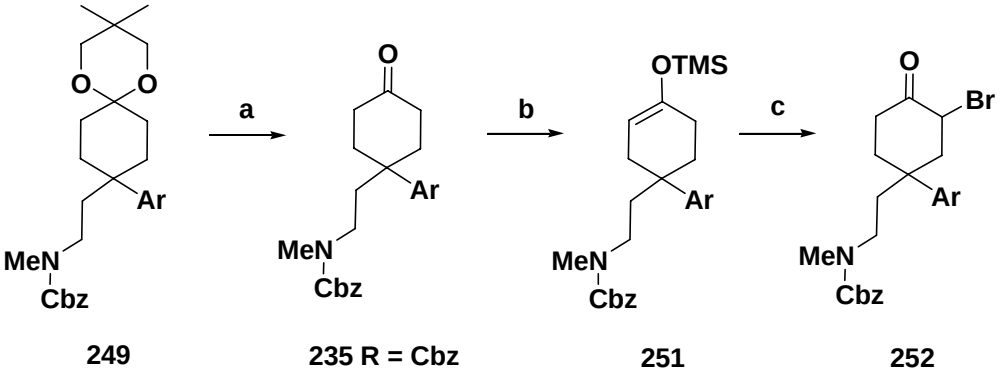
Scheme 45. *Reagents and conditions:* a) DIBAL, DCM, 0 ºC, 1 h, quantitative, b) $Ph_3P^+CH_2I^-$, $NaNH_2$, THF, 0 ºC, 30 min 82%; c) BMS, THF, 0 ºC to r t, overnight, then 30% aq. H_2O_2 and 30% aq. NaOH; d) MsCl, Et_3N, DCM, 0 ºC, 30 min, 100%; e) 40% aq. $MeNH_2$, sealed tube, 100 ºC, 2 h; f) $ClCO_2Bn$, K_2CO_3, THF-H_2O, 0 ºC to r t, 4 h, 88% (2 steps); g) Br_2, $AlCl_3$, THF or MeOH, 0 ºC.

Due to unforeseen problems associated with *α*-bromination of acetal **249**, it was hydrolysed in acetone-water (1:1) system under reflux in the presence of catalytic amount of H_2SO_4 to obtain ketone **235** (R = Cbz) in 85% yields (scheme 46).

IR spectrum of compound **235** showed a broad absorption at 1669 cm^{-1}. This may be due to merger of the carbamate and carbonyl absorption. ^1H NMR spectrum of compound **235** showed disappearance of a doublet at δ 3.48 and a singlet at δ 0.96 corresponding to the acetal function, indicating hydrolysis of acetal. ^{13}C NMR spectrum of compound **235** showed appearance of signal at δ 210.1 indicating the formation of ketone. Further, its molecular formula was confirmed by MS spectrum, which showed a signal at 426 and 425 revealing M+1 and M^+ respectively.

Total Synthesis of (±)-Mesembrine

Silyl enol ether of the ketone **235** was prepared by refluxing a solution of **235** and TMSCl in the presence of Et_3N in CH_3CN for 2 hours in quantitative yields and the crude silyl enol ether **251** was further subjected to bromination with NBS in THF at 0 ºC to give α-bromoketone **252** (scheme 46), which was used as such for further reaction.[44]



249 **235 R = Cbz** **251** **252**

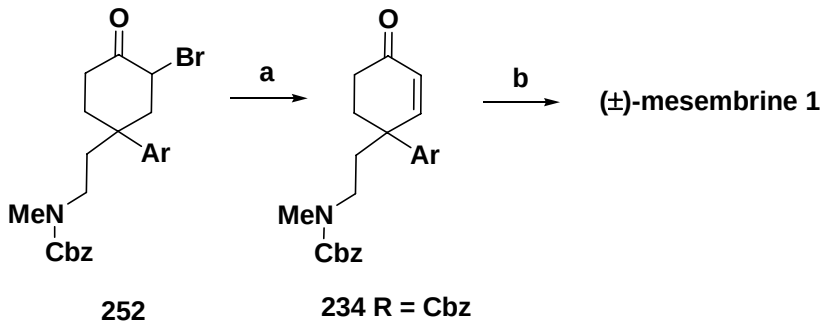
Scheme 46: *Reagents and conditions:* a) Acetone-H_2O, H_2SO_4 (cat.), reflux, 85%; b) TMSCl, Et_3N, CH_3CN, reflux, 2 h, quantitative (crude); c) NBS, THF, 0 ºC, 10 min, quantitative (crude).

The crude α-bromoketone **252** was then subjected to dehydrobromination using DBU as a base in different solvents like DCM, benzene or DME, but surprisingly, it did not furnish the desired enone **234** (R = Cbz). Treatment of α-bromoketone **252** with Li_2CO_3 and LiBr in DMF at 110 ºC furnished the desired enone **234** in 75% yields (scheme 47).[45]

IR spectrum of compound **234** showed a strong absorption at 1690 cm^{-1} characteristic of enone. ^{1}H NMR spectrum of compound **234** showed singlet at δ 7.34 and 7.33 corresponding to five carbamate phenyl protons. The splitting of signals was observed which was attributed to the mixture of the rotamers. Doublet at δ 7.12 corresponded to 0.35 protons, doublet at δ 6.94 corresponded to 0.52 protons. A singlet at δ 6.81 corresponded to two protons and the singlet at δ 6.71 corresponded to one proton. The doublet of doublet at δ 6.13 corresponded to 0.51 protons. The two singlets at δ 5.08 and δ 5.05 corresponding to 1.62 and 0.38 protons constitute benzylic protons. The six methoxy protons appeared at δ 3.88 (two protons), 3.86 (three protons), and 3.80 (one proton). A singlet at δ 3.19 corresponded to 1.48 protons. The singlet at δ 2.86 corresponded to 2.48 protons. The doublet at δ 2.74 corresponded to 0.47 protons. A multiplet at δ 1.98-2.35 corresponded to seven protons. ^{13}C NMR spectrum of compound **234** showed two signals at δ 209.8, 197.9 corresponding to the enone carbonyl. The doublet at δ 154.4 corresponded to the β-carbon of the enone while the α-carbon may be merged with the phenyl carbons of the carbamate. The signal at δ 66.83 revealed the presence of benzylic carbon. *N-Me* appeared at δ 34.18

and 34.67. Appearance of a signal at 424 in MS spectrum corresponding to M+1, further confirmed its structure.

The remaining task was then unmasking the carbamate without affecting the double bond in enone **234**. Thus, according to the literature precedence, enone **234** was treated with TMSI[46] but it resulted in the formation of an inseparable mixture of products. Also, treatment of the enone **234** with 40% KOH in methanol[47] or with $Ba(OH)_2$[48] was not fruitful. Eventually, the carbamate was unmasked using $BF_3{\cdot}OEt_2$ complex[49] in presence of excess DMS in DCM at 0 ºC to get the target molecule **1** in 95% yields (scheme 47).



Scheme 47. *Reagents and conditions:* a) Li_2CO_3, LiBr, DMF, 110 ºC, 75%; b) $BF_3{\cdot}OEt_2$, DCM, Me_2S, 0 ºC, 1 h, 95%.

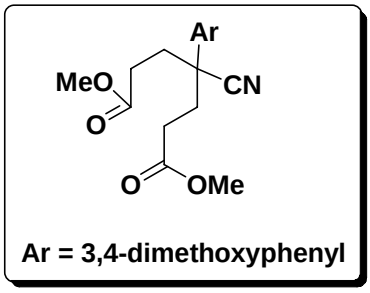
IR spectrum of mesembrine **1** showed absorption at 1716 cm^{-1} characteristic of the ketone function. ^1H NMR spectrum of mesembrine **1** showed two doublets at δ 6.87 and 6.81 and a doublet of doublet at δ 6.85 corresponding to three aromatic protons. The two singlets at δ 3.86 and 3.84 were attributed to the methoxy protons. The signal at δ 2.36 corresponded to N-*Me*. The remaining protons appeared as two triplets at δ 3.04 and 2.64 for four protons and multiplets at δ 3.18-3.22, 2.25-2.31 and 2.13-2.18 for remaining eight protons. ^{13}C NMR spectrum of mesembrine 1, showed signal at δ 210.8 revealing presence of ketone function. Its molecular formula was confirmed by MS spectrum, which showed a signal at 289 indicating presence of M^+.

2.1.4.3. Conclusion

In conclusion, (±)-mesembrine has been efficiently synthesized utilizing readily available materials by double Michael addition employing the protocol under aqueous conditions as the key step in 18% overall yield.

2.1.5. Experimental

Dimethyl 4-cyano-4-(3,4-dimethoxyphenyl)heptanedioate (238)



A mixture of finely powdered 3,4-dimethoxyphenylacetonitrile **45** (5 g, 28.25 mmol) and $TBAHSO_4$ (0.096 g, 0.28 mmol) in 10% aq. NaOH solution (20 ml) was stirred for 30 minutes at room temperature. A dark red colour appeared. The mixture was then cooled in an ice-bath. Methyl acrylate **239** was slowly added dropwise at 0 ^oC, (12.65 ml, 138.95 mmol). After 1 hour a colourless solid was formed, which was filtered and crystallized from EtOAc (7.49 g, 76% yield).

Alternatively, compound **238** was prepared by refluxing a mixture of 3,4-dimethoxyphenylacetonitrile (100 g, 0.564 mol) and methyl acrylate (253 ml, 2.82 mol) in the presence of Triton-B (2.35 ml, 0.006 mol, 40% solution in MeOH) in CH_3CN for overnight in almost quantitative yields (197 g).

Molecular formula : $C_{18}H_{23}NO_6$

Yield : 76%

Mp : 72-3 ^oC

IR (Nujol) : 2961, 2932, 2851, 2232, 1736, 1513, 1459, 1449, 1413, 1195, 1173, 1144, 1024, 889, 823, 768, 701, 657 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.80-6.94 (m, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.58 (s, 6H), 2.04-2.48 (m, 8H)

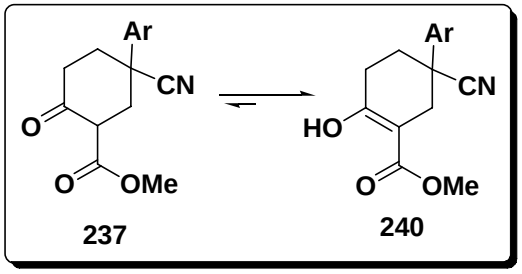
^{13}C NMR (50 MHz, $CDCl_3$) : δ 172.2, 149.5, 148.9, 128.3, 120.9, 118.3, 111.4, 108.8, 55.8, 51.6, 46.4, 35.7, 29.9

MS (EI) *m/z* : 350 (M+1), 318, 286, 259, 208, 149

Analysis : Calculated for $C_{18}H_{23}NO_6$; C-61.88, H-6.64, N-4.01 found, C-61.53, H-6.35, N-3.88

Total Synthesis of (±)-Mesembrine

Methyl 5-cyano-5-(3,4-dimethoxyphenyl)-2-oxocyclohexanecarboxylate (237) and Methyl 5-cyano-5-(3,4-dimethoxyphenyl)-2-hydroxycyclohex-1-enecarboxylate (240)



To a suspension of oil free NaH (57.6 g, 0.69 mol) in DME (200 ml), a solution of Michael adduct **238** (100 g, 0.32 mol) in DME (400 ml) was added drop-wise and refluxed for 3 hours. The solvent was distilled off, the reaction mixture was allowed to cool and NaH was quenched with aqueous saturated NH_4Cl solution, water was added to it and extracted with EtOAc, washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. Crystallization (ethyl acetate) furnished a colourless solid (80.84 g).

Molecular formula : $C_{17}H_{19}NO_5$

Yield : 89%

Mp : 125-6 ^oC

IR (Nujol) : 3365, 2956, 2919, 2850, 2236, 1665, 1515, 1457, 1375, 1337, 1285, 1255, 1209, 1152, 1023 cm^{-1}

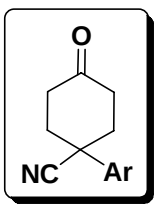
^{1}H NMR (200 MHz, $CDCl_3$) : δ 12.20 (s, 0.83H), 6.95 (m, 2H), 6.84 (d, *J*= 9.0 Hz) 3.89 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 2.49-3.00 (m, 5H), 2.13-2.24 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 171.5, 170.5, 149.2, 148.8, 131.6, 121.7, 117.4, 111.2, 109.1, 94.6, 55.8, 51.5, 40.5, 34.7, 31.4, 26.9

MS (EI) *m/z* : 318 (M+1), 317 (M^+), 285, 189, 174, 146, 119, 91, 77

Analysis : Calculated for $C_{17}H_{19}NO_5$; C-64.34, H-6.03, N-4.41 found C-64.74, H-5.94, N-4.09

1-(3,4-dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (236)



The mixture of tautomers **237** and **240** (75.0 g, 0.24 mol), NaCl (69.20 g, 1.18 mol) in DMSO (419 ml, 5.92 mol) was heated at 140 ^oC for 6 hours in the presence of water (21.29 ml, 1.18 mol). The reaction mixture was allowed to cool, diluted with water, extracted with ether (3x 200 ml), and the combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crystallization from EtOAc afforded a pale yellow solid (53.31 g).

Total Synthesis of (±)-Mesembrine

Molecular formula : $C_{15}H_{17}NO_3$

Yield : 87%

Mp : 111-3 ^oC

IR (Nujol) : 2923, 2855, 2241, 1710, 1516, 1459, 1375, 1263, 1239, 1147, 1021 cm^{-1}

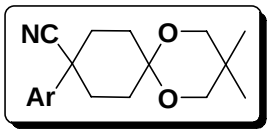
^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.99 (s, 2H), 6.86 (d, *J*= 8.79 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.90 (dt, *J*= 5.86 Hz and 15.14 Hz, 2H), 2.43-2.58 (m, 4H), 2.25 (dt, *J*= 3.90 Hz and 13.67 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 206.4, 149.0, 148.8, 130.7, 121.0, 117.2, 111.0, 108.7, 55.6, 42.2, 38.2, 36.6

MS (EI) *m/z* : 260 (M+1), 259 (M^+), 203, 189, 174, 119, 91, 77, 57

Analysis : Calculated for $C_{15}H_{17}NO_3$; C-69.48, H-6.61, N-5.40 found C-69.21, H-6.34, N-5.27.

Acetal (243)



A mixture of ketone **236** (50 g, 0.19 mol), 2,2-dimethyl-1,3-propanediol (22.08 g, 0.21 mol) and PPTS (4.85 g, 0.019 mol) was refluxed in benzene in a round bottom flask fitted with Dean-Stark apparatus for 7 hours to remove water. The reaction mixture was washed with aq. $NaHCO_3$ solution, and then thoroughly with water, dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure followed by crystallization from EtOAc furnished a colourless solid (67.27 g, 95%).

Molecular formula : $C_{20}H_{27}NO_4$

Yield : 95%

Mp : 131-3 ^oC

IR (Nujol) : 2923, 2857, 2237, 1463, 1377, 1260, 1243, 1142, 1103 cm^{-1}

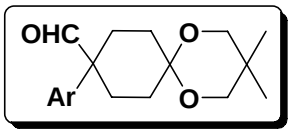
^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.98 (s, 2H), 6.84 (d, *J*= 7.81 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.53 (d, *J*= 14.16 Hz, 4H), 2.39 (d, *J*= 11.23 Hz, 2H), 1.86-2.07 (m, 6H), 0.99 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 148.9, 148.5, 132.6, 122.0, 117.4, 111.1, 109.1, 95.7, 69.7, 55.6, 43.2, 33.4, 30.0, 29.6, 22.4

MS (EI) *m/z* : 346 (M+1), 345(M^+), 317, 259, 189, 141, 128

Analysis : Calculated for $C_{20}H_{27}NO_4$; C-69.54, H-7.88, N-4.05 found, C-69.24, H-7.62, N-3.96

Aldehyde (244)



To a stirred solution of nitrile **243** (60 g, 0.17 mol) in DCM (250 ml), DIBAL (104 ml, 0.21 mol, 2 M in toluene) was added dropwise at 0 ^oC, under argon atmosphere. The reaction mixture was stirred at 0 ^oC for 1 hour. Reaction was quenched with saturated aq. NH_4Cl solution at 0 ^oC and stirred for 20 minutes. Then 10% HCl solution was added, stirred for few minutes and extracted with DCM, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain a white solid in quantitative yields (60.52 g).

Molecular formula : $C_{20}H_{28}O_5$

Yield : 100%

Mp : 148 ^oC

IR (Nujol) : 2928, 2712, 1713, 1598, 1585, 1518, 1466, 1377, 1332, 1258, 1234, 1022, 884, 813, 767, 701, 627 cm^{-1}

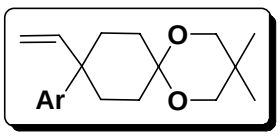
^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.29 (s, 1H), 6.82 (s, 2H), 6.72 (s, 1H), 3.84 (s, 6H), 3.46 (d, *J*= 11.23 Hz, 4H), 1.88-2.34 (m, 6H), 1.53-1.66 (m, 2H), 0.94 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 200.6, 149.1, 148.2, 130.7, 119.3, 111.2, 110.2, 96.6, 69.7, 55.6, 53.1, 30.0, 28.8, 27.0, 22.5

MS (EI) *m/z* : 348 (M^+), 319, 233, 215, 192, 141, 128, 91, 69

Analysis : Calculated for $C_{20}H_{28}O_5$; C-68.94, H-8.10 found, 68.79, H-8.23

Olefin (246)



A mixture of $Ph_3P^+CH_3I^-$ (116.0 g, 0.28 mol) and $NaNH_2$ (10.08 g, 0.26 mol) (250 ml) was stirred in THF under nitrogen atmosphere at room temperature for 2 hours. A dark yellow colour of the ylide appeared. It was cooled with ice-salt mixture. A solution of aldehyde **244** (50 g, 0.14 mol) in THF (200 ml) was added drop-wise with salt-ice cooling. Yellow color of the ylide disappeared soon after the addition of aldehyde solution. The reaction mixture was stirred

for 30 minutes. Solvent was removed under reduced pressure and quenched with saturated aq. NH_4Cl solution, extracted with EtOAc, the combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain a thick red residue which after purification by column chromatography over neutral alumina furnished thick colourless oil (49.71 g).

Molecular formula : $C_{21}H_{30}O_4$

Yield : 82%

IR (Neat) : 2949, 2862, 1594, 1513, 1461, 1259, 1145, 1109, 1029, 909, 886, 871, 806 cm^{-1}

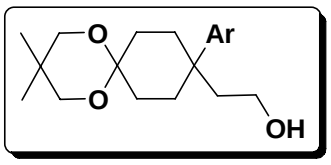
^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.77-6.91 (m, 3H), 5.81 (dd, *J*= 10.73 Hz and 17.55 Hz, 1H), 5.09 (d, *J*= 10.73 Hz 1H), 4.92 (d, *J*= 17.55 Hz, 1H), 3.86 (s, 6H), 3.49 (d, *J*= 9.85 Hz, 4H), 1.85-2.10 (m, 8H), 0.97 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 148.7, 147.3, 146.2, 138.4, 118.8, 112.7, 111.2, 110.9, 97.3, 69.8, 69.7, 55.8, 44.0, 31.7, 30.0, 28.8, 22.6

MS (EI) *m/z* : 347 (M+1), 346 (M^+), 318, 260, 190, 159, 141, 69

Analysis : Calculated for $C_{21}H_{30}O_4$; C-72.80, H-8.73 found, C-72.50, H-8.85

Alcohol (247)



To a stirring solution of olefin **246** (45 g, 130.06 mmol) in THF (150 ml), BMS complex (16.04 ml, 169.08 mmol) was added dropwise *via* syringe at 0 ^oC, under argon atmosphere. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then cooled to 0 ^oC, followed by addition of 30% aq. NaOH (65 ml) and stirred for 30 minutes. Then 30% H_2O_2 (65 ml) was added dropwise and further stirred for 1 hour at 0 ^oC. The reaction mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatographic purification over neutral alumina afforded a thick colourless syrup (35.51 g).

Molecular formula : $C_{21}H_{32}O_5$

Yield : 75%

IR ($CHCl_3$) : 3462, 3016, 2946, 2838, 1589, 1517, 1464, 1255, 1216, 1150, 1117, 1106, 1027, 807, 759, 667 cm^{-1}

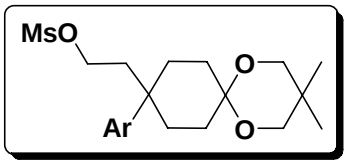
^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.73-6.86 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.41 (d, *J*= 15.14 Hz, 4H), 3.29 (t, *J*= 6.83 Hz, 2H), 2.10 (s, 1H), 1.92-2.05 (m, 5H), 1.48-1.77 (m, 6H), 0.89 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 148.9, 147.1, 137.4, 118.8, 111.2, 110.3, 97.7, 66.7, 59.0, 55.8, 55.6, 45.9, 39.5, 34.8, 32.2, 28.6, 23.7, 6.9

MS (EI) *m/z* : 364 (M^+)

Analysis : Calculated for $C_{21}H_{32}O_5$; C-69.20, H-8.85 found C-69.35, H-8.63

Mesylate (248)



To a stirring solution of alcohol **247** (25 g, 68.68 mmol) and Et_3N (14.33 ml, 103.02 mmol) in DCM (100 ml), MsCl (8.80 ml, 113.64 mmol) was added at 0 ^oC, under nitrogen atmosphere. After 30 minutes, the reaction mixture was washed with water, brine, dried over anhydrous Na_2SO_4, filtered concentrated *in vacuo* to afford a pale yellow syrup in quantitative yields (41.85 g). The crude mesylate was used for further reaction without purification.

Molecular formula : $C_{23}H_{34}O_7S$

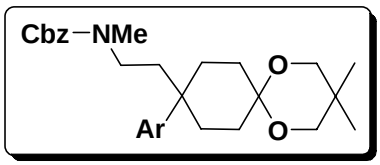
Yield : quantitative

IR : 3021, 2938, 2838, 1518, 1465, 1333, 1256, 1216, 1027 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.78-6.90 (m, 3H), 3.86 (s, 6H), 3.47 (d, *J*= 14.87 Hz, 4H), 2.25 (s, 3H), 1.95-2.12 (m, 5H), 1.48-1.74 (m, 7H), 0.95 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 148.8, 147.0, 137.5, 119.0, 111.0, 97.7, 66.9, 55.9, 55.8, 47.3, 39.9, 36.1, 32.2, 30.1, 28.6, 22.7

Carbamate (249)



A mixture of mesyl ester **248** (30 g, 67.87 mmol) and 40% aq. $MeNH_2$ solution (60 ml) was heated in THF in a sealed tube at 100 ^oC for 2 hours. The reaction mixture was then cooled to 0 ^oC and saturated aq. $NaHCO_3$ solution (25 ml)

added to the reaction mixture, followed by drop-wise addition of $ClCO_2Bn$ (10.65 ml, 74.66 mmol) and stirred for 4 hours. Water was added to the reaction mixture and extracted with EtOAc, washed with water, brine and dried over anhydrous Na_2SO_4, filtered and solvent removed under reduced pressure. Column chromatographic purification over neutral alumina (pet ether/EtOAc, 85:15-70:30) afforded pale yellow oil (30.52 g).

Molecular formula : $C_{30}H_{41}NO_6$

Yield : 88%

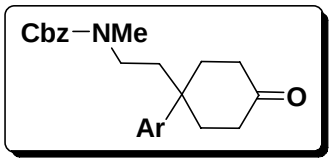
IR ($CHCl_3$) : 3018, 2957, 1694, 1518, 1216, 759 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.36 (s, 2H), 7.33 (s, 3H), 6.80 (bs, 3H), 5.11 (s, 0.38H), 5.06 (s, 1.62H), 3.86 (s, 6H), 3.48 (d, *J*= 13.18 Hz, 4H), 2.93 (bs, 2H), 2.82 (d, *J*= 4.88 Hz, 1H), 2.72 (d, *J*= 10.74 Hz, 3H), 2.18 (s, 1H), 1.88-2.11 (m, 4H), 1.50-1.78 (m, 7H), 0.96 (s, 6H)

MS (EI) *m/z* : 512 (M+1), 511 (M^+), 425, 233, 141, 108, 91, 65

Analysis : Calculated for $C_{30}H_{41}NO_6$; C-70.42, H-8.08, N-2.74 found C-70.23, H- 7.93

Benzyl 2-(1-(3,4-dimethoxyphenyl)-4-oxocyclohexyl)ethyl(methyl)carbamate (235)



A solution of carbamate **253** (20 g, 39.14 mmol) was refluxed for 24 hours in acetone-water (1:1, 100 ml), in the presence of few drops of conc. HCl. Acetone was removed from the reaction mixture, and extracted with EtOAc, washed with saturated $NaHCO_3$ solution, water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatographic purification (pet ether-EtOAc, 7:3) furnished a thick colourless oil (14.14 g).

Molecular formula : $C_{25}H_{31}NO_5$

Yield : 85%

IR ($CHCl_3$) : 3019, 1669, 1216, 895, 759 cm^{-1}

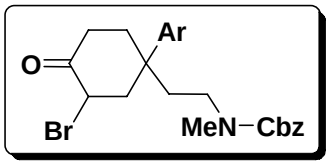
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.25 (s, 5H), 6.85 (s, 1H), 6.77 (s, 2H), 4.98 (s, 2H), 3.01 (bs, 2H), 3.84 (s, 1.40H), 3.81 (s, 2.17H), 3.78 (s, 2.42H), 2.94 (bs, 2H), 2.67 (d, *J*= 12.21 Hz, 3H), 2.11-2.38 (m, 6H), 1.78-1.97 (m, 4H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 210.1, 155.6, 149.1, 147.5, 136.6, 134.9, 128.2, 127.6, 118.6, 111.2, 109.7, 66.7, 55.8, 55.5, 45.1, 44.8, 40.0, 39.2, 37.6, 35.5, 34.1, 33.6, 29.5

MS (EI) *m/z* **:** 426 (M+1), 425 (M^+), 233, 180, 151, 91,71

Analysis **:** Calculated for $C_{25}H_{31}NO_5$; C-70.57, H-7.34, N-3.29 found C-70.50, H-7.11, N-3.35

Benzyl 2-(3-bromo-1-(3,4-dimethoxyphenyl)-4-oxocyclohexyl)ethyl(methyl)carbamate (252)



A solution of ketone **235** (10 g, 23.53 mmol), Et_3N (6.55 ml, 47.06 mmol) and TMSCl (4.47 ml, 35.29 mmol) was refluxed in CH_3CN (65 ml) for 2 hours. CH_3CN was distilled off, the residue was allowed to cool, EtOAc added to it, washed with water, brine, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo* to obtain a thick crimson oil. The crude oil was dissolved in THF and cooled to 0 ^oC. NBS (4.19 g, 23.53 mmol) was added to it in one lot at 0 ^oC and stirred for 10 minutes. The reaction was quenched with brine, THF layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a thick dark crimson syrup (11.84 g), which was used without purification for further reaction.

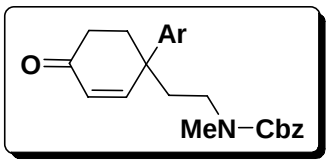
Molecular formula **:** $C_{25}H_{30}BrNO_5$

Yield **:** quantitative (crude)

IR ($CHCl_3$) **:** 3020, 2934, 1698, 1590, 1520, 1465, 1408, 1255, 1216, 1028, 910, 758, 698, 668 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.30 (s, 5H), 6.85 (m, 3H), 5.03 (s, 2H), 4.55 (dd, *J*= 4.88 Hz and 13.19 Hz, 1H), 3.86 (s, 2.36H), 3.85 (s, 0.92H), 3.84 (s, 2.40H), 2.97 (bs, 3H), 2.71 (s, 4H), 2.33 (s, 3H), 1.75 (s, 3H)

Benzyl 2-(1-(3,4-dimethoxyphenyl)-4-oxocyclohex-2-enyl)ethyl(methyl) carbamate (234)



A mixture of α-bromoketone **252** (5.2 g, 10.34 mmol), Li_2CO_3 (2.07 g, 27.91 mmol) and LiBr (1.62 g, 18.61 mmol) was heated in dry DMF at 120 ^oC for 2 hours. The reaction mixture

was allowed to cool, water was added to it and extracted with ether, washed with water, brine, dried over anhydrous Na_2SO_4. Filtration followed by evaporation of the solvent and chromatographic purification over silica gel (pet ether-EtOAc, 3:1) furnished a pale yellow syrup (3.28 g).

Molecular formula : $C_{25}H_{29}NO_5$

Yield : 75%

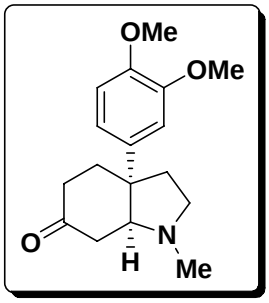
IR ($CHCl_3$) : 3019, 2938, 1690, 1589, 1518, 1461, 1407, 1365, 1305, 1256, 1216, 1055, 835, 756, 699, 668 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.34 (s, 1.40H), 7.33 (s, 3.60H), 7.12 (d, *J*= 9.77 Hz, 0.35H), 6.94 (d, *J*= 12.21 Hz, 0.52H), 6.81 (s, 2H), 6.71 (s, 1H), 6.13 (dd, *J*= 9.77 Hz and 16.12 Hz, 0.51H), 5.08 (s, 1.68H), 5.05 (s, 0.32H), 3.88 (s, 2H), 3.86 (s, 3H), 3.80 (s, 1H), 3.19 (bs, 1.48H), 2.86 (s, 3H), 2.74 (d, *J*= 9.28 Hz, 0.47H), 2.17-2.36 (m, 7H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 209.8, 197.9, 155.2, 153.7, 153.5, 148.8, 147.6, 147.2, 136.2, 134.5, 129.0, 128.0, 127.9, 127.4, 127.3, 118.5, 118.3, 111.0, 110.8, 109.6, 66.4, 55.5, 55.4, 55.3, 55.2, 45.8, 44.5, 41.9, 38.9, 37.3, 35.2, 33.8

MS (EI) *m/z* : 446 (M+Na), 424 (M+1), 382

Mesembrine 1



To a solution of enone **234** (1.5 g, 3.55 mmol), DMS (5.18 ml, 70.92 mmol) in DCM (5 ml), $BF_3{\cdot}OEt_2$ (4.50 ml, 35.46 mmol) was added dropwise *via* syringe at 0 ^oC and stirred at this temperature for 1 hour. The reaction was quenched with 25% NH_4OH solution, extracted with DCM, washed with water, brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent followed by column chromatographic purification over silica gel using MeOH-DCM (1%-5%) system furnished mesembrine **1** as a pale yellow oil (0.97 g).

Molecular formula : $C_{17}H_{23}NO_3$

Yield : 95%

IR ($CHCl_3$) : 2959, 1716, 1519, 1254, 1217, 755, 666 cm^{-1}

Total Synthesis of (±)-Mesembrine

^{1}H NMR (500 MHz, $CDCl_3$) : δ 6.90 (d, *J*= 2.0 Hz, 1H), 6.87 (dd, *J*= 2.0 Hz and 8.3 Hz, 1H), 6.83 (d, *J*= 8.3 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.18-3.22 (m, 1H), 3.04 (t, *J*= 3.7 Hz, 1H), 2.64 (t, *J*= 4.6 Hz, 2H), 2.38-2.43 (m, 2H), 2.36 (s, 3H), 2.25-2.31 (m, 1H), 2.10-2.18 (m, 4H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 210.8, 149.2, 147.7, 139.8, 118.0, 111.3, 110.2, 70.2, 56.1, 55.9, 54.6, 47.6, 40.4, 40.0, 38.8, 36.1, 35.0

MS (EI) *m/z* **:** 289 (M^+), 274, 254, 218, 204, 128, 91, 70, 59

Analysis **:** Calculated for $C_{17}H_{23}NO_3$; C-70.50, H-8.01, N-4.84 found C-70.21, H-7.75, N-4.69

2.1.6. Spectra

2.1.7. References

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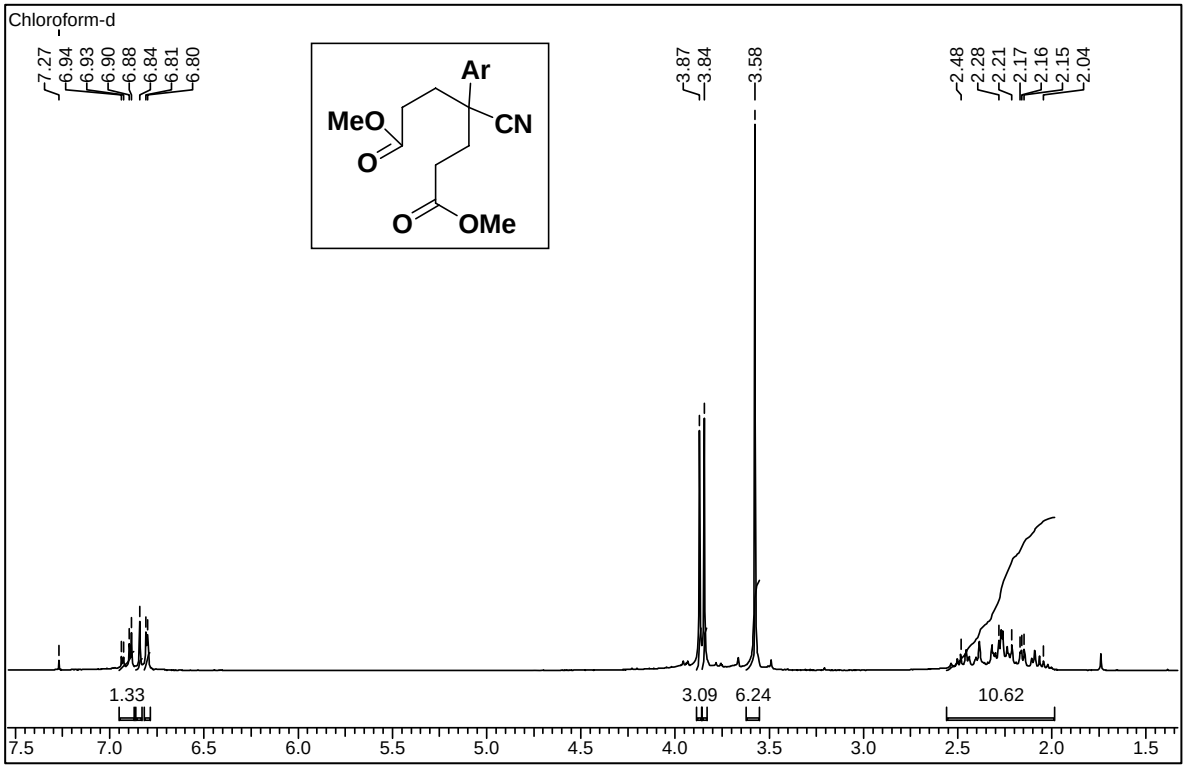
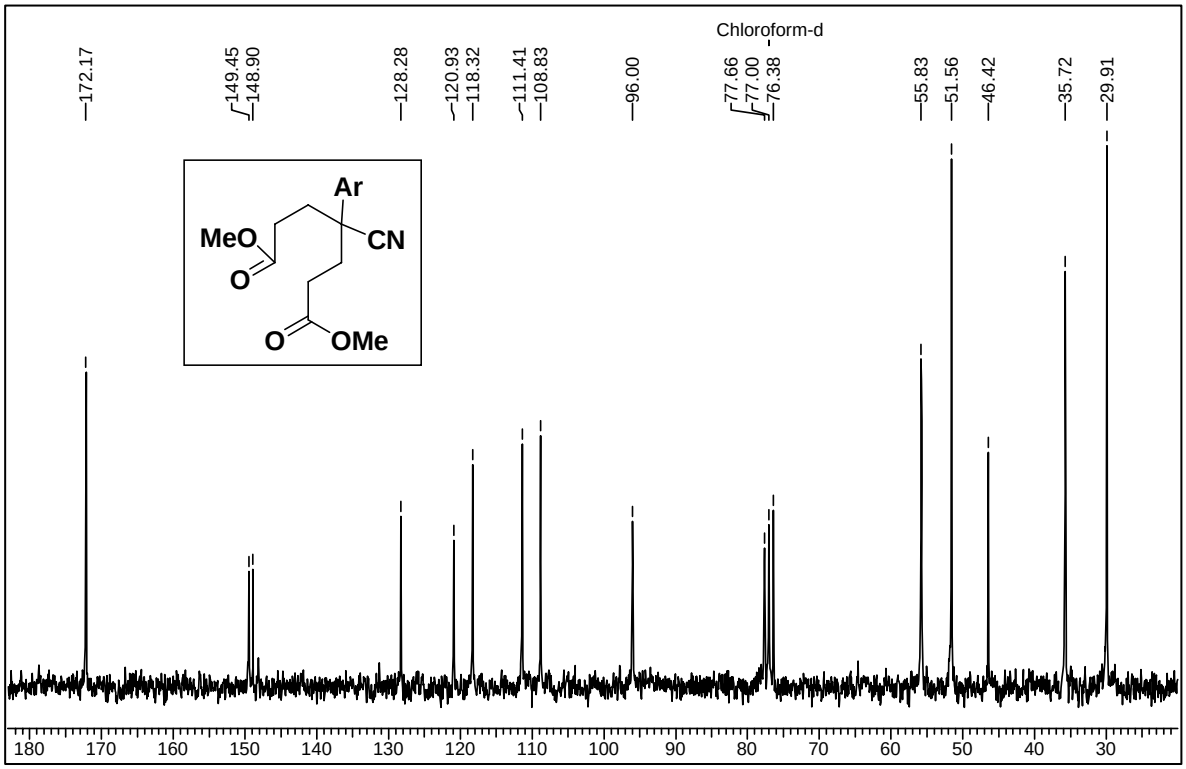
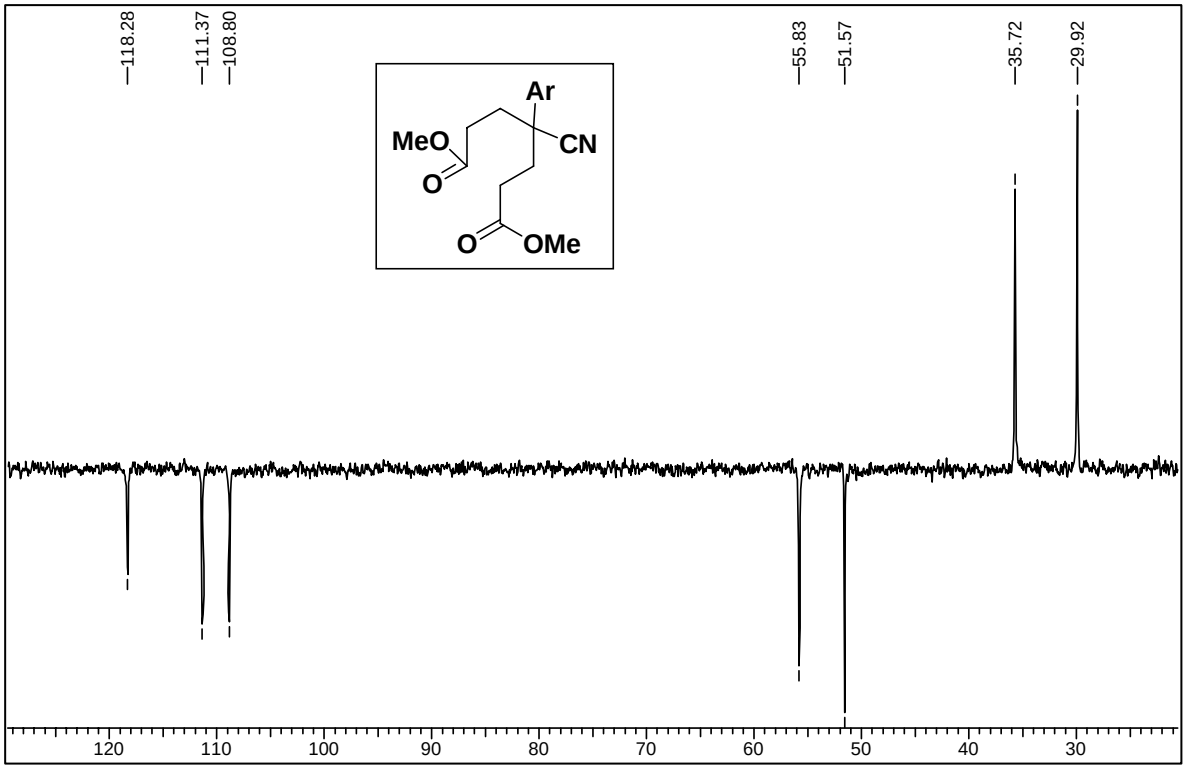


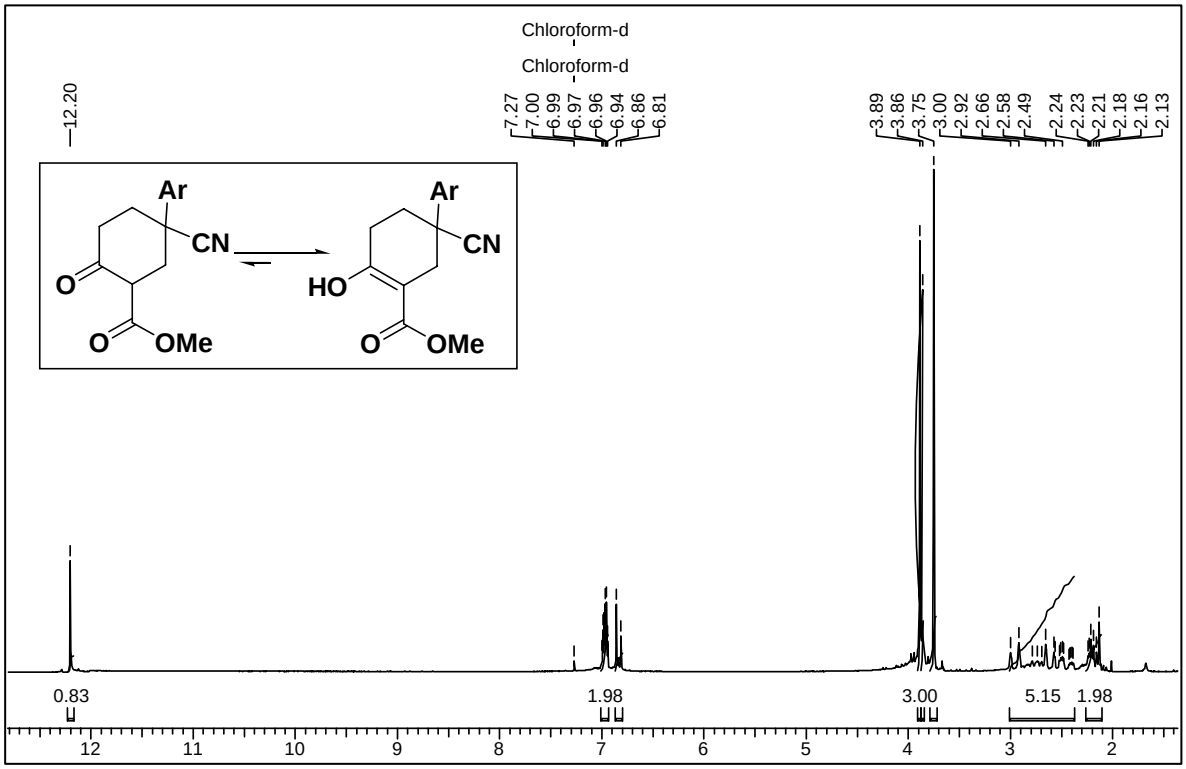
^{1}H NMR Spectrum of Compound 238 (200 MHz, $CDCl_3$)



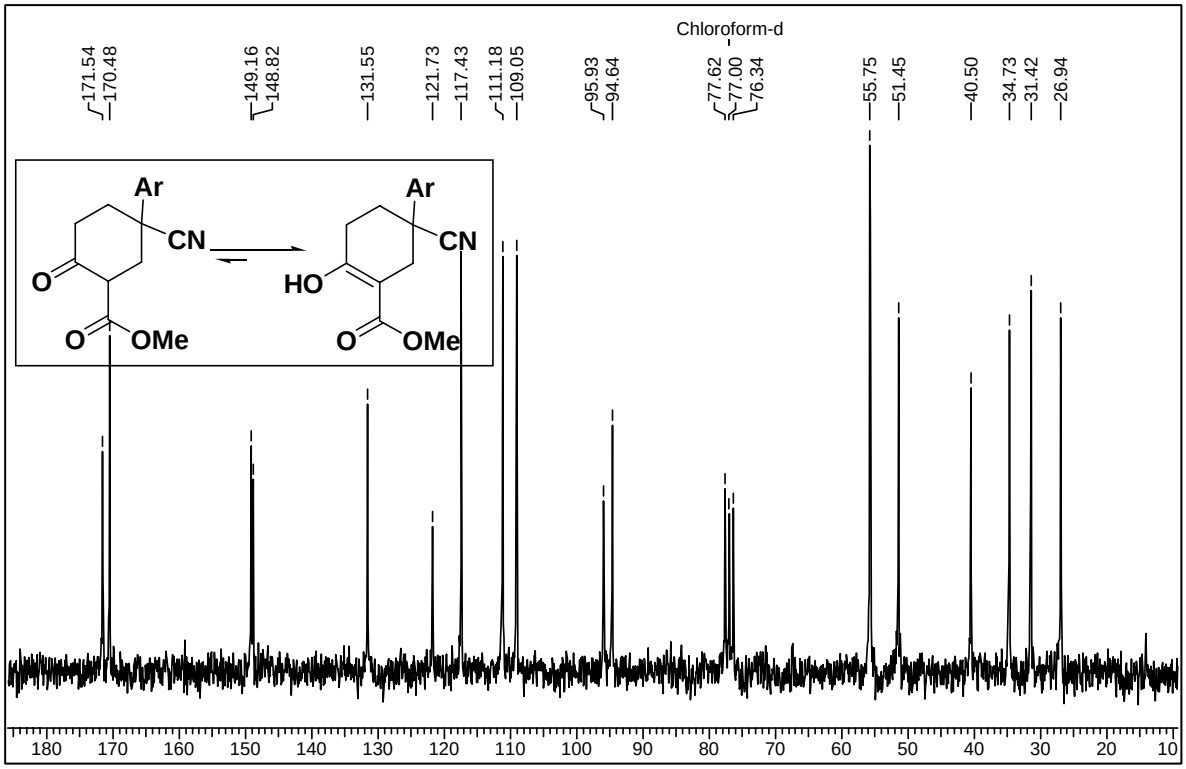
^{13}C NMR Spectrum of Compound 238 (200 MHz, $CDCl_3$ + CCl_4)



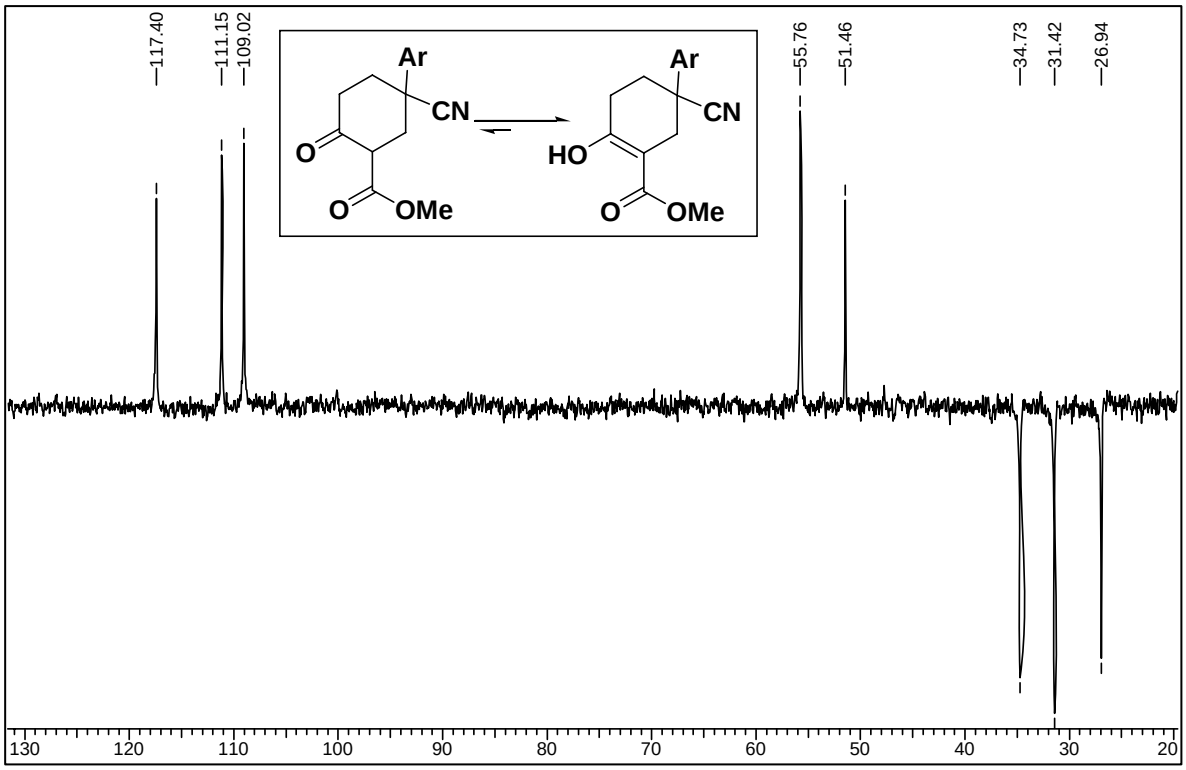
DEPT NMR Spectrum of Compound 238 (200 MHz, $CDCl_3$ + CCl_4)



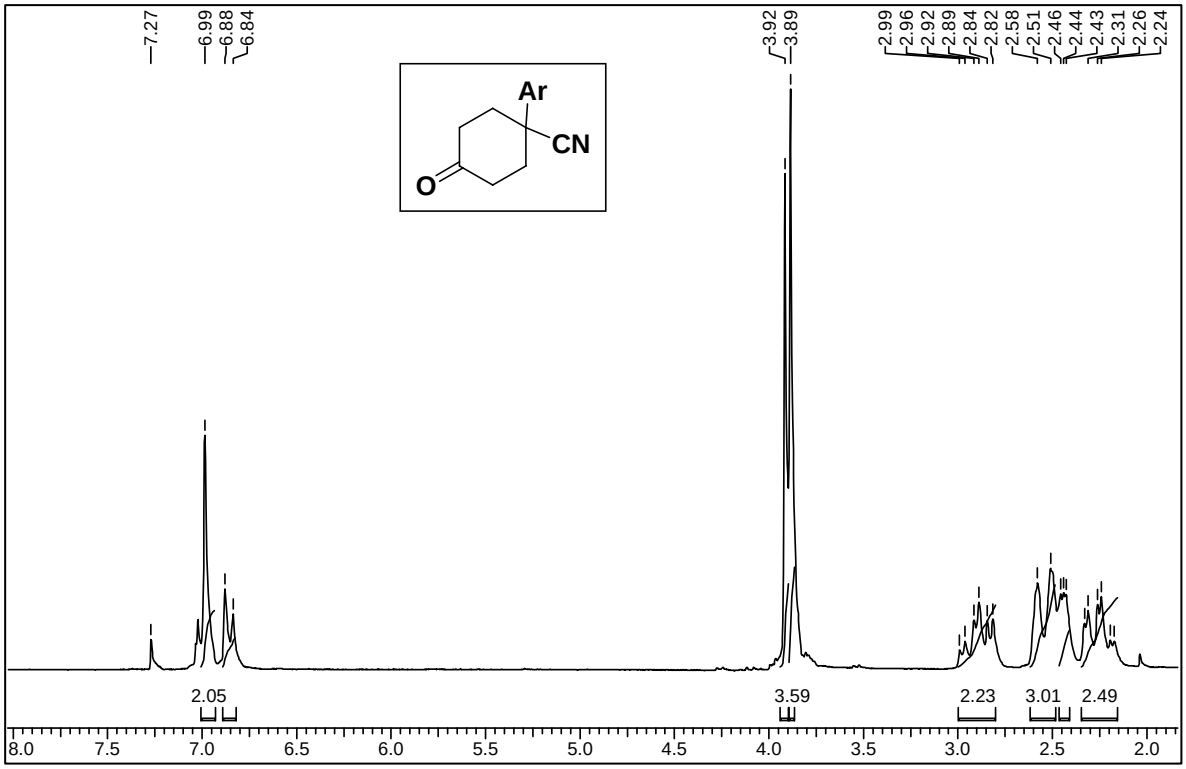
^{1}H NMR Spectrum of Compound 237 + 240 (200 MHz, $CDCl_3$)



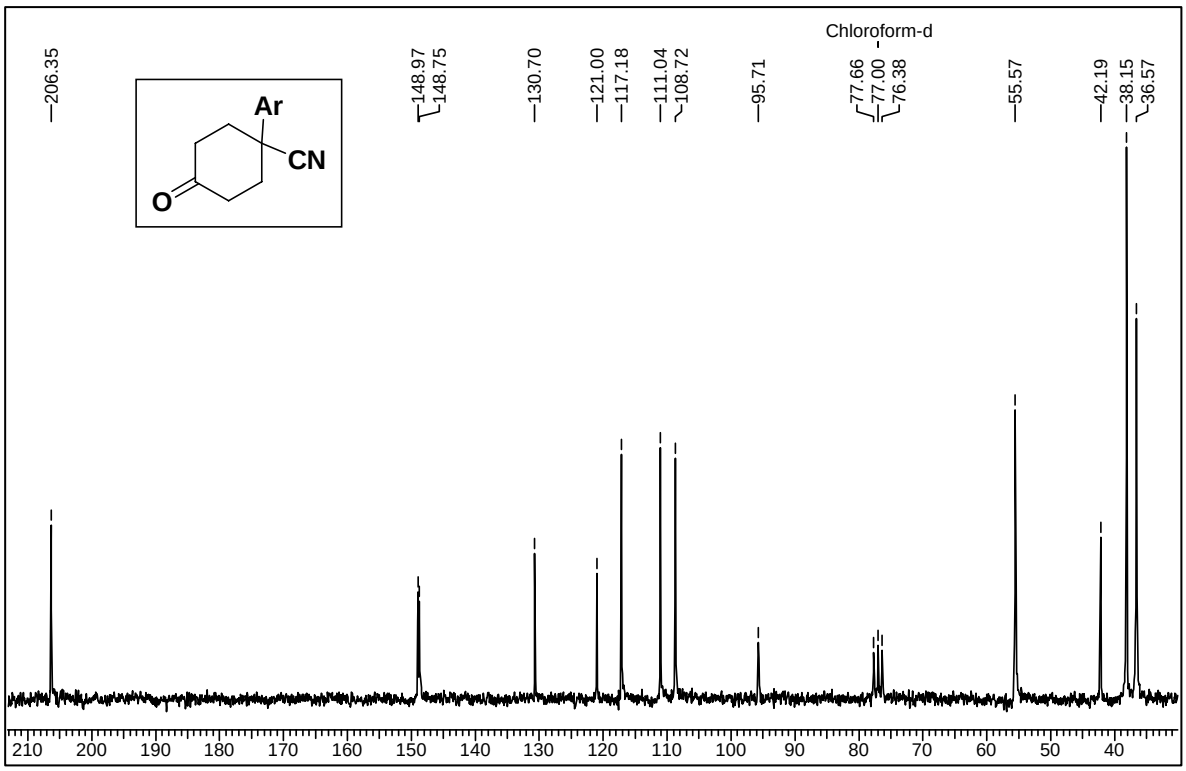
^{13}C NMR Spectrum of Compound 237 + 240 (50 MHz, $CDCl_3$ + CCl_4)



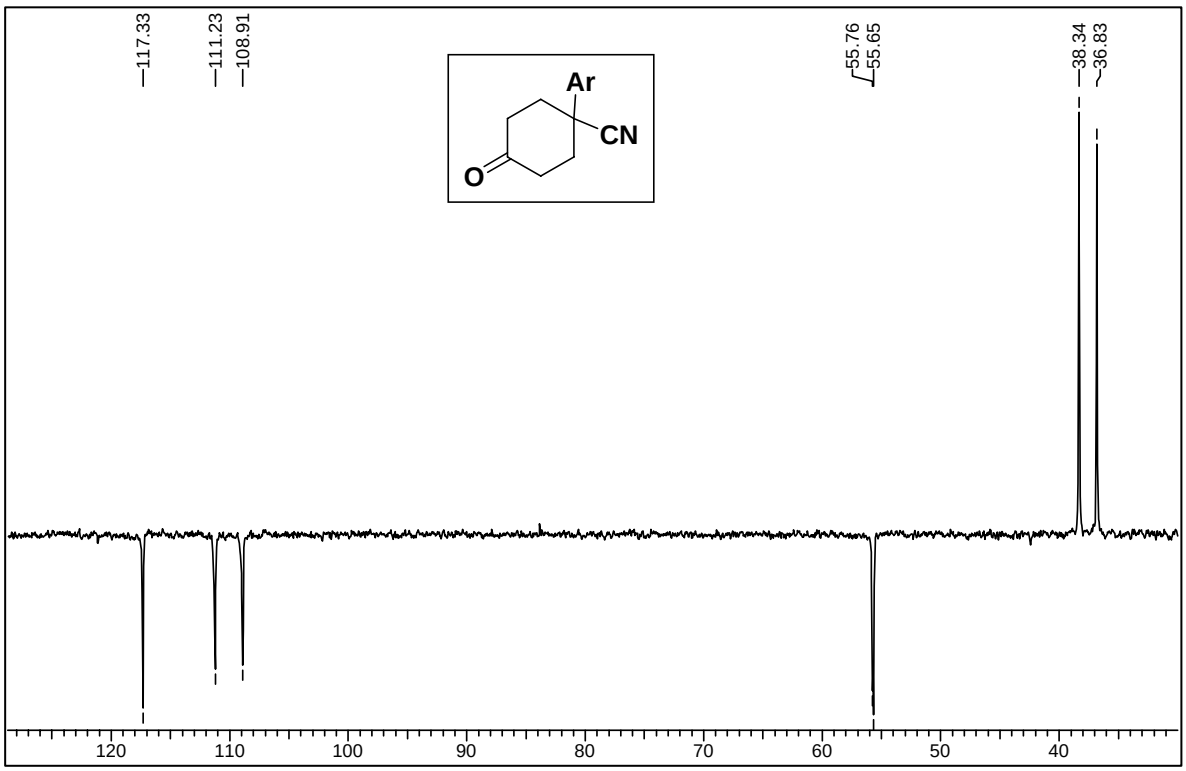
DEPT NMR Spectrum of Compound 237 + 240 (50 MHz, $CDCl_3$ + CCl_4)



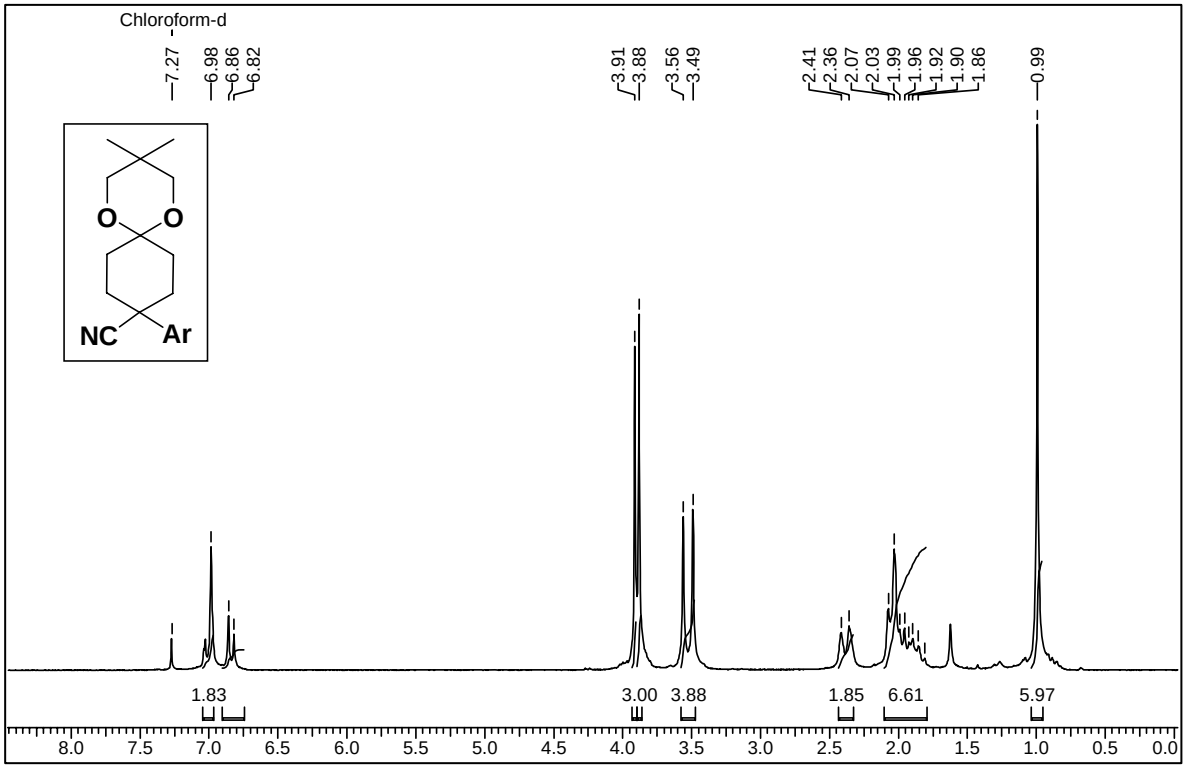
^{1}H NMR Spectrum of Compound 236 (200 MHz, $CDCl_3$)



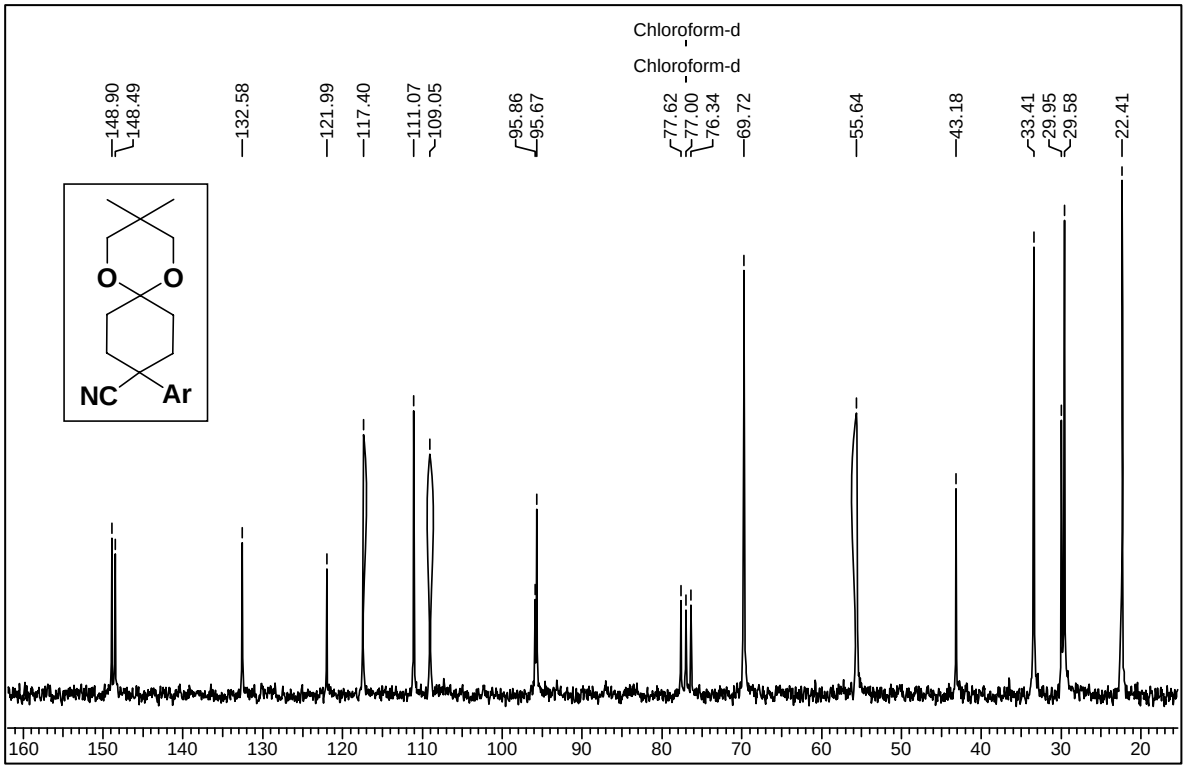
^{13}C NMR Spectrum of Compound 236 (50 MHz, $CDCl_3$ + CCl_4)



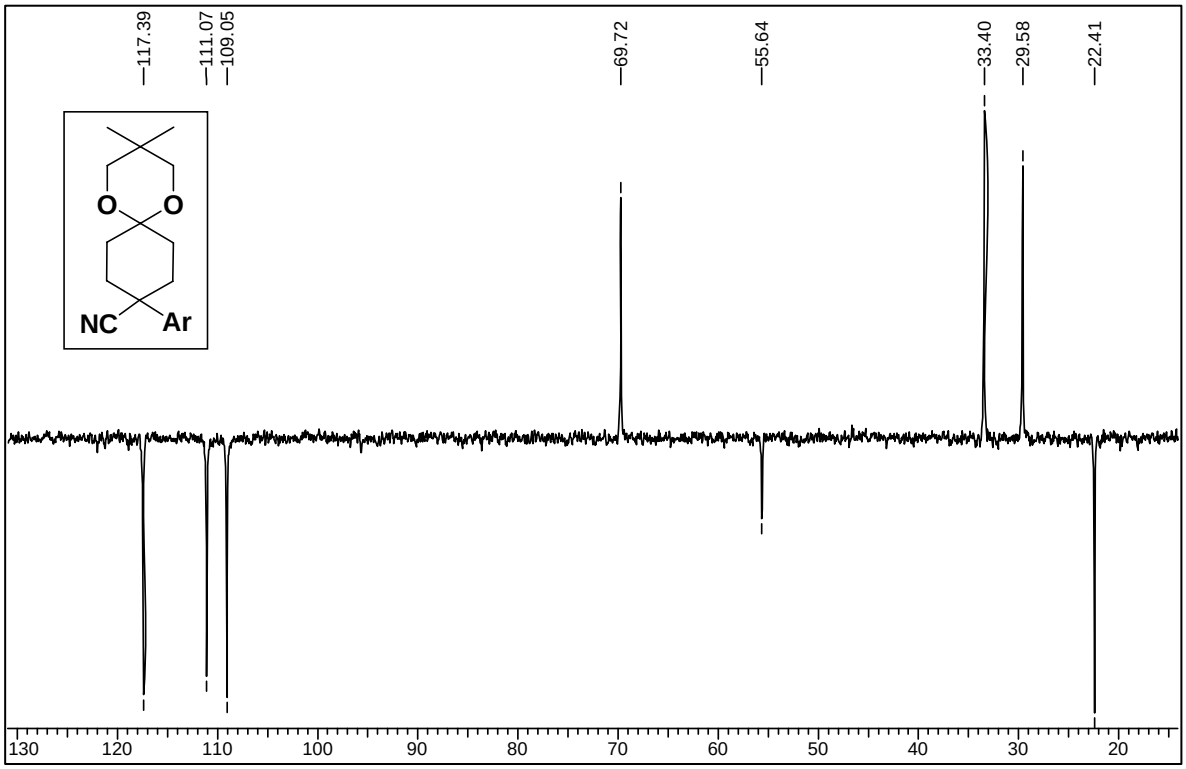
DEPT NMR Spectrum of Compound 236 (50 MHz, $CDCl_3$ + CCl_4)



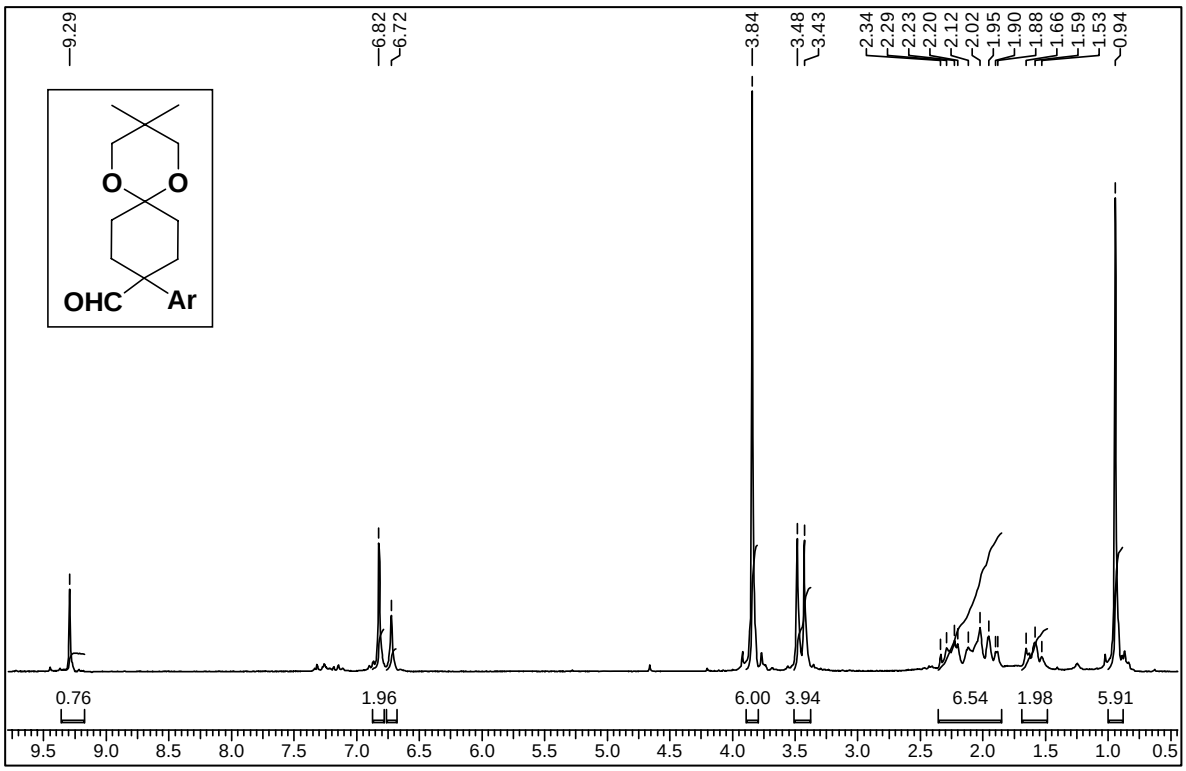
^{1}H NMR Spectrum of Compound 243 (200 MHz, $CDCl_3$)



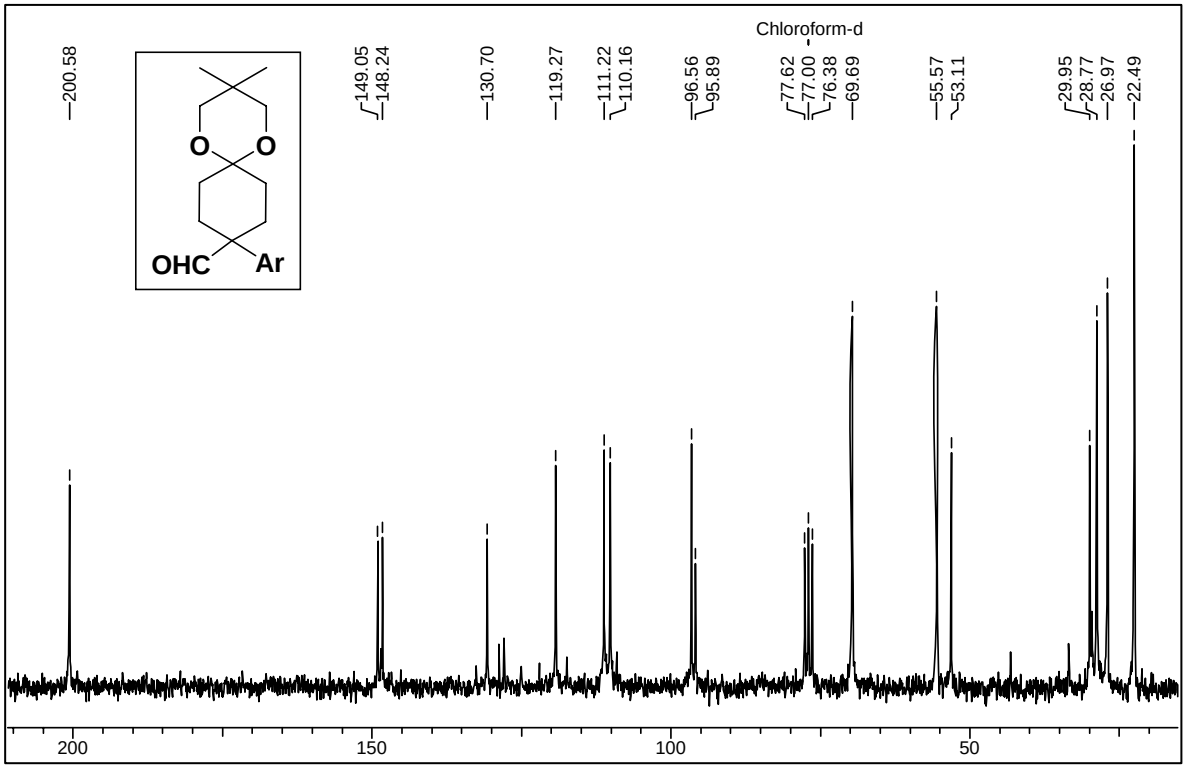
^{13}C NMR Spectrum of Compound 243 (50 MHz, $CDCl_3$ + CCl_4)



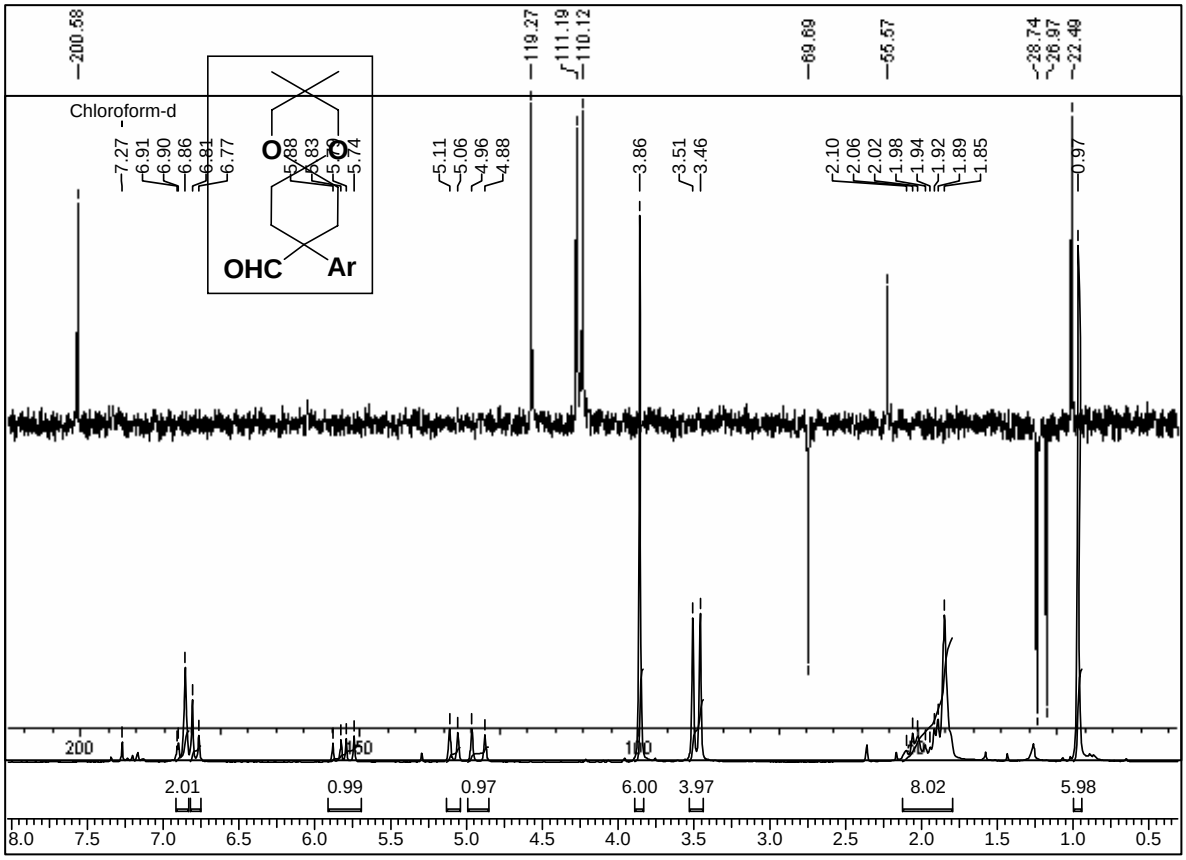
DEPT NMR Spectrum of Compound 243 (50 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR Spectrum of Compound 244 (200 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound 244 (50 MHz, $CDCl_3$ + CCl_4)



DEPT NMR Spectrum of Compound 244 (50 MHz, $CDCl_3$ + CCl_4)

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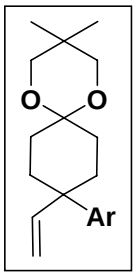

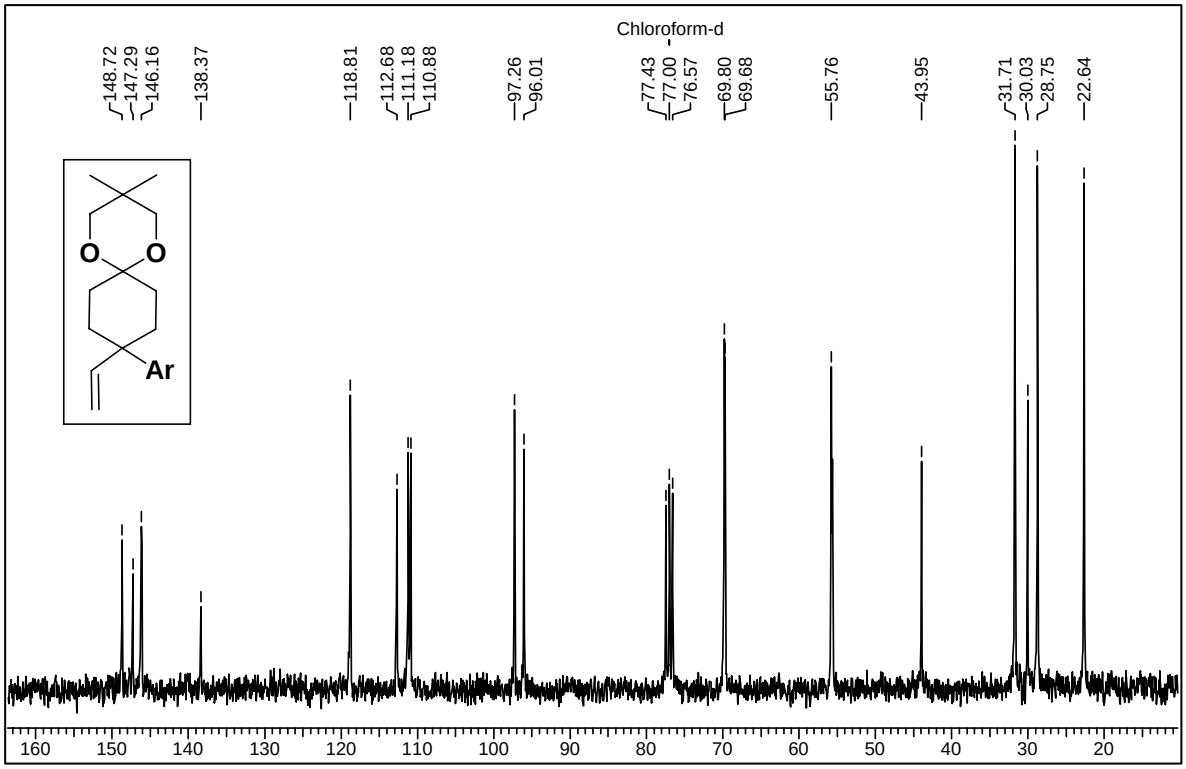

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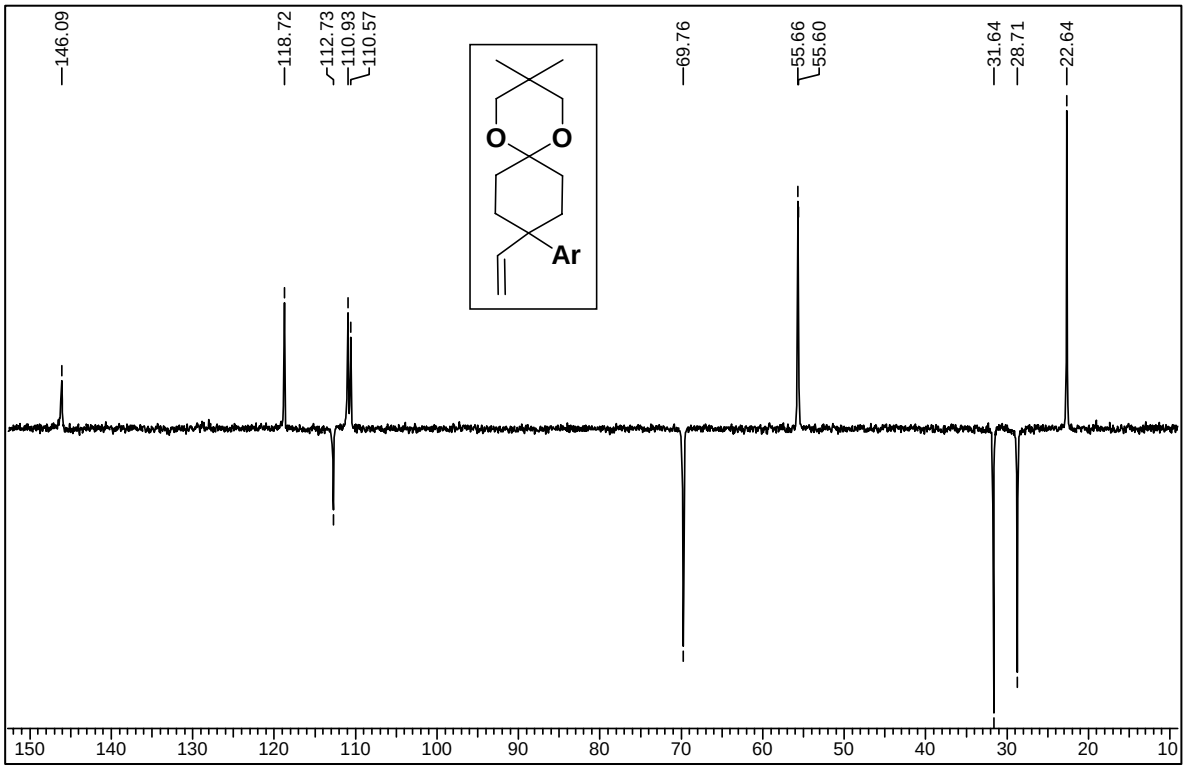

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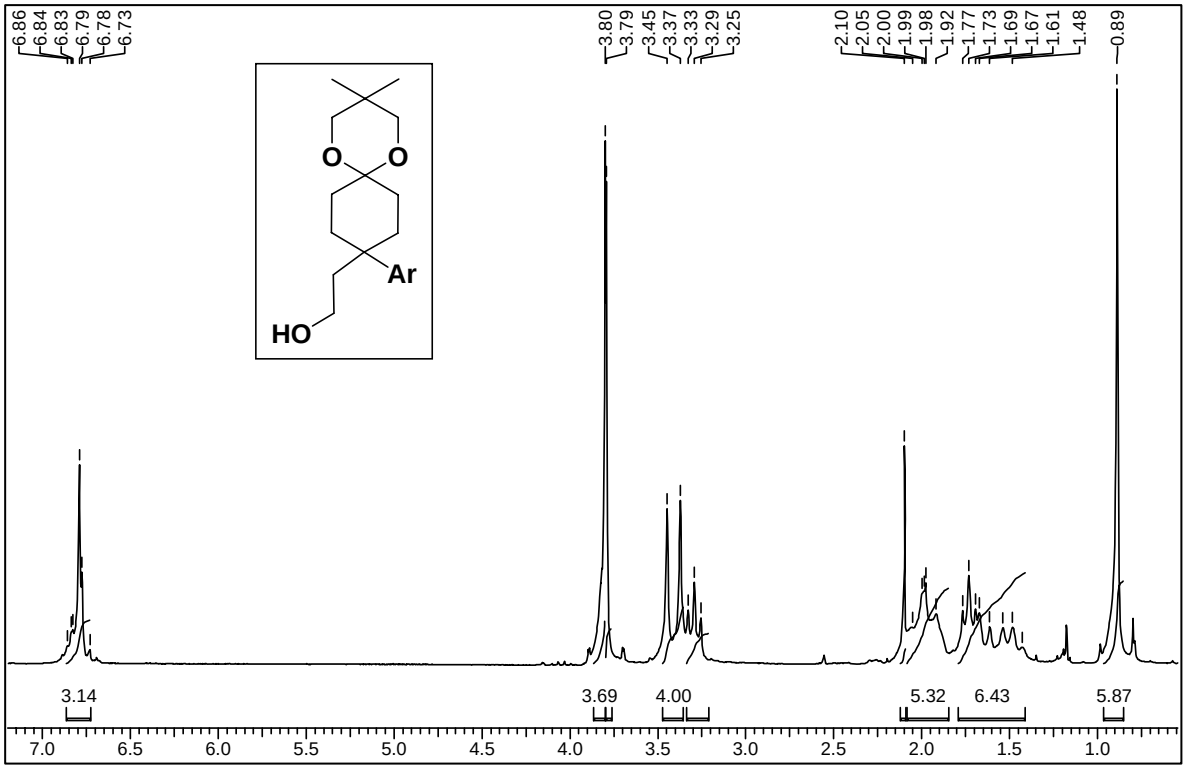

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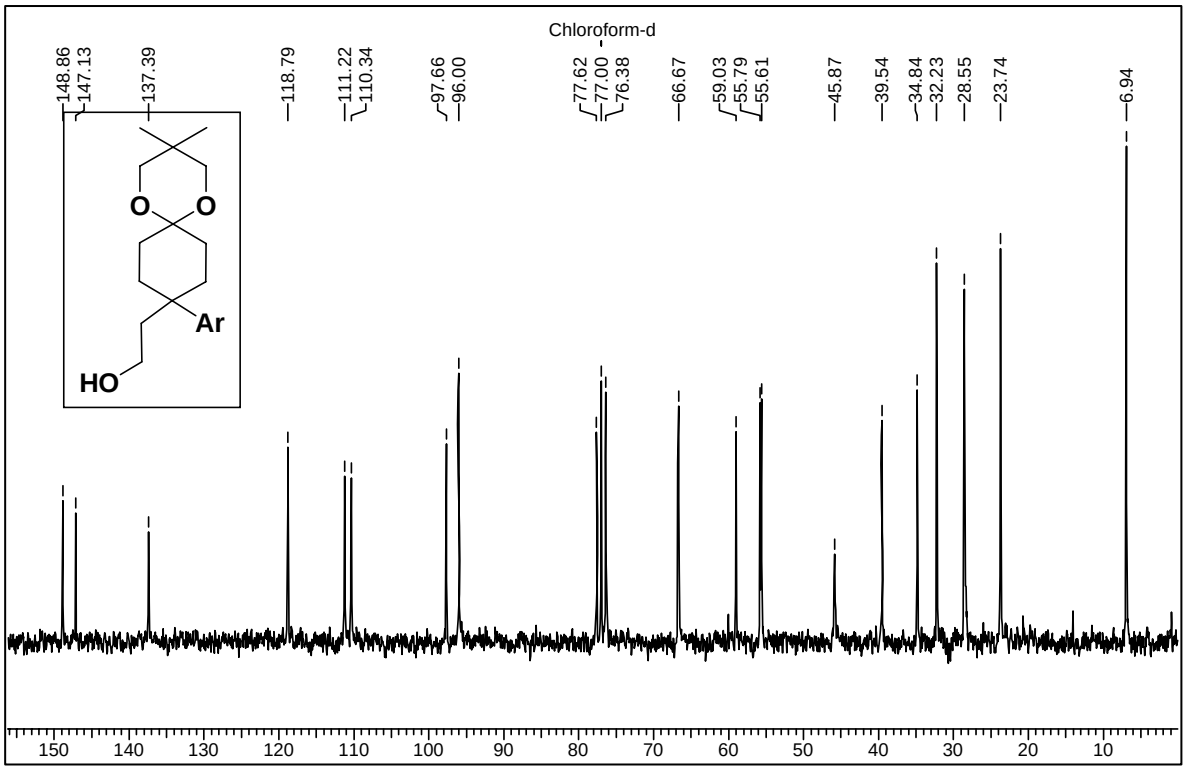
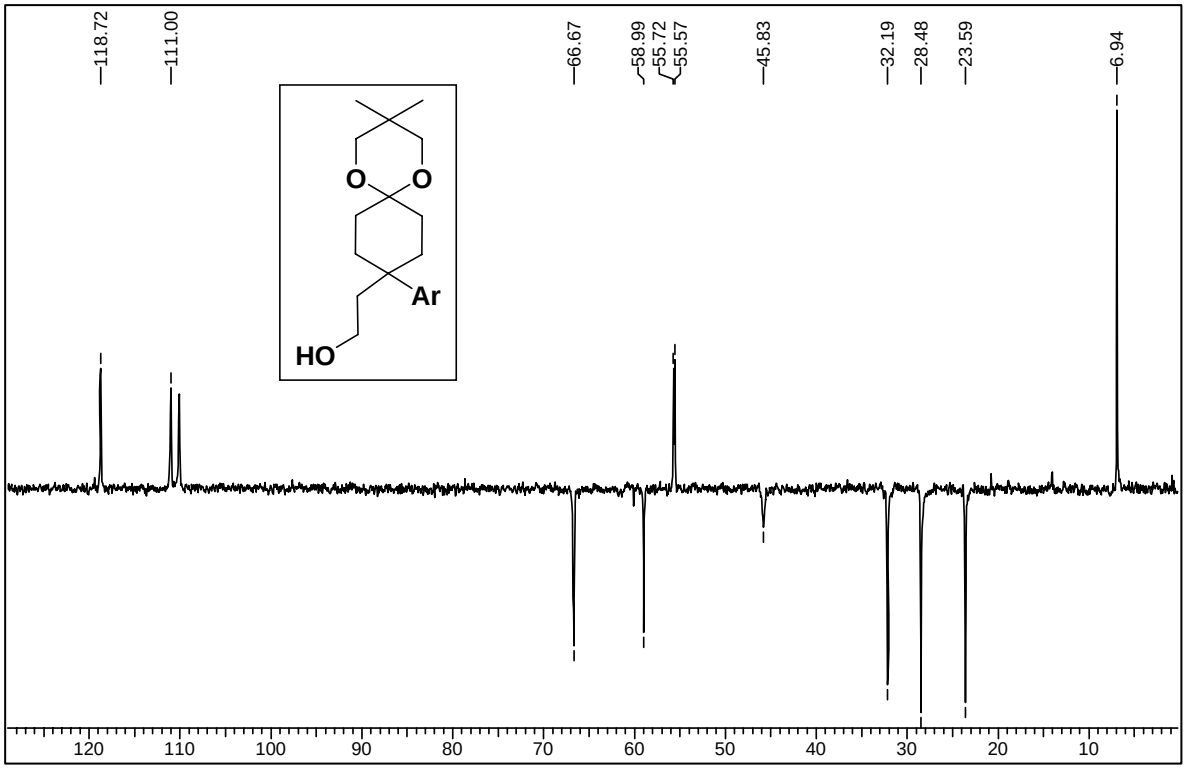
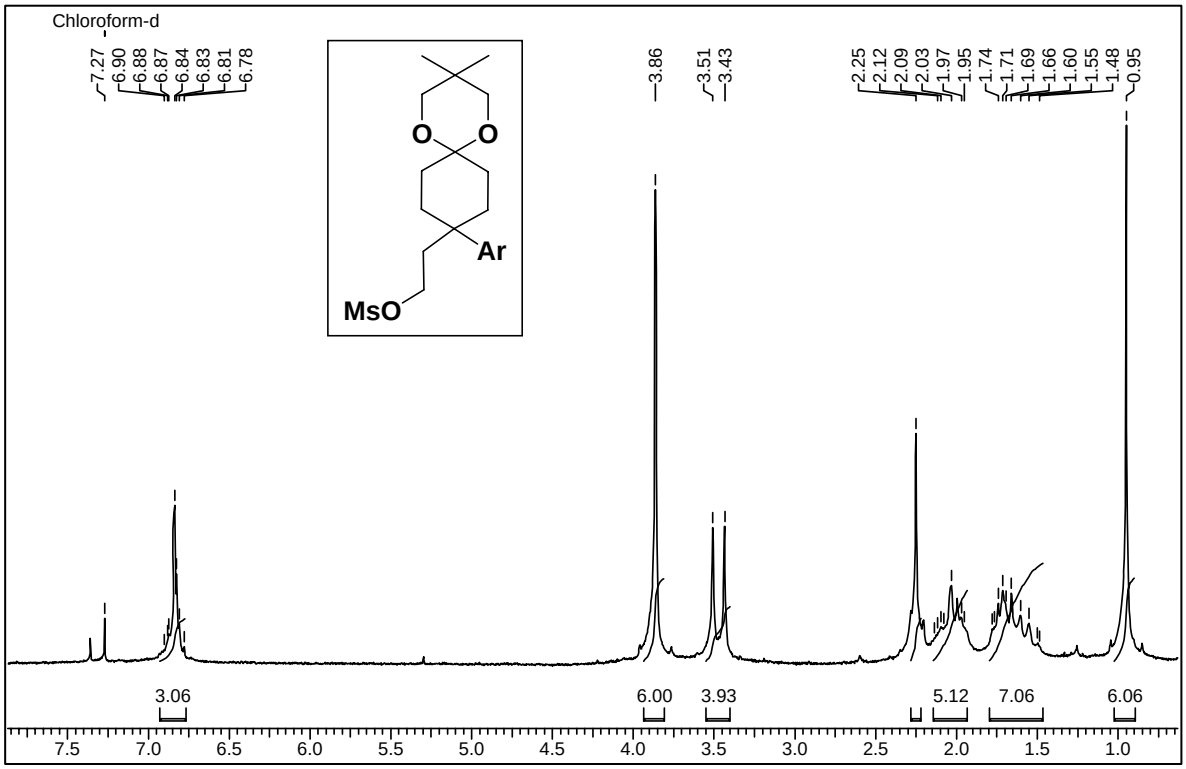


^{13}C NMR Spectrum of Compound 247 (50 MHz, $CDCl_3$ + CCl_4)



DEPT NMR Spectrum of Compound 247 (50 MHz, $CDCl_3$ + CCl_4)



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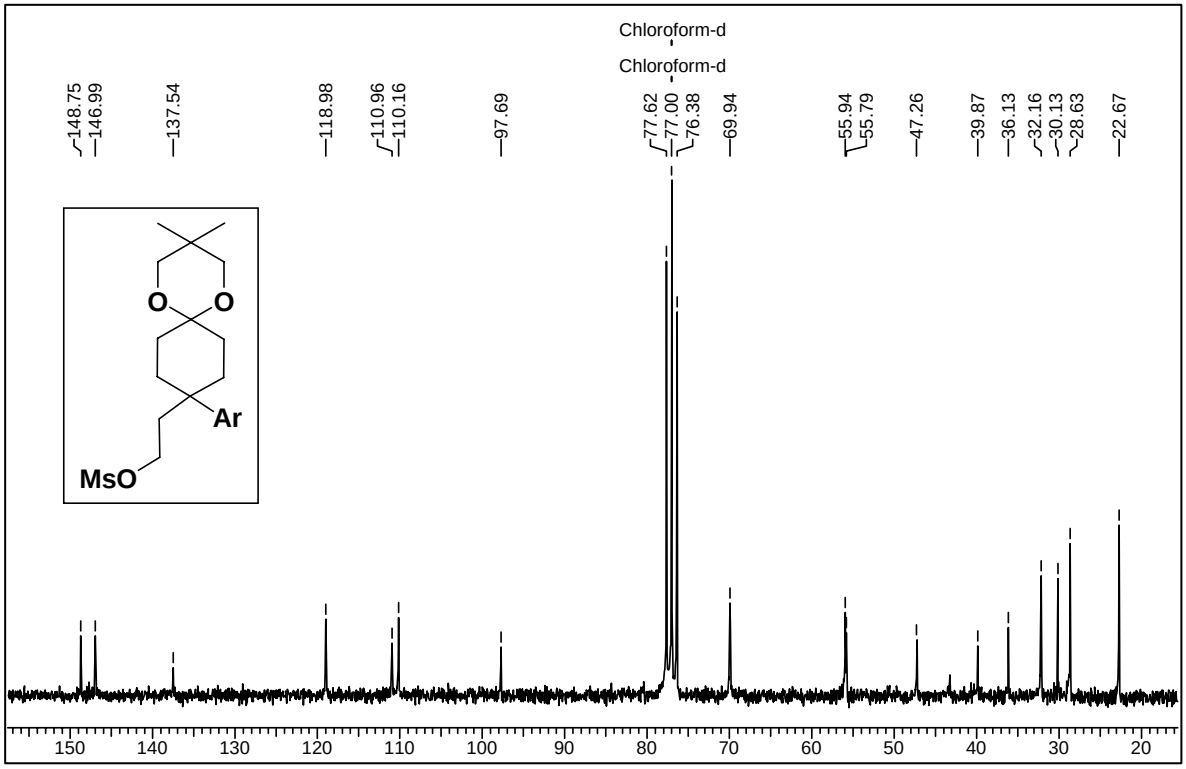
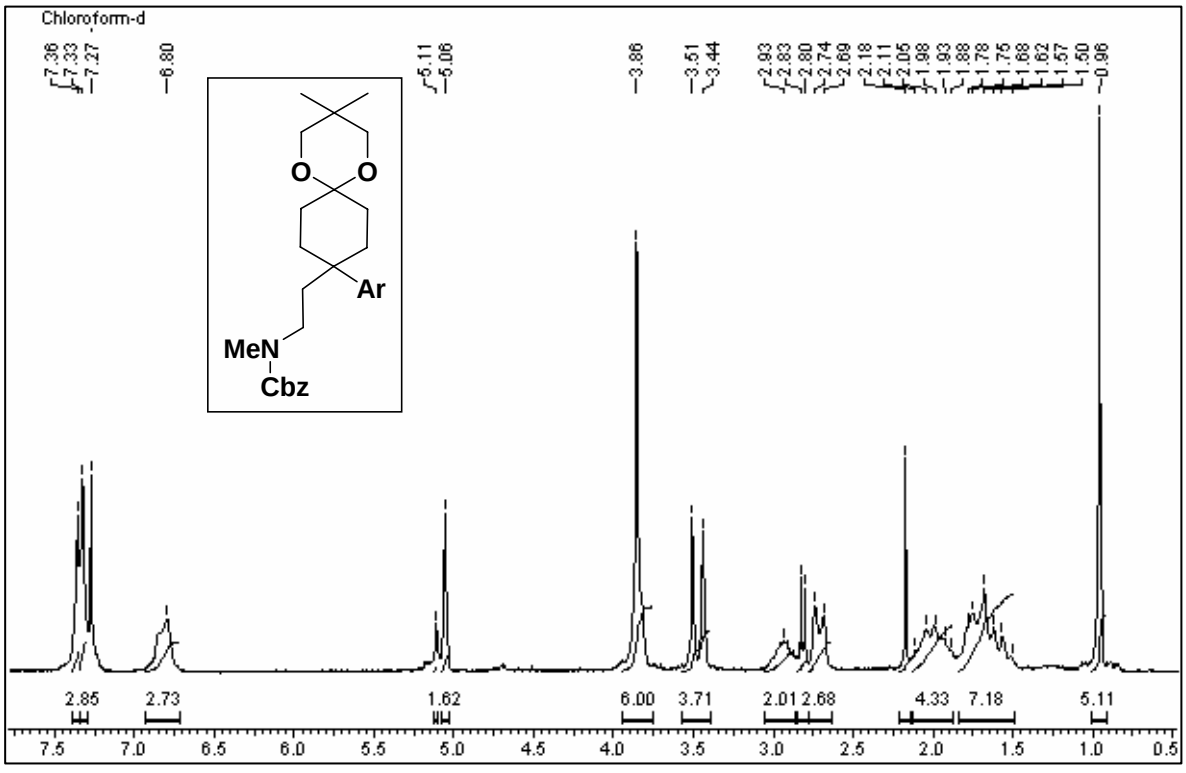
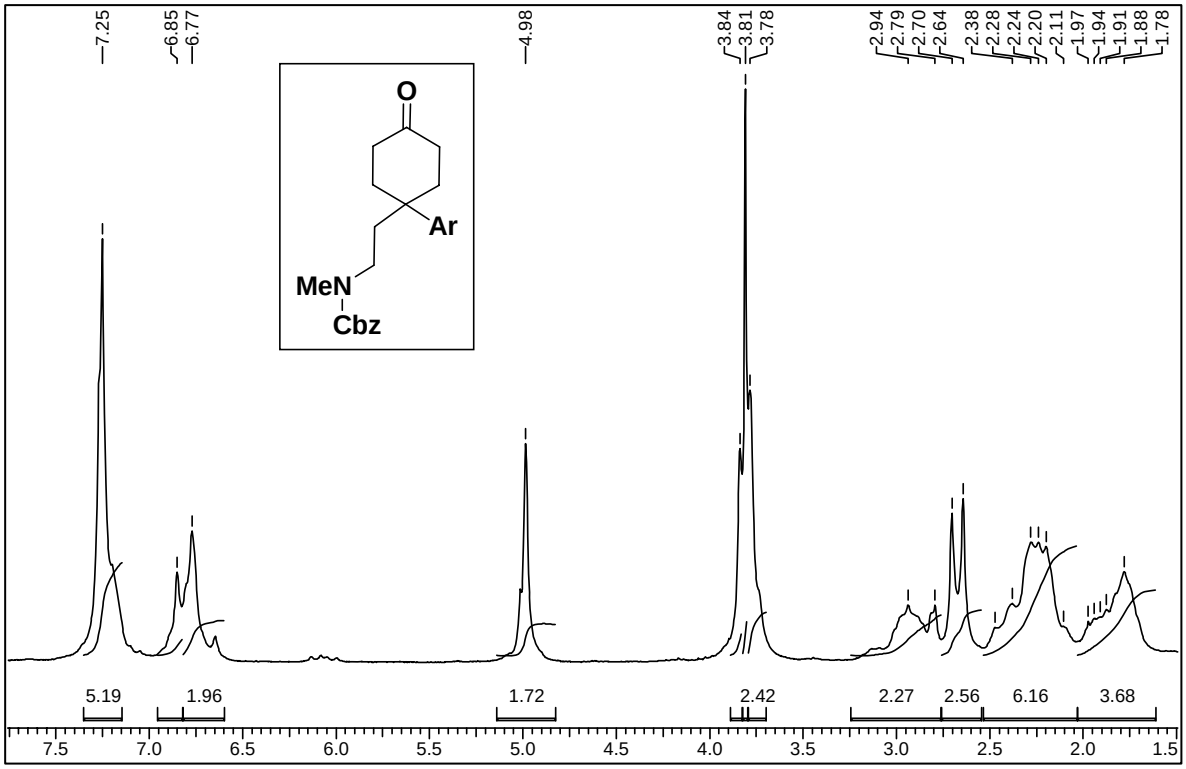


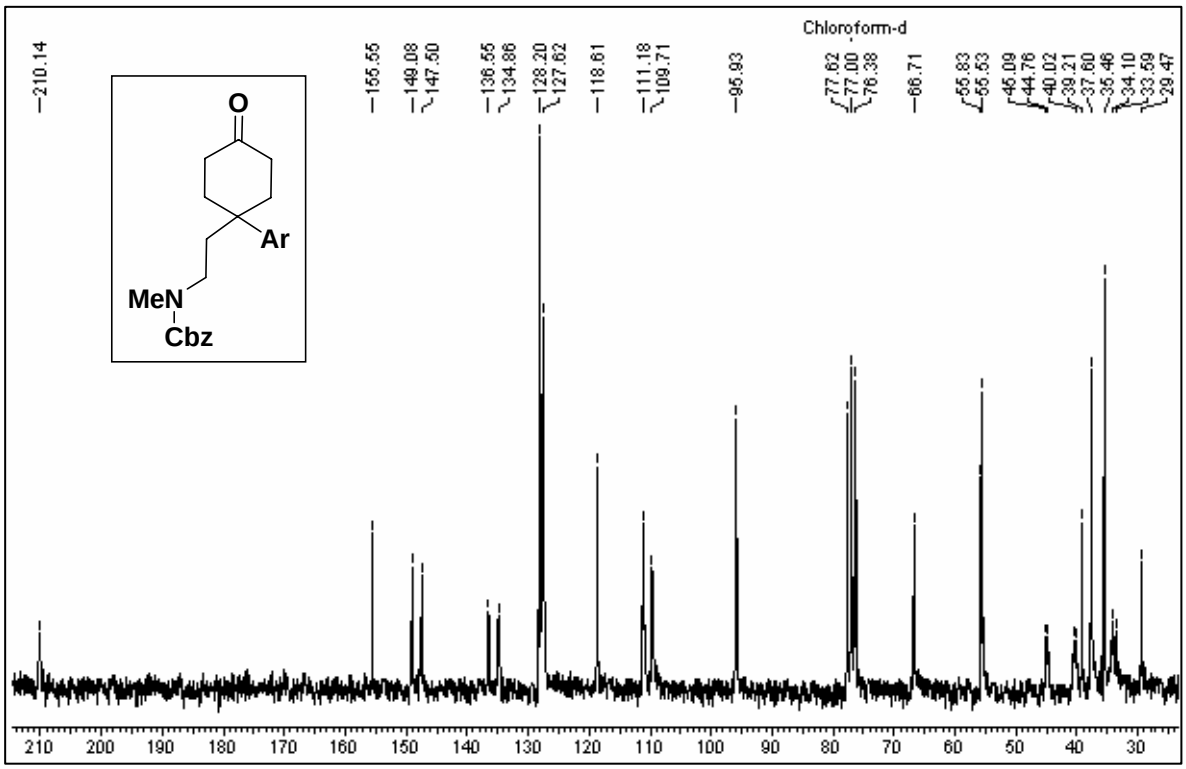
^{13}C NMR Spectrum of Compound 248 (50 MHz, $CDCl_3$)



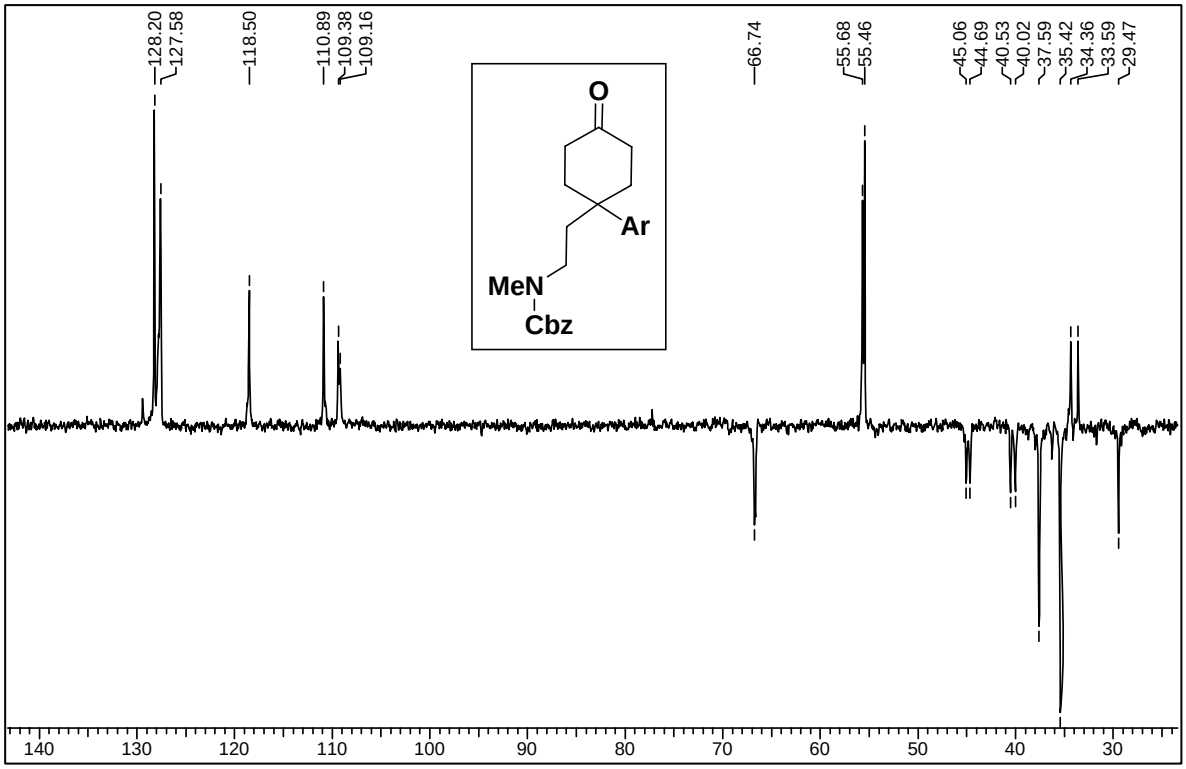
^{1}H NMR Spectrum of Compound 249 (200 MHz, $CDCl_3$)



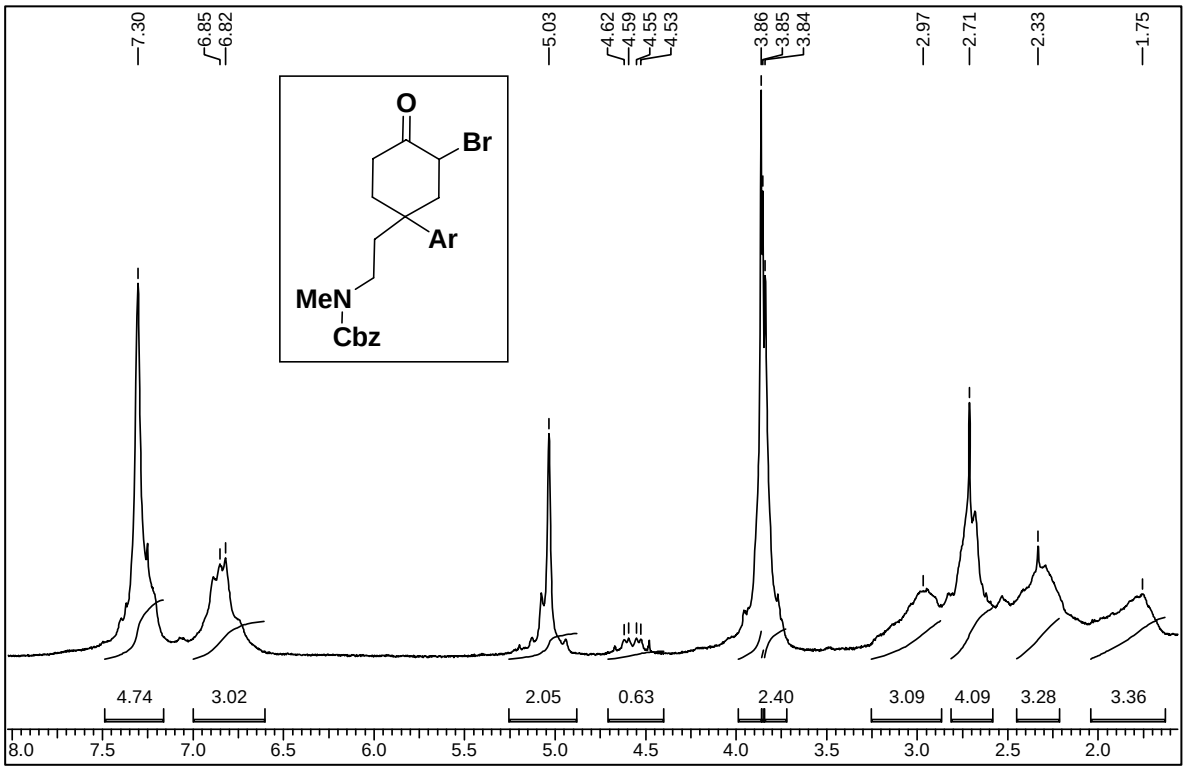
^{1}H NMR Spectrum of Compound 235 (200 MHz, $CDCl_3$)



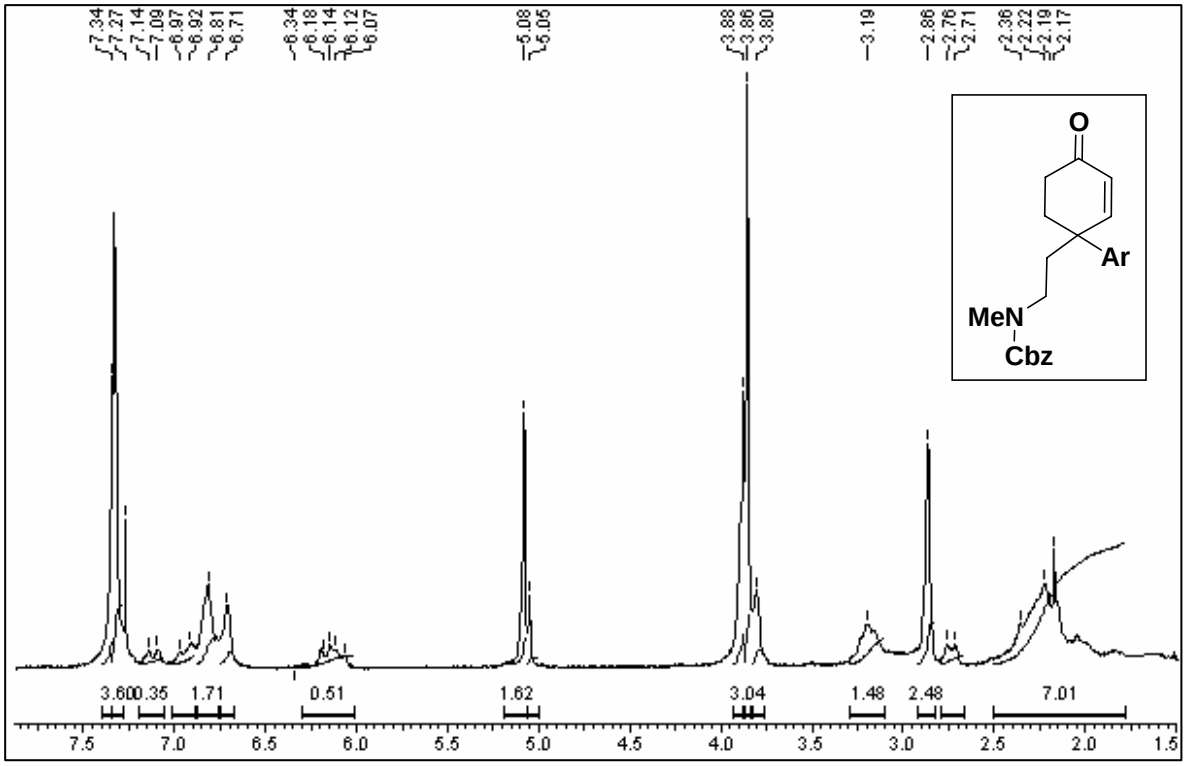
^{13}C NMR Spectrum of Compound 235 (50 MHz, $CDCl_3$ + CCl_4)



DEPT NMR Spectrum of Compound 235 (50 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR Spectrum of Compound 252 (200 MHz, $CDCl_3$)



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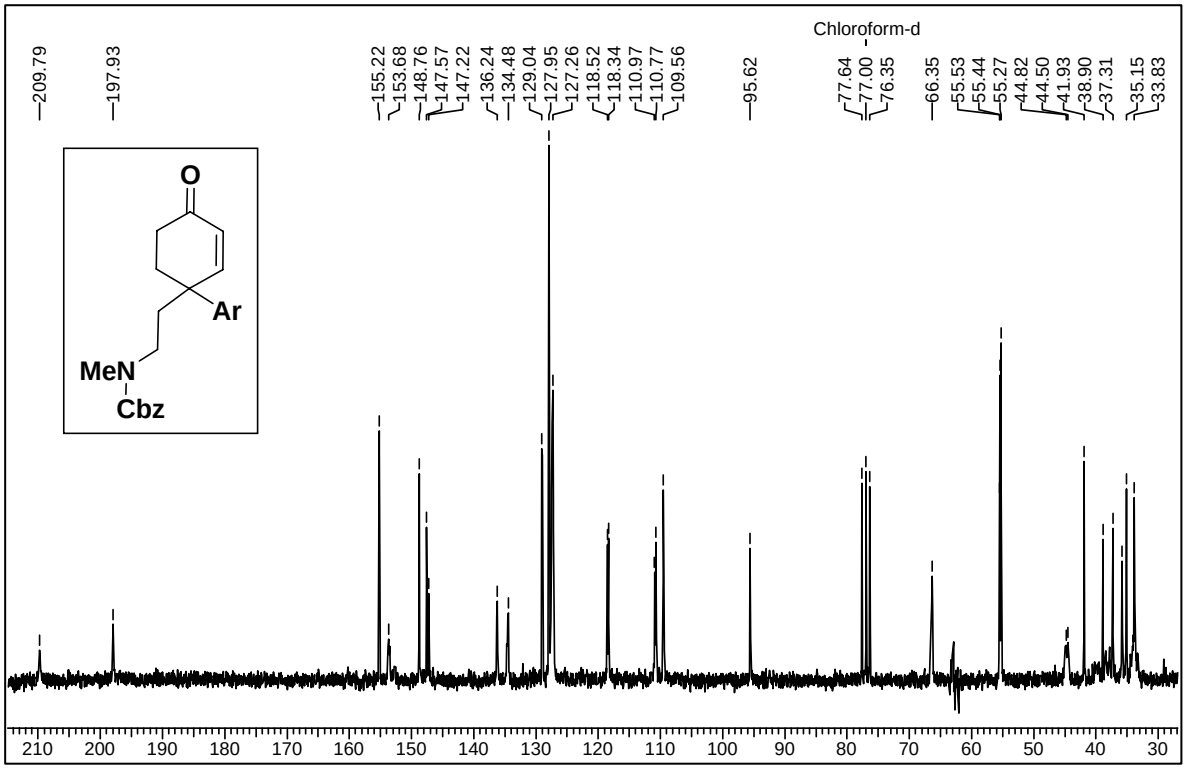
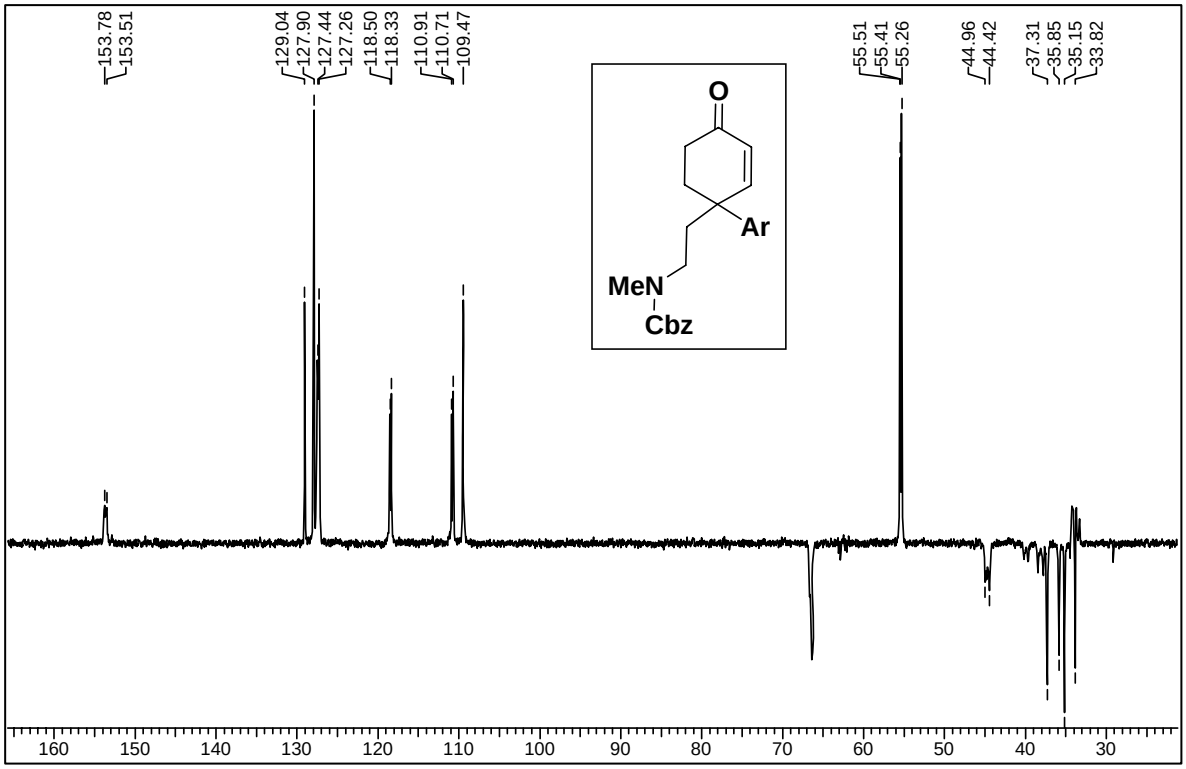
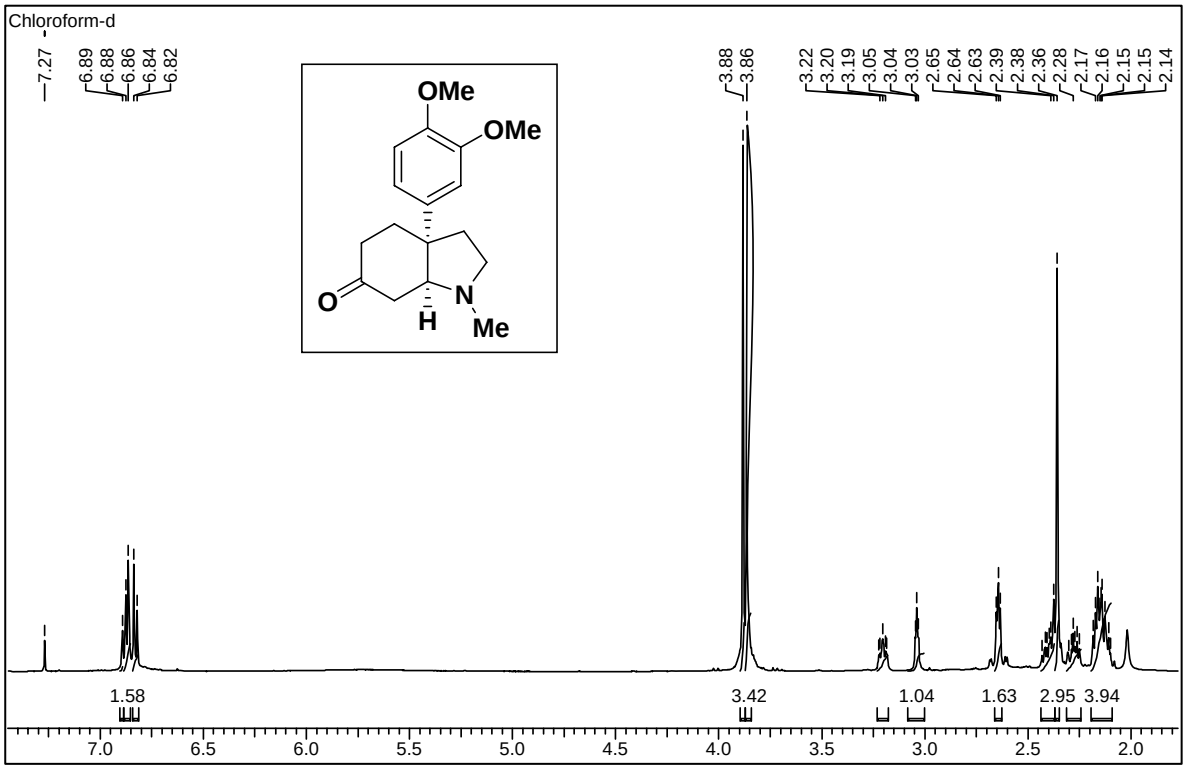


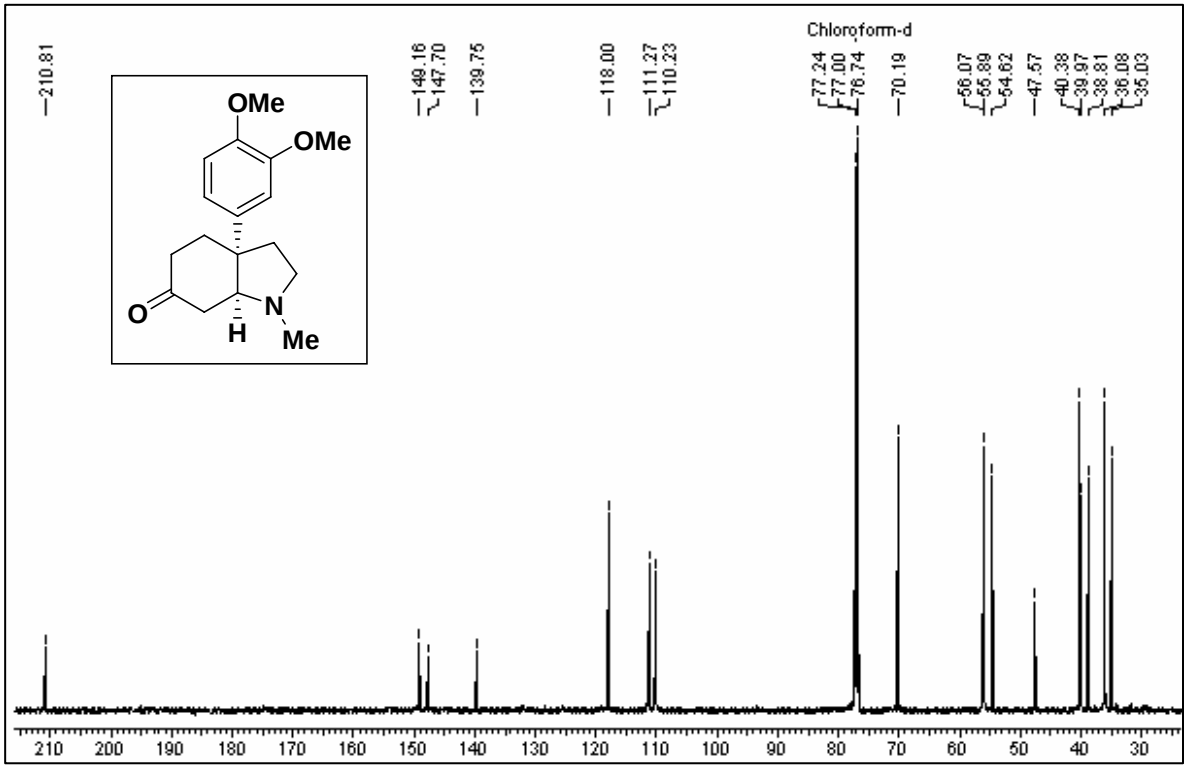
^{13}C NMR Spectrum of Compound 234 (200 MHz, $CDCl_3$ + CCl_4)



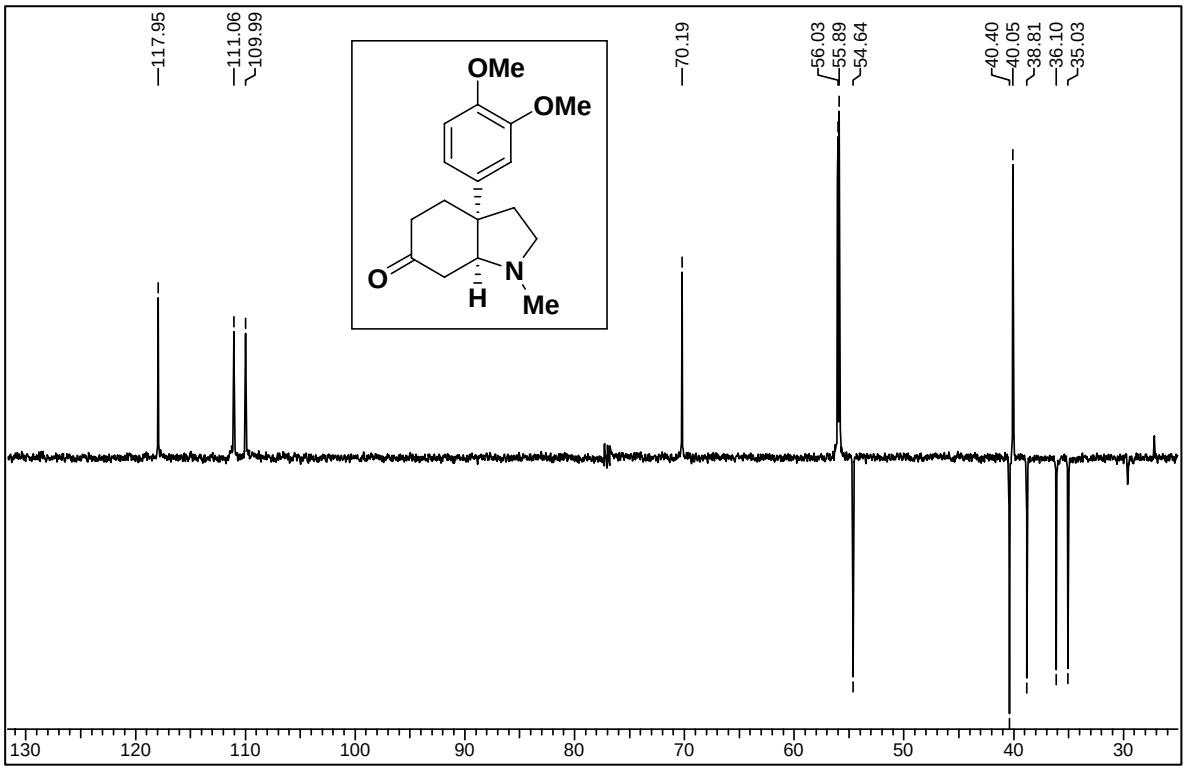
DEPT NMR Spectrum of Compound 234 (200 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR Spectrum of Mesembrine 1 (500 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Mesembrine 1 (125 MHz, $CDCl_3$)



DEPT NMR Spectrum of Mesembrine 1 (125 MHz, $CDCl_3$)

Section-2: Synthetic Studies Towards Zafirlukast

2.2.1. Introduction

2.2.1.1 Asthma

Asthma is a chronic disease[1] in which sufferers have repeated attacks of difficulty in breathing and coughing. Around 100 million people suffer from the chronic lung disease worldwide. People of all ages get asthma but 50 per cent of sufferers are children, mostly boys, under 10. Among adults, women are more likely to develop asthma than men.

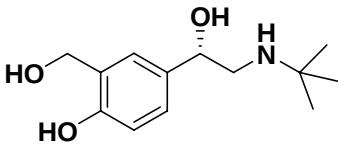
Acute asthmatic attack may be triggered by exertion, cold, smoke, air pollution, air-borne infection or allergies. To acquire asthma, people seem to need to have been born with a predisposition to the disease. It may not reveal itself until they have been exposed to some asthma irritants.

Broncheoles in the lungs are made up of ring-shaped muscles that are capable of contracting or relaxing. Asthmatics tend to be sensitive to various types of irritants in the atmosphere e. g. exertion, colds, air pollution, air-borne infection, allergies etc. that makes these brancheoles contract will narrow the passages, which makes it more difficult for the air to pass through and also gives rise to the characteristic wheezy noise. The inner lining of these brancheoles becomes inflated, which makes the lining swell and produce an excess amount of the mucus (phlegm), also contributing to the airway narrowing.

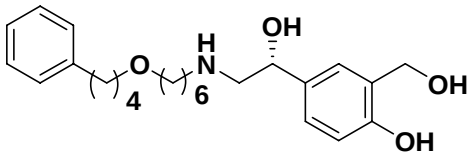
2.2.1.2. Medication: Medicines for asthma are generally divided in two main groups.

1. Relievers (bronchodilators): These are quick-acting medicines that relax the muscles of the airways. This opens the airways and makes it easier to breathe. They are further categorized into three groups.

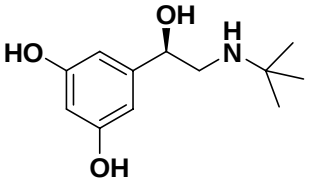
A. *Beta-2 agonists:* Beta-2 agonists act on molecule-sized receptors on the muscle of the broncheoles. Examples are salbutamol **1** (Ventolin) and terbutaline **2** (Bricanyl). These medicines are inhaled from a variety of delivery devices, the most familiar being the pressurised metered-dose-inhaler (MDI). They are used when required to relieve shortness of breath. Longer-acting beta-2 agonists include salmeterol **3** (Serevent) and formoterol **4** (Foradil, Oxis). Their action lasts over 12 hours, making them suitable for twice daily dosage to keep the airways open throughout the day.



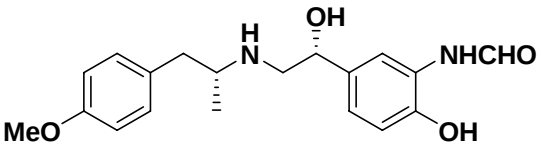
Salbutamol 1



Salmeterol 3

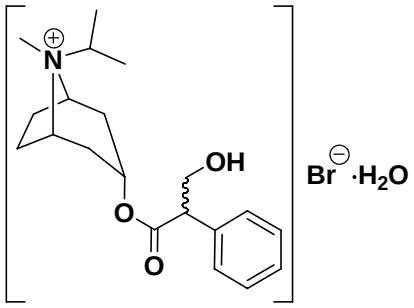


Terbutaline 2



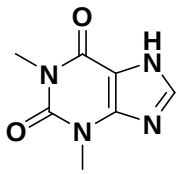
Formoterol 4

B. *Anticholinergics:* The nerve impulses cause the muscles to contract, thus narrowing the airway. Anticholinergic medicines block this effect, allowing the airways to open. The size of this effect is fairly small, so it is most noticeable if the airways have already been narrowed by other conditions, such as chronic bronchitis. An example of an anticholinergic is ipratropium bromide **5** (Atrovent).

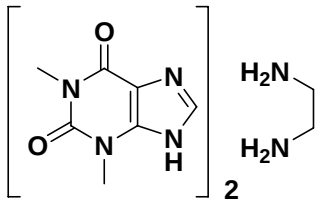


Ipratropium bromide 5

C. *Theophyllines:* Theophylline **6** (Slophyllin) and aminophylline **7** (Phyllocontin continus) are given orally and are less commonly used as they are more likely to produce side effects than inhaled treatment. They are still in very wide use throughout the world. All three types of reliever can be combined if necessary.



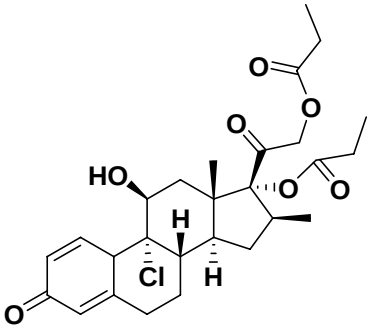
Theophylline 6



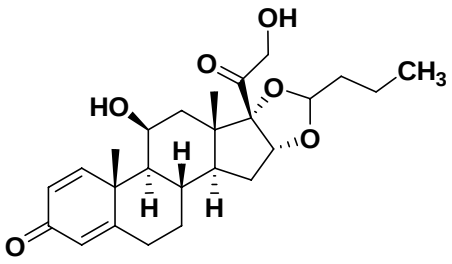
Aminophylline 7

2. Preventers: They are categorized into three main groups.

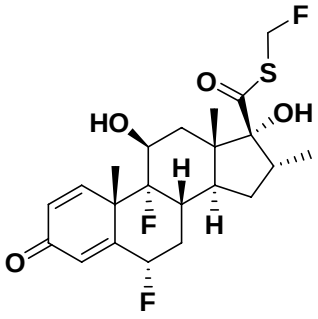
A. *Corticosteroid:* reduce inflammation within the airways, allowing many patients with previously troublesome asthma to lead almost symptom-free lives. Examples include beclometasone **8** (Becotide), budesonide **9** (Pulmicort) and fluticasone **10** (Flixotide). They are usually given as inhaled treatment, although sometimes oral steroid tablets prednisolone **11** (Deltacortril) may be required for severe attacks.



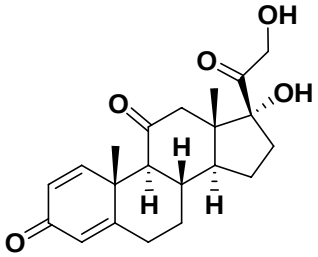
Beclometasone 8



Budesonide 9

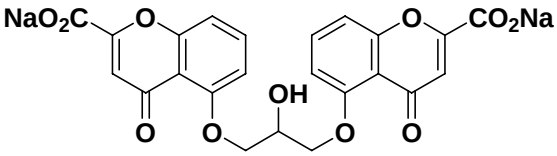


Fluticasone 10

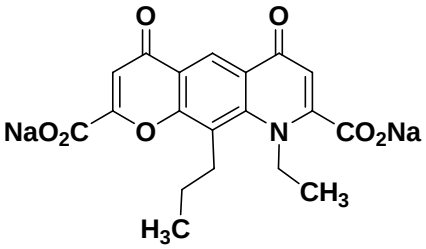


Prednisolone 11

B. *Cromones:* act to reduce inflammation of the airways. They tend to be best for mild asthma and are more effective in children than adults. The medicines are given by inhalation and are usually very well tolerated. Examples include sodium cromoglicate **12** (Intal) and nedocromil sodium (Tilade).

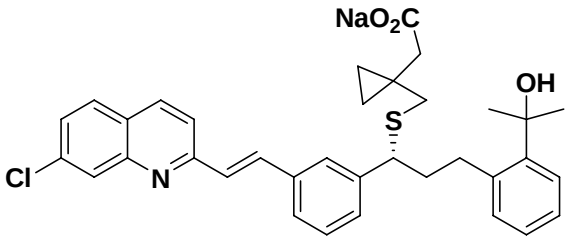


Sodium cromoglicate 12

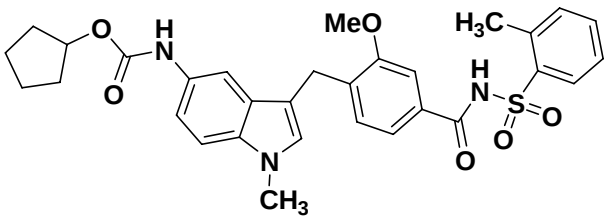


Nedocromil sodium 13

C. *Leukotriene receptor antagonists:* are the compounds released by inflammatory cells within the lungs, which have a powerful constricting effect upon the airways. The examples are montelukast **14** (Singulair) and zafirlukast **15** (Accolate).

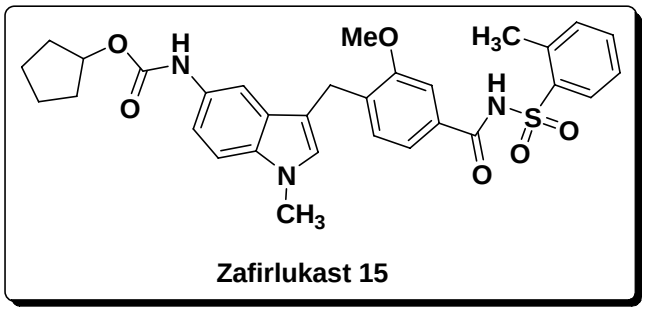


Montelukast 14



Zafirlukast 15

2.2.2. Zafirlukast



Zafirlukast 15

Zafirlukast[2] **15** is a synthetic, selective peptide leukotriene receptor antagonist[3,4] (LTRA), with the chemical name 4-(5-cyclopentyloxy-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-*N*-*o*-tolylsulfonylbenzamide, marketed by AstraZeneca with various brand names Accolate, Accoleit, and Vanticon. It was the first LTRA to be marketed in the USA and is now approved in over 60 countries. Zafirlukast is one of a new class of drugs, which act by blocking the effects of leukotrienes-natural substances, which trigger inflammation, mucus secretion and which cause bronchoconstriction typical of an asthmatic attack. One important factor in the success of the product may be its tablet form, since there are sometimes disadvantages and difficulties associated with the usage of inhalers.

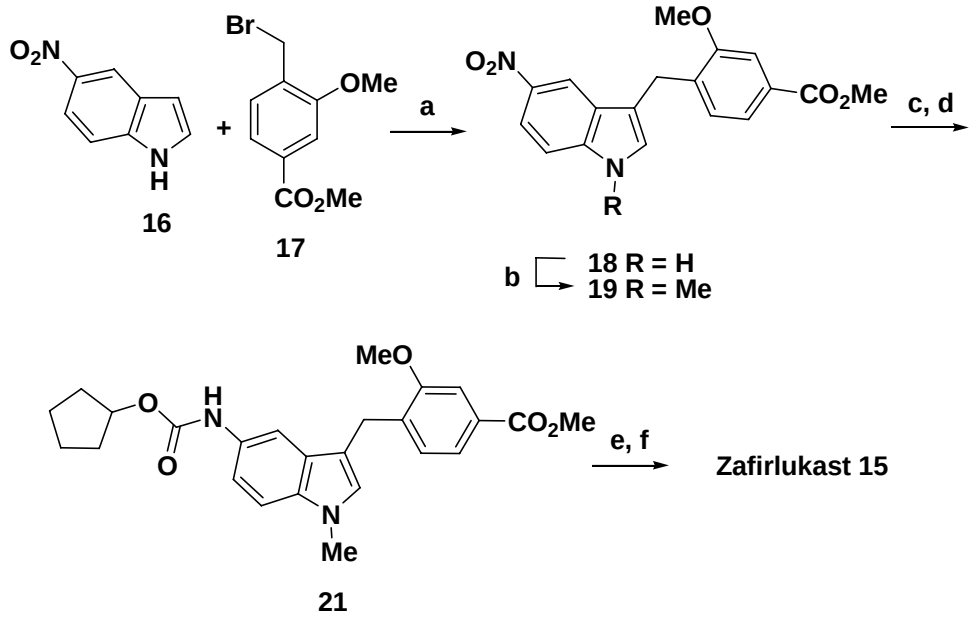
Mechanism of Action[5]: Zafirlukast is a selective and competitive receptor antagonist of leukotriene D4 and E4 (LTD4 and LTE4), components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 25-100 times more sensitive to the bronchoconstricting activity of inhaled LTD4 than nonasthmatic subjects. *In vitro* studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes (LTC4, LTD4 and LTE4) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal LTD4-induced increases in cutaneous vascular permeability and inhibited inhaled LTD4-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway

responses to antigen; this included both the early- and late-phase response and the nonspecific hyperresponsiveness.

In humans, zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment with single doses of zafirlukast attenuated the early- and late-phase reaction caused by inhalation of various antigens such as grass, cat dander, ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyperresponsiveness to inhaled histamine that followed inhaled allergen challenge.

2.2.3. Literature Review

Matassa[5] (*J. Med. Chem.* **1990**, *33*, 1781-1790; U. S. Patent 4,859,692 and U. S. Patent 5,993,859)



Scheme 1. *Reagents and conditions:* a) Ag_2O, dioxane, 60 ºC; b) NaH, MeI, DMF; c) H_2, 10% Pd/C, THF; d) cyclopentyl chloroformate **20**, *N*-methylmorpholine, DCM; e) LiOH, H_2O, THF, MeOH; f) *o*-tolyl sulfonamide **22**, l-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, DMAP, DCM.

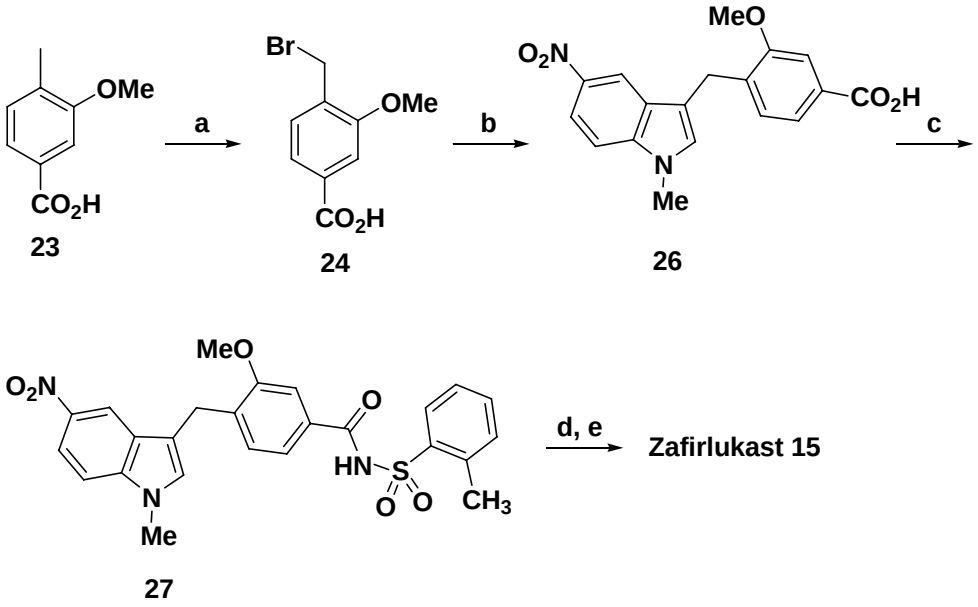
5-Nitroindole **16** was alkylated at C-3 with bromo ester **17,** under catalysis by silver oxide, to give ester **18.** *N*-methylation of the indole was carried out with MeI using NaH in anhydrous DMF to give **19**. Catalytic hydrogenation of the nitro group with Pd-C gave primary amine, which upon acylation with cyclopentyl chloroformate **20** gave urethane **21.** Ester **21** was hydrolyzed at room temperature with LiOH to give the corresponding carboxylic acid, which was coupled with *o*-tolyl sulfonamide **22** in DCM to give zafirlukast **15** in the presence of carbodiimide (Scheme 1).

An improved process[6] was reported by Mosley *et. al.* based on the above described synthesis.

A similar synthesis was also reported in 16% overall yield by Li and Ning[7], employing condensation of bromoester **17** with 5-nitroindole **16** followed by subsequent *N*-methylation, reduction, acylation, hydrolysis and condensation as depicted in scheme 1.

Synthetic Studies Towards Zafirlukast

Reddy[8] (*Org. Proc. Res. Dev.* **2004**, *8*, 952-958)



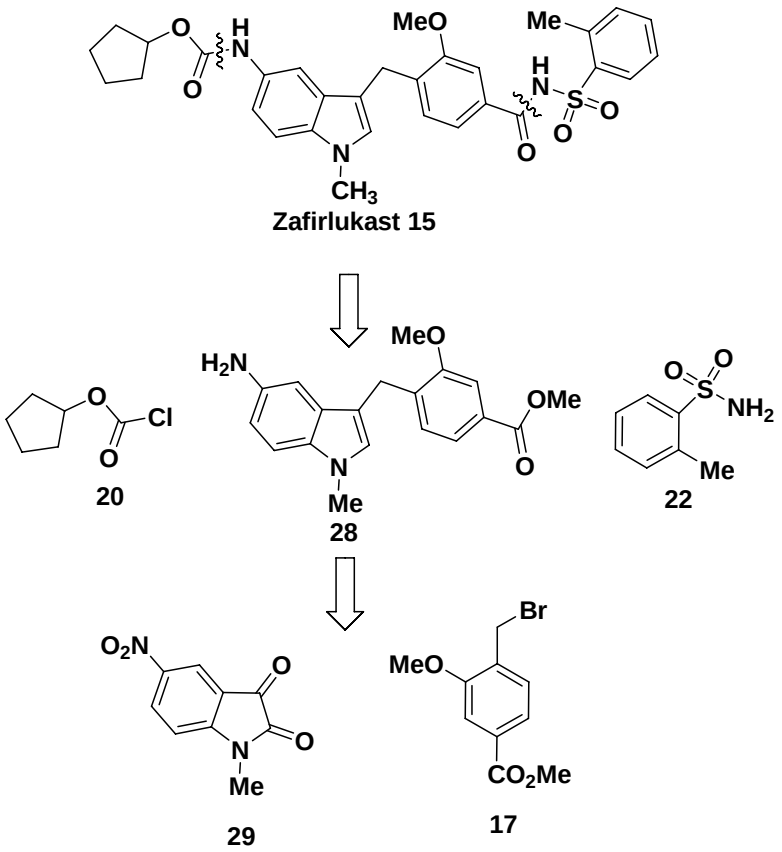
Scheme 2. *Reagents and conditions:* a) DBDMH, AIBN, CH_3Cl, reflux, 81%; b) $ZnBr_2$, dioxane, 60-65 ºC, 62%; c) DCC, DMAP, *o*-toluene sulfonamide **22**, DCM, 63%; d) H_2, Raney Ni, THF, 88%; e) cyclopentyl chloroformate **20**, *N*-methylmorpholine, DCM, 89%.

Reddy *et. al.* reported a total synthesis of zafirlukast **15** by coupling bromide **24**, derived from commercially available 3-methoxy-4-methylbenzoic acid **23** with 1-methyl-5-nitroindole **25**. Bromination of **23** with DBDMH in the presence AIBN in $CHCl_3$, afforded bromomethylbenzoic acid derivative **24** in 81% yield. Alkylation of indole **25** with bromide **24** in dioxane mediated by $ZnBr_2$ at 60-65 °C furnished indole **26** in 62% yield. Acid **26** was coupled with *o*-toluene sulfonamide **22** using DCC in the presence of DMAP as a catalyst to give sulfonamide **27** in 63% yield. Catalytic hydrogenation of **27** using Raney Ni in MeOH smoothly afforded amine, which upon acylation with cyclopentyl chloroformate **20** yielded the target molecule **15** in 89% yield (Scheme 2).

2.2.4. Present work

2.2.4.1. Retrosynthetic analysis

The purpose of the present work was to devise a practical and efficient synthesis of zafirlukast **1** from easily accessible starting materials.

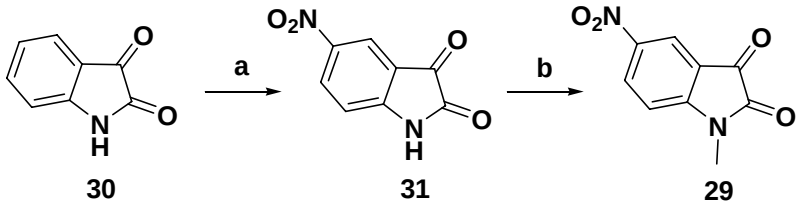


Scheme 3. Retrosynthetic analysis

Retrosynthetic analysis revealed that target molecule **15** could be assembled from fragment **28**, cyclopentyl chloroformate **20** and *o*-tolyl sulfonamide **22**. Ultimately, fragment **28** could be build from 1-methyl-5-nitroisatin **29** and bromide **17** (scheme 3).

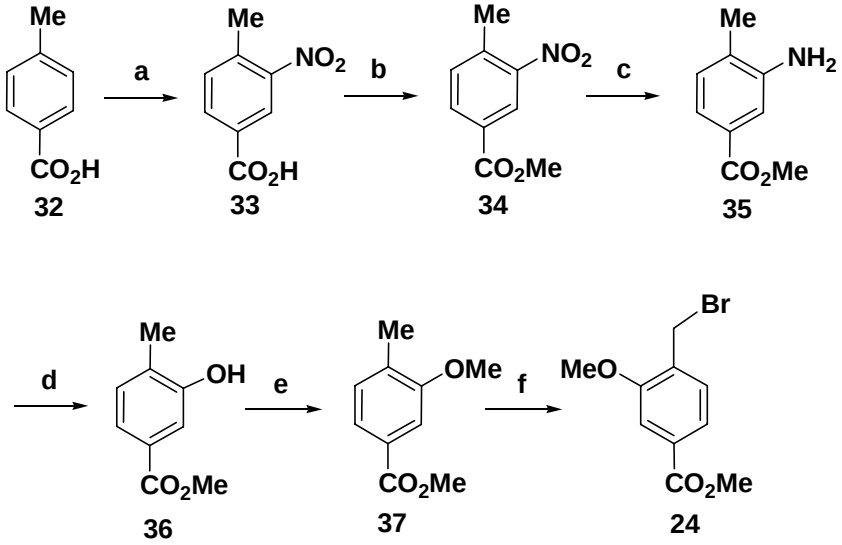
Preparation of 1-methyl-5-nitroindole 29

Isatin **30** was nitrated with fuming HNO_3 and conc. H_2SO_4 at 0 ºC to furnish 5-nitroisatin **31** in 78% yield.[9] 5-Nitroisatin **31** was methylated with MeI in the presence of K_2CO_3 at room temperature to obtain 1-methyl-5-nitroisatin **29** in 82% yield (scheme 4).[10]



Scheme 4. *Reagents and conditions:* a) fuming HNO_3, H_2SO_4, 0 ^oC, 78%; b) K_2CO_3, MeI, DMF, 24 h, r t, 82%.

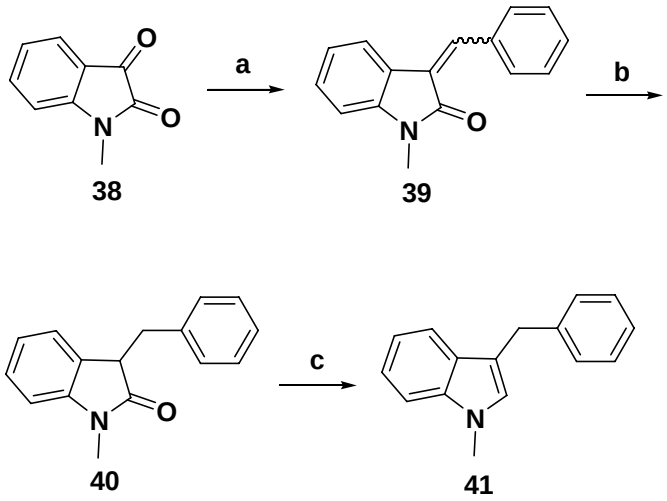
Preparation of bromide 24[11]



Scheme 5. *Reagents and conditions:* a) fuming HNO_3, conc. H_2SO_4, 0 ºC, 80%; b) conc. H_2SO_4, MeOH, reflux, 8 h, 85%; c) H_2 (50 psi), Raney Ni, MeOH, r t, 6 h, 96%; d) $NaNO_2$, Urea, 0 ºC, 44%; e) K_2CO_3, Me_2SO_4, acetone, reflux, 2 h, 72%; f) NBS, $(PhCOO)_2$, CCl_4, reflux, 10 h, 96%.

p-Toluic acid **32** was nitrated with fuming HNO_3 and conc. H_2SO_4 at 0 ºC to obtain 3-nitro *p*-toluic acid **33** in 80% yield.[12] Esterification of acid **33** with catalytic conc. H_2SO_4 in refluxing MeOH furnished ester **34** in 85% yield.[13] Catalytic hydrogenation of the nitro ester **34** with Raney nickel gave amine **35**[14], which was converted into diazonium salt with $NaNO_2$, in the presence of conc. H_2SO_4 to furnish phenol **36**.[15] Subsequent methylation of the resultant phenol with Me_2SO_4 in acetone gave methyl ether **37** in 72% yield.[16] Benzylic bromination of methyl ether **37** was effected with NBS in the presence of catalytic benzoyl peroxide to furnish bromide **17** (scheme 14).[17]

2.2.4.2. Model Study



Scheme 6. *Reagents and conditions:* a) $Ph_3P^+CH_2PhBr^-$, NaH, THF, r t, 24 h, 84%; b) H_2, Raney Ni, MeOH, 6 h, 98%; c) BMS, THF, r t, 2 h, 70%.

Before directly going for actual synthesis of zafirlukast, it was decided to test the efficiency of key step i.e. Wittig reaction as the precious bromide **24** is prepared through a sequence of steps. Accordingly, 1-methylisatin **38** was treated with the ylide generated from the Ph_3P and BnBr to give olefin **39** as a *E/Z* mixture of isomers in 84%. The ratio of *E/Z* mixture was not determined as the double bond was to be destroyed in the subsequent reduction step.

IR spectrum of compound **39** showed strong absorption at 1695 cm^{-1} characteristic of the amide function. ^1H NMR spectrum of compound **39** showed multiplet at δ 8.31-8.35 corresponding to 0.62 protons, a singlet at δ 7.89 corresponding to 0.71 protons, doublet at δ 7.71 corresponding to 0.58 protons, singlet at δ 7.67 corresponding to 1.20 protons, singlet at δ 7.64 corresponding to 0.44 protons, multiplet at δ 7.46-7.57 corresponding to 3.94 protons, multiplet at δ 7.25-7.36 corresponding to 1.68 protons, doublet of triplet at δ 7.08 corresponding to 0.54 protons, doublet at δ 6.95 corresponding to 0.24 protons, doublet at δ 6.91 corresponding to 0.39 protons, singlet at δ 6.87 corresponding to 0.71 protons, doublet at δ 6.83 corresponding to 0.48 protons, and a singlet at δ 3.33 corresponding to *N*-C*H*$_3$. ^{13}C NMR spectrum of compound **39** showed signal at δ 168.3 revealing amide carbonyl. The signals at δ 144.3, 137.1, 137.0, 135.1, 132.0, 130.4, 129.7, 129.4, 129.3, 128.8, 128.6, 128.2, 127.3, 122.8, 121.7, 121.2, 108.1 revealed aromatic carbons. The signal at δ 26.1 corresponded to the *N*-CH_3 carbons. Molecular formula of the

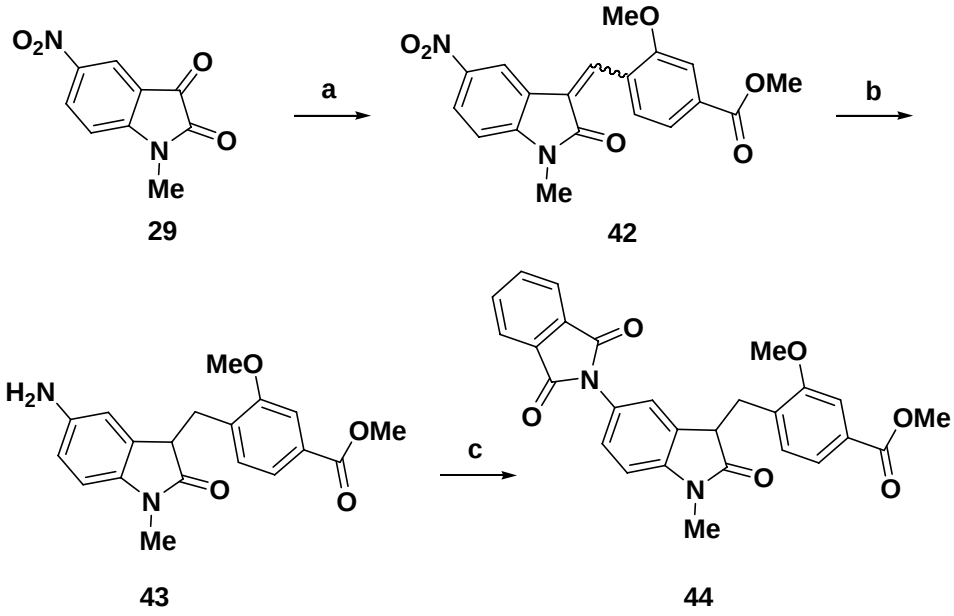
compound **39** was further confirmed by MS spectrum, which showed appearance of signals at 274 (M+K), 258 (M+Na), 235 (M+1), and 232 corresponding to M^+.

The isomeric mixture was subjected to catalytic hydrogenation using Raney Ni to furnish oxindole **40** in 98% yield.

IR spectrum of compound **40** showed a strong absorption at 1706 cm^{-1} characteristic of oxindole carbonyl. ^1H NMR spectrum of compound **40** showed multiplet at δ 7.17-7.30 corresponding to six protons, doublet of triplet at δ 6.93 corresponding to one proton, doublets at δ 6.79 and 6.75 corresponding to one proton each. The three benzylic protons appeared as doublets of doublet at δ 3.74, 3.54 and 2.91. The signal at δ 3.20 revealed *N*-methyl protons. ^{13}C NMR spectrum of compound **40** showed signal at δ 176.7 corresponding to amide function. The signals at δ 144.1, 137.8, 129.3, 128.2, 128.1, 127.8, 126.5, 124.4, 121.9 revealed aromatic carbons. The signal at δ 25.9 indicated the *N*-*C*H_3 carbon. The signals at δ 36.7 and 46.9 revealed the benzylic carbons. Further, molecular formula of the compound was confirmed by MS spectrum,which showed signal at 238 revealing M+1.

Oxindole **40** was then subjected to borane-methyl sulfide reduction to afford indole **41** in 70% yield (scheme 6).[17]

2.2.4.3. Attempted Synthesis of Zafirlukast



Scheme 7. *Reagents conditions:* a) $Ph_3P^+CH_2ArBr^-$, NaH, THF, 24 h, 50%; b) H_2, Raney Ni, MeOH, 6 h, 94%; c) Phthalic anhydride, Et_3N, PhH, reflux, 77%.

With good yield of model Wittig reaction with 1-methyl isatin **38**, it was time to test its efficiency with elaborated bromide **17** and 1-methyl-5-nitroisatin **29**. Thus, to a suspension of **29** in THF was added the ylide generated from salt of Ph_3P with bromide **17**, to furnish the expected olefin **42** in 50% yield as a mixture of isomers. Geometry of the double bond was not significant as it was to be destroyed in the subsequent reduction step.

IR spectrum of compound **42** showed a strong absorption at 1720 cm^{-1} characteristic of ester and amide carbonyl merging together. ^1H NMR spectrum of compound **42** showed following signals for aromatic and olefinic protons: doublet at δ 8.34 corresponding to one proton, multiplet at δ 8.23-8.28 corresponding to one protons, singlet at δ 8.11 corresponding to one proton, doublet at δ 6.92 corresponding to 0.80 protons, a doublet at δ 6.91 corresponding to 0.20 protons. The signals at δ 4.01, 3.99 and 3.96 revealed six methoxy protons. The signals at δ 3.37 and 3.34 corresponded to *N*-C*H*$_3$ protons. Molecular formula of compound **242** was further confirmed by MS spectrum, which showed signal at 368 revealing M^+.

Low yields may be attributed to very low solubility of the 1-methyl-5-nitroisatin **29** in THF. Yields of olefin **42** may be improved with proper choice of solvent system and reaction conditions.

Olefin **42** was then subjected to catalytic hydrogenation using Raney Ni to give oxindole **43** in 94% yield with concomitant reduction of the nitro group. Amine **43** was protected as phthalimide with phthalic anhydride and Et_3N in refluxing benzene to furnish **44** in 77% yield (scheme 16).[17]

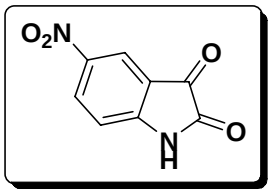
IR spectrum of compound **44** showed a strong absorption at 1721 cm^{-1} characteristic of amide function. ^1H NMR spectrum of compound **44** showed two doublets of doublet at δ 7.96 and 7.82 corresponding to four protons indicating formation of phthalimide and three doublets of doublet at 3.96, 3.63 and 2.91 revealed three benzylic protons. The singlets at δ 3.92 and 3.91 revealed six methoxy protons. The singlet at δ 3.28 revealed N-*CH*$_3$ protons. ^{13}C NMR spectrum of compound **44** showed signal at δ 177.1, 167.4, 167.0 revealing the presence of amide and ester functions. The signals at δ 55.4, 52.1 revealed methoxy carbons. The signal at 44.8 revealed *N*-*C*H$_3$ carbon and the two benzylic carbons appeared at δ 31.9, 26.3. MS spectrum of compound **44** showed signal appearing at 471 corresponding to M+1, further confirmed its molecular formula.

2.2.4.4. Conclusion

An advanced intermediate **44**, adorned with all requisite functionalities for further elaboration, has been synthesized employing Wittig reaction. Due to time constraints, the synthetic plan further could not be investigated. However, with judicious choice of reagents and tuning of reaction conditions phthalimide **44** could be taken to target molecule.

2.2.5. Experimental

5-Nitroisatin (31)

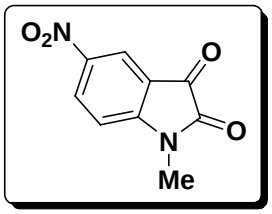


Isatin **30** (14.7 g, 0.1 mol) was added to conc. H_2SO_4 (121 ml) cooled to 0 ºC in an ice-salt bath. Fuming HNO_3 (4.2 ml) was added to this, drop by drop, in such a way that temperature should not rise above 5 ºC. The reaction mixture was allowed to stand for about 30 minutes and then poured over crushed ice (500 g). A yellow precipitate separated immediately. The solid was filtered and washed with water and air dried to a constant weight (15 g).

Yield **:** 85%

Mp **:** 252 ^oC (dec.)[9]

1-Methyl-5-nitroisatin (29)



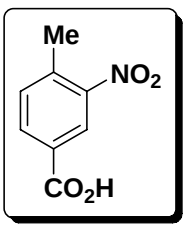
A mixture of nitroisatin **31** (10 g, 0.052 mol), MeI (16.21 ml, 0.260 mol) and K_2CO_3 (21.56 g, 1.56 mol) in anhydrous DMF was stirred overnight at room temperature. Water was added to the reaction mixture and acidified with dilute HCl till acidic to pH paper. A yellow solid separated, which was filtered and washed thoroughly with water till neutral to pH paper and air dried to a constant weight (9.66 g).

Molecular formula **:** $C_9H_6N_2O_4$

Yield **:** 90%

Mp **:** 202-6 ^oC (lit.[10] Mp 203 ºC)

Methyl 4-methy-3-benzoic acid (33)



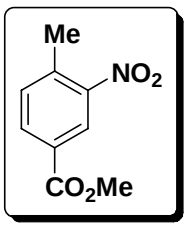
Fuming HNO_3 (39.4 ml, 0.932 mol) was slowly added to conc. H_2SO_4 (98 ml, 1.84 mol) at 0-5 ºC. The cooled nitrating mixture was taken in a beaker equipped with a mechanichal stirrer and addition funnel. *p*-Toluic acid **32** (100 g, 0.735 mol) was added to this mixture, in small portions, over 5 hours at such a rate to maintain the temperature at 0-5 ºC. The reaction mixture was stirred further for additional 2 hours at room temperature and then

poured over ice. The solid that separated was filtered, washed with water till it was free of acid and then air-dried to a constant weight (106.47 g).

Yield **:** 80%

Mp **:** 187.5° C (lit.[12] Mp 190 °C)

Methyl 4-methyl-3-nitrobenzoate (34)

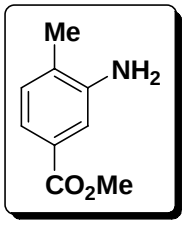


Acid **33** (100 g, 0.552 mol) was dissolved in MeOH (1000 ml). Conc. H_2SO_4 (30 ml) was added cautiously to this solution. The mixture was refluxed for 8 hours. Solvent was distilled off. Ice-cold water was added to the residue. It was then extracted with EtOAc, washed with $NaHCO_3$ solution, water, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo* to furnish faint yellow a solid (91.57 g)

Yield **:** 85%

Mp **:** 45 °C (lit.[13] Mp 51 °C)

Methyl 3-amino-4-methylbenzoate (35)

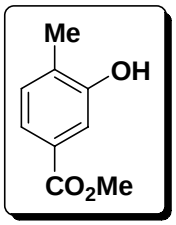


Nitro ester **34** (80 g, 0.410 mol) was subjected to hydrogenation in a Parr shaker in MeOH using Raney Ni as the catalyst (5 g, 20 mol %) at 50 psi for 8 hours. The catalyst was filtered off, washed thoroughly with MeOH and the combined filtrates concentrated under reduced pressure to furnish a yellow solid (65.0 g).

Yield **:** 96%

Mp **:** 114-5 ^{o}C (lit.[14] Mp 116 °C)

Methyl 3-hydroxy-4-methylbenzoate (36)



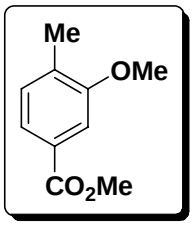
The amino ester **35** (60 g, 0.364 mol) was added to dil. H_2SO_4 (125 ml conc. H_2SO_4 diluted with 1 L water) and warmed on a water bath until all the compound was dissolved. Cold water (800 ml) was added and the mixture was cooled to 0 °C. $NaNO_2$ (62.6 g, 0.907 mol) was added to this mixture with constant stirring. It was then stirred at room temperature for 15 minutes. Then, urea (65.4 g, 1.09 mol) was added in portions. The mixture was warmed at 50 ºC for 15 minutes (temperature was not allowed to rise above 55 ºC). EtOAc was added to the

reaction mixture and washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure to afford a colourless solid (26.56 g).

Yield **:** 44%

Mp **:** 81°C (lit.[15] Mp 82-3 ºC)

Methyl 3-methoxy-4-methylbenzoate (37)

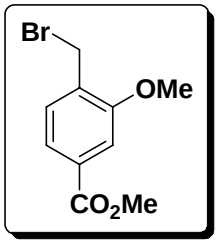


A mixture of methyl 3-hydroxy-4-methylbenzoate **36** (25 g, 0.151 mol), Me_2SO_4 (28.3 ml, 0.386 mol), anhydrous K_2CO_3 (103.5 g, 0.75 mol) was refluxed in acetone for 2 hours. K_2CO_3 was filtered off, washed thoroughly with acetone. The filtrates were combined and concentrated, the residue was redissolved in EtOAc washed with water, dried (anhydrous Na_2SO_4), filtered and concentrated *in vacuo* to furnish a white solid (19.52 g).

Yield **:** 72%

Mp **:** 41-42 °C (lit.[16] Mp 42-3 °C)

Methyl 4-(bromomethyl)-3-methoxybenzoate (24)



A mixture of methyl 3-methoxy-4-methylbenzoate **37** (5 g, 27.8 mmol), NBS (4.94 g, 27.8 mmol), and benoyl peroxide (0.0008 g, 0.003 mmol) was refluxed in CCl_4 (25 ml) for 10 hours. The reaction mixture was allowed to cool and filtered. The residue was washed with CCl_4 and the combined filtrate concentrated *in vacuo*. Purification by column chromatography over silica gel (5-10% EtOAc-pet ether) furnished a colourless solid (7.19 g).

Yield **:** 100%

Mp **:** 69-71 ^{o}C (lit.[11] 73-75 ^{o}C)

Benzyl triphenylphosphonium bromide

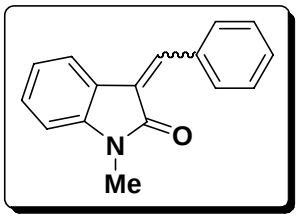
To a solution of Ph_3P (22 g, 0.084 mol) in toluene, BnBr (10 ml, 0.084 mol) was added dropwise with ice-cooling and stirred at room temperature for 2 hours. A solid was formed, which was filtered and washed with toluene and then dry pet ether to remove unreacted Ph_3P. The salt was dried under vacuum (35 g, 96% yield).

Synthetic Studies Towards Zafirlukast

(2-Methoxy-4-(methoxycarbonyl)benzyl)triphenylphosphonium bromide

To an ice-cooled solution of Ph_3P (10.15 g, 0.039 mol) in PhMe, bromide **17** (10 g, 0.039 mol) was added and stirred at room temperature for 2 hours. A solid was formed, which was filtered and washed with PhMe and then dry pet ether to remove unreacted Ph_3P. The salt was dried under vacuum (17.1 g, 85% yield).

3-Benzylidine-1-methylindolin-2-one (39)

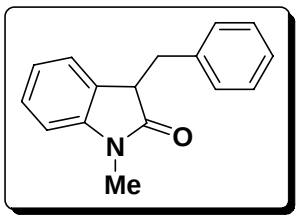


A mixture of benzyl triphenylphosphonium bromide (6.08 g, 13.98 mmol) and NaH (0.522 g, 13.04 mmol) was stirred in THF for 1 hour. A dark red colour developed. To this a solution of 1-methylisatin **38** (1.5 g, 9.32 mmol) in THF (5 ml) was added dropwise *via* syringe. The reaction mixture was stirred for two hours at room temperature and was quenched with saturated NH_4Cl solution, extracted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resultant residue was chromatographed over silica gel (EtOAc-pet ether, 1:9) to furnish a yellow-red solid as a mixture of *E/Z* isomers (2.19 g).

Molecular formula	**:** $C_{16}H_{13}NO$
Yield	**:** 84%
IR	**:** 3020, 1695, 1609, 1472, 1423, 1216, 1091, 1043, 929, 757, 669
^{1}H NMR (200 MHz, $CDCl_3$)	**:** δ 8.31-8.35 (m, 0.62H), 7.89 (s, 0.71H), 7.71 (d, *J*= 2.28 Hz, 0.58H), 7.67 (s, 1.20H), 7.64 (s, 0.44H), 7.46-7.57 (m, 3.94H), 7.25-7.36 (m, 1.68H), 7.08 (dt, *J*= 0.88 Hz and 7.58 Hz, 0.54 H), 6.95 (d, *J*= 1.01 Hz, 0.24H), 6.91 (d, *J*= 0.88 Hz, 0.39H), 6.87 (s, 0.71H), 6.83 (d, *J*= 2.40 Hz, 0.48H), 3.33 (s, 2H), 3.33 (s, 1H)
^{13}C NMR (125 MHz $CDCl_3$)	**:** δ 168.3, 144.3, 137.1, 137.0, 135.1, 132.0, 130.4, 129.7, 129.4, 129.3, 128.8, 128.6, 128.2, 127.3, 122.8, 121.7, 121.2, 108.1, 26.1
MS (EI) *m/z*	**:** 274 (M+39), 258 (M+23), 236 (M+1), 232
Analysis	**:** Calculated for $C_{16}H_{13}NO$; C-81.68, H-5.57, N-5.95 found; C-81.52, H-5.25, N-5.77

Synthetic Studies Towards Zafirlukast

3-Benzyl-1-methylindolin-2-one (40)



The isomeric mixture of olefins **39** (2.0 g, 8.51 mmol) was subjected to hydrogenation (balloon pressure) in the presence of Raney Ni (0.100 g) in MeOH at room temperature for 2 hours. The catalyst was filtered off, washed thoroughly with MeOH and the combined filtrates concentrated under reduced pressure to furnish a yellow solid (2.02 g).

Molecular formula : $C_{16}H_{15}NO$

Yield : 98%

IR ($CHCl_3$) : 3019, 1706, 1614, 1496, 1455, 1471, 1377, 1354, 1216, 1090, 757, 700, 669 cm^{-1}

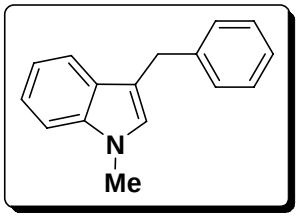
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.20-7.30 (m, 6H), 6.93 (dt, *J*= 1.52 Hz and 7.45 Hz, 1H), 6.77 (dd, *J*= 3.03 Hz and 6.70 Hz, 2H), 3.74 (dd, *J*= 4.55 Hz and 9.48 Hz, 1H), 3.54 (dd, *J*= 4.55 Hz and 13.65 Hz, 1H), 3.20 (s, 3H), 2.91 (dd, *J*= 9.48 Hz and 13.65 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 144.1, 137.8, 129.3, 128.1, 127.8, 126.5, 124.4, 121.9, 107.7, 46.9, 36.7, 25.9

MS (EI) *m/z* : 239 (M+2), 238 (M+1), 184

Analysis : Calculated for $C_{16}H_{15}NO$; C-80.98, H-6.37, N-5.90 found, C-80.79, H-6.09, N-5.63

3-Benzyl-1-methyl-1*H*-indole (41)



To a solution of oxindole **40** (1.0 g, 4.22 mol) in THF, BMS complex was added dropwise at room temperature. The reaction mixture was stirred for 30 minutes. Then the reaction mixture was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was evaporated under reduced pressure. Column chromatographic purification over neutral alumina using EtOAc-pet ether (1:9) gave indole **41** (0.653 g).

Molecular formula : $C_{16}H_{15}N$

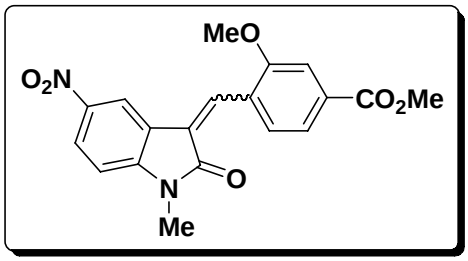
Yield : 70%

Mp : 61 ^oC

IR ($CHCl_3$) **:** 3060, 3027, 2933, 1600, 1500, 1452, 1434, 1364, 1316, 1242, 1125, 1045, 802, 754, 732, 697 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.42 (d, *J*= 7.83 Hz, 1H), 7.07-7.20 (m, 8H), 6.99 (d, *J*= 6.82 Hz, 1H), 4.02 (s, 2H), 3.67 (s, 3H)

Methy 3-methoxy-4-((1-methyl-5-nitro-2-oxoindolin-3-ylidene)methylbenzoate (42)



A mixture of (2-methoxy-4-(methoxycarbonyl)benzyl) triphenylphosphonium bromide (7.59 g, 14.56 mmol) and NaH (0.544 g, 13.59 mmol) was stirred in THF for 1 hour. A dark red colour developed. The suspension was allowed to settle. The supernatant ylide solution was added dropwise *via* syringe to a suspension of 1-methyl-5-nitroisatin **29** (2 g, 9.71 mmol) in THF. The reaction mixture was stirred overnight at room temperature and quenched with saturated NH_4Cl solution, extracted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resultant residue was chromatographed over silica gel to furnish a yellow solid as a mixture of isomers *E/Z* isomers (2.50 g).

Molecular formula **:** $C_{19}H_{16}N_2O_6$

Yield **:** 50%

Mp **:** 197-9 ^oC

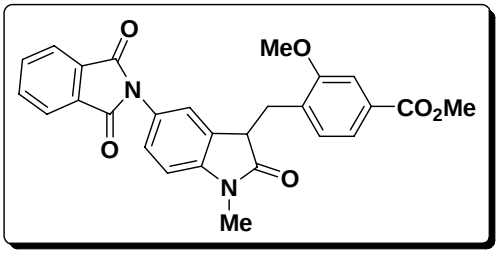
IR ($CHCl_3$) **:** 1720, 1611, 1461, 1377, 1198, 1105, 1023, 979, 749 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.34 (d, *J*= 2.14 Hz, 1H), 8.23-8.28 (m, 1H), 8.11 (s, 1H), 7.73 (d, *J*= 1.24 Hz, 0.19H), 7.69-781 (m, 3H), 6.92 (d, *J*= 8.72 Hz, 0.80H), 6.91 (d, *J*= 8.59 Hz, 0.20H), 4.01 (s, 0.58H), 3.99 (s, 2.42H), 3.96 (s, 3H), 3.37 (s, 2.40H), 3.34 (s, 0.60H)

MS (EI) *m/z* **:** 368 (M^+), 350, 326, 328, 315, 301, 297, 292, 274, 265, 260, 258, 252, 238, 236, 205, 149

Analysis **:** Calculated for $C_{19}H_{16}N_2O_6$; C-61.95, H-4.38, N-7.61; found, C-61.70, H-4.25, N-7.53

Methyl 4-((5-(1,3-dioxoisoindolin-2-yl)-1-methyl-2-oxoindolin-3yl)-methoxybenzoate (44)



The isomeric mixture of olefins **42** (1 g, 2.71 mmol) was subjected to hydrogenation (balloon pressure) in the presence of Raney nickel (0.100 g,) in MeOH at room temperature for 2 hours. The catalyst was filtered off, and the residue was washed thoroughly with MeOH and the combined filtrates were concentrated under reduced pressure to furnish amine **43** as a crimson syrup (0.924 g, 94% yield). Amine **43** was used as such for further reaction. A mixture of amine **43**, phthalic anhydride (0.436 g, 2.94 mol), Et_3N (0.62 ml, 4.40 mol) and DMAP (0.036 g, 0.30 mol) was refluxed overnight in benzene. The reaction mixture was allowed to cool, EtOAc added to it, washed with 3 N HCl followed by water, brine, dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The resultant residue was precipitated from EtOAc-DCM to obtain a pinkish solid (1.06 g).

Molecular formula **:** $C_{27}H_{22}N_2O_6$

Yield **:** 77%

Mp **:** 265 ^oC (dec.)

IR ($CHCl_3$) **:** 3020, 2954, 2401, 1779, 1721, 1621, 1500, 1468, 1437, 1412, 1388, 1369, 1351, 1293, 1216, 1105, 1082, 1038, 930, 877, 759, 721, 669 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.96 (dd, *J*= 3.15 Hz and 5.30 Hz, 2H), 7.82 (dd, *J*= 3.15 Hz and 5.30 Hz, 2H), 7.63 (dd, *J*= 1.27 Hz and 7.71 Hz, 1H), 7.53 (d, *J*= 1.27 Hz, 1H), 7.30 (s, 1H), 7.27 (s, 1H), 6.94 (d, *J*= 8.33 Hz, 1H), 6.74 (s, 1H), 3.96 (dd, *J*= 4.92 Hz and 9.60 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.63 (dd, *J*= 4.92 Hz and 13.26 Hz, 1H), 3.28 (s, 3H), 2.91 (dd, *J*= 9.60 Hz and 13.26 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 167.4, 167.0, 157.5, 144.1, 134.3, 131.8, 131.7, 131.2, 130.0, 129.5, 127.0, 125.6, 123.7, 121.8, 110.9, 108.1, 55.4, 52.1, 44.8, 31.9, 26.3

MS (EI) *m/z* **:** 471 (M+1), 423, 380

Analysis **:** Calculated for $C_{27}H_{22}N_2O_6$; C-68.93, H-4.71, N-5.95; found, C-68.74, H-4.93, N-5.90

Spectra

2.2.6. References

1. This information was obtained through internet search *via* Google search engine and is based on text by Dr Carl J Brandt and Dr Finn Rasmussen.
2. Formerly ICI 204219; AstraZeneca trade name Accolate.
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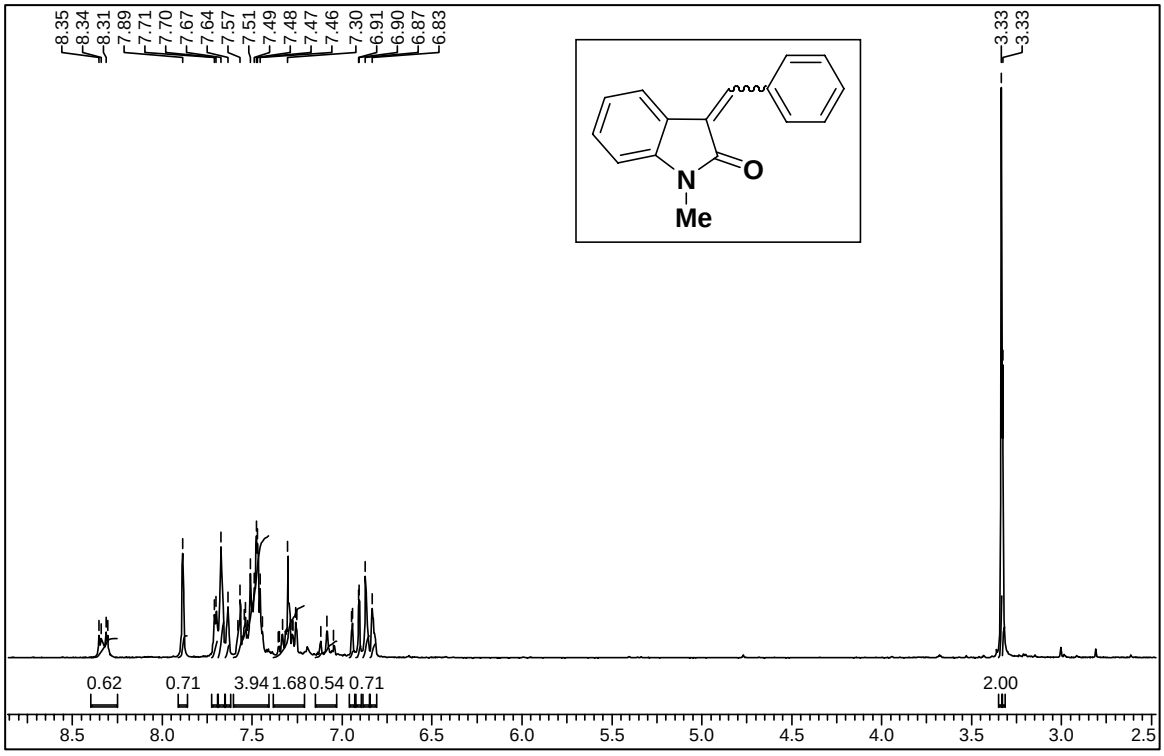
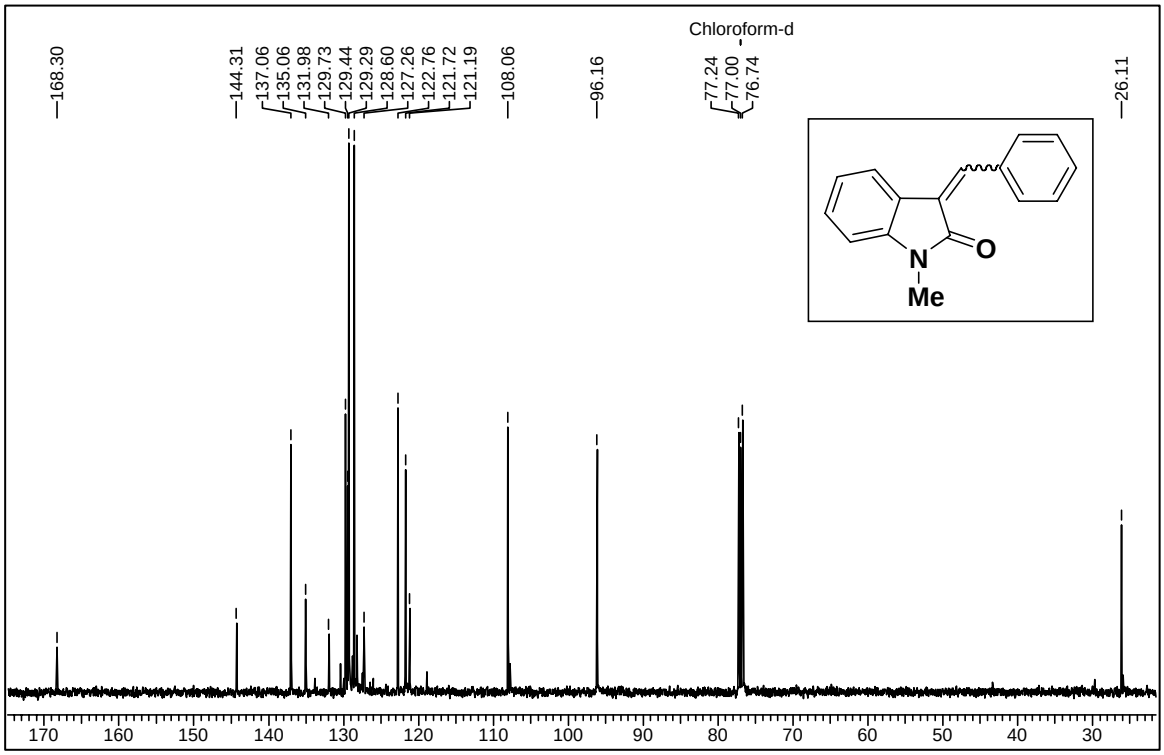
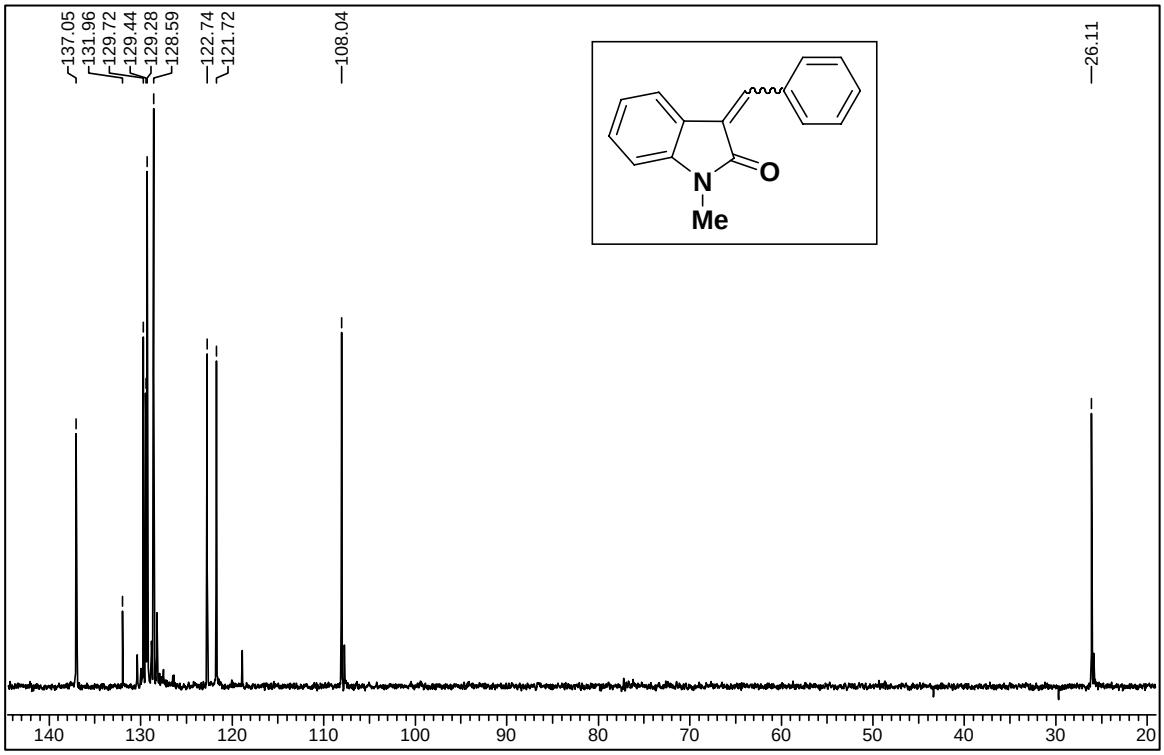


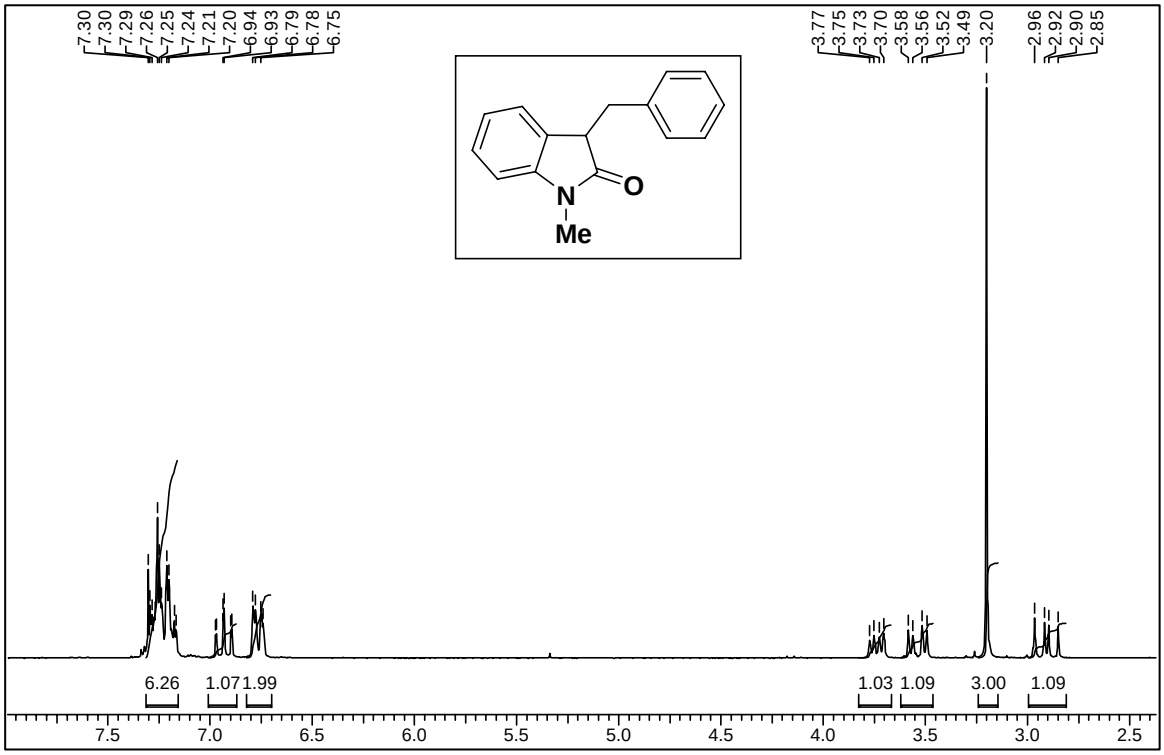
^{1}H NMR Spectrum of Compound 39 (200 MHz, $CDCl_3$)



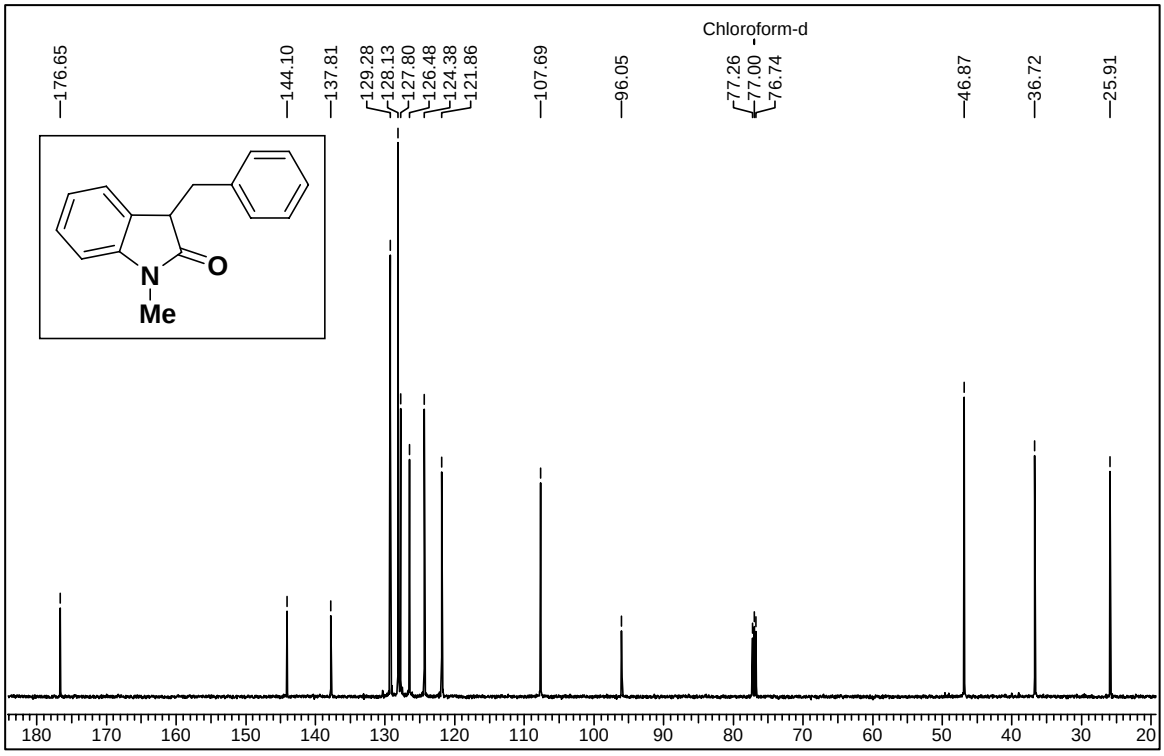
^{13}C NMR Spectrum of Compound 39 (125 MHz, $CDCl_3$ + CCl_4)



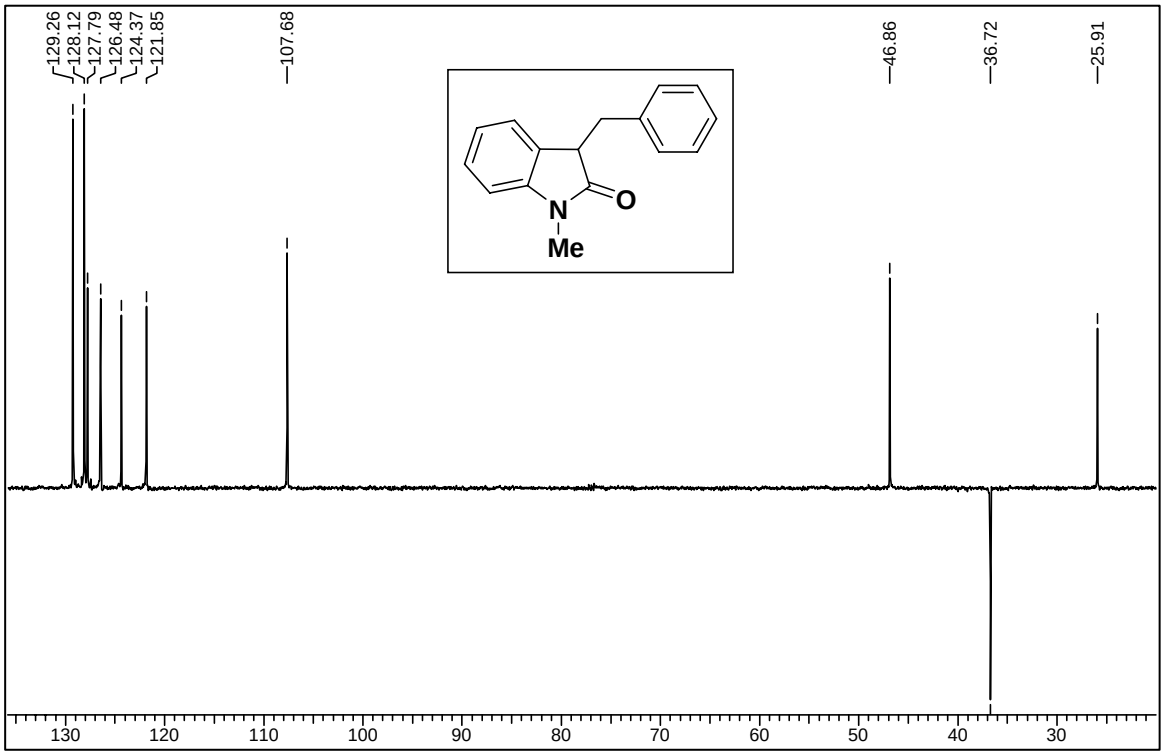
DEPT NMR Spectrum of Compound 39 (125 MHz, $CDCl_3$ + CCl_4)



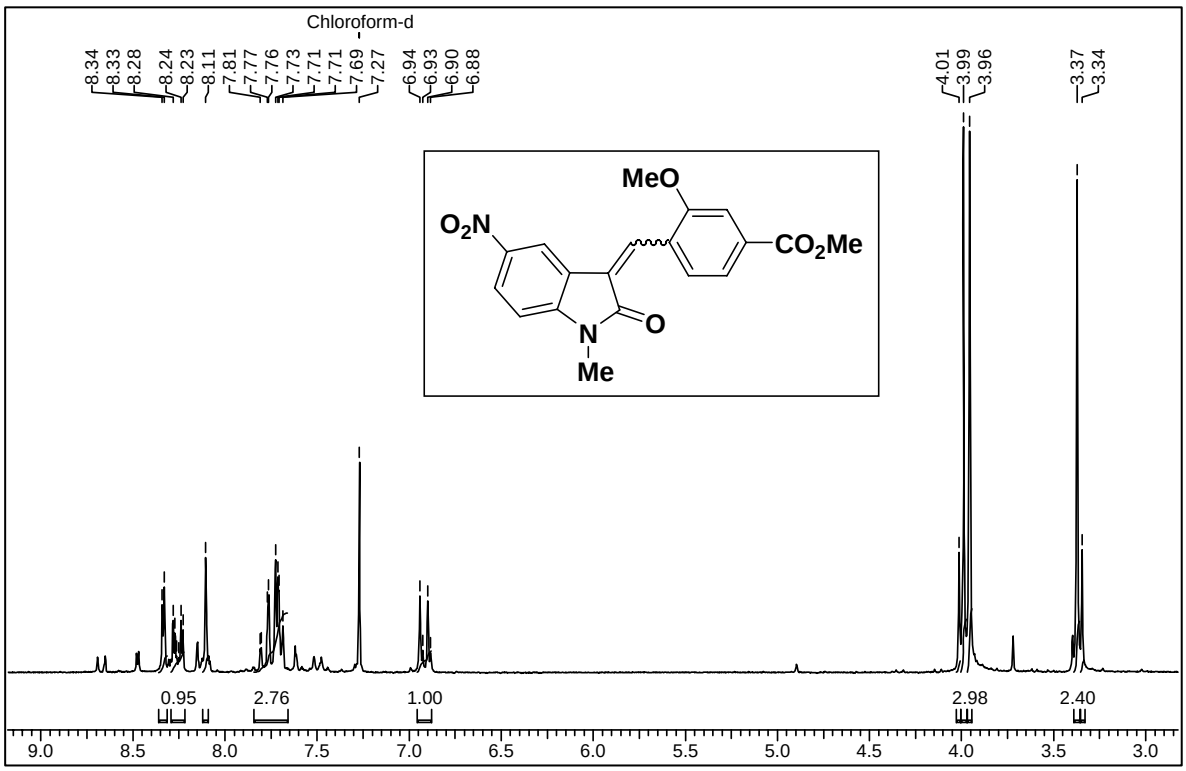
^{1}H NMR Spectrum of Compound 40 (200 MHz, $CDCl_3$)



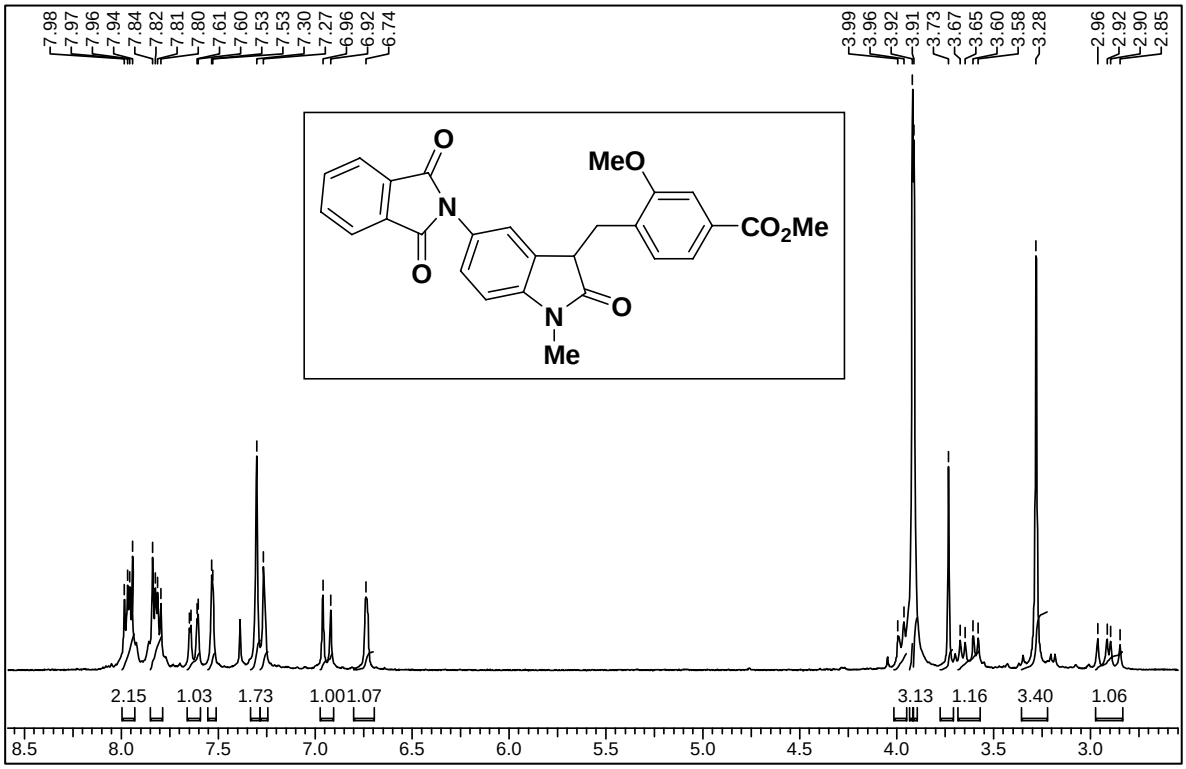
^{13}C NMR Spectrum of Compound 40 (125 MHz, $CDCl_3$ + CCl_4)



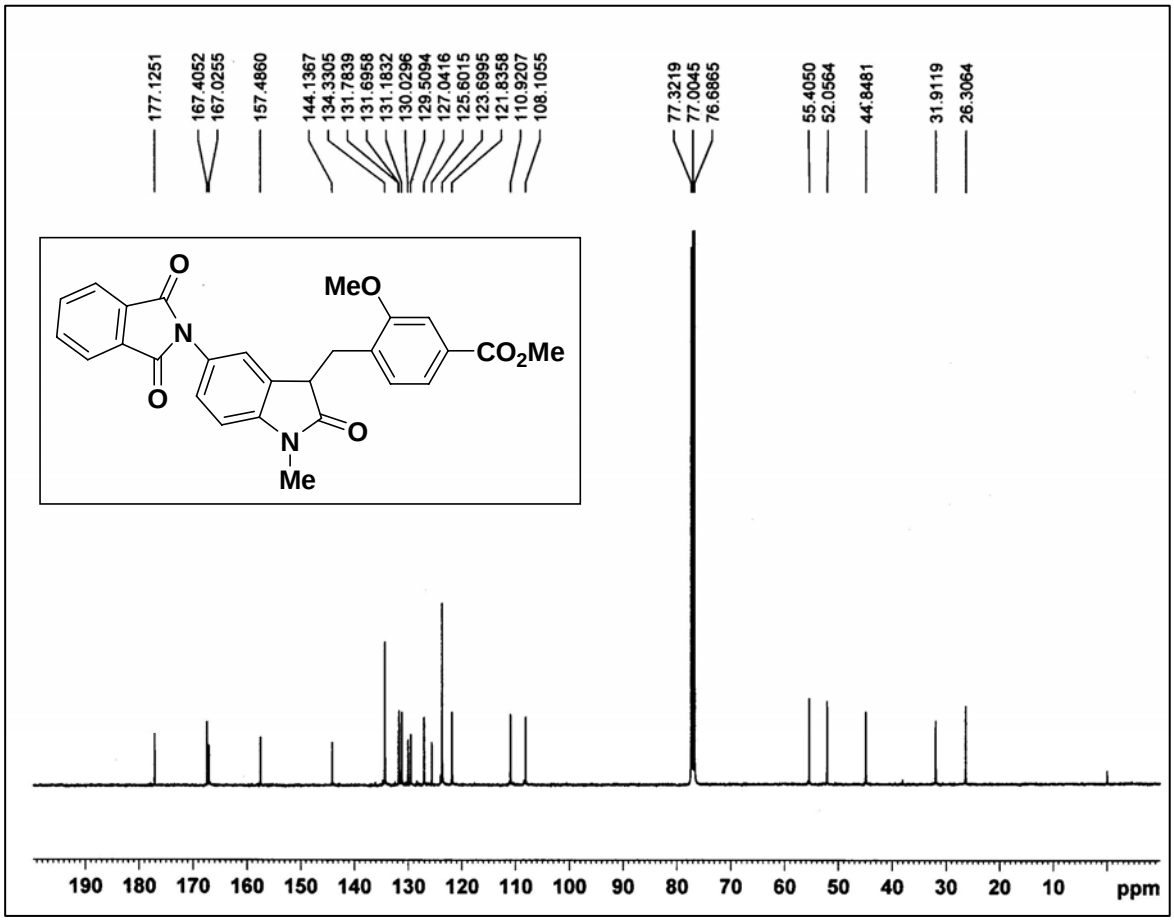
DEPT NMR Spectrum of Compound 40 (125 MHz, $CDCl_3$ + CCl_4)



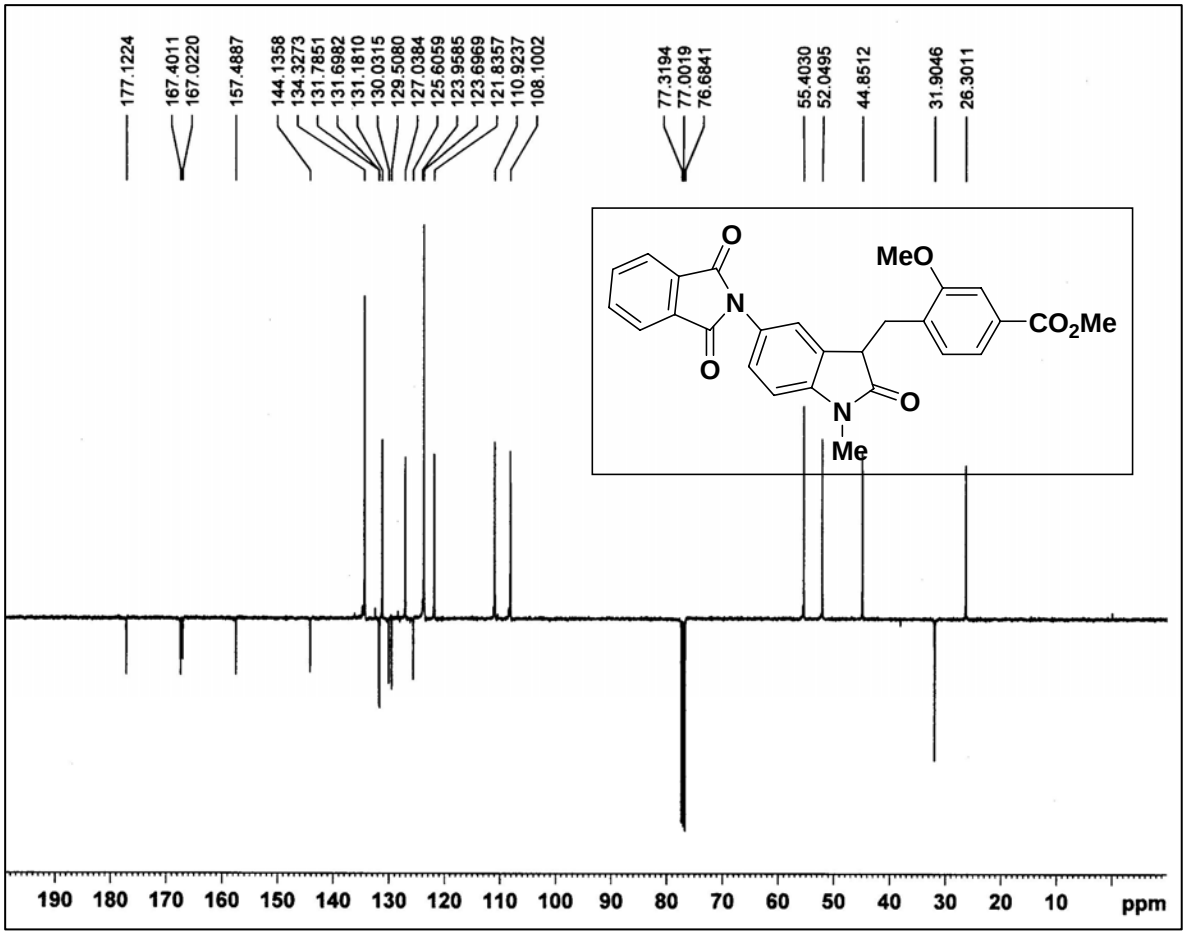
^{1}H NMR Spectrum of Compound 42 (200 MHz, $CDCl_3$)



^{1}H NMR Spectrum of Compound 44 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of Compound 44 (100 MHz, $CDCl_3$)



DEPT NMR Spectrum of Compound 44 (100 MHz, $CDCl_3$)

List of Publications

1. "One-pot Process for the Preparation of 1-[2-Dimethylamino-(4-methoxyphenyl)-ethyl]cyclohexanol" Chavan, S. P.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; **Khobragade, D. A.**; Ravindranathan, T.; Gurjar, M. K.; Kalkote, U. R. US Patent No. 6,350,912 B1 *Chem. Abstr.* **2002**, *136*, 200009.

2. "An Efficient Synthesis of (±)-β-Herbertenol by a 1,3-Cyclopentadione Annelation Strategy" Chavan, S. P.; Kharul, R. K.; Kale, R. R.; **Khobragade, D. A.** *Tetrahedron* **2003**, *59*, 2737-2741.

3. "Process for the Preparation of 1-[Cyano(aryl)methyl]cyclohexanol" Chavan, S. P.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; **Khobragade, D. A.**; Ravindranathan, T.; Gurjar, M. K.; Kalkote, U. R. US Patent No. 6,504,044 B2.

4. "An Efficient and Green Protocol for the Preparation of Cycloalkanols: A Practical Synthesis of Venlafaxine" Chavan, S. P.; **Khobragade, D. A.**; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; Ravindranathan, T.; Gurjar, M. K.; Kalkote, U. R. *Tetrahedron Letters* **2004**, *45*, 7291-7295.

5. "A Simple and Efficient Synthesis of (±)-Mesembrine" Chavan, S. P.; **Khobragade**, **D. A.**; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Letters* **2004**, *45*, 5263-5265.

6. "Convenient Formal Total Synthesis of (±)-Paroxetine" Chavan, S. P.; **Khobragade**, **D. A.**; Pathak, A. B.; Kalkote, U. R. (communicated).

7. "A Practical Synthesis of (±)-Venlafaxine" Chavan, S. P.; **Khobragade**, **D. A.**; Thakkar, M. R.; Kalkote, U. R. (communicated).