NOVEL ORGANIC TRANSFORMATIONS FOR THE THERMAL/SONOCHEMICAL SYNTHESIS OF IMPORTANT INTERMEDIATES AND BIOLOGICALLY ACTIVE MOLECULES

A THESIS SUBMITTED TO THE

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IN

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BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Novel organic transformations for the thermal/sonochemical synthesis of important intermediates and biologically active molecules**" submitted by **K. Venkatesan** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

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Candidate's Declaration

I hereby declare that the thesis entitled "**Novel organic transformations for the thermal/sonochemical synthesis of important intermediates and biologically active molecules**" submitted for the award of degree of **Doctor of Philosophy** in Chemistry to the University of Pune has not been submitted by me to any other university or institution. This work was carried out by me at the National Chemical Laboratory, Pune, India.

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March 31, 2008

DEDICATED

TO MY

Family Members

Contents

List of Publications

Acknowledgements

I thank whole heartedly, the supreme God, the illimitable superior spirit.

It is my great pleasure to express my thanks and appreciations towards the people who have in many ways assisted me to reach this stage. It gives me an immense pleasure to express my deep sense of gratitude and profound thanks to my research guide Dr. K.V. Srinivasan for all the advice, guidance, support and encouragement during every stage of my Ph.D work. I do sincerely acknowledge freedom rendered to me by him for independent thinking, planning and executing the research. Although this eulogy is insufficient, I preserve an everlasting gratitude for him.

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I am very much thankful to my family members for their care, encouragement, support and sacrifice.

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Venkatesan

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Aq.	-	Aqueous
Bbim	-	1,3-di-*n*-butyl imidazolium
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
t-Bu	-	*tert*-Butyl
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DCM	-	Dichloromethane
DHP	-	Dihydropyran
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-yl)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	-	Diasteromreic excess
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol

Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
g	-	Grams
h or hrs	-	Hours
HPLC	-	High pressure liquid chromatography
Hz	-	Hertz
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
IL(s)	-	Ionic Liquid(s)
LDA	-	Lithium diisopropylamide
LC-MS	-	Liquid chromatography mass spectrometry
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min(s)	-	Minute(s)
mL	-	Millilitre
mmol	-	Millimole
MP	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
MEM	-	Methoxyethoxymethyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NMR	-	Nuclear Magnetic Resonance
PCC	-	Pyridinium chlorochromate
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl

p-TSA	-	*par*a-Toluenesulfonic acid
SAD	-	Sharpless asymmetric dihydroxylation
SAE	-	Sharpless asymmetric Epoxidation
satd.	-	Saturated
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
*P*TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H-NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C-NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *e*V using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Büchi rotary evaporator below 40 °C unless otherwise mentioned.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- Numbering of schemes, Figures, Tables and compounds have been done indepently in each chapter.
- The numbering of schemes and compounds in the thesis abstract is different from the individual chapters.

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Title of the thesis	**"Novel organic transformations for the thermal/sonochemical synthesis of important intermediates and biologically active molecules''**
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Date of registration	**April 05, 2004.**

ABSTRACT

The thesis entitled **"Novel organic transformations for the thermal/sonochemical synthesis of important intermediates and biologically active molecules"** is divided into three chapters.

Chapter 1: The first chapter describes the synthesis and characterization of various imidazolium based ionic liquids which are useful in several important organic transformations.

Chapter 2: The second chapter describes the acylation of alcohols, the synthesis of biologically active compounds such as xanthenes, acridines, benzo[b]pyrans and Suzuki/Suzuki-Miyaura coupling reactions.

Chapter 3: Third chapter is divided into three sections; Section-A deals with a brief introduction of Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation. Section-B and Section-C describe the stereoselective synthesis of Pachastrissamine (Jaspine-B) and (*S*)-Dapoxetine respectively.

Chapter I: ***Synthesis and Characterization of ionic liquids***

This chapter is divided into three sections. Section-A deals with a brief introduction and physiochemical properties of ionic liquids. Section-B deals with a brief introduction of sonochemistry in organic synthesis. Section-C deals with the synthesis and characterization of new ionic liquids.

Section A: ***Ionic liquid (IL) - a brief introduction and vis-à-vis green chemistry perspectives***

The past few years has witnessed the evolution of a new era in chemical research by the entry of ionic liquids as potential 'Green Designer Solvents' as novel replacements for volatile organic compounds traditionally used as industrial solvents. Ionic liquids are systems consisting of salts that are liquid at ambient conditions. A brief history of ionic liquids and their emergence as environmentally benign solvents have been discussed in this section. Various types of ILs and their nomenclature are covered. The unique property of this ionic species, which gives liquid character to it, has been discussed in detail. A wide variety of reactions performed in ionic liquids have been summarized.

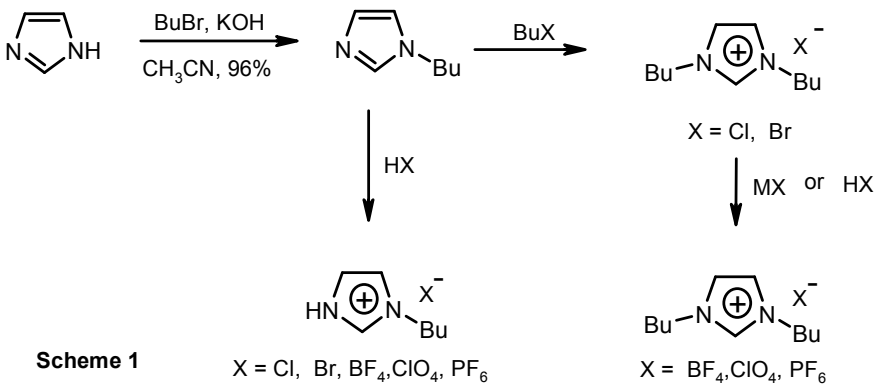
Section B: ***Introduction to Sonochemistry***

Application of ultrasound to chemical transformations may be termed as Sonochemistry. Sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse as mentioned earlier.[14] Ultrasound as non-thermal energy transfer source is well known to enhance reaction rates/yields/selectivity in organic synthesis and has found wide-spread applications in synthetic organic chemistry.

When ultrasonic energy at high power is applied to a liquid, a phenomenon called 'cavitation' occurs. Cavitation is the formation, growth and collapse of bubbles in the liquid.[1,2] This results in the 'cold boiling' of liquid. The role of ultrasound in homogeneous and heterogeneous chemistry has been well documented in the literature.

Section C: ***Synthesis and characterization of novel ILs based on 1-n-butyl and 1,3-di-n-butyl imidazolium salts***

A series of N,N-dialkyl substituted imidazolium and 1-alkylimidazolium based ILs have been synthesized (**Scheme 1**).



Scheme 1

The ionic liquids synthesized were fully characterized by properties such as viscosity, density, polarity and as well as spectral and elemental analyses. The variation of both density and viscosity has been correlated to the change in the basicity of the anion. Melting and decomposition temperatures were measured using TG-DTA techniques. In mass spectra, all the ILs showed $[M\text{-}X]^+$ as the base peak and peaks corresponding to the respective molecular ion were not observed.

Chapter II: ***Acylation of alcohols, synthesis of xanthenes, acridines, benzo[b]pyrans and Suzuki/Suzuki-Miyaura coupling reactions***

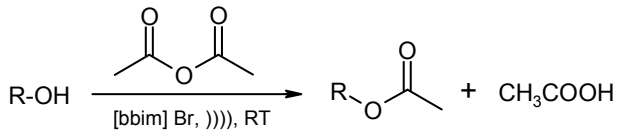
Acylation of alcohol is one of the important useful organic transformations. Kowledge of heterocyclic chemistry is useful in biosynthesis and in drug metabolism as well. There are a large number of synthetic heterocyclic compounds with other important applications and many are valuable intermediates in synthesis. Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. Biaryls are an important class of organic compounds useful as precursors to pharmaceuticals, polymers, materials, liquid crystals, and ligands. The Suzuki-Miyaura coupling, the palladium-catalyzed cross-coupling of Sp^2 hybridised halides, triflates, N_2BF_4, BF_3K, sulfonates with Sp^2 hybridized boronic acids or their esters, is one of the most important, and versatile tools for the synthesis of biaryls and liquid crystals. This chapter is subdivided into five sections.

Section A: ***Acylation of alcohols***

The acetylation of alcohols is one of the most frequently and extensively used transformations in organic synthesis as well as in carbohydrate chemistry as it provides an

efficient and inexpensive means for protecting hydroxyl groups in a multi-step synthetic process. The standard *O*-acetylation reaction uses acetic anhydride as the primary reagent and a wide range of solvents and catalysts. A variety of catalysts ranging from bases such as 4-(dimethylamino)pyridine (DMAP), Lewis acids such as $ZnCl_2$, Zeolites such as H-beta, and enzymes such as Lipases have been reported.

This section deals with the acylaiton of a variety of alcohols including aryl-alkanols, alkanols, cinnamyl alcohol, menthol, and carbohydrates were subjected to the *O*-acetylation with acetic anhydride in the IL, 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) as the solvent at ambient temperature (30 ^{o}C) under ultrasonic irradiation (Scheme **2**).



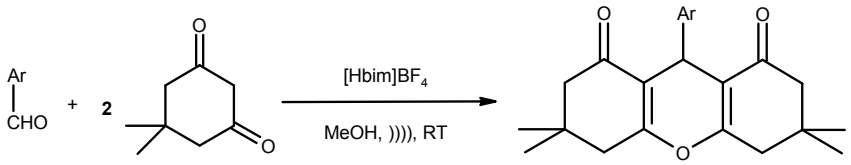
Scheme **2**

The liquid esters could be easily isolated from the reaction mixture either by fractional distillation leaving behind the non-volatile IL pure enough for reuse in several recycles. The solid esters *viz*., esters of D-Glucose and D-Mannitol were selectively extracted into 20% petroleum ether in ethyl acetate leaving behind the IL as an immiscible layer. The boiling points and the melting points of the products are compared with the reported literature values.

Section B: *Synthesis of 1,8-dioxo-octahydroxanthene derivatives*

Xanthene derivatives are parent compounds of a large number of naturally occurring, as well as synthetic derivatives, and occupy a prominent position in medicinal chemistry. In particularly, xanthene-diones constitute a structural unit in a number of natural products, and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring.

Due to the above mentioned importance of these compounds, we have developed a simple, efficient and eco-friendly method for the synthesis of xanthenes. This novel methodology involves the condensation reaction of an aldehyde and diketone which is efficiently promoted by the Ionic liquid, [Hbim]BF_4 at ambient temperature under ultrasonic irradiation to afford the corresponding xanthene derivatives in good to excellent yields (75-95%) as shown in Scheme **3**.



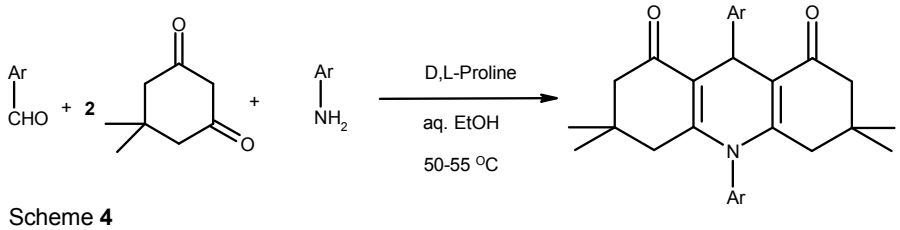
Scheme **3**

The products can be easily isolated by simple work up procedures such as dilution with waster and filtration of the precipitated product. All the known and new products were well characterized by melting point, IR, ^{1}H-NMR and LC-MS analyses. For the known compounds, the values were in agreement with those reported in literature.

Section C: ***Proline catalyzed efficient synthesis of 1,8-dioxodecahydroacridines***

1,8-Dioxo-9-aryl-10-(4-methylphenyl)-decahydroacridines and their derivatives are poly-functionalized 1,4-dihydropyridine derivatives. These compounds exert their spasmolytic and vasodilating activities through their ability to inhibit movement of calcium through certain membrane channels, thus interfering with the calcium dependent processes associated with the contraction of vascular smooth muscle.

We thought that there is scope for further innovation towards mild reaction conditions, short reaction times, increase in variation of the substituents in the components and better yields in the synthesis of 1,8-dioxo-decahydroacridines which can possibly be achieved by choosing Proline as a catalyst for this multi-component reaction (MCR). This method offers the advantages of proceeding in neutral and mild conditions, giving high to very good isolated yields (80-91%) of acridines with easy work-up procedure (**Scheme 4**).



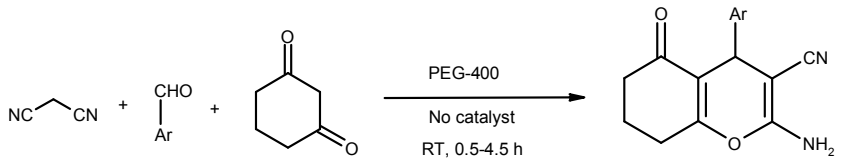
Scheme **4**

All the known and new compounds were well characterized by melting point, IR, ^{1}H-NMR, ^{13}C-NMR and elemental analyses.

Section D: ***PEG-400 promoted one-pot synthesis of tetrahydrobenzo[b]pyrans.***

Poly-functionalized benzo[b]pyrans constitute the structural unit of a series of natural products and because of the inherent reactivity of the inbuilt pyran ring are versatile synthons. They are an important class of compounds, which has received considerable attention in recent years due to their wide range of biological and pharmacological activities such as anti-coagulant, spasmolytic, diuretic, anti-ancaphylactin and anticancer properties. A number of 2-amino-4*H*-benzo[b]pyrans are useful as photoactive materials.

Thus, new routes utilizing a MCR protocol, for the synthesis of these molecules can attract considerable attention in the search of methods for rapid entry to these heterocycles. Consequently, we thought that there is scope for further innovation towards milder reaction conditions, short reaction time and better yields in the synthesis of benzo[b]pyrans which can possibly be achieved by choosing PEG-400 for this multi-component reaction (Scheme **5**).



Scheme **5**

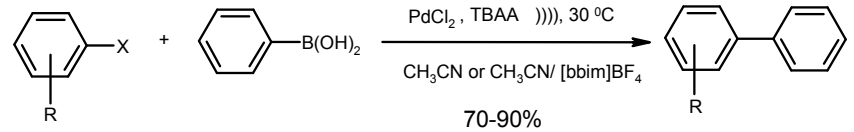
PEG-400 promoted efficient one-pot three component condensation reaction of an aldehyde, malononitrile and a diketone under mild and neutral conditions has been achieved to afford the corresponding benzo[b]pyrans in good isolated yields (77-85%).

Section E: ***Suzuki/Suzuki-Miyaura coupling reactions***

The Palladium-catalyzed cross-coupling reaction of aryl halides and phenylboronic acids has been shown to a powerful and frequently employed method for the formation of carbon-carbon bonds. Biaryls are ubiquitous compounds, their unit being present in a variety of natural products and bioactive molecules as well as in many functional advanced materials; there is wide interest in the development of new synthetic methodologies in spite of the many methods already available.

We have developed a new methodology for a ligand- and amine- free Suzuki reaction at ambient temperature under ultrasound irradiation in a molecular solvent such as acetonitrile as well as a RTIL, 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4), in excellent chemo-selectivity with considerably enhanced reaction rates through the

formation of stable and crystalline clusters of zero-valent Pd nano-particles (Scheme **6**). Under identical silent stirred conditions, in the absence of ultrasound no reaction was observed even after several hours of sonication (6 h).



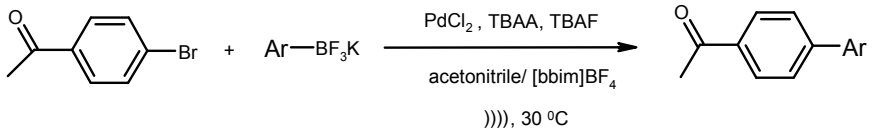
R = H, CH_3,CHO,$COCH_3$,COOH, Cl, NO_2

x = I, Br, Cl

Scheme **6**

All synthesized compounds were well characterized by melting point, ^{1}H-NMR, ^{13}C-NMR and elemental analyses. The formation of Pd(0) nanoparticles is confirmed by TEM (Transmission electron microscopy) analysis.

Aryltrifluoroborates are equally stable compounds as arylboronic acids. Hence, we have also developed a new strategy for the coupling reaction of haloarenes with aryltrifluoroborates (Scheme **7**).



Ar = Aryl

Scheme **7**

Chapter III: ***Asymmetric Synthesis of Jaspine-B and (S)-Dapoxetine***

This chapter is further divided into three sections

Section A: A Brief Introduction to Sharpless Asymmetric dihydroxylation (SAD) and Sharpless Asymmetric Epoxidation (SAE)

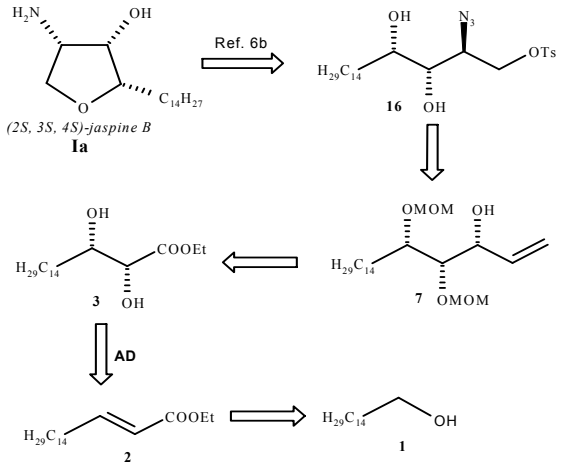
Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetry inducing agents. Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. The Sharpless Asymmetric Dihydroxylation (SAD) reaction is one such reaction developed in early 1990. Likewise, The Sharpless Asymmetric Epoxidation (SAE) reaction is also one of the powerful methods to generate epoxy alcohols in high yields with very high enantiomeric excess. In our synthetic endeavors we have employed SAD reaction towards the synthesis Jaspine B

and similarly we have applied Sharpless Asymmetric Epoxidaiton for the synthesis of (*S*)-dapoxetine respectively.

Section B: ***Stereoselective synthesis of Jaspine-B***

Pachastrissamine **I**, a naturally occurring novel anhydrophytosphingosine derivative, has been isolated recently from the Okinawan marine sponge *Pachastrissa* sp. Shortly thereafter, another research group reported the isolation of the same natural product from a different marine sponge, *Jaspis* sp. and named it as jaspine B. The jaspine B hydrochloride displayed remarkable bioactivity (IC50 = 0.24 μM) against the A549 human lung carcinoma cell line using the ATPlite assay and represented the most potent anticancer agent on this cell line yet isolated from the *Jaspis* genus. This Section deals with stereoselective synthesis of Pachastrissamine (jaspine B), starting from commercially available 1-pentadecanol. Sharpless asymmetric dihydroxylation and a chelation-controlled vinyl Grignard reactions are the key steps in this synthetic strategy.

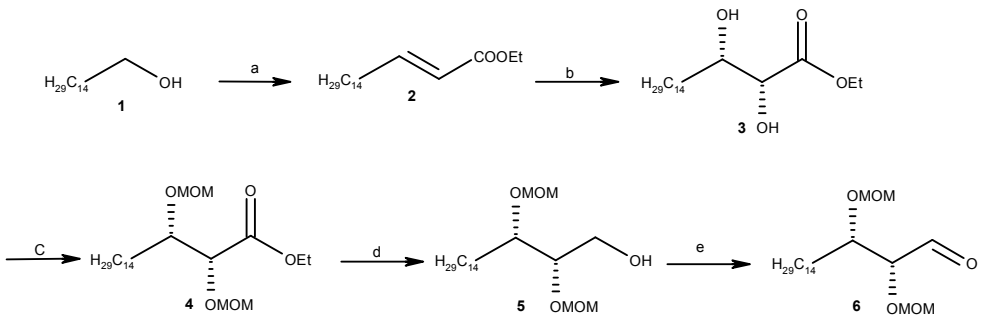
Our synthetic strategy for the synthesis of Pachastrissamine (Jaspine B) is shown below (Scheme **8**).



Scheme **8**. Retrosynthetic approach for (2*S*,3*S*,4*S*)-jaspine B (**I**).

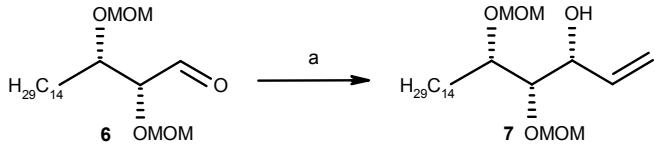
We envisioned that the azido-diol **16** could be prepared from the terminal olefin **7,** which in turn could be prepared from the diol **3** after suitable protection *via* a chelation controlled vinyl Grignard reaction. The diol **3** itself could be prepared by Sharpless asymmetric dihydroxylation of α,β-unsaturated olefin ester **2** which in turn could be obtained from the

commercially available 1-pentadecanol **1**. The intermediate **6** was synthesized from the achiral starting material **1** using the strategy shown in Scheme **9**.



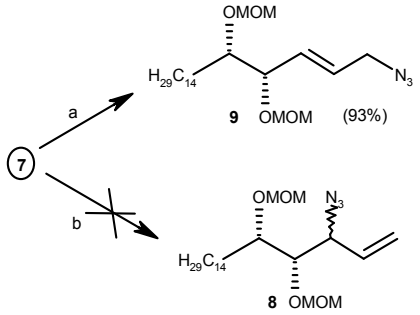
Scheme **9**. Synthesis of intermediate **6** (Sharpless dihydroxylation method as a key step). Reagents and conditions: (a) (i) PCC, dry DCM, 0 ^{o}C-RT, 3h; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 92%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3[Fe(CN)]_6$, $MeSO_2NH_2$, OsO_4 (0.1 M sol. in toluene), t-BuOH/H_2O (1:1), 0 ^{o}C, 24 h, 88%; (c) MOMCl, dry DCM, DIPEA, 0 ^{o}C, over night, 96% ; (d) DIBAL-H, dry DCM, –10 ^{o}C, 1 h, 96%. (e) IBX, EtOAc, reflux, 4 h.

To create the third stereogenic center with the required stereochemistry, a chelation controlled vinyl Grignard reaction was performed (Scheme **10**).



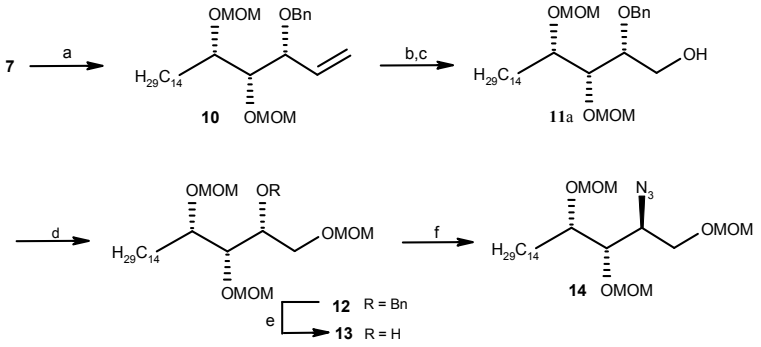
Scheme **10**. Chelation controlled vinyl Grignard reaction: (a) vinyl magnesium bromide, $MgBr_2.OEt_2$, dry THF, –78 ^{o}C, 45 min, 89%.

The allylic alcohol **7** was mesylated using MsCl in the presence of Et_3N and subsequently a nucelophilic displacement with sodium azide furnished only the terminal azide **9** in 93% yield. Also, the one-pot azide formation conducted in DMF medium under the standard conditions (DMF: CCl_4 (7:1), TPP, NaN_3, 75 ^{o}C, 12 h) resulted in no reaction (96% of **7** was recovered back from the reaction medium, Scheme **11**.



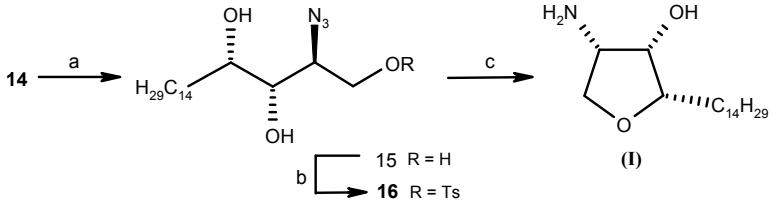
Scheme **11**. *Reagents and conditions*: (a) (i) MsCl, dry CH_2Cl_2, Et_3N, 0 ^{o}C, 3 h; (ii) NaN_3, dry DMF, 65 ^{o}C, 12 h, 93% for two steps. (b) Dry DMF, CCl_4, PPh_3, NaN_3, 75 ^{o}C, 12 h.

High diastereomeric excess (de = >95%) is observed in this case (judged by ^{1}H and ^{13}C-NMR spectral analysis). The allyl alcohol **7** was converted in to azide intermediate **14** using the following synthetic strategy (Scheme **12**).



Scheme **12**. Synthesis of intermediate **14**. Reagents and conditions: (a) BnBr, NaH, THF, 0 ^{o}C, 87%; (b) (i) OsO4 (0.1 M sol. in toluene), t-BuOH/THF/H_2O (3:2:1), NMO, over night; (ii) $NaIO_4$, $NaHCO_3$, water, RT, 3 h; (c) $NaBH_4$, MeOH, 0 ^{o}C, 1 h, 82% from 10; (d) MOMCl, dry DCM, DIPEA, 0 ^{o}C, over night, 94%; (e) 5% Pd(C), H_2, MeOH, RT, overnight, 96% ; (f) (i) TsCl, dry CH_2Cl_2, Et_3N, DMAP (cat.), 0 ^{o}C, 3 h; (ii) NaN_3, dry DMF, 95 ^{o}C, 14 h, 80%.

Deprotection of the MOM groups followed by tosylation provided mono-tosylated compound **16**. The compound **16** was subjected to cyclization and subsequent reduction to furnish jaspine B (**I**) with all desired stereo-centers (88% yield from 1**6**, Scheme **13**).

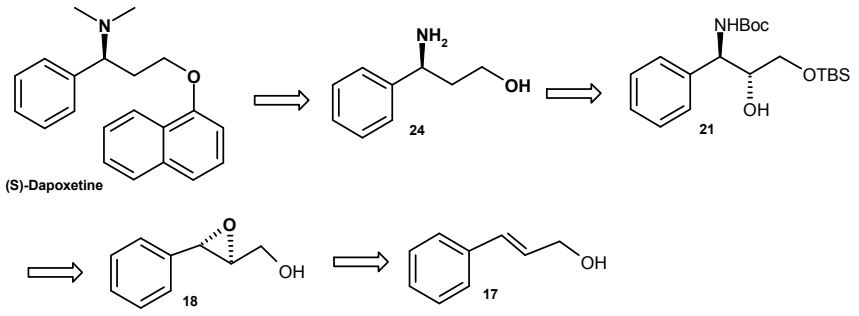


Scheme 13. Synthesis of (2*S*,3*S*,4*S*)-jaspine B (**I**): (a) aq. HCl, THF, 0-RT, 10 h; (b) *p*-Tosyl chloride, CH_2Cl_2, DMAP, 0 ^{o}C, 2 h, 85% from **14**; (c) (i) K_2CO_3, Methanol, 10 ^{o}C- RT; (ii) H_2/Pd-C, DCM: Methanol (1:1), RT, 10 h, 88% from **16**.

Section C: Stereoselective synthesis of (S)-Dapoxetine

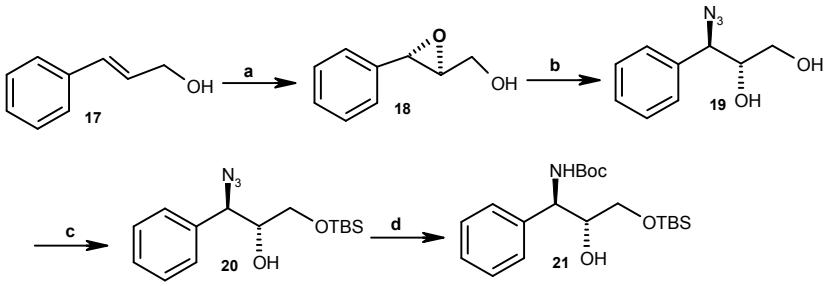
Depression is a common psychiatric disorder and one of the most frequent illnesses in the world-affecting people of all gender, ages, and backgrounds. Phosphodiesterase 5 Inhibitors (PDE5I) are the preferred first line treatment by most patients. Currently three drugs such as Sildenafil (viagra), tadalafil (cialis) and vardenafil (levitra) are available in the market. A newer serotonin reuptake inhibitor, dapoxetine, is now in the pipeline. It has

faster onset of action and shorter half time and may be a better on-demand drug with less side effects. Moreover, (*S*)-Dapoxetine is currently being tested as a treatment for premature ejaculation in men, 23-30% of men are suffering worldwide due to this problem. Very few methods are currently available for the synthesis of this important and potent pharmacologically active (S)-dapoxetine. Our retro synthetic route for the synthesis of (S)-dapoxetine is shown in the Scheme **14**.



Scheme **14**

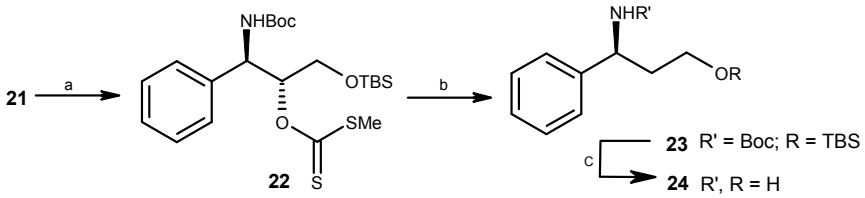
It is envisaged that amino-alcohol **24** could be synthesized from the secondary alcohol **21**, which in turn could be easily prepared from the epoxide **18**. The epoxide **18** could be prepared from Cinnamyl alcohol **17** by employing Sharpless asymmetric epoxidation method. The exact synthetic route followed in the present work is shown in the Scheme **15** and **16**. Sharpless asymmetric epoxidation is the key step of this synthetic strategy.



Scheme **15**. Synthesis of intermediate **21**. ***Reagents and conditions***: (a). (+)-Diethyl tartrate, $Ti(O^{i}pr)_4$, *t*-BuHP, Sharpless asymmetric epoxidation conditions; (b). NaN_3, MeOH, H_2O, NH_4Cl, 65 ^{o}C, 5h; (c). TBSCl, imidazole, DCM, RT, over night; (d). Pd-C/H_2, $(Boc)_2O$, EtOAc.

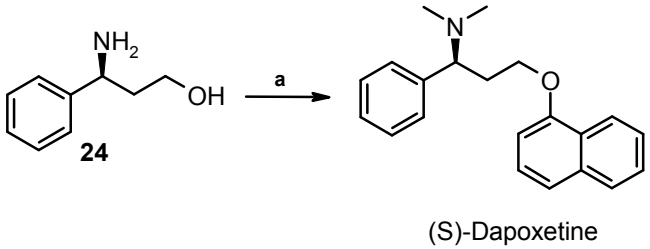
The intermediate **21** was converted into the xanthate derivative **22**, which furtherly subjected to deoxygenation under the Barton-McCombie protocol using n-Bu_3SnH and a catalytic amount of AIBN in toluene under reflux conditions afforded the protected amino

alcohol **23**, which was further treated with AcOH in THF to give the amino alcohol **24** (Scheme **16**).



Scheme **16**. Synthesis of intermediate **24**. Reagents and conditions: (a) MeI, CS_2, NaH, THF, 0 ^oC-RT, over night, 83%; (b) n-Bu_3SnH, AIBN, toluene, reflux, 6 h; (c) TFA, DCM, 0 ^oC-RT, 5 h, 80% (for two steps).

The amino alcohol **24** was converted in to (S)-Dapoxetine by employing the literature procedure (Scheme **17**).



Scheme **17**. **Reagents and conditions**: (a) Ref.: Oliver Torre *et al*, Tetrahedron: *Asymmetry*, **2006**, *17*, 860.

Chapter I

Section A

Introduction to ionic liquids vis-á-vis green chemistry perspectives

1.1.0 Introduction

The growing awareness of environmental issues has focused attention on the need for greener and more sustainable technologies in the chemical industry.[1] The number of environmental laws and regulations has increased over the years, and more specific regulations have been set in order to provide a safer environment. The U.S. Environmental Protection Agency (EPA) has almost twenty different programmes for protecting the environment.[2] Thus one of the most important and challenging area of research in chemistry is the development of green and clean technologies replacing conventional hazardous and volatile organic solvents (VOCs) by alternative non-volatile, non-flammable, non-toxic, safe and environmentally friendly solvents. In this context, much attention has been devoted recently to develop more and more environmentally benign process by using so-called green or neoteric solvents under the concept of green chemistry, which has emerged as an important area of chemistry and has achieved outstanding progress towards the development of green reaction processes.[3]

A green solvent must ideally have negligible vapour pressure, high boiling point, be non-toxic, have high capacity to dissolve wide range of organic, inorganic and organometallic compounds, it should be chemically and physically stable, probably recyclable, inexpensive and eventually easy to handle. In addition to these, solvents that allow more selective and rapid transformations will have a significant impact. Therefore, many attempts have been made to substitute conventional organic solvents with novel alternative reaction media which include: supercritical fluids, perfluorinated solvents, low melting polymers, water and more particularly ionic liquids.

1.1.1 Alternative solvents in organic synthesis

1.1.1.1 Supercritical fluids

A supercritical fluid is any substance at a temperature and pressure above its thermodynamic critical point. It can diffuse through solids like a gas, and dissolve materials like a liquid. Additionally, close to the critical point, small changes in pressure or temperature result in large changes in density, allowing many properties to be "tuned". Supercritical fluids are suitable as a substitute for organic solvents in a range of industrial and laboratory processes. Carbon dioxide and water are the most commonly used

supercritical fluids ($scCO_2$). The critical point of CO_2 is at 73 atm. and 31.1 ºC. These conditions could be easily achieved in the laboratory.

The advantages related to the use of $scCO_2$ are numerous and clearly addressed in a recent article.[4] $ScCO_2$ is non-flammable and less toxic than most organic solvents. It is relatively inert towards reactive compounds and is a natural, unregulated solvent, with high availability; it can be easily removed by depressurization, which renders it an easy separation from the products of a reaction. Furthermore, the selectivity of a reaction can be dramatically changed when conducted in a supercritical fluid as compared to traditional organic solvents.

1.1.1.2 Perfluorinated (fluorous) solvents

Fluorous (perfluorinated) solvents as perfluoroalkenes, perfluoroalkyl ethers and perfluoroalkylamines are generally chemically benign and environmentally-friendly for being non-toxic (unlike the freons), non-flammable, thermally stable, recyclable, and for their high ability to dissolve oxygen gas, which is an advantage used in medical technology. Due to their extremely non-polar characteristics they are not suitable for most organic reactions and tend to be used in conjunction with a traditional organic solvent (or some sort of immiscible solvent) to form a biphasic system.[5]

1.1.1.3 Poly (ethylene glycol)-PEG

Polyethylene glycol (PEG) is the most commercially important polyether. Poly (ethylene glycol) is the linear polymer formed from the polymerization of ethylene oxide. PEG is liquid at room temperature, depending on their molecular weights. PEG usually indicates the polyether of molecular weight less than 20000 (g mol^{-1}) and is known to be inexpensive, thermally stable, recoverable, biologically compatible and non-toxic.[6] Furthermore, PEG and its mono-methylethers have a low vapor pressure, are nonflammable, present simple workup procedures and can be recycled. For these reasons PEG is considered to be an environmentally benign alternative to volatile solvents and a highly practical medium for organic reactions. Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter its properties can not be easily tuned. For instance, they do not possess Lewis/Bronsted acidity to promote organic transformations.

PEG 400 (Polyethylene Glycol 400) is a low molecular weight grade of Polyethylene glycol. It is a clear, colorless, viscous liquid. Due to its low toxicity, PEG 400 is widely used in a variety of pharmaceutical formulations.

1.1.1.4 Water

Not only water is non-toxic and readily available at low cost, it is also non-flammable and environmentally benign, providing opportunities for clean processing and pollution prevention. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., Organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of Breslow[7] and Grieco[8] in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results. For instance, the rates and stereo-selectivities of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. The use of organic co-solvents or surfactants helps to increase the solubility of non-polar reactants in water by disrupting the strong H-bonding network of pure water.[9]

The chemistry community has been mobilized to develop new chemistries that are less hazardous to human health and the environment. One of these approaches is the green chemistry movement, which is based on 12 principles developed by Anastas to prevent pollution.[3a] Green chemistry means nothing but is a way of thinking and doing things better and more efficiently.[3a] Despite all the environmental regulations and broader knowledge about environmental issues, the traditional way of thinking still hinders the application of green chemistry principles as the standard practice in the development of new industry.

1.1.2 Principles of green chemistry:[3a]

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible, and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient pressure and temperature.
7. Raw material for feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and they break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time in process monitoring and control prior to formation of hazardous substances.
12. Substances and the form of substances used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

The fifth principle concerns the use of auxiliary substances in order to reduce or eliminate solvent waste in the chemical industry.[2] Because solvents are often necessary in chemical reactions, alternative solvents have been developed. The ideal solvent should have very low volatility, and it should be chemically and physically stable, recyclable and easy to handle. One such candidate is an ionic liquid (IL).

1.1.3 Ionic Liquids (ILs)

Unlike volatile organic compounds, ionic liquids have a low vapour pressure and they do not evaporate easily. An ionic liquid (IL) is a liquid containing only ions, but it is different from the classic definition of a molten salt.[10] More recently melting point criterion has been proposed to distinguish between molten salts and ionic liquids. Molten salts are

usually defined as a highly-melting, highly viscous and highly corrosive liquid medium, while ionic liquids are defined as pure compounds, consisting only of cations and anions (i.e., salts), which melts at or below 100 ^{o}C and has lower viscocity.[11] In few cases ionic liquids are free-flowing liquid at room temperature, in such case they are regarded as room temperature ionic liquids (RTILs). Most characteristics feature of ionic liquids which is not included in definition of ionic liquid is that, usually they are composed of a bulky organic cation with low degree of symmetry and bulky inorganic/organic anion. Although estimates vary, there is no doubt that the number of combinations of anions and cations that can give rise to potential ILs is vast.[12] The high possibility for synthetic variations has led to ILs being described as 'designer solvents'.[13]

Since it is not possible to make every combination of ions and measure their properties (the number is >1014), in order to be able to exploit their potential it is necessary to establish the physico-chemical properties of the already synthesized ILs and the correlation between these and molecular structure.[12]

1.1.3.1 Brief History of ILs

The earliest discovery of an ionic liquid can be dated to the middle of the nineteenth century, when some "red oil" was observed in a Friedel-Crafts reaction.[14] A few decades later, in 1914, the first room-temperature IL ethylammonium nitrate,[15] $[EtNH_3][NO_3]$, was synthesized. This salt is liquid at room temperature but usually contains a small amount of water (200-600 ppm). In 1951 $AlCl_3$-based ionic liquids were developed by Hurley and Wier[16] at Rice Institute in Texas as a bath solution for electroplating aluminium. In 1963 the U.S. Air Force Academy became interested in that work and developed it further with the aim of finding new electrolytes for batteries. As early as 1967, a publication by Swain *et al* described the use of tetra-*n*-hexylammonium benzoate as a solvent for kinetic and electrochemical investigations.[17] Even though this liquid salt was a hemi-hydrate at room temperature, this research work had a pioneering significance because it already contained a quantitative determination of the ionization strength of the ionic medium. In 1970s Osteryoung[18] and Wilkes[19] succeeded in preparing room-temperature liquid chloroaluminate melts. In the 1980s Hussey and Seddon[20-22] started to use these alkylpyridinium tetrahalidoaluminate, $[Rpy][AlCl_3X]$, ionic liquids as solvents in transition metal complex studies. It is because of Seddon's work that ionic liquids became more

familiar to a broad public. The first publications in which ionic liquids were described as new reaction media and catalysts for organic synthesis appeared at the end of the 1980s. Acidic ionic liquids with chloroaluminate ions proved to be effective Friedel-Crafts catalysts,[23] phosphonium halide melts were used successfully in nucleophilic aromatic substitution reactions.[24] The use of ionic liquids as solvents for homogeneous transition metal catalysts was described for the first time in 1990 by Chauvin *et al*. Chauvin's group dissolved nickel catalysts in weakly acidic chloroaluminate melts and investigated the resulting ionic catalyst solutions for the dimerization of propene.[25] Wilkes *et al.* used also weakly acidic chloroaluminate melts and studied therein the ethylene polymerization with Ziegler-Natta catalysts.[26]

The concept of ionic liquids received a substantial boost by the work of Wilkes's group when they described in 1992 the synthesis of systems with significantly enhanced stability against hydrolysis, for example low melting tetrafluoroborate melts.[27a] In contrast to chloroaluminate ionic liquids, these systems offer high tolerance versus functional groups which opens up a much larger range of applications especially for transition metal catalysis. Ionic liquids with tetrafluoroborate ions have been successfully used, for example, in the rhodium-catalyzed hydroformylation of olefins.[28] Based on Wilkes's work, it became clearly apparent that ionic liquids were by no means limited to chloroaluminate melts, quite to the contrary, a whole range of cation/anion combinations can form low-melting salts.

The most recent publications are concerned with the synthesis of new ionic liquids,[29] with the systematic investigation of their physical and chemical properties,[30] and with further applications as solvents and catalysts.[31] Two excellent reviews by Welton[32] and by Seddon and Holbrey[33] have been already published describing in special detail the use of chloroaluminate ionic liquids in synthetic and catalytic applications. Electrochemical[34] and complex chemistry[35] investigations in ionic liquids have already been reviewed too. The review article published by Keim *et al*[11] describes the synthesis, properties, and potential of ionic liquids with respect to their application as solvent in transition metal catalysis in "non-chloroaluminate" systems.

In general, ionic liquids are equally or more polar in nature when compared to organic solvents. Their water miscibility depends on their cation and anion composition. In

addition, many catalysts are miscible with ILs and do not leach from them. Hence, ILs are ideal solvents for two-phase catalysis. When an IL contains a catalyst and a product forms its own layer above the IL phase, separation of the product is easy and recycling of the IL and the catalyst is possible. In case of non-volatile IL, volatile products could be distilled or products could be separated by precipitation with a suitable solvent, that is miscible with the IL, but not with the product. After precipitation the applied solvent can be distilled from the non-volatile IL that can be recycled for a next reaction.

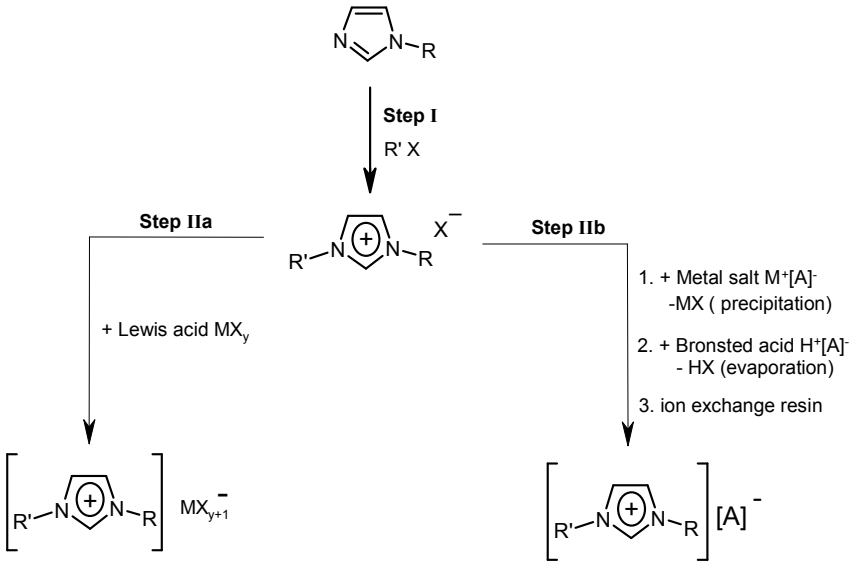
1.1.3.2 Lewis acid-based ionic liquids

In general, Lewis acid-based ionic liquids are prepared by mixing appropriate amounts of a quaternary halide salt and a Lewis acid, and no solvent is needed. The reaction is exothermic, and hence the build-up of excess local heat may result in decomposition and discoloration of the ionic liquid. Since the reagents and the product are water-sensitive, the reaction should be carried out in a dry box. The use of $AlCl_3$ as a Lewis acid in the preparation of an ionic liquid is mostly studied, but also other Lewis acids such as $EtAlCl_2$,[36] BCl_3,[37] CuCl,[38] $SnCl_2$ & $GeCl_2$[39] and $InCl_3$[40]can be used.

1.1.3.3 Synthesis of Ionic Liquids

The synthesis of ionic liquids normally consists of two major steps. In the first step, desired cation has to be generated, usually by direct alkylation/quaternization of a nitrogen or phosphorus atom. In the second step, the anion resulting from the alkylation reaction can be exchanged for a different one by metathesis reaction or by direct combination with Lewis acid. Since imidazolium based ILs have reached some kind of standard in the IL community, because of weak interaction between anion and cations and good thermal stability as compared to other ammonium salts, the general and detailed synthesis of imidazolium-based ionic liquids is represented in Scheme **1** and discussed further.

Imidazolium salts with different anions are obtained by the quaternization reaction depending upon the alkylating reagent (step **I**). In case where it is not possible to obtain imidazolium salt with required anion then there further steps IIa and IIb (Scheme **1**) are required.



Scheme 1. Synthetic pathways for the preparation of ILs exemplified as imidazolium salt[11]

Two different paths are possible to replace anion formed resulting from initial quaternization step. First is the imidazolium salts directly treated with Lewis acids, this leads to the formation of first generation ionic liquids of the type $[RR'im][MX_{y+1}]$ (step IIa Scheme **1**). Alternatively it is possible to exchange anion with desired anion by addition of metal salt $M^+[A]^-$ (with the precipitation of M^+X^-), by displacement of anion by a strong acid $H^+[A]^-$ (with evaporation of HX) or by passing over ion exchange resin (step IIb, Scheme **1**).

1.1.3.4 Cations and anions of ILs

Commonly used cations are large and unsymmetric, e.g., derivatives of ammonium, sulfonium, phosphonium, imidazolium, pyridinium, pyrrolidinium, and quinazolinium ions (Fig. **1**). Typical inorganic anions are e.g. halides, tetrachloroaluminate, hexafluorophosphate, tetrafluoroborate and bis(trifluoromethylsulfonyl)imide and typical organic anions are trifluoroacetate (triflate), alkylsulfonate, *p*-toluenesulfonate (tosylate) and alkylsulfate (Fig. **2**).

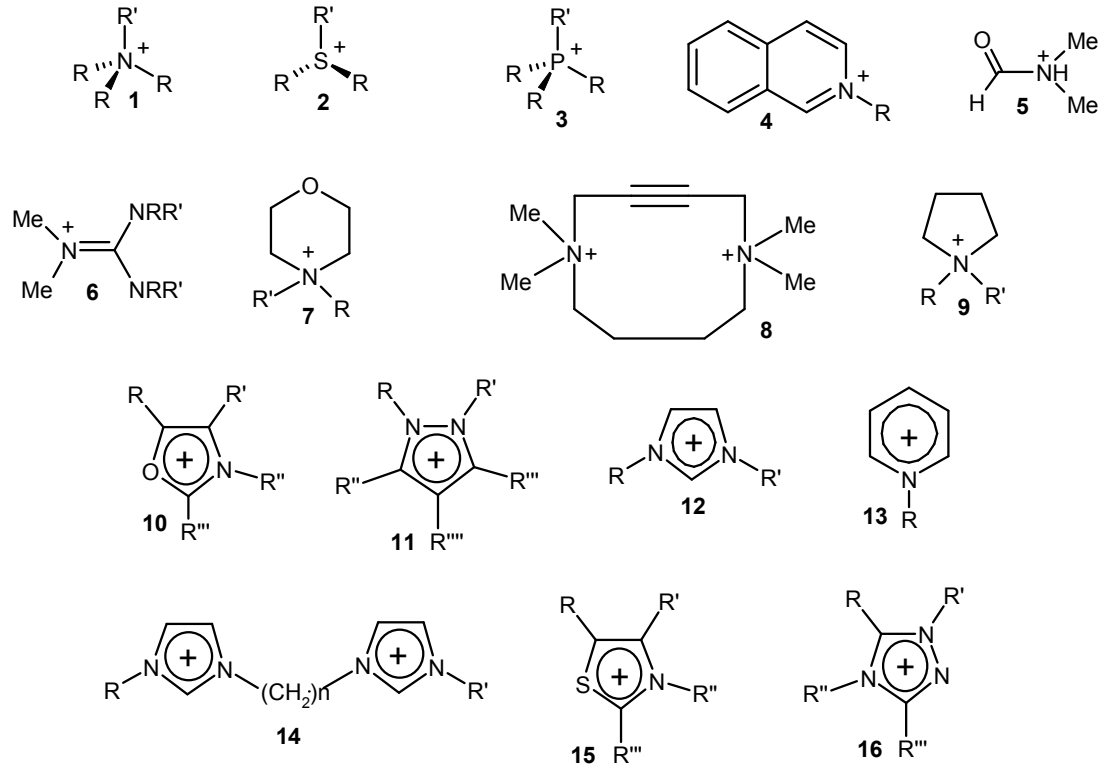


Fig. 1. Some commonly used cations

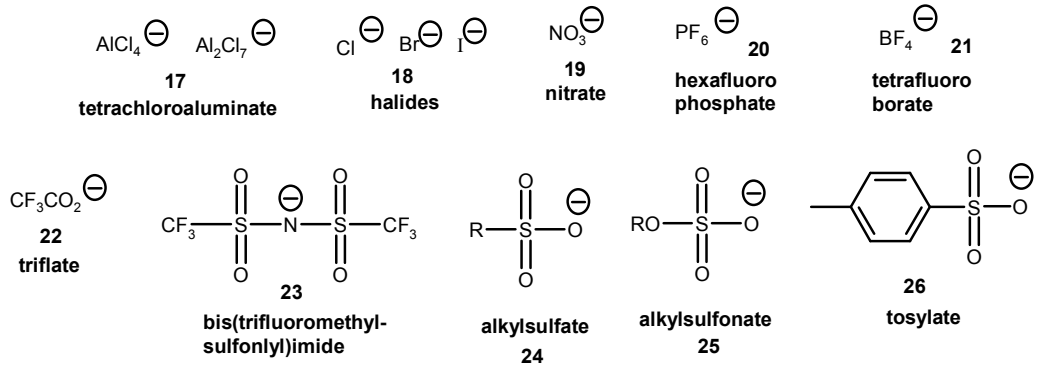


Fig. 2. Very commonly used anions

Recently, some more new anions are also reported in the literature.[41] In the near future, list of cations and anions will be extended to a nearly limitless number. Various combinations of cations and anions provide finely designed ionic liquids for different applications.

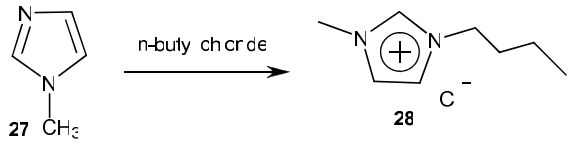
1.1.3.5 Quality and Characterization of ILs

The purity of an ionic liquid is of paramount importance, since impurities influence its chemical and physical properties.[42] Hence, special attention is to be paid for the characterization of the ionic liquids. The ionic liquids can be analyzed with NMR, MS

(ESI^+ and/or ESI^-) and elemental analysis. Their thermal stability may be determined with TGA in order to know their upper temperature limit. The determination of a liquid range of an ionic liquid is necessary in order to know a temperature range, where IL can be utilized. It is important to use purified starting materials in their preparation in order to get a pure ionic liquid. The main contaminants of ionic liquids are halides, water, organic compounds or inorganic salts. A colorimetric method has been recently developed to determine the level of unreacted alkylimidazole (<0.2 mol%) in the ionic liquid.[43] The application where an ionic liquid will be used determines the level of purity of the ionic liquid required.

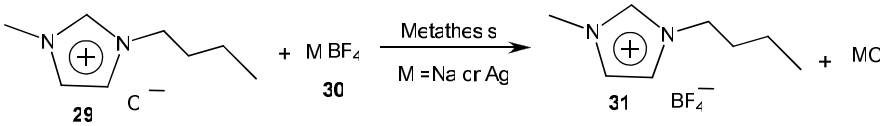
1.1.3.5.1 Halides, organic compounds and inorganic salts

Halides, organic compounds and inorganic salts present in a prepared IL are the result of unfinished reactions. For e.g., in the preparation of [C_4mim]Cl **28**, the possible impurities are unreacted organic starting compounds, *N*-methylimidazole **27** and *n*-butyl chloride (Scheme **2**).[44] Their presence can be detected quite easily by ^{1}H-NMR spectroscopy. Volatile compounds, such as butyl chloride in this reaction, are easily removed by distillation. *N*-methylimidazole has a high boiling point (196 ºC) and, therefore, its removal by extraction with a volatile solvent (diethyl ether, dichloromethane or ethyl acetate) is preferred. The remains of extraction solvents can be removed in a high vacuum. In the case that the prepared ionic liquid is a solid at room temperature, it can be crystallized from an organic solvent.



Scheme 2

When the metathesis reaction is done with $AgBF_4$, the ionic liquid contains lesser impurities than when $NaBF_4$ is used, but the drawback is that silver salts are very expensive to use in a large amount.



Scheme 3. Metathesis reaction of [C_4mim]Cl **29** to [C_4mim]BF_4 **31.**

1.1.3.6 Solubility in water

Miscibility with water depends on the nature of the ionic liquid. Some ionic liquids are totally soluble in water, while others are not miscible at all.[45] Most ionic liquids contain some water that might originate from its preparation or purification process. In addition, many ILs are hygroscopic. A large amount of water could be detected by ^{1}H-NMR spectroscopy and a small amount by using a Karl-Fisher titrator.[46] Water is removed from ionic liquids by heating at 60-80 ºC in a high vacuum for at least three hours, preferably overnight. Recently, it has been noticed that some ionic liquids have a tendency to decompose when heated in the presence of water. For example, ILs that contain hexafluorophosphate ions may form hydrogen fluoride when heated.[47] This could be detected through pH measurement directly from the ionic liquid or from aqueous washings. Hydrogen fluoride is toxic and consequently the use of hexafluorophosphate-based ionic liquids may be avoided. [48]

1.1.3.7 Color

Impurities sometimes affect the coloration of ionic liquids. The chemical nature of coloring impurities is not clear, but they are assumed to be oxidation products or thermal degradation products of starting materials.[42,49] Even if the amount of the impurity is so small that it cannot be detected by ^{1}H-NMR or CHN microanalysis it might have significance on the application IL is used. Colored impurities can be eliminated by using distilled reagents and a low reaction temperature. Especially amines very easily take on a yellowish color upon standing, but distillation normally removes the color. When the prepared IL is colored, it can be purified with activated charcoal followed by filtration through activated alumina or silica.[50]

1.1.4 Physicochemical properties of ILs

Physical properties such as melting point, boiling point, density and viscosity are related to the mechanics and engineering components associated with a process. For example, densities, viscosities and surface tensions will determine important parameters including rates of liquid-liquid phase separation, mass transfer, power requirements of mixing and pumping. Other physical properties, such as refractive index are related to certain chemical properties despite providing a bulk property description. Chemical properties such as the structuredness, polarity and relative hydrogen bonding, donating and accepting ability are

more obviously related to the molecular chemistry of their application.[51] Due to the obvious intermolecular interactions that these parameters measure, these chemical properties are believed to play a major role in determining solubilities, partition constants and reaction rates. Thus it is necessary to understand how the physico-chemical properties of ionic liquids are able to affect organic reactivity as well as how they depend upon their structural features. This will be illustrated on the basis of a few selected examples which are as follows:

1.1.4.1 Melting point

By definition, ionic liquids are the salts whose melting points are below 100 ^{o}C. Thus the melting point is the key criteria for the evaluation of an ionic liquid. Low melting point is an important reason that ILs have become popular as a medium in organic reactions and other chemical processes. Both cations and anions contribute to the low melting points of the ILs.

By the variation of the alkyl chain length in the cation, fine-tuning of the melting point can be achieved.[11,41] Longer the alkyl chain, lower is the melting point, but only up to a certain extent (rule of thumb for imidazolium cations: C_8 gives the lowest melting points).[41] Beyond that, prolongation of the alkyl chain raises the melting point again. In addition to this, a good distribution of charge in cation and weak intermolecular interaction such as weak hydrogen bonding are also responsible for the lowering of melting points of ILs.[11] Comparison of the melting points of different salts clearly illustrate that, cation size, symmetry, charge distribution and alkyl chain length affects the melting points of ILs (Table **1**).

Table 1 Melting points of various salts

Entry	Salt	M. P. ^{o}C
1	NaCl	803
2	KCl	772
3	[Mmim]Cl	125
4	[Emim]Cl	87
5	[Bmim]Cl	65
6	[NMe_4]Br	> 300
7	[NEt_4]Br	284
8	[NBu_4]Br	124-128
9	[$NHex_4$]Br	99-100
10	[$NOct_4$]Br	95-98

Besides the cation, the anion also influences the melting point. With a given cation, the choice of anion has a strong effect on the melting point (Table **2**).[11] Strongly co-ordinating and hydrophilic anions like the halides lead to high melting points, whereas weakly co-ordinating and hydrophobic anions result in low melting points. Also increase in size of the anion with same charge leads to a decrease in melting point.

Table 2 Influence of different anions on the melting point of imidazolium salts

Entry	Imidazolium salts	M. P. ^{o}C	Ref.
1	[Emim]Cl	87	19
2	[Emim]NO_2	55	27a
3	[Emim]NO_3	38	27a
4	[Emim]$AlCl_4$	7	27b
5	[Emim]BF_4	6[a]	30d
7	[Emim]CF_3SO_3	-9	29a
8	[Emim]CF_3CO_2	-14	29a

[a]Glass transition

1.1.4.2 Viscosity

Generally viscosity of ILs is higher than that of common molecular solvent or water and their viscosity ranges from 10-500 cP at room temperature, similar to those of oil. A high viscosity may produce a reduction in the rate of reactions and reduction in the diffusion rate of the redox species. Thus the recent efforts have been made to develop low viscous ILs.[52] The viscosity of ionic liquids is determined by van der Waals forces and hydrogen bonding. Electrostatic forces may also play an important role. Comparing viscosity of different ILs (based upon the imidazolium cation) shows that increase in length of the alkyl chain and fluorination in the cation/anion strongly influences the viscosity of ILs[45] (Table **3**). This is due to stronger van der Waals forces between cations leading to increase in the energy required for molecular motion. Also, the ability of anions to form hydrogen bonding has a pronounced effect on viscosity. The fluorinated anions such as BF_4^- and PF_6^- form viscous ionic liquids due to the formation of hydrogen bonding. In general, all ionic liquids show a significant decrease in viscosity as the temperature increases.[45]

Table 3 Influence of alkyl chain length, fluorination in anion and strength of hydrogen bonding on viscosity of different imidazolium based ILs

Entry	Ionic Liquid	Viscosity (cP)
1	[Emim]BF_4	43[a]
2	[Bmim]BF_4	91[a]
3	[Hexmim]BF_4	177[a]
4	[Bmim]CF_3SO_3	90[b]
5	[Bmim] [*n*-$C_4F_9SO_3$]	373[b]
6	[Bmim]CF_3CO_2	73[b]
7	[Bmim] [*n*-$C_3F_7CO_2$]	182[b]
8	[Bmim]PF_6	450[b]
9	[Bmim]Tf_2N	52[b]

[a]Measurements were done at 30 °C.
[b]Measurements were done at 25 °C.

As is evident from Table **3**, that viscosity increases with increasing alkyl chain length (Entry 1-3 Table **3**), also fluorination in anions causes increase in viscosity (Entry 4-7 Table **3**). Strength of hydrogen bonding decreases in the order $[PF_6]^-$ > $[BF_4]^-$ > $[NTf_2]^-$ which results in decrease in the viscosity (Entry 8, 2, 9 Table **3**).

1.1.4.3 Density

Generally ILs are denser than water with values ranging from 1 to 1.6 g cm^{-3}. Density is one of the most often measured properties of ILs, probably because nearly every application requires knowledge of the density. The molar mass of the anion, alkyl chain length and bulkiness in the cation significantly affects the overall density of ILs. Density of ILs decreases with increase in length of the alkyl chain in cation and increases with increase in molar mass of anion (Table **4**).[45]

Table 4. Densities of different ILs at 25 °C

Entry	Ionic Liquid	Density (g/mL)
1	[Bmim]Cl	1.08
2	[Hexmim]Cl	1.03
3	[Octmim]Cl	1.00
4	[Bmim]I	1.44
5	[Bmim]BF_4	1.12
6	[Bmim]PF_6	1.36
7	[Bmim]Tf_2N	1.43
8	[Bmim]CF_3CO_2	1.21
9	[Bmim]CF_3SO_3	1.29

The density of ionic liquids is also temperature dependent. In general, the density of ILs decreases linearly as the temperature increases.

1.1.4.4 Polarity of Ionic Liquids and Solvent properties

Solvent polarity[53,54] is the most commonly used criterion for solvent classification. Even when considering molecular solvents it is poorly understood and often confused. The simplest qualitative definition is that a polar solvent is one that will dissolve and stabilize dipolar or charged solutes. It is widely thought, though yet to be generally demonstrated, that under this definition, ionic liquids will be highly polar solvents. Further information regarding the recent developments in this context may be obtained from the review article published by Greaves *et al.*[55]

1.1.4.5. Conductivity

Ionic liquids have reasonably good ionic conductivities compared with those of organic solvents/electrolyte systems (up to ~10 mS cm^{-1}).[41] At elevated temperatures of e.g. 200 ^{o}C a conductivity of 0.1 Ω^{-1} cm^{-1} can be achieved for some systems. However, at room temperature their conductivities are usually lower than those of concentrated aqueous electrolytes. Based on the fact that ionic liquids are composed solely of ions, it would be expected that ionic liquids have high conductivities. This is not the case since the conductivity of any solution depends not only on the number of charge carriers but also on their mobility. The large constituent ions of ionic liquids reduce the ion mobility which, in turn, leads to lower conductivities. Furthermore, ion pair formation and/or ion aggregation lead to reduced conductivity. The conductivity of ionic liquids is inversely linked to their viscosity. Hence, ionic liquids of higher viscosity exhibit lower conductivity. Increasing the temperature increases conductivity and lowers viscosity.

1.1.4.6 Electrochemical window

The electrochemical window is an important property and plays a key role in using ionic liquids in electro-deposition of metals and semiconductors. By definition, the electrochemical window is the electrochemical potential range over which the electrolyte is neither reduced nor oxidized at an electrode. This value determines the electrochemical stability of solvents. As known, the electro-deposition of elements and compounds in water

is limited by its low electrochemical window of only about 1.2 V. On the contrary, ionic liquids have significantly larger electrochemical windows, e.g., 4.15 V for [Bmim]PF_6[56] and 4.10 V for [Bmim]BF_4[56] at a platinum electrode and 5.5 V for [BmPy]Tf_2N at a glassy carbon electrode.[57] In general, the wide electrochemical windows of ionic liquids have opened the door to electro-deposit metals and semiconductors at room temperature which were formerly obtained only from high temperature molten salts.

1.1.4.7. Stability of Ionic Liquids

Considering the different applications where ionic liquids can be used, it is essential to know about their stability. Stability can be evaluated in terms of thermal or chemical reactivity according to the temperatures and reaction conditions they withstand. The stability of ionic liquids also depends on their purity. Especially water and halide impurities will affect physical properties such as density, viscosity, melting point and degradation temperature. In reference to these, it can be concluded that impurities also affect chemical properties, and hence thermal stability and reactivity.

1.1.4.7.1. Thermal stability

The thermal stability of an ionic liquid is determined by the strength of the formed heteroatom-carbon or heteroatom-hydrogen bonds and the stability of the formed ion species. A *N-C* bond is stronger than a N-H bond and accordingly, the stability of ammonium cations decreases in the following order: quaternary>tertiary>secondary> primary.[58] The degradation temperature is measured by using thermo-gravimetric analysis (TGA) or differential thermal analysis. The reported degradation temperature values of a certain ionic liquid has reportedly shown large variations.[29a,44-45,52,59-61] The values depend on both the measuring method and the interpretation of the data. Measurements have been done with different heating rates, ranging from 2-20 ºC/min, in air or nitrogen atmosphere and by using different pan materials (aluminium, alumina, ceramic). Isothermal measurements have shown that the actual decomposition occurs at a lower temperature than fast scan TGA measurements indicate.[63] More accurate measurements have been done during the last two years on the real stability of ionic liquids.[64,65]

The degradation temperatures of some 1-alkyl-3-methylimidazolium-based ionic liquids are presented in Table **5**. The degradation temperature increases only slightly when the

alkyl chain is changed from ethyl to octadecane, but the anion has a much stronger effect on the degradation temperature.

Table 5. Effect of an anion and the length of an alkyl substituent on degradation temperatures with some imidazolium-based ionic liquids.[41]

$[C_n mim]X^a$	T ^oC
1-alkyl-3-methylimidazolium chloride	240-290
1-alkyl-3-methylimidazolium hexafluorophosphate	330-420
1-alkyl-3-methylimidazolium tetrafluoroborate	350-410
1-alkyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	400-480

[a]Chain length of alkyl substituent, Cn: C_2-C_{18}

1.1.4.7.2. Chemical Stability

The chemical stability of ionic liquids has been studied with acids, bases and some other reagents. An ionic liquid is considered to be chemically stable when it does not react or decompose under reaction conditions. Until now, imidazolium-based ionic liquids have been the most studied and used. Research has shown that most imidazolium-based ILs withstand acidic conditions, but not basic ones.[65] The reason is the acidic proton at the carbon atom between nitrogen atoms in the imidazolium ring. Even a mild base can remove it and decompose the ionic liquid. Stability towards bases slightly increases when this carbon atom is alkylated. When higher stability is needed, phosphonium-based ionic liquids are a good choice, since they are compatible even with strong bases.[66]

Most ionic liquids are considered as inert solvents, but there are some studies where ILs have been reported to react with some reagents. In Heck reactions ionic liquids seem to react with metal catalysts and form an *in situ* carbene-palladium complex.[67] In nucleophilic reactions some ionic liquids are not only inert solvents.[68] This is the case when the ionic liquid contains a nucleophilic anion that might act as a nucleophile instead of added nucleophile. On the other hand, the added nucleophile might react with an imidazolium cation and dealkylate it. This has been reported to happen at elevated temperatures accompanied by a distinct color change in ionic liquids.[68] A similar phenomenon was observed when $[C_4mim]Cl$ was prepared with microwave irradiation at elevated temperatures[69] leading to the formation of new and undesired imidazolium-based cations during the reaction.

1.1.4.8 Salient features of ILs which make so attractive:

1. Low or negligible vapour pressure and non-flammable, in general.
2. They have high thermal stability.
3. They serve as a good medium to solubilize gases such as H_2, CO, O_2 and CO_2 and many reactions are now being performed using ionic liquids and supercritical CO_2.
4. Their ionic character enhances the reaction rates to a great extent in many reactions including microwave assisted and ultrasound promoted organic synthesis.
5. Their ability to dissolve a wide range of inorganic, organic, organometallic compounds and even polymeric materials.
6. Highly polar yet non-coordinating solvents.
7. Most of the ionic liquids may be stored without decomposition for a long period of time.
8. They exhibit Brønsted, Lewis and Franklin acidity, as well as superacidity.
9. They are immiscible with a number of organic solvents and provide a non-aqueous, polar alternative for two-phase systems. Hydrophobic ionic liquids can also be used as immiscible polar phases with water.
10. Because of their non-volatile nature, products could be easily isolated by vacuum distillation, leaving behind the IL pure enough for recycling after the reaction.
11. They are relatively cheap, and easy to prepare.
12. ILs may be termed as "designer" and 'neoteric' solvents since their properties can be adjusted to suit for the particular process by changing anion/cation or both.

1.1.4.9 Applications of ILs

A detailed information about the physical properties of ionic liquids can be found, e.g. in the book "Ionic Liquids in Synthesis" by Wasserscheid and Welton.[41] The most important properties of ionic liquids are: thermal stability, low vapour pressure, electric conductivity, tunable solubility (possibility for biphasic systems), liquid crystal structures, high electro-elasticity, high heat capacity and inflammability. These properties enable the use of ionic liquids in a wide range of applications, as shown in **Fig. 3**.[70]

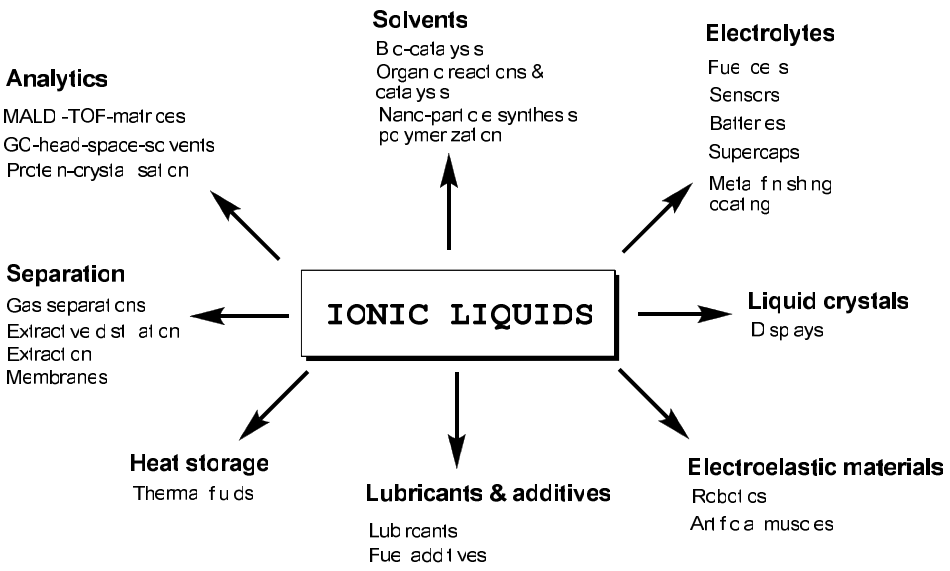


Fig. 3. Application of ILs in various fields[70]

Recently, ILs have been utilized in some industrial applications.[71a] BASF was one of the first companies that employed ILs. The process is called BASIL and it uses *N*-methylimidazole as a base to neutralize a formed hydrogen chloride, and as a result, 1-hydrogen-3-methylimidazolium chloride, IL is synthesized. The Dimersol/ Difasol process developed by the IFP (Commereuc *et al.*)[71b] is widely used industrially for the dimerization of alkenes, typically propene and butenes, to the more valuable branched hexenes and octenes, with twenty-five plants in operation world-wide producing *ca.* $3x10^6$ tonnes per annum. Although this process is used widely, the separation of products from the catalyst is a major problem and leads to increased operational costs and environmental impact. Chauvin *et al.*[71c] at the IFP in France reasoned that chloroaluminate ionic liquids would be good solvents for the nickel catalyst, and discovered that by using a ternary ionic liquid system ([bmim]Cl-$AlCl_3$-$EtAlCl_2$) (bmim = 1-butyl-3-methylimidazolium), it is possible to form the active catalyst from a $NiCl_2L_2$ precursor and that most importantly, the ionic liquid solvent stabilizes the active nickel species.

All the potential uses of ILs have not been fully exploited. Nevertheless some of the important applications for which the unique properties of ILs will be advantageous are described below.

1.1.5 Organic Reactions in ILs

A wide variety of reactions have been reported in ILs. Many reactions resulted in higher rates and better selectivity as compared with molecular solvents. Indeed these solvent systems suit well for catalysis as well.[72]

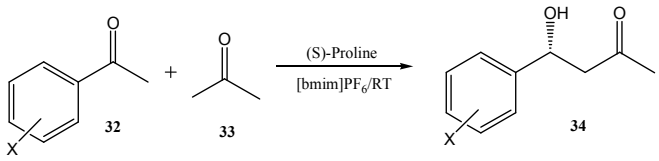
1.1.5.1 Friedel-Crafts reaction

Earlier investigations of the Friedel-Crafts reaction of simple benzene derivatives were carried out by Wilkes[23] in an [emim]Cl-$AlCl_3$ system. This was followed by the work of Seddon and Adams, who carried out the acetylation reactions of carbocyclic aromatic compounds with acetyl chloride in acidic compositions of [emim][Cl]-$AlCl_3$.[73] These reactions worked efficiently giving the stereo-electronically favored products. In the acetylation reaction of naphthalene, the major product was the thermodynamically unfavoured 1-acetylnaphthalene and the minor product as 2-acetylnaphthalene with only 2% yield. This is in accordance with the best literature yield and selectivity.[74]

1.1.5.2 Aldol condensation reactions

The self-condensation reaction of 1-propanal to form 2-methylpent-2-enal (Aldol I) has been carried out in non-coordinating imidazolium ionic liquids.[75] The reaction progressed through an aldol intermediate and produced the unsaturated aldehyde under the applied reaction conditions. Of the various ionic liquids tested, the highest product selectivity was found for [bmim][PF_6].

The proline-catalysed asymmetric direct aldol reaction of different aromatic aldehydes with acetone and several other ketones in the ionic liquid [bmim][PF_6] achieved good yields of aldolization products with reasonable enantioselectivities, even when 1–5% of proline was used as a catalyst (Scheme **4**).[76]



Scheme 4

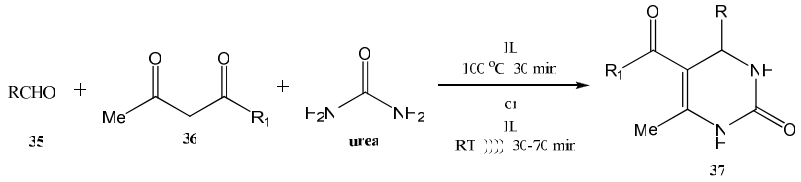
1.1.5.3 Wittig reactions

The ionic solvent [bmim][BF_4] has been used as a medium to carry out Wittig reactions using stabilized ylides allowing easier separation of the alkenes from Ph_3PO and also

recycling of the solvent.[77] Further, a similar *E*-stereo-selectivity was observed in the ionic liquid solvents as that observed in organic solvents.

1.1.5.4 Biginelli reaction

Ionic liquids such as [bmim][BF_4] and [Hbim]BF_4 have been used as catalysts for the Biginelli condensation reaction (Scheme **5**).[78a,b] With [bmim]Cl and TBACl as the catalysts, low and negligible yields of the products were obtained, respectively.

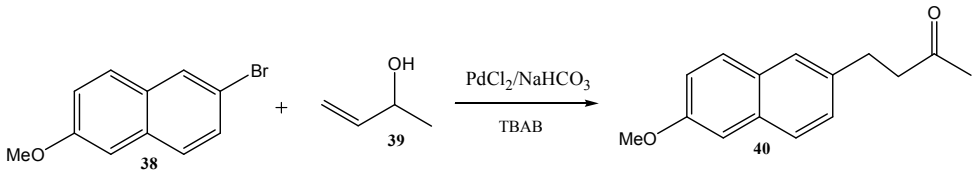


Scheme 5

1.1.5.5 Palladium-catalyzed C-C coupling reactions

1.1.5.5.1 Heck reaction

The Heck reaction has received a great attention due to its major importance in organic synthesis and in the manufacture of fine chemicals.[79,80] Of late, quaternary ammonium,[81] pyridinium[82a] and imidazolium[67] salts have been used as solvents for the Heck reaction of mono-substituted alkenes with aryl halides. The first example of a Heck reaction in ionic liquids was reported for the synthesis of *trans*-cinnamate by the reaction of bromobenzene with butyl acrylate catalysed by palladium salts in molten tetraalkylammonium and tetraalkylphosphonium bromide salts.[81] No formation of palladium metal was observed and the product was isolated by distillation from the ionic liquid. The Heck coupling of aryl halides with allylic alcohols catalyzed by $PdCl_2$ in molten tetraalkylammonium bromide gave the corresponding β-arylated carbonyl compounds (Scheme **6**).[82b]



Scheme 6

1.1.5.5.2 Sonogashira reaction

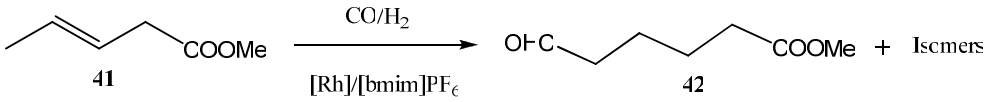
Ryu *et al*. reported a Sonogashira coupling reaction in an ionic liquid, namely, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6].[83a] Using Pd[(PPh_3)$_2$]Cl_2 as catalyst and diisopropylamine or piperidine as base, the Sonogashira coupling reaction

proceeded efficiently without using a copper co-catalyst. In this case the products were extracted with hexane, the resulting ionic liquid layer was washed with water to remove ammonium salts. The resulting ionic liquid containing the Pd catalyst could be reused successfully several times with only a slight loss in its activity.

Srinivasan *et al*. have demonstrated that the *copper*- and *ligand*-free Sonogashira reaction catalyzed by Pd(0) nanoparticles proceeds under ultrasound irradiation in the ionic liquid [bbim][BF_4].[84b] The formation of Pd(0) nanoparticles was investigated in this reaction by subjecting the reaction mixture (after a successful Sonogashira reaction between iodobenzene and 1-ethynylbenzene in [bbim][BF_4] under sonochemical conditions) to *in situ* TEM analysis.

1.1.5.6 Hydroformylation

The hydroformylation of olefins is an industrially important catalytic chemical process. The oxo-process is usually performed in industry using cobalt and rhodium complexes in homogeneous conditions or by aqueous rhodium complexes under biphasic conditions.[84] This reaction is the first one investigated using molten salts as immobilizing agents, but employing Ru-catalyst precursors (Scheme **7**).[85,86]



Scheme 7

1.1.5.7 Olefin metathesis

Olefin metathesis has become a powerful tool for the cleavage, as well as the formation of C=C bonds in fine chemicals, macrocycles or polymers[87] and in natural products.[88] Several well-defined homogeneous ruthenium-carbene complexes **43(**a-f) are efficient catalyst precursors, air stable and extremely tolerant towards different organic functional groups (Fig. **4**).[89]

Buijsman and co-workers reported that the Grubbs ruthenium catalyst precursor **43**a dissolved in [bmim][PF_6] promoted the ring-closing metathesis (RCM) of several dienes for at least three cycles.[90] In the light of these results, another strategy for RCM in ionic liquids was employed by the introduction of an ionic liquid pattern (as an alkylimidazolium salt, **43**f) directly bound to the ligand to avoid the problem of catalyst

leaching. The resulting ionic catalyst was found to be completely soluble in [bmim][PF_6] and allowed the RCM reaction to be carried out under standard homogeneous conditions (Fig. **4**).[91]

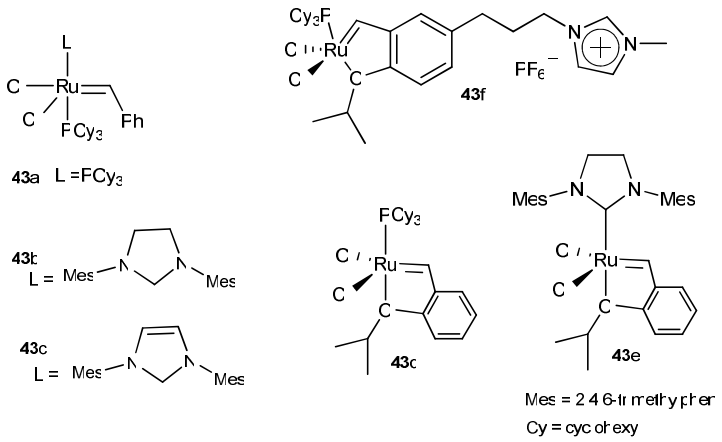
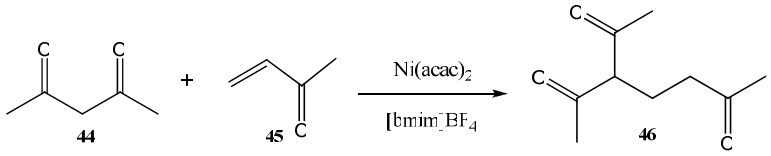


Fig. 4. Ruthenium ionic liquid catalyst used in RCM reaction

1.1.5.8 The Michael addition reactions

The Michael addition reaction is one of the most useful C-C bond-forming reactions[91] and has wide synthetic applications in organic synthesis[92] involving many homogenous[93] as well as heterogeneous catalysis.[94,95] The Lewis acids $Ni(acac)_2$, $Yb(OTf)_3$, and $FeCl_3{\cdot}6H_2O$ have been used for the metal-catalysed Michael addition in the ionic liquid [bmim][BF_4], focusing mainly on the addition of acetylacetone (Hacac) to methyl vinyl ketone as a model reaction (Scheme **8**).[96]



Scheme **8**

1.1.5.9 Asymmetric dihydroxylation of the olefins

Osmium catalysts have been used in asymmetric dihydroxylation reactions of the olefins. The high cost and toxicity of, and contamination of the product with, the osmium catalyst, however, restrict the use of the asymmetric dihydroxylation reactions in industry.[97] Different methods have been developed for immobilization of the osmium catalyst such as by microencapsulation of OsO_4 in polystyrene-type capsules[98] or on silica-anchored tetrasubstituted olefins[99] or by ion exchangers.[100] In an attempt to solve this problem, two independent groups have simultaneously reported the asymmetric dihydroxylation of

olefins based on the anchoring of the osmium ligand catalyst in a room temperature ionic liquid.[101-102] Before this work, OsO_4-catalysed olefin dihydroxylation using 4-methylmorpholine-*N*-oxide (NMO) as the co-oxidant in [bmim][BF_4] had already been reported.[103]

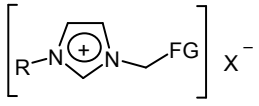
1.1.6 Other reactions in Ionic Liquids

1.1.6.1 Co-polymerization of styrene and CO catalyzed by cationic Pd-catalysts

The insertion polymerization of alkenes is typically catalyzed by cationic metal complexes with weakly coordinated anions.[104] Polar non-coordinating ionic liquids are attractive solvents for these reactions, since they may stabilize the solvent-separated ion pairs that are necessary for a high activity. Chloroaluminate ionic liquids have been applied to the cationic,[105] metal-catalyzed oligomerization and polymerization of alkenes.[106] Ethylene oligomerisation and ethylene-linked polymerization have been studied in air- and moisture-stable [C_4mim][PF_6].[107,108]

1.1.7 Task specific ionic liquids [TSILs]

Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the ILs.[41] These ILs can then act as reagents or catalysts in organic reactions. Recently, many attempts have been made to explore functional ionic liquids through incorporation of additional functional groups as a part of the cation and/or anion. Recently, various types of ‘‘task-specific’’ ionic liquids (TSILs) have been designed and synthesized for specific purposes such as catalysis, organic synthesis, separation of specific materials as well as for the construction of nanostructure materials and ion conductive materials etc.[109] Many of them were focused on the incorporation of functionality into a branch appended to the cation, especially imidazolium cation (Fig. **5**).



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FG = Functional Group

FG = NH_2, OH, OR, SH, PPh_3, $Si(OR)_3$, metal complex, CN, COOH, SO_3H, SO_2Cl, SCN etc

R = alkyl chain

Fig. **5** Task specific ILs

The imidazolium salts are defined as TSILs when they have the following features: (i) ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the imidazolium salts, which behave not only as a reaction medium but also as a reagent or catalyst. (ii) A conventional ionic liquid solution of a functionalized imidazolium salt, which is not a liquid form at ambient temperature, could also be defined as a TSIL since the functionalized imidazolium salt become integral elements of the overall ionic liquid solution and can introduce a functional group into the liquid.

1.1.8 Chiral ionic liquids

Chiral ionic liquids are quite attractive for their potential application to chiral discrimination including asymmetric synthesis and optical resolution of racemates. New chiral ionic liquids, directly derived from the 'chiral pool', have been synthesized and are interesting solvents for enantioselective reactions and useful in chiral separation techniques.[110] The first reported chiral ionic liquid was 1-butyl-3-methylimidazolium ([BMIM]) lactate III by Seddon *et al*. in 1999.[111] The [bmim][lactate], synthesized from [bmim][Cl] and sodium (*S*)-2-hydroxypropionate, was used in asymmetric Diels-Alder reactions between ethyl acrylate and cyclopentadiene. The Diels-Alder adducts were simply isolated by decanting off the upper organic layer. A good *endo*:*exo* selectivity of 4.4/1 was obtained. The ionic liquids prepared by this method meet the following criteria:

(a) easy preparation by direct synthesis in enantiopure form and low melting points.

(b) good chemical stability towards water and common organic substrates,

(c) relatively low viscosity and good thermal stability.

The use of ionic liquids with chiral anions is somehow more obvious, since some of these are readily available as sodium salts.[111] Recently, few examples of chiral ionic liquids (CILs) have been reported in the literature.[112] Some representative examples are shown in Fig **6**. Due to their ease of synthesis and their peculiar properties, these new chiral solvents should play a central role in enantioselective organic synthesis and hopefully expand the scope of chiral solvents. Chiral ILs can be particularly attractive if one considers their potential applications to chiral discrimination, including asymmetric syntheses and optical resolution of racemates. For example, one can expect a significant transfer of chirality in these solvents due to their high degree of organization. Most reports deal with the synthesis

and properties of the new chiral ILs and only a few deals with their application in organic reactions.

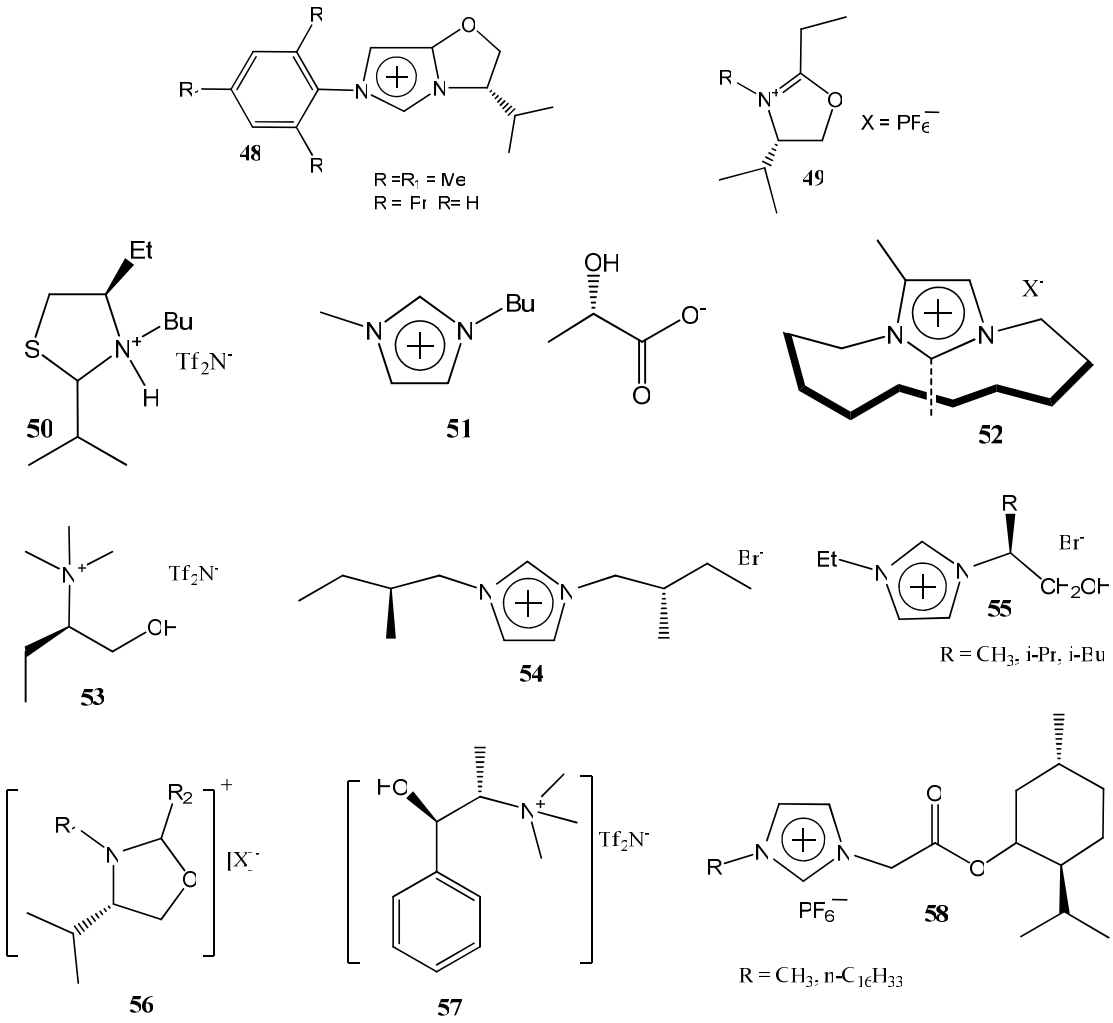

Fig. 6 Some of the **c**hiral ILs reported in the literature

1.1.9 Biodegradability of ionic liquids

The chemical and physical properties of ionic liquids have been studied intensively since their discovery. Diverse modifications of cations and anions have provided ionic liquids with desired properties for many technical applications.[113] Yet, the design of an ionic liquid with suitable properties for a specific application in view is not enough and more attention needs to be paid to the total life-cycle impacts of ionic liquids. Studies on the biodegradation of ionic liquids and their potential accumulation in the environment have begun only recently.[114,115] Degradation of organic compounds can be either aerobic or anaerobic. In both processes micro-organisms require a source of nitrogen and other

essential nutrients in order to decompose an organic substrate into carbon dioxide and water. A difference of the processes is that an aerobic treatment requires a source of oxygen and an anaerobic treatment requires an electron acceptor such as Fe^{3+}.[3c]

1.1.10 Recycling of ionic liquids

Environmental considerations require the recovery of ionic liquids after their use. Ionic liquids are quite expensive, and hence their recycling is also necessary due to economic reasons. A review by Olivier-Bourbigou and Magna indicates that ILs have been successfully recycled in many reactions.[116] Several procedures for recycling ionic liquids have been reported, and the efficiency of the recycling varies from poor to very good recovery. Examples of reactions using recyclable IL included palladium-catalyzed Heck reactions,[66,82a] oxidations of benzaldehyde and alkylbenzene,[117] Friedel-Crafts acylations,[73,118] co-polymerization of styrene and carbon monoxide,[119] Biginelli reaction,[78b] and dimerization of propene.[25]

Recyclability requires rates and yields to be maintained at a reasonable level after repeated reactions. In particular, reactions containing a transition metal catalyst immobilized into the ionic liquid of a biphasic reaction system have proved to be recyclable. Generally, recycling is based on the non-volatile nature of ionic liquids and the solubility differences between ionic liquids, organic compounds and water. Products can be extracted from ionic liquids with a non-polar solvent or they can be separated by distillation. A water-immiscible ionic liquid can be washed with water to get a water soluble product or side products out of the reaction mixture.

1.1.11 Benign ionic liquids

Until now, research on ionic liquids has mainly focused on imidazolium-based ionic liquids because they have good, adjustable properties for many applications and they are easy to prepare. Growing concerns about environmental issues have led the design of ionic liquids into a direction where more attention is paid to eco-toxicology. New anion candidates have been suggested on the basis of the first toxicological and eco-toxicological studies. Imidazolium-based ionic liquids with acetate **59** and lactate **60**,[120] saccharinate **61** and acesulfamate **62**[121] and amino acid-based anions[122] have been designed (Fig. **7**). These anions form non-toxic, readily biodegradable and water-soluble ionic liquids. Combining these anions with non-toxic, biodegradable cations, e.g. butyryl choline **63**, could result in

new ionic liquids with benign properties. The need remains for poorly coordinating, hydrophobic anions that could replace commonly used fluorous anions such as $[PF_6]^-$ and $[NTf_2]^-$, until now, no potential candidates have been discovered.

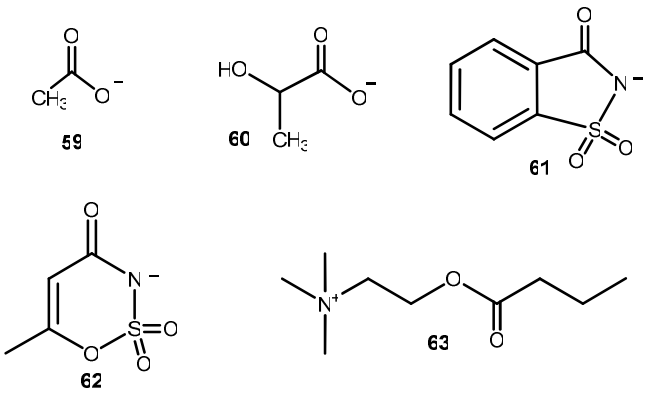

Fig. 7 Some examples of biodegradable anions and cation

1.1.12 Summary and Conclusions

The chemistry of room-temperature ionic liquids is at an incredibly exciting stage in its development. No longer mere curiosities, ionic liquids are beginning to be used as solvents for a wide range of synthetic procedures. The advent of systems that are easy to handle will allow those without specialist knowledge of the field to use them for the first time. The small number of reactions that have been investigated so far show the potential of the ionic liquids but are just a beginning. The solvent environment that is provided by the ionic liquids is quite unlike any other available at or close to room temperature. Already, startling differences have been seen between reactions in ionic liquids and molecular solvents. As the number of investigations increases, we will be able to tell if there is any general "ionic liquid effect". Potentially any reaction may produce interesting results in ionic liquids, and the discovery of the new chemistry waiting to be found will be a mammoth task.[32]

In addition to the above mentioned advantages of ILs, they have some limitations such as in most of the cases separation of the products from the ILs usually require extraction with non-polar volatile organic solvents. Their high viscosity as compared to conventional solvents make stirring and homogenization of reaction medium difficult, which causes slow dissolution of solids reactant which results reduction in the rate of reactions. Other drawbacks are their higher cost as compared to most commonly used organic solvents and

also little is known about their toxicity. Further, there is a lack of information regarding the role of ILs in many reactions.

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Chapter I

Section B

Introduction to Sonochemistry

1.2.0 Introduction to Sonochemistry

When ultrasonic energy at high power is applied to a liquid, a phenomenon called 'cavitation' occurs. Cavitation is the formation, growth and collapse of bubbles in the liquid.[1,2] This results in the 'cold boiling' of liquid. Ultrasonic vibration reduces the thickness of liquid films, enhances gas transfer and reduces bubble coalescence, which increases the interfacial area of gas transfer.[3-6] This can be used to separate gases as lighter molecules in an ultrasonic field will travel further than heavier ones. Ultrasonic energy can also be used to remove contaminants from air and to break down toxic components in soil and water. The role of ultrasound in homogeneous and heterogeneous chemistry has been well documented in the literature.

Ultrasounds are waves at frequencies above those within the hearing range of the average person, i.e., at frequencies above 16 kHz. Ultrasonic energy (high frequency sound waves) produces an alternating adiabatic compression and rarefaction of the liquid media being irradiated. In the rarefaction part of the ultrasonic wave (when the liquid is unduly stretched or "torn apart"), microbubbles form because of reduced pressure (i.e. sufficiently large negative pressures). These microbubbles contain vaporized liquid or gas that was previously dissolved in the liquid. The micro-bubble can be either stable about their average size for many cycles (stable cavitation) or transient when they grow to certain size and violently collapse or implode during the compression part of the wave (transition cavitation). The critical size depends on the liquid and the frequency of the sound; at 20 kHz, for example, it is roughly 100-170 μm. The energy put into the liquid to create microvoids is released during implosion creating high local pressures upto 1000 atm. and high transitory temperatures up to 5000 K.[7-11] This energy-releasing phenomena of the bubble formation and collapse is termed as acoustic cavitation.[12-14]

Cavitation can also be achieved by throttling a valve downstream from a pump. When the pressure at an orifice or any other mechanical constriction falls below the vapour pressure of the liquid, cavitations are generated which then collapse downstream with a recovery of pressure, giving rise to high temperature and pressure pulses. This cavitation is termed as hydrodynamic cavitation.[15]

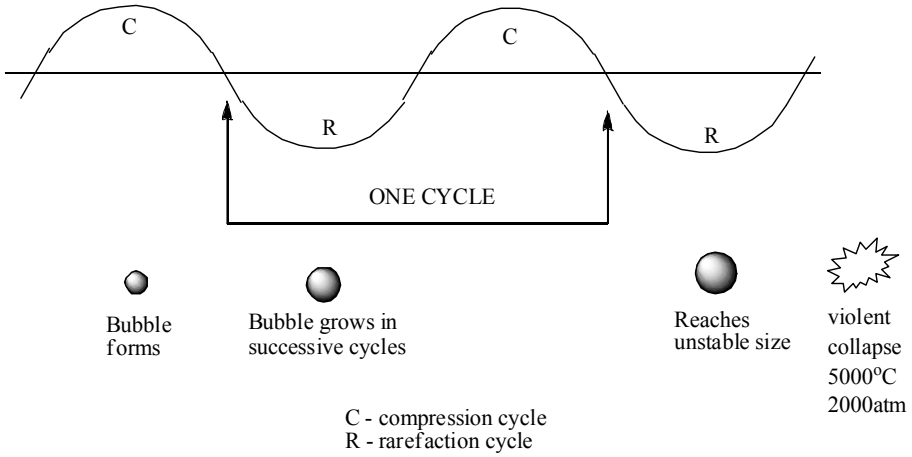


Fig. 8 Sound propagation in a liquid showing cavitation bubble formation and collapse

1.2.1 Sonochemical reactions

Application of ultrasound to chemical transformations may be termed as Sonochemistry. Sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse as mentioned earlier.[14] Ultrasound as non-thermal energy transfer source is well known to enhance reaction rates/yields/selectivity in organic synthesis and has found wide-spread applications in synthetic organic chemistry.[16]

1.2.2. Factors influencing Sonochemical processes

Application of ultrasound to chemical transformations may be termed as Sonochemistry. Sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse.[14]

1.2.2.1 Effect of solvent

Cavities are readily formed when using solvents with high vapour pressure, low viscosity and low surface tension. The intermolecular forces in the liquid must be overcome in order to form the bubbles. Thus, solvents with high densities, surface tensions and viscosities generally have higher threshold for cavitation but more harsh condition when cavitation begins.[12]

1.2.2.2 Effect of ambient gas

There are several properties of gases that can affect sonochemical activities.[5] The heat capacity ratio C_p/C_v or polytropic ratio of the gas in the bubble affects the amount of

heat released and, hence the final temperature produced in an adiabatic compression and the cause of reaction. Higher temperatures and pressures are generated with monoatomic gases with higher polytropic ratio than those with polyatomic gases with lower polytropic ratio.[5] Another parameter that affects cavitational collapse is the thermal conductivity of gases. A gas with low thermal conductivity reduces heat dissipation from cavitation site following adiabatic collapse and should favour higher collapse temperature compared with high thermal conductivity gas.[1] The solubility of gas is also an important aspect. The more soluble the gas, the more likely it is to diffuse in to the cavitation bubble. Soluble gases should result in the formation of larger number of cavitation nuclei and extensive bubble collapse since these gases are readily forced back to the bulk phase.[1]

1.2.2.3 Effect of temperature

Unlike most of the reaction systems, lowering of reaction temperature increases the rate of reaction. This is attributed to the lowering of the solvent vapor pressure, which increases the intensity of cavitation. At low vapor pressure, less vapour has an opportunity to diffuse into the bubble and making the implosion more violent. Also, as liquid temperature decreases, the amount of gas dissolved increases and the vapor pressure of the liquid decreases. Very volatile solvents lead to relatively high pressures in the bubble and also 'cushion' the collapse.[17]

1.2.2.4 Effect of pressure

Effect of pressure in reaction can cause some increase in the rate of sonochemical reaction due to the magnified effect of cavitation implosions. Too much pressure reduces the rate of reaction by decreasing the frequency or efficiency of bubble formations.[14]

1.2.2.5 Effect of acoustic intensity

An increase in ultrasound intensity implies an increase in the acoustic amplitude. The collapse time, the temperature and the pressure of collapse are all dependent on the acoustic amplitude. The cavitation bubble collapse will be more violent at higher acoustic amplitudes. So an increase in intensity will result in greater sonochemical effects in the collapsing bubble.[5,16a]

1.2.2.6 Effect of acoustic power

Power delivered to the system can increase the sonochemical activity to an optimum level after which it falls.[18,19] When acoustic power increases and simultaneously

increases amplitude of vibration, the maximum radius of the cavity bubble also increases as well as its time of collapse and this bubble is not able to collapse within time equal half of the period i.e. before the sound field reverses itself, the rarefaction phase begins acting on the collapsing bubble.[20,21]

1.2.2.7 Frequency of ultrasonic irradiation

Frequency has significant effect on the cavitation process because it alters the critical size of the cavitational bubble.[22-27] At high frequencies, the cavitational effect is reduced because either (i) the rarefaction cycle of the sound wave produces a negative pressure which is insufficient in its duration and/or intensity to initiate cavitation or (ii) the compression cycle occurs faster than the time for the microbubble to collapse. Lower frequency ultrasound produces more violent cavitation, leading to higher localized temperature and pressure.

1.2.3 Fundamentals of Sonochemical Reactions

The influence of ultrasonic energy on chemical activity may involve any of the following: [2-3,28-29]

i. **Production of heat**
ii. **Promotion of mixing (stirring) or mass transfer**
iii. **Promotion of intimate contact between materials**
iv. **Production of free radicals**

The physical effects of ultrasound can enhance the reactivity of a catalyst by enlarging its surface area or accelerate a reaction by proper mixing of reagents. The chemical effects of ultrasound enhance reaction rates because of the formation of highly reactive radical species formed during cavitation.[4,11] Homogeneous sonochemistry examines, mainly in the liquid phase, the activity of radicals or excited species formed in the bubble gas phase during the violent implosion and their possible release into the liquid.[16a] The cavitation event also gives rise to acoustic micro-streaming or formation of miniature eddie current that enhances the mass and heat transfer in the liquid, and also causes velocity gradients that results in shear forces. In heterogeneous sonochemistry, the mechanical effects of cavitation resulting from the erosion action of microjets formed during the asymmetric collapse of bubbles at the vicinity of interfaces are also important.[16a]

The following theories have been proposed to explain the sonochemical events.

(a) Hot-spot theory

(b) Electrical theory

(c) Plasma discharge theory

(d) Super-critical theory

The hot-spot theory suggests that a pressure of the order of 1000 atm is generated and a temperature of about 5000 K results during violent collapse of the bubble.[7-9] The electrical theory suggested by Margulis[30] says that during bubble formation and collapse, enormous electrical field gradients are generated and these are sufficiently high to cause bond breakage and chemical activity.

The plasma theory by Lepoint and Mullie[31] also suggests that the extreme conditions associated with the fragmentative collapse is due to intense electrical fields and seems to involve a true implosion which is related to corona-like discharges caused by fragmentation process and the formation of microplasmas inside the bubbles.

Hoffmann[32] proposed super-critical theory, in which the existence of a layer in the bubble-solution interface where temperature and pressure may be beyond the critical conditions of water and which may have physical properties intermediate between those of a gas and a liquid. They also proved that supercritical water is obtained during the collapse of cavitation bubbles generated sonolytically.

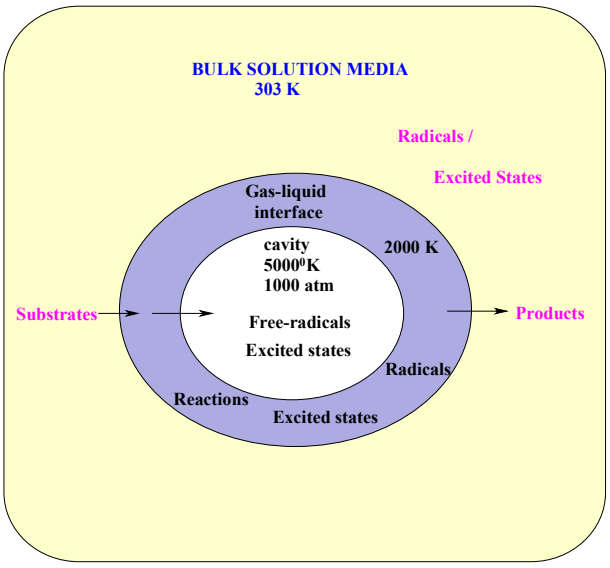


Fig. 9 Schematic diagram of cavitation bubble

In general, most studies have adopted 'hot spot' concept for experimental result interpretation. Hot spot theory suggests a sonochemical reaction as a highly heterogeneous reaction in which reactive species and heat are produced from a well defined micro-reactor i.e. 'cavitation bubble'.[11,33] In the figure, three regions for occurrence of reactions are postulated

(i) A hot gaseous nucleus
(ii) An interfacial region and radial gradient in temperature and local radical density
(iii) The bulk solution at ambient temperature.

Reactions involving free radicals can occur within the collapsing bubble, at the interface of the bubble and in the surrounding liquid. Within the center of the bubble, harsh conditions generated on bubble collapse cause bond breakage and/or dissociation of the water and other vapors and gases, leading to the formation of free radicals to the formation of excited states.

Solvent and/or substrates suffer homolytic bond breakage to produce reactive species. High temperatures and pressures created during cavitation provide the activation energy required for the bond cleavage. The radicals generated either react with each other to form new molecules and radicals or diffuse into the bulk liquid to serve as oxidants. The second reaction site is the liquid shell immediately surrounding the imploding cavity, which has been estimated to heat up to approximately 2000 K during cavitation implosion. In this solvent layer surrounding the hot bubble, both combustion and free-radical reactions (involving **.**OH derived from decomposition of water) occur. Pyrolysis in the interfacial region is predominant at high solute concentrations, while at low solute concentrations, free-radical reactions are likely to predominate. At the interface between bubble and bulk liquid, surface-active reagents also accumulate and species produced in the bubble first react with chemicals in the bulk liquid. It has been shown that the majority of degradation takes place in the bubble-bulk interface region.[34-35]

1.2.4 Rules of sonochemistry

As mentioned in earlier section, the sonochemistry involves mainly the cavitation phenomena, which results in hot spots and micro reactors. With this theory many conclusions are derived by many workers to generalize the reactions, which are activated by ultrasound. Considering all possibilities in the formation and collapse of cavitation

bubble as main mechanism, the sonochemical reactions can be classified into three groups.[36]

a. Homogeneous systems which proceed via radical or radical-ion intermediates – this implies that sonication is able to effect reactions proceeding through radicals and further it is unlikely to effect ionic reactions.
b. Heterogeneous systems proceeding via ionic intermediates – the reaction is influenced primarily through mechanical effects of cavitation such as surface cleaning, particle size reduction and improved mass transfer.
c. Heterogeneous reactions, which include a radical pathway or a mixed mechanism i.e. radical and ionic – radical reactions will be chemically enhanced by sonication but the general mechanical effect referred to above in b may still apply. If the radical and ionic mechanisms lead to different products ultrasound should favour the radical pathway and this could lead to a switch in the nature of the reaction products.

1.2.5 Equipment

The first requirement for sonochemistry is a source of ultrasound energy. This is usually generated via an ultrasonic transducer. This is a device which converts mechanical or electrical energy to sound energy. There are three main types of transducers used in sonochemistry: Liquid-driven (effective liquid whistling), magnetostrictive (reduction of size of metal when placed in magnetic field e.g. Ni) and piezoelectric. Most of the current equipments utilize piezoelectric ceramic tranducers. Two piezoelectric ceramic plates are clamped between metallic plates to form a piezoelectric sandwich, which provides an added mechanical motion. Piezoelectric transducers are very efficient and depending on their dimensions, can be made to operate over the whole ultrasonic range. The two commonly used sources of ultrasound in laboratory are ultrasonic cleaning bath and the ultrasonic horn or probe system.[37] These generally operate at frequencies of around 40 and 20 kHz, respectively.

1.2.5.1 Ultrasonic cleaning bath

A simple ultrasonic cleaning bath is the simple and cheapest source of ultrasound. It usually consists of a tank fitted with transducers at the bottom. The reaction flask can be immersed into the tank filled with some liquid mostly water. The amount of energy, which

reaches the reaction through the vessel walls, is low – normally between 1 and 5 W cm^{-2}. Temperature control in the commercial cleaning bath is very poor and may require additional thermostatic control.

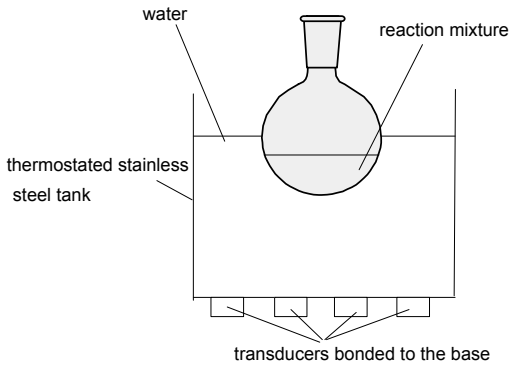


Fig. 10 Ultrasonic cleaning bath

1.2.5.2 Ultrasonic probe

This apparatus allows acoustic energy to be introduced directly into the system rather than rely on its transfer through water in the tank and through the walls of the tank. It is more expensive and less convenient because of the requirement of special seals for the closed reaction vessels which carry inert atmospheres or pressures above ambient or reflux temperatures. The maximum power out put can be as high as several hundreds W cm^{-2} and is tunable.

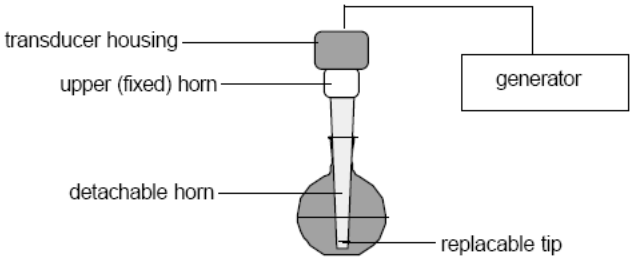
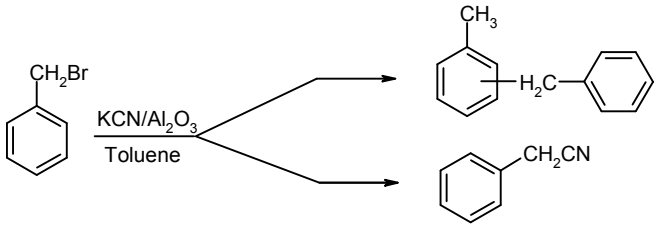


Fig. 11 Ultrasonic Probe

1.2.6 Reactions promoted by ultrasound

Ando *et.al*[38] demonstrated for he first time the sonochemical promoted reaction when a suspension of benzyl bromide and alumina supported potassium cyanide in toluene as solvent resulted in benzyl cyanide in 77% yield under sonication. The room temperature stirring results in 75% of diphenyl methane products via Friedel-Crafts reaction of benzyl

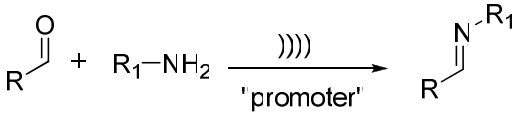
bromide with solvent toluene. The explanation is based upon the structural change to the catalytic sites of the solid support under sonication, possibly by masking them through cavitationally induced cyanide absorption (Scheme **9**).



Scheme 9

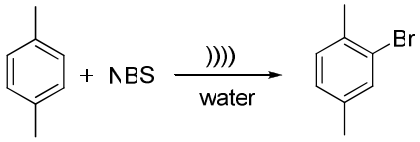
1.2.6.1 Recent applications of ultrasound in Organic Synthesis

Guzen *et al.*[39] synthesized a series of imines by an ultrasound-assisted reaction of aldehydes and primary amines using silica as the promoter in eco-friendly manner. Products were obtained in high yields even in large scale synthesis as shown in Scheme **10**.



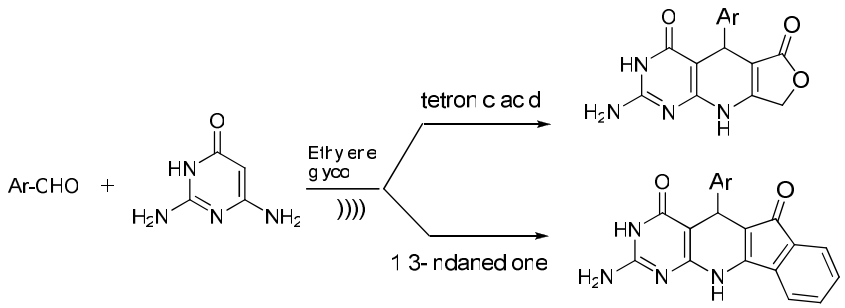
Scheme 10

Ultrasound assisted bromination reactions of various alkylaryls with *N*-bromosuccinimide, either neat or in water, shows chemoselectivity. Ring substitution occurs in water with ultrasound (Scheme **11**).[40]



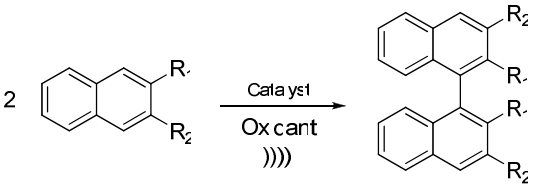
Scheme 11

Tu *et al.*[41] synthesized a series of pyrido[2,3-*d*]pyrimidine derivatives and related compounds *via* the condensation reaction of an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one and either tetronic acid or 1,3-indanedione under ultrasonic irradiation without catalyst. This protocol has the advantages of higher yields, lower cost and convenient procedure (Scheme **12**).



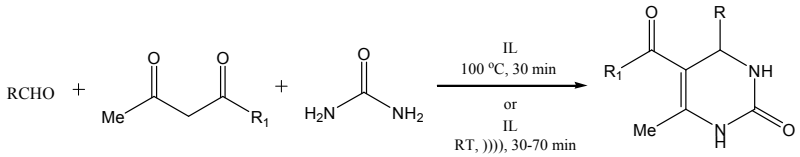
Scheme 12

Naphthols were selectively coupled under sonication using Fe^{3+} impregnated pillared Montmorillonite K-10 and TBHP as an oxidant. Considerable enhancement in the reaction rate was observed under sonication as compared to the reaction performed under silent condition (Scheme **13**).[42]



Scheme 13

Srinivasan *et.al*[43] synthesized 1,4-dihydropyrimidin-(4*H*)ones in the ionic liquid *viz*. [Hbim]BF_4 which was well promoted by ultrasound at ambient conditions (Scheme **14**).



Scheme 14

1.2.6.2 Enzymatic synthesis

Enzyme or whole cell reactivity under ultrasound irradiation is an emerging field. High power ultrasound will break biological cell walls releasing the contents but it can also denature enzymes. So it is very important that conditions of sonication must be carefully regulated to tolerate the biological cell.

Controlled sonication has been used to stimulate a suspension of Baker's yeast to produce an inexpensive source of sterol cyclase.[44] Significantly, sonication has no effect on the activity of the isolated cell-free cyclase system, a result which demonstrates how cell membrane disruption can occur without damage of the contents. Sonication is very

effective in solvent combinations in peptide synthesis where two immiscible solvents when sonicated forms an emulsion which facilitates the reaction.[45]

1.2.7 Specification of Ultrasonic cleaning bath used in Section A, B and E of Chapter II:

The reactions were carried out in a thermostated (30±1 ^{o}C) ultrasonic cleaning bath at 50 kHz. The ultrasonic cleaner had an output power of 120 W and a power supply of 450 W. The tank dimensions were 290 X 240 X 150 mm with a liquid holding capacity of 9.5 L. The reactions were carried out in a RB flask of 10 mL capacity suspended at the center of the cleaning bath, 5 cm below the surface of the liquid.

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Chapter I

Section C

Synthesis and characterization of novel ILs based on 1-n-butyl and 1, 3-di-n-butyl imidazolium salts

1.3.0 Introduction

In the previous Section **A** a brief introduction to ILs vis-à-vis green chemistry elements including a definition, brief history of ILs, their characteristic physico-chemical properties, application of ILs in organic synthesis, task specific ionic liquids (TSILs), chiral ionic liquids (CILs), stability of ILs, biodegradation of ILs and a new concept of benign ILs have been described. More over, ILs based upon imidazolium cation have good thermal stability, large electrochemical window, most of them are liquids at room temperature, have low viscosity and high polarity as compared to other ILs. Thus considering these important features of ILs based upon imidazolium cations, we synthesized several ILs based upon this class of cations with different anions of varying basicity and studied their efficacy in various important organic transformations. Inherent Brønsted acidity of imidazolium ring protons and Lewis acidity of imidazolium nucleus due to positive charge delocalization prompted us to explore their use in various organic transformations catalyzed by both Lewis and Brønsted acids. These investigations are described in Section-A, Section-B and Section-E of **Chapter II**.

1.3.1 Present work

In this section synthesis and characterization of several ionic liquids based upon the imidazolium cations has been described. Two sets of ILs based on N,N-di-*n*-butylimidazolium $[bbim]^+$ and N-butylimidazolium $[Hbim]^+$ salts with varying basicity of the anions are synthesized (Fig. **12**).

64 **65**

[bbim]X **[Hbim]X**

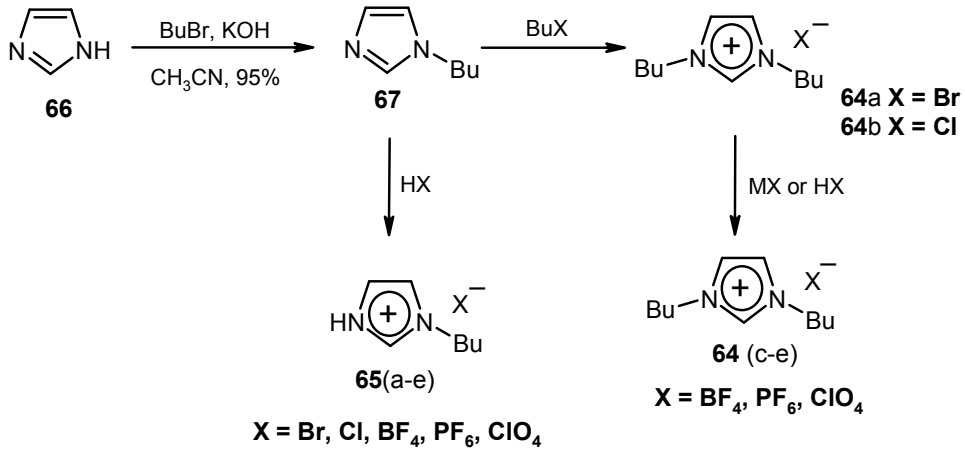
X = Br, Cl, BF_4, PF_6, ClO_4

Fig. 12 Ionic liquids synthesized, characterized, and studied their efficacy for important organic transformations

1.3.2 Results and discussion

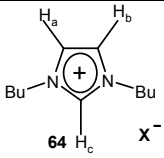
1.3.2.1. Synthesis of imidazolium based Ionic Liquids (ILs)

The ILs were synthesized from an inexpensive raw material such as imidazole **66**. N-butylation of imidazole **66** by the reaction of imidazole with *n*-butyl bromide in the presence of potassium hydroxide as the base in acetonitrile gave 1-*n*-butylimidazole **67** selectively in excellent yield (96%). Quaternization of 1-*n*-butylimidazole **67** with *n*-butyl bromide or chloride afforded a 1,3-di-*n*-butyl imidazolium bromide **64a** or chloride **64b** respectively. Metathesis of 1,3-di-*n*-butylimidazolium bromide **64a** with sodium tetrafluoroborate, potassium hexafluorophosphate and perchloric acid gave 1,3-di-*n*-butyl imidazolium $[bbim]^+$ ILs **64c-e** with the corresponding anions. The direct quaternization of 1-*n*-butyl imidazole **67** with inorganic acids such as HBr, HCl, HBF_4, HPF_6 and $HClO_4$ gave 1-*n*-butyl imidazolium salts $[Hbim]^+$ ILs **65a-e** with corresponding anion of the acids (Scheme **15**).



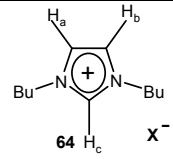
Scheme 15

Table 6a. Relation between chemical shifts and pK_a values [bbim]X ILs

 [bbim]X series	Yield of [bbim]X ILs (%)	pK_a of the acid of the anion	Chemical shift, δ (ppm)	
			H_a and H_b	H_c
[bbim]Br (**64a**)	98	-9	7.47	10.08
[bbim]Cl (**64b**)	95	-7	7.48	10.38
[bbim]BF_4 (**64c**)	98	0.5	7.87	9.20
[bbim]PF_6 (**64d**)	92	_	7.35	8.86
[bbim]ClO_4 (**64e**)	95	-11	7.40	9.02

It is well known that the formation of hydrogen bonding causes a downfield chemical shift of proton. Hydrogen bonding in imidazolium ring depends on the basicity of anion. It is logical to assume that H_c proton is less electron rich than H_a and H_b because it is attached to a carbon atom in between two electronegative nitrogen atoms. Thus, H_c proton is more prone for H-bonding with counter anion than others. This is so the case as evidenced from NMR shifts of H_c proton.

Table 6b. Relation between chemical shifts and pK_a values, [Hbim]X ILs

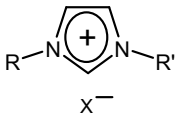
 **[Hbim]X series**	Yield of [Hbim]X ILs (%)	pK_a of the acid of the anion	**Chemical shift δ (ppm)**			
			H_a	H_b	H_c	-NH
[Hbim]Br (**65a**)	92	-9	7.15	7.42	8.57	11.83
[Hbim]Cl (**65b**)	95	-7	7.39	7.64	9.18	12.22
[Hbim]BF_4 (**65c**)	94	0.5	7.11	7.47	8.69	12.17
[Hbim]PF_6 (**65d**)	91	_	7.18	7.18	8.56	12.61
[Hbim]ClO_4 (**65e**)	90	-11	7.12	7.12	8.16	14.59

When we recorded ^{1}H-NMR of [Hbim]X series of ILs in $CDCl_3$ as deuterated solvent the –N*H* proton shift was observed at variable chemical shifts depending upon the concentration (this may be due to the –N*H* proton which is more labile for exchange). Consequently, the ^{1}H-NMR of the [Hbim]X ionic liquids are recorded as neat samples using D_2O as an external lock (D_2O was filled in capillary and it was blocked and inserted into neat compound). We found that the chemical shift of the –N*H* proton of [Hbim]BF_4 went downfield to 14.59 δ ppm. It can be observed from the chemical shifts recorded in Table **6**b, that with increasing basicity of the anion (increasing pK_a of the corresponding acid) there is a progressive shifting of the –N*H* proton toward downfield region. As the sample was neat and viscous no splitting in *butyl* chain was observed giving rise to only broad signals. The chemical shifts of various protons on imidazolium ring and -N*H* protons co-related with basicity of anions in terms of pK_a values of corresponding acid of the anions as shown in Table **6**b.

1.3.3. Density of Ionic Liquids

The overall density of IL heavily depends on the molar mass of anion. The contribution of the larger hydrophobic anions decreases the density of the IL. This may be due to weaker molecular attraction and weak hydrogen bonding which decreases molecular agglomeration.

Table 7 Density of [bbim]X and [[Hbim]X ILs

IL				**Density (g/cm^3)[a]**
	R-	**R′-**	**X**	
64a	Bu	Bu	Br	1.23
64b	Bu	Bu	Cl	1.02
64c	Bu	Bu	BF_4	1.15
64d	Bu	Bu	PF_6	1.23
64e	Bu	Bu	ClO_4	1.19
65a	Bu	H	Br	1.21
65b	Bu	H	Cl	1.11
65c	Bu	H	BF_4	1.20
65e	Bu	H	ClO_4	1.29

[a]Density was determined at 27 °C

1.3.4 Viscosity of Ionic Liquids

Viscosity is probably the most important physical property for initially determining the processability of a solvent. Ideally one would like the viscosity of a fluid to be as low as possible allowing the fluid to be pumped easily. In addition it is desired for the fluid to have only small changes in viscosity in the normal operating temperature range. Previous studies show that the viscosity of ILs is mainly controlled by hydrogen bonding, van der Waals forces, molecular weight and mobility (Table **8**).

Table 8 Viscosity of [bbim]X and [Hbim]X ILs

IL	IL		Viscosity (cP)[a]
	Cation	Anion X^-	
64a	[bbim]	Br	373.1
64b	[bbim]	Cl	549.6
64c	[bbim]	BF_4	105.6
64d	[bbim]	PF_6	132.0
64e	[bbim]	ClO_4	57.6
65a	[Hbim]	Br	98.6
65b	[Hbim]	Cl	149.6
65c	[Hbim]	BF_4	68.8
65e	[Hbim]	ClO_4	28.2

[a]viscosity was determined at 27^{o}C

Viscosity is on a higher side for ILs with more basic anion. This is clearly demonstrated from the data recorded as shown in Table **8**. In BF_4 based ILs because of less basic anion, the van der Waals forces dominates over the H-bonding due to better charge delocalization. This will reduce the viscosity of the IL, whereas in Cl based ILs because of more basic anion and smaller size, the van der Waals forces dominates over the H-bonding due to less charge delocalization. This will increase the viscosity of the IL.

1.3.5 Thermal Analysis of Ionic Liquids

The ILs have low or negligible vapour pressure and as a result it decomposes on heating. In general the ILs hitherto reported are thermally stable up to 400 ^{o}C after which it tends to decompose and at around 480 ^{o}C it completely decomposes. From our experimental results, it is clear that halide ions dramatically decrease the thermal stability by almost 100 ^{o}C. Decomposition started at around 220 ^{o}C and the ILs fully decomposed at around 330

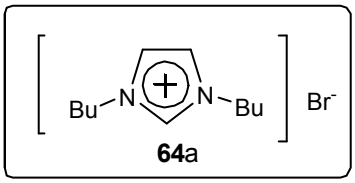
^{o}C. In the case of BF_4 salts, decomposition started at 335 ^{o}C and at 480 ^{o}C complete weight loss was observed. However decomposition of 1-*n*-butylimidazolium ionic liquids started at around 130 ^{o}C itself.

Usually the complete weight loss should occur with the absorption of heat, which will result in an endotherm. In the case of BF_4 salts, there may be some side reaction, which can result in a more thermodynamically stable product. From the weight loss calculated from the exact decomposition temperature, it can be concluded that the decomposition of BF_4^- species into more stable BF_3 and F^- may have resulted in the endotherm.

1.3.6 Experimental section

Preparation and characterization of different ionic liquids (ILs):

(1) Synthesis of 1, 3-Di-*n*-butylimidazolium Bromide [bbim]Br (64a):

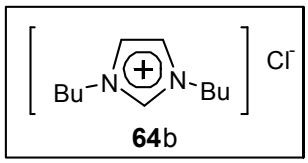


64a

A mixture of 1-*n*-butylimidazole (12.41 g, 0.1 mol) and *n*-butyl bromide (11.3 mL, 0.11 mol) was heated with stirring at 85-90 °C for 4 h. Excess *n*-butyl bromide was removed at 85 °C under reduced pressure (10 mm Hg) over 1 h leaving behind the ionic liquid, [bbim]Br, as a colorless liquid (25.6 g; yield 98%).

IR (KBr) υ_{max}	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753 cm^{-1}
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 0.86 (t, *J* = 7.0 Hz, 6H), 1.23-1.42 (m, 4H), 1.78-1.93 (m, 4H), 4.28 (t, *J* = 7.0 Hz, 4H), 7.54 (s, 2H), 10.41 (s, 1H).
^{13}C-NMR ($CDCl_3$, 200 MHz)	δ 12.9, 18.8, 31.6, 49.1, 121.9, 135.9.
Elemental analysis ($C_{11}H_{21}N_2Br$)	Calcd.: C, 50.58; H, 8.10; Br, 30.59; N, 10.72%. Found: C, 50.66; H, 8.03; Br, 30.53; N, 10.79%.
LC-MS	181 (M–X, 31%), 165 (3%), 151 (6%), 138 (37%), 124 (53%), 109 (8%), 97 (100%), 81 (87%), 68 (21%), 57 (29%).

(2) 1, 3-Di-*n*-butylimidazolium Chloride [bbim]Cl (64b):

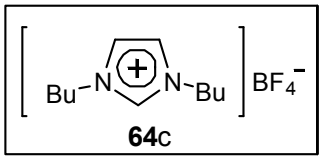


64b

This ionic liquid was synthesized by adopting the same procedure reported above for [bbim]Br; the reaction was performed with *n*-butyl chloride instead of *n*-butyl bromide to get [bbim]Cl as a viscous oily liquid (19.7 g; yield 95%).

IR (KBr) υ_{max}	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753 cm^{-1}
^{1}H-NMR ($CDCl_3$, 500 MHz)	**δ** 0.80 (t, *J* = 7.0 Hz, 6H), 1.24 (m, 4H), 1.72 (m, 4H), 4.22 (t, *J* = 7.0 Hz, 4H), 7.48 (s, 2H), 10.38 (s, 1H).
^{13}C-NMR ($CDCl_3$, 200 MHz)	**δ** 13.1, 19.1, 31.9, 49.3, 122.2, 136.9.
Observed Elemental analysis ($C_{11}H_{21}N_2Cl$)	Calcd.: C, 60.95; H, 9.77; Cl, 16.36; N, 12.92%. Found: C, 60.86; H, 9.84; Cl, 16.25; N, 12.99%.
LC-MS	181 (M–X, 31%), 165 (3%), 151 (6%), 138 (37%), 124 (53%), 109 (8%), 97 (100%), 81 (87%), 68 (21%), 57 (29%).

(3) Synthesis of 1, 3-Di-*n*-butylimidazolium Tetrafluoroborate [bbim]BF_4 (64c):



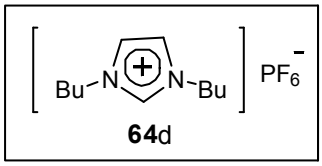
64c

To a solution of 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) (26.01 g, 0.10 mol) in water (150 mL) was added a solution of sodium tetrafluoroborate (12.10 g, 0.11 mol) in water (60 mL), and the mixture was stirred at 30 °C for 12 h. The ionic liquid [bbim]BF_4 separated out as an immiscible layer. The reaction mixture was extracted with dichloromethane (3X50 mL). The combined DCM (dichloromethane) layer, which was separated, was washed with water and brine and dried over anhydrous sodium sulfate. The solvent DCM was removed under *vacuo* leaving behind the pure IL [bbim]BF_4 as viscous oil (26.3 g; yield 98%).

IR (KBr) υ_{max}	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753 cm^{-1}
^{1}H NMR ($CDCl_3$, 500 MHz)	**δ** 0.91 (t, *J* = 7.0 Hz, 6H), 1.27-1.46 (m, 4H), 1.81-1.96 (m, 4H), 4.21-4.29 (t, 4H), 7.52 (s, 2H), 8.99 (s, 1H).
^{13}C NMR ($CDCl_3$, 200 MHz)	**δ** 13.1, 19.1, 31.8, 49.6, 122.3, 135.4.

Elemental analysis ($C_{11}H_{21}N_2BF_4$)	Calcd.: C, 49.28; H, 7.90; B, 4.03; F, 28.34; N, 10.45%. Found: C, 49.36; H, 7.81; B, 3.94; F, 28.41; N, 10.56%.
LC-MS	181 (M–X, 100%), 165 (15%), 151 (12%), 138 (61%), 124 (40%), 107 (33%), 97 (65%), 81 (62%), 68 (16%), 57 (42%).

(4) Synthesis of 1, 3-Di-*n*-butylimidazolium hexafluorophosphate [bbim]PF_6 (64d):



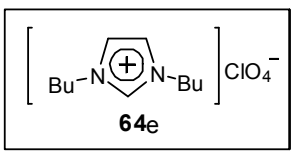
64d

To a solution of 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) (26.01 g, 0.10 mol) in 150 mL of water was added a solution of potassium hexafluorophosphate (20.23 g, 0.11 mol) in water (50 mL), and the mixture was stirred at 30 °C for 8 h. The ionic liquid [bbim]PF_6 separated out as an immiscible layer. The reaction mixture was extracted with dichloromethane (3X50 mL). The combined DCM layer, which was separated, was washed with water and brine and dried over anhydrous sodium sulfate. The solvent DCM was removed under *vacuo* leaving behind the pure IL [bbim]PF_6 as a viscous oil (30.0 g; yield 92%).

IR (KBr) υ_{max}	3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623 cm^{-1}
^{1}H-NMR ($CDCl_3$, 500 MHz)	**δ** 0.92 (t, *J* = 7 Hz, 6H), 1.27-1.46 (m, 4H), 1.79-1.94 (m, 4H), 4.15-4.23 (t, 4H), 7.33 (s, 2H), 8.79 (s, 1H).
^{13}C-NMR ($CDCl_3$, 200 MHz)	**δ** 13.2, 19.3, 31.8, 49.9, 122.3, 135.3.
Elemental analysis ($C_{11}H_{21}N_2PF_6$)	Calcd.: C, 40.49; H, 6.49; F, 34.94; N, 8.59; P, 9.49%. Found: C, 40.55; H, 6.39; F, 35.00; N, 8.67; P, 9.30%.
LC-MS	181 (M–X, 100%), 165 (15%), 151 (12%), 138 (61%), 124 (40%), 107 (33%), 97 (65%), 81 (62%), 68 (16%), 57 (42%).

(5) Synthesis of 1, 3-Di-*n*-butylimidazolium perchlorate [bbim]ClO_4 (64e):

This ionic liquid was synthesized by adopting the same procedure reported above for [bbim]BF_4; the reaction was performed with perchloric acid instead of sodium tetrafluoroborate to get [bbim]ClO_4 as a viscous oil (26.7 g; yield 95%).

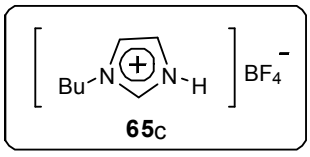


64e

IR: (KBr) υ_{max}	3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623 cm^{-1}

^{1}H NMR (CDCl$_3$, 500 MHz)	**δ** 0.88 (t, *J* = 7 Hz, 6H), 1.29-1.36 (m, 4H), 1.80-1.85 (m, 4H), 4.16 (t, *J* = 7 Hz, 4H), 7.42 (s, 2H), 9.03 (s, 1H).
^{13}C NMR (CDCl$_3$, 200 MHz)	**δ** 13.2, 19.3, 31.9, 49.8, 122.4, 135.6.
Elemental analysis $C_{11}H_{21}N_2ClO_4$	Calcd.: C, 47.06; H, 7.54; Cl, 12.63; N, 9.98%. Found: C, 47.14; H, 7.63; Cl, 12.74; N, 9.89%.
LC-MS	181 (M–X, 100%), 165 (15%), 151 (12%), 138 (61%), 124 (40%), 107 (33%), 97 (65%), 81 (62%), 68 (16%), 57 (42%).

(6) Synthesis of 1-Butylimidazolium Tetrafluoroborate [Hbim]BF$_4$ (65c):

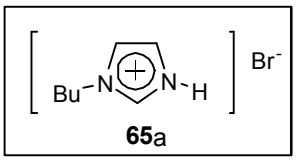


65c

Tetrafluoroboric acid (8.78 g, 0.1 mol) as 48% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (12.4 g, 0.1 mol) at 0 °C under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water was removed from the reaction mixture by subjecting it to evaporation for 4 h at 80 °C under reduced pressure (10 mm Hg) to give the product [Hbim]BF$_4$ as a viscous oil (19.9 g; yield 94%).

IR: (KBr) υ_{max}	3607, 3153, 2876, 1580, 1466, 894, 762 cm^{-1}
^{1}H-NMR (Neat, 200 MHz) D$_2$O as an external lock	δ 0.56 (s, 3H), 0.95 (s, 2H), 1.47 (s, 2H), 3.87 (s, 2H), 7.12 (s, 2H), 8.16 (s, 1H), 14.59 (br s, 1H).
^{13}C-NMR (Neat, 200 MHz) D$_2$O as an external lock	δ 13.1, 19.2, 32.1, 48.5, 120.9, 122.8, 135.2
Elemental analysis ($C_7H_{13}N_2BF_4$)	Calcd.: C, 39.66; H, 6.18; B, 5.10; F, 35.85; N, 13.21%. Found: C, 39.53; H, 6.30; B, 5.01; F, 35.72; N, 13.29%.
LC-MS :	124 (M–X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(7) 1-butylimidazolium bromide [Hbim]Br (65a):

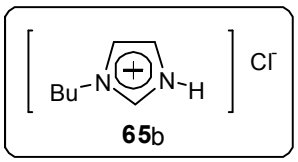


65a

This ionic liquid was synthesized by adopting the same procedure reported above for [Hbim]BF_4; the reaction was performed with hydrobromic acid (40% aqueous solution) instead of tetrafluoroboric acid to get [Hbim]Br as a viscous oil (18.9 g; yield 92%).

IR (KBr) υ_{max}	3607, 3153, 2876, 1580, 1466, 894, 762 cm^{-1}
^{1}H-NMR (Neat, 200 MHz) D_2O as an external lock	δ 0.21 (s, 3H), 0.64 (s, 2H), 1.31 (s, 2H), 4.03 (s, 2H), 7.39 (s, 1H), 7.64 (s, 1H), 9.18 (s, 1H), 12.22 (br s, 1H).
^{13}C-NMR (Neat, 200 MHz) D_2O as an external lock	δ 13.1, 19.1, 32.4, 47.3, 120, 124.7, 136.1
Elemental analysis ($C_7H_{13}N_2Br$)	Calcd.: C, 40.99; H, 6.39; Br, 38.96; N, 13.66%. Found: C, 40.88; H, 6.47; Br, 38.90; N, 13.75%.
LC-MS	124 (M - X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(8) 1-butylimidazolium chloride [Hbim]Cl (65b):

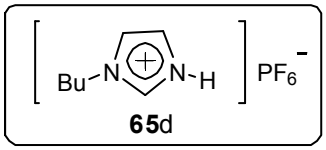


65b

This ionic liquid was synthesized by adopting the same procedure reported above for [Hbim]BF_4; the reaction was performed with hydrochloric acid (35% aqueous solution) instead of tetrafluoroboric acid to get [Hbim]Cl as a viscous oil (15.3 g; yield 95%).

IR: (KBr) υ_{max}	3607, 3153, 2876, 1580, 1466, 894, 762 cm^{-1}
^{1}H-NMR (Neat, 200 MHz) D_2O as an external lock	δ 0.48 (s, 3H), 0.88 (s, 2H), 1.42 (s, 2H), 4 (s, 2H), 7.11 (s, 1H), 7.47 (s, 1H), 8.69 (s, 1H), 12.17 (br s, 1H).
^{13}C-NMR (Neat, 200 MHz) D_2O as an external lock	δ 11.7, 17.7, 30.9, 45.7, 118.3, 123.7, 134.7.
Elemental analysis ($C_7H_{13}N_2Cl$)	Calcd.: C, 52.34; H, 8.16; Cl, 22.07; N, 17.44%. Found: C, 52.27; H, 8.25; Cl, 22.00; N, 17.53%.
LC-MS	124 (M - X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(9) 1-Butylimidazolium hexaflouorphosphate [Hbim]PF_6 (65d):

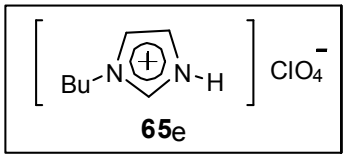


65d

This ionic liquid was synthesized by adopting the same procedure reported above for [Hbim]BF_4; the reaction was performed with hexafluoroboric acid (65% aqueous solution) instead of tetrafluoroboric acid to get [Hbim]PF_6 as a viscous oil (24.6 g; yield 91%).

IR: (KBr) υ_{max}	3607, 3153, 2876, 1580, 1466, 894, 762 cm^{-1}
^{1}H-NMR (Neat, 200 MHz) D_2O as an external lock	δ 0.42 (s, 3H), 0.84 (s, 2H), 1.43 (s, 2H), 3.96 (s, 2H,), 7.18 (s, 2H), 8.56 (s, 1H), 12.61 (br s, 1H).
^{13}C-NMR (Neat, 200 MHz) D_2O as an external lock	δ 12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7
Elemental analysis ($C_7H_{13}N_2PF_6$)	Calcd.: C, 31.12; H, 4.85; F, 42.19; N, 10.37; P, 11.47%. Found: C, 31.20; H, 4.92; F, 42.08; N, 10.44; P, 11.53%.
LC-MS	124 (M–X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(10) 1-Butylimidazolium perchlorate [Hbim]ClO_4 (65e**):**



65e

This ionic liquid was synthesized by adopting the same procedure reported above for [Hbim]BF_4; the reaction was performed with perchloric acid (70% aqueous solution) instead of tetrafluoroboric acid to get [Hbim]ClO_4 as a viscous oil (20.2 g; yield 90%).

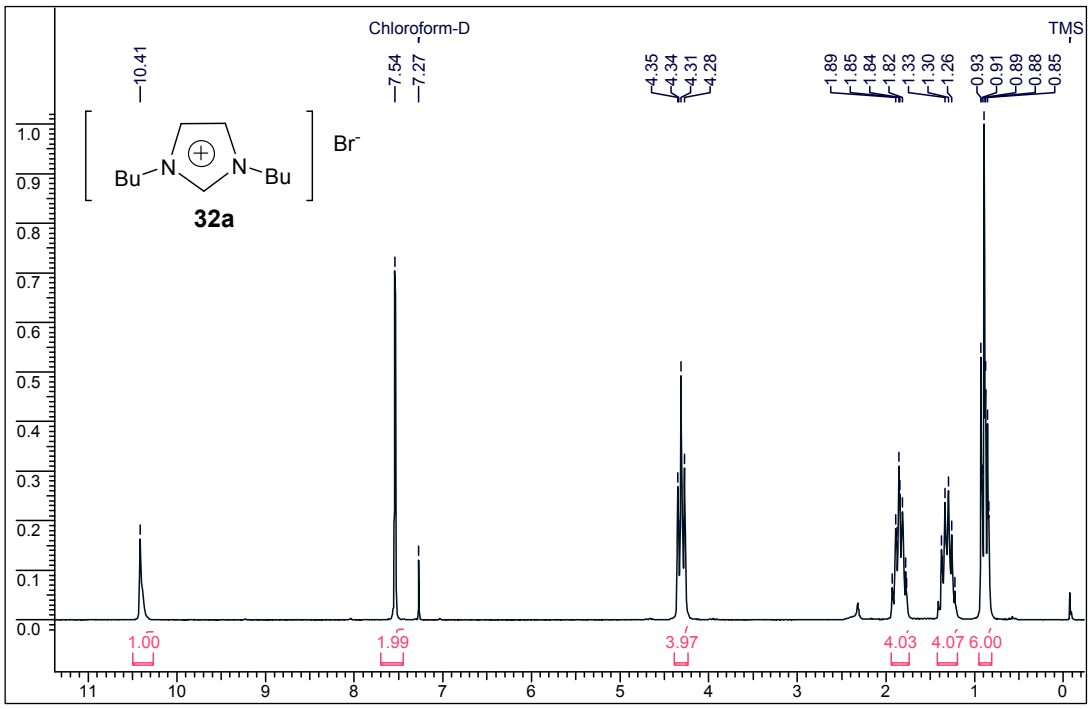
IR (KBr) υ_{max}	3607, 3153, 2876, 1580, 1466, 894, 762 cm^{-1}
^{1}H-NMR (Neat, 200 MHz) D_2O as an external lock	δ 0.71 (t, *J* =7.0 Hz, 3H); 1.17 (m, 2H), 1.73 (m, 2H,), 4.16 (t, *J* = 7.0 Hz, 2H), 7.15 (s, 1H), 7.42 (s, 1H), 8.57 (s, 1H), 11.83 (br s, 1H).
^{13}C-NMR (Neat, 200 MHz) D_2O as an external lock	δ 12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7
Elemental analysis ($C_7H_{13}N_2ClO_4$)	Calcd.: C, 37.43; H, 5.83; Cl, 15.78; N, 12.47%. Found: C, 37.36; H, 5.89; Cl, 15.69; N, 12.54%.
LC-MS	124 (M–X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

1.3.7. Spectra

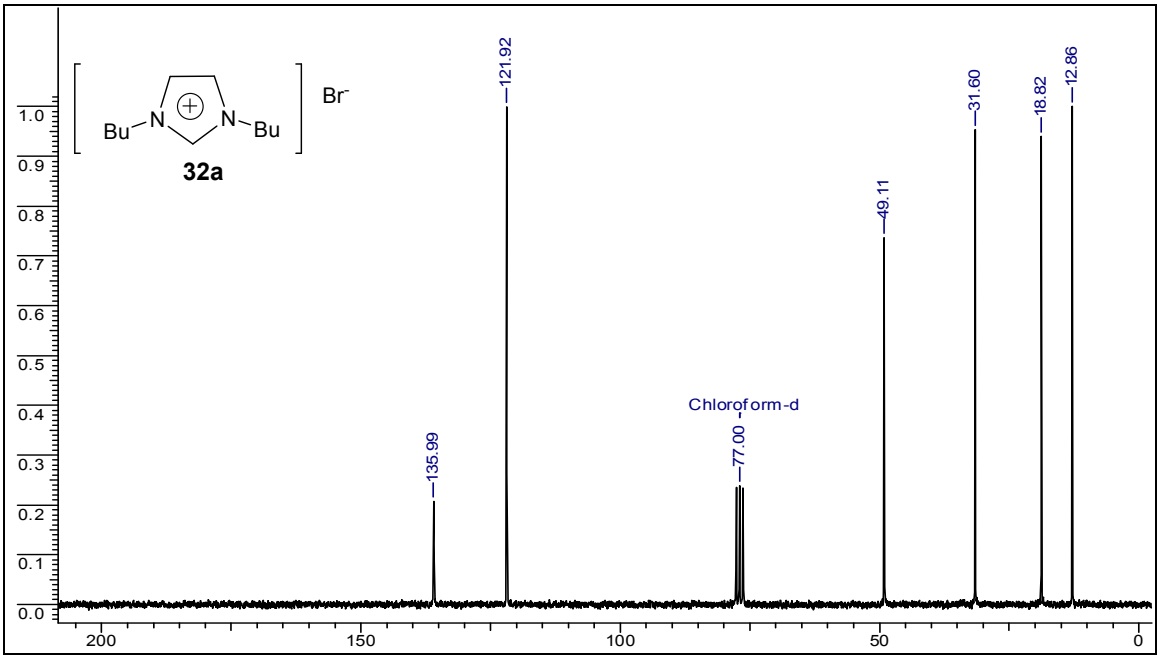
Table 11 ^{1}H & ^{13}C spectra of some selected ILs are given below:

Sr. No.	Spectra	
1	^{1}H & ^{13}C spectra of **[bbim]Br**	**(64**a**)**
2	^{1}H & ^{13}C spectra of **[bbim]BF_4**	**(64**c**)**
3	^{1}H & ^{13}C spectra of **[bbim]PF_6**	**(64**d**)**
4	^{1}H & ^{13}C spectra of **[bbim]ClO_4**	**(64**e**)**
5	^{1}H & ^{13}C spectra of **[Hbim]Br**	**(65**a**)**
6	^{1}H & ^{13}C spectra of **[Hbim]Cl**	**(65**b**)**
7	^{1}H & ^{13}C spectra of **[Hbim]BF_4**	**(65**c**)**
8	^{1}H & ^{13}C spectra of **[Hbim]PF_6**	**(65**d**)**
9	^{1}H & ^{13}C spectra of **[Hbim]ClO_4**	**(65**e**)**
10	TGA, DTG and DTA curves for **[Hbim]BF_4**	**(65**c**)**

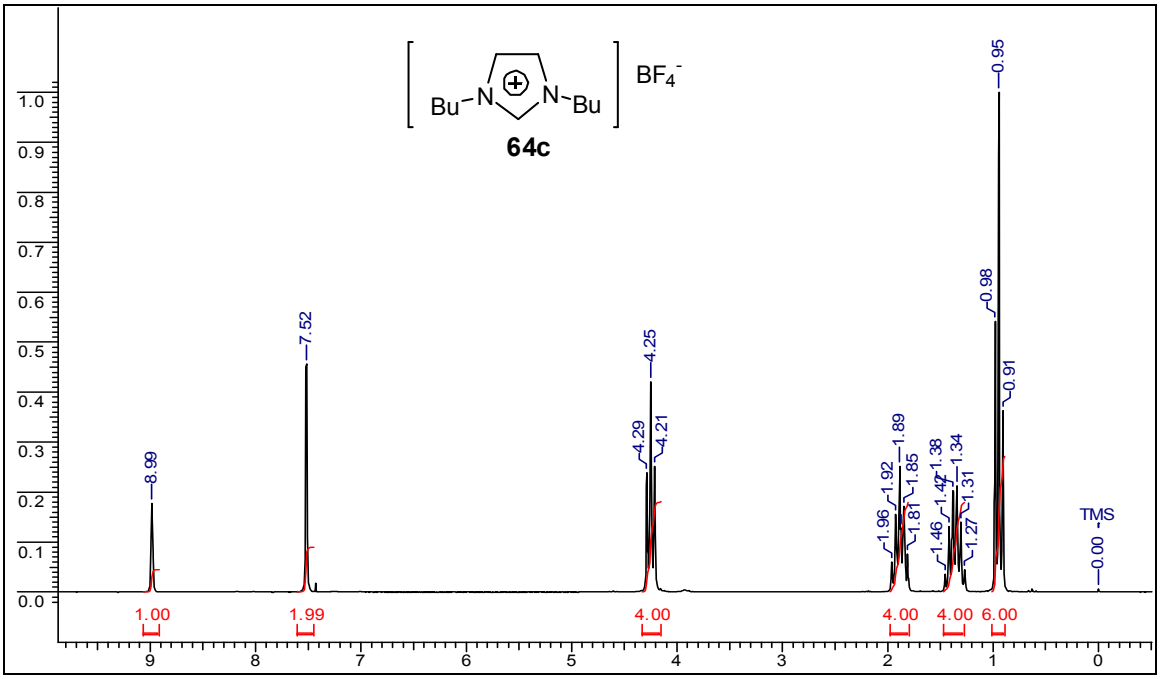
^{1}H-NMR spectrum of [bbim]Br (**64**a)



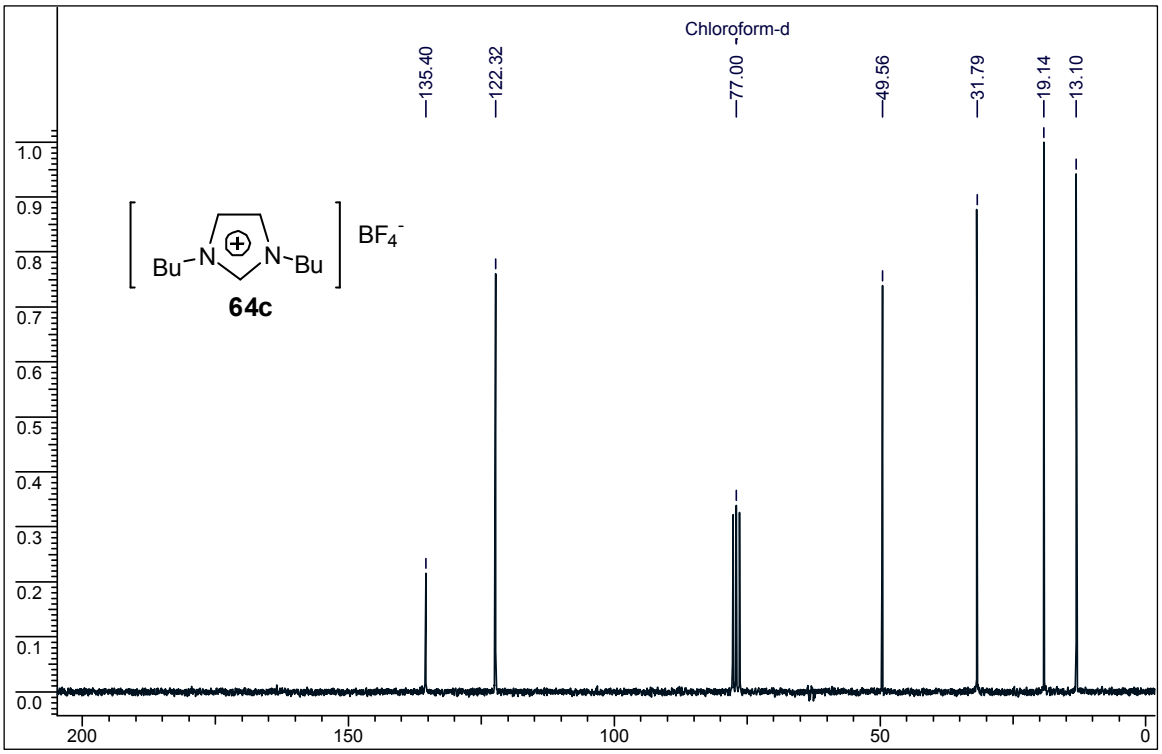
^{13}C-NMR spectrum of [bbim]Br (**64**a)



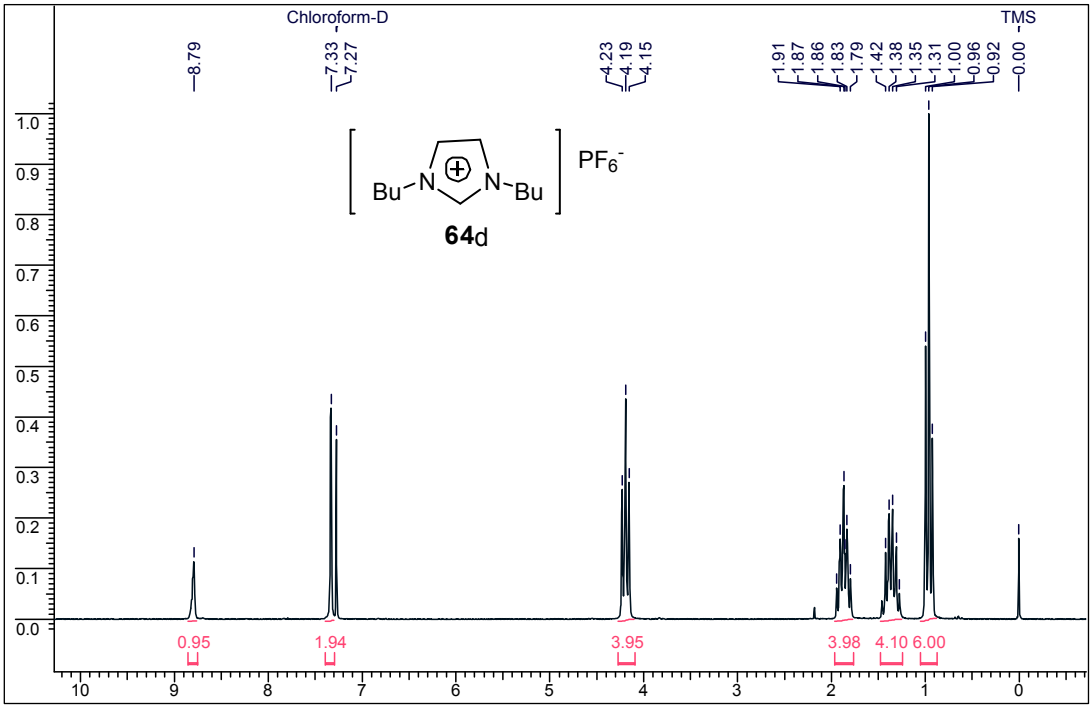
^{1}H-NMR spectrum of [bbim]BF_4 (**64c**)



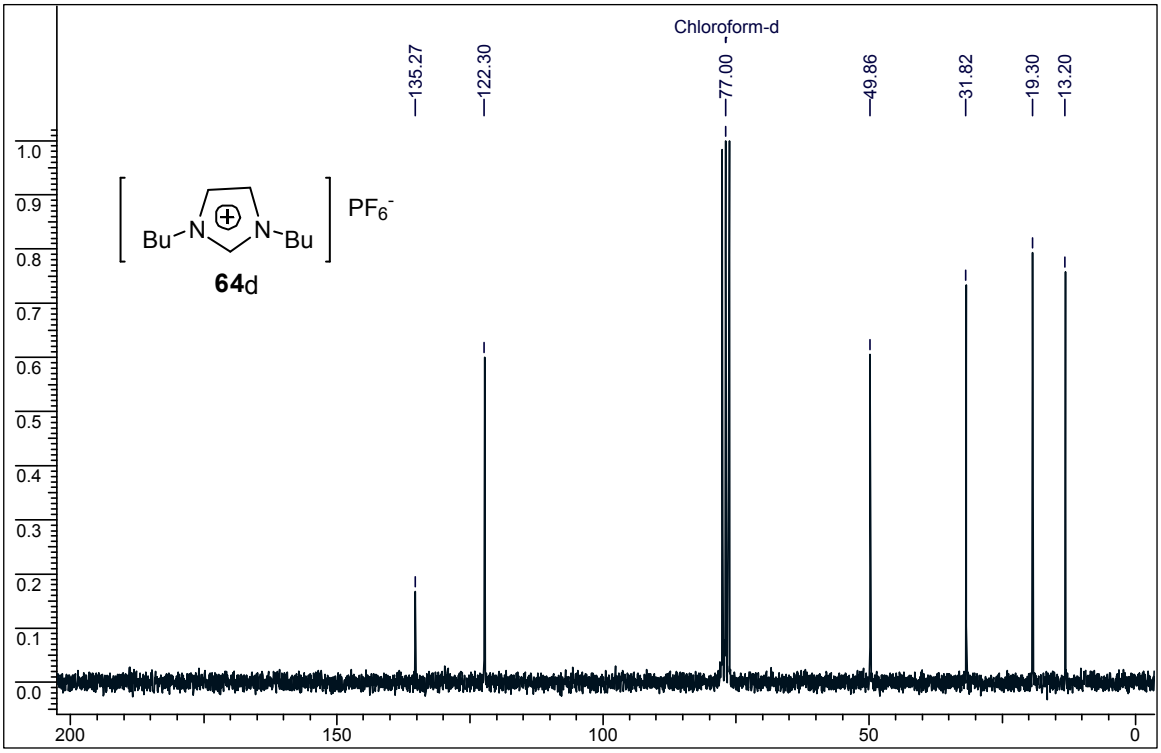
^{13}C-NMR spectrum of [bbim]BF_4 (**64c**)



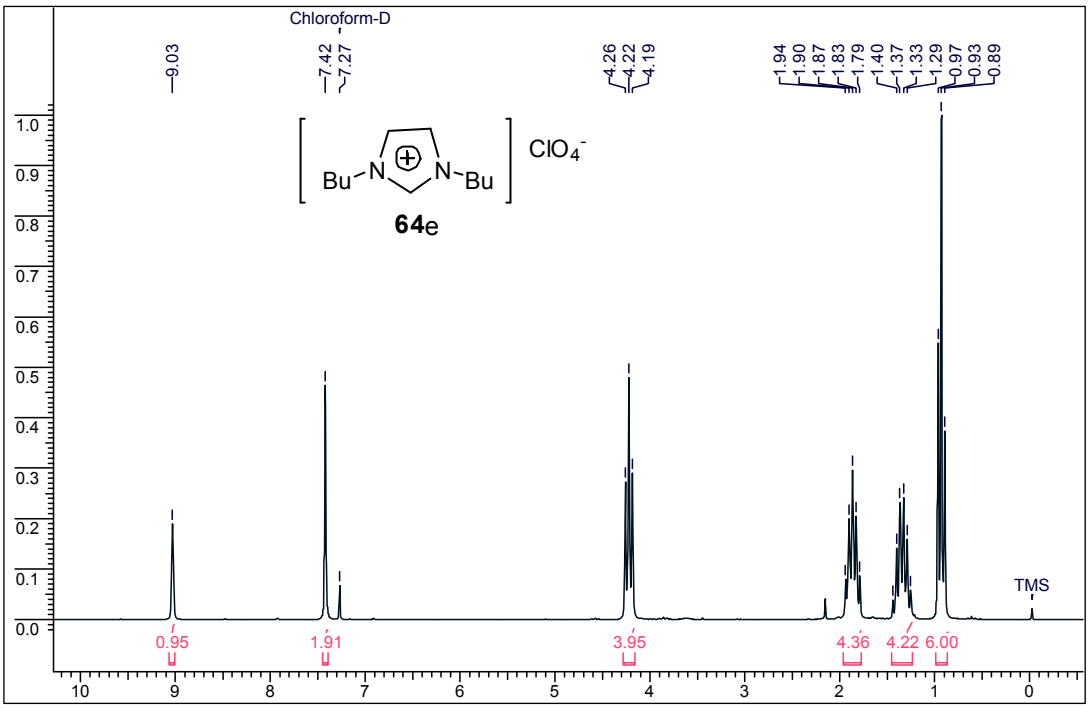
^{1}H-NMR spectrum of [bbim]PF_6 (**64**d)



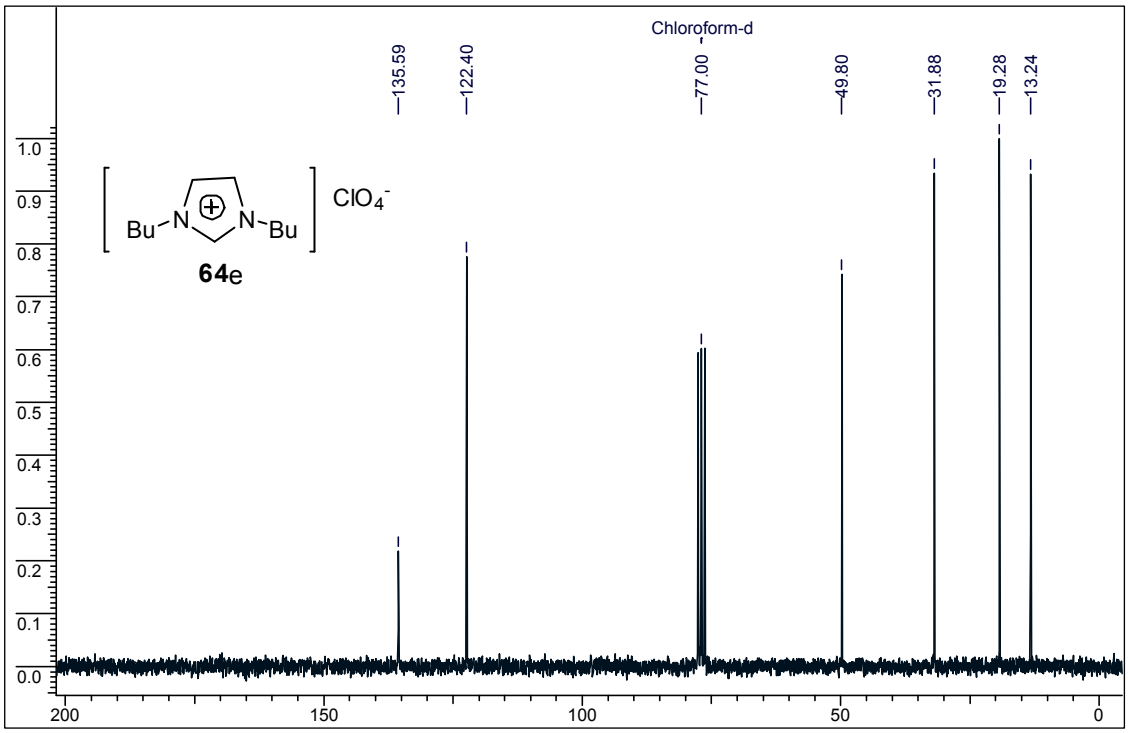
^{13}C-NMR spectrum of [bbim]PF_6 (**64**d)



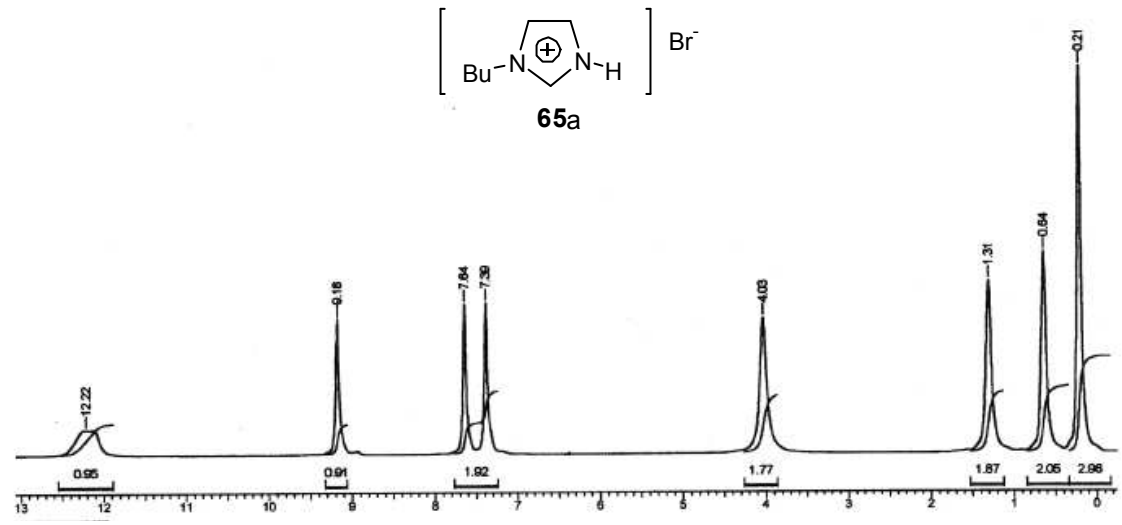
^{1}H-NMR spectrum of [bbim]ClO_4 (**64**e)



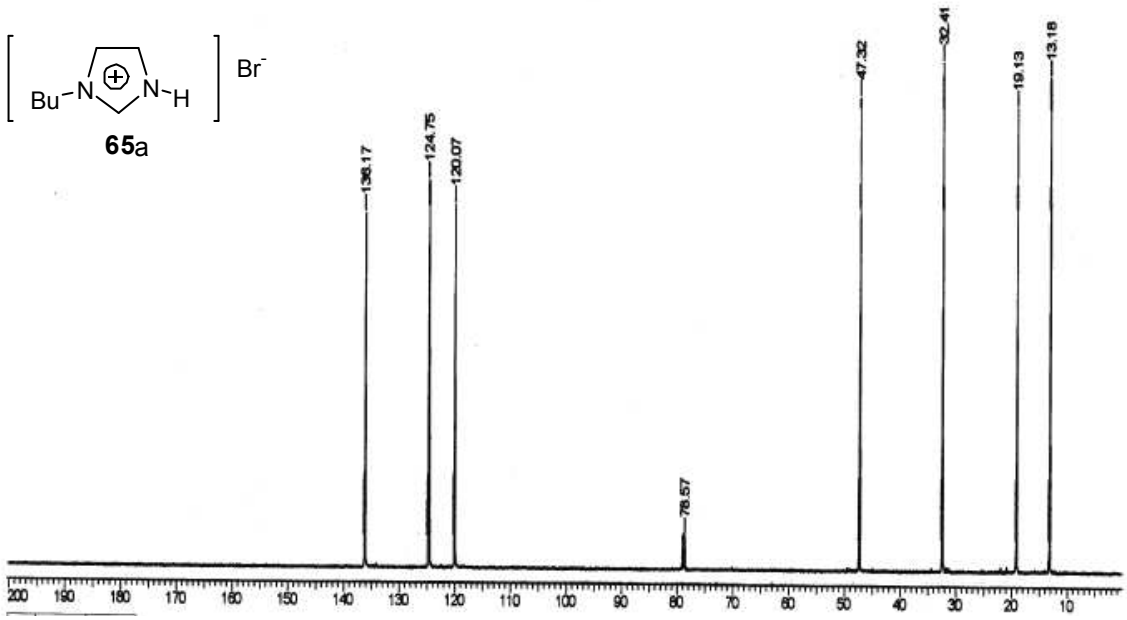
^{13}C-NMR spectrum of [bbim]ClO_4 (**64**e)



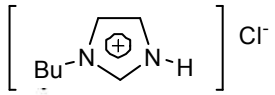
^{1}H-NMR spectrum of [Hbim]Br (**65**a)



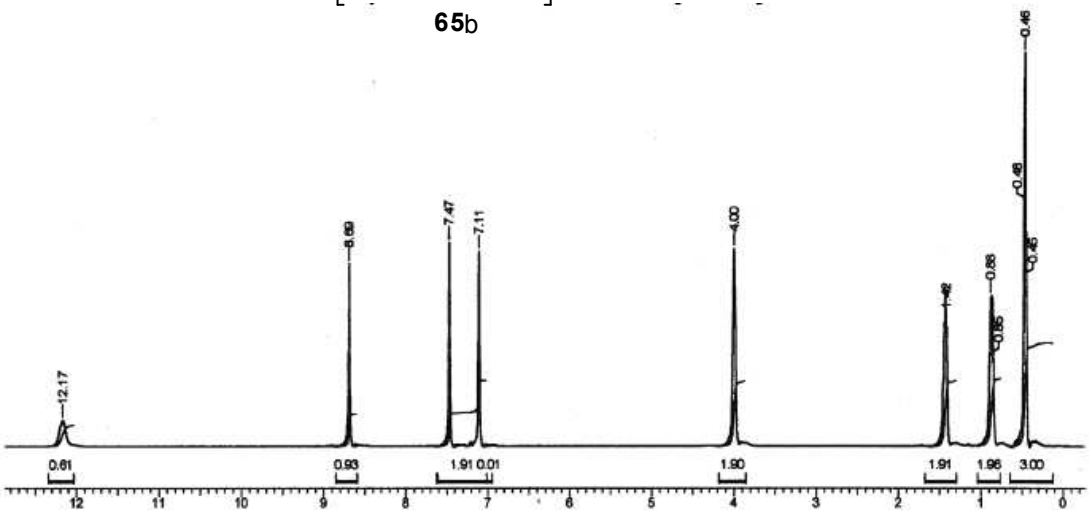
^{13}C-NMR spectrum of [Hbim]Br (**65**a)



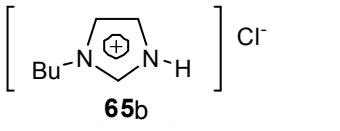
^{1}H-NMR spectrum of [Hbim]Cl (**65**b)



65b

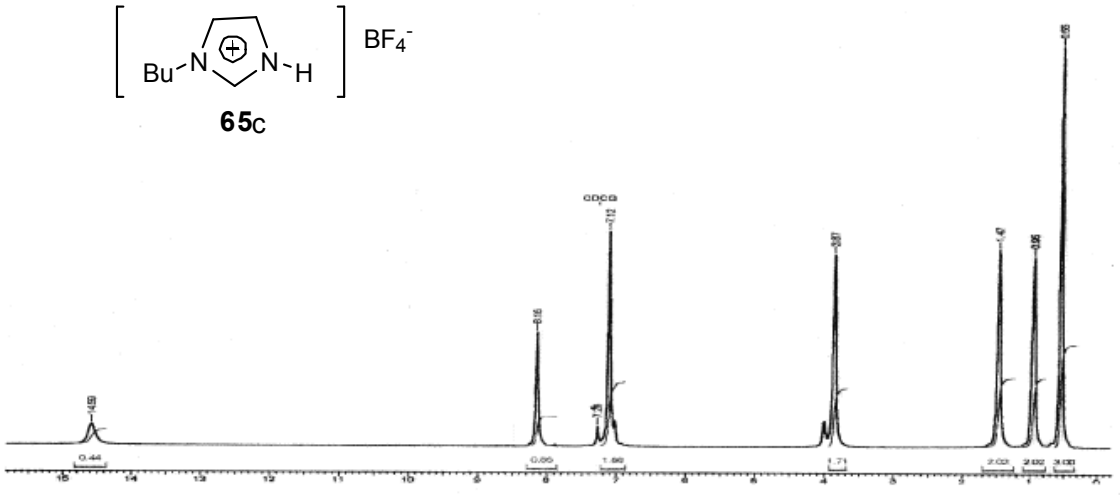


^{13}C-NMR spectrum of [Hbim]Cl (**65**b)

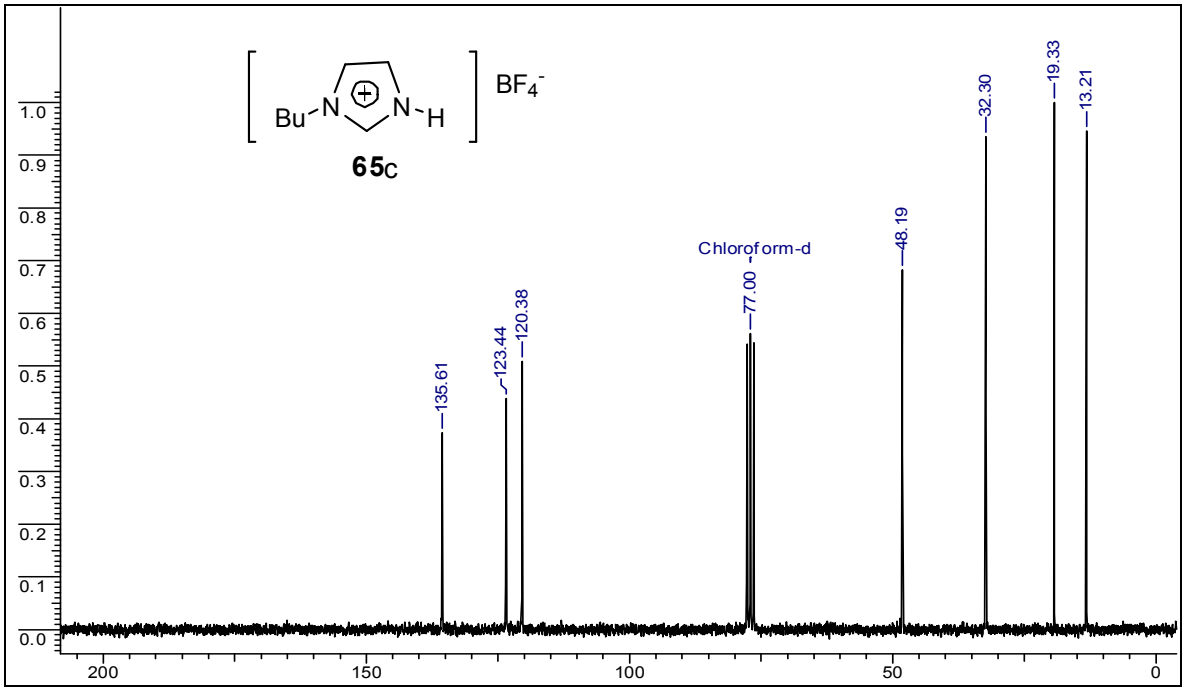


65b

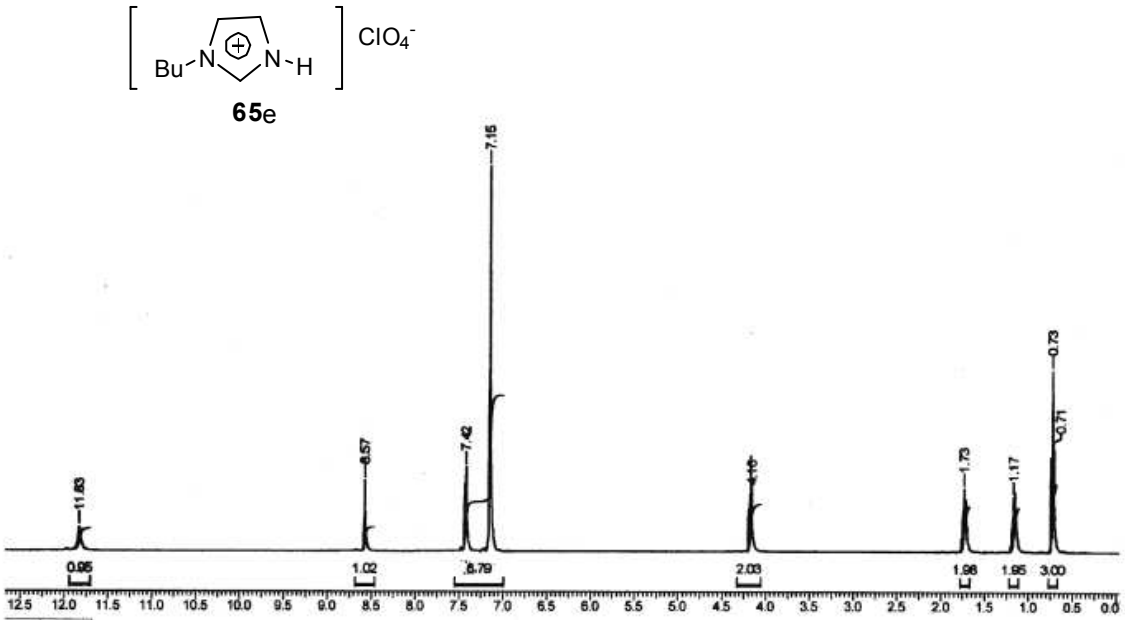
^{1}H-NMR spectrum of [Hbim]BF_4 (**65**c)



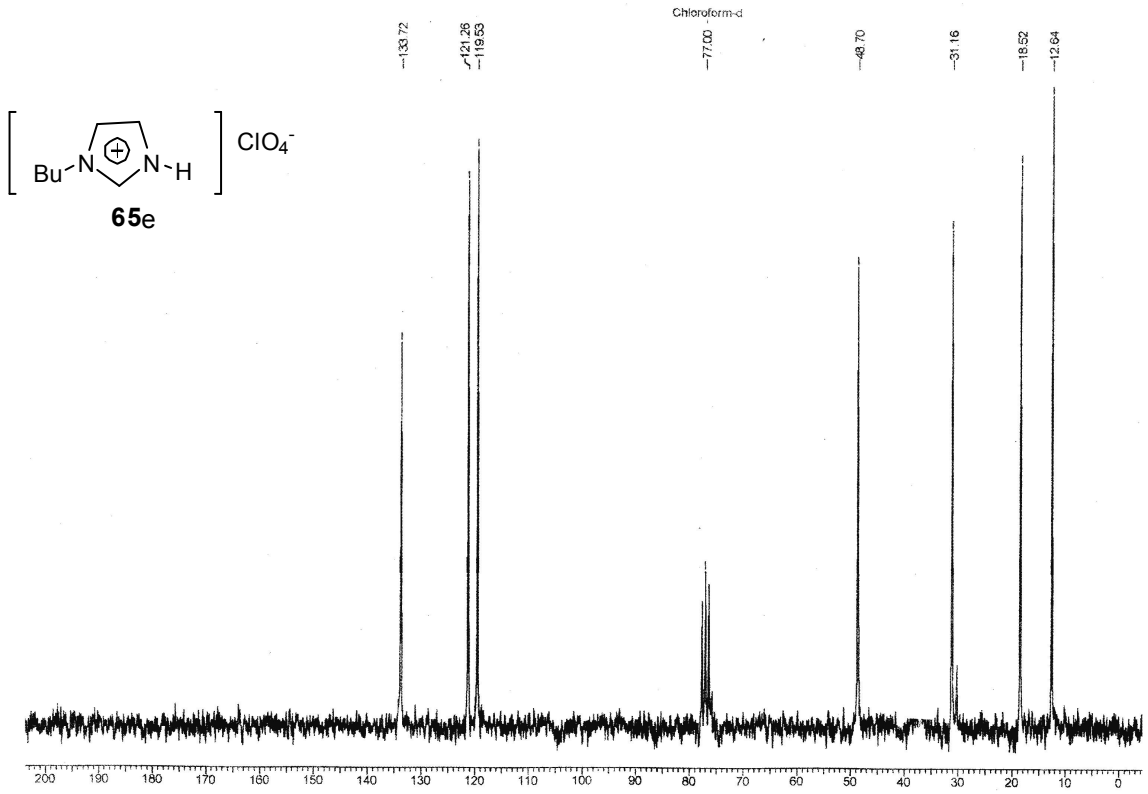
^{13}C-NMR spectrum of [Hbim]BF_4 (**65**c)



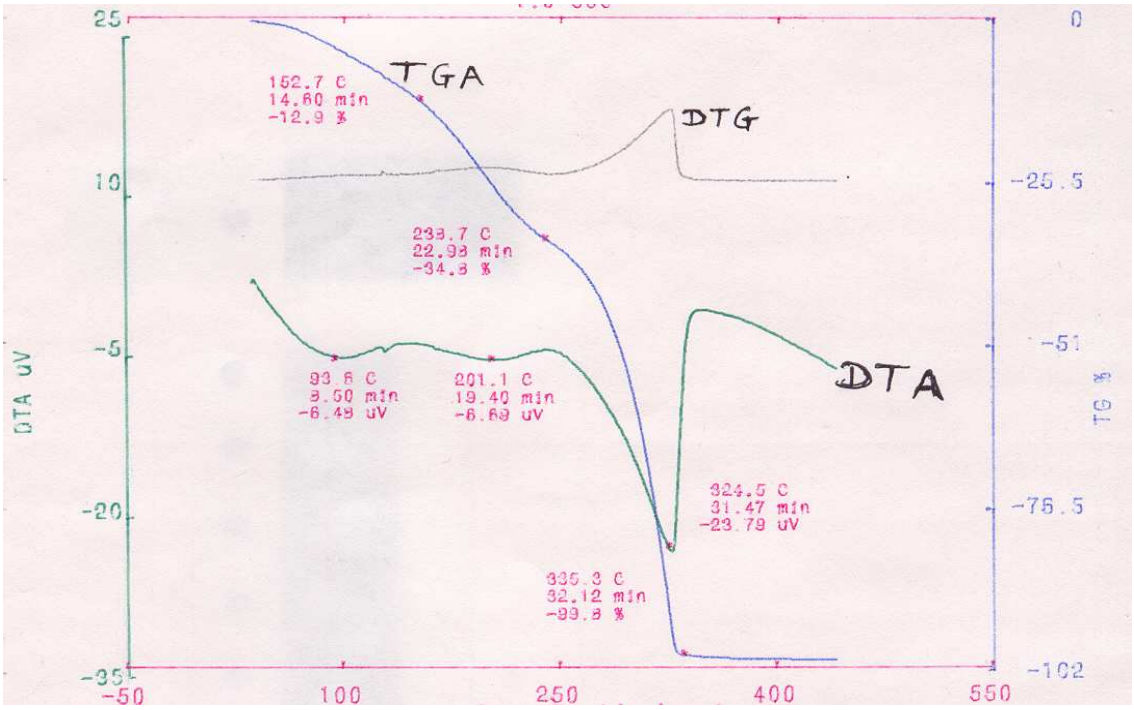
^{1}H-NMR spectrum of [Hbim]ClO_4 (**65**e)



^{13}C NMR spectrum of [Hbim]ClO_4 (**65**e)



TGA, DTG and DTA curves for [Hbim]BF_4 (65c)



Chapter-II

Sec-A

Acetylation of alcohols

2.1.0 Introduction

The ester moiety is a common functional group in polymers, drugs, and biologically relevant compounds such as sugars etc. In addition, the ester functionality serves as a protecting group for alcohols,[1a] among the various protecting groups which have been reported for alcohols, acetyl is the most common protecting group for this purpose because acetylation of alcohols is very easy under acidic condition. On the other hand, the deprotection *viz.*, hydrolysis of acetates will occur quantitatively under mild alkaline conditions.[1b] Obviously, thus the acylation of alcohols is one of the important and routinely utilized transformations in organic synthesis.[1a] Acid anhydrides have been the most commonly used reagents for the acylation of alcohols in the presence of an acid or base catalyst[2] and the utility of this protocol was boosted by the discovery of the (dimethylamino)pyridine (DMAP) catalyst.[3a] Bu_3P is a highly active promoter,[3b] and recently it has been shown that the optically active phosphine catalyst is efficient for kinetic resolution of racemic allyl alcohols.[3c] The aminophosphine superbase is another basic catalyst which is able to accelerate acetylation of alcohols with Ac_2O with high efficiency.[3d] Although the catalysts are very useful, some of them suffer from a number of drawbacks. For instance, even though the above mentioned phosphorus catalysts are useful with regard to high catalytic activities, the procedure is tedious because all the manipulation should be performed under anhydrous and degassed conditions due to the instability of the phosphorus catalysts in air. In parallel $Sc[(OTf)_3]$[3e] is highly active so that even tertiary alcohol could be acylated smoothly. However, the acylation with this catalyst must be carried out under anhydrous conditions and occasionally at low temperatures to suppress elimination. Although $Me_3Si(OTf)$[3f] is one of the most powerful activators of acid anhydrides, the silyl triflates are labile toward moisture, and therefore the silyl triflate-catalyzed acylation must be carried out under strictly anhydrous conditions. Moreover, Lewis acids such as $ZnCl_2$,[4] Zeolites such as H-beta,[5] and enzymes such as Lipases have also been reported for the acetylation reaction of alcohols.[6]

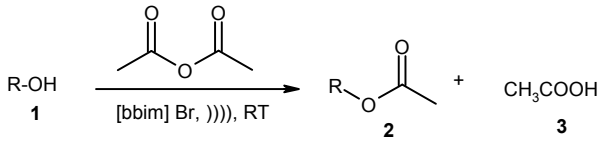
2.1.1 Present work

Despite a number of precedents, new efficient methodologies for acylation are still in strong demand. The sonochemical methodology developed by us circumvents all the above mentioned drawbacks since the non-volatile IL can be efficiently recovered and reused and

the process does not require any additional catalyst since the IL itself promotes the reaction.

2.1.2 Results and discussion

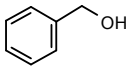
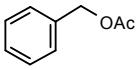
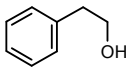
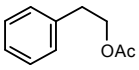
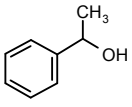
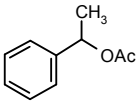
A variety of alcohols including aryl-alkanols, alkanols, cinnamyl alcohol, menthol, and carbohydrates were subjected to the *O*-acetylation with acetic anhydride in the IL, 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) as the solvent at ambient temperature (30 ^{o}C) under ultrasonic irradiation (Scheme **1**).

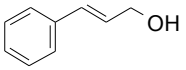
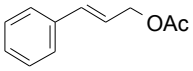
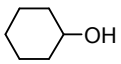
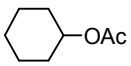
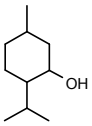
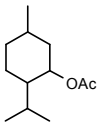
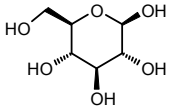
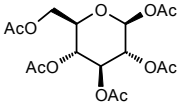
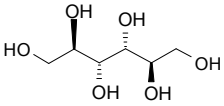
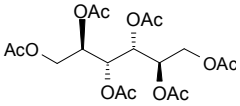
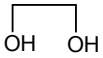
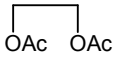
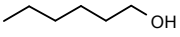
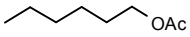
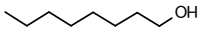
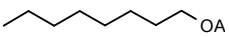


Scheme **1**

The reactions were monitored by TLC and taken to completion. The same reactions were performed under stirring without ultrasound (silent reactions) maintaining similar conditions. The time taken for complete conversion and the isolated yields are recorded in Table **1**. All the isolated products are known compounds reported in the literature. They were well characterized by their physical constants such as boiling points, melting points and additionally optical rotation for the chiral compounds. Their IR, ^{1}H-NMR, mass spectral and elemental analyses were in conformity with their structures.

Table 1 *O*- acetylation of alcohols under sonication and silent conditions

Entry	Alcohol (**1**a – k)	Time for complete conversion, min		Product (**2**a – k)	Yield (%)[a]		Physical Constants
		)))))	Silent		)))))	Silent	
1	 1a	5	60	 2a	95	91	Bp 132 ^{o}C at 102mmHg[7]
2	 1b	5	60	 2b	94	93	Bp 104 ^{o}C at 20mmHg[8]
3	 1c	5	55	 2c	92	90	Bp 94 ^{o}C at 12mmHg[8]

Entry	Alcohol (**1**a – k)	Time for complete conversion, min		Product (**2**a – k)	Yield (%)[a]		Physical Constants
		)))))	Silent		)))))	Silent	
4	 1d	5	20	 2d	93	90	Bp 263 °C at 760mmHg[9]
5	 1e	10	60	 2e	95	80	Bp 170 °C at 760mmHg[9]
6	 1f	30	180	 2f	90	50	Bp 116 °C at 25mmHg[10]
7	 1g	10	120	 2g	91	74	Mp 131 °C[11] $[\alpha]_{D=}$ +5.33° (c=5 in $CHCl_3$)
8	 1h	30	120	 2h	80	72	Mp 123 °C[12] $[\alpha]_{D=}$ +25° (c=5 in $CHCl_3$)
9	 1i	30	180	 2i	95	90	Bp 187 °C at 760mmHg[13]
10	 1j	65	600	 2j	65	61	Bp 168 °C at 1mmHg[9]
11	 1k	60	600	 2k	62	59	Bp 43 °C at 0.3mmHg[14]

[a]isolated yields.

All the reactions proceed to completion in just 5 to 30 min under ambient temperature except for 1-hexanol and 1-octanol for which 60 min of sonication was necessary under the same conditions. The respective esters were isolated in high purity and excellent yields (Table **1**). Importantly, most of the esters, which are liquids, were isolated by simple process of fractional distillation under reduced pressure leaving behind the ionic liquid. The solid esters viz., the carbohydrate esters (Table **1**, Entry **7** and **8**) were selectively extracted into 20% petroleum ether (bp 60-80 °C) in ethyl acetate leaving behind the IL as an immiscible layer. The separation of the organic layer and removal of the solvent under reduced pressure furnished the pure esters. The recovery of the IL in each case was 98%.

The IL, thus recovered, could be reused at least four times in the *O*-acetylation of benzyl alcohol without loss of activity.

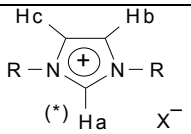
The role of ultrasound in promoting the *O*-acetylation is evident from the fact that the corresponding reactions under stirred conditions without ultrasound (silent reactions) needed relatively much longer time for complete conversion, in many cases in lowered yields (Table **1**). Likewise, the unique role of ionic liquid in promoting the sonochemical reaction was evident from the fact that the *O*-acetylation of benzyl alcohol with acetic anhydride in molecular solvents such as dichloromethane, acetonitrile, chloroform, toluene and hexane under ultrasonic irradiation did not show any conversion even after several hours of sonication.

Significantly, it was observed that the sonochemical acetylation of the carbohydrates *viz.*, D-(+)-glucose and D-(+)-mannitol gave the corresponding esters *viz.*, 1,2,3,4,6-pentaacetyl-β-D-glucose and D-(+)-mannitol hexaacetate respectively stereo specifically with retention of configuration. This was indicated by comparing their melting points and optical rotation with values reported in literature (Table **1**).

The sonochemical acetylation of benzyl alcohol was carried out in non-imidazolium ILs such as ethylammonium nitrate and 1-*n*-butyl-pyridinium tetrafluoroborate respectively. In both the cases, the reaction did not proceed beyond 50% conversion even after several hours of sonication. This highlights the role of the imidazolium IL used in the present work which by virtue of its inherent Lewis /Brønsted acidities of the imidazolium ring and its ring protons promoted the reaction to complete conversion.

The efficacy of the ILs to promote these sonochemical acetylation reactions was correlated to the nature of the anions. It was assumed that the nature of the anion will govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidities of the ILs. Thus the sonochemical acetylation of benzyl alcohol was performed in different 1,3-di-*n*-butyl imidazolium ILs, [bbim]X, with varying anions. The results are recorded in Table **2**. The time for the complete conversion was then correlated to the most deshielded imidazolium proton (H_a) chemical shifts (Table **2**) indicative of the Lewis/ Brønsted acidities of the different ILs. It was observed that the reaction becomes progressively faster with increasing Lewis/ Brønsted acidity of the ILs as indicated by the increasing downfield shift of the imidazolium proton H_a.

Table 2 *O*-acetylation of benzyl alcohol (**1a**) to benzyl acetate (**2a**) in various ionic liquids under sonication

Entry	Ionic Liquid	 (a)	Time for complete conversion/ min	Yield (%)[b]
1	[bbim]Cl	10.6	5	90
2	[bbim]Br	10.3	5	95
3	[bbim]ClO_4	9.02	15	89
4	[bbim]BF_4	8.87	25	90
5	[bbim]PF_6	8.86	30	91

[a]chemical shift, δ-value, of H_a Proton in ppm.
[b]isolated yields.

The possible hydrogen bond (Lewis/Brønsted acid) interaction of the most acidic hydrogen, H_a, of the imidazolium cation with the oxygen of the acetic anhydride as shown in Fig. **1,** facilitates the generation of an acetyl cation required for the reaction. The influence of the acidity of this H_a proton for promoting the reaction was unequivocally established by conducting the sonochemical acetylation of benzyl alcohol in the ILs 1-*n*-butyl-2,3-dimethylimidazolium tetrafluoroborate, ([bdmim]BF_4) and 1,3-di-*n*-butyl-2-methylimidazolium bromide ([bbmim]Br) respectively. The conversions do not go beyond 50 and 54% respectively even after 5 h of sonication.

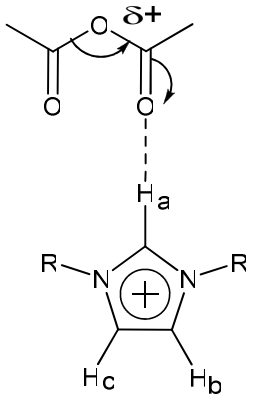


Fig. **1** The H_a (most acidic) hydrogen bond interaction of imidazolium cation with oxygen of acetic anhydride.

2.1.3 **Conclusion**

The *O*-acetylation of alcohols with acetic anhydride to the corresponding esters has been achieved in short reaction times with excellent isolated yields under ambient conditions without the need for any additional catalyst by the combined use of ultrasonic irradiation and a 'green' room temperature ionic liquid as a reaction medium and promoter. The esters could be easily isolated from the reaction mixture either by fractional distillation or selective extraction leaving behind the non-volatile IL pure enough for reuse in several recycles. Thus, this novel methodology is an improved practical alternative to conventional acid/base catalyzed thermal processes and is environment friendly with minimal waste. This work is already peer reviewed and published in *Green Chemistry*, **2003**, *5*, 693.

2.1.4 **Experimental**

2.1.4.1 Preparation of different ionic liquids

The ILs [bbim]X (where X = Br, Cl, BF_4, ClO_4 and PF_6) were prepared as per the methods reported in **Chapter-I** (Sec-C). The IL, [bdmim]BF_4, was procured from ACROS Organics and used as such.

2.1.4.2 Synthesis of 1-butyl-2-methylimidazole

2-methylimidazole (10g, 122 mmol) and KOH (7.5g, 134 mmol) in 25 mL of acetonitrile was stirred for 1 h. *n*-butyl bromide (16g, 122 mmol) was added drop wise to the above mixture over 45 min maintaining the temperature of the reaction mixture by external cooling at 10-15 ^oC. The resulting mixture was further stirred for 3 h at 30 ^oC. The reaction mixture was filtered to remove KBr and the solvent was distilled off under reduced pressure to leave behind a pale brown liquid. This was further subjected to distillation under reduced pressure (170 ^oC/5mm) to yield pure product as a colorless liquid.

Yield	13.25g, 79%
IR($CHCl_3$, cm^{-1}) υ_{max}	3369, 2960, 2933, 2874, 1667, 1618, 1525, 1499, 1465, 1425, 1364, 1276, 1219, 1144, 1099, 1072, 985, 949, 918,

	753, 729.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.30 (m, 2H), 1.65 (m, 2H), 2.31 (s, 3H), 3.76 (t, *J* = 2.0 Hz, 2H), 6.75 (s, 1H), 6.84 (s, 1H).
Elemental Analysis	Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27%. Found: C, 69.42; H, 10.30; N, 20.35 %.

2.1.4.3 Synthesis of 1,3-di-*n*-butyl-2-methylimidazolium bromide, [bbmim]Br

A mixture of 1-butyl-2-methylimidazole (12g, 87 mmol) and *n*-butyl bromide (12.5g, 91 mmol) was heated at 90 ^oC for 6 h and the reaction was followed by TLC using 2% methanol in ethyl acetate as eluent. After completion of the reaction, excess *n*-butyl bromide was removed at 80 ^oC under reduced pressure (10 mmHg) to afford the required ionic liquid as a colorless thick viscous liquid.

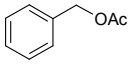
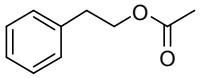
Yield	21.8g, 95.4%.
IR($CHCl_3$, cm^{-1}) υ_{max}	3662, 3393, 3173, 3062, 3018, 2961, 2934, 2876, 2453, 1667, 1619, 1583, 1530, 1465, 1383, 1336, 1296, 1245, 1216, 1197, 1136, 1116, 1083, 947, 925, 881, 751.
^{1}H NMR (300 MHz, $CDCl_3$)	δ 0.89 (t, *J*=7.2 Hz, 6H), 1.32 (m, 4H), 1.75 (m, 4H), 2.76 (s, 3H), 4.23 (t, *J* = 7.2 Hz, 4H), 7.59 (s, 1H).
Elemental Analysis	Anal. Calcd. for $C_{12}H_{23}N_2Br$: C, 52.36; H, 8.36; N, 1018 %. Found: C, 52.15; H, 8.64; N, 10.33 %.

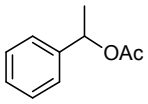
2.1.4.4 General procedure for the sonochemical acetylation

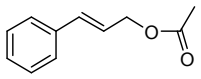
A mixture of alcohol (10 mmol) and acetic anhydride (11.1 mmol) in 1,3-di-*n*-butyl imidazolium bromide ([bbim]Br, 2.0g) was sonicated in an atmosphere of argon at ambient conditions in a thermostated (30 ± 1 ^oC) ultrasonic cleaning bath. The reactions were monitored by TLC and taken to completion. The same reactions were performed under stirring without ultrasound (silent reactions) maintaining similar conditions. After the complete conversion, all the esters except those of carbohydrates (Entries **7** and **8**), which

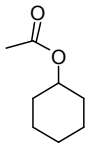
are liquids, were isolated by subjecting the reaction mixture to fractional distillation under reduced pressure leaving behind the non-volatile IL. After the recovery of acetic acid as the first fraction, esters were distilled out at their respective boiling points as indicated in Table **1**. Alternatively, the solid esters (Table **1**, Entries **7** and **8**) were completely and selectively extracted into 20% petroleum ether (bp 60-80 ^{o}C) in ethyl acetate (2 × 25 ml) leaving behind the IL as an immiscible layer. The separation of the organic layer and removal of the solvent under reduced pressure furnished the pure esters. In both the cases the recovered IL was pure enough for use in several recycles.

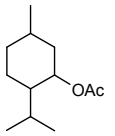
2.1.5 Characterization data

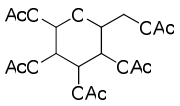
Benzyl acetate, 2a	
IR ($CHCl_3$, υ_{max})	2936, 1727, 1357, 1240 cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$)	δ 2.00 (s, 3H), 5.01 (s, 2H), 7.19-7.30 (m, 5H).
Elemental Analysis	Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%. Found: C, 71.91; H, 6.63%.
MS (m/z)	150 (M^+)
Phenylethyl acetate, 2b	
IR($CHCl_3$, υ_{max})	3032, 3025, 1742, 1385, 1240, 1053749 cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 2.05 (s, 3H), 3.0 (t, 2H), 4.30 (t, 2H), 7.25-7.40 (m, 5H).
Elemental Analysis	Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37%. Found: C, 73.22; H, 7.31%.

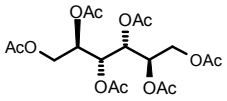
1-phenylethyl acetate, 2c	
IR($CHCl_3$, υ_{max})	2960, 1758, 1426, 1372, 1213, 1033 cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 1.45 (d, 3H), 1.99 (s, 3H), 5.78 (q, *J* = 6.0 Hz, 1H), 7.17-7.28 (m, 5H).
Elemental Analysis	Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37%. Found: C, 73.21; H, 7.44%.
MS (m/z, rel. int. %)	164 (M^+)

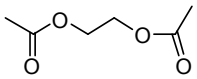
Cinnamyl acetate, 2d	
IR($CHCl_3$, υ_{max})	3025, 2875, 1730, 1488, 1382, 1232, 1025, 966, 746 cm^{-1}.
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 2.11 (s, 3H), 4.75 (d, 2H), 6.27-6.30 (m, 1H), 6.65 (d, 1H), 7.25-7.41 (m, 5H).
Elemental Analysis	Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86%. Found: C, 74.92; H, 6.93%.
MS (m/z, rel. int. %)	176 (M^+)

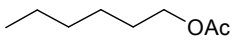
Cyclohexyl acetate, 2e	
IR($CHCl_3$, cm^{-1}) υ_{max}	2980, 1740, 1464, 1215 cm^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 1.20-1.25 (m, 1H), 1.32-1.39 (m, 4H), 1.49-1.53 (m, 1H), 1.69-1.71 (m, 2H), 1.82-1.84 (m, 2H), 2.01 (s, 3H), 4.71 (m, 1H).
Elemental Analysis	Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92%. Found: C, 67.52; H, 9.99%.
MS (m/z)	142 (M^+)

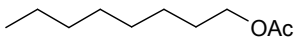
Menthol acetate, 2f	
IR($CHCl_3$, υ_{max})	2926, 1715, 1225, 1007 cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$)	δ 0.75 (d, *J* = 6.5 Hz, 3H), 0.85 (s, 3H), 0.9 (s, 3H), 0.95-2.1 (m, 9H), 2.2 (s, 3H), 4.7 (m, 1H).
Elemental Analysis	Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%. Found: C, 72.60; H, 11.25%.
MS (m/z)	198 (M^+)

D-glucose penta-*O*-acetate, 2g	
IR($CHCl_3$, υ_{max})	2955, 2335, 1747, 1371, 1218, 1146 cm^{-1}
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 2.00-2.25 (s, 15H), 4.09-4.13 (m, 2H), 4.24-4.29 (m, 1H), 5.06-5.20 (m, 2H), 5.48 (t, 1H), 6.35 (d, 1H).
Elemental Analysis	Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68%. Found: C, 49.30; H, 5.74%.

D-mannitol hexa-*O*-acetate, 2h	
IR($CHCl_3$, υ_{max})	3065, 1759, 1363, 1200 cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$)	δ 2.04 (s, 6H), 2.06 (s, 6H), 2.08 (s, 6H), 4.04 (d, *J* = 5.0 Hz, 1H), 4.06 (d, *J* = 5.0 Hz, 1H), 4.20 (m, 2H), 5.06 (m, 2H), 5.43 (d, 2H).
Elemental Analysis	Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03%. Found: C, 49.72; H, 5.95%.
MS (m/z)	375 [M^+-59]

Glycol diacetate, 2i	
IR($CHCl_3$, υ_{max})	3065, 2948, 1734, 1366, 1217, 1040 cm^{-1}
^{1}H-NMR (300 MHz, $CDCl_3$)	δ 2.09 (s, 6H), 4.27 (s, 4H).
Elemental Analysis	Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90%. Found: C, 49.37; H, 6.99%.
MS (m/z)	146 (M^+)

1-hexyl acetate, 2j	
IR ($CHCl_3$, υ_{max})	3020, 2956, 1720, 1250 cm^{-1}.
^{1}H-NMR (500 MHz, $CDCl_3$)	δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.25-1.45 (m, 6H), 1.5-1.7 (m, 2H), 2.1 (s, 3H), 4.1 (t, *J* = 6.9 Hz, 2H).
Elemental Analysis	Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18%. Found: C, 66.55; H, 11.27%.

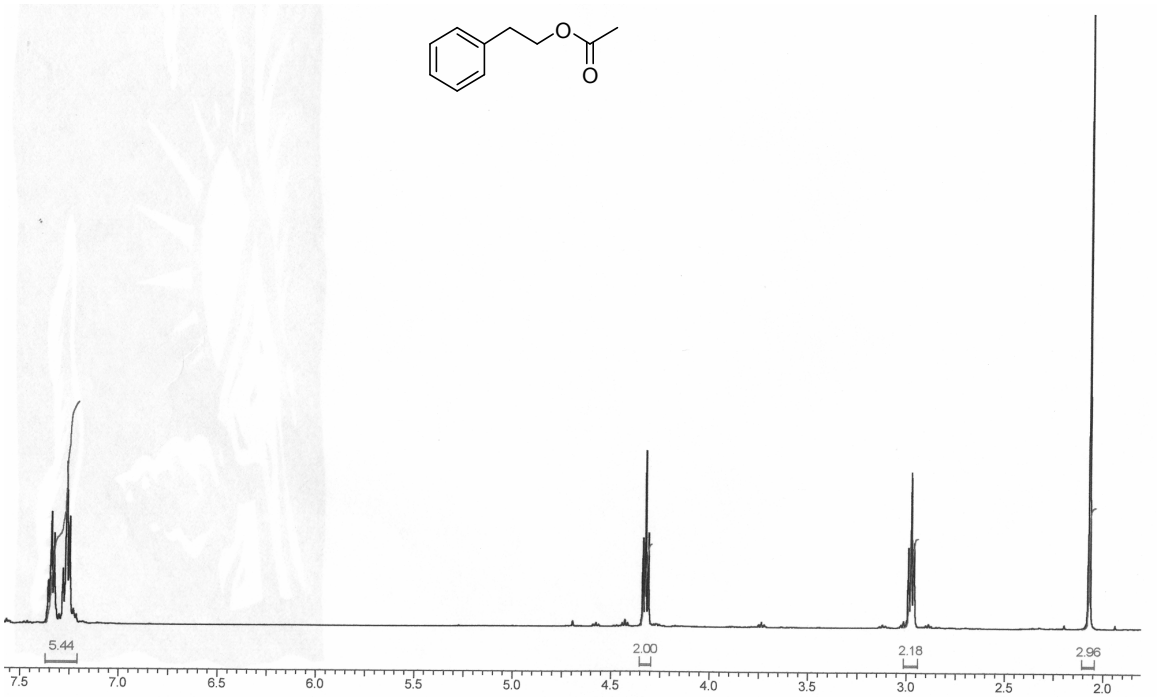
1-octyl acetate, 2k	
IR ($CHCl_3$, υ_{max})	3020, 2955, 1721, 1252 cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$)	δ 0.86 (t, *J* = 7.4 Hz, 3H), 1.20-1.30 (m, 11H), 1.56-1.63 (m, 2H), 2.02 (s, 1H), 4.01 (t, *J* = 7.4 Hz, 2H).
Elemental Analysis	Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%. Found: C, 69.79; H, 11.79%.

2.1.6 Spectra

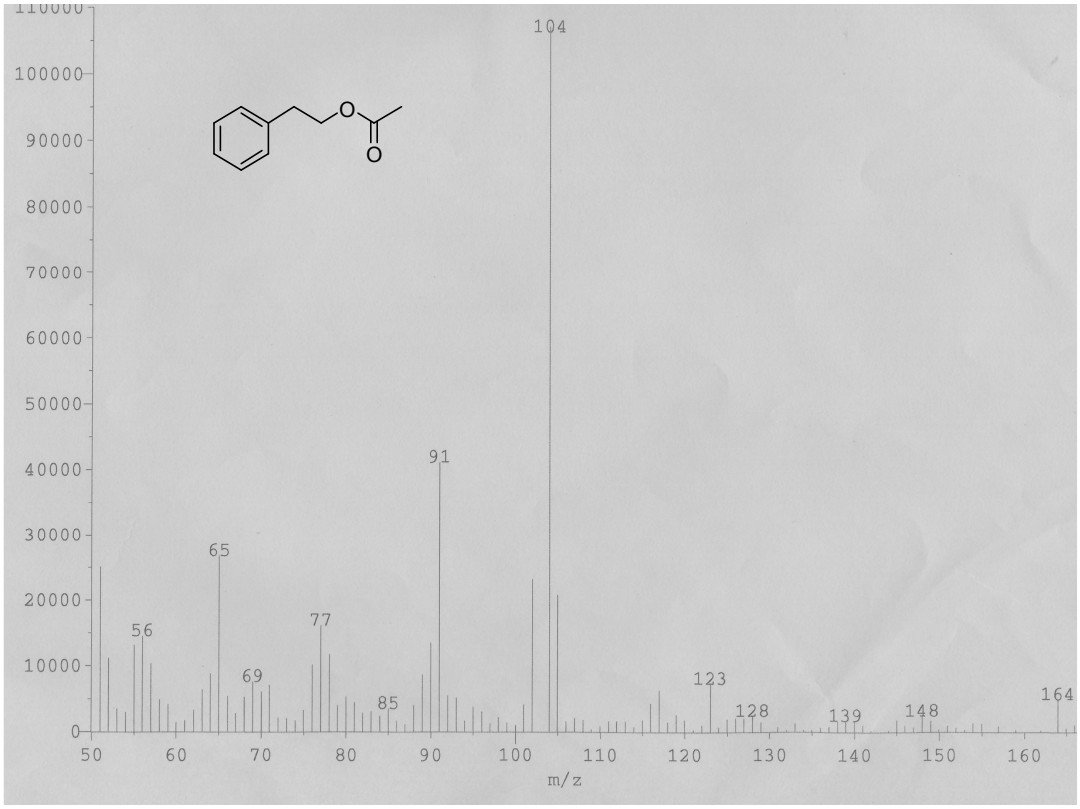
Table 3: ^{1}H-NMR spectrum /MS of some selected acetates are given below:

S No.	Spectra
1	^{1}H-NMR spectrum of **2b**
2	MS of **2b**
3	^{1}H-NMR spectrum of **2d**
4	MS of **2d**
5	^{1}H-NMR spectrum of **2g**
6	^{1}H-NMR spectrum of **2h**
7	^{1}H-NMR spectrum of **2i**
8	^{1}H-NMR spectrum of **2k**

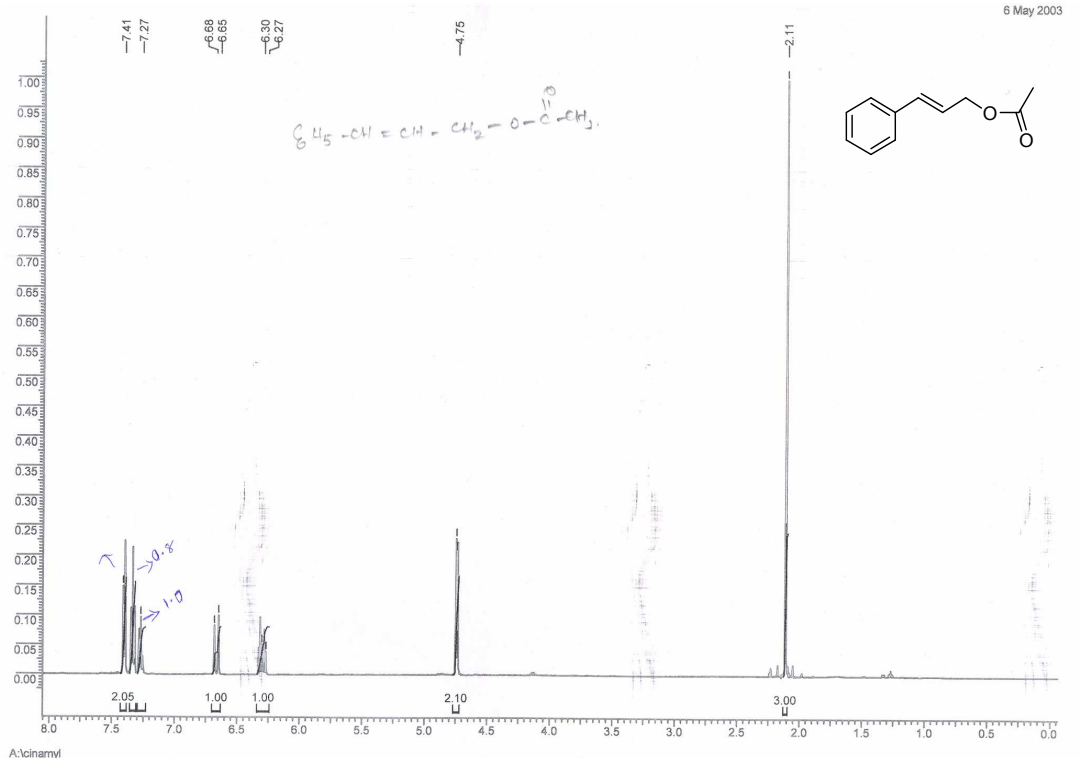
^{1}H-NMR spectrum of **2b**



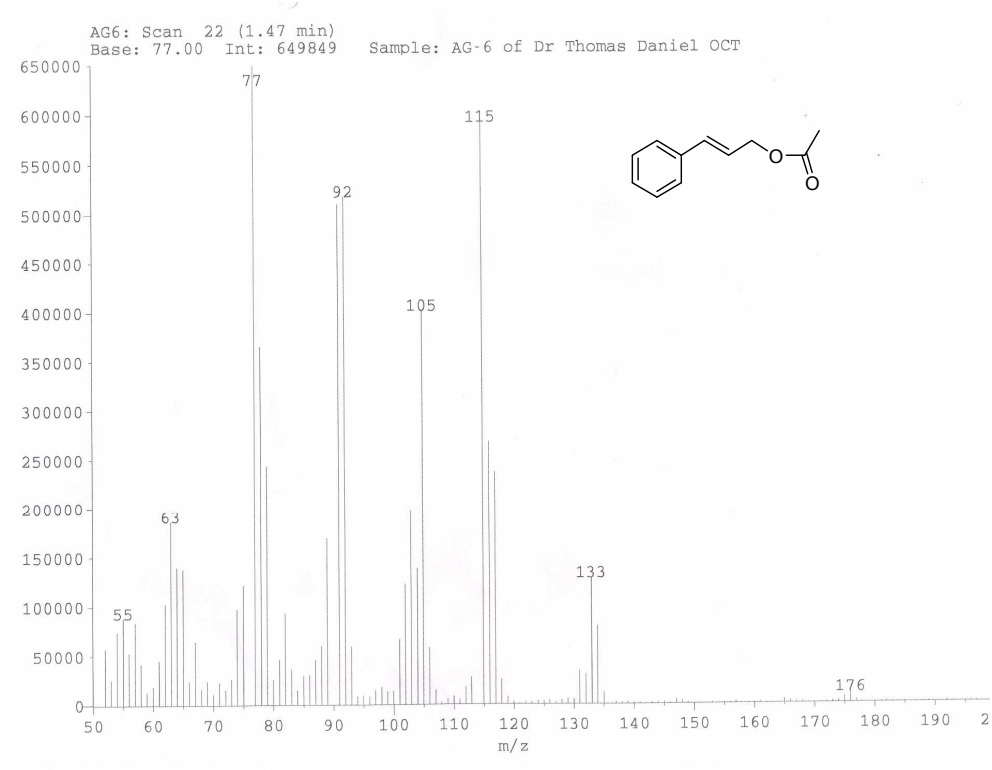
MS of **2b**



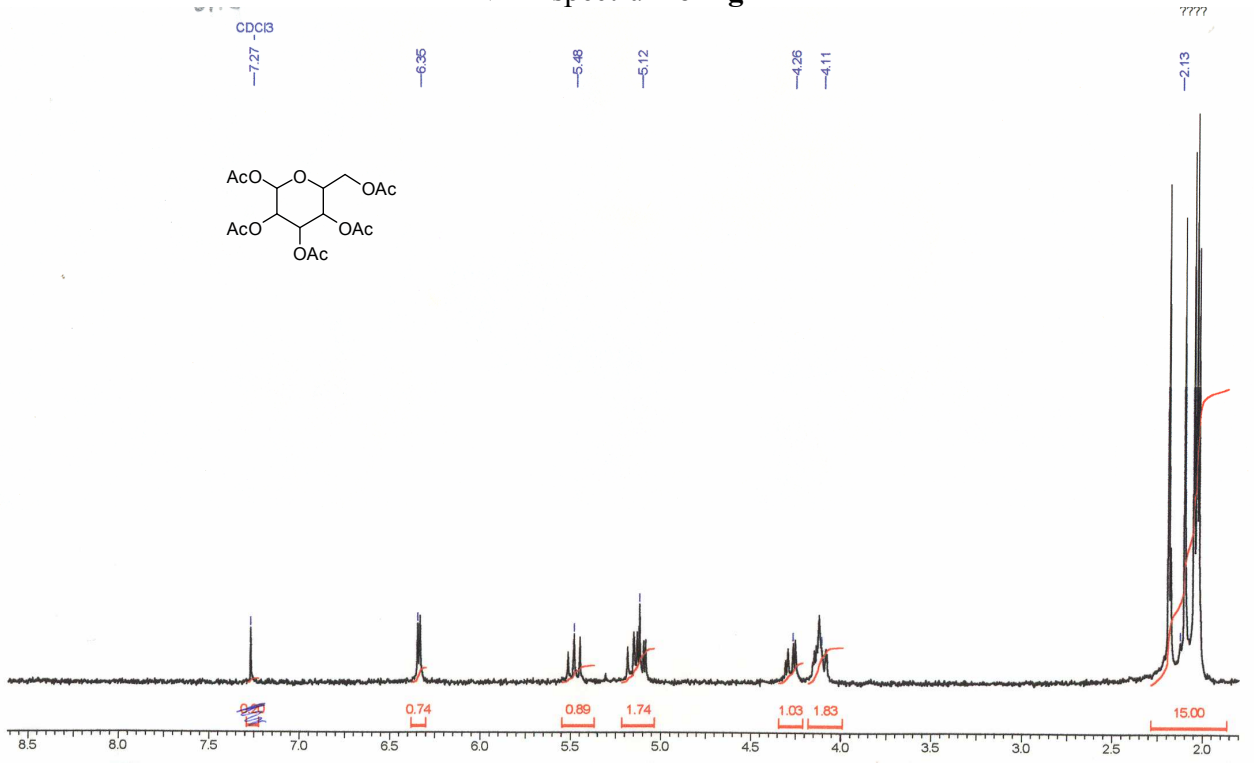
^{1}H-NMR spectrum of **2d**



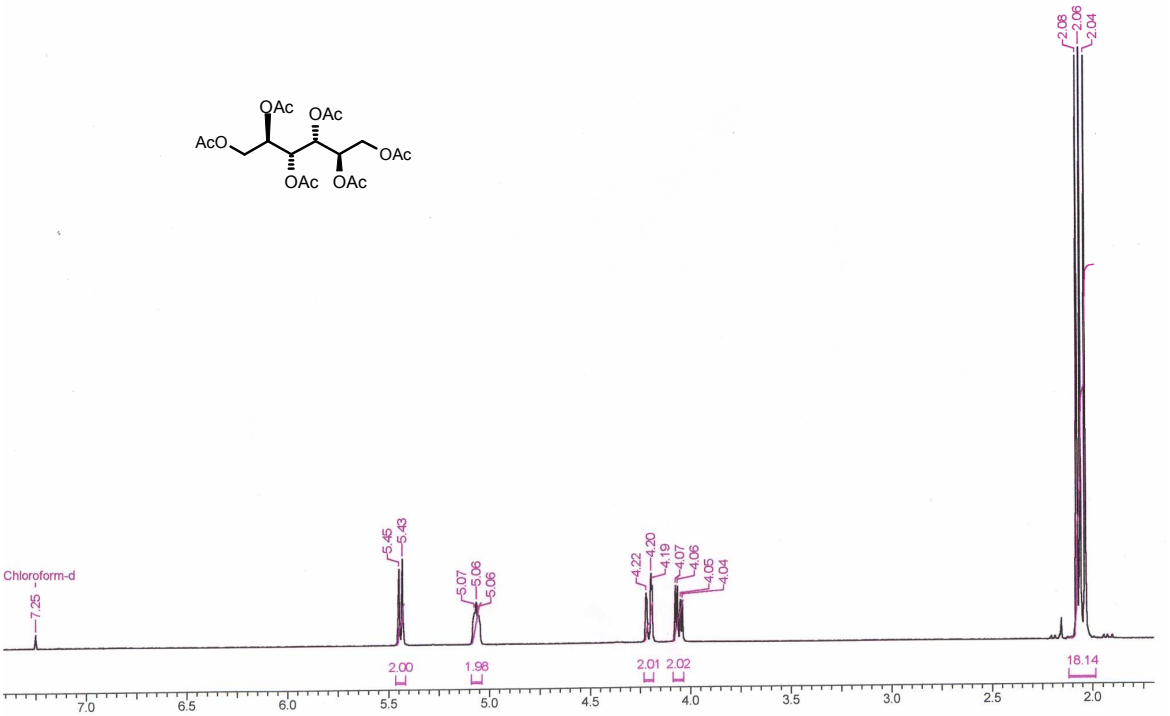
MS of **2d**



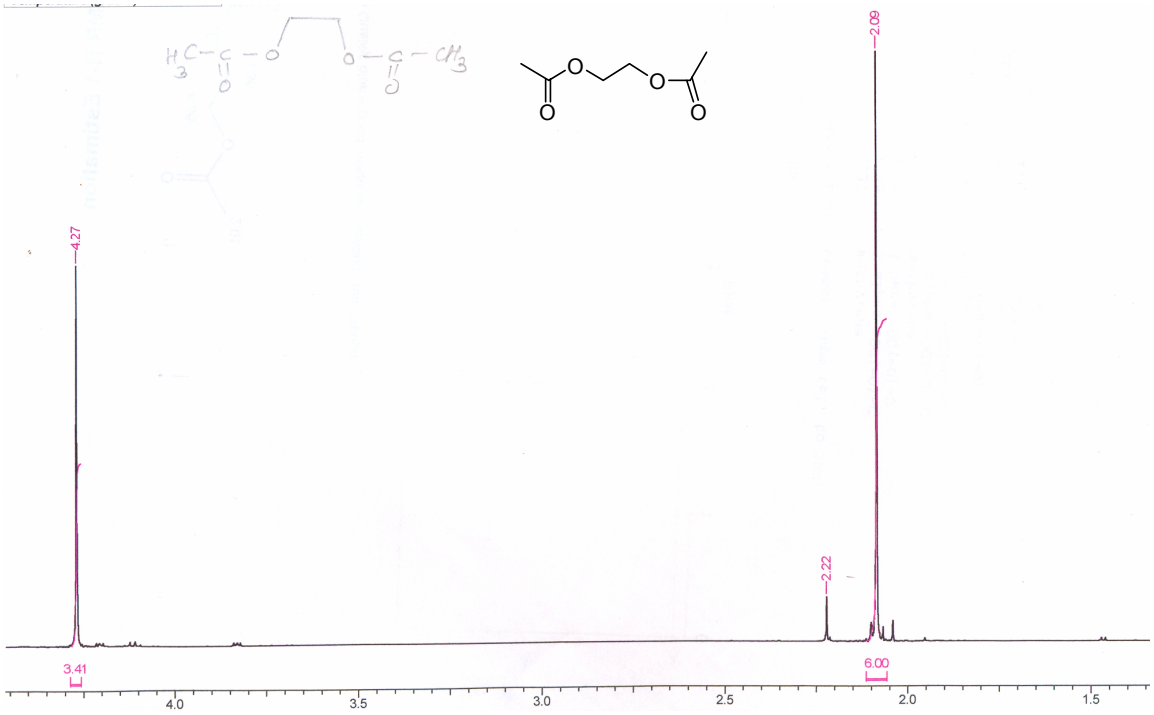
^{1}H-NMR spectrum of **2g**



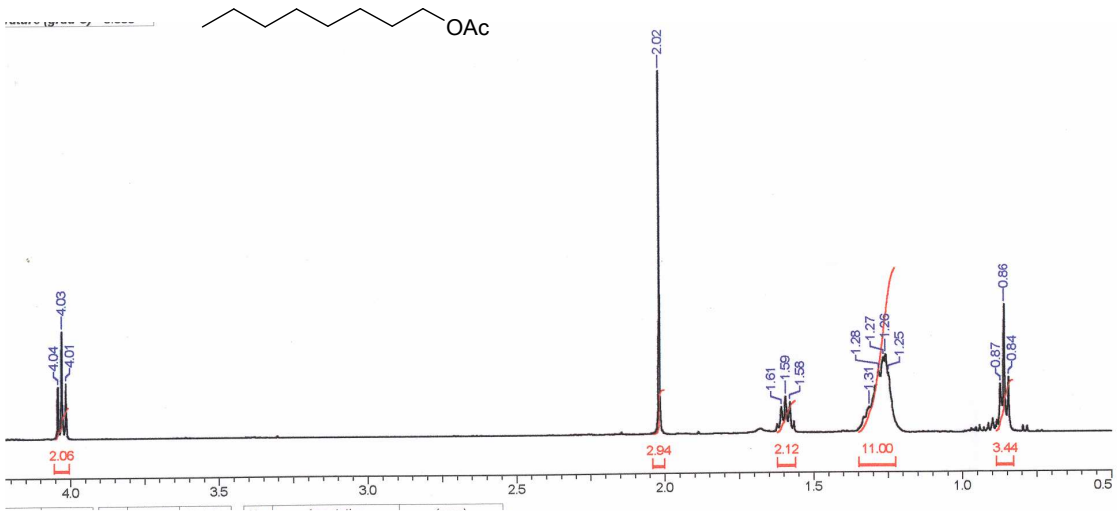
^{1}H-NMR spectrum of **2h**



^{1}H-NMR spectrum of **2i**



^{1}H-NMR spectrum of **2k**



2.1.7 References

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Chapter-II

Sec-B

Synthesis of 1,8-dioxo-octahydroxanthene derivatives

2.2.0 Introduction

Xanthene derivatives have attracted considerable interest in recent years because of their promising activity as positive allosteric modulators of metabotropic (mGlu) receptors[1] and potent non-peptidic inhibitors of recombinant human calpain I.[2] They have been used as rigid carbon skeletons for the construction of new chiral bidentate phosphine ligands with potential applications in catalytic processes.[3] In particular, xanthene-diones constitute a structural unit in a number of natural products[4] and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring.[5]

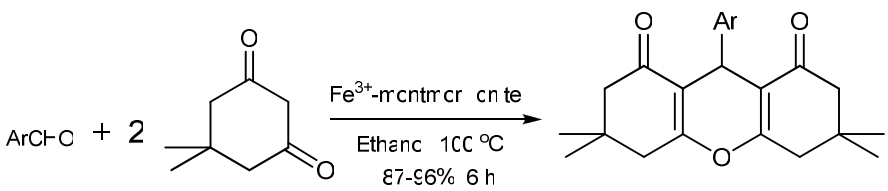
The use of ultrasound in organic transformation is now well known to enhance reaction rates and yields/selectivity of reactions, and in several cases facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure.[6a-b] The driving energy is provided by cavitation, the formation and collapse of bubbles, which liberates considerable energy in short times (For a brief review, see **Chapter I, Sec-B**). In recent times, the use of room temperature ionic liquids (ILs) as 'green' solvents in organic synthetic processes has gained considerable importance due to their negligible vapour pressure, solvating ability and easy recyclability[6c-d] (**Chapter I, Sec-A**). These ionic liquids have no vapour pressure, which should change considerably the characteristics of cavitation in the bulk.

2.2.1 Review of Literature

In recent years, several improved procedures have been reported for the synthesis of xanthenes, some of the recent methods are discussed below.

Yang's approach (2007)[7]

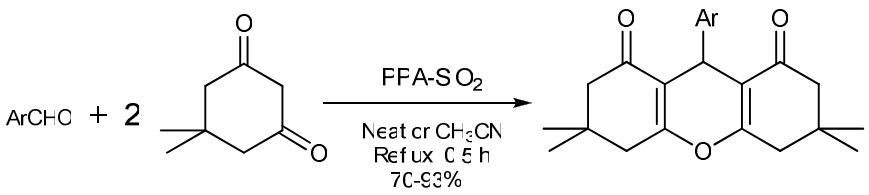
Yang *et al.* synthesized xanthene derivatives through the condensation reactions between aromatic aldehydes and dimedone using Fe^{3+}-montmorillonite as a catalyst (Scheme **2**).



Scheme 2

Srinivas's approach (2007)[8]

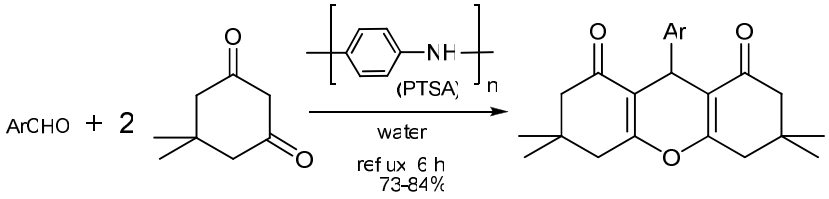
Srinivas and co-workers synthesized xanthene derivatives utilizing polyphosphoric acid–SiO_2 as an efficient catalyst (Scheme **3**).



Scheme 3

Palaniappan's approach (2006)[9]

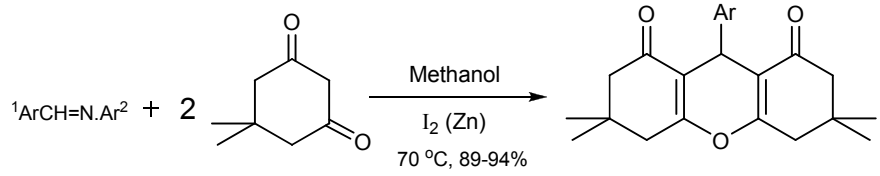
An efficient and straightforward procedure for the synthesis of 1,8-dioxo-dodecahydroxanthene was achieved through one-pot condensation of arylaldehyde and 1,3-cyclohexanedione in the presence of polyaniline-*p*-tolulenesulfonate salt as polymeric solid acid catalyst (Scheme **4**).



Scheme 4

Rong's approach (2006)[10]

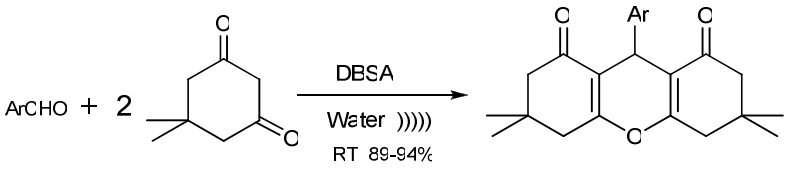
Rong and co-workers employed the molecular iodine and a catalytic amount of zinc powder as the catalyst to synthesize the xanthenediones derivatives in excellent yields (Scheme **5**).



Scheme 5

Jin's approach (2006)[11]

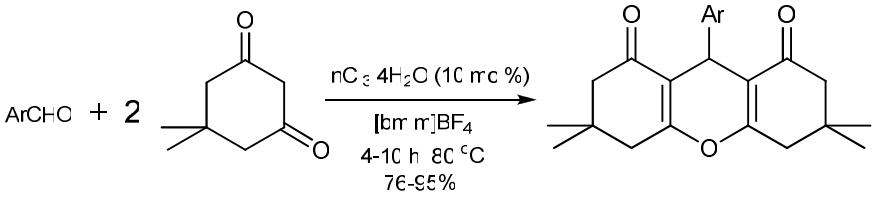
Jin and co-workers reported an efficient synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthene derivatives using p-dodecylbenzenesulfonic acid (DBSA) as the catalyst (10 mol.%) under ultrasound irradiation (Scheme **6**).



Scheme 6

Wang's approach (2005)[12]

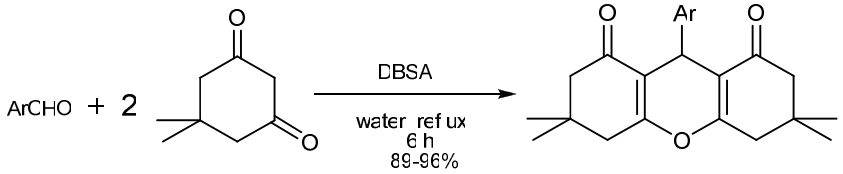
Wang and co-workers reported a green procedure for the synthesis of xanthenedione derivatives through $InCl_3 \cdot 4H_2O$-promoted condensation of aldehydes and 5,5-dimethyl-1,3-cyclohexanedione in ionic liquids (Scheme **7**).



Scheme 7

Jin's approach (2004)[13]

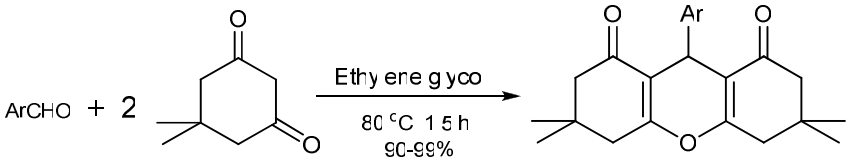
An efficient and convenient approach to the synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthene derivatives using *p*-dodecylbenezenesulfonic acid (DBSA) as the catalyst (10 mol%) is described (Scheme **8**).



Scheme 8

Tu's approach (2002)[14]

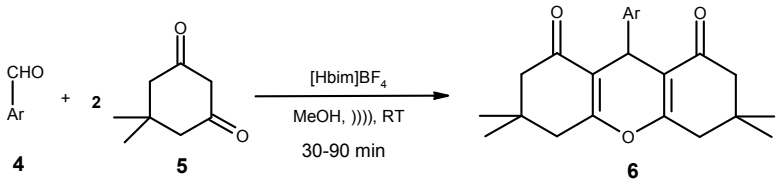
The condensation of aromatic aldehyde with 5,5-dimethyl-1,3-cyclohexanedione is carried out in ethylene glycol as solvent without catalyst (Scheme **9**).



Scheme 9

2.2.2 Present work

Even though there are many methods reported in the literature for the synthesis of xanthenes,[7-14] we thought that there is scope for further innovation towards milder reaction conditions, short reaction times and better yields in the synthesis of xanthenes, which was achieved by using "green" imidazolium ionic liquid, $[Hbim]BF_4$ (IL) as reaction media as well as promoter in the absence of any added catalyst under ultrasound irradiation at ambient conditions. We have compared the reaction times and yields for the *p*-TSA catalyzed synthesis of xanthenes under thermal conditions. It is noteworthy that the products, xanthenes, were isolated in excellent yields in short reaction times employing simple workup procedures and the non-volatile IL could be efficiently recovered and reused, and the process does not need any additional acidic/basic catalyst (Scheme **10**).



Scheme 10

2.2.3 Results and discussion

The Ionic liquid, $[Hbim]BF_4$, was synthesized by the method described in Chapter-I, Sec-C. A model reaction involving 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and benzaldehyde to afford the xanthene **6k** under various reaction conditions was performed for an appropriate time. The results are recorded in Table **4**.

Table **4**: The synthesis of xanthene **6k** under various reaction conditions**:**

S. No	Catalyst/Solvent	Reaction Conditions	Product	Yield (%)[a]
1	2 mL of MeOH + No catalyst	RT, 6h,)))))	**6k**	0
2	2 mL of $[Hbim]BF_4$ + No co-solvent	RT, 6h,)))))	**6k**	5[b]
3	2 mL of $[Hbim]BF_4$ + 0.5 mL of MeOH	RT, 6h,)))))	**6k**	85
4	2 mL of DMSO + No catalyst	RT, 6h,)))))	**6k**	0
5	2 mL of hexadecane + No catalyst	RT, 6h,)))))	**6k**	0
6	2 mL of NMP + No catalyst	RT, 6h,)))))	**6k**	0
7	2 mL of PEG-400 + No catalyst	RT, 6h,)))))	**6k**	0
8	2 mL of $[Hbim]BF_4$ + 0.5 mL of MeOH	RT stirring, 6h	**6k**	<5[c]

S. No	Catalyst/Solvent	Reaction Conditions	Product	Yield (%)[a]
9	*p*-TSA (5 mol%) + 4 mL of MeOH + 2 mL of water	50 ^{o}C, 20 min	**6k**	80
10	*p*-TSA (5 mol%) + 4 mL of MeOH + 2 mL of water	RT stirring, 24 h	**6k**	0
11	4 mL of MeOH + 2 mL of water + No catalyst	75-80 ^{o}C, 1h	**6k**	0
12	*p*-TSA (5 mol%) + 2 mL of water	75-80 ^{o}C, 1h	**6k**	0

[a] isolated yields.
[b] the substrate, dimedone, is sparingly soluble under this condition.
[c] dimedone (92%) and benzaldehyde (86%) were recovered back from the reaction mixture.

The sonochemical synthesis of xanthenes using IL containing 25 vol. % of MeOH in the IL was observed to be the most optimum condition for the synthesis of xanthenes in maximum yields at ambient temperature in the absence of any added catalyst. Hence, all further reactions with other aldehydes were carried out under these conditions. The IL acts as a Brønsted acid catalyst as well as a solvent at ambient temperature (30 ^{o}C) under ultrasonic irradiation (Scheme **10**). The MeOH was added as co-solvent to solubilize dimedone under this condition. A variety of aldehydes including aryl-, cinnamyl- and furyl- were subjected to the sonochemical conditions in the IL to afford the products (xanthenes) in very good yields in short reaction times. All the reactions were monitored by TLC and taken to completion. The time taken for complete conversion and the isolated yields are recorded in Table **5**. We also compared our results with the reaction rates for the p-TSA catalyzed synthesis of xanthenes under thermal conditions (Table **5**), which were comparable. However, this reaction did not proceed at ambient temperature under silent conditions. All the known and new products were well characterized by melting point, IR, ^{1}H-NMR and LC-MS analyses. For the known compounds, the values were in agreement with those reported in literature. No significant formation of product (**6**k) was observed, when the reaction was conducted under silent conditions, even after 6 h of stirring (stirring at 30 °C under silent conditions). The replacement of IL by molecular solvents such as DMSO, MeOH, hexadecane and PEG-400 did not result in the formation of the product (**6k**) even after 6 h of sonication and the unreacted starting materials were recovered.

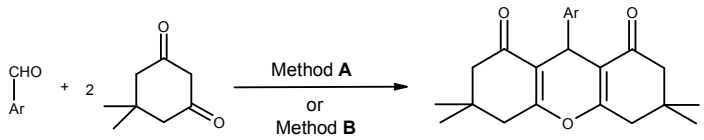
The process tolerates aromatic aldehydes containing both electron donating and electron withdrawing substituents. It can be observed that all the aldehydes have reacted in short

reaction times under ambient conditions to afford the xanthenes in good isolated yields. The products were easily isolated in almost pure state by dilution with excess of chilled water and filtration of the precipitated xanthenes. The xanthenes, thus isolated were homogeneous on TLC and were pure enough for all practical purposes. The mother liquor was subjected to distillation to remove methanol and water at 70 ^{o}C under high vacuum (10 mm Hg) to recover the IL pure enough for recycle. The IL was recycled three times without any loss in activity.

Thus, it becomes evident that it is the synergy of the combined use of the IL and ultrasound irradiation that has facilitated this efficient protocol. The synergy of the combined use of IL and ultrasound is best explained in terms of the 'hot spot' model of the cavitation phenomenon. Due to the non-volatility of the IL, the atmosphere of the cavitation bubble will contain only the vapour of the solute with none of the solvent vapours. It may be noted that in the case of molecular solvents which have significant vapour pressure, the atmosphere of the bubble will consist in addition to the vapours of the solute, the vapours of the solvent also which may retard the actual sonochemical process as well as bring about a decrease in selectivity with the solvent itself participating in the reaction or by its sonochemical degradation. The solvent vapours also exert a cushioning effect limiting the efficiency of cavitation. The exclusion of the solvent vapours in the cavitation bubble will lead to the increased intensity of cavitational collapse enhancing the reaction rates and selectivity. Thus, a logical conclusion is that cavitation bubbles in ILs should contain essentially the molecules of the solute, leading to their preferential activation without participation of the solvent. This activation should result in increased rates of the thermolytic processes, if the whole reaction occurs inside the cavity. If this is not so, the increased intensity of cavitation leading to high intensity micro-streaming enhances mass and heat transfer in the IL which in turn can generate reactive intermediates, nano-particles etc species which can take part in reactions at the interface and bulk of the medium. On the other hand, it is also possible that the strong polarity of the ILs should stabilize charges in reaction intermediates, broadening thus the domain of the sonochemistry to polar pathways, of low sensitivity to sonication up to now. It can thus be deduced that sonochemistry in ILs should offer a number of advantages which was indeed found to be the case in the present work wherein enhanced reaction rates and

selectivity/yields at ambient temperature was achieved whereas no reaction was observed when the reaction was performed in high boiling molecular solvents such as DMSO, NMP, hexadecane and PEG-400.

Table 4: **The Synthesis of xanthene derivatives 6(a-n) under sonochemical thermal and conditions:**

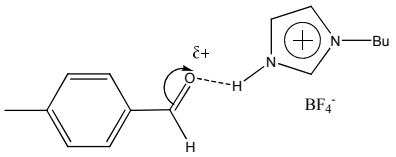


S. No	Ar-	Reaction time (min)		Product	Yield (%)[a]		mp (°C)
		IL catalysis, Method-A	*p*-TSA catalysis, Method-B		IL catalysis, Method-A	*p*-TSA catalysis, Method-B	
1	4-methylphenyl-	60	25	**6a**	75	70	216-217[13]
2	4-methoxyphenyl-	45	30	**6b**	88	79	241-243[13]
3	3,4,5-trimethoxy phenyl-	60	30	**6c**	82	76	187-189*
4	3-nitrophenyl-	60	60	**6d**	80	75	167-168[13]
5	2-chlorophenyl-	60	60	**6e**	94	65	226-228[13]
6	3-bromophenyl-	60	50	**6f**	95	98	190-192*
7	4-nitrophenyl-	60	30	**6g**	88	85	221-223[13]
8	2,5-dimethoxy phenyl-	30	25	**6h**	92	93	172-174*
9	2-hydroxy,3-methoxyphenyl-	45	20	**6i**	82	78	224-226*
10	3-methoxy,4-hydroxyphenyl-	90	30	**6j**	86	84	225-227[13]
11	Phenyl-	45	20	**6k**	85	80	205-206[13]
12	4-hydroxyphenyl-	75	25	**6l**	78	73	246-248[13]
13	Cinnamyl-	60	10	**6m**	93	92	177-179[13]
14	2-furyl-	30	30	**6n**	81	85	62-64*

[a] Isolated yields.
* New compounds.

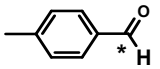
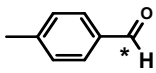
The IL has not only acted as a favorable medium with improved energetics of cavitation for this sonochemical reaction, but also promoted the reaction with its inherent Brønsted acidity thus obviating the necessity of using any additional acid catalyst. The Brønsted acidity is conferred by the –NH proton of $[Hbim]BF_4$ (chemical shift of 14.59 ppm)

capable of bonding with the carbonyl oxygen of the aldehydes as shown in Scheme **11**. Evidence for this was obtained by recording the ^{13}C-NMR spectra of *p*-tolualdehyde with an external lock of D_2O and with one equivalent of the IL under similar conditions. The results are recorded in Table **6**. A significant shift of ~ 3 ppm for the carbonyl carbon of the aldehyde by the interaction with the IL were observed. Additional evidence was obtained by recording their IR spectra neat wherein also a significant shift to a lower wave number by 7-18 cm^{-1} was observed (Table **6**).



Scheme **11**

Table **6.** ^{13}C-NMR chemical shifts and IR data for the carbonyl group:

S.No	Substrate	Chemical shift, (ppm)[a]	IR values[b], ν, cm^{-1}
1		204.3	1703.2
2	 + [Hbim]BF_4	207.4	1685.3

[a] Recorded neat with D_2O as external lock. [b] Recorded with neat sample.

On the basis of these evidences, a plausible mechanism for this novel protocol is shown in Fig. **2**.

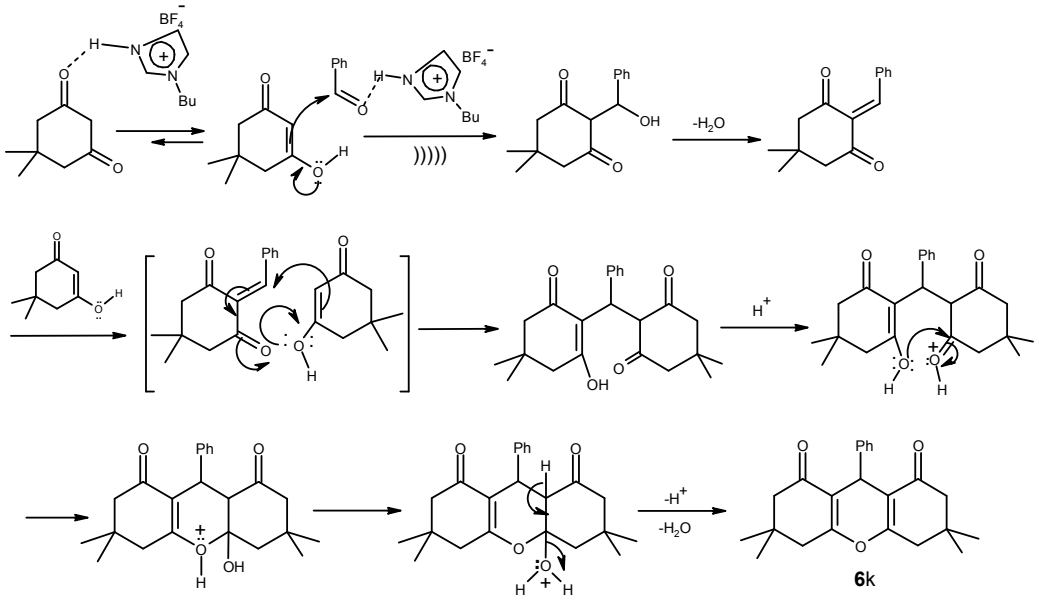


Figure 2 Plausible mechanism for the one-pot synthesis of Xanthene derivatives under MCR conditions

2.2.4 Conclusion

In conclusion, we have developed an efficient and convenient sonochemical synthesis of xanthene derivatives by the reaction of a cyclic diketone and aldehyde at ambient conditions by using [Hbim]BF_4 as solvent as well as promoter. The synergy of the combined use of ultrasound and IL has brought about successfully in enhanced reaction rates, the synthesis of a library of xanthenes. We also evaluated our results in terms of reaction times and yields for the *p*-TSA catalyzed synthesis of xanthenes under thermal conditions (Table **3**), which were comparable. The advantages of the method include the simple reaction conditions, the use of non-volatile ionic liquid which can be recovered and recycled, and the process is also amenable for scale up. The products can be easily isolated by simple work up procedures such as dilution with water and filtration of the precipitated product. The ambient conditions, non-volatile reusable IL, high reaction rates, excellent isolated yields and easy work up procedures makes this methodology an improved practical alternative to generate a library of a diverse array of poly-substituted xanthenes as compared to the conventional acid catalyzed thermal processes. This work is already peer reviewed and published in *Ultrasonics Sonochemistry* **2008,** *15,* 548.

2.2.5 Experimental

2.2.5.1 Typical procedure for the synthesis of 6k under sonochemical conditions: (Method A):

A mixture containing benzaldehyde **4a** (212 mg, 2.0 mmol), dimedone **5** (560 mg, 4.0 mmol), 2 mL of IL ([Hbim]BF_4) to which 0.5 mL of methanol was added as a co-solvent, was sonicated in an atmosphere of argon at ambient conditions in a thermostated (30±1 °C) ultrasonic cleaning bath for 45 min. After completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (~40 g) and stirred for about 1 h. The solid separated was filtered through a sintered funnel under suction, washed with ice-cold water (20 ml) and then recystallized from hot ethanol to afford **6**k (0.225 g, 85%). The combined aqueous filtrate was subjected to distillation to remove water under reduced

pressure (70 °C, 10 mmHg, 2 h) to leave behind the IL in near complete recovery, pure enough for recycle.

2.2.5.2 Typical procedure for the *p*-TSA catalyzed synthesis of 6k under thermal conditions (Method B)

A mixture of benzaldehyde **4**a (212 mg, 2 mmol), dimedone **5** (560 mg, 4 mmol), *p*-TSA (2 mg, 5 mol %), 4 mL of MeOH containing 2 mL of water was heated to 50 ^{o}C in an atmosphere of argon for about 20 min. After completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (~30 g) and stirred for about 1 h. The solid separated was filtered through a sintered funnel under suction, washed with ice-cold water (30 ml) and then recystallized from hot ethanol to afford **6**k (0.213 g, 80%).

2.2.6 Characterization data of xanthene derivatives:

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-*p*-tolyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6a:

Nature of compound; mp	**:**	White solid; mp: 216-217 ^{o}C.
IR: ($CHCl_3$)υ_{max}	**:**	3148, 2958, 1720, 1590, 1378, 1192, 1081 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.99 (s, 6H). 1.09 (s, 6H), 2.18-2.20 (d, *J* = 3.54 Hz, 4H), 2.24 (s, 3H), 2.45 (s, 4H), 4.70 (s, 1H), 6.99 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1, Hz, 2H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 20.9, 27.3, 29.2, 32.1, 40.8, 50.7, 115.6, 128.1, 128.7, 135.7, 141.1, 162.1, 196.4.
LC-MS	**:**	387 [M+23] (M+Na)
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74%. Found: C, 79.01; H, 7.83%.

3,4,6,7-tetrahydro-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6b:

Nature of compound; mp	**:**	Colorless solid; mp: 241-243 ^{o}C.
IR: ($CHCl_3$)υ_{max}	**:**	3014, 2958, 2873, 1891, 1667, 1624, 1510, 1360, 1215 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.99 (s, 6H), 1.10 (s, 6H), 2.19 (d, *J* = 3.43 Hz, 4H), 2.45 (s, 4H), 3.73 (s, 3H), 4.70 (s, 1H), 6.73 (d, *J* = 8.71 Hz, 2H), 7.18 (d, *J* = 8.71 Hz, 2H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 27.3, 29.2, 32.1, 40.2, 50.7, 55.0, 113.4, 115.7, 129.3, 136.4, 157.9, 162.0, 196.5.
LC-MS	**:**	403 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42%. Found: C, 75.83; H, 7.35%.

3,4,6,7-tetrahydro-9-(3,4,5-trimethoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6c:

Nature of compound; mp	**:**	Pale yellow solid; mp: 187-189 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3008, 2958, 2930, 2872, 1667, 1587, 1506, 1374 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.12 (s, 6H), 1.24 (s, 6H), 2.36 (d, *J* = 11.7 Hz, 8H), 3.75 (s, 6H), 3.81 (s, 3H), 5.49 (s, 1H), 6.34 (s, 2H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 26.7, 30.0, 31.01, 32.7, 46.3, 55.8, 60.8, 104.0, 115.5, 133.7, 152.8, 189.3, 190.4.
LC-MS	**:**	463 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32%. Found: C, 70.83; H, 7.39%.

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6d:

Nature of compound; mp	**:**	Pale yellow solid; mp: 167-168 ^{o}C.
IR: ($CHCl_3$)υ_{max}	**:**	3019, 2961, 1666, 1595, 1529, 1351, 1197, 1003 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.00 (s, 6H), 1.11 (s, 6H), 2.19 (d, *J* = 5.6 Hz, 4H), 4.84 (s, 4H), 5.25 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.97-8.01 (m, 2H)
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 27.2, 29.2, 32.2, 40.7, 50.6, 114.5, 121.6, 122.5, 128.8, 135.7, 146.2, 163.0, 196.4.
LC-MS	**:**	417 [M+23]
Elemental analysis	**:**	Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54%. Found: C, 69.80; H, 6.46; N, 3.65%.

9-(2-chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6e:

Nature of compound; mp	**:**	White solid; mp: 226-228 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3392, 3064, 2960, 2929, 2253, 1719, 1664, 1595, 1380, 1166 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.02-1.19 (br s, 12H), 2.25-2.44 (m, 8H), 5.62 (s, 1H), 7.09-7.44 (m, 4H).
LC-MS	**:**	406 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{23}H_{25}ClO_3$: C, 71.77; H, 6.55; Cl, 9.21%. Found: C, 71.70; H, 6.63; Cl, 9.14%.

9-(3-bromophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6f:

Nature of compound; mp	**:**	White solid; mp: 190-192 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3019, 2964, 2890, 1594, 1372, 1215 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.10 (s, 6H), 1.23 (s, 6H), 2.32-2.44 (m, 8H), 5.49 (s, 1H), 6.99-7.32 (m, 4H).
LC-MS	**:**	446 [M+18], 452 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{23}H_{25}BrO_3$: C, 64.34; H, 5.87; Br, 18.61%. Found: C, 64.27; H, 5.95; Br, 18.51%.

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(4-nitrophenyl)-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6g:

Nature of compound; mp	**:**	White solid; mp: 221-223 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3019, 2961, 1666, 1595, 1530, 1351, 1197, 1003 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.12 (s, 6H), 1.24 (s, 6H), 2.37-2.50 (m, 8H), 5.55 (s, 1H), 7.23 (d, J = 8.6 Hz, 2H), 8.12 (d, J = 8.8, 2H).
LC-MS	**:**	418 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54%. Found: C, 69.80; H, 6.29; N, 3.63%.

3,4,6,7-tetrahydro-9-(2,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6h:

Nature of compound; mp	**:**	Colorless solid; mp: 172-174 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3384, 3019, 2961, 2836, 1719, 1662, 1596, 1497, 1371, 1216 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.96 (s, 6H), 1.09 (s, 6H), 2.16 (d, J = 4.4 Hz, 4H), 2.40 (d, J = 4.8 Hz, 4H), 3.75 (br s, 6H), 4.83 (s, 1H), 6.65-6.67 (m, 2H), 6.95 (d, J = 2.5 Hz, 1H).
LC-MS	**:**	433 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37%. Found: C, 73.06; H, 7.30%.

3,4,6,7-tetrahydro-9-(2-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6i:

Nature of compound; mp	**:**	White solid; mp: 224-226 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3649, 3626, 3019, 2964, 1650, 1615, 1582, 1390, 1215, 1098 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.93-1.06 (m, 8H), 1.11 (s, 4H), 2.30-2.60 (m, 8H), 3.88 (s, 3H), 4.65 (s, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H).
LC-MS	**:**	418 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12%. Found: C, 72.62; H, 7.18%.

3,4,6,7-tetrahydro-9-(4-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthen-e-1,8-(5*H*,9*H*)-dione, 6j:

Nature of compound; mp	**:**	Colorless solid; mp: 225-227 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3696, 3582, 3155, 2962, 2253, 1663, 1502, 1362, 1199 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.01 (s, 6H), 1.11 (s, 6H), 2.21 (d, *J* = 2.0 Hz, 4H), 2.46 (s, 4H), 3.90 (s, 3H), 4.67 (s, 1H), 5.49 (br s, 1H), 6.55 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 27.2, 29.3, 31.3, 32.2, 40.8, 50.7, 55.8, 112.2, 113.9, 115.8, 119.9, 136.4, 143.9, 162.1, 196.6.
LC-MS	**:**	419 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12%. Found: C, 72.78; H, 7.19%.

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione, 6k:

Nature of compound; mp	**:**	White solid; mp: 225-227 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3019, 2964, 1667, 1625, 1361, 1215, 1137 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.03 (s, 6H), 1.14 (s, 6H), 2.24 (s, 4H), 2.50 (s, 4H), 4.79 (s, 1H), 7.13-7.35 (m, 5H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 27.3, 29.2, 32.1, 40.8, 50.7, 115.6, 126.3, 127.9, 128.3, 144.0, 162.2, 196.3.
LC-MS	**:**	373 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48%. Found: C, 78.75; H, 7.57%.

3,4,6,7-tetrahydro-9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6*l*:

Nature of compound; mp	**:**	White solid; mp: 246-248 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3684, 3608, 3019, 2964, 1665, 1511, 1426, 1362, 1215, 1197 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.99 (s, 6H), 1.09 (s, 6H), 2.20 (s, 4H), 2.45 (s, 4H), 4.66 (s, 1H), 6.53 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.50 Hz, 2H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 27.3, 29.1, 30.9, 32.2, 40.7, 50.6, 115.2, 115.8, 129.2, 135.3, 154.8, 162.5, 197.4.
LC-MS	**:**	389 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15%. Found: C, 75.30; H, 7.24%.

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-styryl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione, 6m:

Nature of compound; mp	**:**	Pale yellow solid; mp: 177-179 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3019, 2963, 2930, 1668, 1597, 1372, 1216 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.12 (s, 12H), 2.32 (s, 4H), 2.44 (s, 4H), 4.42 (s, 1H), 6.27-6.35 (m, 2H), 7.18-7.30 (m, 5H).
LC-MS	**:**	399 [M+23]
Elemental analysis (%)	**:**	Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.75; H, 7.50%. Found: C, 79.79; H, 7.60%.

9-(2-furanyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8-(5*H*,9*H*)dione, 6n:

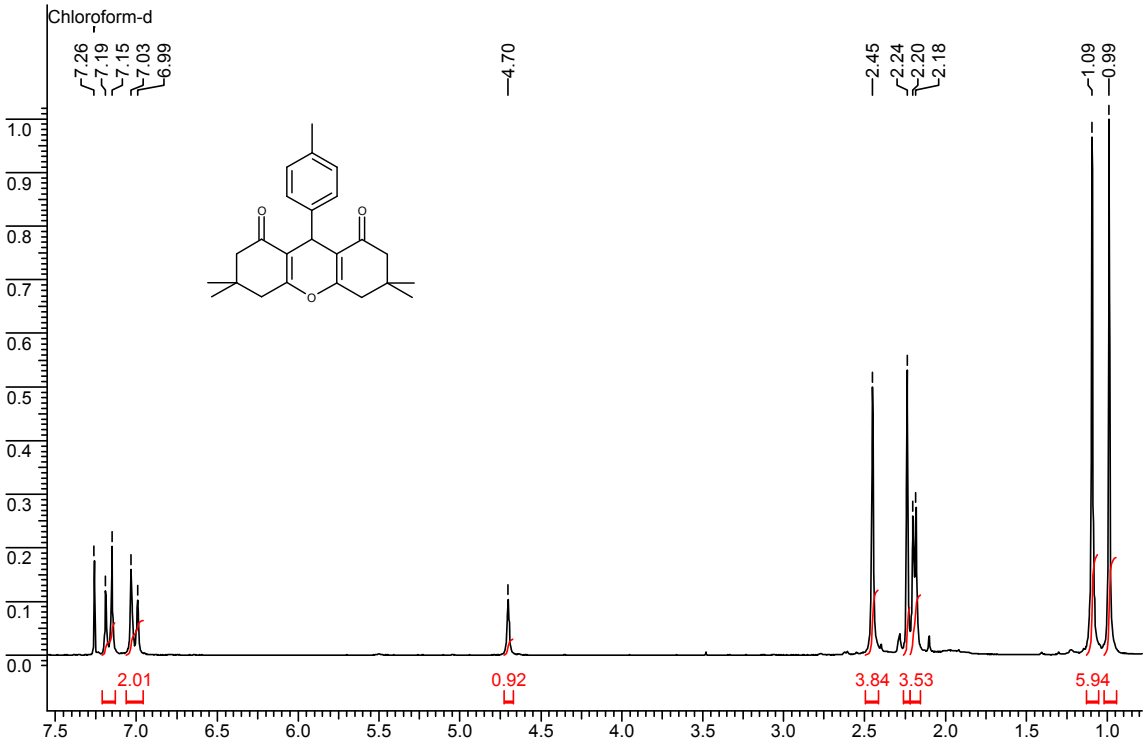
Nature of compound; mp	**:**	Pale brownish solid; mp: 62-64 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3019, 2963, 2890, 1667, 1600, 1359, 1215, 1165, 927, 762, 669 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.03 (s, 6H), 1.12 (s, 6H), 2.35 (br s, 8H), 4.96 (s, 1H), 5.38 (s, 1H), 5.83-6.27 (m, 2H).
LC-MS	**:**	362 [M+23]
Elemental analysis	**:**	Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11%. Found: C, 74.15; H, 7.17%.

2.2.7 **Spectra**

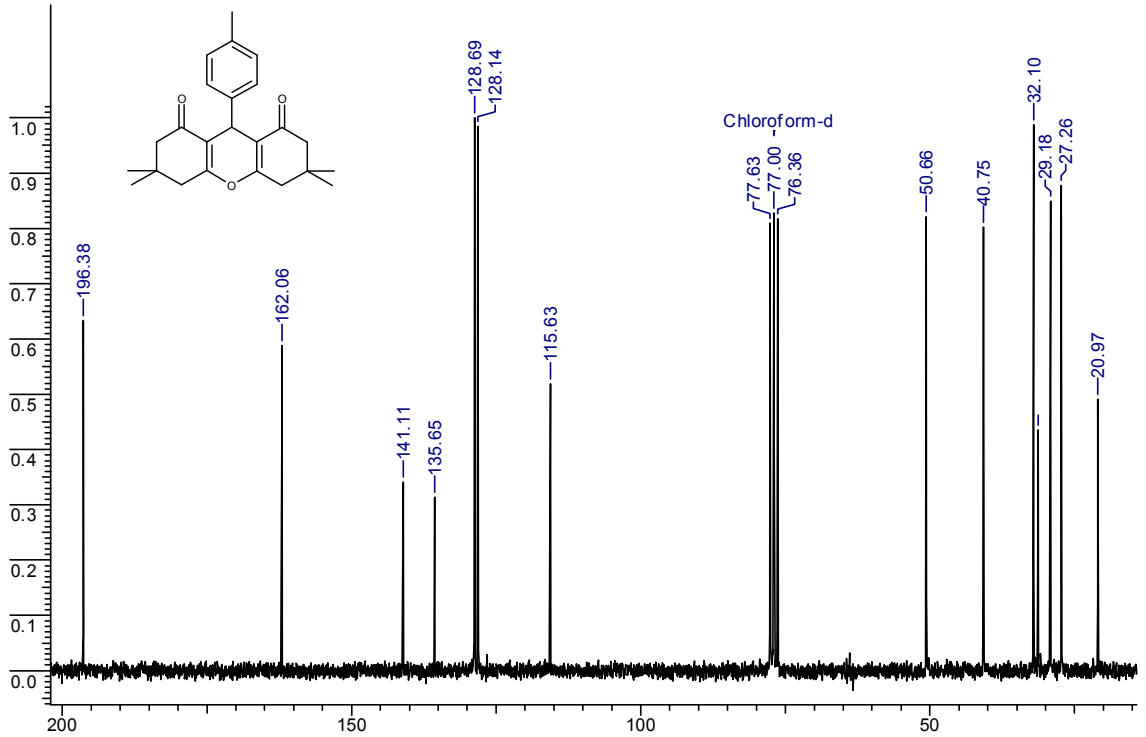
Table 7: ^{1}H & ^{13}C/LC-MS spectra of some selected Xanthenes are given below:

S No.	Spectra
1	^{1}H & ^{13}C spectra of **6a**
2	^{1}H & ^{13}C spectra of **6b**
3	^{1}H & ^{13}C spectra of **6c**
4	^{1}H-NMR spectrum & MS of **6f**
5	^{1}H & ^{13}C spectra of **6j**
6	^{1}H & ^{13}C spectra of **6k**

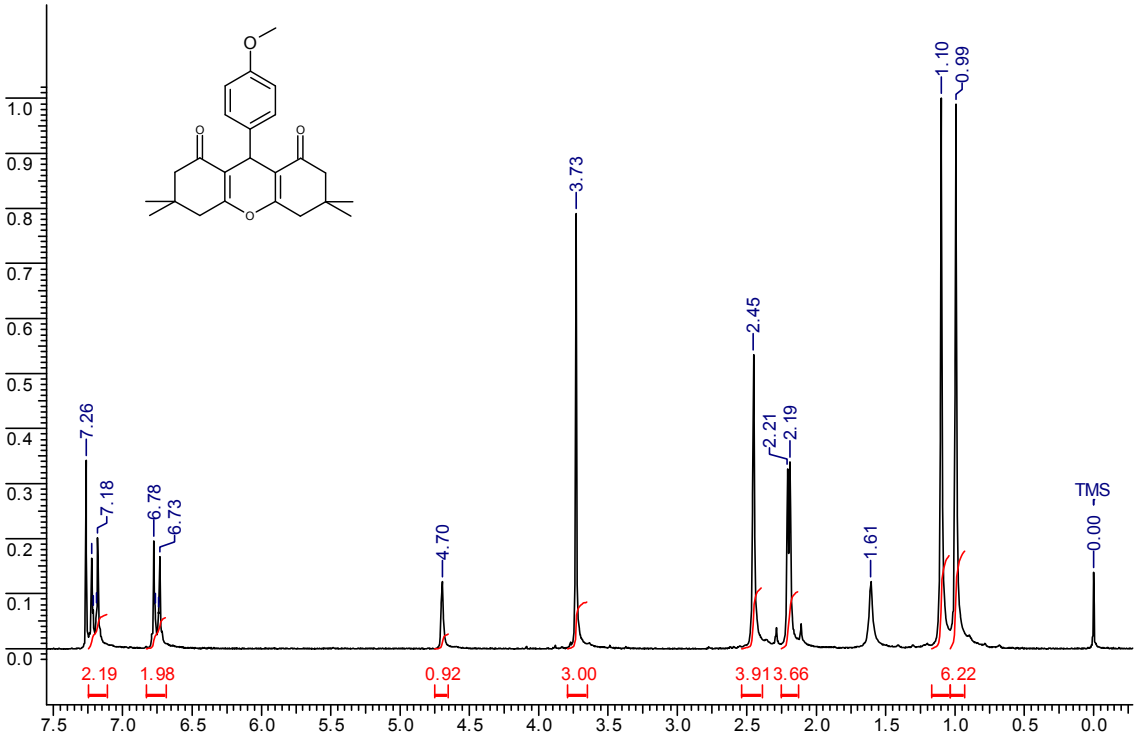
^{1}H-NMR spectrum of **6a**



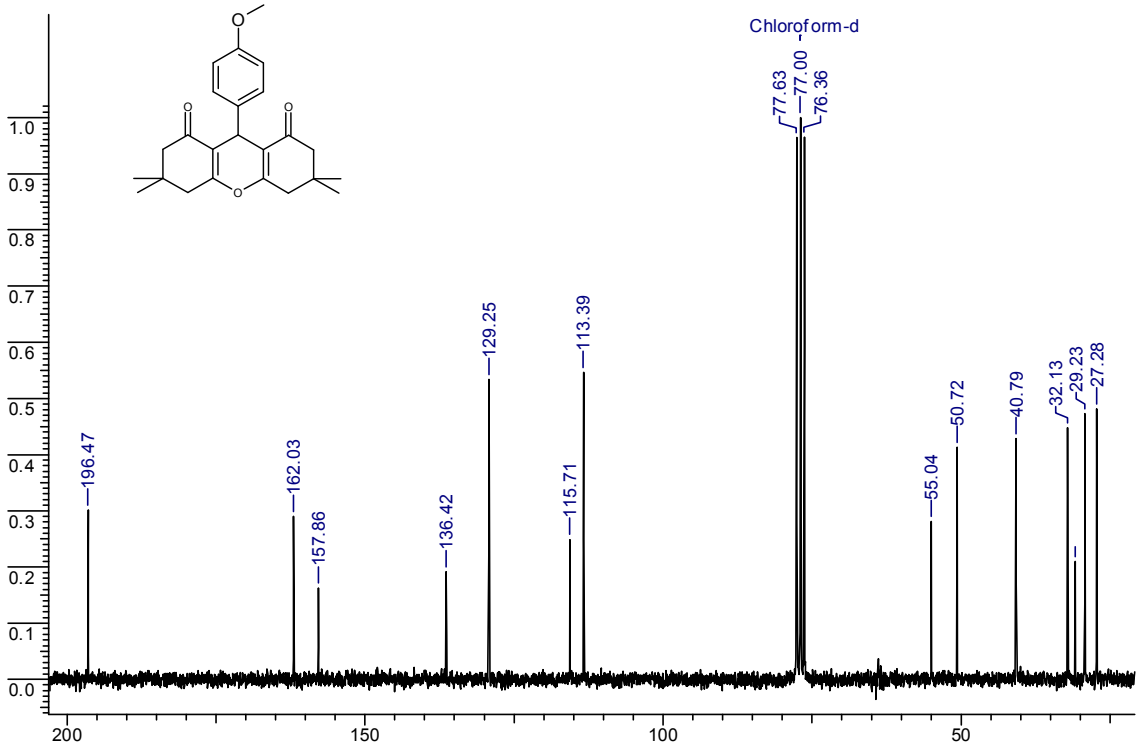
^{13}C-NMR spectrum of **6a**



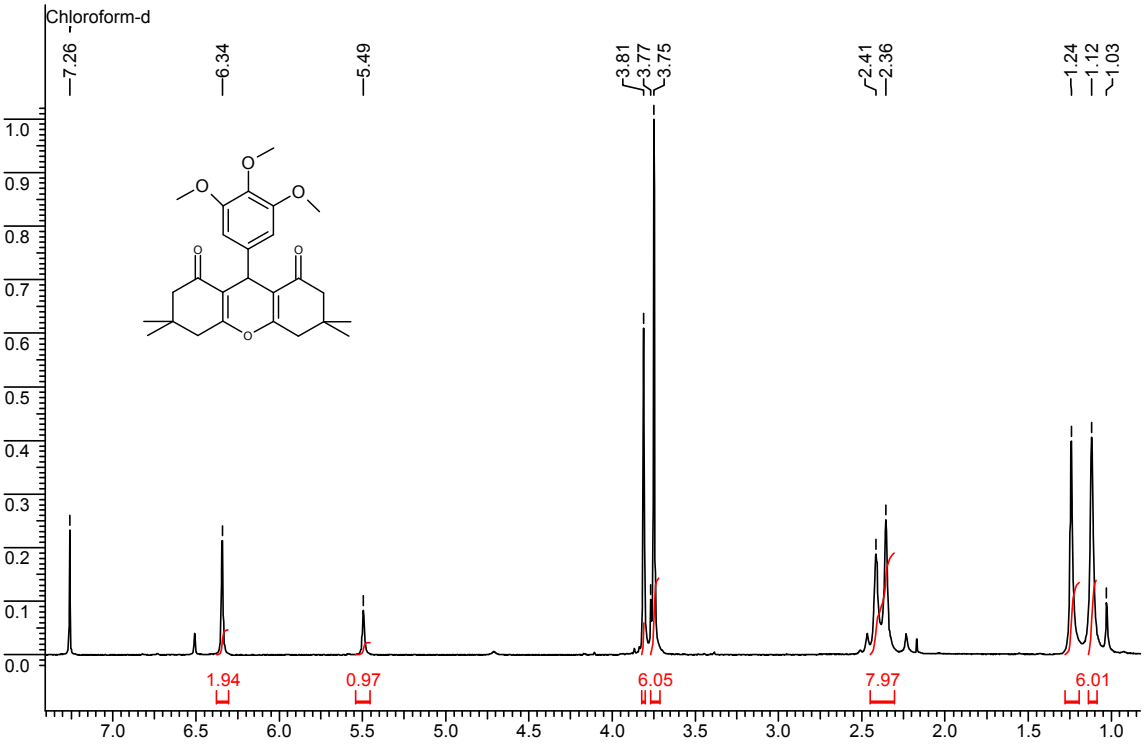
^{1}H-NMR spectrum of **6b**



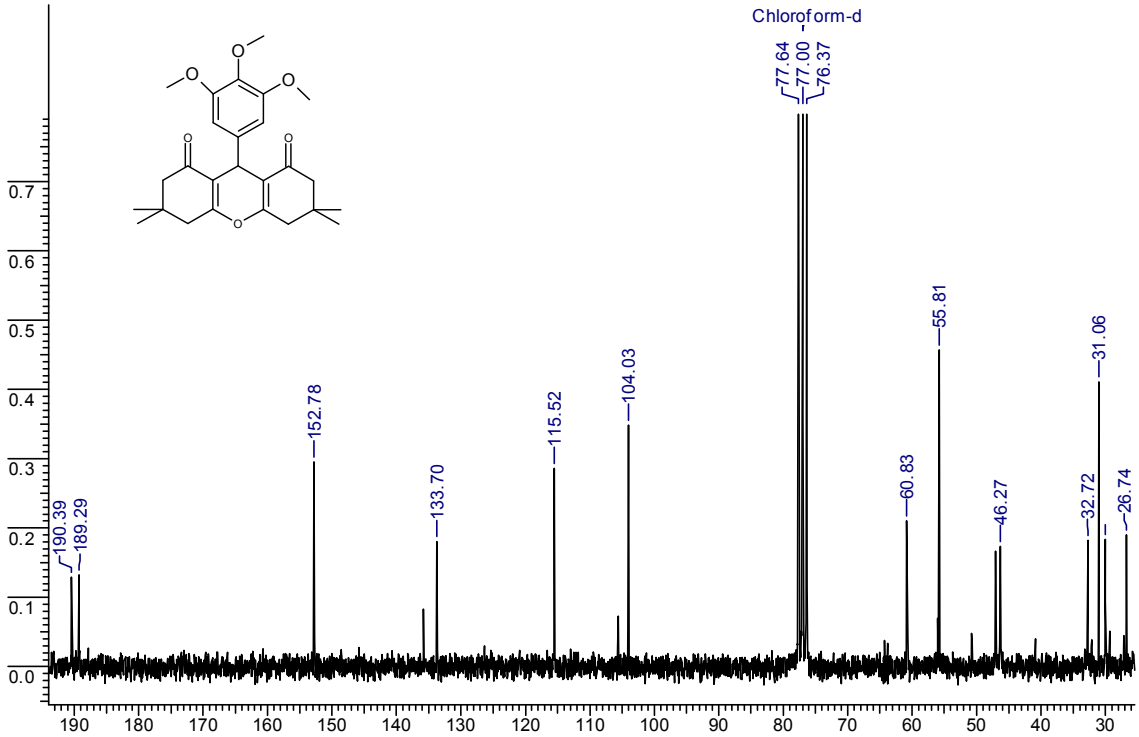
^{13}C-NMR spectrum of **6b**



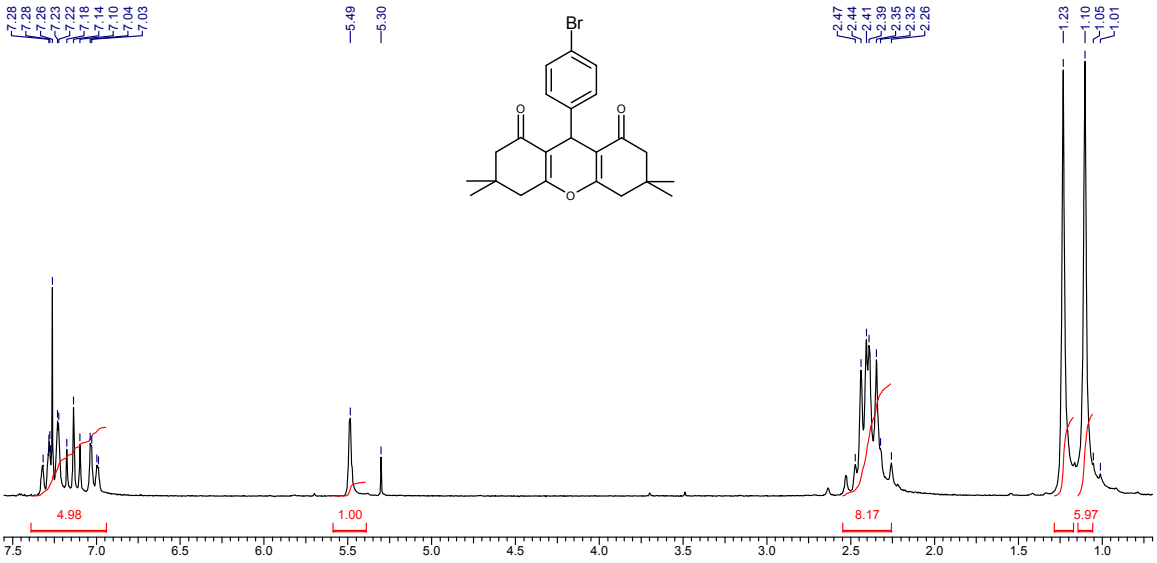
^{1}H-NMR spectrum of **6c**



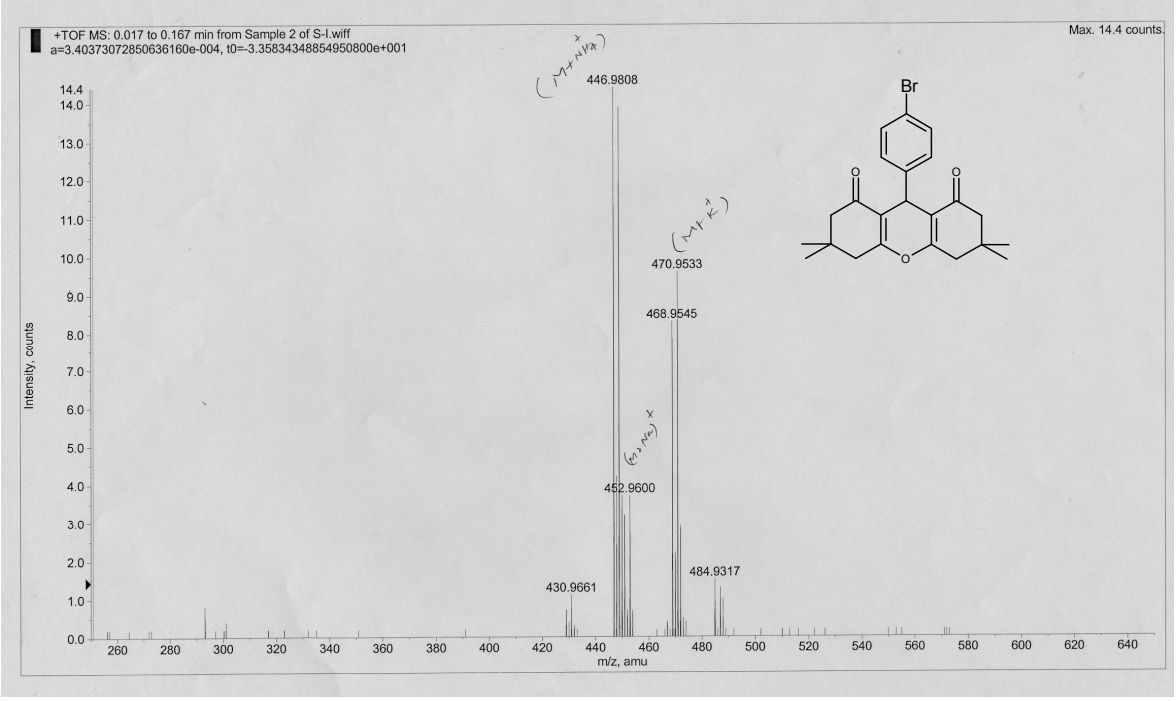
^{13}C-NMR spectrum of **6c**



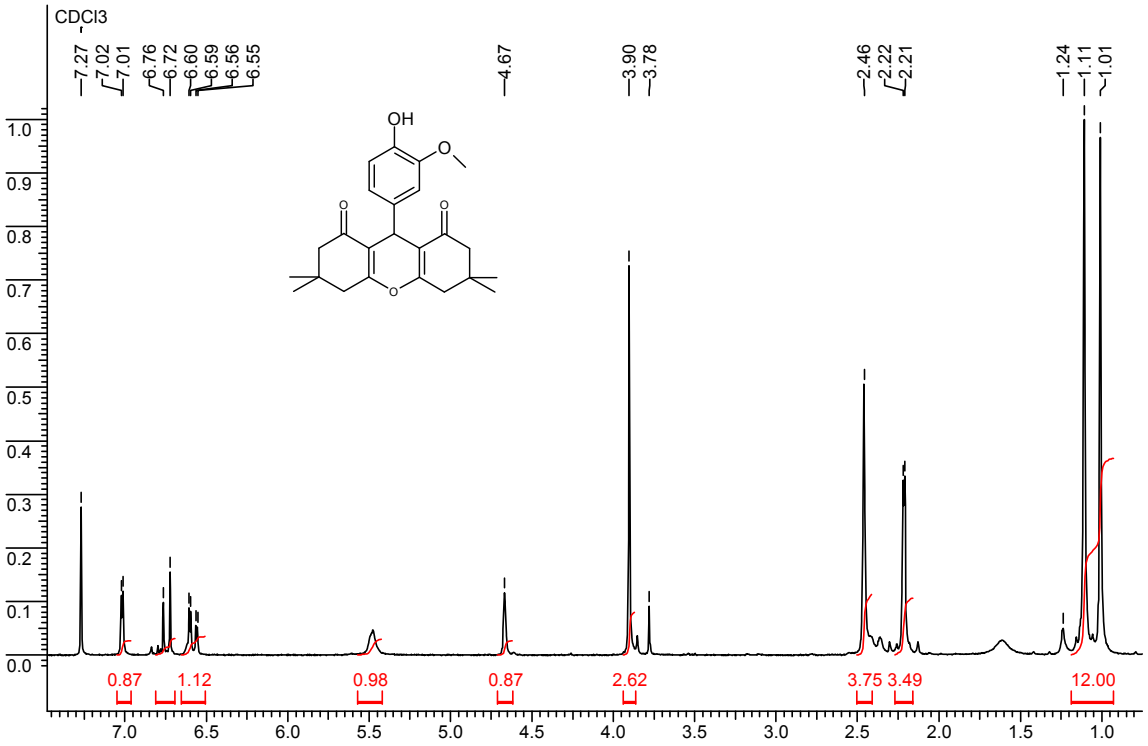
^{1}H-NMR spectrum of **6f**



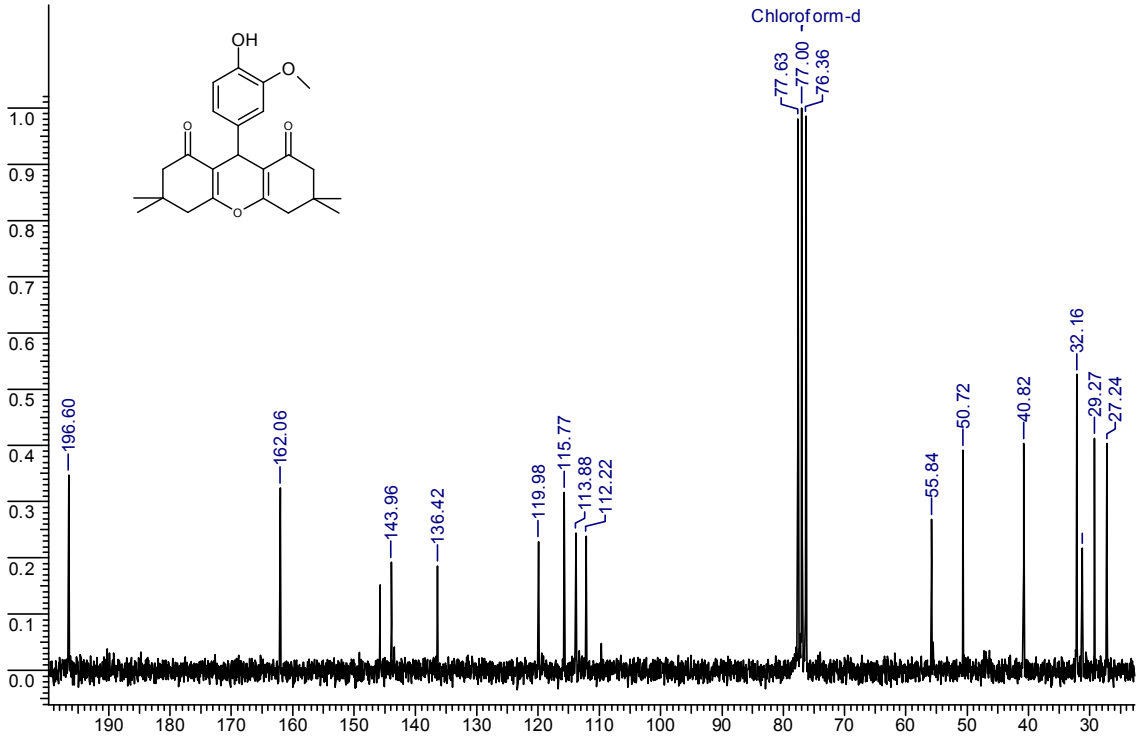
LC-MS of 6f



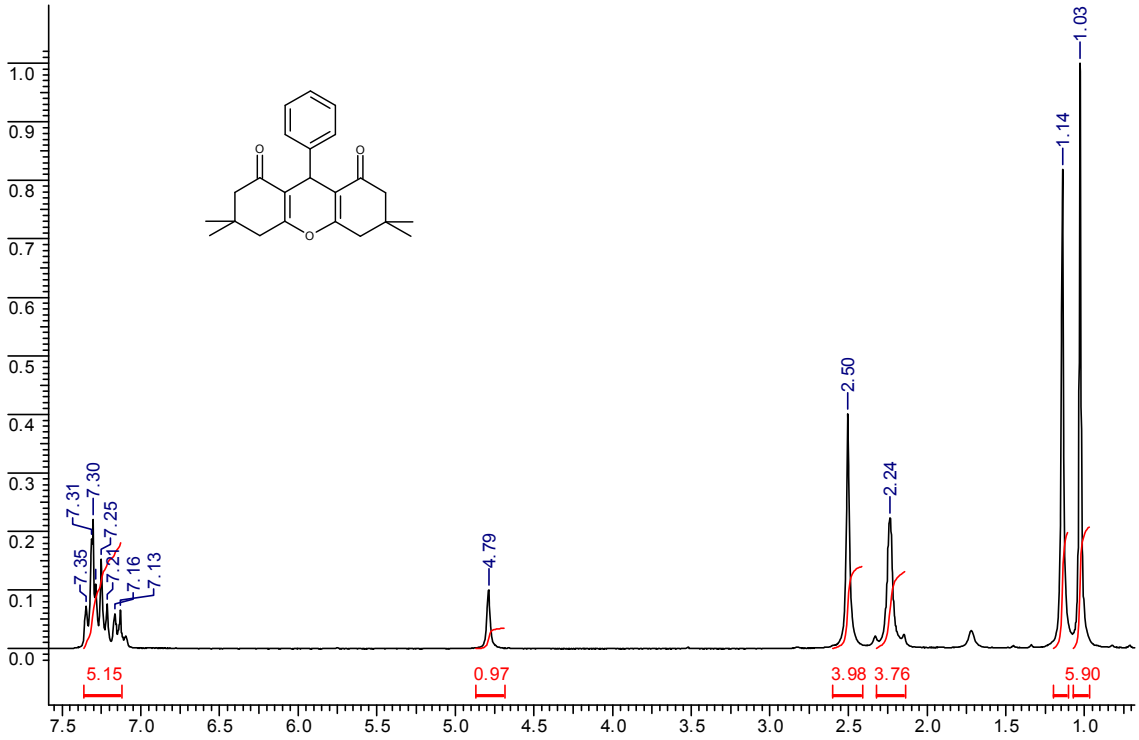
^{1}H-NMR spectrum of **6j**



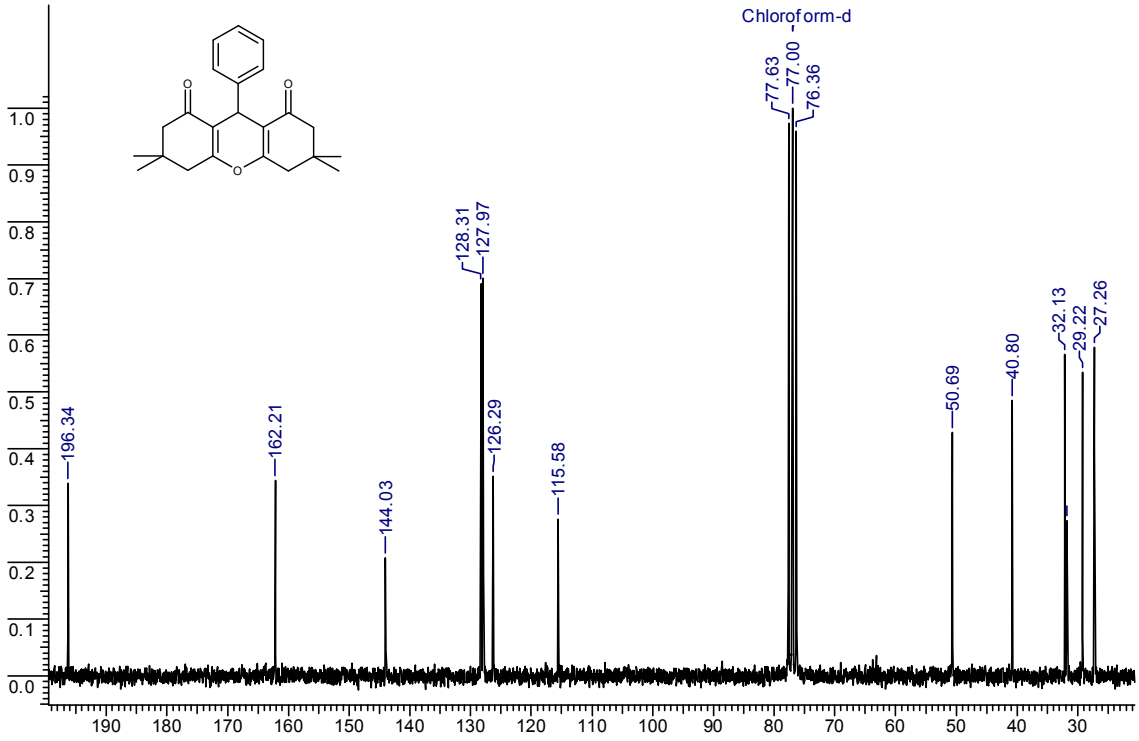
^{13}C-NMR spectrum of **6j**



^{1}H-NMR spectrum of **6k**



^{13}C-NMR spectrum of **6k**



2.2.8 References

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Chapter-II

Sec-C

Proline catalyzed efficient synthesis of 1,8-dioxo-decahydroacridines

2.3.0 Introduction

1,8-Dioxo-9-aryl-10-aryl-decahydroacridines and their derivatives are poly-functionalized 1,4-dihydropyridine derivatives. In recent years, 1,4-dihydropyridines and their derivatives have attracted strong interest due to the treatment of cardiovascular diseases, such as angina pectoris[1] and hypertension.[2] Acridine derivatives have been used to synthesize labeled conjugates with medicinals, peptides, proteins, and nucleic acids[3-5] that exhibit anti-tumor and DNA-binding properties.

The chemical industry is a major contributor to environmental pollution. With increasing regulatory pressure focusing on organic solvents, the development of non-hazardous alternatives is of great importance.[7] Recently, organic reactions conducted in aqueous media have received much attention[8] because water is nontoxic, cheap, abundantly available and benign to the environment. Although water not only increased the rate and the yield of a reaction but also, enhanced enantioselectivity in chiral synthesis.[9] The major drawbacks of using water as a solvent are its poor ability to solubilize organic reactants and unsuitability for use with moisture sensitive organic compounds and catalysts. One of the more efficient and versatile methods of increasing solubility and one that does not require modification of the solute is to use an organic co-solvent. Some of the most commonly used co-solvents are the lower alcohols, DMF, acetone, and acetonitrile. Proline is an abundant bi-functional chiral molecule that is inexpensive and available in both enantiomeric forms. The two functional groups *viz*., secondary NH and COOH groups act as acid or base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis.[10] Reportedly, the conventional synthesis of acridines and their derivatives has been performed in an organic solvent such as HOAc.[11] Recently few methodologies are reported in the literature for the synthesis of decahydroacridines.[12]

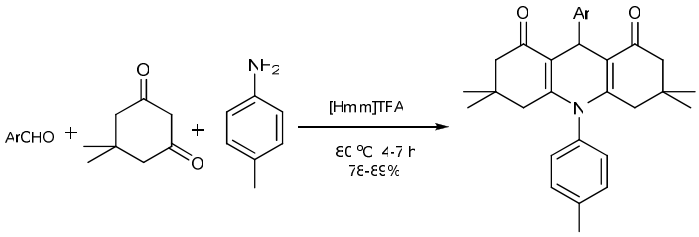
Many of these literature reports incorporate multi-component reactions (MCR) as their synthetic protocol. MCRs are especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and the diversity can be achieved simply by varying the reacting components[6]. Thus, new routes utilizing a MCR protocol, for the synthesis of these molecules can attract considerable attention in the search of methods for rapid entry to these heterocycles.

2.3.1 Literature Review

Some of the recent literature reports are described below.

Dabiri's approach (2007)[12a]

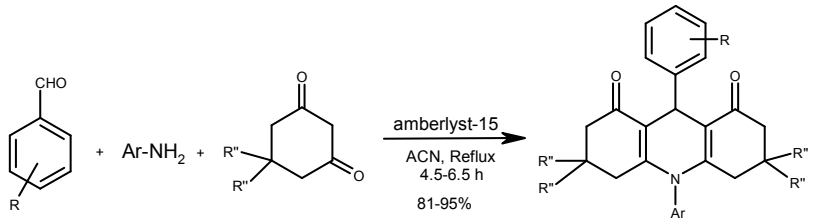
Dabiri and co-workers synthesized decahydroacridines in an Bronsted acidic ionic liquid, viz., [Hmim]TFA as shown in Scheme **12**.



Scheme **12**

Das's approach (2006)[12b]

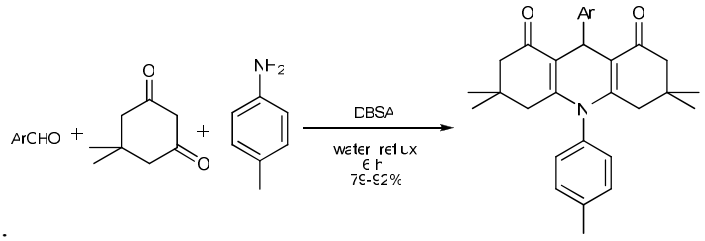
Das and co-workers utilized amberlyst-15 as an efficient catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes and 1,8-dioxo-decahydroacridines in excellent yields (Scheme **13**).



Scheme **13**

Jin's approach (2004)[12c]

Reaction of aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione and *p*-toluidine in water were successfully carried out in the presence of *p*-dodecylbenezenesulfonic acid (DBSA) as a Bronsted acid-surfactant-combined catalyst for the synthesis of decahydroacridines (Scheme **14**).

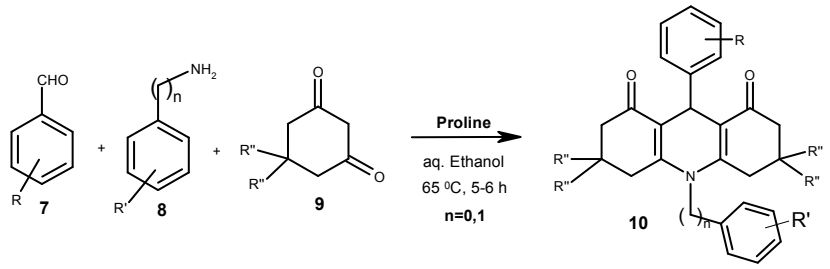


Scheme **14**

2.3.2 Present Work

The reported methods have limitations of poor yields in some cases, cumbersome work-up procedure and generation of polluting effluents. Consequently, we thought that there is scope for further innovation towards milder reaction conditions, short reaction times, increase in variation of the substituents in the components and better yields in the synthesis of 1,8-dioxo-decahydroacridines which can possibly be achieved by choosing D,L-Proline as a catalyst for this multi-component reaction (MCR).

We developed for the first time a facile synthesis of 1,8-dioxodecahydroacridines catalyzed by Proline in aqueous ethanolic medium toward a clean and efficient synthesis of acridines (Scheme **15**).

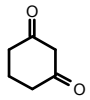
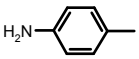
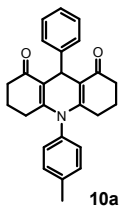


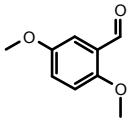
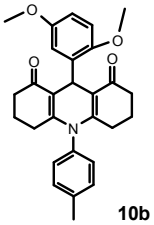
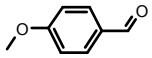
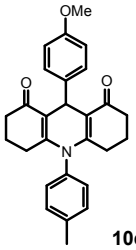
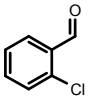
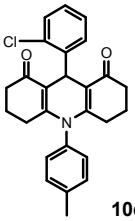
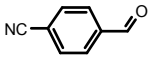
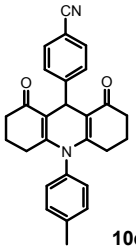
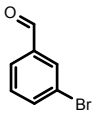
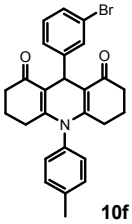
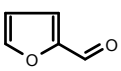
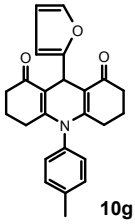
Scheme 15

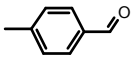
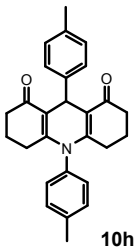
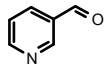
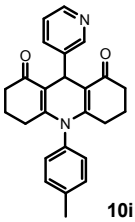
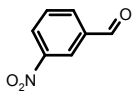
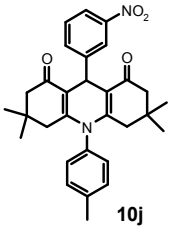
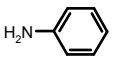
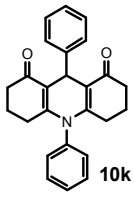
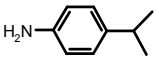
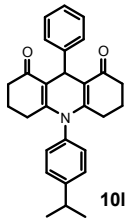
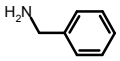
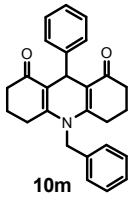
2.3.3 Results and Discussion

In order to determine the scope of the designed novel protocol, a number of commercially available aldehydes were condensed with cyclic ketones and aryl amines under optimized reaction conditions and the results are summarized in Table **8**. We investigated further the electronic effect of different substituents present on the aldehyde component. We observed that a wide range of aldehydes having both electron-donating and electron-withdrawing groups are equally facile for the reaction resulting in the formation of decahydroacridine derivatives in very good isolated yields.

Table 8: Proline catalyzed one-pot synthesis of 1,8-Dioxodecahydroacridines 10(a-m) in aqueous media

Entry	Aldehyde 7	Diketone 8	Aryl amine 9	Product 10	Reaction Time (h)	Yield (%)[a]	MP/ °C
1	 **7a**	 **8a**	 **9a**	 **10a**	5	83	204-206

2	 **7b**	**8a**	**9a**	 **10b**	6	80	236-238
3	 **7c**	**8a**	**9a**	 **10c**	6	84	235-238
4	 **7d**	**8a**	**9a**	 **10d**	5	82	226-229
5	 **7e**	**8a**	**9a**	 **10e**	6	79	230-233
6	 **7f**	**8a**	**9a**	 **10f**	5	84	208-210
7	 **7g**	**8a**	**9a**	 **10g**	6	73	163-166

8	 **7h**	**8a**	**9a**	 **10h**	6	83	196-198
9	 **7i**	**8a**	**9a**	 **10i**	5	81	214-217
10	 **7j**	**8b**	**9a**	 **10j**	6	80	284-285 Lit.: [285-286][12c]
11	**7a**	**8a**	 **9b**	 **10k**	5	83	246-248
12	**7a**	**8a**	 **9c**	 **10l**	6	85	196-198
13	**7a**	**8a**	 **9d**	 **10m**	6	88	292-294

[a]**y**ields reported are after recrystallization.

We also observed that various amines such as aniline, *p*-toludine, benzyl amine and *p*-isopropylaniline reacted smoothly under our conditions. All the known and new compounds were well characterized by melting point, IR, ^{1}H-NMR, ^{13}C-NMR and

elemental analyses. For the known compounds, the values were in agreement with those reported in literature. A plausible mechanistic pathway of this MCR is shown in Fig. **3**.

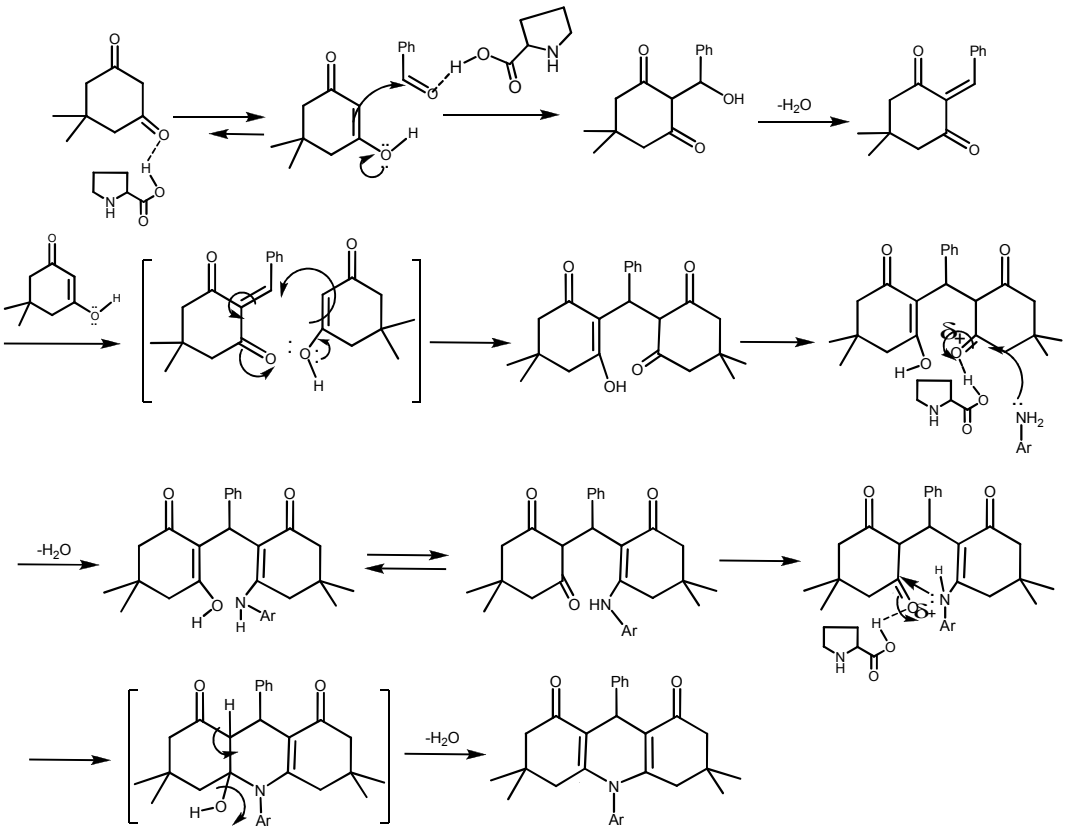


Fig. 3

2.3.4 Conclusion

In conclusion, the commercially available, inexpensive D,L-Proline has proved to be a useful and novel catalyst for the synthesis of 1,8-dioxodecahydroacridines by the three component coupling of aldehydes, amines, and cyclic diketones under neutral aqueous alcoholic conditions. The experimental procedure is simple, convenient and the reaction conditions are amenable to scale-up. This method provides an easy access to substituted decahydroacridines with diverse chemical structures. The current methodology has the advantages of operational simplicity, neutral reaction conditions, excellent yields of products and the absence of toxic effluents. This work is already peer reviewed and accepted for publication in *Synthetic Communications*.

2.3.5 EXPERIMENTAL

2.3.5.1 General procedure for the synthesis of 1,8-dioxo-decahydroacridines (10):

A mixture of aromatic aldehyde **7** (1 mmol), diketone **8** (2 mmol), aromatic amine **9** (1 mmol) , and Proline (10 mol%) in 15 mL of ethanol containing 3 mL of water was heated at 65 ^{o}C for the appropriate time. After completion of the reaction (as indicated by TLC), the volume of the solution was reduced to half, and H_2O (10 mL) was added and stirred for 30 min. The reaction mixture was extracted with ethyl acetate (3X10 mL) and the organic solvent was separated, dried over Na_2SO_4 and concentrated in *vacuo* to get the product as a residue. The resulting crude product was recystallized from hot ethanol to afford acridines **10** (products) in very good isolated yields. The decahydroacridines thus isolated were homogeneous on TLC and were pure enough for all practical purposes.

2.3.6 Characterization Data

3,4,6,7-tetrahydro-9-phenyl-10-*p*-tolylacridine-1,8-(2*H*,5*H*, 9*H*, 10*H*)-dione (**10**a)**:**

Nature and mp	White solid; mp 204-206 ^{o}C
IR ($CHCl_3$) υ_{max}	3012, 2960, 2930, 2874, 1636, 1571, 1510, 1454, 1379, 1363, 1285, 1233, 1182, 1108, 816, 756, 700, 667 cm^{-1}
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.64-1.83 (m, 4H), 1.99-2.28 (m, 8H), 2.37 (s, 3H), 5.31 (s, 3H), 7.01-7.36 (m, 9H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 20.9, 21.1, 28.2, 31.9, 36.7, 115.3, 125.8, 127.6, 128.1, 136.2, 139.4, 146.5, 151.8, 196.1.
Elemental analysis	Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%. Found: C, 81.49; H, 6.51; N, 3.58%.

3,4,6,7-tetrahydro-9-(2,5-dimethoxyphenyl)-10-*p*-tolylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (**10**b)**:**

Nature and mp	Pale yellow solid; mp 236-238 ^{o}C
IR ($CHCl_3$) υ_{max}	3017, 2952, 2930, 2833, 1635, 1572, 1510, 1454, 1377, 1363, 1236, 1216, 1183, 1108, 1019, 956, 756, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.64-1.77 (m, 4H), 1.97-2.02 (m, 4H), 2.12-2.22 (m, 2H), 2.38 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 5.35 (s, 1H), 6.55-6.61 (m, 1H), 6.70-6.75 (m, 1H), 7.00-7.22

	(m, 5H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.2, 28.5, 30.7, 36.7, 55.5, 57.5, 112.1, 113.9, 114.7, 117.1, 135.9, 136.8, 139.2, 151.8, 153.4, 196.0.
Elemental analysis	Anal. Calcd. for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16%. Found: C, 75.88; H, 6.52; N, 3.25%.

3,4,6,7-tetrahydro-9-(4-methoxyphenyl)-10-*p*-tolyl-acridine-1,8-(2H,5H,9H,10H)-dione (10c):

Nature and mp	White solid; mp 235-238 ^oC
IR ($CHCl_3$) υ_{max}	3015, 2956, 2936, 2873, 1635, 1571, 1509, 1455, 1362, 1287, 1216, 1182, 1108, 1034, 955, 858, 756, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.69-1.81 (m, 4H), 1.98-2.11 (m, 4H), 2.18-2.28 (m, 4H), 2.38 (s, 3H), 3.68 (s, 3H), 5.24 (s, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.20-7.28 (m, 4H)
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.1, 28.2, 31.2, 36.7, 55.1, 113.5, 115.6, 128.7, 136.4, 139.1, 139.4, 151.5, 157.7, 196.2
Elemental analysis	Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39%. Found: C, 78.49; H, 6.64; N, 3.47%.

9-(2-chlorophenyl)-3,4,6,7-tetrahydro-10-*p*-tolyl-acridine-1,8(2*H*,5*H*,9*H*,10*H*)dione (10d):

Nature and mp	White solid; mp 226-229 ^oC
IR ($CHCl_3$) υ_{max}	3017, 2960, 2930, 2875, 1636, 1567, 1511, 1470, 1361, 1288, 1216, 1183, 1135, 1080, 1034, 1002, 958, 858, 754, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.66-1.75 (m, 4H), 1.93-2.02 (m, 4H), 2.14-2.21 (m, 4H), 2.38 (s, 3H), 5.43 (s, 1H), 6.93-7.27 (m, 8H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.3, 28.5, 35.0, 36.7, 113.4, 126.1, 127.4, 134.0, 136.6, 139.5, 142.3, 152.7, 196.2.
Elemental analysis	Anal. Calcd for $C_{26}H_{24}ClNO_2$: C, 74.72; H, 5.79; Cl, 8.48; N, 3.35%. Found: C, 74.66; H, 5.73; Cl, 8.40; N, 3.41%.

4-(1,2,3,4,5,6,7,8,9,10-decahydro-1,8-dioxo-10-*p*-tolylacridin-9-yl)benzonitrile (10e):

Nature and mp	White solid; mp 230-233 ^{o}C
IR ($CHCl_3$) υ_{max}	3014, 2950, 2930, 2227, 1637, 1571, 1509, 1452, 1364, 1283, 1216, 1182, 1135, 1073, 1016, 958, 754, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.69-1.81 (m, 4H), 1.99-2.10 (m, 4H), 2.19-2.27 (m, 4H), 2.38 (s, 3H), 5.30 (s, 1H), 7.03 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.45 (m, 4H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 20.9, 28.2, 32.9, 36.6, 109.4, 114.3, 128.6, 132.0, 135.9, 139.8, 151.8, 152.4, 195.9.
Elemental analysis	Anal. Calcd. for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86%. Found: C, 79.33; H, 5.97; N, 6.80%.

9-(3-bromophenyl)-3,4,6,7-tetrahydro-10-*p*-tolyl-acridine-1,8(2*H*,5*H*,9*H*,10*H*)dione (10f):

Nature and mp	White solid; mp 208-210 ^{o}C
IR ($CHCl_3$) υ_{max}	3015, 2953, 2871, 1636, 1570, 1510, 1455, 1378, 1362, 1287, 1215, 1182, 1135, 1071, 1018, 956, 858, 759, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.70-1.85 (m, 4H), 2.00-2.10 (m, 4H), 2.25-2.30 (m, 4H), 2.38 (s, 3H), 5.27 (s, 1H), 7.03-7.08 (m, 3H), 7.15-7.36 (m, 4H), 7.39-7.41 (m, 1H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.0, 28.2, 32.0, 36.6, 114.9, 122.3, 126.8, 136.1, 139.6, 148.8, 152.1, 196.0.
Elemental analysis	Anal. Calcd for $C_{26}H_{24}BrNO_2$: C, 67.54; H, 5.23; Br, 17.28; N, 3.03%. Found: C, 67.49; H, 5.31; Br, 17.17; N, 3.11%.

9-(furan-2-yl)-3,4,6,7-tetrahydro-10-*p*-tolylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione (10g):

Nature and mp	White solid; mp 163-166 ^{o}C

IR ($CHCl_3$) υ_{max}	3008, 2949, 2871, 1637, 1572, 1510, 1454, 1359, 1287, 1228, 1181, 1134, 1008, 955, 858, 754, 665 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.69-1.86 (m, 4H), 1.99-2.31 (m, 8H), 2.37 (s, 3H), 5.45 (s, 1H), 6.01 (d, *J* = 3.2 Hz, 1H), 6.15-6.17 (m, 1H), 7.05-7.26 (m, 5H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 20.9, 25.8, 28.0, 36.6, 104.5, 110.1, 112.1, 136.1, 139.4, 140.7, 152.9, 157.4, 195.9.
Elemental analysis	Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75%. Found: C, 77.25; H, 6.28; N, 3.69%.

3,4,6,7-tetrahydro-9,10-di-*p*-tolylacridine-1,8-(2*H*, 5*H*,9*H*,10*H*)dione (10h):

Nature and mp	Pale yellow solid; mp 196-198 ^oC
IR ($CHCl_3$) υ_{max}	3018, 2953, 2871, 1636, 1572, 1511, 1454, 1428, 1378, 1362, 1286, 1215, 1182, 1135, 1039, 955, 755, 668 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.65-1.89 (m, 4H), 1.98-2.10 (m, 4H), 2.16-2.18 (m, 2H), 2.20 (s, 3H), 2.25-2.30 (m, 2H), 2.37 (s, 3H), 5.26 (s, 1H), 6.96-7.07 (m, 4H), 7.19-7.26 (m, 4H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.0, 28.2, 31.5, 36.7, 115.5, 127.6, 128.9, 135.0, 136.4, 139.4, 143.7, 151.6, 196.1.
Elemental analysis	Anal. Calcd. for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52%. Found: C, 81.65; H, 6.79; N, 3.58%.

3,4,6,7-tetrahydro-9-(pyridin-3-yl)-10-*p*-tolyl-acridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione(10i):

Nature and mp	Pale yellow solid; mp 214-217 ^oC
IR ($CHCl_3$) υ_{max}	3017, 2959, 2874, 1637, 1574, 1510, 1427, 1379, 1362, 1286, 1182, 1134, 956, 756, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.64-1.87 (m, 4H), 2.00-2.31 (m, 8H), 2.38 (s, 3H), 5.25 (s, 1H), 7.06-7.14 (m, 3H), 7.22-7.28 (m, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 8.26-8.29 (m, 1H), 8.47 (d, *J* = 1.9 Hz, 1H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 20.9, 28.1, 30.6, 36.5, 114.4, 123.0, 135.9, 136.3, 139.6, 142.0, 146.8, 148.7, 149.3, 152.3, 195.9.

Elemental analysis	Anal. Calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29%. Found: C, 78.03; H, 6.20; N, 7.37%.

3,3,6,6-tetramethyl-9-(3-nitrophenyl)-10-*p*-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*, 5*H*)dione (10j):

Nature and mp	Pale yellow solid; mp 284-286 ^oC
IR ($CHCl_3$) υ_{max}	3017, 2979, 2872, 1641, 1579, 1535, 1510, 1459, 1365, 1304, 1211, 1152, 831, 765, 730 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 0.79 (s, 6 H), 0.96 (s, 6H), 1.90 (d, *J* = 16.2 Hz, 2H), 2.07 (d, *J* = 16.2 Hz, 2H), 2.21 (q, *J* = 9.0 Hz, 4H), 2.53 (s, 3H), 5.41 (s, 1 H), 7.11 (d, *J* = 6.4 Hz, 2H), 7.22-7.31 (m, 4H), 7.33 (d, *J* = 6.4 Hz, 2H).
Elemental analysis	Anal. Calcd. for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78%. Found: C, 74.30; H, 6.60; N, 5.85%.

3,4,6,7-tetrahydro-9,10-diphenylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione (10k):

Nature and mp	White solid; mp 246-248 ^oC
IR ($CHCl_3$) υ_{max}	3019, 2948, 2890, 1637, 1593, 1569, 1492, 1429, 1363, 1286, 1216, 1135, 1074, 955, 858, 756, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.71-2.28 (m, 12H), 5.32 (s, 1H), 7.03-7.50 (m, 10H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.0, 28.2, 31.9, 36.7, 115.4, 125.9, 127.6, 128.1, 129.3, 138.9, 146.4, 151.6, 196.2.
Elemental analysis	Anal. Calcd. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79%. Found: C, 81.35; H, 6.20; N, 3.84%.

3,4,6,7-tetrahydro-10-(4-isopropylphenyl)-9-phenyl-acridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (10*l*):

Nature and mp	Pale yellow solid; mp 196-198 ^oC
IR ($CHCl_3$) υ_{max}	3010, 2962, 2891, 1635, 1604, 1571, 1508, 1454, 1379, 1364, 1286, 1182, 1135, 1073, 1016, 956, 859, 755, 666 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.22 (s, 3H), 1.26 (s, 3H), 1.71-1.82 (m, 4H), 1.99-2.28 (m, 8H), 2.87-3.00 (m, 1H), 5.31 (s, 1H), 7.04-7.37 (m, 9H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 21.0, 23.8, 28.2, 31.8, 33.7, 36.7, 115.3, 125.9, 127.6, 128.1, 136.5, 146.5, 150.2, 151.9, 196.1.
Elemental analysis	Anal. Calcd. for $C_{28}H_{29}NO_2$: C, 81.72; H, 7.10; N, 3.40%. Found: C, 81.66; H, 7.18; N, 3.49%.

10-benzyl-3,4,6,7-tetrahydro-9-phenylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (**10**m)**:**

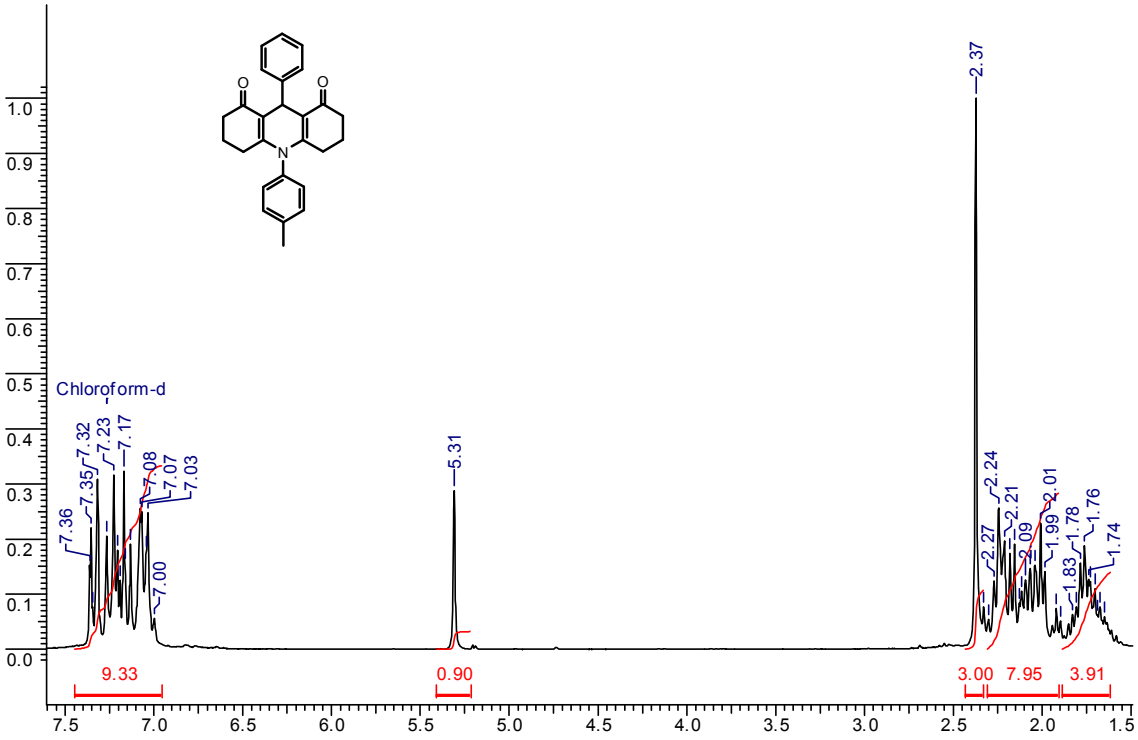
Nature and mp	Pale yellow solid; mp 292-294 ^oC
IR ($CHCl_3$) υ_{max}	3017, 2954, 2891, 1630, 1568, 1510, 1454, 1381, 1361, 1281, 1216, 1176, 1052, 956, 859, 756, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 1.87-2.02 (m, 4H), 2.29-2.35 (m, 4H), 2.52-2.79 (m, 4H), 4.99 (s, 2H), 5.26 (s, 1H), 6.95-6.99 (m, 2H), 7.08-7.16 (m, 4H), 7.30-7.41 (m, 4H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	δ 20.3, 25.6, 29.7, 35.5, 47.7, 114.8, 124.4, 126.5, 127.6, 128.1, 134.0, 135.9, 142.2, 151.9, 194.8.
Elemental analysis	Anal. Calcd. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%. Found: C, 81.34; H, 6.50; N, 3.73%.

2.3.7 Spectra

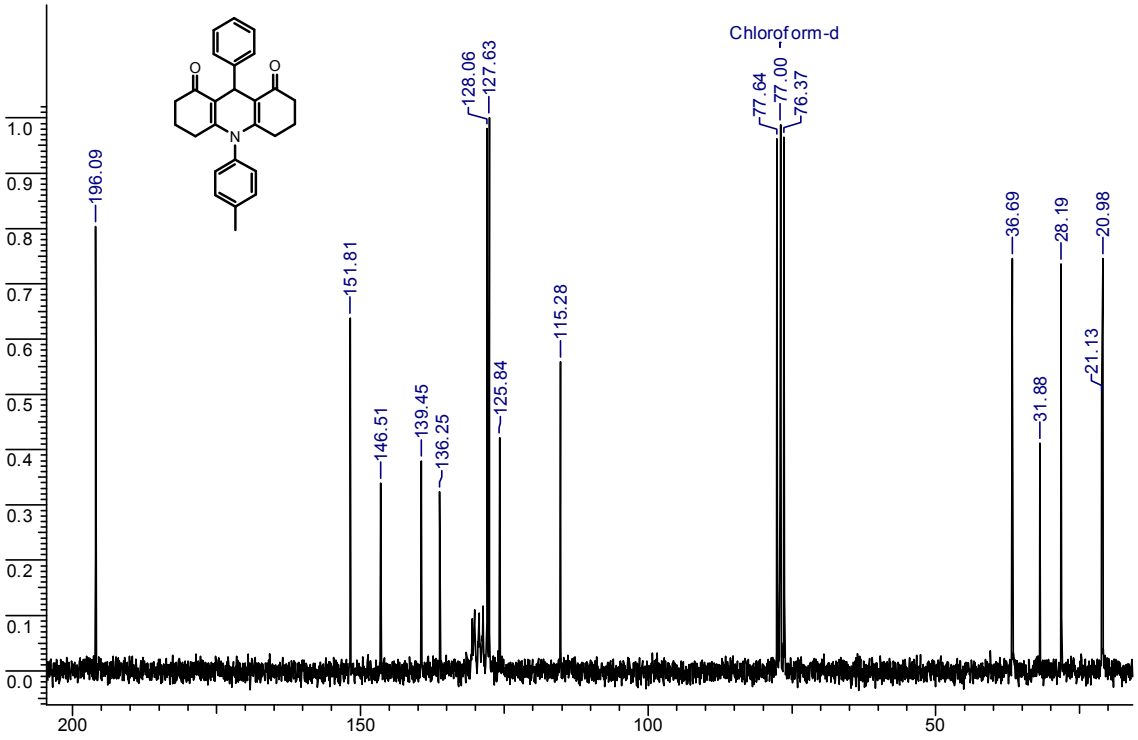
Table 9: ^{1}H & ^{13}C spectra of some selected acridines are given below:

Sr. No.	Spectra
1	^{1}H & ^{13}C spectra of **10**a
2	^{1}H & ^{13}C spectra of **10**e
3	^{1}H & ^{13}C spectra of **10**f
4	^{1}H & ^{13}C spectra of **10**g
5	^{1}H & ^{13}C spectra of **10**k
6	^{1}H & ^{13}C spectra of **10***l*
7	^{1}H & ^{13}C spectra of **10**m

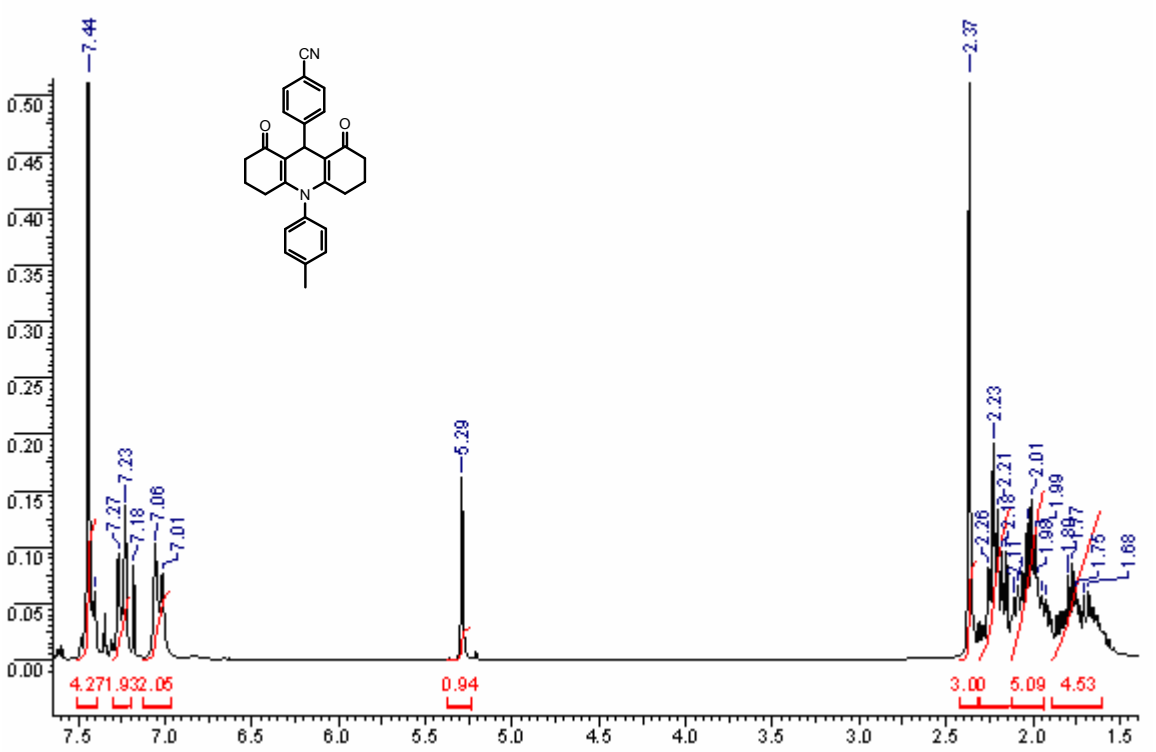
^{1}H-NMR spectrum of **10a**



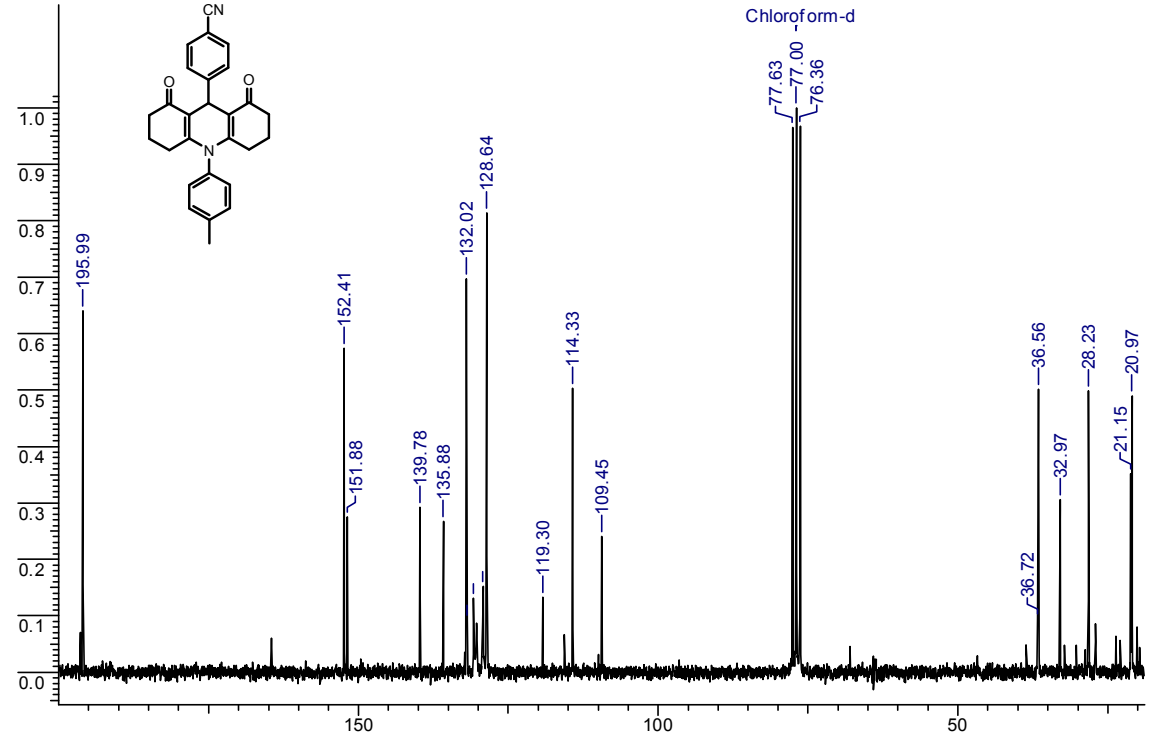
^{13}C-NMR spectrum of **10a**



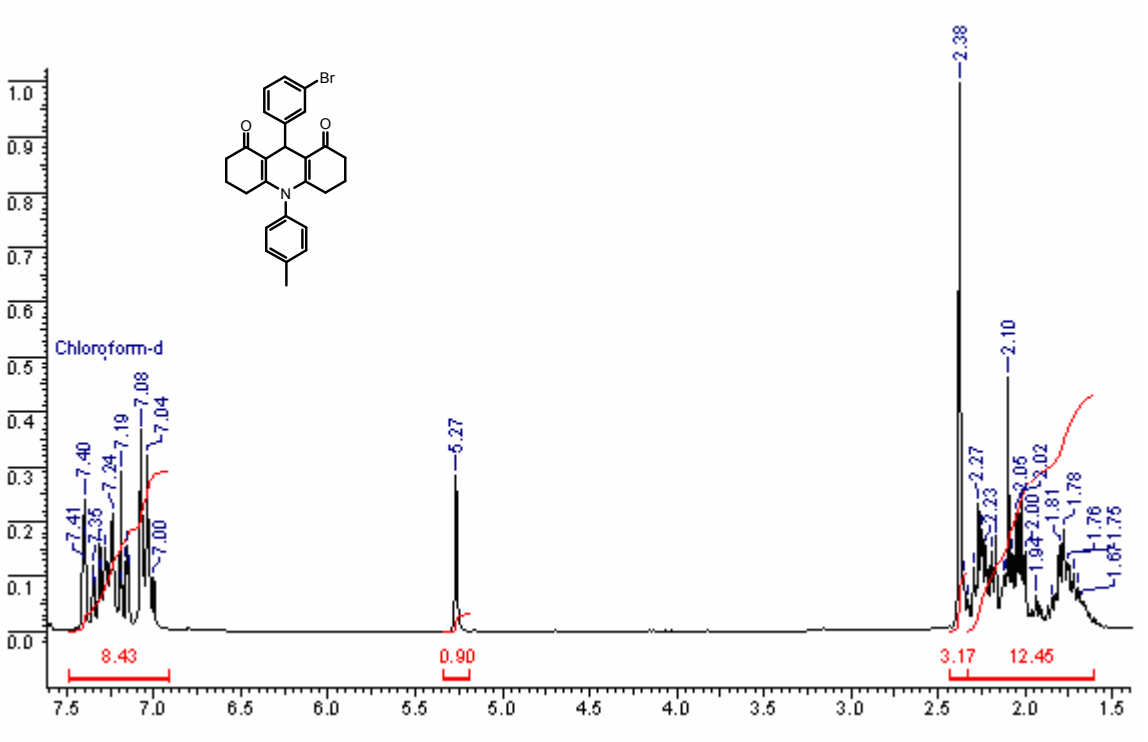
^{1}H-NMR spectrum of **10e**



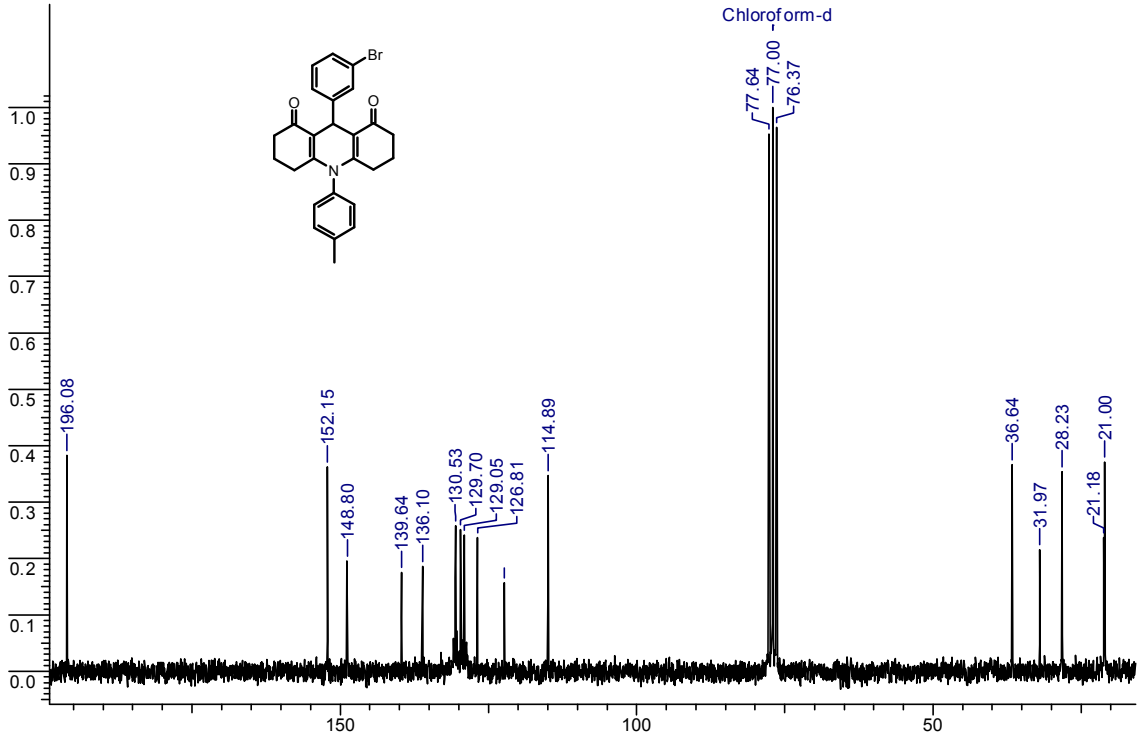
^{13}C-NMR spectrum of **10e**



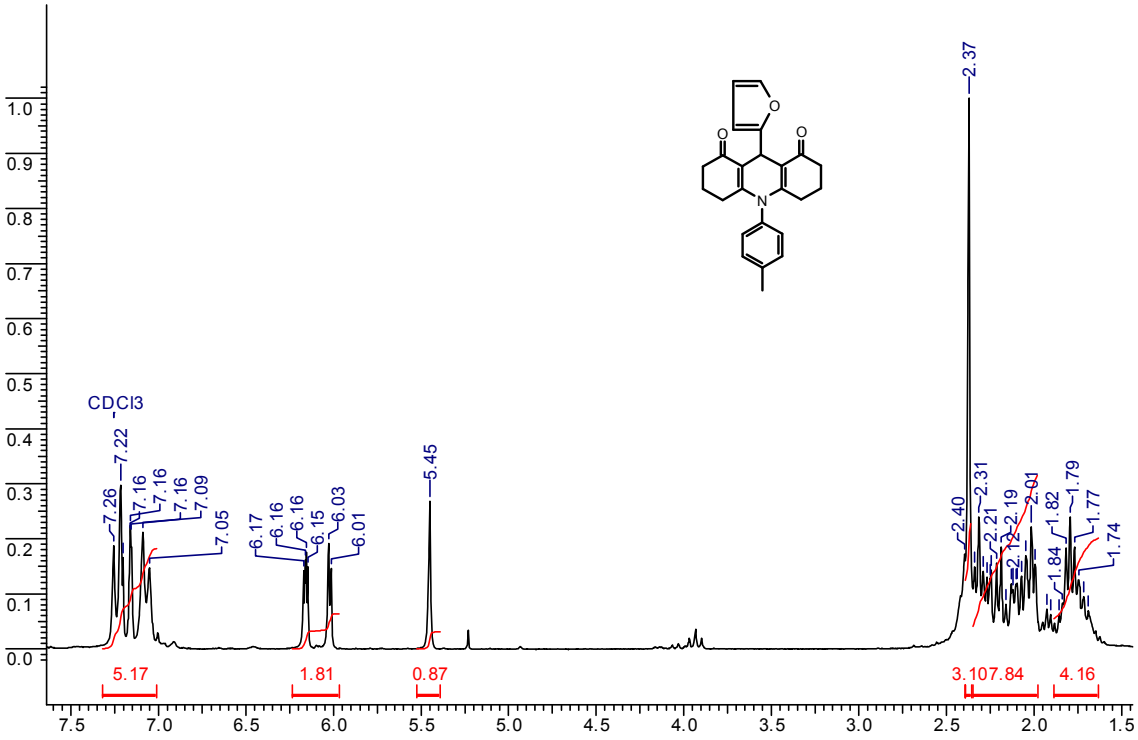
^{1}H-NMR spectrum of **10f**



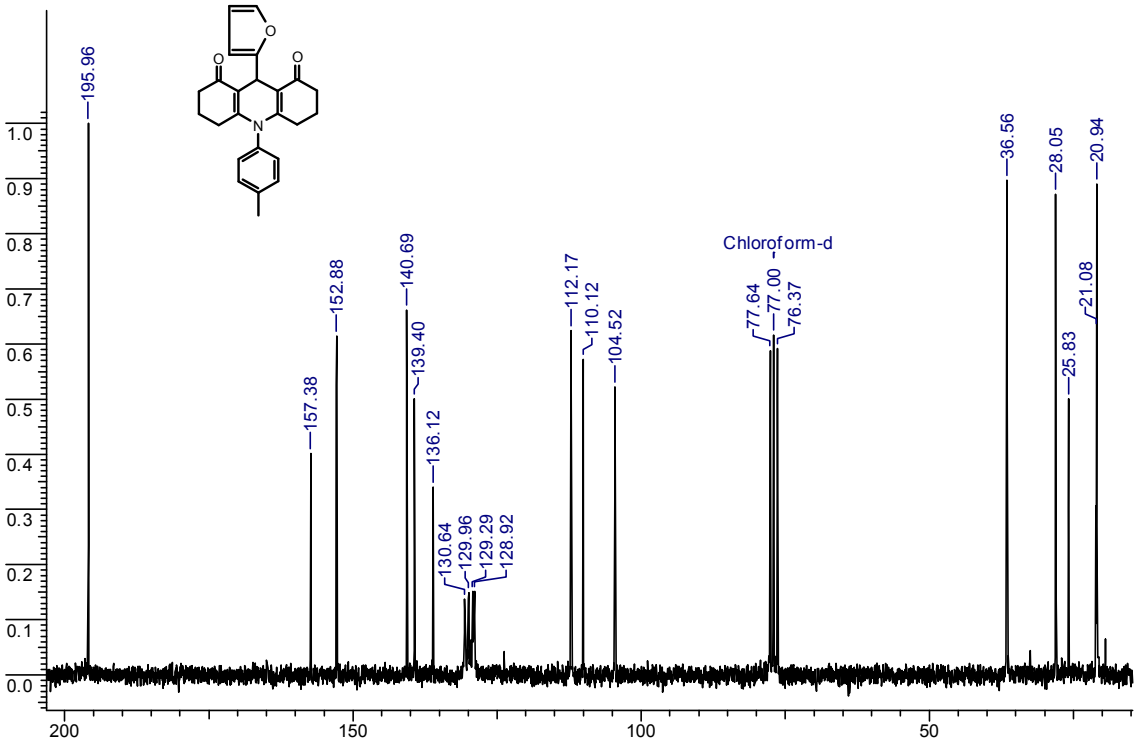
^{13}C-NMR spectrum of **10f**



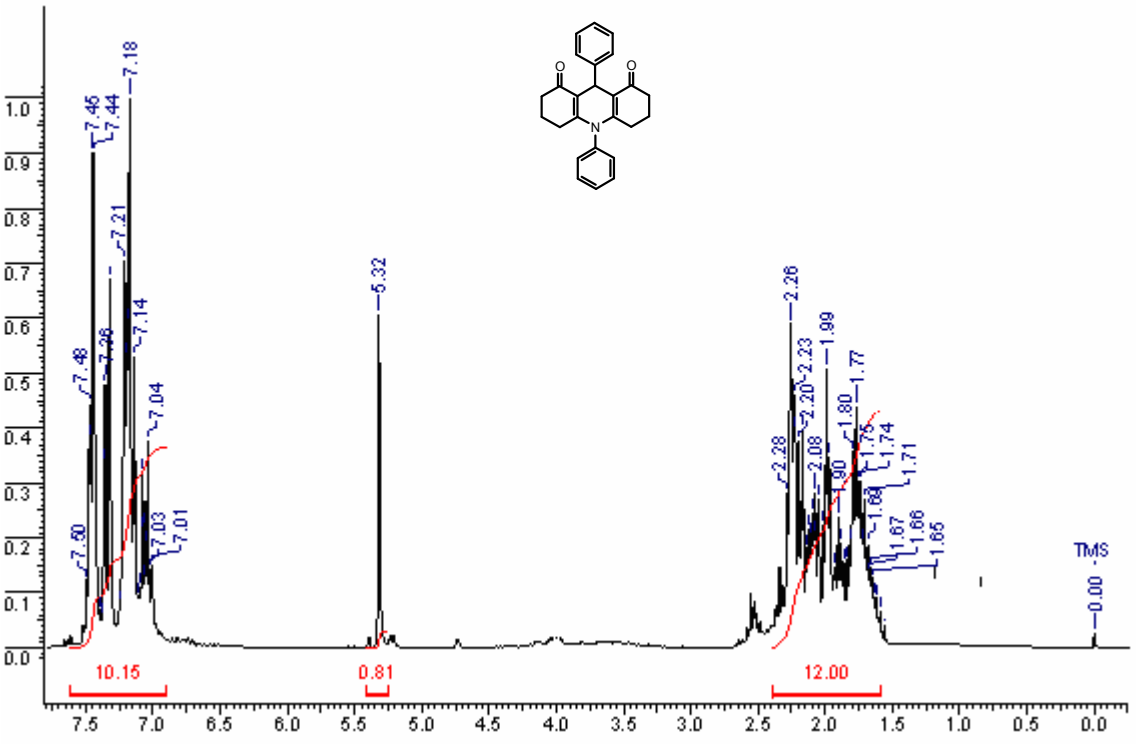
^{1}H-NMR spectrum of **10g**



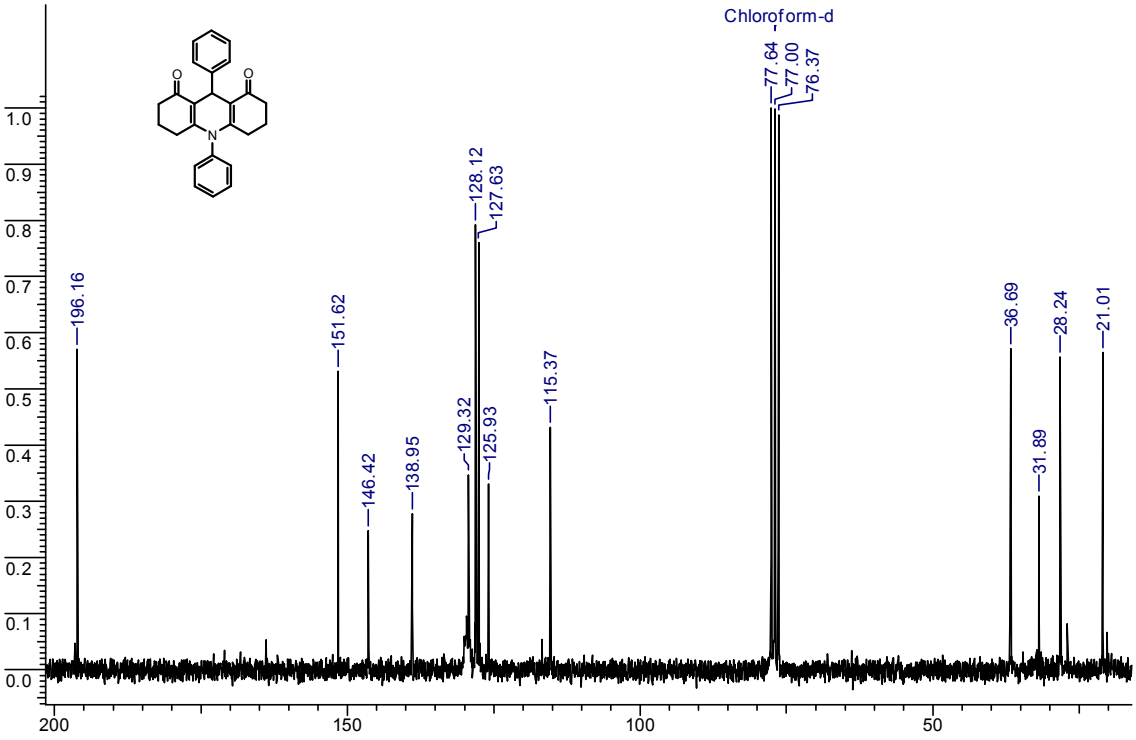
^{13}C-NMR spectrum of **10g**



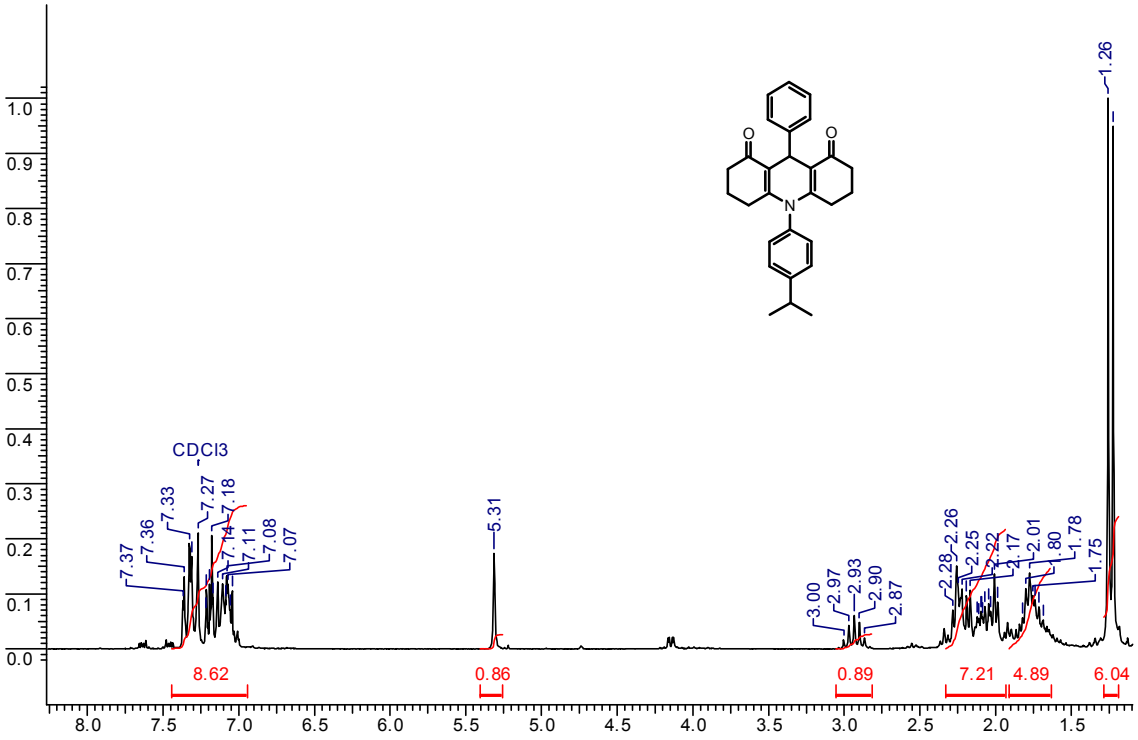
^{1}H-NMR spectrum of **10k**



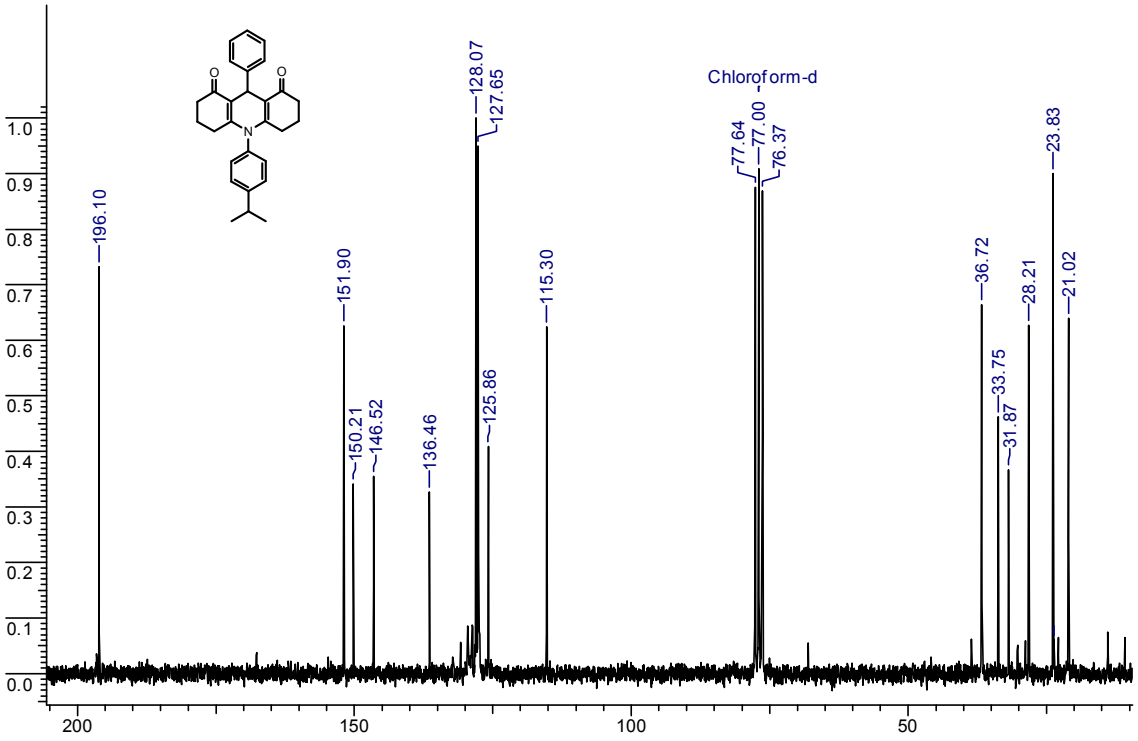
^{13}C-NMR spectrum of **10k**



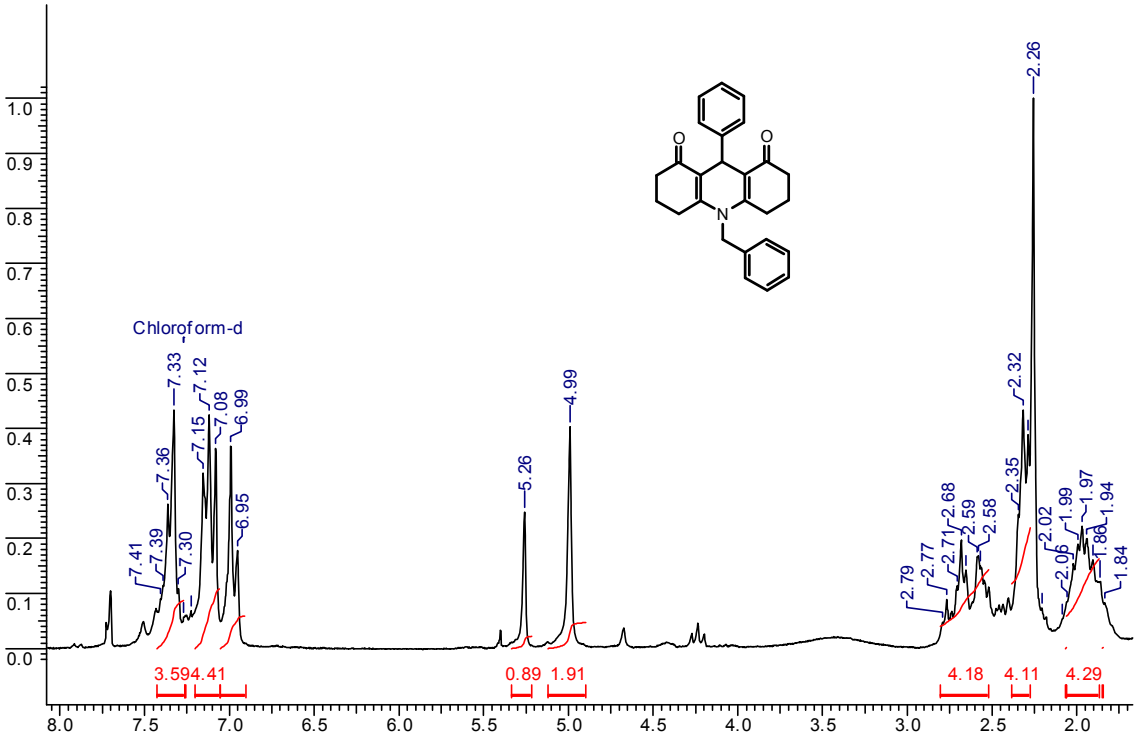
^{1}H-NMR spectrum of **10*l***



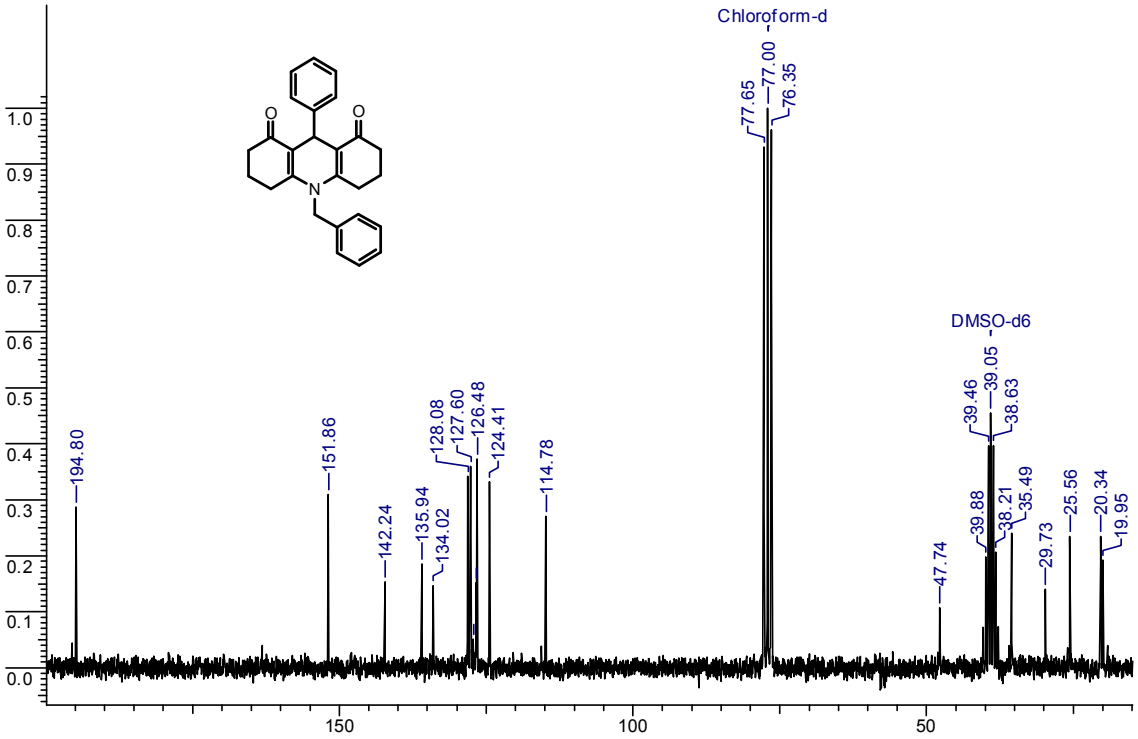
^{13}C-NMR spectrum of **10*l***



^{1}H-NMR spectrum of **10m**



^{13}C-NMR spectrum of **10m**



2.3.8 References

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Ch-II

Sec-D

PEG-400 promoted one-pot synthesis of tetrahydrobenzo[b]pyrans

2.4 Introduction

Poly-functionalized benzo[b]pyrans constitute the structural unit of a series of natural products and are versatile synthons because of the inherent reactivity of the inbuilt pyran ring.[1] They are an important class of compounds, which has received considerable attention in recent years due to their wide range of biological and pharmacological activities such as anti-coagulant, spasmolytic, diuretic, anti-ancaphylactin and anticancer properties.[2] A number of 2-amino-4*H*-benzo[b]pyrans are useful as photoactive materials.[3a] Also, they can be used as cognitive enhancers for the treatment of neurodegenerative disease, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS-associated dementia, and Down syndrome, as well as for the treatment of schizophrenia and myoclonus.[3b] In the conventional reported synthesis of benzo[b]pyrans, the use of organic solvents like DMF/acetic acid make the work-up procedure complicated, leads to poor yields of the products besides polluting the environment and also base catalyzed reactions were reported with lower yields.[4] Many of the other procedures employ catalysts such as HTMAB,[5a] Proline,[5b] $Yb(PFO)_3$,[5c] HDMBAB,[5d] TMAH,[5e] $(NH_4)_2HPO_4$[5f] and TEBA.[5g] Recently, Kaupp *et al.* reported a novel method for the synthesis benzo[*b*]pyrans utilizing the reactants in solid or molten state.[6] In addition methods employing microwave,[7a,b] ultrasound,[7c] and ionic liquid mediated[8] syntheses have also been reported. To the best of our knowledge, only one report exists in the literature which utilizes water as solvent in the absence of a catalyst.[9] Some of the methods reported above use expensive catalysts, strong acidic conditions, higher temperatures, require longer reaction times, resulting in unsatisfactory yields and involved cumbersome product isolation procedures.

From the point of view of environmentally friendly chemical synthesis, the replacement of toxic and volatile organic solvents by alternatives such as water, ionic liquids and PEG and carrying out organic transformations under solvent-less conditions has emerged as a new area in modern organic synthesis.[10,11] Polyethylene glycol promoted reactions have attracted the attention of organic chemists due to their ease of workup, the ability to act as phase transfer catalysts and their inexpensive, readily available and eco-friendly nature.[10e,12-13]

Multi-Component Reactions (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and the diversity can be achieved simply by varying the reacting components.[14] Thus, new routes utilizing a MCR protocol, for the synthesis of benzo[b]pyrans can attract considerable

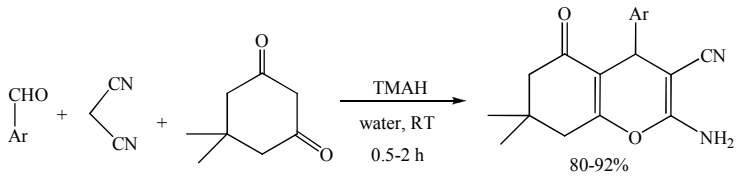
attention in the search of methods for rapid entry to these heterocycles. Consequently, we thought that there is scope for further innovation towards milder reaction conditions, short reaction time and better yields in the synthesis of benzo[b]pyrans which can possibly be achieved by choosing PEG-400 for this multi-component reaction (MCR).

2.4.1 Literature work

Reported syntheses of tetrahydrobenzo[b]pyrans have burgeoned in recent years because of increasing recognition of their biological relevance. Some of the recent syntheses of tetrahydrobenzo[b]pyrans are described below.

Balalaie's approach (2007)[5e]

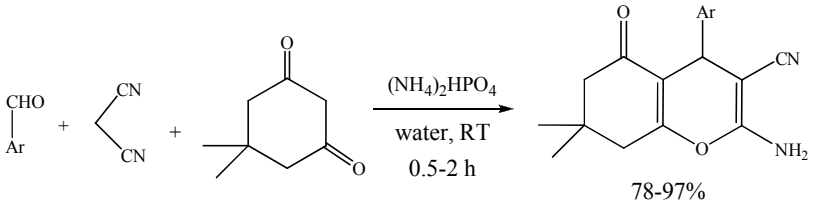
Tetra-methyl ammonium hydroxide (TMAH) has been used as a mild, efficient, neutral and cheap catalyst for the synthesis of various tetrahydrobenzo[b]pyran derivatives via a one-pot three-component condensation in aqueous media.



(Scheme **16**)

Balalaie's approach (2007)[5f]

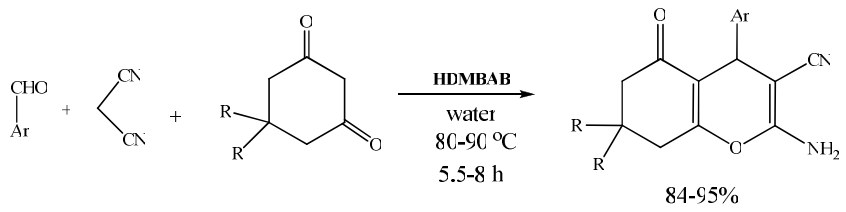
Diammonium hydrogen phosphate was used as a mild, efficient, neutral, and cheap catalyst for the synthesis of various tetrahydrobenzo[b]pyran derivatives *via* an one-pot strategy in aqueous media.



(Scheme **17**)

Jin's approach (2006)[5d]

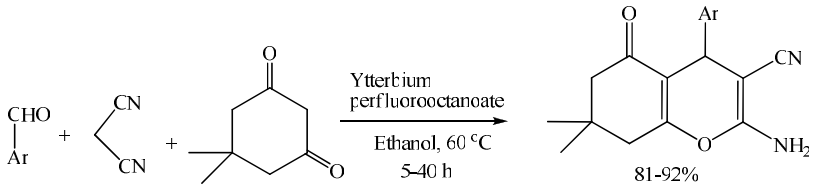
A clean and efficient method for the synthesis of tetrahydrobenzo[b]pyran derivatives using hexadecyldimethylbenzylammonium bromide (HDMBAB) as the catalyst is described.



(Scheme **18**)

Wang's approach (2006)[5c]

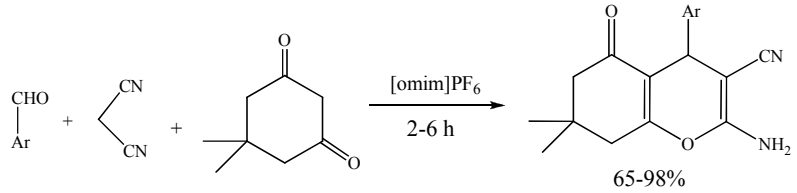
Rare earth perfluorooctanoate, [Yb(PFO)$_3$], catalyzes facile condensation of dimedone, aldehydes and malononitrile under mild conditions to afford the corresponding 5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran derivatives in good to high yields.



(Scheme **19**)

Jiang's approach (2005)[8b]

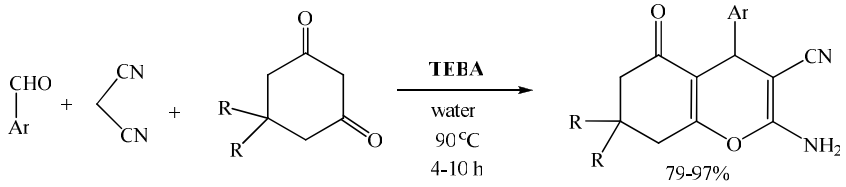
A one-pot synthesis of a series of tetrahydrobenzo[*b*]pyran derivatives via *via* an one-pot strategy in room temperature ionic liquids (RTILs) without any catalyst has been reported.



(Scheme **20**)

Shi's approach (2004)[5g]

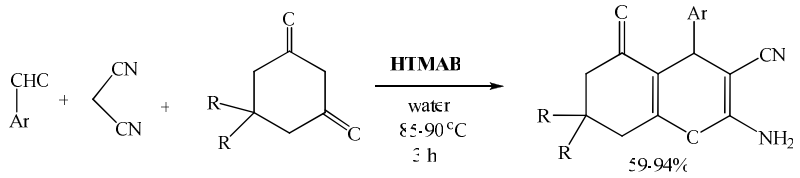
The reaction of aromatic aldehyde, malononitrile and 1,3-cyclohexanediones in water in the presence of triethylbenzylammonium chloride (TEBA) provides an efficient access to tetrahydrobenzo[b]pyranas.



(Scheme **21**)

Jin's approach (2004)[5a]

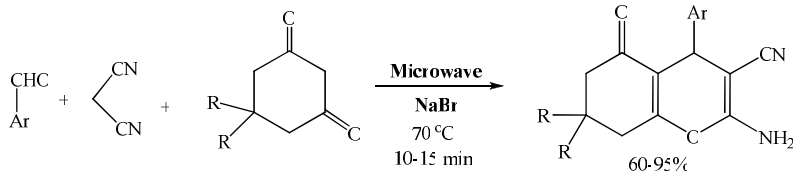
Jin and co-workers described an efficient and convenient approach to the synthesis of tetrahydrobenzo[*b*]pyran derivatives using hexadecyltrimethylammoniumbromide (HTMAB) as the catalyst (10 mol%).



(Scheme **22**)

Devi's approach (2004)[7a]

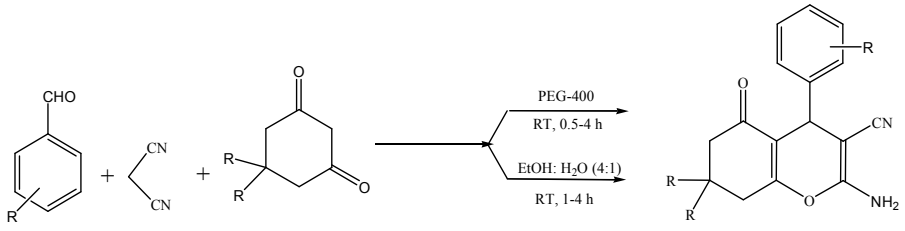
Sodium bromide catalyzed one-pot strategy proceeds under microwave irradiation in solvent free conditions to give highly functionalized benzo[b]pyrans in excellent yields.



(Scheme **23**)

2.4.2 Present work

In our present work, we have developed an one-pot three-component cyclocondensation of aromatic aldehydes (**11**), malononitrile (**12**) and a diketone (**13**a or **13**b) at ambient conditions in PEG-400 and EtOH:H_2O (4:1) as solvents respectively to afford the corresponding benzo[b]pyrans in excellent yields as shown in Scheme **24**.



Scheme 24

2.4.3 Results and discussion

A model reaction involving benzaldehyde (**11**a), malononitrile (**12**), 1,3-cyclohexanedione (**13**a) to afford the 4*H*-benzo[b]pyran **14**a under ambient temperature conditions in different solvents and solvent mixtures was performed. The results are recorded in Table **10**.

Table 10. Synthesis of benzo[b]pyran (14a) under various reaction conditions

Entry	Reaction conditions	Yield (%)[a]
1	3 mL of acetonitrile, No catalyst, Reflux, 6 h	0
2	**ethanol: water (4:1, 3 mL), RT, 1 h**	**81**[b]
3	ethanol: water (4:1, 3 mL), Reflux, 1 h	82[b]
4	3 mL of water, RT, 24 h	<5[c]
5	2 mL of ethanol, RT, 6 h	79
6	**2 mL of PEG-400, RT, 1 h**	**94**

[a]Isolated yields. [b]Yields after recrystallization from ethanol. [c]The starting materials 1,3-cyclohexanedione (89%) and benzaldehyde (86%) were recovered back from the reaction mixture.

Among the various conditions, the reaction performed in PEG-400 at ambient conditions was observed to be the most suitable condition for this MCR which afforded the best yield (94%) in the shortest possible reaction time (1 h). Surprisingly, the reactions also proceeded smoothly under ambient temperature, in the innocuous and non-toxic ethanol as solvent in which some water has been added, in just 1 h albeit in relatively lower yields as compared to PEG-400. It was observed that refluxing in this solvent mixture, no appreciable increase in yield was observed. It must be noted that the reaction was very sluggish in water alone as solvent with very poor yields of the product (**14**a) and in absolute ethanol as a solvent even after 6 h, the product was obtained in slightly lowered yield. Hence, all further reactions with other aldehydes were carried out by using PEG-400 as a promoter and with ethanol: water (4:1) at ambient conditions respectively.

A variety of aldehydes such as aryl-, furyl- and pyridyl- were condensed with malononitrile and 1,3-cyclohexanedione (or dimedone **13**b) in a one-pot three component MCR protocol at ambient temperature in PEG-400 medium (Procedure-A) and in ethanol: water (4:1) (Procedure-B) respectively as shown in the Scheme **24**. All the reactions were monitored by TLC and taken to completion. The results are recorded in Table **11**. All the compounds were well characterized by melting point, IR, ^{1}H-NMR and elemental analyses. In case of known compounds, the physical and spectral data are compared with the literature values. It was observed that all the aldehydes reacted in short reaction times (0.5-

4 h) under ambient conditions to afford the benzo[b]pyrans in very good to excellent isolated yields. These processes tolerate aromatic aldehydes containing both electron donating and electron withdrawing substituents. Notably, the complex aldehydes such as 5-iodovanilin and 4-benzyloxybenzaldehyde (Entry **16** and **17**) also reacted in short times giving rise to the corresponding novel products in excellent isolated yields. The structure of the new benzo[b]pyran **14**n was confirmed by X-ray crystallography (Fig. **4**).

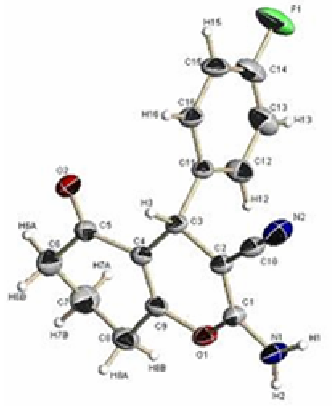
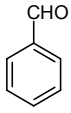
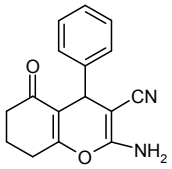
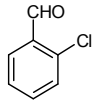
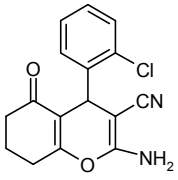
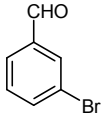
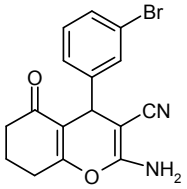
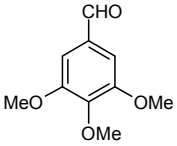
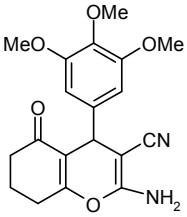
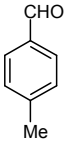
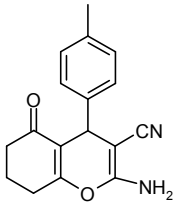
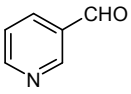
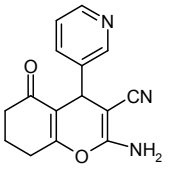
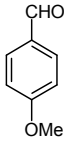
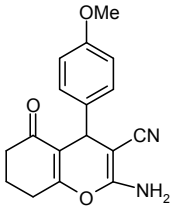
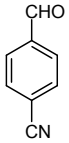
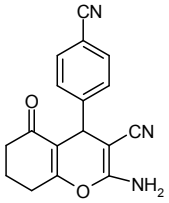


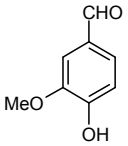
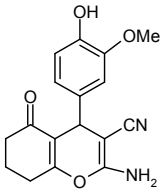
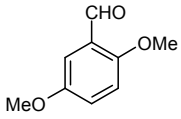
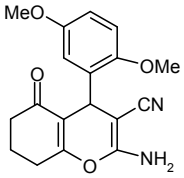
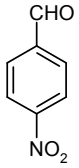
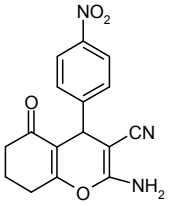
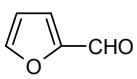
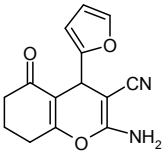
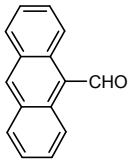
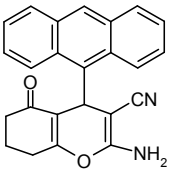
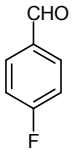
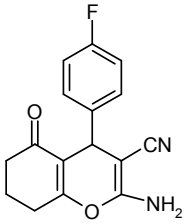
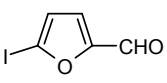
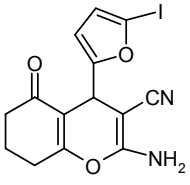
Fig. 4. ORTEP diagram of the X-ray crystal structure of compound **14**n with thermal ellipsoids at 30% probability.

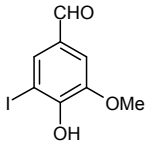
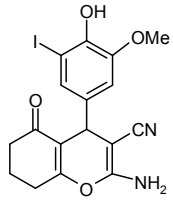
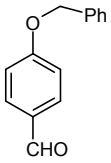
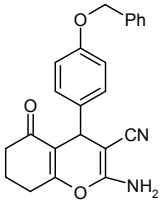
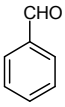
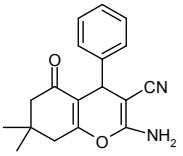
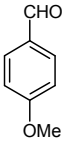
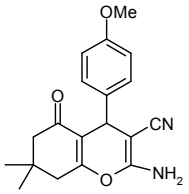
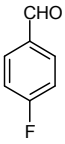
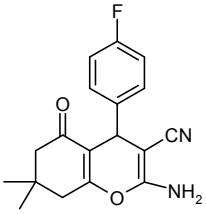
Since PEG-400 was miscible with water in all proportions, the product isolation was carried out by simply diluting the reaction mixture with excess of water, filtering off and drying the precipitated benzo[b]pyrans. The benzo[b]pyrans, thus isolated were homogeneous on TLC and were pure enough for all practical purposes. However, the compounds **14**j and **14**m were subjected to further purification by recrystallization from hot ethanol for characterization and in this case, the yields reported are after this procedure (Table **11**).

Table 11. Synthesis of benzo[b]pyran derivatives **14**(a-t) by using the Procedures 'A' and 'B' at room temperature

Entry	Aldehyde	Solvent: PEG-400		Product	Solvent: EtOH:H_2O (4:1)		MP/^oC (lit.)
	(12)	Time (h)	Yield (%)[a]	**(14)**	Time (h)	Yield (%)[b]	
1	 **12**a	1.0	94	 **14a**	1.0	81	238-240[c]

2		0.75	96	 **14b**	1.5	83	211-213[5d]
3		1.0	95	 **14c**	2.0	85	244-246[c]
4		0.5	89	 **14d**	1.5	80	227-229[c]
5		1.5	95	 **14e**	3.5	83	225-227[c]
6		0.5	90	 **14f**	1.0	80	230-232[c]
7		1.5	86	 **14g**	2.5	77	196-198[5d]
8		0.75	92	 **14h**	1.5	81	235-237[c]

9		1.5	93	 **14i**	3.5	85	230-232[c]
10		3.0	94[b]	 **14j**	3.5	84	223-225[c]
11		1.0	89	 **14k**	1.25	80	232-234[5d]
12		1.0	97	 **14l**	3.0	83	238-240[c]
13		0.5	88[b]	 **14m**	3.0	79	109-112[c]
14		1.0	93	 **14n**	2.0	86	235-236[c]
15		1.0	94	 **14o**	3.0	81	182-184[c]

16		1.0	89	 **14p**	4.0	83	232-234[c]
17		1.5	89	 **14q**	2.5	78	198-200[c]
18		1.5	95	 **14s**	3.0	84	226-228[5a]
19		1.5	91	 **14s**	2.5	81	196-198[5d]
20		1.0	92	 **14t**	2.0	85	188-190[c]

[a]Isolated yields.
[b]Yields reported are after recrystallization from ethanol.
[c]New compounds.

The aqueous filtrate containing PEG-400 was subjected to distillation at 70 °C under reduced pressure (10 mmHg) over 4 h to leave behind the PEG-400 in near complete recovery, pure enough for recycle. The recovered PEG-400 was found to be effective for at least three recycles in the synthesis of **14**a. Since the removal of large quantities of water is an energy intensive process adding to its cost, we tried to selectively extract the products from the PEG-400 medium with the solvents such as DCE, Ethyl acetate and diethyl ether to leave behind PEG-400 as an immiscible layer to recover and recycle further for successive reactions. This did not work out in practice, since the products were found to be sparingly soluble in these solvents.

We also evaluated our results in terms of reaction times and yields for the aqueous ethanol mediated, catalyst free synthesis of benzo[b]pyrans under ambient conditions (Table **11**). The PEG-400 promoted reactions (Procedure-A) are faster than aqueous ethanol mediated reactions (Procedure-B) resulting in better yields in most of the cases. In Procedure-B also, the products are isolated by dilution with water. In both the procedures (Procedure-A and Procedure-B), it is significant that in many of the cases, the products (benzo[b]pyrans) were completely precipitated from the reaction medium after completion of the reaction.

2.4.4 Conclusion

In conclusion, we have evolved a novel efficient and eco-friendly synthesis for the preparation of benzo[b]pyran derivatives by a one-pot three component cyclocondensation reaction of malononitrile, an aldehyde and a cyclic diketone in PEG-400 which acts as reaction medium cum promoter at ambient conditions. The products can be easily isolated by simple work up procedures such as dilution and filtration of the precipitated product. From the aqueous filtrate, PEG-400 could be easily recovered and reused three times without any loss of activity. The reaction times and yields are also compared with aqueous ethanol mediated synthesis of pyrans under ambient conditions (1:4 ratio, water: ethanol), which is also reported for the first time under our reaction conditions. The ambient conditions, eco-friendly solvent, absence of a catalyst, short reaction times, excellent isolated yields and easy work up make this methodology a facile and superior method for the synthesis of poly-substituted benzo[b]pyrans. This methodology is environment friendly with minimal or no waste. This work is communicated to *ARKIVOC*.

2.4.5 Experimental

2.4.5.1 Procedure-A: **Typical procedure for the PEG-400 assisted one-pot synthesis of tetrahydrobenzo[b]pyran (14a):**

A mixture of benzaldehyde (**11**a, 0.106 g, 1.0 mmol), malononitrile (**12**, 0.100 g, 1.5 mmol), and 1,3-cyclohexanedione (**13**a, 0.112 g, 1.0 mmol) in 2 mL of PEG-400 was stirred at RT in an atmosphere of nitrogen at ambient conditions for 1 h. After completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (~50 g) and stirred for about 0.5 h. The solid separated was filtered through a sintered funnel under suction, washed with ice-cold water (50 mL) and dried at vacuum to afford the benzo[b]pyran **14**a (0.251 g, 94%). The aqueous filtrate containing PEG-400 was

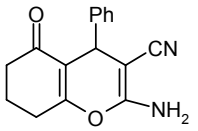
subjected to distillation at 70 °C under reduced pressure (10 mmHg) over 4 h to leave behind the PEG-400 in near complete recovery, pure enough for recycle. The recovered PEG-400 was found to be effective for at least three recycles in the synthesis of **14**a.

2.4.5.2 Procedure-B: **Typical procedure for the aqueous ethanol mediated one-pot synthesis of tetrahydrobenzo[b]pyran (4a):**

A mixture of benzaldehyde (**11**a, 0.106 g, 1.0 mmol), malononitrile (**12**, 0.100 g, 1.5 mmol), and 1,3-cyclohexanedione (**13**a, 0.112 g, 1.0 mmol) in 4 mL of ethanol containing 1 mL of water was stirred at RT for 1 h. After completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (~50 g) and stirred for about 1 h. The solid separated was filtered through a sintered funnel under suction and washed with ice-cold water (50 mL). The resulting crude product was then recystallized from ethanol to afford the benzo[b]pyran **14**a (0.237 g, 81%).

2.4.6 Characterization data for the synthesized compounds

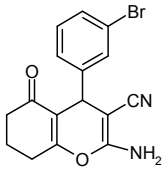
2-amino-4-phenyl-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile, 14a:



White solid
mp: 238-240 °C

IR ($CHCl_3$), υ_{max}	3300, 3167, 2924, 2854, 2193, 1683, 1650, 1610, 1462, 1374, 1245, 1210, 1000, 700 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	δ 2.33-2.45 (m, 2H), 2.67 (t, *J* =7.0Hz, 2H), 2.94-3.01 (m, 2H), 4.71 (s, 1H), 6.36 (br s, 2H), 7.51-7.64 (m, 5H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 19.2, 26.1, 34.6, 35.8, 59.2, 113.8, 118.8, 125.8, 126.5, 127.4, 143.3, 157.6, 162.9, 195.1.
Elemental analysis	Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.04; H, 5.21; N, 10.63%.

2-amino-4-(3-bromophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbo-nitrile, 14c:



White solid

mp: 244-246 °C

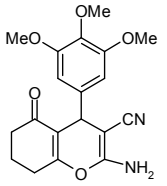
IR ($CHCl_3$), υ_{max} 3300, 3150, 2924, 2854, 2196, 1680, 1640, 1611, 1460, 1421, 1373, 1242, 1214, 1136, 1000, 697 cm^{-1}.

^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz) δ 2.01-2.14 (m, 2H), 2.38 (t, *J* = 6.0 Hz, 2H), 2.65-2.77 (br t, 2H), 4.36 (s, 1H), 6.62 (br s, 2H), 7.24 (d, *J* = 6.0 Hz, 2H), 7.37-7.39 (m, 2H).

^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz) δ 18.7, 25.6, 34.2, 35.3, 57.2, 112.7, 118.3, 120.8, 125.1, 128.4, 128.8, 128.9, 145.6, 157.4, 162.9, 194.6.

Elemental analysis Anal. Calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; Br, 23.15; N, 8.12%. Found: 55.52; H, 3.86; Br, 23.04; N, 8.24%.

2-amino-5,6,7,8-tetrahydro-4-(3,4,5-trimethoxy-phenyl)-5-oxo-4*H*-chromene-3-carbonitrile, 14d:



Pale yellow Solid

mp: 227-229 °C

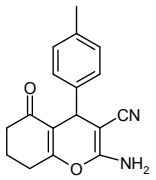
IR ($CHCl_3$), υ_{max} 3372, 3200, 2924, 2854, 2196, 1650, 1640, 1611, 1460, 1421, 1373, 1242, 1210, 1122, 1000, 723 cm^{-1}

^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz) δ 2.09-2.23 (m, 2H), 2.46-2.51 (m, 2H), 2.71-2.77 (m, 2H), 3.85 (s, 3H), 3.93 (s, 6H), 4.39 (s, 1H), 6.49-6.59 (m, 4H).

^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz) δ 18.7, 25.6, 34.3, 35.3, 54.5, 57.6, 58.9, 102.9, 112.7, 112.9, 118.5, 134.9, 138.6, 151.5, 157.3, 162.7, 194.7.

Elemental analysis Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86%. Found: 64.14; H, 5.57; N, 7.92%.

2-amino-5,6,7,8-tetrahydro-5-oxo-4-(*p*-tolyl)-4*H*-chromene-3-carbonitrile, 4e:

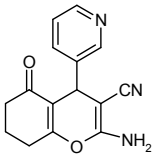


White solid

mp: 225-227 ^{o}C

IR ($CHCl_3$), υ_{max}	3300, 3200, 2924, 2854, 2195, 1655, 1604, 1460, 1377, 1200, 1167, 1070, 1000, 723 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6) (200 MHz)	δ 1.98-2.10 (m, 2H), 2.33 (br s, 5H), 2.63 (br t, 2H), 4.27 (s, 1H), 6.63 (br s, 2H), 7.12 (br s, 4H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.4, 19.3, 25.3, 33.4, 35.0, 57.5, 112.9, 118.3, 125.6, 127.3, 128.5, 129.3, 134.2, 140.0, 146.9, 162.3, 194.2.
Elemental analysis	Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99%. Found: C, 72.77; H, 5.69; N, 9.84%.

2-amino-5,6,7,8-tetrahydro-5-oxo-4-(pyridin-3-yl)-4*H*-chromene-3-carbo-nitrile, 14f:

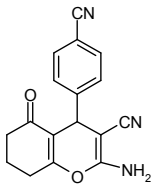


White solid

mp: 230-232 ^{o}C

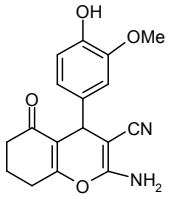
IR ($CHCl_3$), υ_{max}	3350, 3300, 2924, 2854, 2192, 1678, 1665, 1612, 1588, 1460, 1431, 1365, 1210, 1198, 1177, 1000, 840, 715 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.91-2.09 (m, 2H), 2.25 (t, *J* = 6.0 Hz, 2H), 2.56 (t, *J* = 6.0 Hz, 2H), 4.30 (s, 1H), 6.54 (br s, 2H), 7.19-7.26 (m, 1H), 7.50 (d, *J*= 8.0 Hz, 1H), 8.35-8.43 (m, 2H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.7, 25.6, 32.3, 35.3, 56.8, 112.4, 118.3, 122.2, 133.8, 146.5, 147.6, 157.6, 163.2, 194.6.
Elemental analysis	Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72%. Found: C, 67.30; H, 4.81; N, 15.79%.
LC-MS	268 $[M+H]^+$

2-amino-5,6,7,8-tetrahydro-4-(4-cyanophenyl)-5-oxo-4*H*-chromene-3-carbonitrile, 14h:



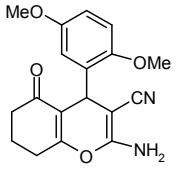
	White solid
	mp: 235-237 ^{o}C
IR ($CHCl_3$), υ_{max}	3300, 3200, 2924, 2854, 2227, 2199, 1687, 1651, 1461, 1365, 1260, 1170, 1019, 1000, 837, 745 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.74-1.84 (m, 2H), 2.09 (t, *J*= 6.0 Hz, 2H), 2.36 (t, *J*= 6.0 Hz, 2H), 4.19 (s, 1H), 5.88 (br s, 2H), 7.12 (d, *J*= 8.2 Hz, 2H), 7.33 (d, *J*= 8.2 Hz, 2H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	19.2, 26.3, 35.2, 35.8, 58.1, 109.6, 113.1, 118.1, 118.5, 127.7, 131.5, 148.7, 157.9, 163.7, 195.2.
Elemental analysis	Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42%. Found: 70.18; H, 4.41; N, 14.35%.

2-amino-5,6,7,8-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-4*H*-chromene-3-carbonitrile, 14i:



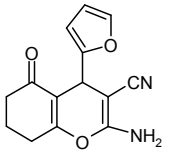
	White solid
	mp: 230-232 ^{o}C
IR ($CHCl_3$) υ_{max}	3420, 3300, 3150, 2924, 2854, 2193, 1672, 1637, 1523, 1596, 1462, 1375, 1365, 1276, 1248, 1215, 1131, 1074, 1000, 724 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.87-2.05 (m, 2H), 2.26 (t, *J*= 6.4 Hz, 2H), 2.52-2.58 (m, 2H), 3.77 (s, 3H), 4.18 (s, 1H), 6.14 (br s, 1 H), 6.51 (dd, *J*= 2.0, 8.0 Hz, 1H), 6.66 (s, 1H), 6.69-6.71 (m, 1H), 8.25 (br s, 1H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.8, 25.7, 33.7, 35.5, 54.5, 58.6, 110.2, 114.1, 118.3, 118.7, 134.5, 144.0, 145.9, 157.3, 162.3, 194.8.
Elemental analysis	Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97%. Found: C, 65.29; H, 5.08; N, 9.07%.

2-amino-5,6,7,8-tetrahydro-4-(2,5-dimethoxy-phenyl)-5-oxo-4*H*-chromene-3-carbonitrile, 14j:



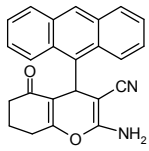
	Pale yellow solid
	mp: 223-225 ^{o}C
IR ($CHCl_3$) υ_{max}	3480, 3320, 3171, 2924, 2854, 2188, 1673, 1660, 1596, 1499, 1463, 1365, 1276, 1248, 1208, 1139, 1068, 1000, 806, 714 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.96-2.07 (m, 2H), 2.27 (t, *J*= 6.0 Hz, 2H), 2.54-2.68 (m, 2H), 3.70 (s, 3H), 3.77 (s, 3H), 6.48 (br s, 2H), 6.53 (d, *J*= 3.0 Hz, 1H), 6.65-6.71 (m, 1H), 6.81 (d, *J*= 8.8 Hz, 1H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.5, 25.2, 28.5, 35.0, 53.6, 54.8, 56.5, 109.6, 111.0, 111.7, 113.3, 118.3, 132.1, 149.6, 151.7, 163.1, 194.0.
Elemental analysis	Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58%. Found: C, 66.18; H, 5.49; N, 8.68%.

2-amino-4-(furan-2-yl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile, 14l:



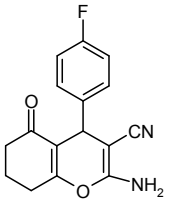
	Pale brownish solid
	mp: 238-240 ^{o}C
IR ($CHCl_3$), υ_{max}	3398, 3325, 3213, 2924, 2854, 2186, 1677, 1651, 1603, 1459, 1360, 1240, 1211, 1162, 1066, 1015, 1001, 926, 824, 749 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.89-2.02 (m, 2H), 2.31 (t, *J* = 6.5 Hz, 2H), 2.53-2.61 (m, 2H), 4.36 (s, 1H), 6.01 (d, *J* = 3.2 Hz, 1H), 6.25-627 (m, 1H), 6.87 (br s, 2H), 7.36 (s, 1H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.1, 25.0, 27.3, 34.6, 53.9, 103.4, 108.6, 110.0, 117.9, 139.7, 154.0, 157.6, 163.2, 193.7.
Elemental analysis	Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93%. Found: C, 65.55; H, 4.64; N, 11.07%.

2-amino-4-(10-anthracenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile, 14m:



	Orange colored solid mp: 109-112 ^{o}C
IR ($CHCl_3$) υ_{max}	3450, 3335, 3171, 2924, 2854, 2191, 1678, 1654, 1594, 1462, 1377, 1350, 1203, 1139, 1067, 994, 881, 723 cm^{-1}.
^{1}H-NMR-(200 MHz) ($CDCl_3$+DMSO-d_6)	δ 1.83-2.22 (m, 4H), 2.67 (br s, 2H), 5.93 (s, 1H), 6.76 (br s, 2H), 7.35-7.64 (m, 5H), 7.96-8.10 (m, 4H).
^{13}C-NMR ($CDCl_3$+ DMSO-d_6, 50 MHz)	δ 18.7, 25.3, 28.2, 35.1, 39.5, 56.9, 68.5, 90.7, 113.5, 118.0, 121.7, 123.6, 124.8, 126.6, 127.1, 127.8, 129.2, 130.2, 133.3, 135.5, 156.6, 161.3, 162.5, 194.4.
Elemental analysis	Anal. Calcd. for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65%. Found: 78.52; H, 4.89; N, 7.71%.

2-amino-5,6,7,8-tetrahydro-5-oxo-4-(4-fluorophenyl)-4*H*-chromene-3-carbonitrile, 14n:



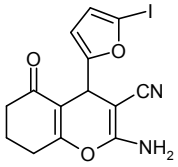
	White solid mp 235-236 ^{o}C
IR ($CHCl_3$) υ_{max}	3413, 3335, 2193, 1682, 1653, 1603, 1506, 1459, 1367, 1360, 1262, 1208, 1069, 1002, 820, 762 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.92-2.12 (m, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 6.1 Hz, 2H), 4.33 (s, 1H), 6.20 (br s, 2H), 6.91-7.00 (m, 2H), 7.16-7.25 (m, 2H).
^{13}C-NMR	δ 19.2, 26.1, 34.3, 35.9, 38.5, 58.2, 113.7, 114.1,

($CDCl_3$+DMSO-d_6, 50 MHz)	114.3, 118.9, 128.4, 139.7, 157.8, 159.3, 161.7, 163.2, 194.9.
Elemental analysis	Anal. Calcd. for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; F, 6.68; N, 9.85%. Found: 67.64; H, 4.66; F, 6.60; N, 9.90%.

Crystal data for 14n:

$C_{16}H_{13}FN_2O_2$, M = 284.28, crystal dimensions 0.52 x 0.34 x 0.25 mm, Monoclinic, space group C2/c, a = 13.254(3), b = 10.927(2), c = 19.860(4) Å, β = 101.895(4)°, V = 2814.3(11) $Å^3$, Z = 8; ρ_{calcd} = 1.342 gcm^{-3}, μ (Mo-K_α) = 0.099 mm^{-1}, $2\theta_{max}$ = 51°, 7012 reflections collected, 2585 unique, 2268 observed (I > 2σ (I)) reflections, 198 refined parameters, R value 0.0536, wR2 = 0.1400 (all data R = 0.0595, wR2 = 0.1458), S = 1.051, minimum and maximum transmission 0.9504 and 0.9757 respectively, maximum and minimum residual electron densities +0.238 and –0.188 e $Å^{-3}$. X-ray data intensity were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{MoK\alpha}$ = 0.71073 Å at T = 293(2) K. All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model except for the nitrogen.

2-amino-4-(5-iodofuran-2-yl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile, 14o:



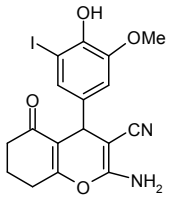
Pale brownish solid

mp: 182-184 °C

IR ($CHCl_3$) υ_{max}	3386, 3196, 2924, 2854, 2193, 1682, 1654, 1608, 1460, 1377, 1245, 1213, 1015, 722 cm^{-1}.

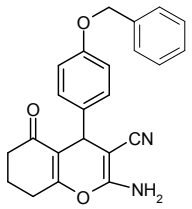
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 2.05-2.14 (m, 2H), 2.39-2.53 (m, 2H), 2.63-2.76 (m, 2H), 4.48 (s, 1H), 6.06 (d, *J*= 3.2 Hz, 1H), 6.48 (d, *J*= 3.2 Hz, 1H), 6.81 (br s, 2H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.4, 25.3, 27.8, 34.9, 53.9, 86.1, 106.9, 109.9, 117.9, 119.1, 123.4, 140.5, 151.4, 157.8, 159.5, 163.5, 193.9.
Elemental analysis	Anal. Calcd. for $C_{14}H_{11}IN_2O_3$: C, 44.00; H, 2.90; I, 33.21; N, 7.33%. Found: C, 44.08; H, 2.99; I, 33.11; N, 7.42%.

2-amino-5,6,7,8-tetrahydro-4-(4-hydroxy-5-iodo-3-methoxyphenyl)-5-oxo-4*H*-chromene-3-carbonitrile, 14p:



	Pale yellow solid mp: 232-234 ^oC
IR ($CHCl_3$) υ_{max}	3500, 3320, 3183, 2924, 2855, 2189, 1677, 1650, 1609, 1460, 1379, 1245, 1162, 1000, 722 cm^{-1}.
^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz)	δ 1.78-1.86 (m, 2H), 2.09-2.19 (m, 2H), 2.35-2.42 (m, 2H), 4.01 (s, 1H), 5.96 (br s, 2H), 6.56 (d, *J*=1.90 Hz, 1H), 6.79 (d, *J*=1.90 Hz, 1H), 7.45 (br s, 1H).
^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz)	δ 18.0, 24.8, 32.8, 34.6, 54.1, 56.2, 68.1, 82.4, 109.4, 112.0, 117.9, 126.4, 135.7, 143.1, 144.9, 156.7, 162.2, 193.
Elemental analysis	Anal. Calcd. for $C_{17}H_{15}IN_2O_4$: C, 46.59; H, 3.45; I, 28.96; N, 6.39%. Found: C, 46.65; H, 3.37; I, 28.85; N, 6.47%.

2-amino-4-(4-(benzyloxy)phenyl)-5,6,7,8-tetrahydro-5-oxo-4H-chromene-3-carbonitrile, 14q:



White solid

mp: 198-200 ^{o}C

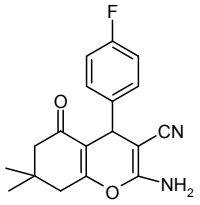
IR ($CHCl_3$) υ_{max} 3320, 3171, 2925, 2855, 2190, 1681, 1651, 1606, 1459, 1376, 1260, 1210, 1002, 694 cm^{-1}.

^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz) δ 2.01-2.06 (m, 2H), 2.35-2.41 (m, 2H), 2.56-2.62 (m, 2H), 4.40 (s, 1H), 4.56 (br s, 2H), 5.02 (s, 2H), 6.98 (d, *J*= 8.7 Hz, 2H), 7.14-7.44 (m, 8H).

^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz) δ 19.2, 26.1, 33.9, 35.9, 59.6, 68.9, 113.7, 118.9, 126.6,127.6, 135.8, 136.1, 156.6, 157.6, 162.7, 195.

Elemental analysis Anal. Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%; Found: C, 74.10; H, 5.49; N, 7.63%.

2-amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*chromene-3-carbo-nitrile, 14t:



White solid

mp: 188-190 ^{o}C

IR ($CHCl_3$) υ_{max} 3360, 3310, 3184, 2925, 2854, 2190, 1712, 1685, 1652, 1605, 1505, 1461, 1415, 1372, 1252, 1215, 1154, 1038, 850, 717 cm^{-1}.

^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz) δ 1.29 (s, 3H), 1.38 (s, 3H), 2.46 (d, *J*= 5.31 Hz, 2H), 2.75 (s, 2H), 4.59 (s, 1H), 6.45 (br s, 2H), 7.19-7.28 (m, 2H), 7.44-7.52 (m, 2H).

^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz) δ 26.5, 27.9, 31.1, 34.1, 49.6, 58.8, 112.5, 113.8, 114.3, 118.7, 128.1, 128.2, 139.1, 139.2, 157.6, 158.0, 161.1, 194.9.

Elemental analysis Anal. Calcd. for $C_{18}H_{17}FN_2O_2$: C, 69.22; H, 5.49; F, 6.08; N, 8.97%; Found: C, 69.14; H, 5.41; F, 5.92; N,

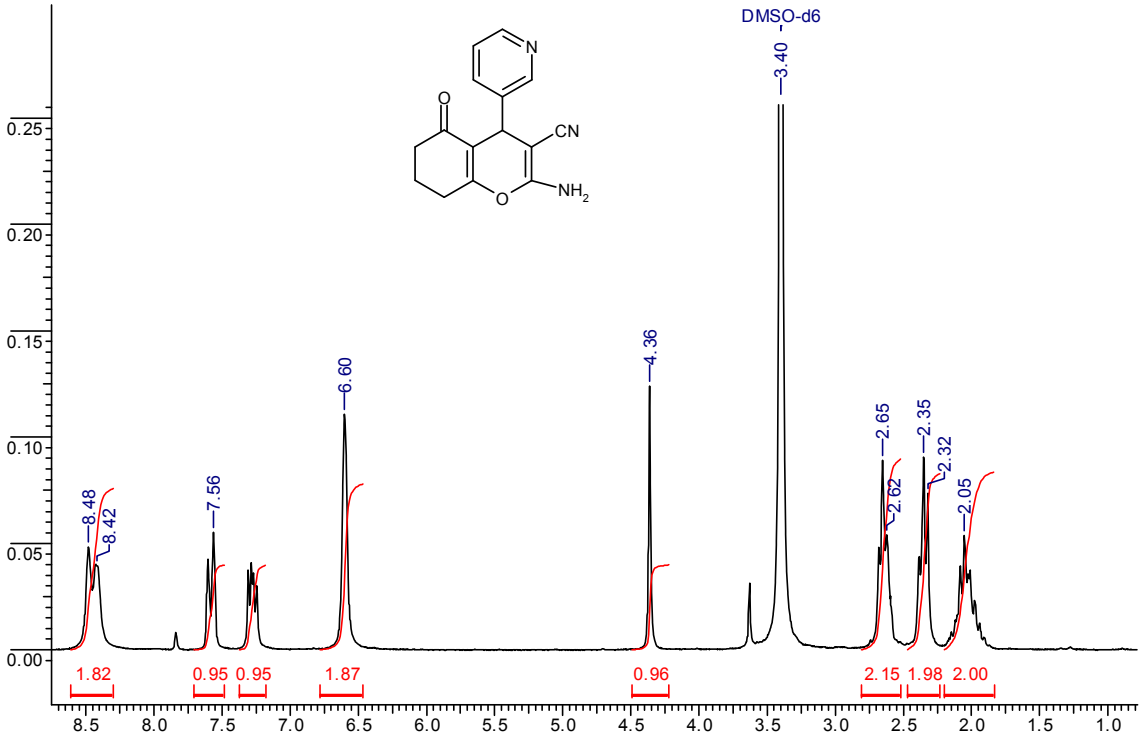
9.05%.

2.4.7 Spectra

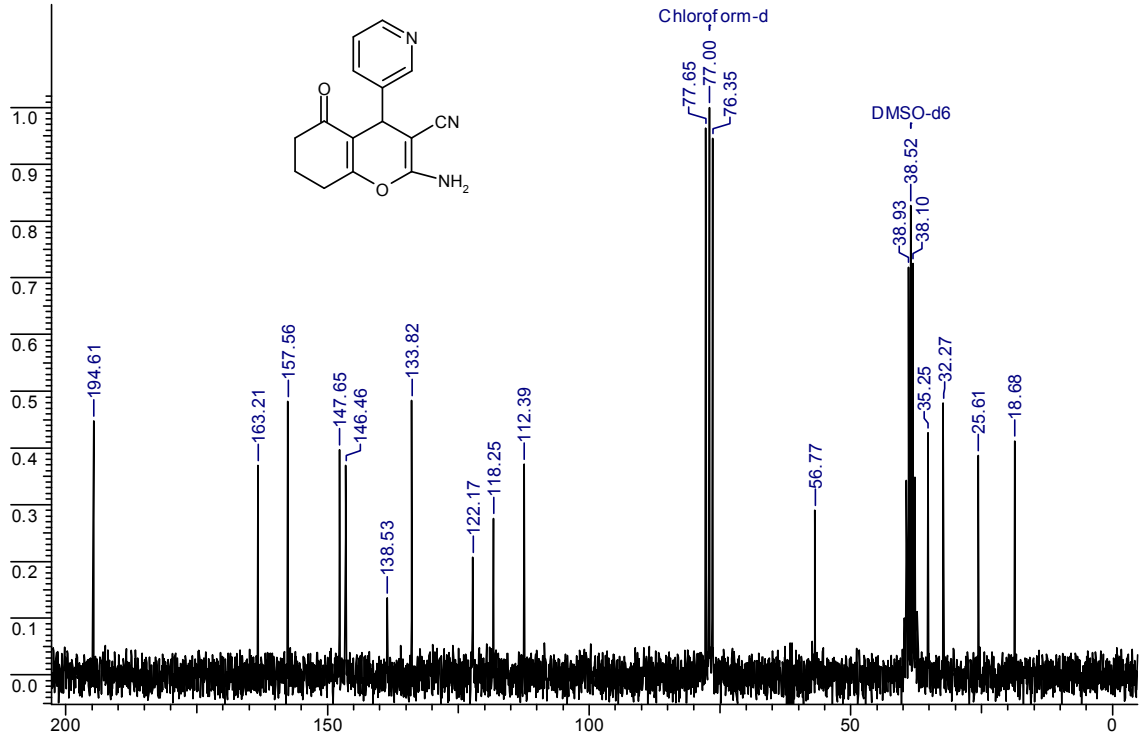
Table 12: ^{1}H & ^{13}C spectra of some selected tetrahydrobenzo[b]pyrans (**14**) are given below:

S. No.	Spectra
1	^{1}H & ^{13}C spectra of **14**f
2	^{1}H & ^{13}C spectra of **14**g
3	^{1}H & ^{13}C spectra of **14**k
4	^{1}H & ^{13}C spectra of **14**l
5	^{1}H & ^{13}C spectra of **14**n
6	^{1}H & ^{13}C spectra of **14**q

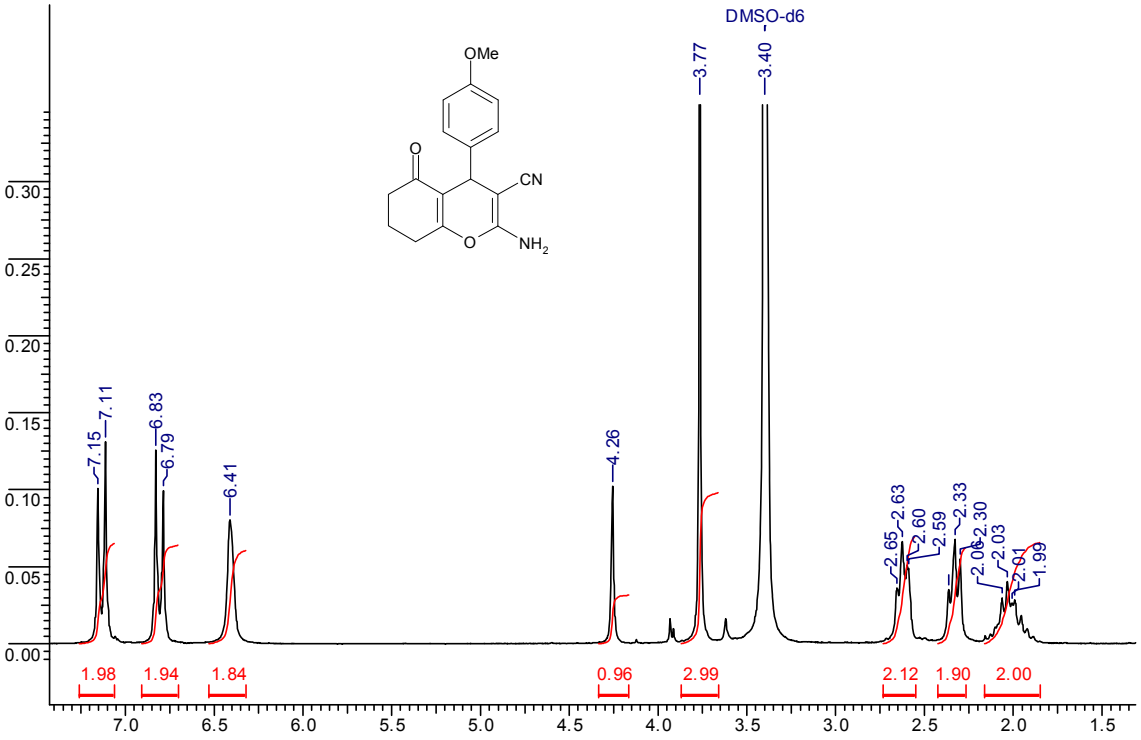
^{1}H-NMR spectra of **14**f:



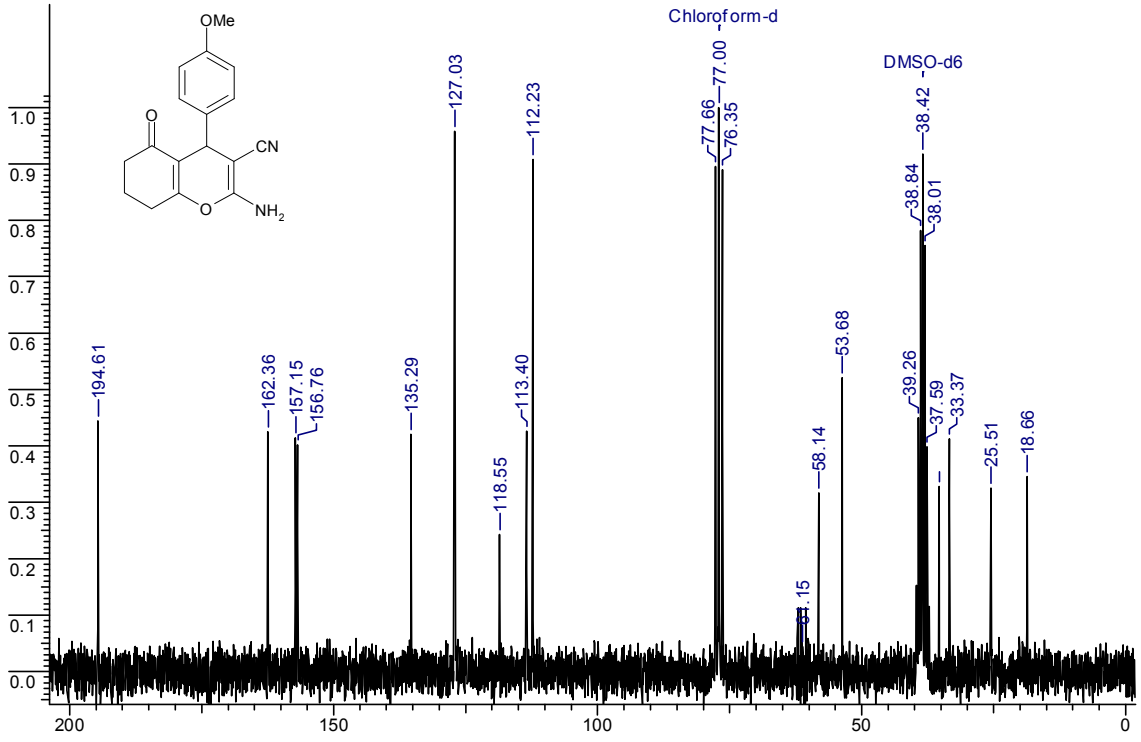
^{13}C-NMR spectra of **14**f:



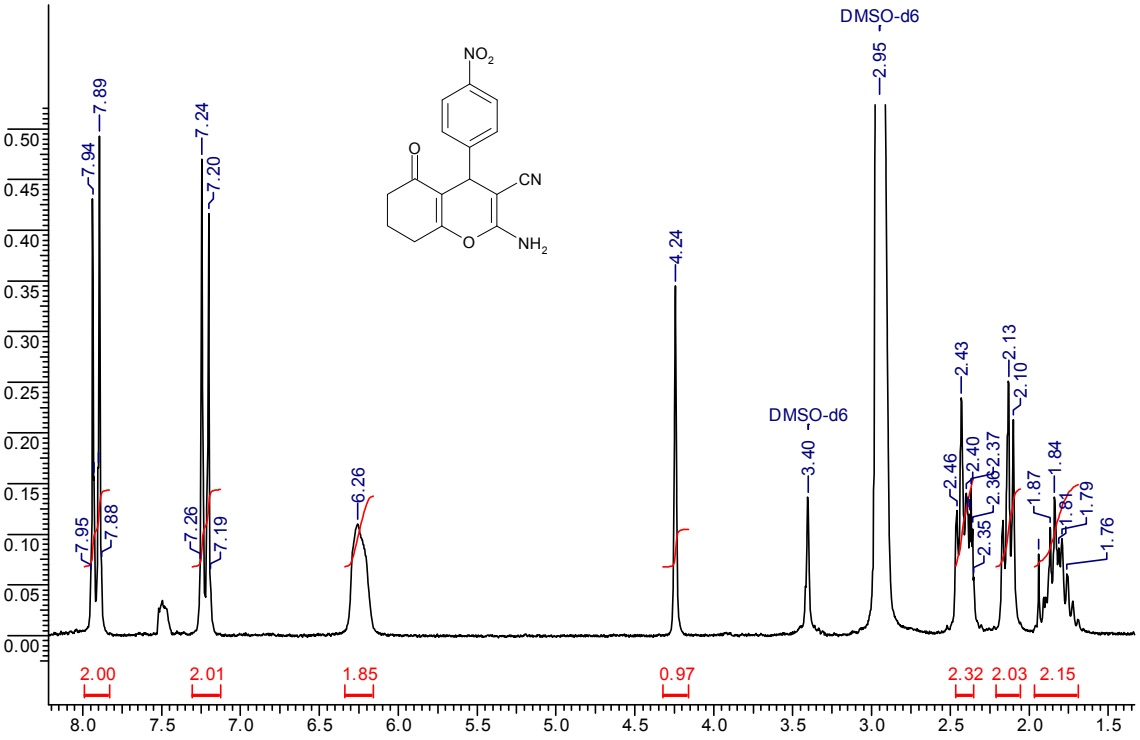
^{1}H-NMR spectra of **14**g:



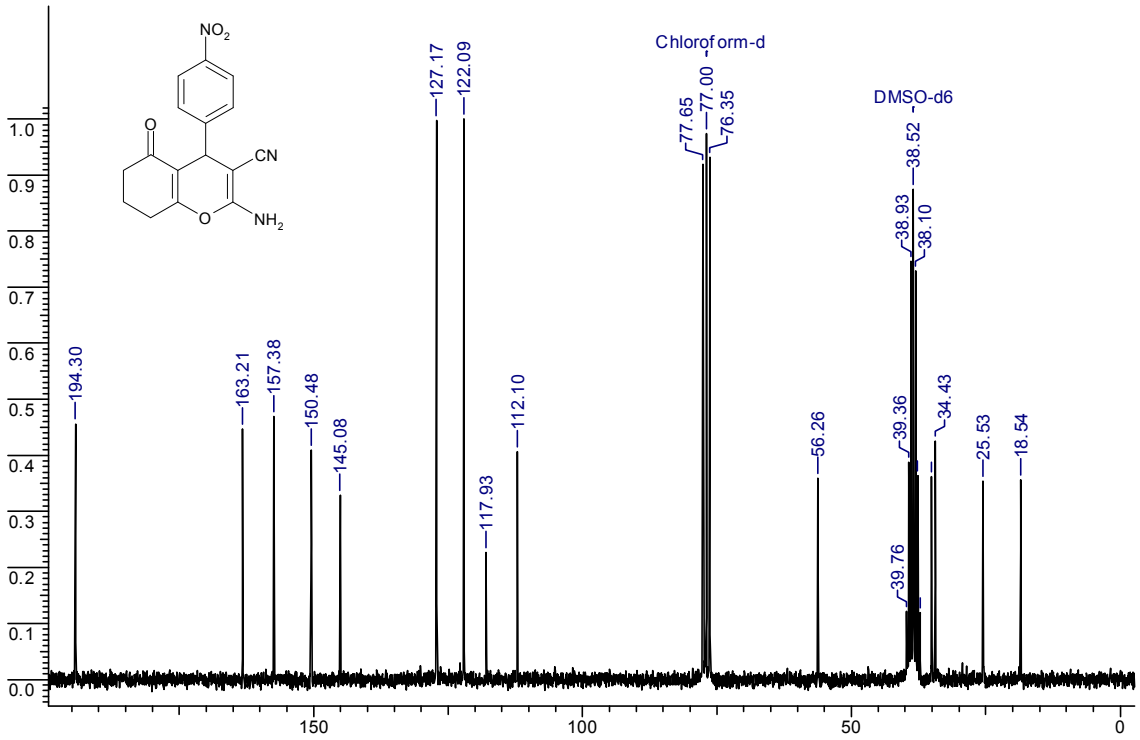
^{13}C-NMR spectra of **14**g:



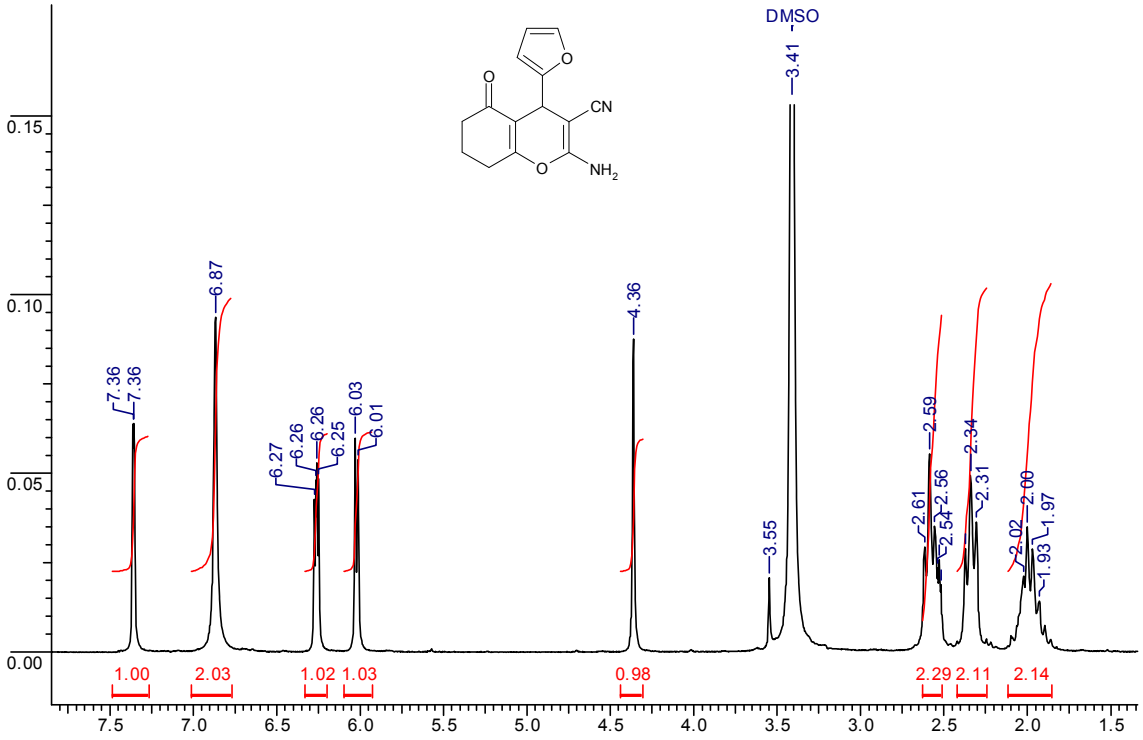
^{1}H-NMR spectra of **14**k:



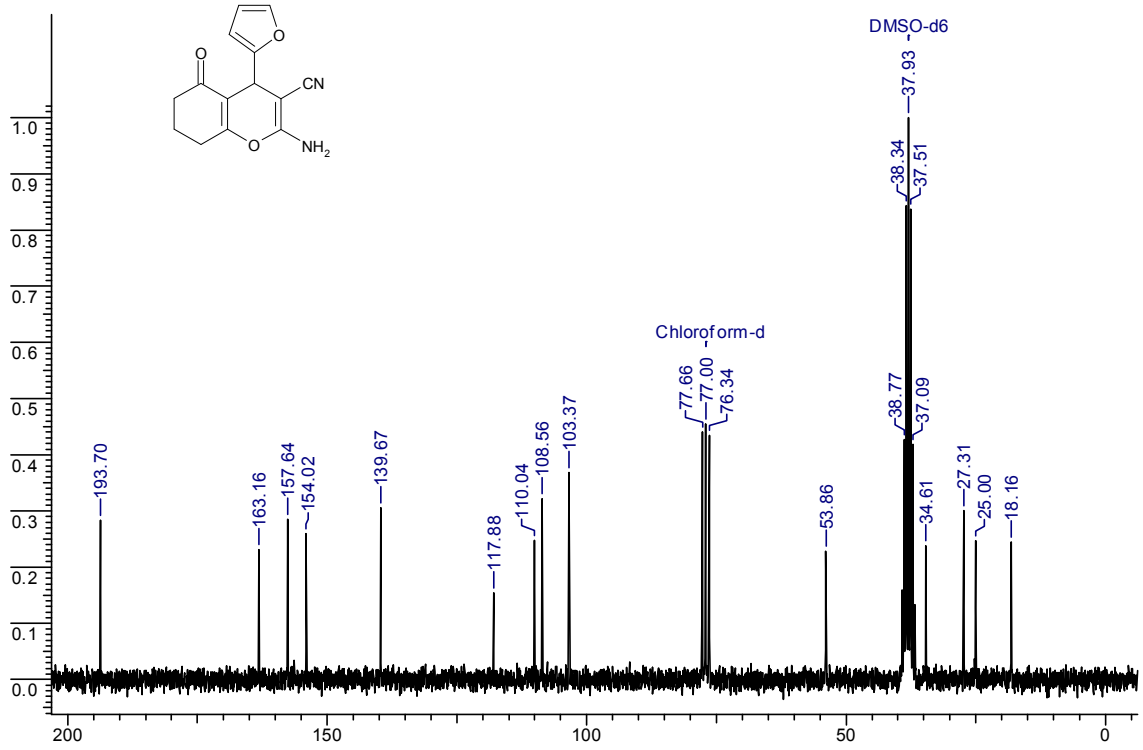
^{13}C-NMR spectra of **14**k:



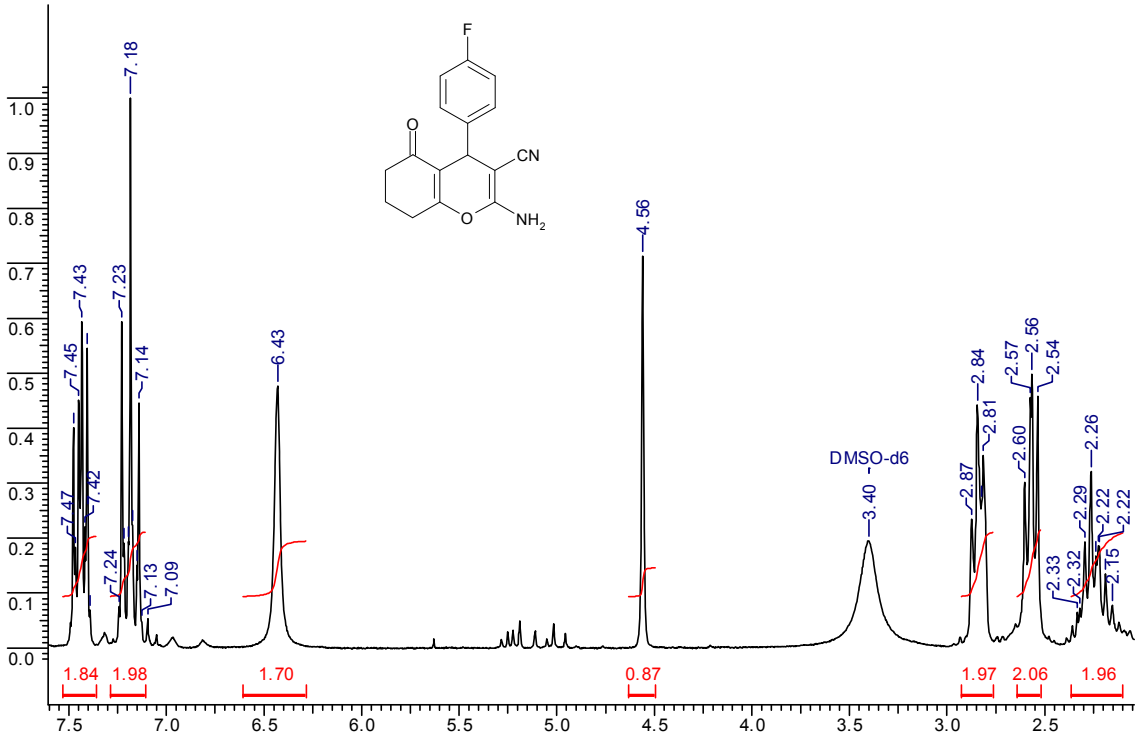
^{1}H-NMR spectra of **14l**:



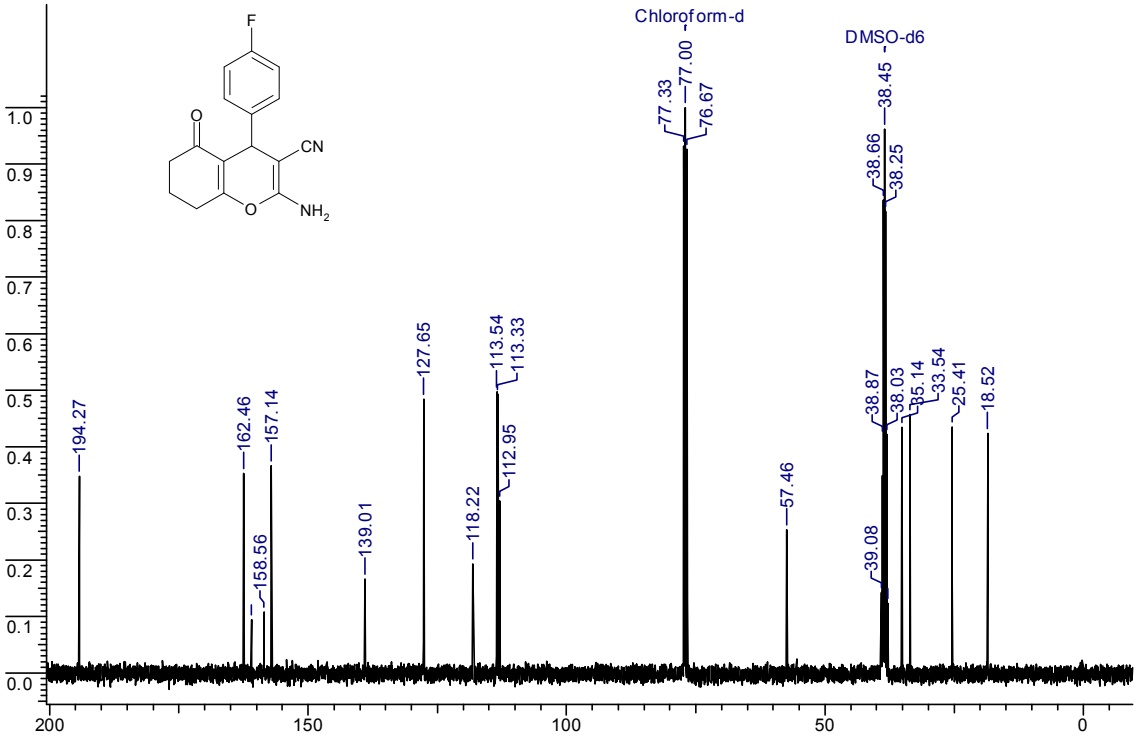
^{13}C-NMR spectra of **14l**:



^{1}H-NMR spectra of **14**n:



^{13}C-NMR spectra of **14**n:



2.4.8 References

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Chapter-II

Sec-E

Suzuki/Suzuki Miyaura Coupling Reactions

2.5.0 Introduction

The Suzuki-Miyaura coupling, the palladium-catalyzed cross-coupling of Sp^2 hybridised halides, triflates, N_2BF_4, BF_3K, sulfonates with Sp^2 hybridized boronic acids or their esters, is one of the most important, and versatile tools for the synthesis of biaryls and liquid crystals.[1-2] Its tolerance to a wide range of functional groups on both substrates extended its scope to wide variety of biologically active compounds. Further more, the key advantages of Suzuki-Miyaura coupling are the commercial availability of the diverse boronic acids that are environmentally safer than the other organometallic reagents. In addition, the handling and removal of boron-containing byproducts is easy when compared to other organometallic reagents, especially in a large-scale synthesis.[3] Biaryls are an important class of organic compounds useful as precursors to pharmaceuticals, polymers, materials, liquid crystals, and ligands.[2b] Biaryls are ubiquitous compounds, their unit being present in a variety of natural products and bioactive molecules as well as in many functional advanced materials. Therefore there is a wide interest in the development of new synthetic methodologies in spite of the many methods already available.[4]

There are many useful reviews available to cover Suzuki-Miyaura coupling up to 1998.[3] Kotha *et al.*[5a] reviewed the recent development in Suzuki coupling from 1999 to late 2001. During the last 6 years, a number of advances have taken place with reference to the catalyst development. Coupling of electron rich or electron neutral aryl halides and arene boronic acids is also possible by using Pd-complexes with sterically hindered, electron rich, or carbene ligands such as those developed by Buchwald,[5b] Fu[5c] and Herrmann[5d] respectively. Cross coupling reactions involving electron deficient aryl fluorides,[6a-b] phosphine free Suzuki reactions,[6c-i] and the cross coupling of aryl chlorides with boronic acids using various palladium catalyst systems[7] were also reported. Ambient temperature ionic liquids promoted,[8a-b,7c] microwave assisted[8c-g] Suzuki coupling reactions have also been reported. Even, super paramagnetic nanoparticles-supported catalysis of Suzuki cross-coupling reaction was reported by Gao *et al.*[9a] Recently Ganesan *et al.*[9b] reported ionic liquid accelerated solid-phase Suzuki-Miyaura coupling reactions. Tertiary phosphane ligands based on phospha-adamantane framework for Suzuki-Miyaura coupling was reported by Capretta *et al.*[9c] Air stable planar chiral ferrocenyl monophosphine ligand for Suzuki Miyaura coupling reactions has been reported by Johannsen *et al.*[9d] Yang *et*

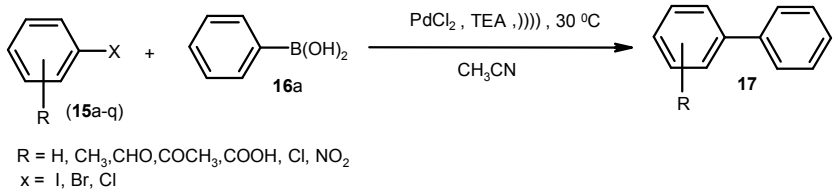
al.[9e] regioselectively synthesized 2-aryl-6-chloronicotinamides *via* $PXPd_2$ catalyst. Hollis *et al.* [9f] used imidazolylbenzene based bidentate carbenes in Suzuki-Miyaura coupling reaction. Chan *et al.*[9g] explored ionic liquids as soluble support for Suzuki-Miyaura coupling.

2.5.1 Present Work

The traditional Suzuki reaction usually requires toxic phosphine ligands, and high temperature conditions and the catalyst systems often suffer from low activities, and to achieve satisfactory results, high reaction temperatures, high catalyst concentrations, and prolonged reaction times are required. Catalyst decomposition often prevents repeat catalytic runs, and decreases reactivity. However, no general solution to these problems has been reported, even though many recent developments have taken place in this area.[10,11,12] From the scientific and environmental points of view, development of a new catalytic system without use of stabilizing phosphine ligands under mild conditions has attracted much attention. We have developed for the first time a ligand-free Suzuki as well as Suzuki-Miyaura reactions at ambient temperature under ultrasound irradiation in a molecular solvent such as acetonitrile as well as a room-temperature ionic liquid (IL), 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4), in excellent chemoselectivity with considerably enhanced reaction rates through the formation of stable and crystalline clusters of zero-valent Pd nanoparticles.

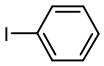
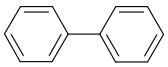
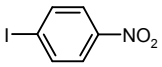
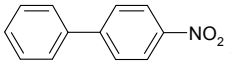
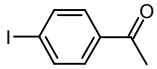
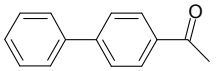
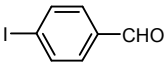
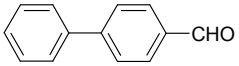
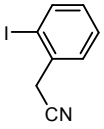
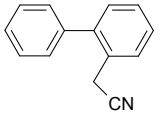
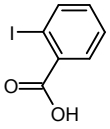
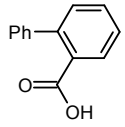
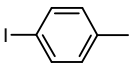
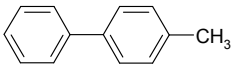
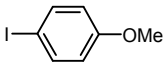
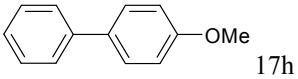
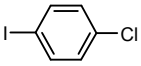
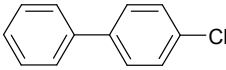
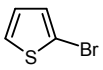
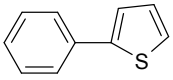
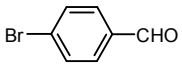
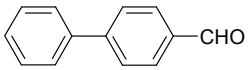
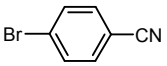
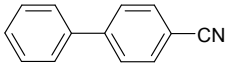
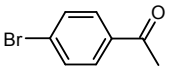
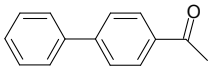
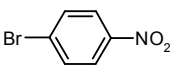
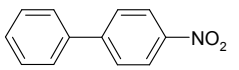
2.5.2 Results and discussion

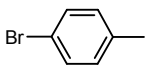
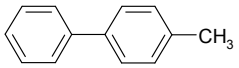
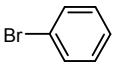
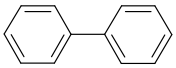
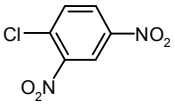
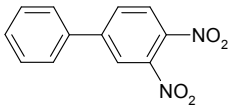
A variety of aryl halides consisting of substituted iodo, bromo, and chloro- benzenes were reacted with phenylboronic acid in the absence of any added ligand in acetonitrile as a solvent using $PdCl_2$ as catalyst and triethylamine as a base under ultrasonic irradiation as shown in Scheme **25**. The results are recorded in Table **13.**



Scheme 25

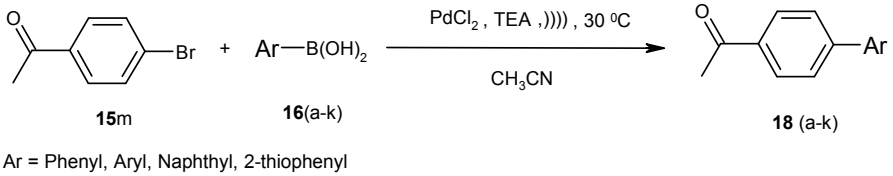
Table 1. Synthesis of Biphenyls 17

Entry	Ar-X **15**	Product **17**	Time (min)	Yield (%)[a]
1	 15a	 17a	10	94
2	 15b	 17b	20	88
3	 15c	 17c	10	90
4	 15d	 17d	15	88
5	 15e	 17e	15	87
6	 15f	 17f	10	88
7	 15g	 17g	10	93
8	 15h	 17h	10	93
9	 15i	 17i	10	89
10	 15j	 17j	20	87
11	 15k	 17k	15	86
12	 15l	 17l	15	88
13	 15m	 17m	10	89
14	 15n	 17n	10	88

15	 15o	 17o	15	92
16	 15p	 17p	20	83
17	 15q	 17q	45	49

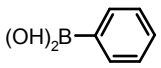
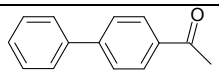
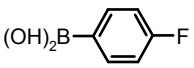
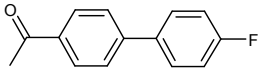
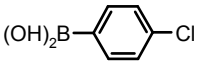
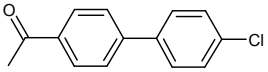
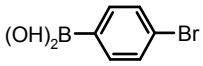
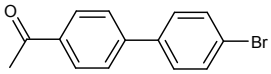
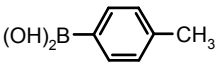
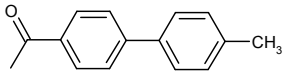
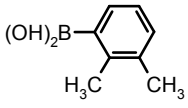
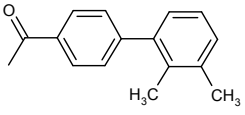
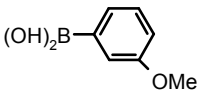
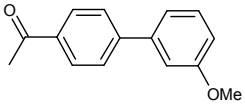
[a] Isolated yields after column chromatography

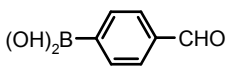
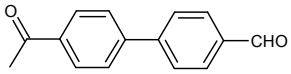
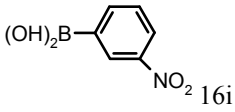
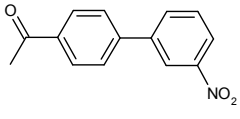
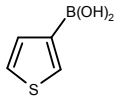
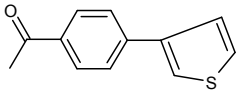
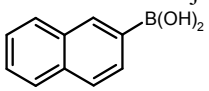
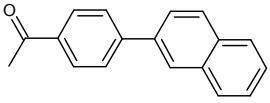
A variety of arylboronic acids were reacted with 2-bromoacetophenone in the absence of any added ligand in acetonitrile as solvent using $PdCl_2$ as catalyst and triethylamine as a base under ultrasonic irradiation (Scheme **26**). The results are recorded in Table **14.**



Scheme 26

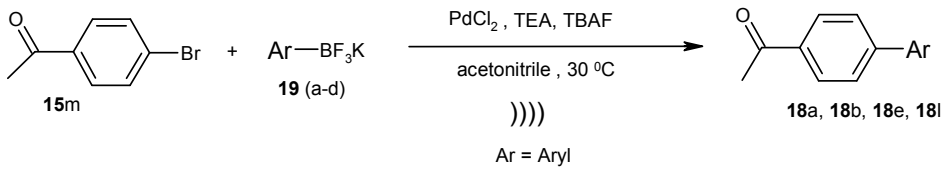
Table 2. Synthesis of Biphenyl derivatives 18(a-k)

Entry	**Ar**-B(OH)$_2$ **16**	Product **18**	Time (min)	Yield (%)[a]
1	 16a	 18a	10	86
2*	 16b	 18b	20	87
3*	 16c	 18c	20	87
4	 16d	 18d	20	87
5*	 16e	 18e	15	88
6*	 16f	 18f	20	89
7*	 16g	 18g	15	90

8	 16h	 18h	25	87
9	 16i	 18i	20	88
10	 16j	 18j	25	90
11	 16k	 18k	25	91

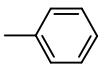
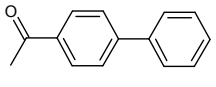
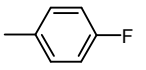
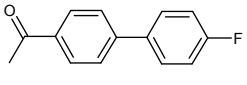
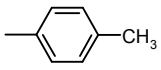
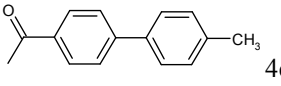
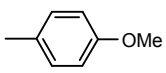
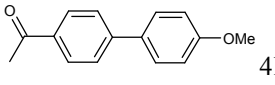
*New compounds. [a] Isolated yields after column chromatography

Also, various aryltrifluorborates **19** were reacted with 2-bromoacetophenone (**15**m) in the absence of any added ligand in acetonitrile as solvent using $PdCl_2$ as catalyst and triethylamine as a base under ultrasonic irradiation as shown in Scheme **27**. The results are recoded in Table **15.**



Scheme 27

Table 15. Synthesis of Biphenyl derivatives (18a, **18**b, **18**e and **18**l)

Entry	**Ar**-BF_3K **19**	Product **18**	Time (min)	Yield (%)[a]
1		 4a	18	86
2*		 4b	20	89
3*		 4e	20	89
4		 4l	20	90

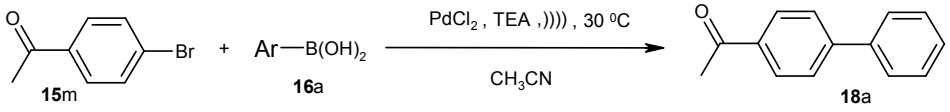
*New compounds. [a] Isolated yields after column chromatography

After completion of the reaction, the solvent was evaporated to get the crude product as a residue which was further purified by silica gel column chromatography using petroleum ether/EtOAc to afford pure products. In all the cases, pure products were well characterized by melting point, spectral, and elemental analyses. It is important to note that

the reaction of 4-iodoacetophenone with phenylboronic acid in acetonitrile at room temperature under similar conditions but in the absence of ultrasound (silent conditions) did not show the formation of any cross-coupled product even after several hours (6 h) of stirring. Moreover, in a blank experiment, Pd(0) nanoparticles were formed by sonicating a mixture of $PdCl_2$ and triethylamine in acetonitrile. To this was added the reactants viz., 4-iodoacetophenone and phenylboronic acid and the mixture was stirred for 6 h at ambient temperature under silent conditions (RT strring). The cross-coupled product 4-acetylbiphenyl was obtained to an extent of 20% as against the 86% yield obtained in the total sonochemical reaction. This implies that ultrasound not only brings about the formation of highly crystalline, active Pd(0) nanoparticles required for the Suzuki reaction but also promoted the activity of the catalytic species in the oxidative insertion, *trans*-metallation and reductive elimination catalytic cycle of the Suzuki reaction. This is made possible by the phenomenon of acoustic cavitation generating transient cavitation bubbles of very short life times ($\sim 10^{-9}$ s), the implosive collapse of which under adiabatic conditions gives rise to high temperatures and pressures.[13]

The Pd-catalyst in the form of Pd(0) nanoparticles was difficult to recover and recycle. However, from the point of view of ease of recovery and recycle of the expensive Pd catalyst, the reactions were performed in acetonitrile/IL mixture (Procedure-B). The recovered Pd-catalyst along with the IL could be recycled three times with practically no loss in activity.

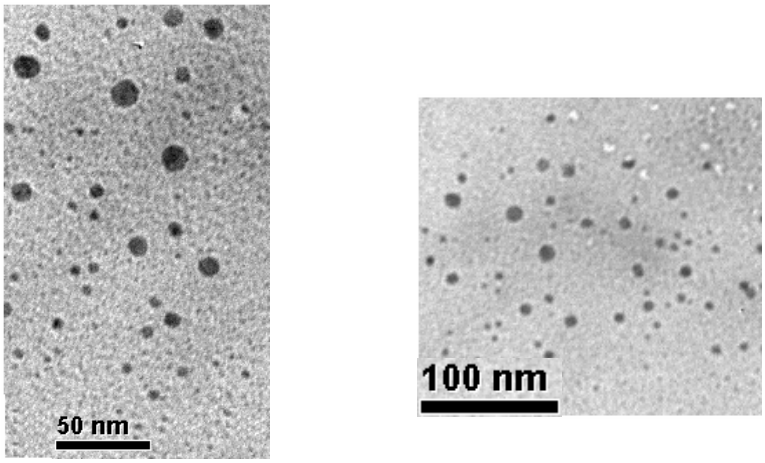
Table 16. Recycling of Pd-catalyst system for the synthesis of diaryl from phenylboronic acid and *p*-bromoacetophenone in acetonitrile/[bbim]BF_4:



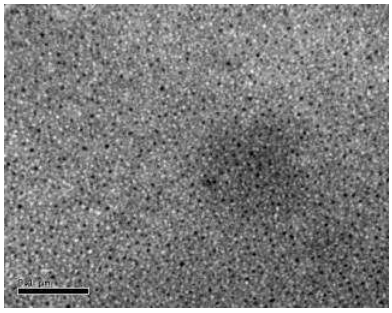
Recycling	Batch 1	Batch 2	Batch 3
Isolated yield (%)	89	88	87

2.5.3 Sample Preparation and TEM analysis

The TEM analysis was carried out in a Transmission Electron Microscope operating at 100 kV at different magnifications varying from 100 to 300 k. After completion of the reaction a sample is removed from the reaction mixture and after appropriate dilution with acetonitrile, was directly deposited on carbon coated 400 mesh Copper TEM grids. TEM pictures of each sample were taken at 100 kV operating voltage at multiple random locations in the sample and at two different magnifications.



TEM-Images of Pd(0) nanoparticles in acetonitrile medium



TEM-Images of Pd(0) nanoparticles in methanol medium

The average particle size of Pd(0) nano-particles generated in acetonitrile medium was observed to be 15 nm and in that of methanol medium is 30 nm.

2.5.4 Conclusion

In conclusion, the Suzuki reaction has been achieved in short reaction times, excellent chemoselectivity and high isolated yields at ambient temperature under ultrasonic irradiation in a molecular solvent as well as a room temperature ionic liquid even in the

absence of any added ligand. The formation of stable and crystalline Pd(0) nanoparticles under the sonochemical conditions has been shown by TEM measurements and could be recycled by using IL/acetonitrile mixture. In case of iodobenzenes and bromobenzenes no traces of homocoupled product (Suzuki Homocoupling reaction) were detected, whereas in the case of chloroarenes the homocoupled product was formed to the extent of 8-10% only. It was ascertained that ultrasound not only generated the Pd(0) nanoparticles as the active catalyst for the reaction but also promoted and enhanced the catalytic activity of this species in the catalytic cycle of the Suzuki cross-coupling reaction. The short reaction times, high isolated yields and easy work up procedure make this sonochemical methodology an efficient protocol for the rapid synthesis of substituted biphenyl libraries.

2.5.5 Experimental Section

2.5.5.1. Suzuki coupling reactions

2.5.5.1.1 General procedure for the coupling reaction of arylboronic acids with haloarenes in Acetonitrile medium (Procedure-A)

A mixture of haloarene (1 mmol), arylboronic acid (1 mmol), $PdCl_2$ (0.004 g) and triethylamine (2 mmol) in 2 mL of acetonitrile was sonicated in a thermostated ultrasonic cleaning bath for the appropriate time under argon at 30 ^oC. The reaction was monitored by TLC and after completion of reaction, acetonitrile was removed from reaction mixture (at 45 ^oC) under reduced pressure to get crude product as a residue which was further purified by silica-gel column chromatography using a mixture of 30% ethyl acetate in petroleum ether (bp 60-80 ^oC) as eluent to afford the pure product.

2.5.5.1.2 General procedure for the coupling reaction of arylboronic acids with haloarenes in in [Bbim]BF_4/acetonitrile medium (Procedure-B)

A mixture of haloarene (1 mmol), arylboronic acid (1 mmol), $PdCl_2$ (0.003 g) and triethylamine (2 mmol) in 2 mL of dry ionic liquid containing 1 mL of acetonitrile was sonicated in a thermostated ultrasonic cleaning bath for the appropriate time under argon at 30 ^oC. The reaction was monitored by TLC, and after completion of reaction, acetonitrile was removed from the reaction mixture under reduced pressure, and the product was selectively extracted with 30% ethyl acetate in petroleum ether (bp 60-80 ^oC) from the reaction mixture leaving behind ionic liquid consisting of the Pd-catalyst as an immiscible

layer. The hydrophobic ionic liquid layer was washed with water to remove the amine hydrochloride salt and the ionic liquid was dried under reduced pressure (5 mm Hg) at 60 ^{o}C for 30 min and used as such for further reaction. The separated organic layer was dried over anhyd Na_2SO_4 and concentrated in a vacuum. The crude product obtained was further purified by column chromatography through a column of silica gel using an appropriate mixture of petroleum ether and ethyl acetate to afford the pure product.

2.5.5.2. Suzuki-Miyaura coupling reactions

2.5.5.2.1 General procedure for the coupling of aryltrifluoroborates with bromoarenes (Procedure-C)

The General procedure for the synthesis of biphenyls from Arylboronic acids was employed. An additional amount of tetrabutylammonium fluoride (0.1 mL of 0.1 M solution in THF) was used.

2.5.6 Characterization data for some of the representative biaryls

4-acetylbiphenyl, 17c:

Nature of compound; mp	**:**	White solid; mp: 118-120 ^{o}C.
IR: ($CHCl_3$)υ_{max}	**:**	3012, 1673, 1515, 1492, 1357, 1211, 1187, 1092 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.71-7.61 (m, 4H), 7.52-7.41 (m, 3H), 2.64 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.3, 144.2, 138.6, 136.2, 131.9, 128.9, 128.6, 126.8, 122.5, 26.4.
Elemental analysis	**:**	Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16%. Found: C, 85.60; H, 6.10%.

4-biphenylcarboxaldehyde, 17d:

Nature of compound; mp	**:**	Pale yellow solid; mp: 56-58 ^{o}C [lit.: dictionary of organic compounds 55-56 ^{o}C).
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 10.03 (s, 1H), 8.00-7.30 (m, 9H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 191.5, 146.9, 139.5, 135.1, 130.0, 128.9, 127.5, 127.2.
Elemental analysis	**:**	Anal. Calcd. for $C_{13}H_{10}O$: C, 85.69; H, 5.53%. Found: C, 85.77; H, 5.61%.

4-acetyl-4′-fluoro-biphenyl, 18b:

Nature of compound; mp	**:**	White solid; mp: 106-108 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3401, 3019, 1681, 1605, 1270, 1216, 823, 755 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.58-7.48 (m, 4H), 7.12 (t, *J* = 8.6 Hz, 2H), 2.56 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.3, 164.5, 161.2, 144.5, 135.8, 128.8, 128.7, 126.9, 115.9, 115.6, 26.3.
Elemental analysis	**:**	Anal. Calcd for $C_{14}H_{11}FO$: C, 78.49; H, 5.18; F, 8.87%. Found: C, 78.49; H, 5.18; F, 8.87%.

4-acetyl-4′-chloro-biphenyl, 18c:

Nature of compound; mp	**:**	White solid; mp: 120-121 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3400, 3018, 1684, 1609, 1272, 1215, 822, 754, 668 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 7.94-7.90 (d, *J* = 8.0 Hz, 2H), 7.55-7.30 (m, 6H), 2.53 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.2, 144.2, 138.2, 136.1, 129.0, 128.8, 126.9, 26.4.
Elemental analysis	**:**	Anal. Calcd for $C_{14}H_{11}ClO$: C, 72.89; H, 4.81; Cl, 15.37%. Found: C, 72.89; H, 4.81; Cl, 15.37%.

4-acetyl-4′-methylbiphenyl, 18e:

Nature of compound; mp	**:**	White solid; mp: 121-123 ^{o}C
IR: ($CHCl_3$)υ_{max}	**:**	3401, 3020, 1678, 1605, 1270, 1217, 808, 756, 668 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = *8.2* Hz, 2H), 2.54 (s, 3H), 2.32 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.2, 145.4, 137.9, 136.7, 135.5, 129.5, 128.6, 126.6, 26.2, 20.8.
Elemental analysis	**:**	Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71%. Found: C, 85.68; H, 6.71%.

4-acetyl-2′,3′-dimethylbiphenyl, 18f:

Nature of compound; mp	**:**	Yellow oil.
IR: ($CHCl_3$)υ_{max}	**:**	3352, 3015, 2933, 1682, 1605, 1581, 1266, 1120, 1030, 754, 667 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 8.00 (m, 2H), 7.65 (m, 2H), 7.14-7.09 (m, 1H), 6.95 (m, 2H), 3.80 (s, 3H), 3.48 (s, 3H), 2.52 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.4, 153.0, 143.0, 135.6, 129.3, 127.9, 124.0, 122.1, 112.3, 60.4, 55.7, 26.3.
Elemental analysis	**:**	Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19%. Found: C, 85.68; H, 7.19%.

4-acetyl-3′-methoxybiphenyl, 18g:

Nature of compound; mp	**:**	White solid; mp 157-159 ^oC.
IR: ($CHCl_3$)υ_{max}	**:**	3336, 2959, 1674, 1603, 1401, 1217, 1032, 817, 770, 668 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.05-6.93 (m, 2H), 6.78 (d, *J* = 8.7 Hz), 3.66 (s, 3H), 2.41 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.5, 160.0, 145.4, 135.4, 132.3, 128.9, 128.3, 126.6, 114.5, 55.4, 26.5.
Elemental analysis	**:**	Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24%. Found C, 79.62; H, 6.24%.

1-(4'-(naphthalen-2-yl)phenyl)ethanone, 18k:

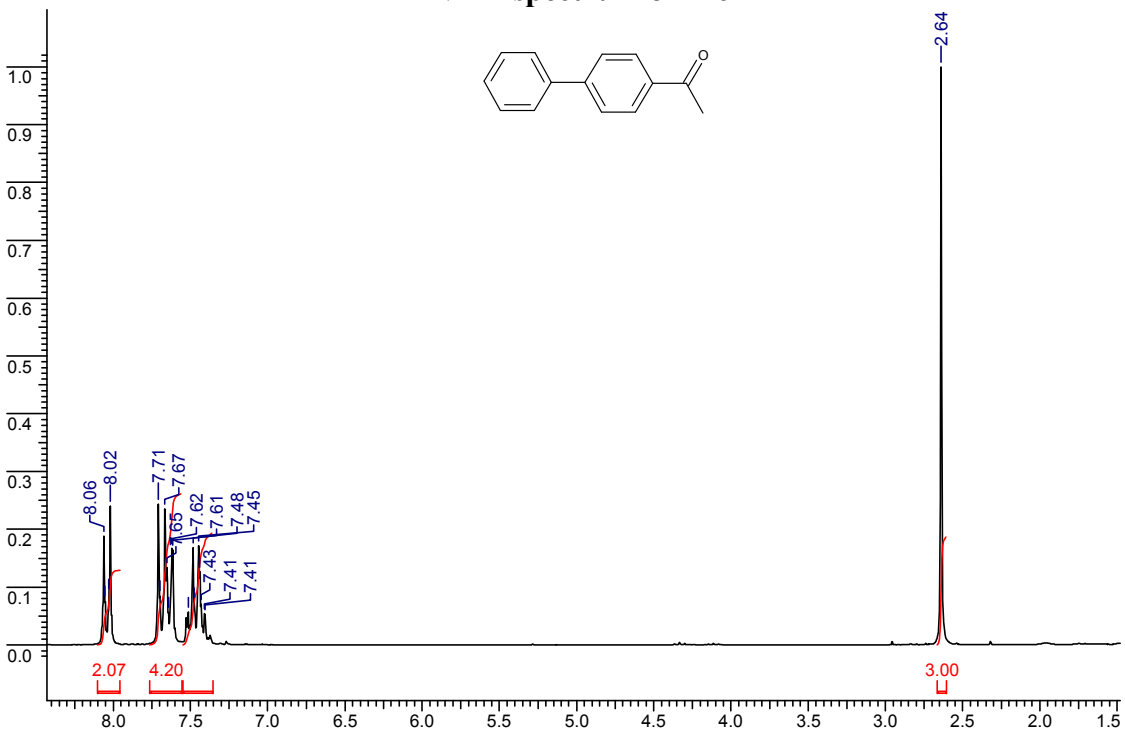
Nature of compound; mp	**:**	White solid; mp 138-140 ^oC.
IR: ($CHCl_3$)υ_{max}	**:**	3346, 3019, 2928, 1680, 1604, 1270, 1216, 1018, 758, 669 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz)	**:**	δ 8.04 (d, *J* = 1.9 Hz, 2H), 8.01 (t, *J* = 2.0 Hz, 1H), 7.91-7.67 (m, 6H), 7.50-7.44 (m, 2H), 2.60 (s, 3H).
^{13}C-NMR ($CDCl_3$, 50 MHz)	**:**	δ 197.2, 145.2, 136.8, 135.6, 133.3, 128.6, 127.0, 126.2, 125.9, 124.8, 26.2.
Elemental analysis	**:**	Anal. Calcd. for $C_{18}H_{14}O$: C, 87.78; H, 5.73%. Found C, 87.78; H, 5.73%.

2.5.7 Spectra

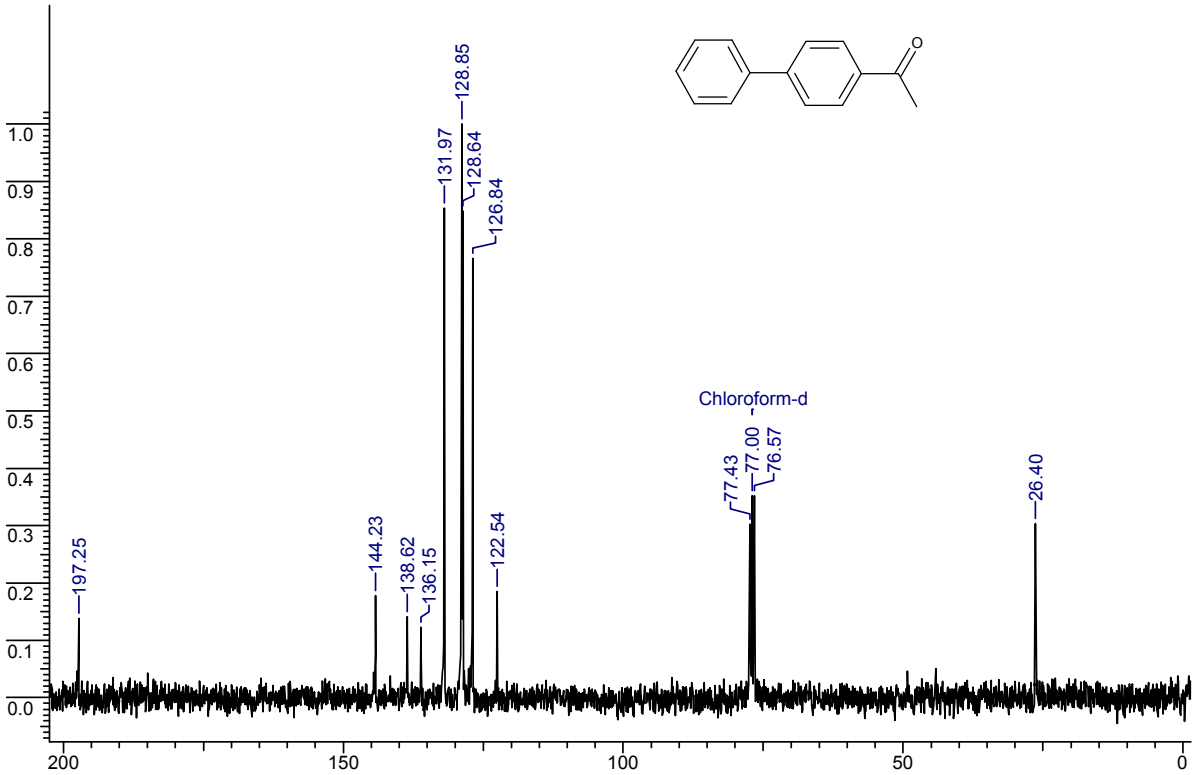
Table 17: ^{1}H & ^{13}C spectra of some selected biaryls are given below:

S. No.	Spectra
1	^{1}H & ^{13}C spectra of **17**c
2	^{1}H & ^{13}C spectra of **17**d
3	^{1}H & ^{13}C spectra of **18**b
4	^{1}H & ^{13}C spectra of **18**c
5	^{1}H & ^{13}C spectra of **18**e
6	^{1}H & ^{13}C spectra of **18**f
7	^{1}H & ^{13}C spectra of **18**g
8	^{1}H & ^{13}C spectra of **18**k

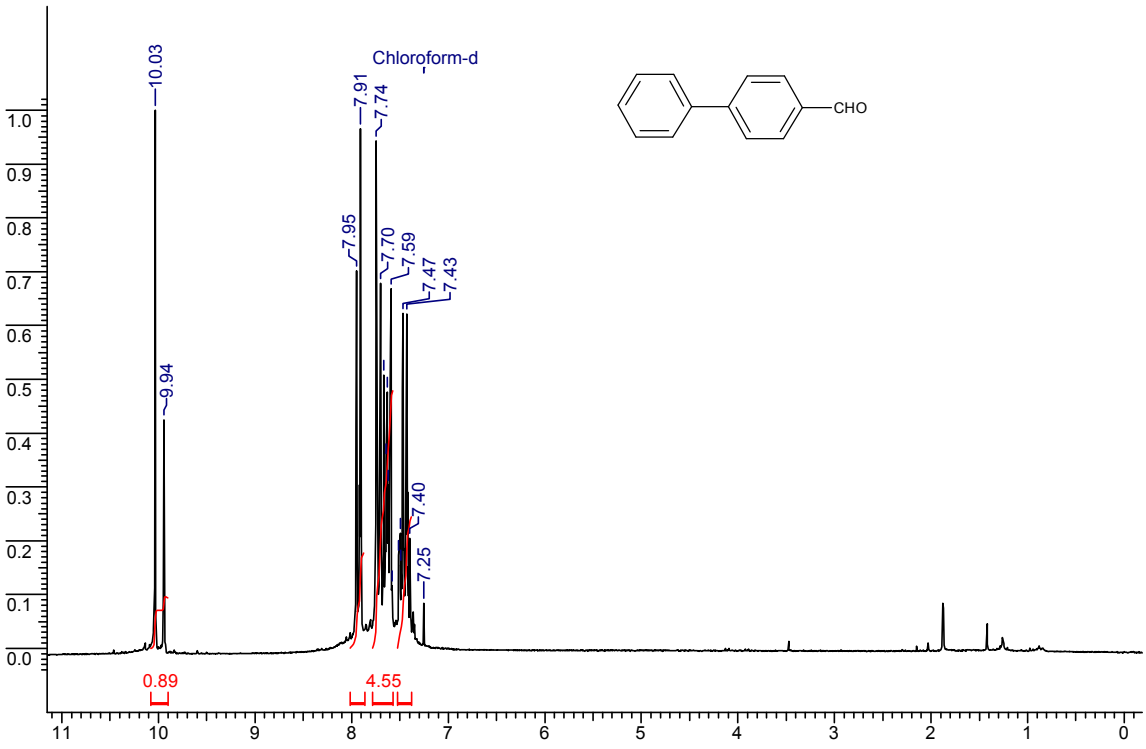
^{1}H-NMR spectrum of 17c



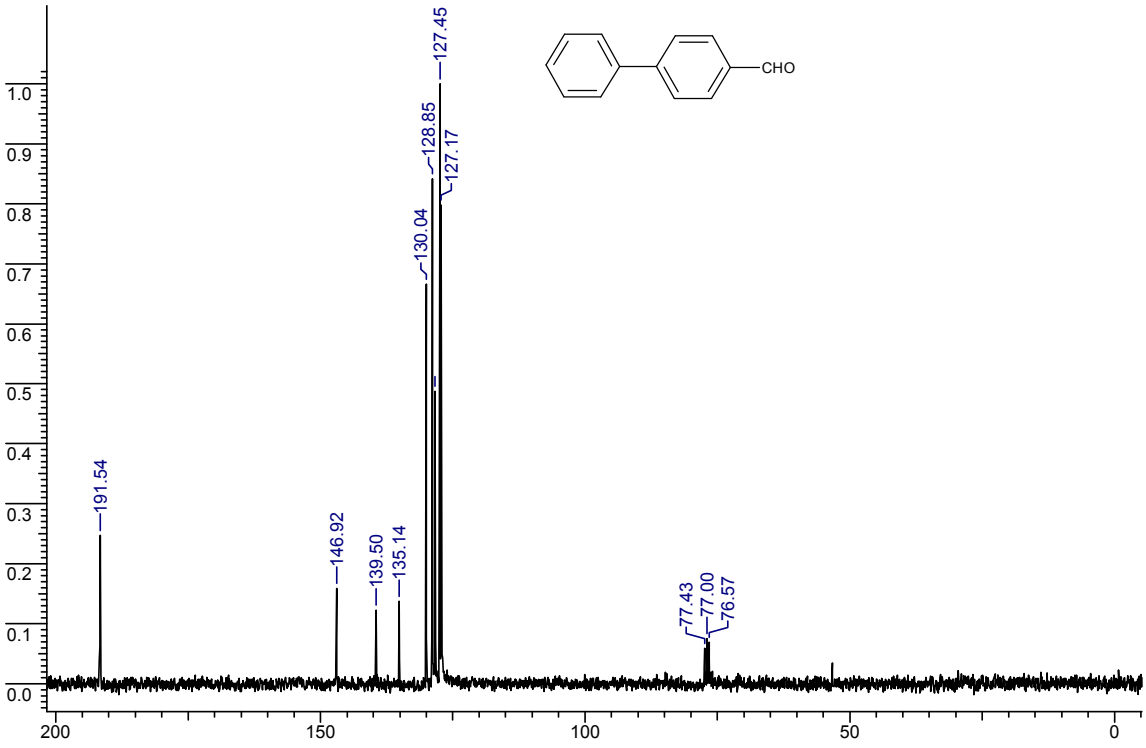
^{13}C-NMR spectrum of 17c



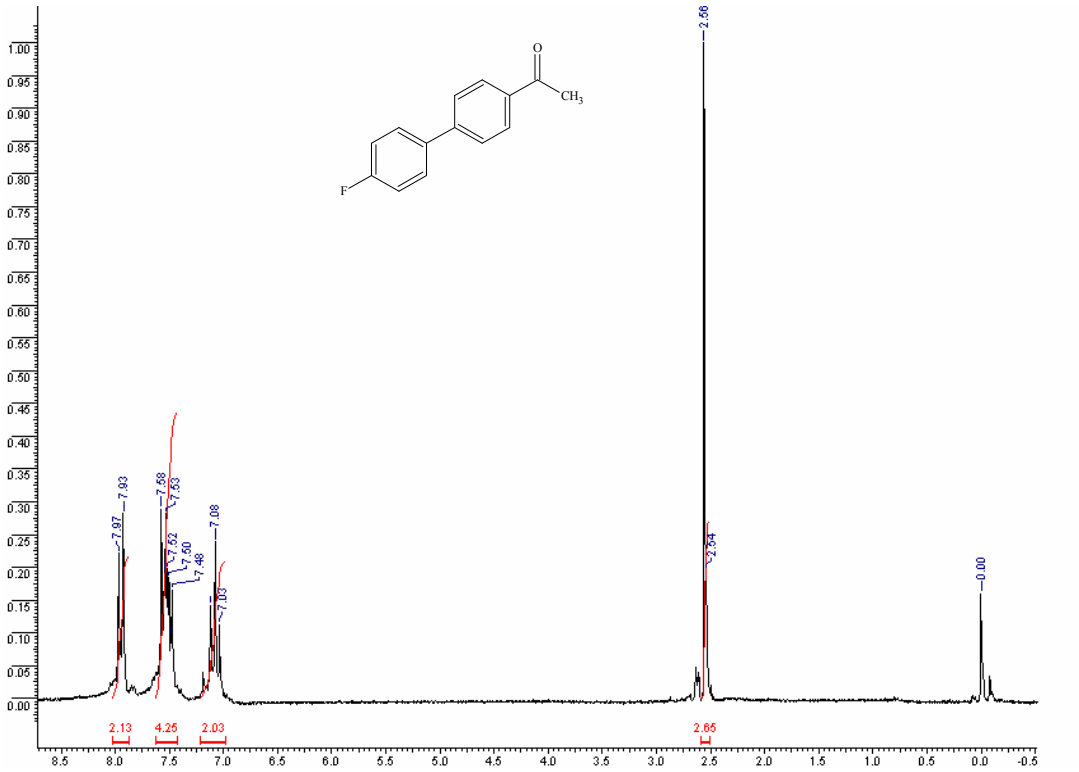
^{1}H-NMR spectrum of 17d



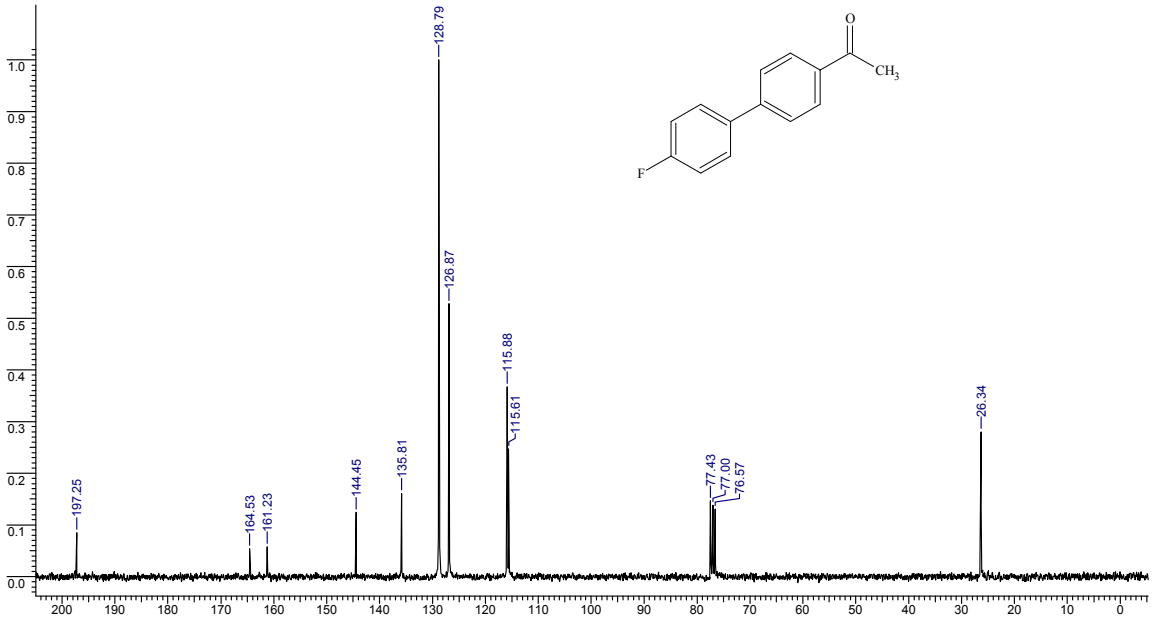
^{1}H-NMR spectrum of 17d



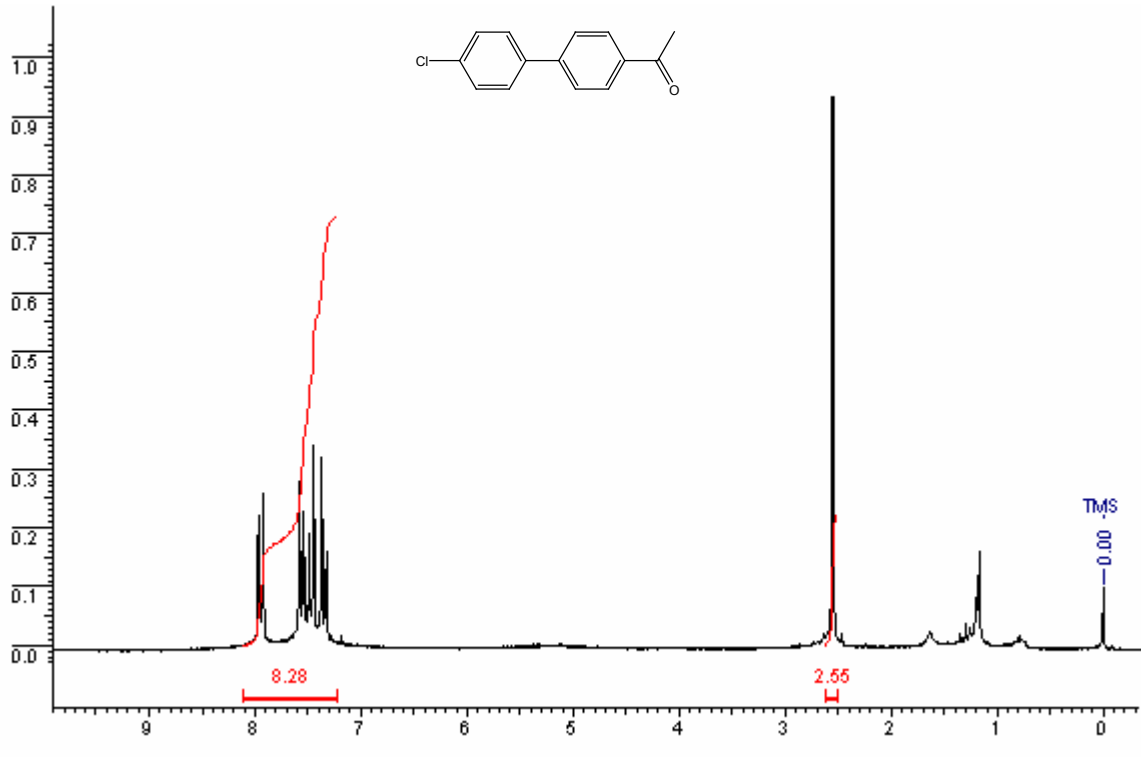
^{1}H-NMR spectrum of 18b



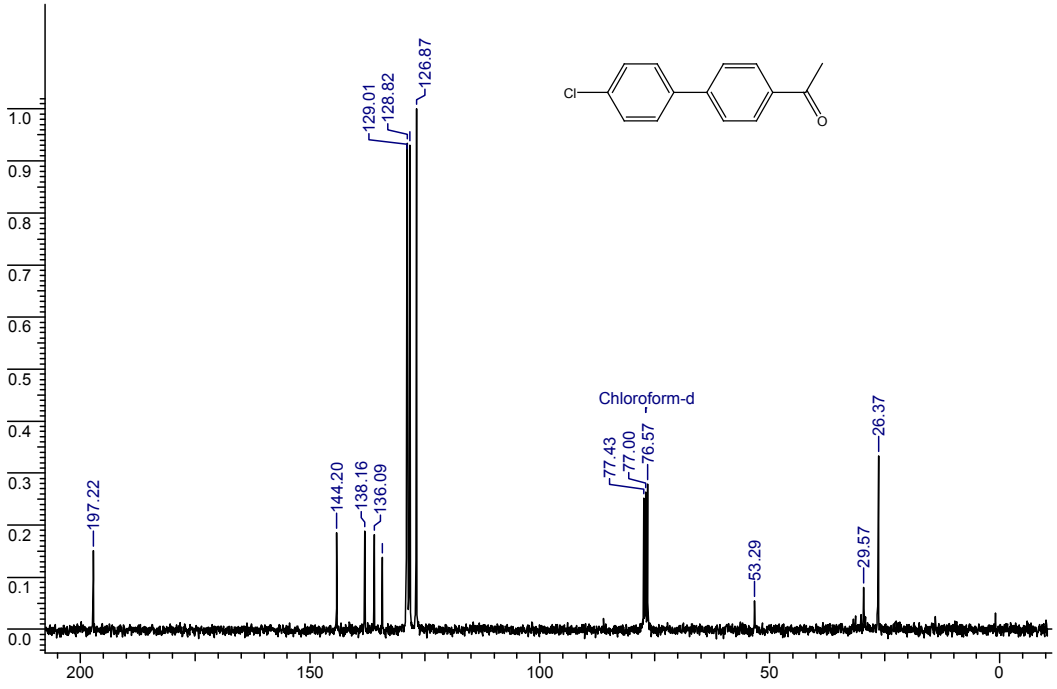
^{13}C-NMR spectrum of 18b



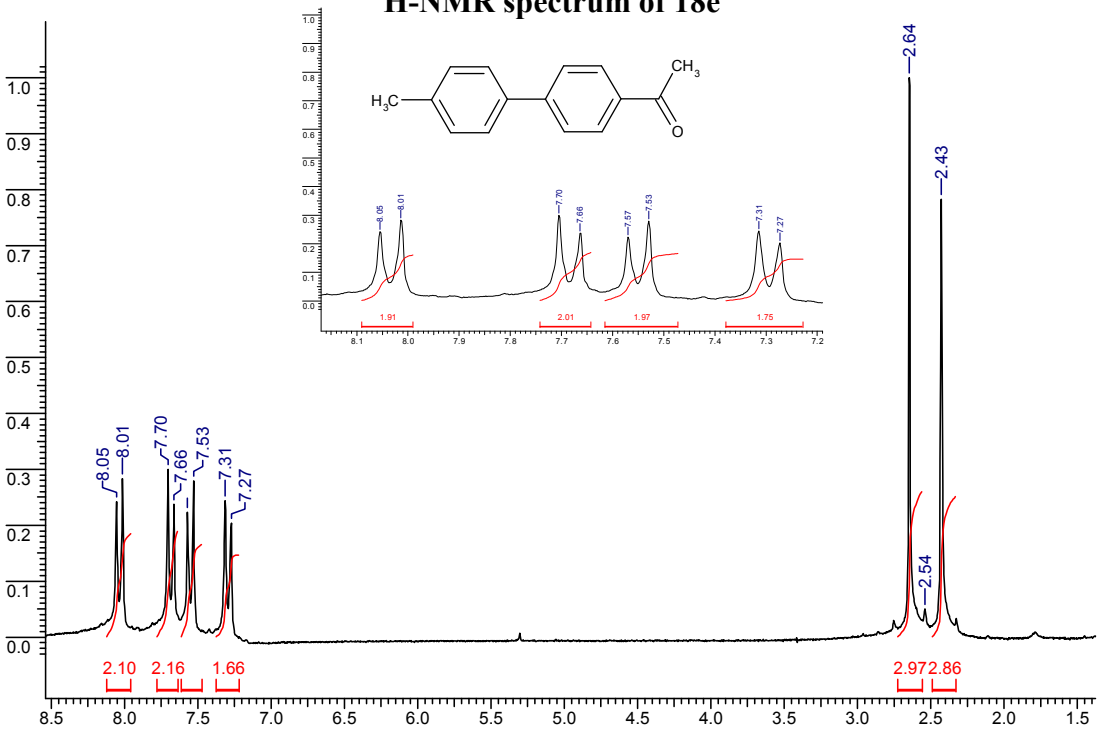
^{1}H-NMR spectrum of 18c



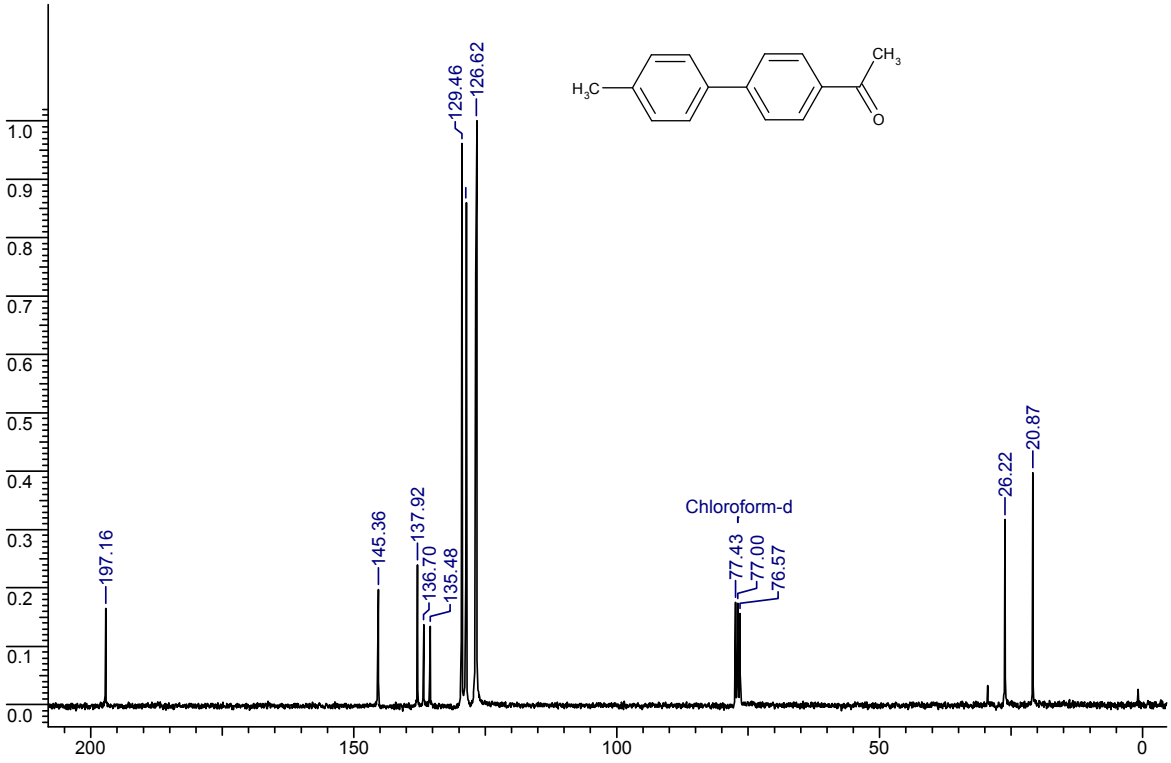
^{13}C-NMR spectrum of 18c



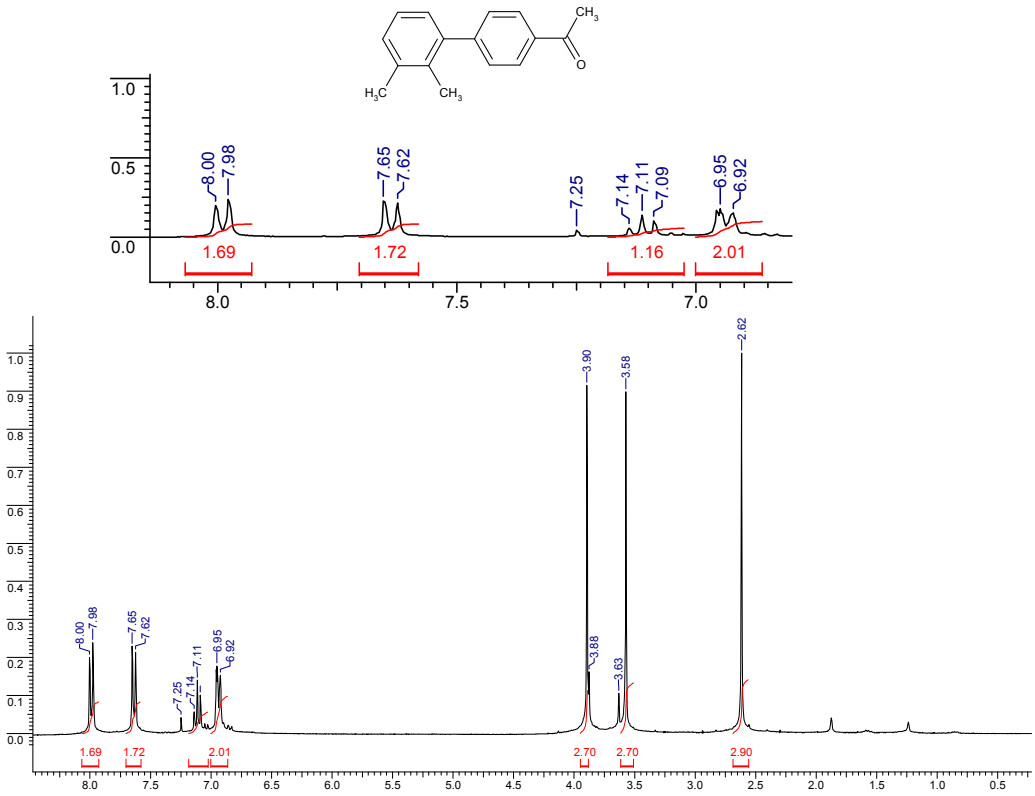
^{1}H-NMR spectrum of 18e



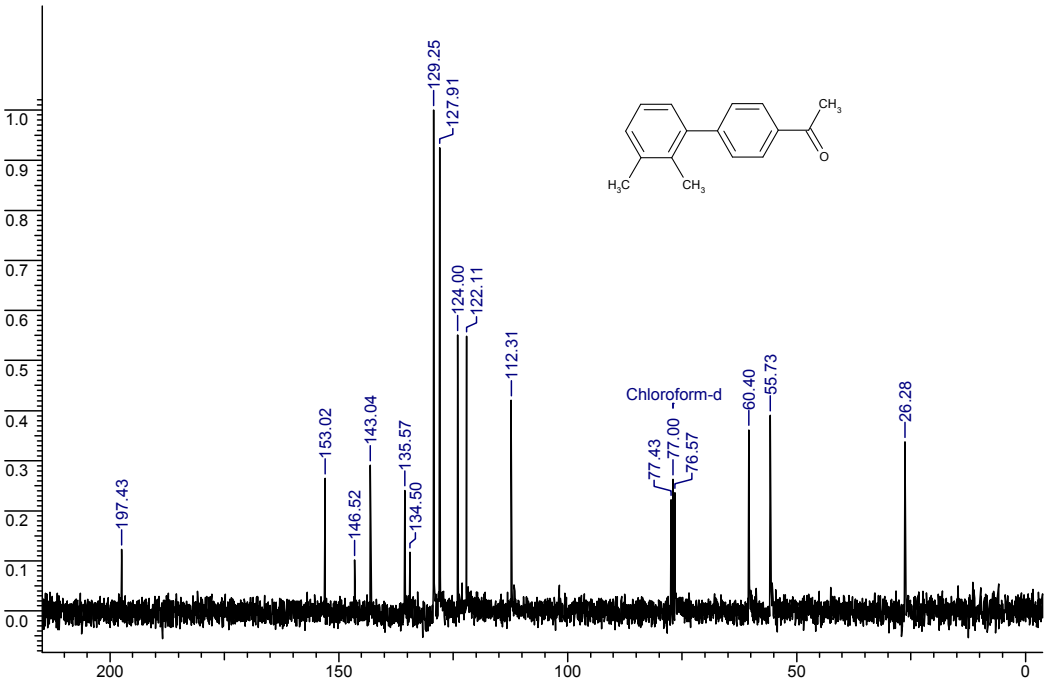
^{13}C-NMR spectrum of 18e



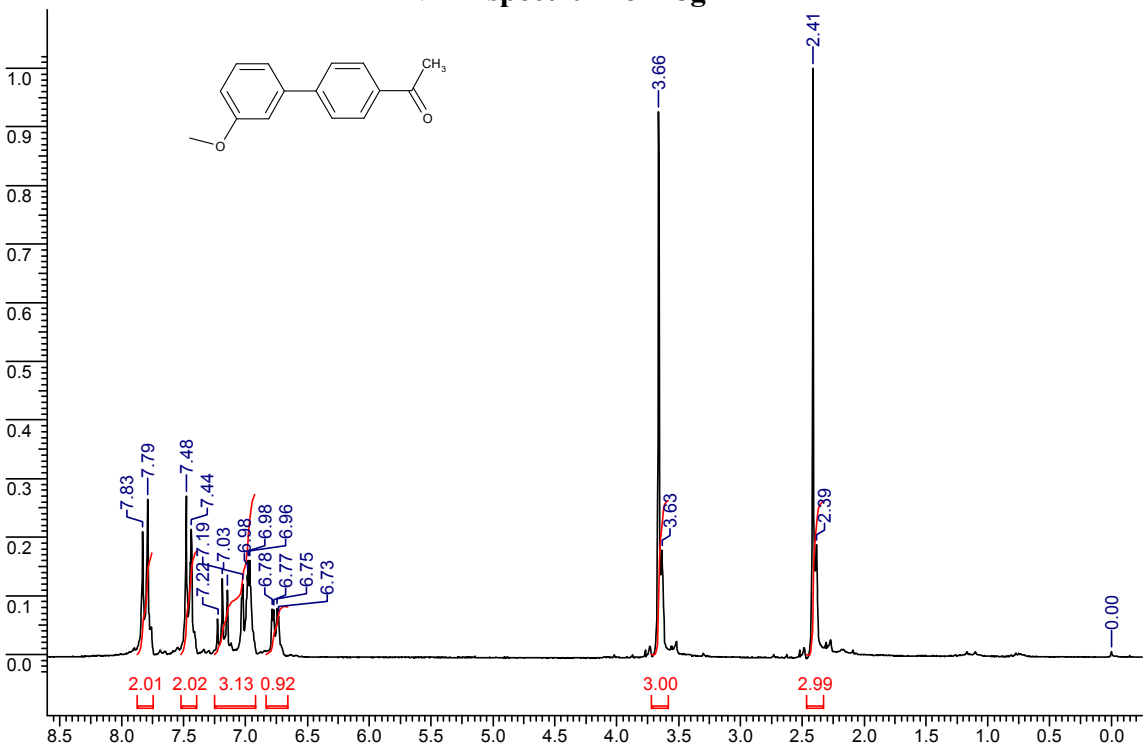
^{1}H-NMR spectrum of 18f



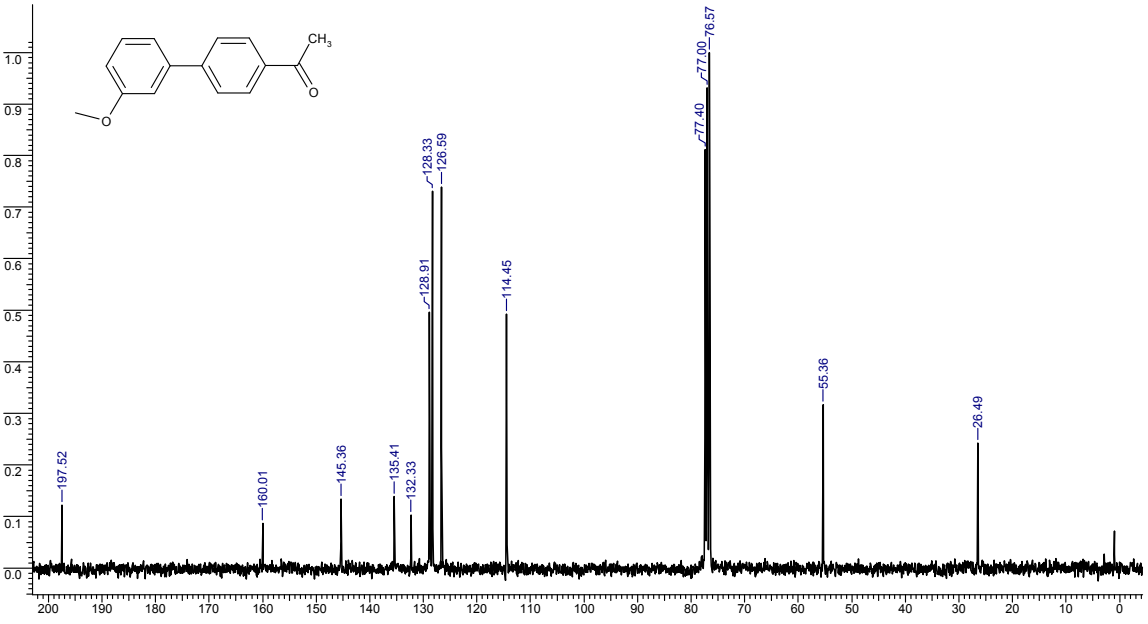
^{13}C-NMR spectrum of 18f



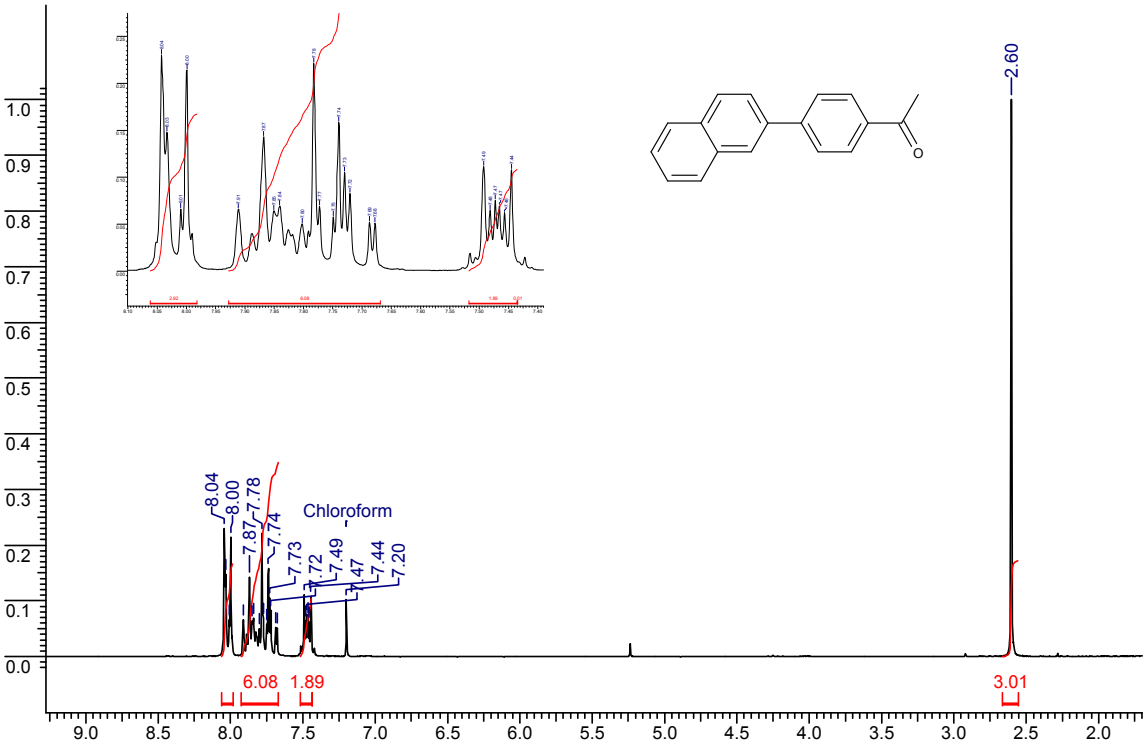
^{1}H-NMR spectrum of 18g



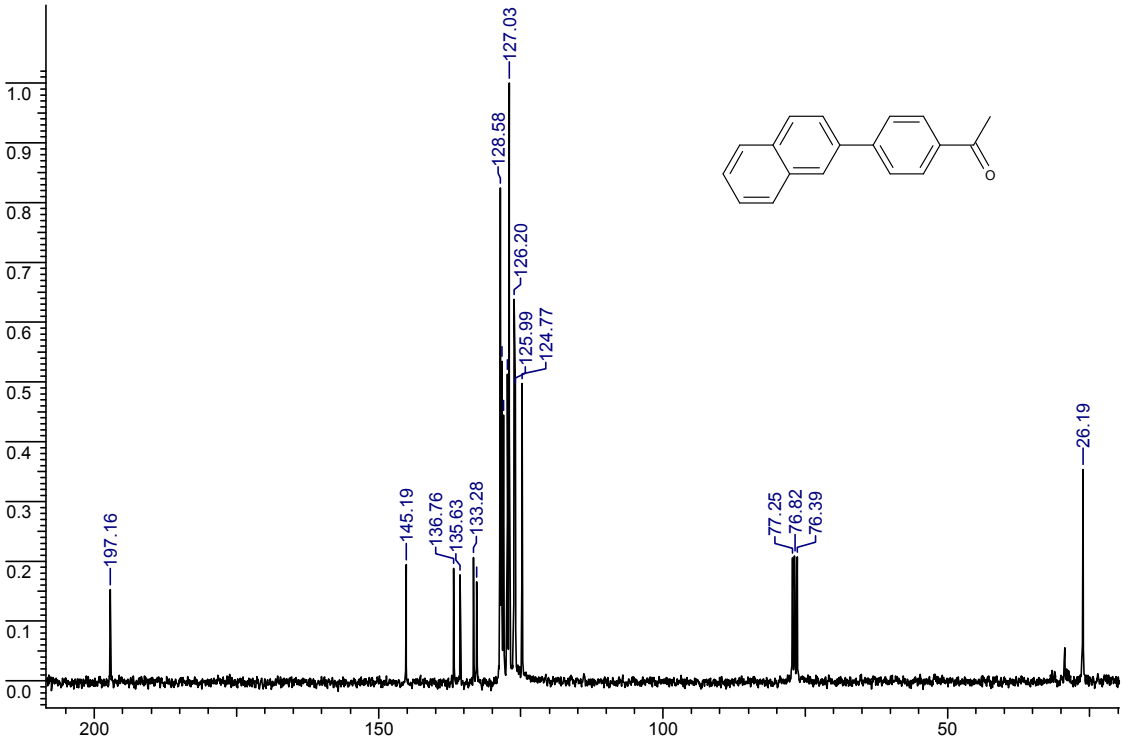
^{13}C-NMR spectrum of 18g



^{1}H-NMR spectrum of 18k



^{13}C-NMR spectrum of 18k



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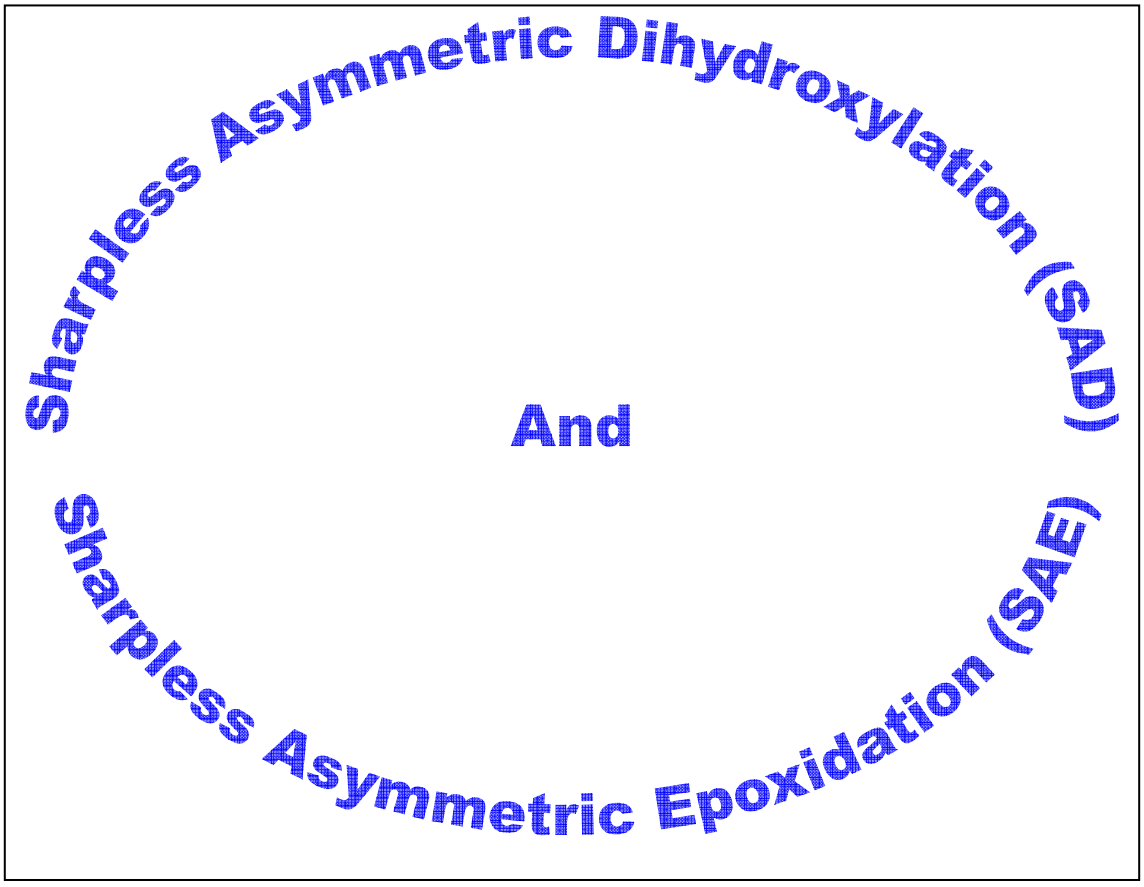
14. Dictionary of organic compounds.

SECTION-A

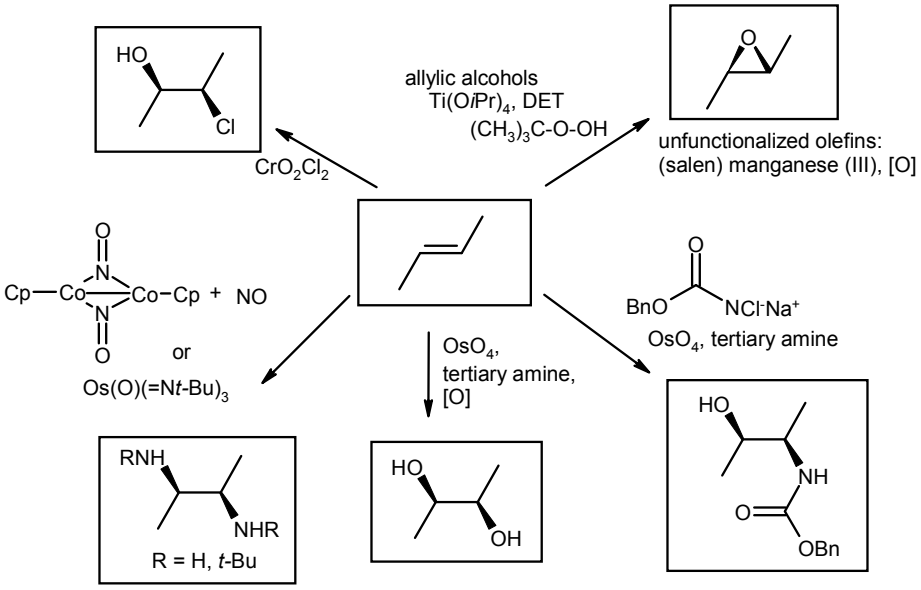

Sharpless Asymmetric Dihydroxylation (SAD)
And
Sharpless Asymmetric Epoxidation (SAE)

3.1.0 Introduction

As the total synthesis of Jaspine-B and (S)-Dapoxetine involve Sharpless asymmetric dihydroxylation (SAD) and Sharpless asymmetric epoxidation (SAE) respectively as the key step in the present work, it is important to describe the salient features of both of the above phenomena.

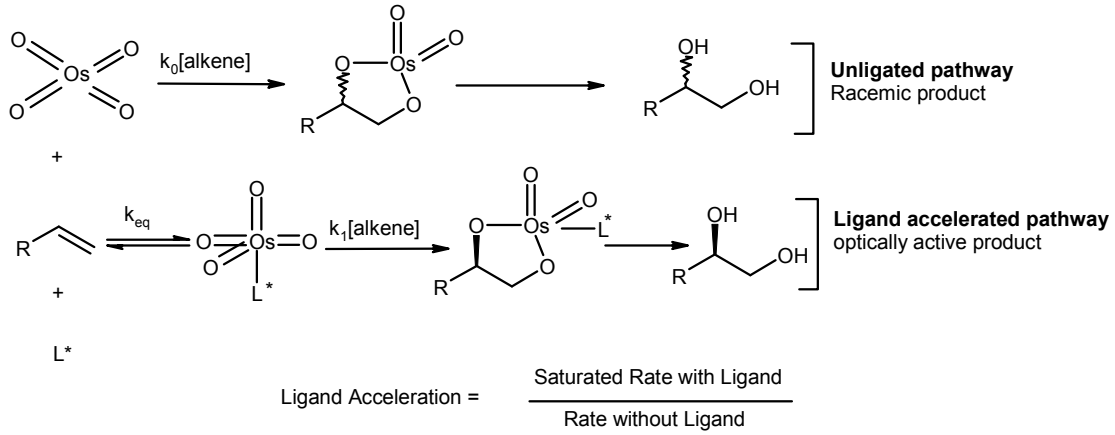
3.1.1 Sharpless Asymmetric Dihydroxylation

Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries and biotechnologies. The goal of asymmetric synthesis-whether it is done in an academic or an industrial setting-is to prepare stereo-chemically-enriched compounds in the most efficient and practical manner possible. In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions offer a practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially the useful one is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of hetero-atoms to olefins has been a fruitful area in recent years (**Scheme 1**).



Scheme 1 Transition metal mediated suprafacial 1,2-difunctionalization of olefins

A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of ***ligand acceleration***,[7] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand (**Scheme 2**). This causes the reaction to be channeled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereo-selectivity of the reaction in a profound way.



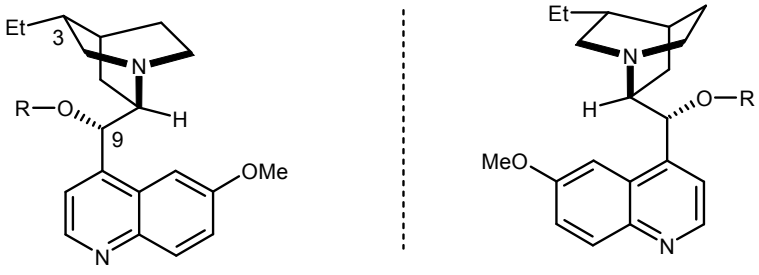
Scheme 2 Ligand accelerated catalysis-dihydroxylation of olefins.[7]

The osmium tetroxide catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is one of the most reliable and selective transformations in organic chemistry. In the stoichiometric reaction of OsO_4 with olefins, Criegee[8] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[5b] Inorganic co-oxidants such as sodium or potassium chlorate[9a] or hydrogen peroxide,[9b,c] were among the first to be introduced, but in some cases diminished yields resulted due to over-oxidation. Much better results were obtained with alkaline *t*-BuOOH, introduced by Sharpless and Akashi,[10] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[11] Tsuji *et al*.[12] demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

Initial efforts by Sharpless *et al.* to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[13] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[14] Moderate to good enantiomeric excess was obtained by utilizing the chiral ligands such as acetate esters of cinchona alkaloids.[13]

Apart from the cinchona alkaloid catalyzed AD, there are a number of methods employing chiral monodentate[15] and bidentate diamine[16] ligands. Despite the good to excellent enantio-selectivities that could be achieved by using diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os(VI)glycolate products and as a consequence prevent *in situ* recycling of the Os and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric with both OsO_4 and the chiral ligand[16] (Fig. **1**).

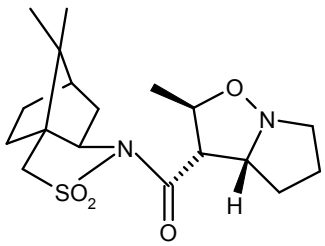
(a) Cinchona Alkaloid Ligands for asymmetric dihydroxylation reaction used under Catalytic Conditions



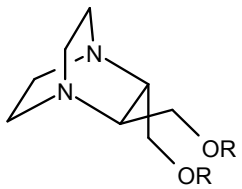
Dihydroquinidine (R = H)
DHQD

Dihydroquinine (R = H)
DHQ

(b) Mono-dentate ligands for asymmetric dihydroxylation reaction used under catalytic conditions



Murahashi et al.[16n]



R = *t*-$BuPh_2Si$
Hirama et al.[15]

(c) Chiral diamine ligands for asymmetric dihydroxylation reaction under *Stoichiometric* conditions

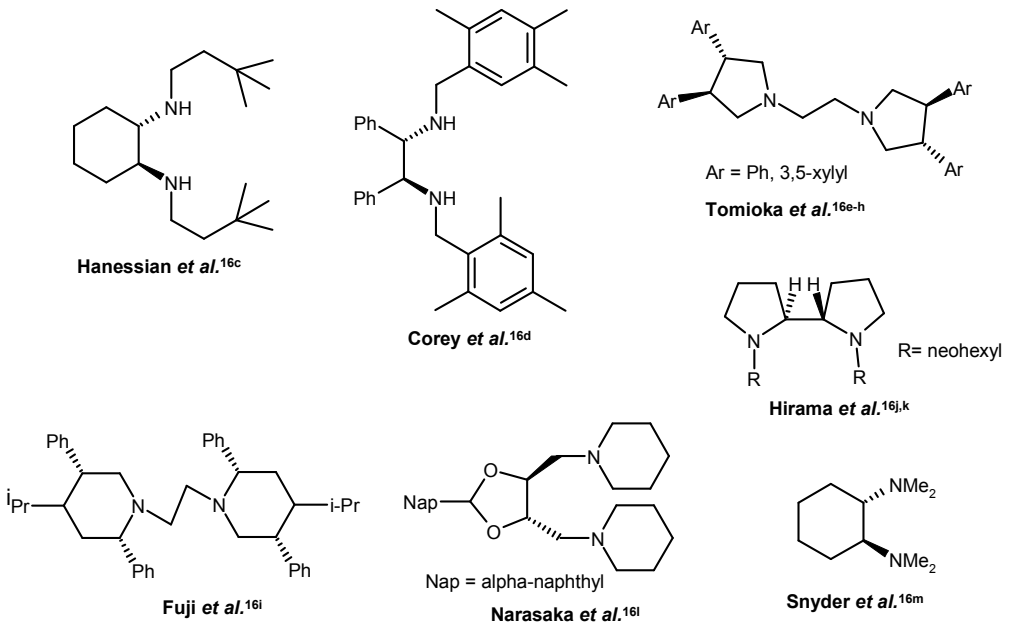


Figure 1 Some of the ligands for Asymmetric Dihydroxylation reaction.[13,16]

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was conducted under stoichiometric conditions, but in 1987 Marko and Sharpless[17] found that the process became catalytic when NMO was employed as the co-oxidizing agent. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was initially lower than that produced by the *stoichiometric* reaction. The origin of this discrepancy was observed to be the presence of a second catalytic cycle,[18] (Fig. **2**) which resulted in low or no enantioselectivity.

Wai[18] discovered a partial solution by adding the olefin substrate slowly to the reaction mixture. Kwong[19] observed that the participation of second catalytic cycle can be practically eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO AD-conditions. Since the actual osmylation takes place in this layer, the resulting osmium (VI) mono-glycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os(VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (Fig. **3**).

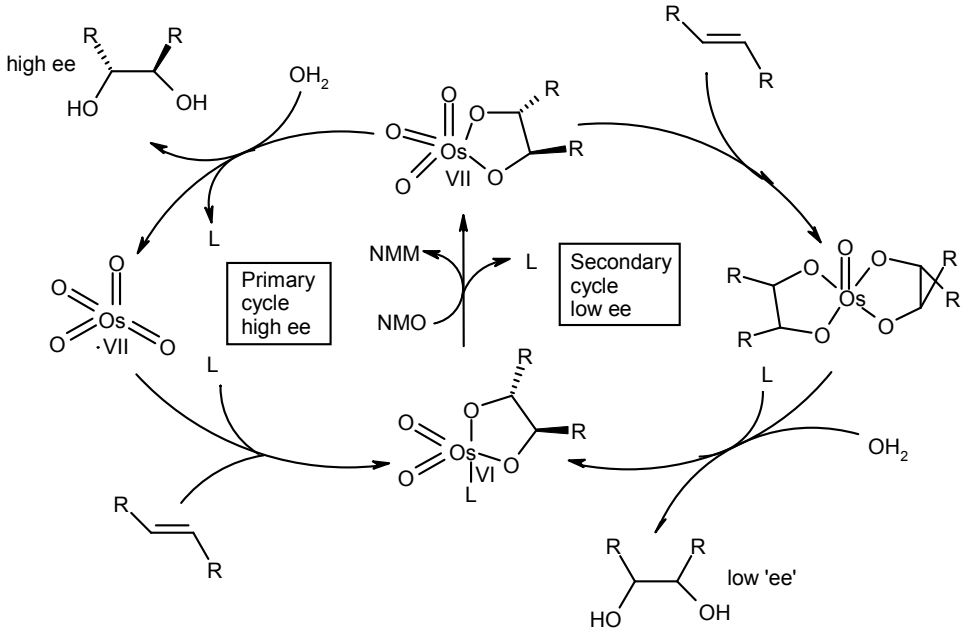


Figure 2 The schematic representation of the catalytic cycles for the SAD reaction using NMO as the co-oxidizing agent

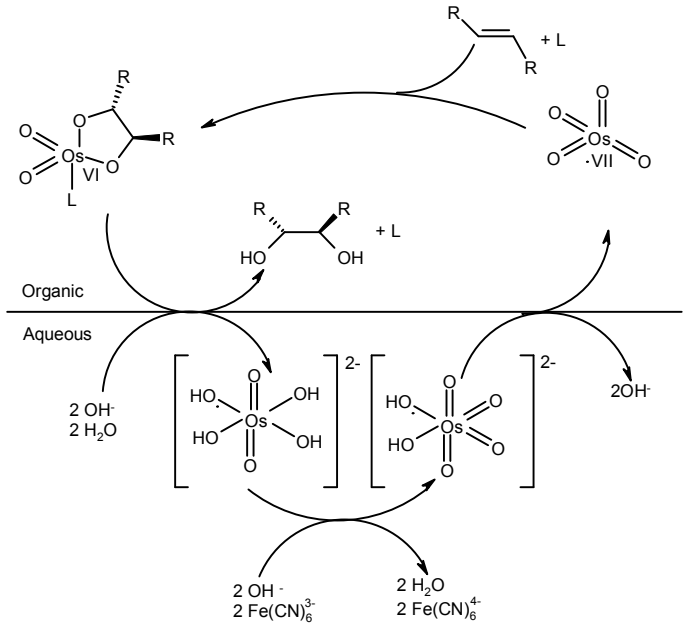


Figure 3 The schematic representation of Catalytic cycle of *SAD* reaction with $K_3Fe(CN)_6$ as the co-oxidizing agent

Sharpless *et al*.[20] found that the hydrolysis of the osmium(VI) glycolate product could be accelerated considerably by using methanesulfonamide ($MeSO_2NH_2$). The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high

catalytic turnover even with sterically overloaded substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0 °C rather than at room temperature, which may have beneficial influence on the selectivity.[21] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed. The discovery of ligands with two independent cinchona alkaloid units by Hartung[20] (phthalazine core) and Crispino[22] (diphenylpyrimidine core) attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (Fig. **4**).

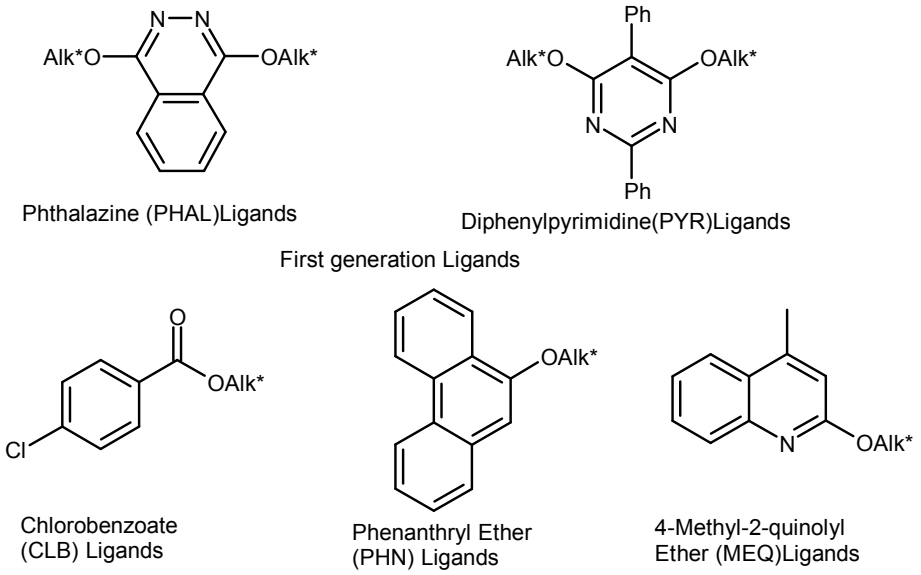
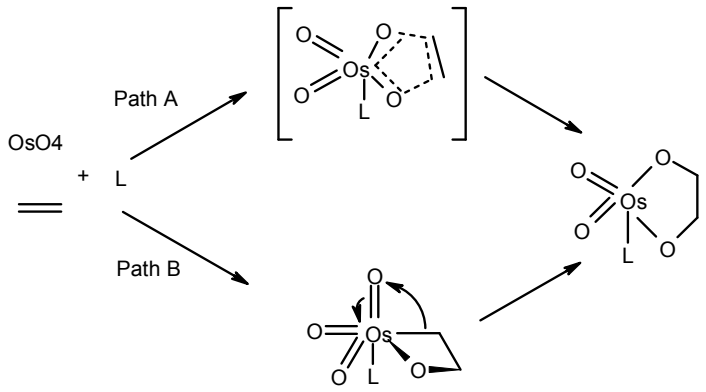


Figure 4 The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Figure **1**)

3.1.1.2 The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken[23a] and Criegee[8] originally proposed a concerted [3+2] pathway, (**Scheme 3**, **Path A**) while Sharpless *et al*.[23b] and Jorgensen *et al*.[23c] suggested a stepwise reaction which is initiated by a [2+2] like addition of the olefin across an Os=O bond (**Path B**), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

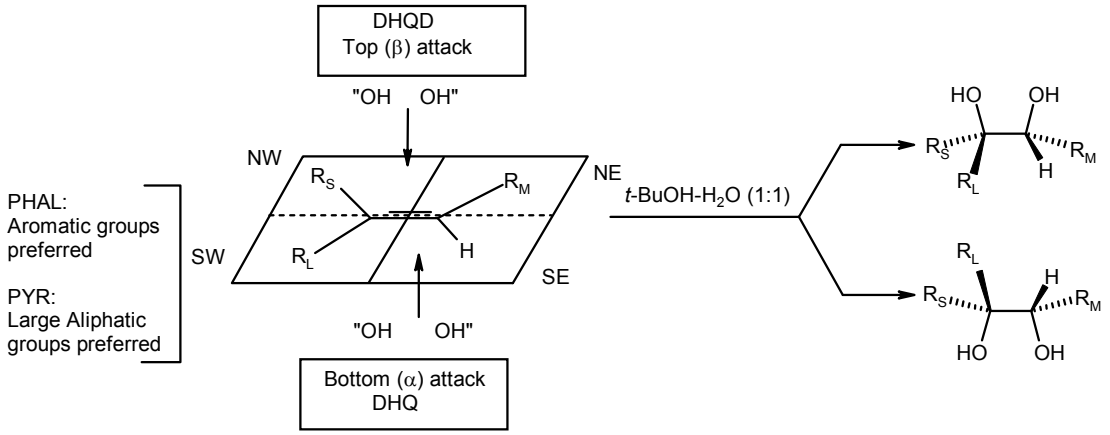


Scheme 3 Schematic presentation of the corrected [3+2] mechanism[23a] (Path A) and the stepwise osmaoxetane mechanism (Path B).[23b,c]

The recent observation of a non-linear Erying relationship between enantiomeric excess and temperature[21] is in consistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighted differently according to temperatures owing to their different activation parameters, ΔH and ΔS. Hence, this observation suggests that the stepwise [2+2]-like mechanism is operative. High level *ab initio* calculations have indeed shown that osmaoxetanes are energetically accessible minima on the potential energy surface.[24]

3.1.1.3 Empirical rules for predicting the face selectivity

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (Scheme **4**).[25] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[25c] An olefin which is placed into this olefin according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (**Scheme 4**).



Scheme 4 The mnemonic device for predicting the face selectivity

3.1.1.4 Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1 M.[20] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% of osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined organic layers are extracted with 3% aq. H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base, and the volume of aqueous ligand solution added to the reaction mixture.

3.1.1.5 The Cinchona Alkaloid Ligands and their Substrate Preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[26] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantio-selectivities were observed when the aromatic substituents appear in certain optimal locations[27] like in *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[28] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are especially well suited for almost all olefins having aliphatic substituents.[29] Even diols derived from allyl halides or allyl alcohols can now be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[30]

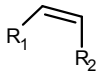
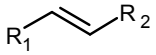
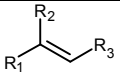
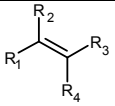
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantio-selectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PRY ligands.[31] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[32] However, in certain cases better results are obtained with the new second generation ligands.[33]

Table 1 Recommended ligands for each olefin class

Olefin Class						
Preferred Ligands	<u>R=Aromatic</u> DPP, PHAL <u>R=Aliphatic</u> AQN <u>R=Branched</u> PYR	<u>R_1, R_2 =Aromatic</u> DPP, PHAL <u>R_1, R_2 =Aliphatic</u> AQN <u>R_1, R_2 = Branched</u> PYR	<u>Acyclic</u> IND <u>Cyclic</u> PYR, DPP, AQN	<u>R_1, R_2 = Aromatic</u> DPP, PHAL <u>R_1, R_2 = Aliphatic</u> AQN	PHAL, DPP, AQN	PYR, PHAL

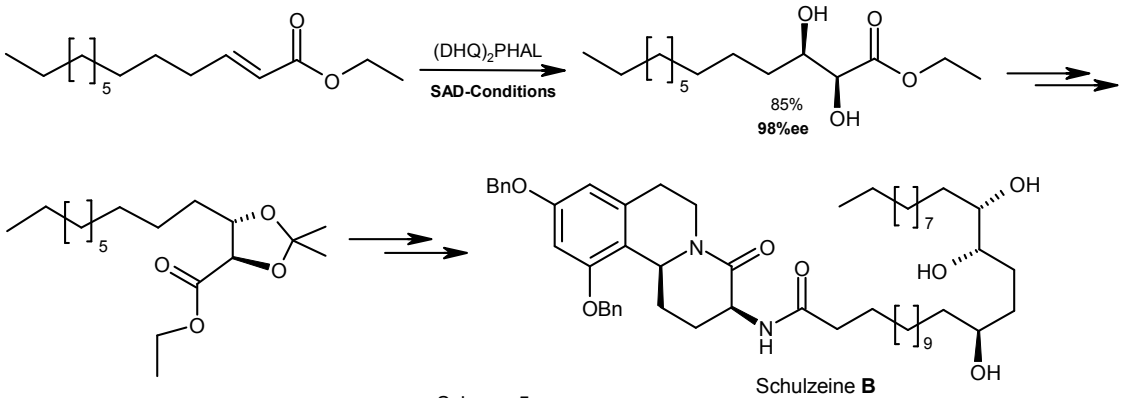
3.1.1.6 Recent Applications of Sharpless Asymmetric Dihydroxylation (SAD) Reaction in Organic Synthesis

Asymmetric dihydroxylation offers some important advantages over the use of chiral pool materials in enantioselective synthesis.

1. SAD, catalytic in both OsO_4 and the chiral ligand, provides either of the enantiomer as the product.
2. SAD is not limited to a certain number of standard starting materials (e.g. carbohydrates, tartrates, etc.), since virtually any olefin can be regarded as a substrate.
3. Third, most enantio-specific syntheses from the chiral pool require an elaborate protecting group strategy. However with SAD, the diol can be carried through the synthesis "masked" as an olefin, ready to be released at any point.

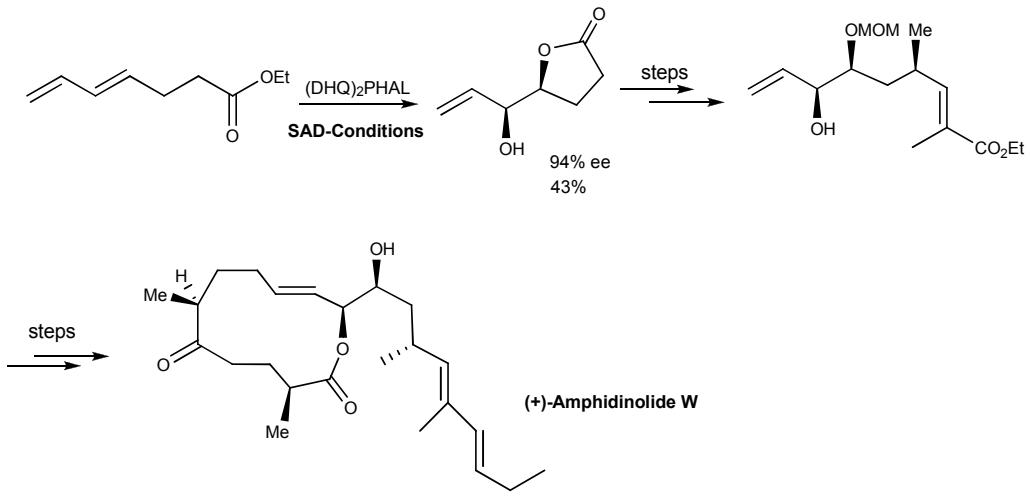
In most instances, diols are not the final products and their synthetic elaboration requires some further transformations. Commonly, these involve the selective manipulation of one of the two OH groups either by protecting it or by converting it into a leaving group, suitable for displacement by a nucleophile. Over the last decade, several applications of SAD reaction in the syntheses of bioactive molecules and natural products have been documented in the literature. While most of the synthetic applications of SAD are covered in the review article by Sharpless *et al.*[5a] a few recent applications are documented below:

(1). Gurjar *et al.*[34] reported the synthesis of Schulzeines-B which inhibit yeast R-glucosidase at concentrations as low as 48 nM and their strategy involves **SAD** as the key step.



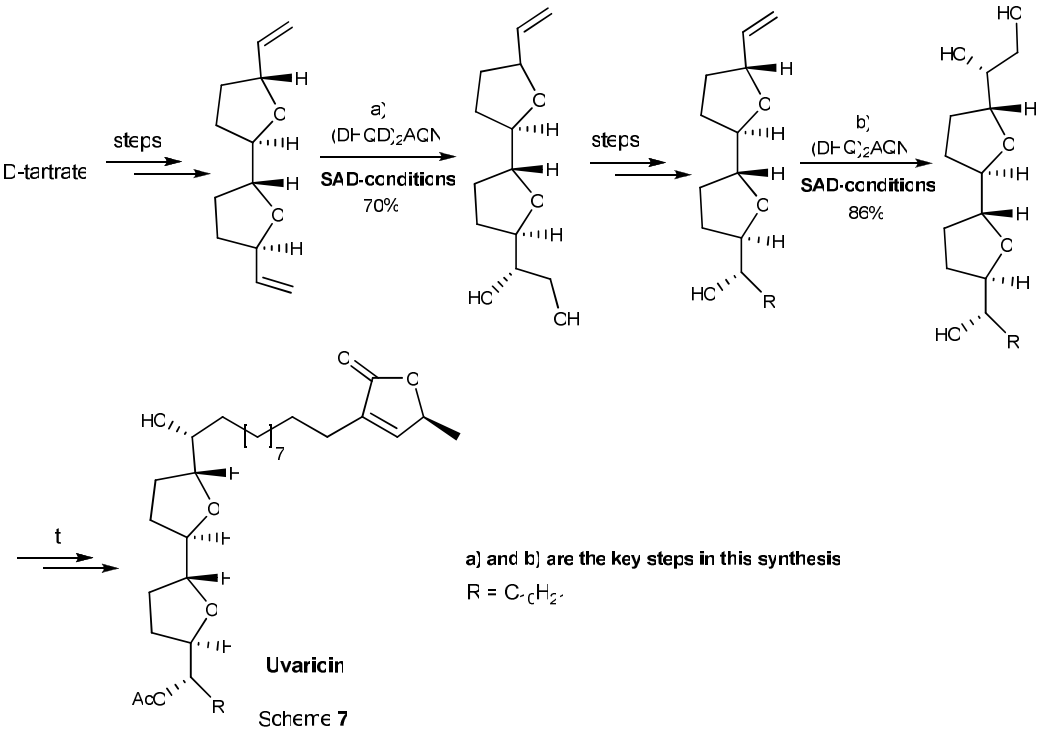
Scheme **5**

(2). Amphidinolides are symbionts of Okinawan marine acoel flatworms *Amphiscolops* sp. They are extremely scarce and have potent antitumor properties. Ghosh *et al.*[35] reported the synthesis of (+)-Amphidinolide-W and the key step of the synthetic strategy involves **SAD**.



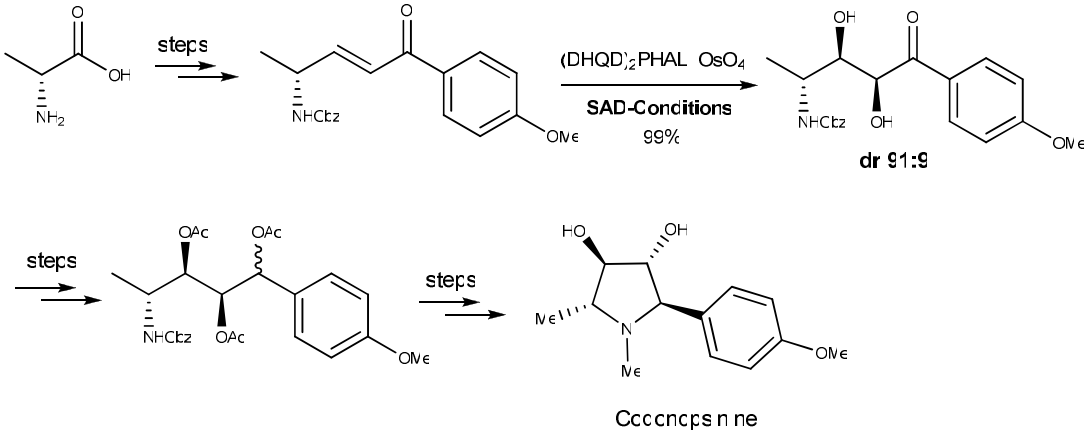
Scheme **6**

(3). Annonaceous acetogenins constitute a new class of compounds that has shown extremely diverse biological activities including cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and anti-feedant agents. Burke *et al.*[36] reported the synthesis of formal synthesis of Uvaricin and the key steps involve **SAD**.



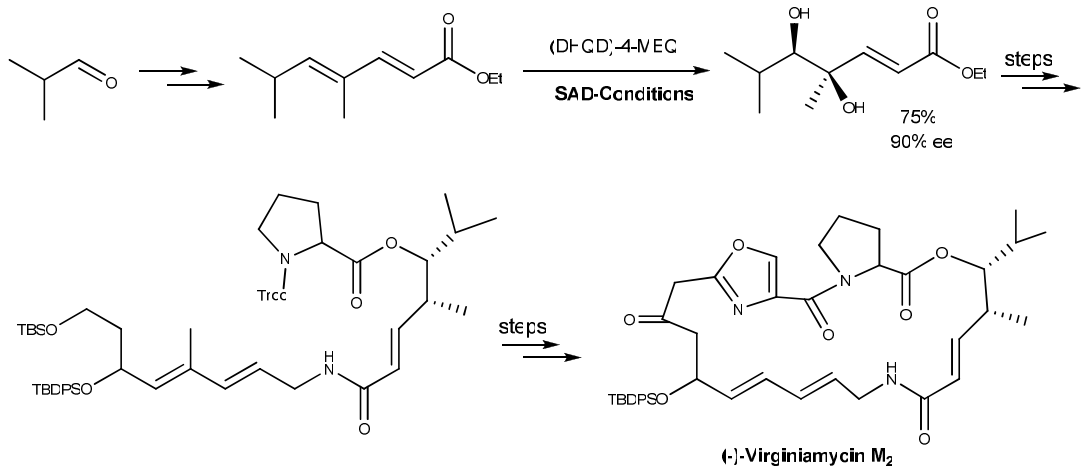
Scheme **7**

(4). Reddy *et al.*[37] synthesized (-)-Codonopsinine starting from D-alanine and their synthetic strategy involved **SAD** as a key step.



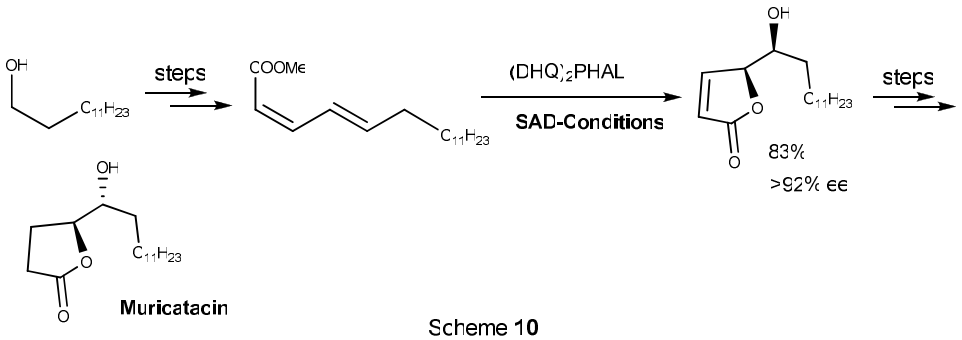
Scheme 8

(5). Mortensen *et al.*[38] reported the new antibacterial agent, Virginiamycin M_2. In this synthetic strategy the **SAD** is being utilized as a key step for the generation of stereogenic chiral centres.



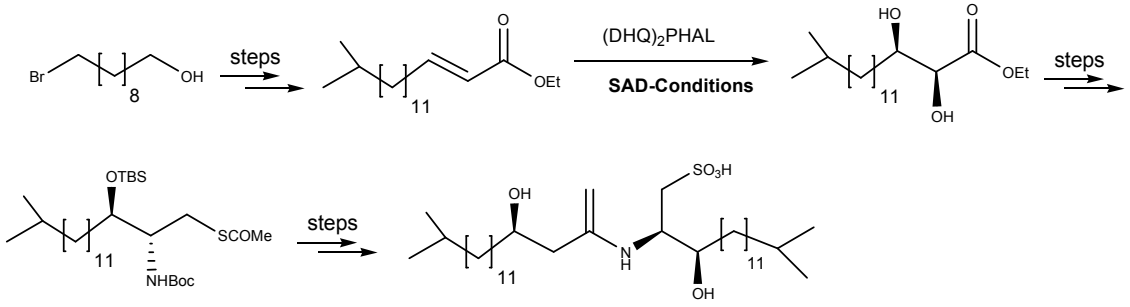
Scheme 9

(6). The muricatacins are a class of naturally occurring 5-hydroxy-γ-butyrolactones with potent cytotoxicity (1-10 μg/mL) against several human tumor cell lines. Ahmed *et al.*[39] synthesized the Muricatacin *via* a synthetic strategy which involves SAD as the key step.



Scheme 10

(7). Naidu *et al.*[40] synthesized Sulphabacin-A enantioselectively starting from 1-bromodecanol and the synthesis of the important key intermediate involved **SAD**.



Scheme 11

3.1.1.7 Conclusion

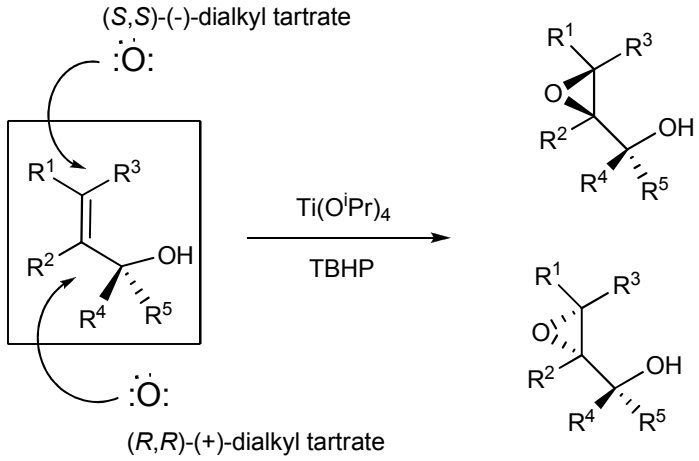
Thus, Sharpless asymmetric dihydroxylation has become a powerful tool for catalytic oxidation reaction. With the proper choice of ligands and the amount of primary oxidant, the catalytic oxidation reaction leading to chiral diols has proved very promising in terms of both yields and enantio-selectivities. It has contributed to rapid advances in synthetic organic chemistry giving access to new molecules which are needed to investigate hitherto unexplained and undiscovered phenomena in the molecular world.

3.1.2 Sharpless Asymmetric Epoxidation

Asymmetric synthesis of optically pure organic compounds is a challenging task for organic chemists. Nature provides thousands of enantiomerically pure compounds, but quite a few of them are either not easily isolated or not available in useful amounts. However it is more elegant and more economical to prepare just the wanted enantiomer by asymmetric synthesis. Epoxides are versatile and important intermediates in organic chemistry. The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. Sharpless and katsuki discovered a system for the asymmetric epoxidation of primary and secondary allylic alcohols that utilizes titanium tetraisopropoxide, a diakyl tartrate as a chiral ligand, and *tert*-butyl hydroperoxide as the oxidant.[41] Notably, this reaction exhibits high levels of enantioselectivity. Like other metal catalyzed epoxidations, this reaction also proceeds under mild conditions with good chemical yield and with high regio-and chemoselectivity.

3.1.2.1 Asymmetric epoxidation with the titanium (IV) tartrate catalyst

The combination of $Ti(OPri)_4$, a dialkyl tartrate, and *tert*-butyl hydroperoxide epoxidizes most of the allyic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in Scheme **12**. When an allylic alcohol (R_4, R_5 = H) is drawn in a plane with the hydroxymethyl group positioned at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2*S*)-epoxide if an (*R*,*R*)-dialkyl tartrate is used as the chiral auxiliary. When an (*S*,*S*)-dialkyl tartrate is employed, oxygen is delivered from the top side resulting in (2*R*)-epoxide. The enantiofacial selectivity of the reaction is > 90% ee for substrate without a Z-olefinic substituent (R_3 = H). The degree of facial selectivity for a Z-allylic alcohol depends on the nature of the Z substituent R_3. The enantioselectivity for substrate with unbranched R_3 substituents ranges from 80 to 94% ee, but that for substrates with branched substituent is lower.[42]

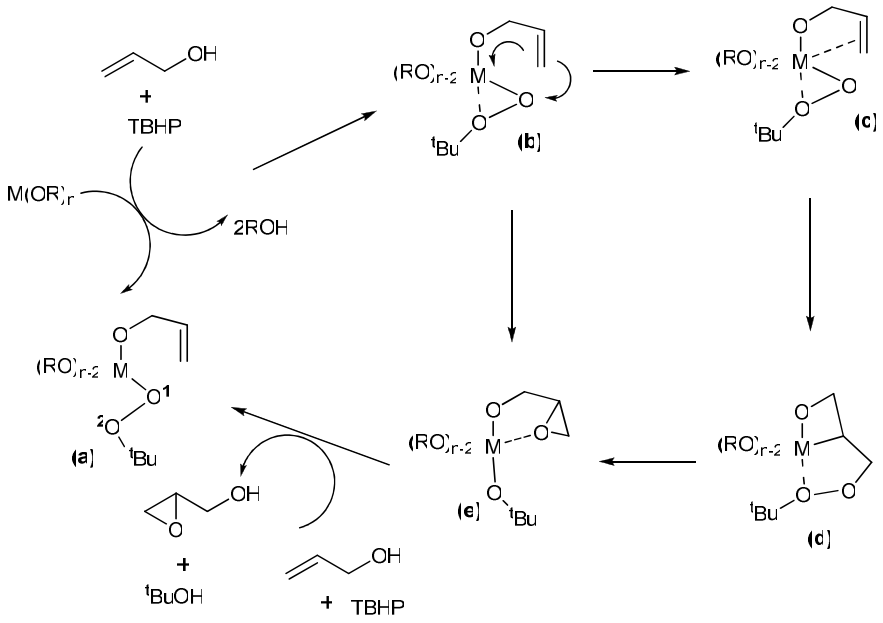


Scheme 12

3.1.2.2 Mechanism of epoxidation reaction

The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in **Scheme 13**.[43] Metal alkoxides generally undergo rapid ligand exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes M(OR)n-x-y-$(OCH_2CH{=}CH_2)_x(OOR)_y$. Among them, only species such as '**a**', bearing both allylic alkoxide and alkyl hydroperoxide groups, is responsible for the epoxidation. The incorporated alkyl hydroperoxide is thought to be further activated by coordination of the second oxygen atom (O-2) to the metal center. The ensuing transfer of (O-1) to the double bond of the allylic alcohol occurs in an intramolecular fashion, is supported by comparison of the epoxidation rate of allylic alcohol with that of allyl methyl ether.[44] However, controversy still surrounds the oxygen transfer process (**b-e**).

One suggestion is that the olefin first coordinates to the metal center and then get inserted into the μ-2-alkyl hydroperoxide ligand to give an epoxide *via* the peroxometallocycle intermediate.[45] An alternative proposal is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken.[42,43d,45] Frontier molecular orbital treatment of peroxometal complexes also suggests that d-transition metal complexes of ROO- exhibit electrophilic behaviour.[46] Finally, exchange of *tert*-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle. The titanium tartrate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of **Scheme 13**.



Scheme 13

Therefore the remaining mechanistic question is how oxygen is transferred enantioselectively to the substrate. To answer this question, structures of titanium-dialkyl tartrate complexes,[45,47] as well as those prepared from $Ti(OPr^i)_4$ and (*R,R*)-*N,N'*-dibenzyltartramide and from $Ti(OEt)_4$, (*R,R*)-diethyl tartrate, and Ph(CO)N(OH)Ph were determined.[48] Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst has been proposed as shown in Fig. **5**.

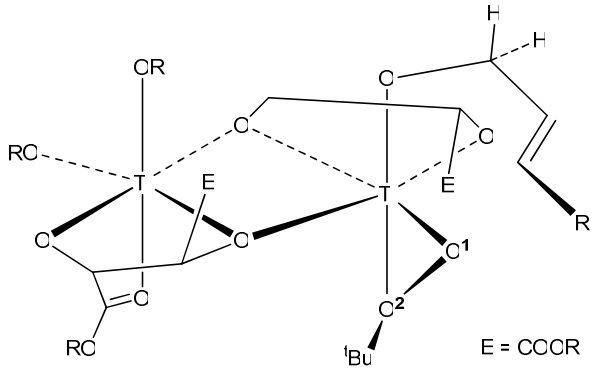


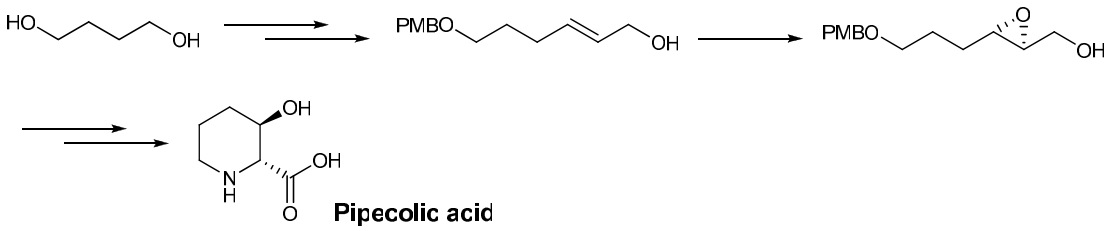
Figure 5

When structure shown in Fig. **5** is viewed down the distal peroxide oxygen-titanium bond axis (O^1-Ti), the symmetry of the tartrate "windmill arms" becomes apparent. Detailed mechanistic pathways are well documented in the literature.[49]

3.1.2.3 Applications of epoxidation in the synthesis of bioactive molecules

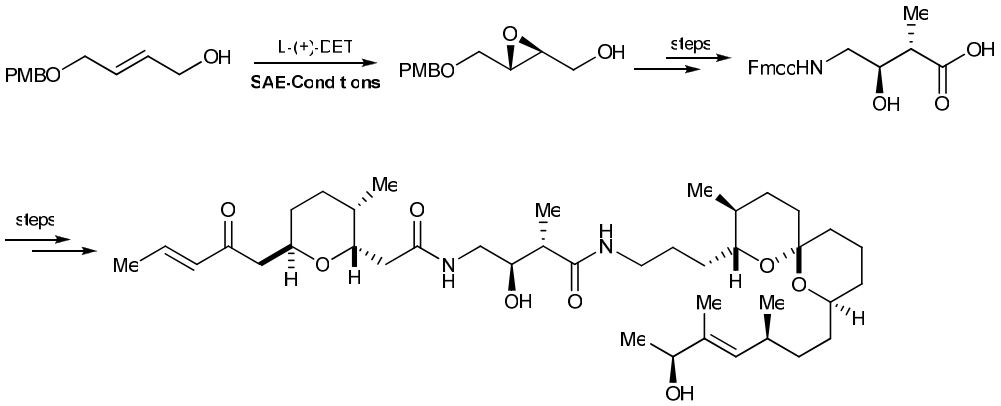
A few selected literature report of the application of AE reaction are described below:

(1). Kumar *et al*.[50] have synthesized *trans*-3-hydroxypipecolic acid employing Sharpless asymmetric epoxidation as the key step (Scheme **14**).



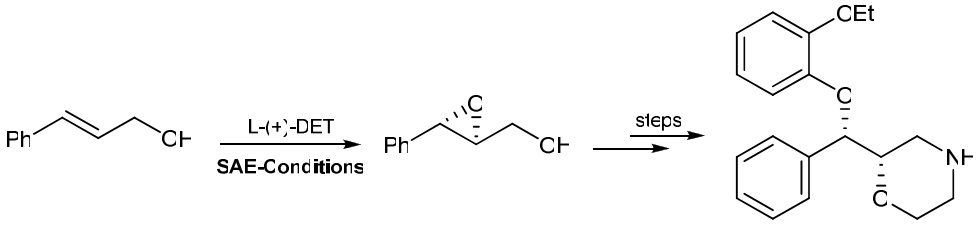
Scheme 14

(2). Bistramide-A is a member of a new class of bioactive molecules isolated from the marine ascidian *Lissoclinum*. *bistratum*. Crimmins *et al.*[51] synthesized Bistramide A utilizing Sharpless asymmetric epoxidation as the key step (Scheme **15**).



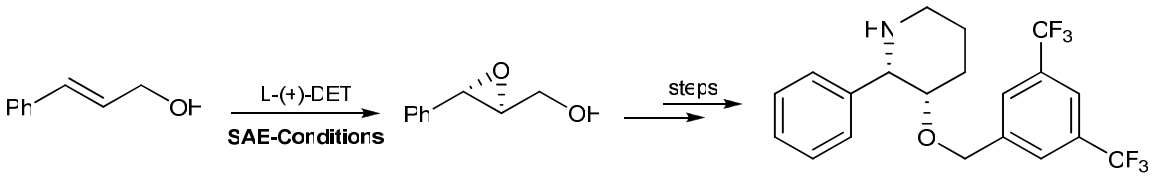
Scheme 15

(3). Reboxetine mesylate is a selective norepinephrine uptake inhibitor (NRI) currently marketed as the racemate. Henegar *et. al*[52] synthesized (S)-Reboxetine succinate via., Sharpless asymmetric epoxidation (Scheme **16**).



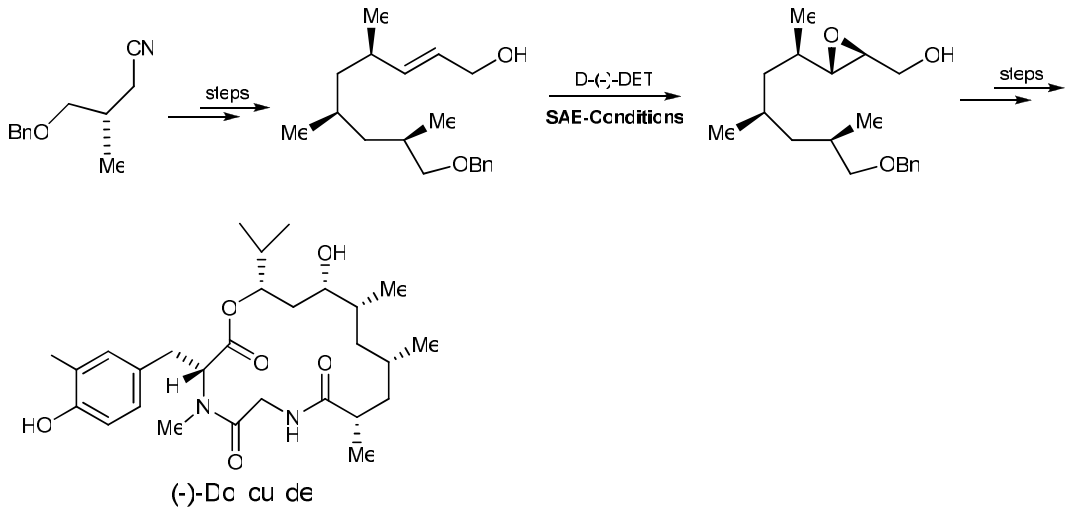
Scheme 16

(4). Shijo *et al.*[53] synthesized (+)-L-733,060 in an enantioselective manner utilizing Sharpless asymmetric epoxidation in their key intermediate step (Scheme **17**).



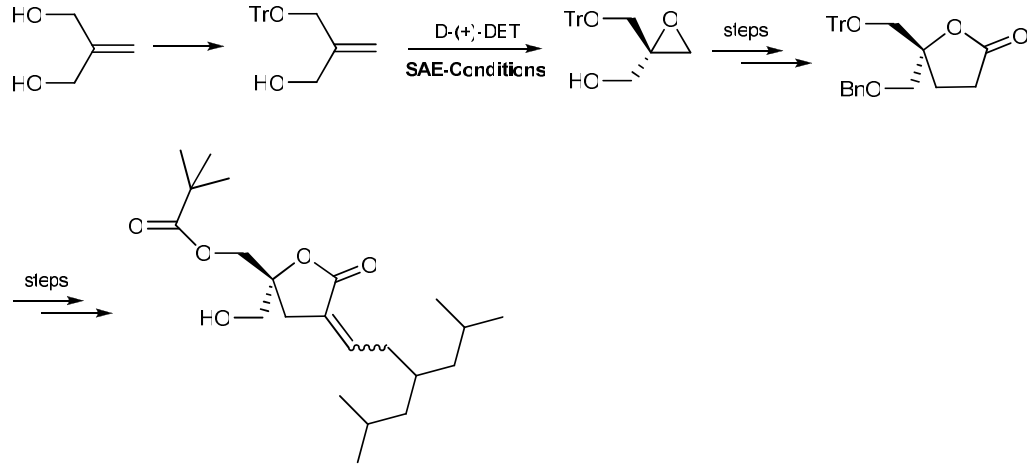
Scheme 17

(5). Ghosh *et al.*[54] synthesized (-)-Doliculide, a potent antitumor agent, stereo-selectively in a convergent manner. The synthesis of the polyketide fragment was achieved by using Sharpless asymmetric epoxidation as the key step (Scheme **18**).



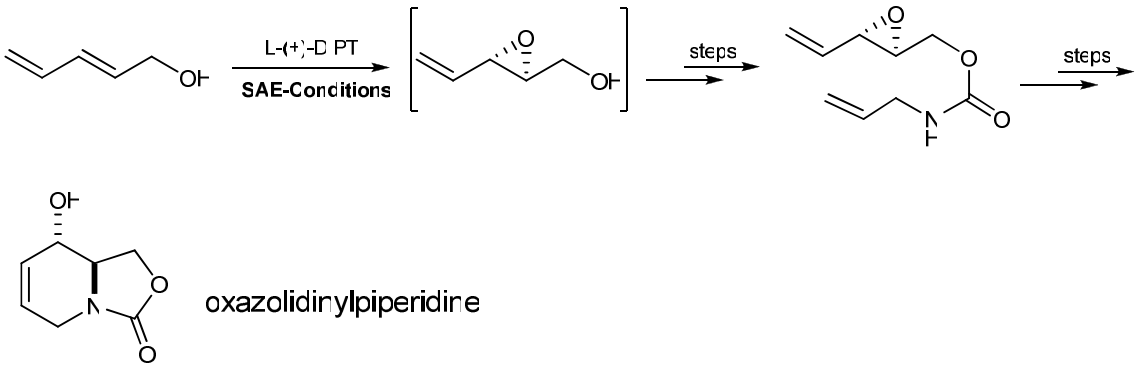
Scheme 18

(6). Kang *et al.*[55] utilized Sharpless asymmetric epoxidation to convert commercially available 2-methylenepropane-1,3-diol to (*R*)-enantiomeric DAG-lactone (Scheme **19**).



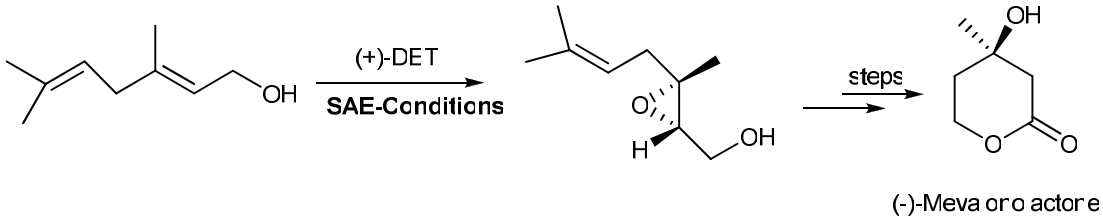
Scheme 19

(7). A concise enantioselective preparation of oxazolidinylpiperidine, a key intermediate in the synthesis of glycosidase inhibitors such as 1-deoxymannojirimycin or 1-deoxygalactostatin, has been developed. Martin *et. al*[56] synthetic strategy involved Sharpless asymmetric epoxidation as the key step (Scheme **20**).



Scheme 20

(8). Mevalonolactone is the biosynthetic precursor of most of the terpenoids, steroids, carotenoids, isoprenoids and pentanoids. Mori *et al*.[57] employed the SAE reaction in the key step of their strategy towards the synthesis of (-)-Mevalonolactone(Scheme **21**).



Scheme 21

3.1.2.4 Conclusion

Thus, Sharpless asymmetric epoxidation is also a powerful tool for the catalytic oxidation reaction. With the proper choice of ligands and the amount of primary oxidant, the catalytic oxidation reaction leading to chiral epoxide has proved very promising in terms of both yields and enantio-selectivities.

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SECTION-B

Stereoselective synthesis of Jaspine B

3.2.0 Introduction

Sphingoid bases are long-chain (typically C_{18}) aminopolyols that constitute the backbone of sphingolipids, ubiquitous components of eukaryotic cell membranes.[1] Once *N*-acylated with a fatty acid they give rise to ceramides, precursors of Sphingomyelin **VII** and Glycosphingolipid through C-1 functionalisation. Most of the sphingoid bases are of the D-*erythro*-sphingosine type but the less prevalent D-*ribo*-phytosphingosine subclass has attracted great interest (Fig. **6**).[2] Notably, the participation of simpler sphingolipids in signal transduction and cell growth regulation has been established. Ceramide is recognized as a second messenger causing various *anti*-mitogenic effects, including apoptosis.[3] In contrast, sphingosine-1-phosphate has emerged as a key mitogenic regulator.[4] These observations suggest that the pharmacological manipulation of the sphingolipid metabolism represents a promising approach for the development of novel anticancer therapies.[5]

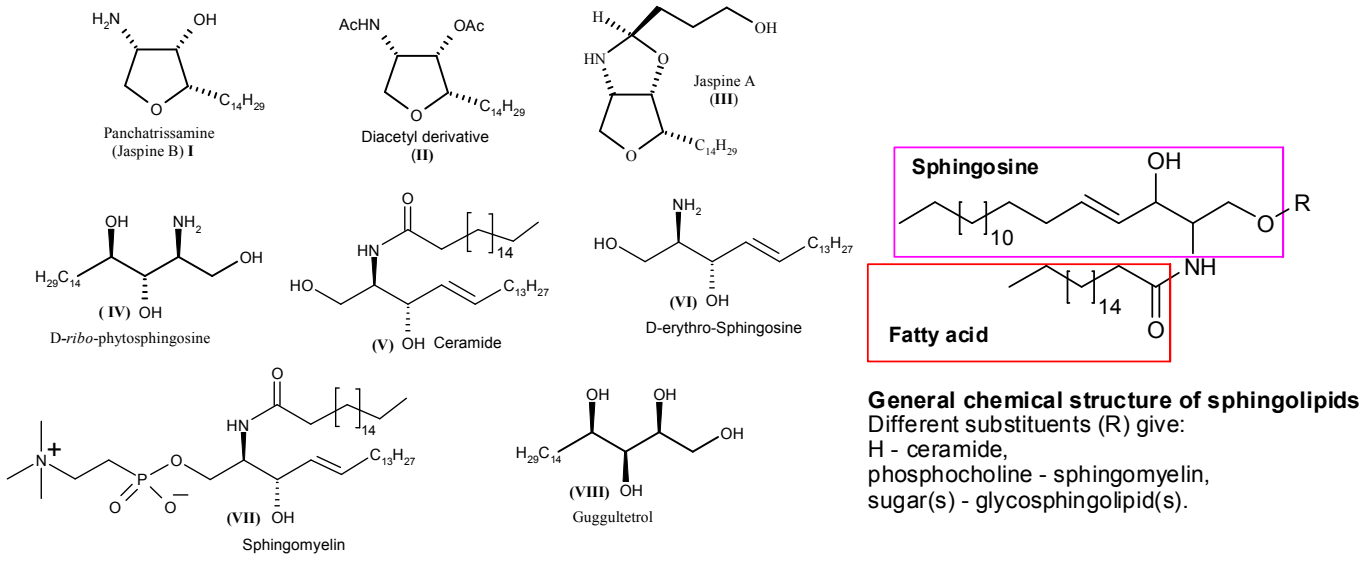


Figure 6 Bio-active Sphingoid bases, Ceramide and Sphingomyelin

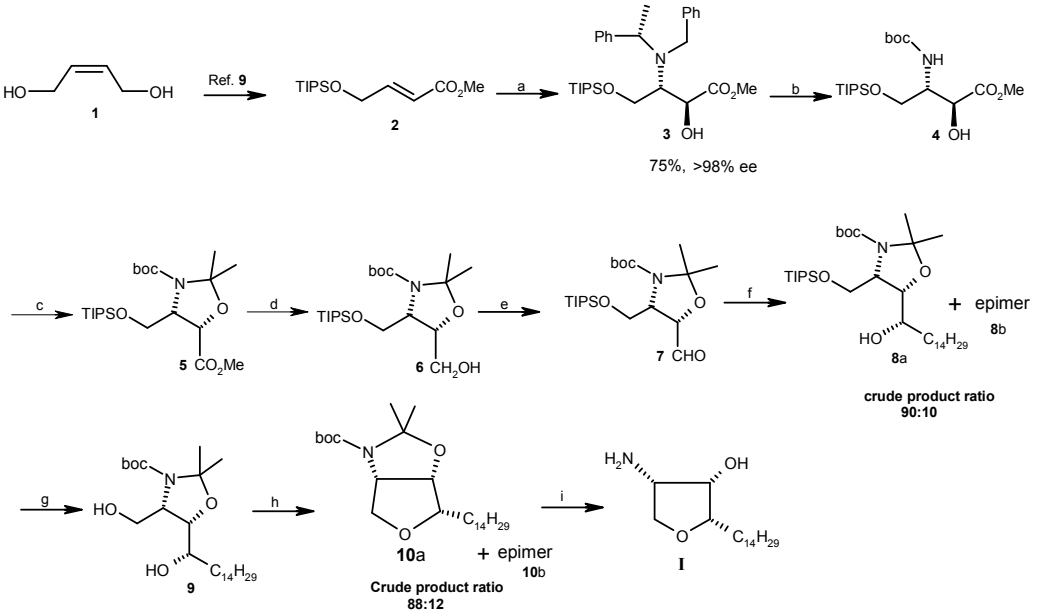
Recent studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers[6] led to the isolation of the cyclic anhydrophytosphingosine Pachastrissamine **I**. Subsequently, Debitus and co-workers independently reported the isolation of jaspine B **I** from the marine sponge *Jaspis* sp,[7] Pachastrissamine and jaspine B are identical (Fig. **6**). Either the free base or the hydrochloride displayed a pronounced cytotoxicity towards several cell lines with IC_{50} values in the submicromolar range (IC_{50} = 0.34 μM).[7] We targeted a biologically relevant

analogue of sphingosine, jaspine B (Fig. **6**). Jaspine B possesses three contiguous stereogenic centers and is structurally similar to the open chain sphingolipid D-*ribo*-phytosphingosine **IV**. It might be very likely that D-*ribo*-phytosphingosine **1V** is the biosynthetic precursor to **I** and **III**. Interestingly, Guggultetrol **VIII**, a naturally occurring lipid isolated from the gum-resin of the tree *Commiphoru mukul (guggulu*), known in Ayurveda, the Indian traditional system of medicine, for the treatment of arthritis, inflammation, obesity, and disorders of lipid metabolism closely resembles the sphingolipid Phytosphingosine **IV**. The tri-substituted tetrahydrofuran structural framework and the proven bioactivity of jaspine B **I** prompted extensive synthetic studies, resulting in a handful of approaches reported very recently.

3.2.1 Review of literature

Abraham *et al* (2007)[8] Scheme 22

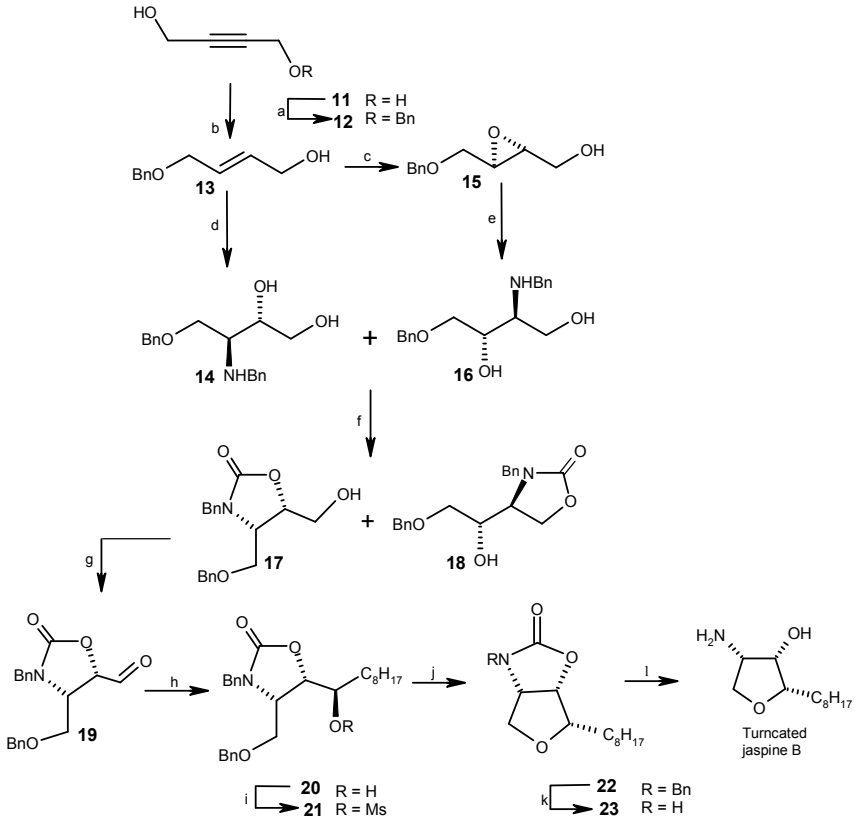
Abraham and co-workers synthesized jaspine B starting from cis-2-butene-1,4-diol **1** in ten steps. The key step of this strategy is the conjugate addition of lithium (S)-N-benzyl-N-(α-methylbenzyl)amide over the enolate ester **2**.



Scheme **22**. Reagents and conditions: (a) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-(camphorsulfonyl)oxaziridine, −78 °C to rt, 12 h; (b) H_2 (5 atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 12 h; (c) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, reflux, 12 h; (d) DIBAL-H, DCM, 0 °C, 6 h; (e) IBX, DMSO, rt, 12 h. (f) $C_{14}H_{29}MgBr$, THF, 0 °C to rt, 6 h; (g) TBAF, THF, rt, 12 h; (h) TsCl, DMAP, pyridine, reflux, 8 h; (i) HCl (2 M, aq), MeOH, 50 °C, 6 h, then KOH (2 M, aq).

Génisson *et al* (2007)[10] Scheme 23

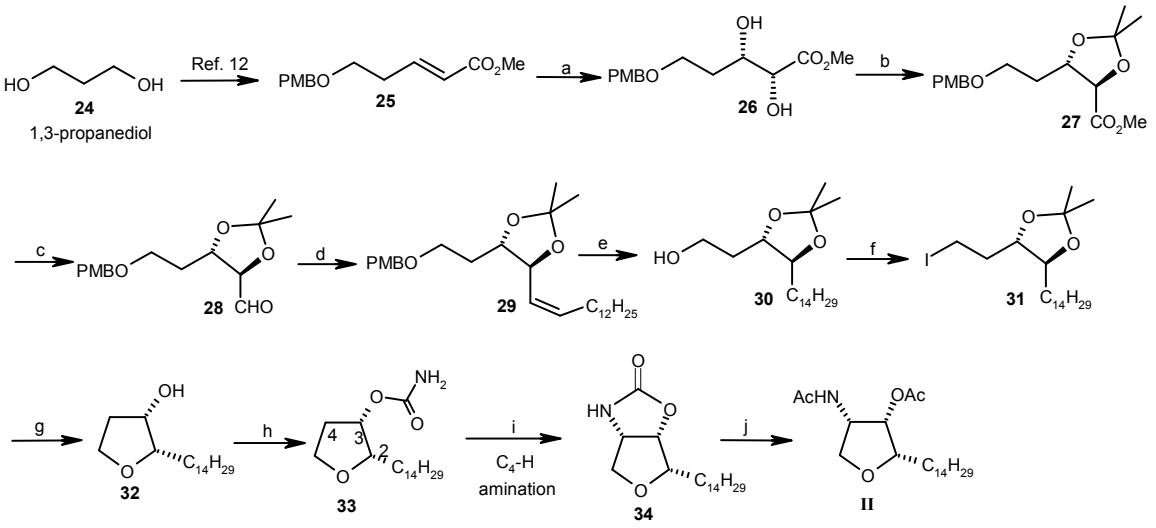
The synthetic strategy of Génisson and co-workers include the preparation of the versatile aldehyde **19** *via* a concise route based on a formal *anti*-asymmetric amino-hydroxylation and its use in the synthesis of a cytotoxic C_{12}-analogue of the **jaspine** B.



Scheme **23**.Reagents and conditions: (a) BnBr, KOH, H_2O, rt, 2 days, 70% based on the bromide; (b) $LiAlH_4$, THF, −20 °C to rt, 6 h, 60%; (c) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuHP, 4 Å MS, CH_2Cl_2, −23 °C, 3.5 days, 90%; (d) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuO_2H, 4 Å MS, CH_2Cl_2, −23 °C, 3 days, then Me_2S, rt, 3 h, then Ti(O*i*-Pr)$_4$, $BnNH_2$, rt, 1.5 days, 60% of a 70:30 mixture of **14** and **16**; (e) Ti(O*i*-Pr)$_4$, $BnNH_2$, CH_2Cl_2, reflux, 24 h, 75% of a 70:30 mixture of **14** and **16**; (f) (i) K_2CO_3, MeOCOCl, THF, rt, 18 h; (ii) 80% KOH in MeOH, rt, 5 h, 60% overall yield of **17**, 23% overall yield of **18**; (g) DMP, CH_2Cl_2, rt, 3 h, 90%; (h) $C_8H_{17}MgBr/CeCl_3$, THF, −78 °C, 5 h, then 0 °C, 1 h, 56%; (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1.5 h, 90%; (j) 10 bar H_2, $Pd(OH)_2$, EtOH, 2 days, 75%; (k) Na/NH_3, THF, −78 °C, 4 h, 83%; (l) KOH, $EtOH/H_2O$, 85 °C, 7 h, 95%.

Yakura *et al* (2007)[11] Scheme 24

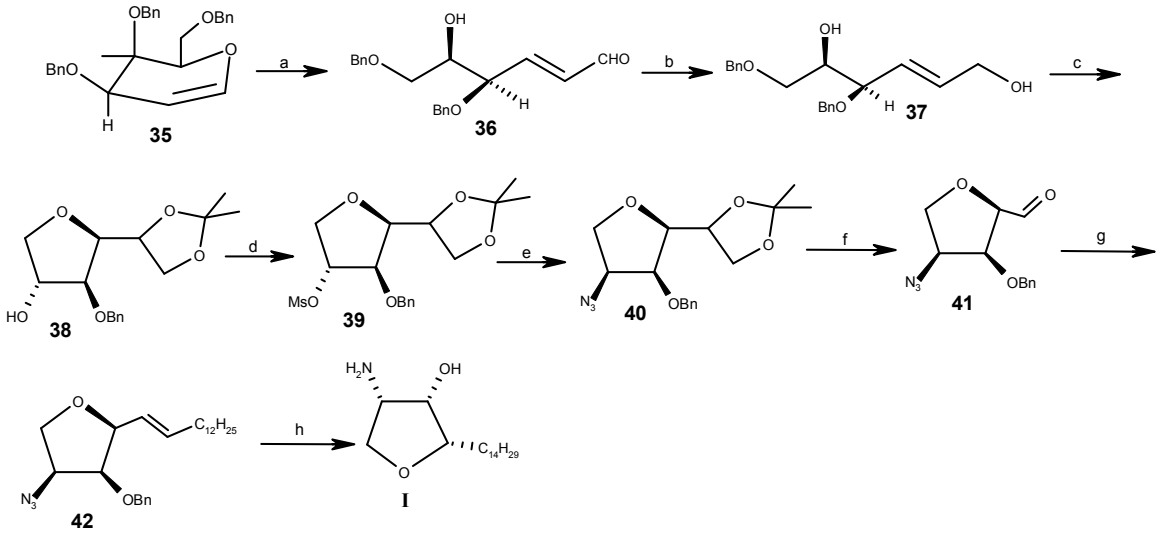
Yakura *et al* synthesized jaspine B starting from the diol **24**, Sharpless asymmetric dihydroxylation being the key step of this synthetic strategy.



Scheme **24**. Reagents and conditions: (a) AD-mix-α-BuOH-H_2O, 0 °C, overnight (89%); (b) DMP, Camphorsulfonic acid, rt, 12 h (quant); (c) DIBAL-H, DCM, −78 °C, 1 h (97%); (d) $Ph_3PCH_2C_{12}H_{25}Br$, *n*-BuLi, THF, −20 °C, 1 h (88%); (e) H_2 (3 atm), Pd/C, Boc_2O, EtOAc, rt, 3 h (87%); (f) I_2, TPP, imidazole, DCM, rt, 1 h (quant); (g) Conc. HCl, THF, rt, 2.5 h then K_2CO_3, MeOH, rt, 3 h (79%); (h) $CCl_3CON{=}C{=}O$, DCM, rt, 1 h then neutral Al_2O_3 (quant); (i) 10 mol% of $Rh_2(OCOCPh_3)_4$, 4.2 eq of $PhI(OAc)_2$, and 6.9 eq of MgO, Benzene, reflux (19%); (j) (i) aq. KOH, EtOH, reflux, 3 h; (ii) Ac_2O, Pyridine, rt, 12 h, 85% (2 steps).

Reddy *et al* (2007)[13] Scheme 25

Reddy and co-workers synthesized Pachastrissamine (jaspine B) starting from 3,4,6-tri-*O*-benzyl-D-galactal **35** in eight steps and 11% overall yield.

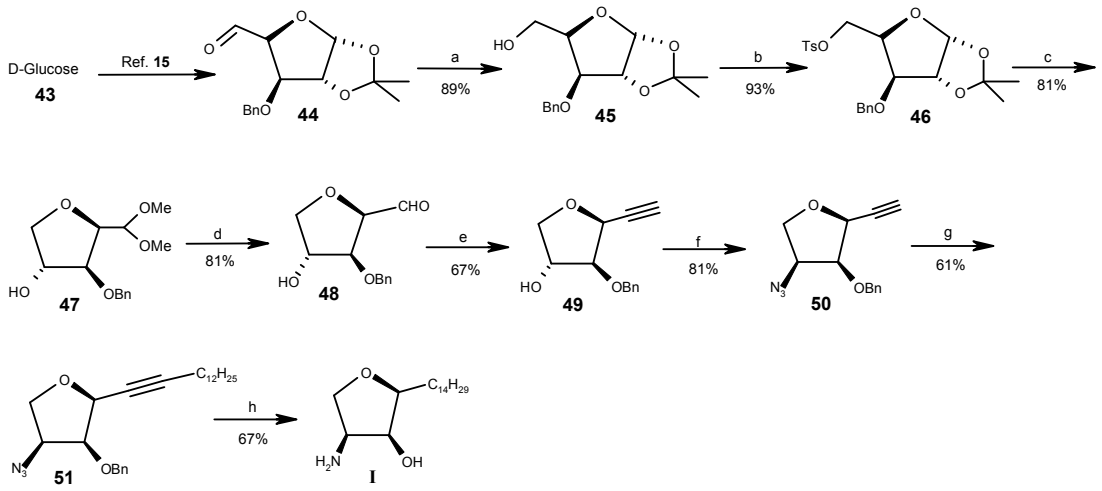


Scheme **25**. Reagents and conditions: (a) $HgSO_4$ (cat.), 0.01 N H_2SO_4, 1,4-dioxane, 0 °C to rt, 8 h, (b) $NaBH_4$ (0.5 equiv), $CeCl_3{\cdot}7H_2O$ (1.0 equiv), EtOH, 0 °C to rt, 3 h, 65% for two steps; (c) $Ti(O^iPr)_4$ (1.0 equiv), L-(+)-DET (1.2 equiv), *t*-BuHP (2.0 equiv), MS 4 Å, CH_2Cl_2, −25 °C to 0 °C 2.5 h, satd. citric acid in acetone, 2 h, 48%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1.5 h; (e) NaN_3, Bu_4NCl (cat.), DMF, 120 °C, 3 days, 62% for

two steps; (f) H_5IO_6 (1.3 equiv), EtOAc, 3 h; (g) $[(C_{13}H_{27})Ph_3P]Br$, *n*-BuLi, dry THF, −78 °C, 82% for two steps; (h) HCO_2NH_4, MeOH, Pd/C, reflux, 18 h, 72%.

Ramana *et al.* (2007)[14] Scheme 26

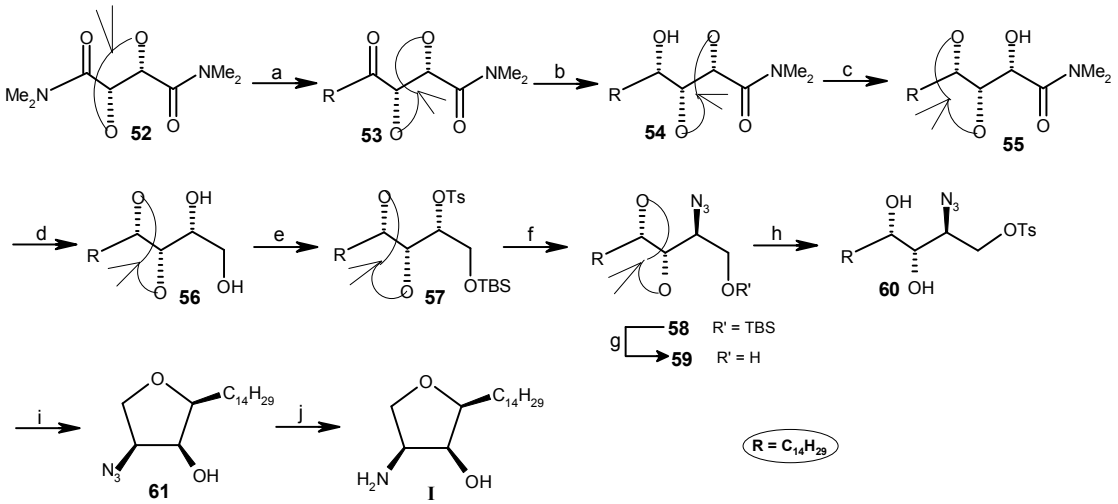
Ramana and co-workers synthesized jaspine B starting from D-Glucose **43**. The stereoselective construction of the central tetrahydrofuran units was based on the pseudo-desymmetrization of a pentodialdo-1,4-furanose derivative taking the advantage of latent symmetry present.



Scheme **26**. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 2 h; (b) *p*-TsCl, pyridine, DMAP, CH_2Cl_2, 5 h; (c) *p*-TSA, methanol, reflux, 6 h; (d) 2 N, H_2SO_4, 50% AcOH, 9 °C, 2 h; (e) $(MeO)_2P(=O)C(=N_2)COCH_3$, methanol, K_2CO_3, rt, 7-9 h; (f) (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 6 h; (ii) LiN_3, DMF, rt, 12 h; (g) *n*-BuLi, THF:HMPA (7:1), $C_{12}H_{25}Br$, −78 to −40 °C, 1 h; (h) 10% Pd/C, ammonium formate, MeOH, reflux, 10 h.

Prasad *et al.* (2007)[21] Scheme 27

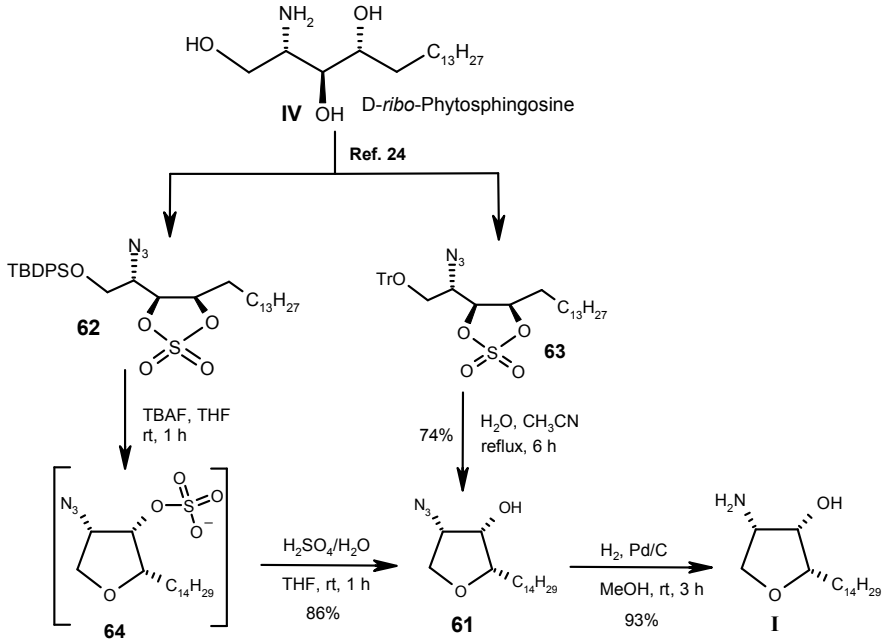
Prasad and co-workers achieved the synthesis of jaspine B in 48% overall yield from D(-)-tartaric acid in 12 steps.



Scheme **27**. Reagents and conditions: (a). *n*-$C_{14}H_{29}MgBr$, THF, –15 ^oC, 0.5 h, 86%; (b) $NaBH_4$, $CeCl_3$, MeOH, –15 ^oC, 2 h, 97%; (c) *p*-TSA, DMP, benzene, reflux, 12 h, 86%; (d) $NaBH_4$, MeOH, –15 ^oC to rt, 3 h, 94%; (e) (i) TBSCl, Imidazole, DMF, rt, 12 h, 92%; (ii) *p*-TsCl, DMAP, DCM, 14 h, rt, 98%; (f) NaN_3, DMF, 12 h, 100 ^oC; (g) TBAF, THF, 0 ^oC to rt, 88%; (h) (i) *p*-TsCl, TEA, DCM, 0 ^oC to rt, 5 h; (ii) $FeCl_3.6H_2O$, DCM, rt, 8 h, 94% for two steps; (i) K_2CO_3, MeOH, 0 ^oC to rt, 4 h, 97%; (j) Pd/C, H_2, MeOH, DCM, rt, 3 h, 94%.

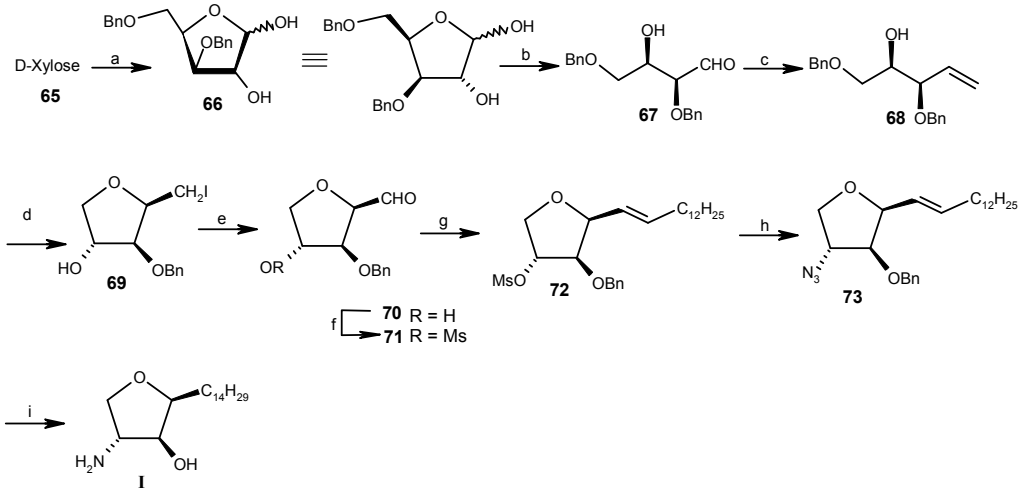
Lee *et al.* (2007)[23] Scheme 28

Lee and co-workers synthesized Jaspine-B starting from a natural Phytosphingosine. The relatively unstrained cyclic sulfate intermediate smoothly underwent the 5-*endo* cyclization to yield the 2,3,4-trisubstituted tetrahydrofuran ring system of Jaspine-B.



Liu *et al.* (2006)[16] Scheme 29

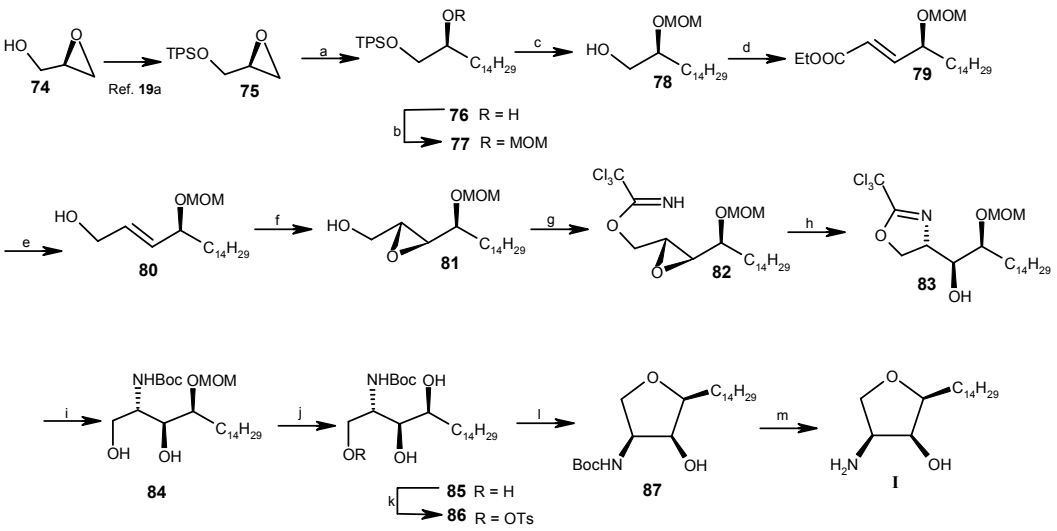
Liu and co-workers stereo-selectively synthesized jaspine B from D-xylose **52** in 11 linear steps with a 23.9% overall yield. The key step in the synthesis involves an iodine-induced debenzylation of a primary alcohol and the subsequent 2,5-cyclization to fit the required configuration of jaspine B.



Scheme **29**. Reagents and conditions: (a) Ref. **17**, 72% in three steps; (b) $NaIO_4$, MeOH, H_2O; (c) $CH_3Ph_3P^+Br^-$, *n*-BuLi, dry THF, −40 °C to rt, 82% for two steps; (d) I_2, $NaHCO_3$, CH_3CN, 80%; (e) $NaHCO_3$, dry DMSO, 150 °C, 6 min; (f) MsCl, Pyridine, rt, 30 min, 74% for two steps; (g) $C_{13}H_{27}Ph_3P^+Br^-$, *n*-BuLi, dry THF, −40 °C to rt, 90%, *Z*/*E* ratio >10/1; (h) NaN_3, NH_4Cl, DMF, 120 °C, 20 h, 80%; (i) Pd/C, H_2, MeOH, TFA, 5 h, 95%.

Celia Ribes (2006)[18] Scheme 30

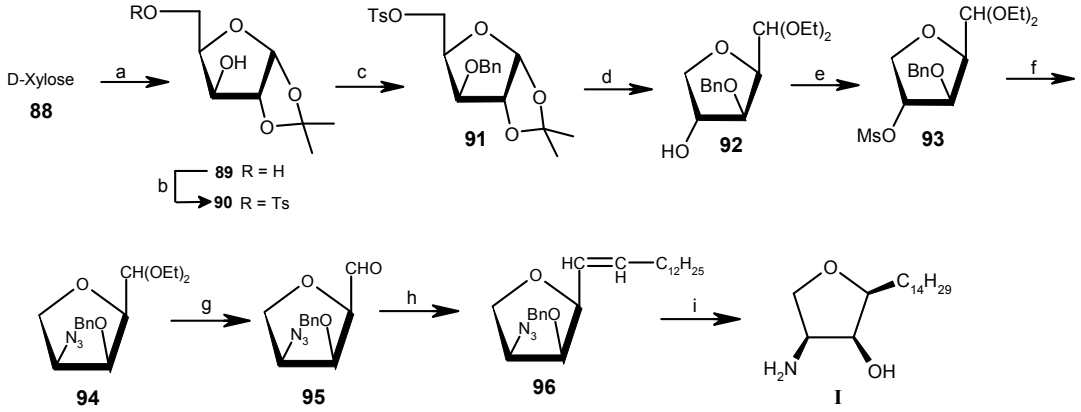
Celia Ribes and co-workers started with the chiral epoxide (*R*)-glycidol **74** in their synthetic strategy towards jaspine B. The key steps of this synthesis are a Sharpless asymmetric epoxidation, an intramolecular stereospecific epoxide opening mediated by a trichloroacetimidate group, and the formation of a tetrahydrofuran ring *via* intramolecular nucleophilic displacement.



Scheme **30**. Reagents and conditions: (a) $CH_3(CH_2)_{12}MgBr$, CuI, THF, −10° to 0 °C, 82%; (b) MOMCl, EtN^iPr_2, CH_2Cl_2, 24 h, rt, 94%; (c) TBAF, THF, 3 h, rt, 94%; (d) Ref. **19**b; (e) DIBAL, hexane, 0 °C, 2.5 h, 95%; (f) *t*-BuHP, (−)-diethyl tartrate, $Ti(^iPrO)_4$, CH_2Cl_2, −20 °C, 24 h, 89%; (g) Cl_3CCN, DBU, CH_2Cl_2, 30 min, 0 °C; (h) Et_2AlCl, CH_2Cl_2, 0 °C to rt, 5 h, 72% overall yield from **81**; (i) aq 1 M HCl, THF, 5 h, rt, then $NaHCO_3$, Boc_2O, 16 h, rt, 96%; (j) TMSBr, CH_2Cl_2, −78 °C, 30 min, 75%; (k) TsCl, Et_3N, DMAP, CH_2Cl_2, 20 min, rt; (l) K_2CO_3, MeOH, 16 h, rt, 70% overall from **85**; (m) TFA, CH_2Cl_2, 0 °C to rt, 45 min, 75%.

Du *et al.* (2006)[22] Scheme 31

Du and co-workers synthesized jaspine B stereo-selectively from D-xylose in ten linear steps with 25.7% overall yield.

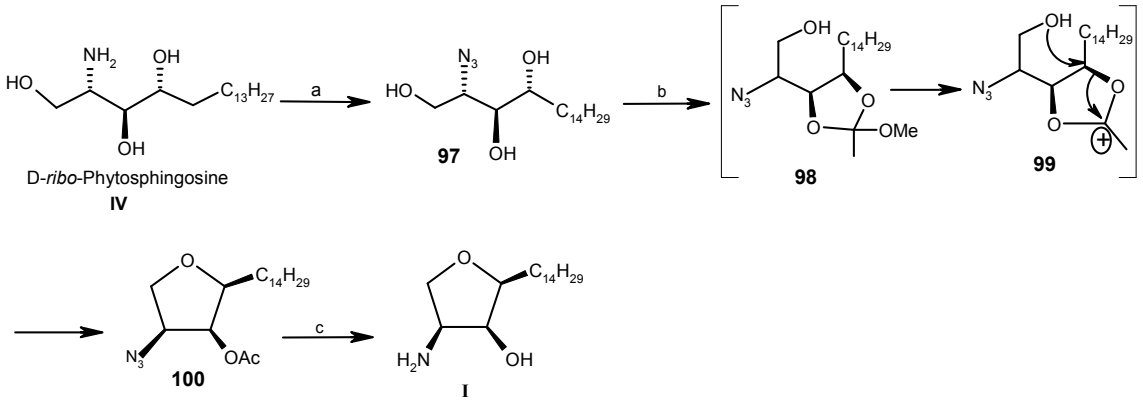


Scheme **31**. Reagents and conditions: (a) Conc. H_2SO_4, acetone, then Na_2CO_3, 82%; (b) tosylimidazolide, MeOTf, *N*-methylimidazole, THF, 93%; (c) benzyl trichloroacetimidate, 1 mol % of TMSOTf, dry CH_2Cl_2, –40 °C, 75%; (d) 5% hydrochloric acid in ethanol (v/v), reflux, 3 h, 89%; (e) MsCl, pyridine, rt, 4 h; (f) NaN_3, NH_4Cl, dry DMF, 120 °C, 20 h, 71% for two steps; (g) aq. 50% TFA, CH_2Cl_2, room temperature, 30 min,

90%; (h) $C_{13}H_{27}Ph_3P^+Br^-$, *n*-BuLi, dry THF, –40 °C, 86%, *Z*/*E* > 10/1; (i) $Pd(OH)_2/C$, H_2, MeOH/EtOAc, 5 h, 92%.

Richard *et al.* (2006)[25] Scheme 32

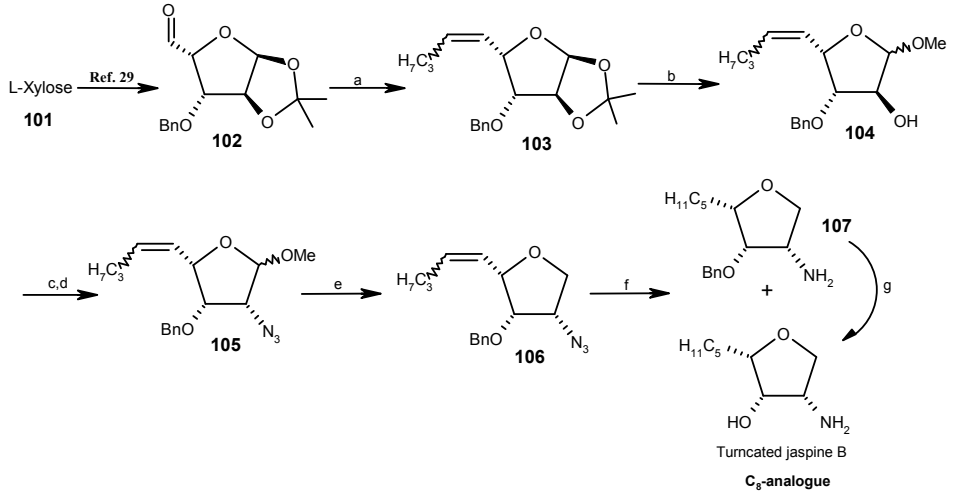
Richard co-workers reported the synthesis of Jaspine-B starting from D-*ribo*-Phyto-sphingosine in four steps.



Scheme **32**. Reagents and conditions: (a) TfN_3, Na_2CO_3, $CuSO_4$, DCM, MeOH, H_2O, rt, 16 h, 96%; (b) TMOA (1.2 equiv), $BF_3.OEt_2$, (0.1 equiv), DCM, 0 °C to rt, 16 h, 92%; (c) ^{t}BuOK, MeOH; (ii) Me_3P, toluene/H_2O (24:1), rt, 16 h, 82%.

Chandrasekhar *et al.* (2006)[28] Scheme 33

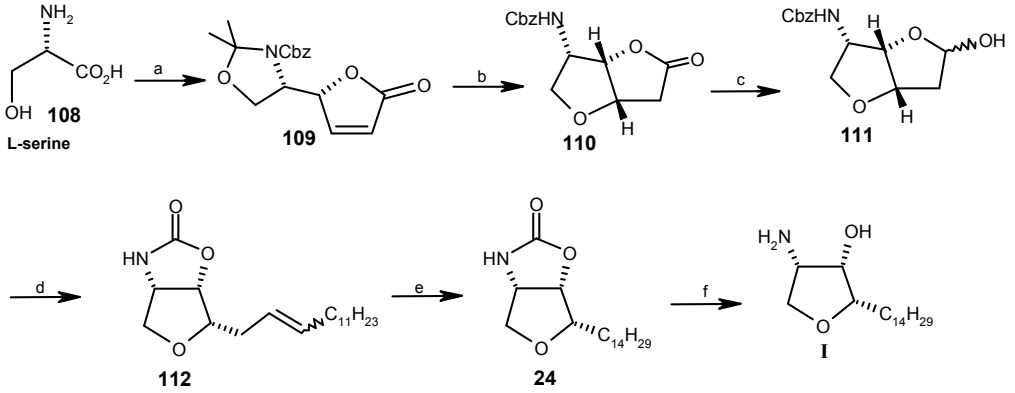
Chandrasekhar and co-workers achieved a short and efficient stereoselective synthesis of *truncated* Pachastrissamine using a Wittig olefination, azidation through imidazole sulfonate ester and one-pot reductive hydrogenation as the key steps.



Scheme **33**. Reagents and conditions: (a) $[C_4H_9PPh_3]Br$, *n*-BuLi, THF-HMPA, –40 ^oC, 4 h, 86%; (b) CH_3COCl (cat), MeOH, 60 ^oC, 8 h, 95%; (c) SO_2Im_2, NaH, DMF, –40 ^oC, 3 h; (d) NaN_3, TBACl, DMF, 110 ^oC, 12 h, 58% (for two steps); (e) $BF_3.OEt_2$, Et_3SiH, CH_2Cl_2, 0 ^oC to rt, 2 h, 94%; (f) Pd/C, H_2, MeOH, rt, 6 h, 70%; (g) Pd/C, H_2, MeOH, rt, 6 h.

Bhaket *et al.* (2005)[26] Scheme 34

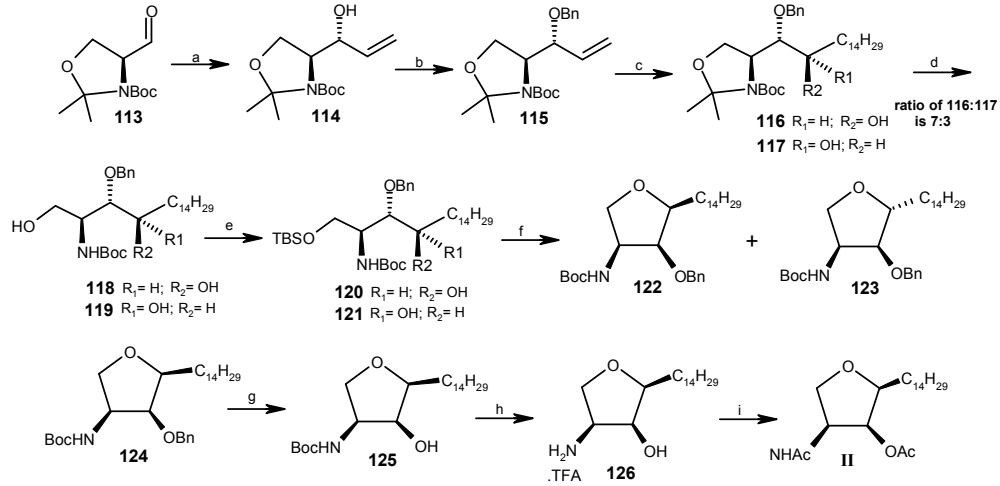
Bhaket and co-workers reported the stereoselective synthesis of Pachastrissamine starting from L-serine in 6 steps.



Scheme **3**4. Reagents and conditions: (a) Ref. **27**, 42%; (b) (i) HCO_2H, CH_2Cl_2, 0 ^oC; (ii) EtOAc, aq. $NaHCO_3$, 79%; (c) DIBAL-H, –78 ^oC, 83%; (d) $[H_{25}C_{12}PPh_3]Br$, *n*-BuLi, THF, –78 ^oC to rt, 81%; (e) Pd-C, H_2, EtOAc, rt, 90%; (f) aq. KOH, EtOH, reflux, 77%.

Sudhakar *et al.* (2005)[20] Scheme 35

Sudhakar and co-workers achieved the synthesis of the **jaspine** B from Garner's aldehyde in 9 steps.



Scheme **35**. Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C to rt, 12 h, (b) BnBr, THF, NaH (60% w/w), 0 °C to rt, 12 h, 92%, (c) (i) O_3, DCM, −78 °C, 1 h, $(CH_3)_2S$, (ii) $C_{14}H_{29}MgBr$, THF, 12 h, rt (83% for two steps), (d) 80% AcOH, 0 °C to rt, 12 h, 91%, (e) TBSCl, imidazole, dry DCM, DMAP, 0 °C to rt, 12 h, 86%, (f) (i) MsCl, Et_3N, DCM, 0 °C to rt, 2 h, (ii) TBAF, THF, rt, 2 h, 88% (overall yield 28.3% for compound **122** and 12.1% for compound **123**), (7:3 diastereo-isomeric mixture for **122** and **123**). (g) Na/liq. NH_3, THF, −78 °C, 30 min, 96%, (h) 50% TFA-DCM, rt, 6 h, 87%, (i) Et_3N, Ac_2O, DCM, 0 °C to rt, 4 h, 94%.

PRESENT WORK

3.2.2 Objective

Given the vast chemistry, structural modifications and biological activities associated with the sphingolipids, the synthesis of this class of vicinal amino alcohols has aroused considerable interest among several research groups around the world. Although a few syntheses are reviewed above, several more are getting documented everyday in the literature. This explains the importance of the research work in sphingolipid chemistry.

3.2.3 Results and Discussion

Our retro synthetic approach is shown in Fig. **7**.

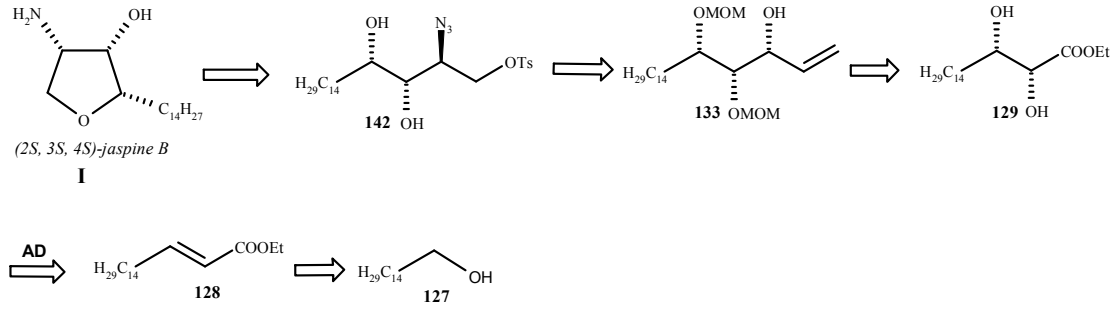
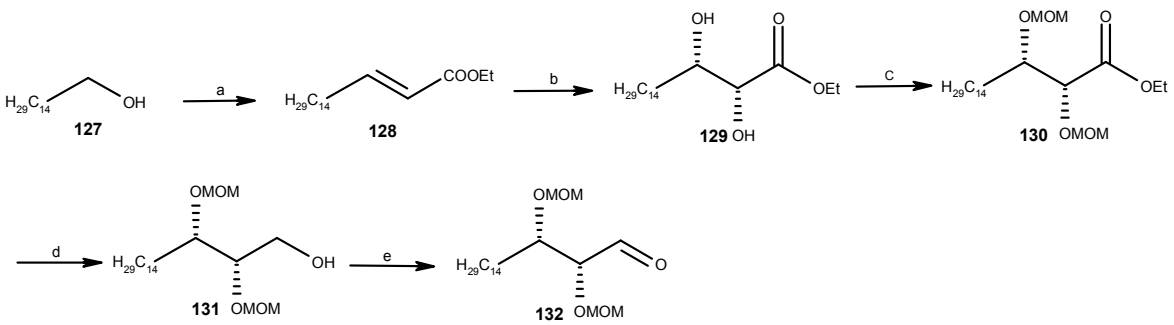


Figure 7 Retrosynthetic pathway towards the synthesis of jaspine-B

We envisioned that the azidodiol **142** could be prepared from the terminal olefin **133**, which in turn could be prepared from the diol **129** after suitable protection *via* a chelation controlled vinyl Grignard reaction. The diol **129** itself could be prepared by Sharpless asymmetric dihydroxylation of α,β-unsaturated olefin ester **128** which in turn could be obtained from the commercially available 1-pentadecanol **127**.

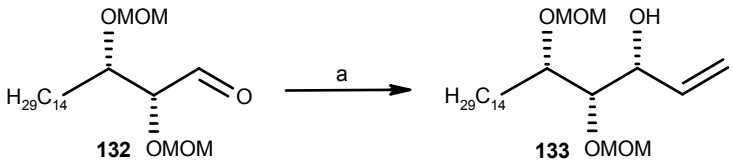
1-pentadecanol **127** after subjecting to oxidation with PCC, followed by a Wittig olefin reaction furnished *trans*- α,β-unsaturated ester **128** in 92% yield. The Olefin **128** was treated with Osmium tetroxide and potassium ferricyanide as a co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under Sharpless Asymmetric Dihydroxylation (SAD) conditions[30] to give diol **129** in 88% yield and 97% ee.[31] Treatment of the diol with MOMCl in the presence of DIPEA gave the di-OMOM derivative **130**, which on reduction with DIBAL-H resulted in the alcohol **131** in 96% yield. The alcohol **131** was oxidized with IBX to afford

the aldehyde **132**. Due to the less-stable nature of the aldehyde **132**, it was immediately taken to the next step as such without further purification (Scheme **36**).



Scheme **36**. Synthesis of intermediate **132** (Sharpless Asymmetric Dihydroxylation method as a key step). Reagents and conditions: (a) (i) PCC, dry DCM, 0 ^{o}C, 3h; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 92%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3[Fe(CN)]_6$, $MeSO_2NH_2$, OsO_4 (0.1 M sol. in toluene), ^{t}-BuOH/H_2O (1:1), 0 ^{o}C, 24 h, 88%; (c) MOMCl, dry DCM, DIPEA, 0 ^{o}C-RT, over night, 96%; (d) DIBAL-H, dry DCM, –10 ^{o}C, 1 h, 96%. (e) IBX, EtOAc, reflux, 3 h.

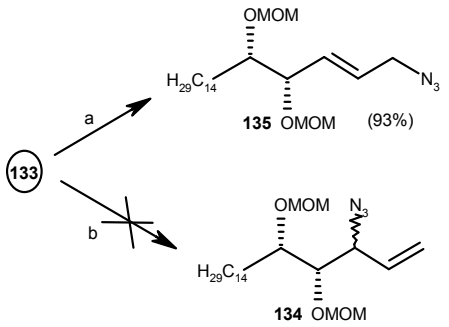
To create the third stereogenic center with the required stereochemistry, a chelation controlled vinyl Grignard reaction[32] was performed (Scheme **37**).



Scheme **37**. Chelation controlled vinyl Grignard reaction: (a) vinyl magnesium bromide, $MgBr_2.OEt_2$, dry THF, –78 ^{o}C, 45 min, 89%.

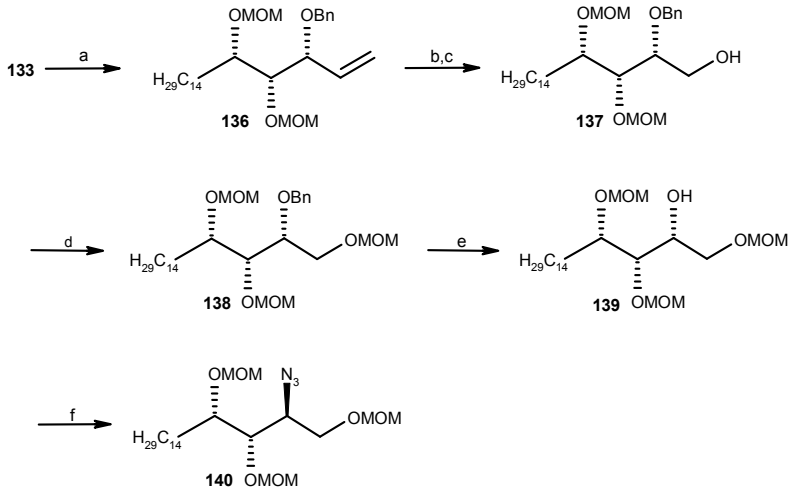
Thus the crude aldehyde **132** was subjected to vinylation reaction using vinyl magnesium bromide in the presence of $MgBr_2.Et_2O$ at –78 ^{o}C to furnish the *syn*-isomer (allylic alcohol **133**) in 89% yield with high diastereomeric excess (de = >95%) as judged by ^{1}H and ^{13}C-NMR spectral analysis of the product.

The allylic alcohol **133** was mesylated using MsCl in the presence of Et_3N and subsequently a nucelophilic displacement with sodium azide furnished the terminal azide **135** only in 93% yield. Also, the one-pot azide formation conducted in DMF medium under the standard conditions[33] (DMF: CCl_4 (7:1), TPP, NaN_3, 75 ^{o}C, 12 h) resulted in no reaction (96% of **133** was recovered back from the reaction medium) as shown in Scheme **38**.



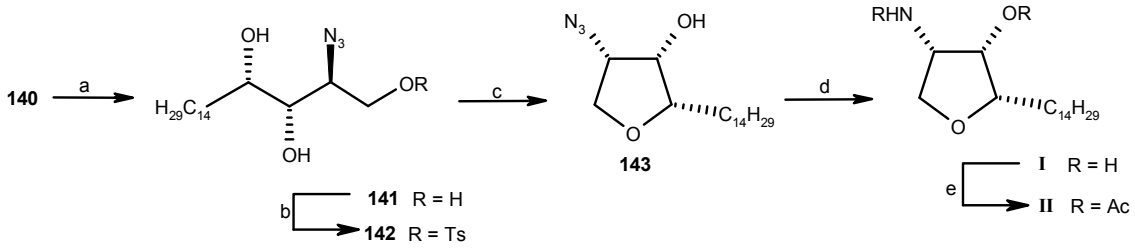
Scheme **38**. *Reagents and conditions*: (a) (i) MsCl, dry CH_2Cl_2, Et_3N, 0 ^oC, 3 h; (ii) NaN_3, dry DMF, 65 ^oC, 12 h, 93%. (b) DMF: CCl_4 (7:1), PPh_3, NaN_3, 75 ^oC, 12 h.

Thus, the allyl alcohol **133** was benzylated to give the terminal olefin **136** in 87% yield. The olefin **136** was subjected to oxidative cleavage[34] followed by reduction with $NaBH_4$ in MeOH to afford the terminal alcohol **137** in 82% yield, which was protected as MOM ether using MOMCl to furnish MOM-protected alcohol **138** in 94% yield and subsequently the benzyl moiety of **138** was deprotected with 5% Pd/C in methanol to give the secondary alcohol **139** in 96% yield. The secondary alcohol **139** was tosylated using *p*-TsCl in the presence of Et_3N and subsequently a nucelophilic displacement with sodium azide furnished the required azide **140** in 83% yield (Scheme **39**).



Scheme **39**. Synthesis of intermediate **140**. Reagents and conditions: (a) BnBr, NaH, THF, 0 ^oC, 4h, 87%; (b) (i) OsO4 (0.1 M sol. in toluene), t-BuOH/THF/H_2O (3:2:1), NMO, over night; (ii) $NaIO_4$, $NaHCO_3$, water, RT, 3 h; (c) $NaBH_4$, MeOH, 0 ^oC-RT, 1 h, 82% from **136**; (d) MOMCl, dry DCM, DIPEA, 0 ^oC-RT, 6 h, 94%; (e) H_2/Pd-C, MeOH, RT, overnight, 96%; (f) (i) *p*-TsCl, dry CH_2Cl_2, Et_3N, DMAP (cat.), 0 ^oC-RT, 3 h; (ii) NaN_3, dry DMF, 95 ^oC, 14 h, 83%.

Deprotection of the MOM groups followed by mono-tosylation furnished the tosyl derivative **142**. The spectral and analytical data of **142** are in conformity with the reported data in the literature.[21] The compound **142** was subjected to cyclization and subsequent reduction, by employing the literature procedure[21] to furnish jaspine B (**I**) with all the desired stereo-centers (Scheme **40**).



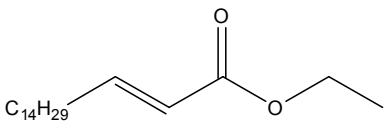
Scheme **40**. Synthesis of (2*S*,3*S*,4*S*)-jaspine B (**I**): (a) aq. HCl, THF, 0 ^{o}C-RT, 5 h; (b) *p*-TsCl, CH_2Cl_2, DMAP, 0 ^{o}C-RT, 4 h, 80% from **140**; (c) K_2CO_3, MeOH, 0 ^{o}C-RT, 6 h, 92%; (d) H_2/Pd-C, MeOH:CH_2Cl_2 (2:1), RT, 7h, 90%; (e) Ac_2O, pyridine, 15 ^{o}C-RT, 24 h, 95%.

3.2.4 Conclusion

In conclusion, we have developed a novel stereoselective synthesis of jaspine B using Sharpless asymmetric dihydroxylation as the source of chirality and a chelation controlled vinylmagnesium Grignard reaction which are the key steps of this stereoselective synthesis. Sharpless asymmetric dihydroxylation of ethyl ester of (E)-2-heptadecenoic acid has been reported for the first time by us in this synthesis and it gave excellent enantioselectivity. Thus, the results described here constitute straight forward selective synthesis of jaspine B in 16 linear steps with an overall yield of % in good to excellent yields in individual reaction steps. This work is already peer reviewed and published in *Tetrahedron: Asymmetry* **2008,** *19***,** 209.

3.2.5 Experimental

Synthesis of *trans*- 2-heptadecenoic acid ethyl ester (128).



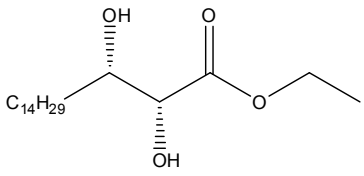
To an ice cold solution of 1-pentadecanol **127** (8.0 g, 35 mmol) in dry CH_2Cl_2 was charged PCC (11.32 g, 52.5 mmol) and the reaction mixture was stirred at 0 ^{o}C for 3 h. The organic solvent was evaporated in *vacuo* and to the residue obtained, was charged 100 mL of diethyl ether, stirred at RT for 15 min and filtered through a short neutral alumina

bed. The organic solvent was dried over Na_2SO_4 and concentrated in *vacuo*. The crude aldehyde (1-pentadecanal) obtained was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl-phosphorane (14.67 g, 42.23 mmol) in dry benzene (120 mL) was added a solution of the above aldehyde in dry benzene (100 mL). The reaction mixture was refluxed for 4 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to afford the α, β-unsaturated olefin **128** as a colorless oily liquid.

Yield	(9.55 g, 92%)
IR($CHCl_3$, υ_{max})	3133, 3020, 2927, 2855, 1732, 1515, 1466, 1389, 1215, 1030, 759, 670 cm^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.0 Hz, 3H), 1.18 (br s, 24H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.33-1.42 (m, 2H), 2.06-2.17 (m, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 5.69 (td, *J* = 15.1, 1.6 Hz, 1H), 6.88-6.97 (m, 1H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ 14.2, 14.3, 22.7, 28.0, 29.2, 29.4, 29.5, 29.6 (several overlapping peaks), 31.9, 32.2, 60.1, 121.2, 149.6, 166.8.
Elemental Analysis	Anal. Calcd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24%; Found C, 76.88; H, 12.31%.

Synthesis of (2*R*,3*S*)-2,3-dihydroxyheptadecanoic acid ethyl ester (129).

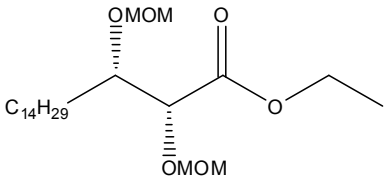


To a mixture of $K_3[Fe(CN)]_6$ (15.99 g, 48.55 mmol), K_2CO_3 (6.70 g, 48.55 mmol) and $(DHQ)_2PHAL$ (13.6 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 80 mL) cooled to 0 °C, was added OsO_4 as a 0.1 M solution in toluene (0.70 mL, 0.4 mol %) followed by methanesulfonamide (1.54 g, 16.2 mmol). After stirring for 30 min at 0 °C, the (*E*)-α,β-unsaturated ester **128** (4.80 g, 16.19 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 (22 g). Stirring was continued for 60 min and the solution was extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated.

The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) to afford the diol **129** as a colorless solid.

Yield	(4.71 g, 88%)
M. Pt (^{o}C)	56-58 °C
$[\alpha]_D^{25}$	-7.06^o (*c* 0.8, $CHCl_3$)
IR($CHCl_3$, υ_{max})	3400, 3133, 3020, 2927, 2855, 1732, 1515, 1466, 1389, 1215, 1030, 759, 670 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.0 Hz, 3H), 1.18 (br s, 24H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.49-1.57 (m, 2H), 2.0 (br s, 2H), 3.78 (dt, *J* = 7.1, 2.1 Hz, 1H), 4.01 (dd, *J* =2.1 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 14.1, 22.6, 25.7, 29.3, 29.5 (several overlapping peaks), 29.6, 31.9, 33.7, 61.9, 72.6, 73.1, 173.7
Elemental Analysis	Anal. Calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59%; Found C, 69.12; H, 11.50%

Synthesis of (2*R*,3*S*)-2,3-bis(methoxymethoxy)-heptadecanoic acid ethyl ester (130).

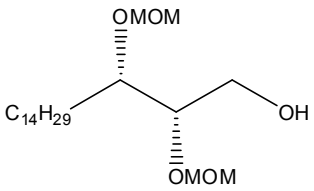


To a CH_2Cl_2 solution of protected diol **129** (4.50 g, 13.62 mmol) taken into a flame dried RB flask under argon atmosphere. DIPEA (9.5 mL, 54.48 mmol) was charged slowly over 5 min at RT and then 3.20 mL of MOMCl (42.22 mmol, 3.1 eq) was slowly added to the reaction mixture at to 0 ^{o}C over a period of 10 min. The reaction was stirred at RT for about 12 h and quenched with 20 mL of water. The organic layer was separated, dried over Na_2SO_4 and concentrated in *vacuo*. The residue obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (20:1) to give **130** as a pale yellow liquid.

Yield	(5.47 g, 96%)
$[\alpha]_D^{25}$	$+43.6^o$ (*c* 1.0, $CHCl_3$)
IR($CHCl_3$, υ_{max})	2927, 2855, 1748, 1466, 1370, 1216, 1153, 1112, 1032, 759, 667 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.18 (br s, 24H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.55-1.59 (m, 2H), 3.28 (s, 3H), 3.34 (s, 3H), 3.83-3.92 (m, 1H), 4.10-4.18 (m, 3H), 4.59 (d, *J* = 2.4 Hz, 2H), 4.66 (d, *J* = 3.2 Hz, 2H)
^{13}C NMR (100 MHz, $CDCl_3$)	δ 14.1, 14.2, 22.7, 25.4, 29.3, 29.5, 29.6 (several overlapped peaks), 30.9, 31.9, 55.7, 56.2, 60.9, 76.8, 78.4, 96.4, 96.5, 171.0
Elemental Analysis	Anal. Calcd for $C_{23}H_{46}O_6$: C, 65.99; H, 11.08%; Found C, 65.90; H, 11.15%.

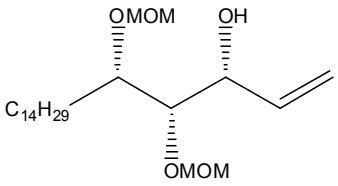
Synthesis of (2*S*,3*S*)-2,3-bis(methoxy-methoxy)heptadecan-1-ol (131).



To a solution of **130** (5.30 g, 12.66 mmol) in dry CH_2Cl_2 (75 mL) at –10 ^oC was added drop wise DIBAL-H (19 mL, 18.98 mmol, 1.0 M solution in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 1 h, then re-cooled to 0 ^oC and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of Celite and concentrated in *vacuo*. Silica gel column chromatography of the crude product (residue) using petroleum ether/EtOAc (10:3) as eluent gave alcohol **131** as a colourless oil.

Yield	(4.58 g, 96%)
$[\alpha]_D^{25}$	–10.53^o (*c* 1.0, $CHCl_3$)
IR($CHCl_3$, υ_{max})	3300, 3019, 2957, 2928, 2856, 1463, 1378, 1261, 1216, 1099, 1026, 838, 759, 669 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.18 (br s, 24H), 1.55-1.59 (m, 2H), 1.88 (br s, 1H), 3.34 (s, 3H), 3.37 (s, 3H), 3.59-3.67 (m, 4H), 4.61-4.72 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.8, 29.3, 29.5, 29.6 (several overlapping peaks), 30.4, 31.9, 55.8, 55.9, 62.7, 78.4, 82.4, 96.8, 97.7.
Elemental Analysis	Anal. Calcd for $C_{21}H_{44}O_5$: C, 66.98; H, 11.78%; Found C, 66.89; H, 11.87%.

Synthesis of (3*R*,4*S*,5*S*)-4,5-bis(methoxymethoxy)-nonadec-1-en-3-ol (133).



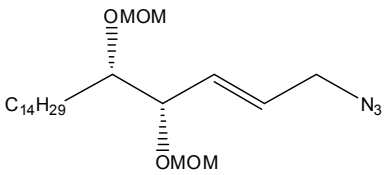
A mixture of 4.10 g of alcohol **131** (10.89 mmol) and 4.57 g of IBX (16.34 mmol) in 40 mL of EtOAc was refluxed for 3 h. The reaction mixture was filtered off and washed with excess of EtOAc. The solvent was evaporated from the filtrate in vacuo to afford the crude aldehyde **132** which was then, directly taken to the next step without any further purification.

The crude aldehyde **132** dissolved in CH_2Cl_2 under argon was added *via* cannula to a stirred suspension of $MgBr_2.Et_2O$ at 0 °C. After stirring for 10 min, the flask was cooled to –78 °C and vinyl magnesium bromide (11 mL, 10.89 mmol; purchased from Aldrich as 1.0 M solution in THF) was added slowly at –78 °C and the reaction was stirred further at this temperature for 45 min. Then, the solvent was removed in *vacuo*, the residue was diluted with CH_2Cl_2 and allowed to warm to 0 °C. Then, the reaction mixture was diluted with saturated aq. NH_4Cl and extracted with CH_2Cl_2 (3X50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/ EtOAc (10:1) as eluent gave *syn*- isomer of the allylic alcohol **133** as a pale yellow viscous oil.

Yield	(3.90 g, 89%)
$[\alpha]_D^{25}$	$+1.85^o$ (*c* 0.56, $CHCl_3$)
IR($CHCl_3$, υ_{max})	3450, 3019, 2927, 2855, 1466, 1378, 1216, 1030, 761, 669 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.18 (br s, 24H), 1.55-1.59 (m, 2H), 1.8 (br s, 1H), 3.06 (dd, *J* = 4.4 Hz, 1H), 3.33 (s, 3H), 3.37 (s, 3H), 3.58-3.66 (m, 1H), 4.21-4.28 (m, 1H), 4.61-4.76 (m, 4H), 5.13 (td, *J* = 1.6, 10.3 Hz, 1H), 5.30 (td, *J* = 1.53, 11 Hz, 1H), 5.81-5.97 (m, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.7, 29.3, 29.5 (several overlapping peaks), 29.6, 30.9, 31.9, 55.9, 56.3, 71.8, 78.4, 83.7, 96.7, 98.5, 116.3, 137.7
Elemental Analysis	Anal. Calcd for $C_{23}H_{46}O_5$: C, 68.61; H, 11.52%. Found:

	C, 68.66; H, 11.61%.
LC-MS (ESI-TOF)	*m/z*: 425.04 (M+Na)

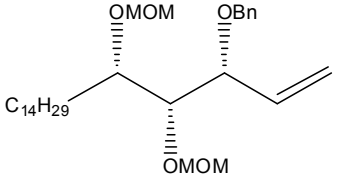
Synthesis of *trans*-(5S,6S)-5-((E)-3-azidoprop-1-enyl)-6-tetradecyl-2,4,7,9-tetraoxa-decane (135).



To the CH_2Cl_2 solution of **133** (250 mg, 0.621 mmol) under argon, Et_3N (0.18 mL, 1.24 mmol) was added slowly at RT. The reaction flask was cooled to 0 ^oC and MsCl (0.06 mL, 0.714 mmol) was added. The reaction mixture was stirred at 10 ^oC for about 2 h and quenched with 2 mL of water. The organic solvent was separated, dried over Na_2SO_4, concentrated in *vacuo* and the residue obtained was dissolved in 2 mL of DMF. To this, NaN_3 (0.049 g, 0.745 mmol) was added and the reaction mixture was heated to 65 ^oC under argon atmosphere for 12 h. Then, the reaction mixture was concentrated to half of its volume *in vacuo*, the residue obtained was dissolved in 10 mL of EtOAc and washed with brine solution. The organic solvent was separated, dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was then purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) to afford the azide **135** as a pale yellow oily compound.

Yield	(0.247, 93%)
$[\alpha]_D^{25}$	+ 8.25^o (*c* 0.15, $CHCl_3$).
IR($CHCl_3$, υ_{max})	2959, 2927, 2855, 2103, 1262, 1216, 1150, 1098, 1027, 760, 669 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.18 (br s, 24H), 1.45-1.57 (m, 2H), 3.30 (s, 3H), 3.33 (s, 3H), 3.47-3.55 (m, 1H), 3.73 (d, *J* = 4.6 Hz, 2H), 4.08 (t, *J* = 5.1 Hz, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.60-4.70 (m, 3H), 5.69-5.74 (m, 2H)
^{13}C NMR (100 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.5, 29.4, 29.6 (several overlapping peaks), 29.7, 30.7, 31.4, 31.9, 36.5, 52.3, 55.7, 55.8, 79.8, 94.3, 96.9, 127.0, 132.2, 162.5
Elemental Analysis	Anal. Calcd. for $C_{23}H_{45}N_3O_4$: C, 64.60; H, 10.61; N, 9.83%. Found: C, 64.68; H, 10.55; N, 9.90%

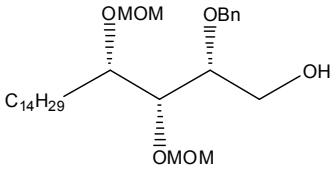
Synthesis of (5*R*,6*S*)-5-((R)-1-(benzyloxy)allyl)-6-tetradecyl-2,4,7,9-tetraoxadecane (136).



To the DMF solution of the allyl alcohol **133** (3.80 g, 9.44 mmol) under argon, 0.680 g of NaH (50% assay, 14.16 mmol) was added slowly at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^{o}C. To this was added slowly the DMF solution of BnBr (1.3 mL of BnBr in 5 mL of DMF, 10.86 mmol), tetra *n*-butylammonium iodide (0.348 g, 0.94 mmol) and the stirring was further continued for 4 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C and was concentrated to half of its volume *in vacuo*. To this was charged diethyl ether and the mixture was stirred well for 10 min. The organic layer was separated, dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was then purified by silica gel column chromatography using petroleum ether/EtOAc (20:1) to afford pure terminal olefin **136** as a colorless oily liquid.

Yield	(4.05g, 87%)
$[\alpha]_D^{25}$	-2.10^{o} (*c* 0.80, $CHCl_3$)
IR($CHCl_3$, υ_{max})	3019, 2927, 2854, 1466, 1215, 1150, 1099, 1027, 927, 757, 669 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.18 (br s, 24H), 1.45-1.57 (m, 2H), 3.23 (s, 3H), 3.34 (s, 3H), 3.49 (m, 2H), 3.92-4.00 (m, 1H), 4.27 (d, *J* = 10.5 Hz, 1H), 4.42-4.53 (m, 1H), 4.57 (d, *J* = 2.1 Hz, 1H), 4.60 (s, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 5.26 (d, *J* = 3.8 Hz, 1H), 5.70-5.88 (m, 1H), 7.24 (br s, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.3, 29.3, 29.6 (several overlapping peaks), 29.7, 31.1, 31.9, 55.8, 56.2, 70.6, 78.4, 80.5, 81.0, 96.9, 98.4, 118.8, 127.5, 127.7, 127.9, 128.3, 135.4, 138.2
Elemental Analysis	Anal. Calcd for $C_{30}H_{52}O_5$: C, 73.13; H, 10.64%; Found C, 73.22; H, 10.73%

Synthesis of (2*R*,3*R*,4*S*)-2-(benzyloxy)-3,4-bis-(methoxymethoxy)-octadecan-1-ol (137).



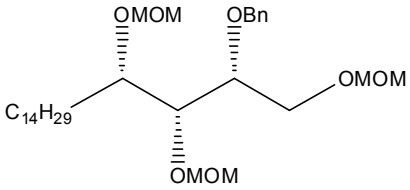
The oxidative cleavage of the terminal olefin **136** (3.50 g, 7.08 mmol) was performed using standard conditions to afford the crude aldehyde (3.01 g) as a pale yellow liquid.

IR ($CHCl_3$, υ_{max}): 2925, 2854, 1732, 1455, 1377, 1212, 1151, 1102, 1029, 734, 698 cm^{-1}

The crude aldehyde obtained was used as such in the next step without further purification. To the methanolic solution of the above crude aldehyde, $NaBH_4$ (250 mg, 7.08 mmol) was added at 0 ^oC. The reaction mixture was further stirred at RT for 1 h and was concentrated to half of its volume *in vacuo*. Then, the reaction mixture was quenched with brine solution and the product was extracted with diethyl ether (3X25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the crude alcohol, which was then purified by silica-gel column chromatography using petroleum ether/EtOAc (7:1) to afford pure alcohol **137** as a pale yellow oily liquid.

Yield	(2.89g, 82%)
$[\alpha]_D^{25}$	-15.49^o (*c* 2.0, $CHCl_3$)
IR($CHCl_3$, υ_{max})	3459, 3018, 2926, 2854, 1466, 1455, 1215, 1150, 1101, 1027, 919, 758, 668 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.18 (br s, 24H), 1.51-1.60 (m, 2H), 3.30 (s, 3H), 3.36 (s, 3H), 3.59-3.77 (m, 5H), 4.51-4.73 (m, 6H), 7.26 (br s, 5H)
^{13}C NMR (100 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.2, 29.3, 29.5, 29.6 (several overlapping peaks) 29.7, 30.7, 31.9, 55.9, 56.2, 60.8, 72.9, 78.4, 79.1, 79.3, 96.9, 98.8, 128.0, 128.4, 138.0.
Elemental Analysis	Anal. Calcd for $C_{29}H_{52}O_6$: C, 70.12; H, 10.55%. Found: C, 70.19; H, 11.55%.
LC-MS (ESI-TOF)	*m/z*: 518.86 (M+Na)

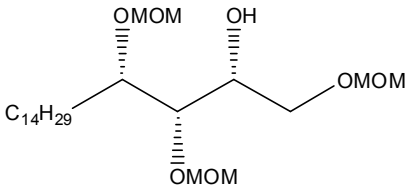
Synthesis of (5*S*,6*R*,7*R*)-7-(benzyloxy)-6-(methoxymethoxy)-5-tetradecyl-2,4,9,11-tetraoxadodecane (138).



To the CH_2Cl_2 solution containing **137** (1 g, 2.0 mmol) under argon atmosphere, DIPEA (0.70 mL, 4.0 mmol) was charged at RT and then, MOMCl (1.8 mL, 2.2 mmol) was added to the reaction mixture at to 0 ^oC. The reaction mixture was stirred at RT for 6 h and quenched with 0.5 mL of cold water. The organic layer was separated, dried over Na_2SO_4 and concentrated in *vacuo*. The residue obtained was purified by silica-gel column chromatography using petroleum ether/EtOAc (9:1) to give triOMOM **138** as a colorless oily liquid.

Yield	(1.02g, 94%)
$[\alpha]_D^{25}$	+ 5^o (*c* 0.5, $CHCl_3$)
IR($CHCl_3$, υ_{max})	2925, 2854, 1466, 1261, 1213, 1151, 1106, 1034, 919, 801, 698, 734 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.10-1.26 (m, 24H), 1.45-1.48 (m, 2H), 3.30 (s, 6H), 3.34 (s, 3H), 3.60-3.76 (m, 5H), 4.52-4.84 (m, 8H), 7.16-7.33 (m, 5H)
^{13}C NMR (100 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.5, 29.3, 29.6 (several overlapping peaks), 29.8, 30.9, 31.9, 55.3, 55.9, 56.2, 67.6, 73.1, 77.9, 78.6, 96.6, 96.8, 98.5, 127.6, 128.0, 128.3, 138.4
Elemental Analysis	Anal. Calcd for $C_{31}H_{56}O_7$: C, 68.85; H, 10.44%. Found: C, 68.80; H, 10.51%.
LC-MS (ESI-TOF)	*m/z*: 562.83 (M+Na)

Synthesis of (6*R*,7*S*,8*S*)-7-(methoxymethoxy)-8-tetradecyl-2,4,9,11-tetraoxadodecan-6-ol (139).

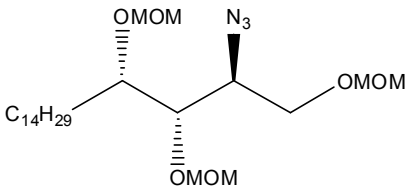


To a solution of **138** (0.760 g, 1.41 mmol) in MeOH (10 mL) was added a catalytic amount of 5% Pd/C and the reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm. balloon pressure) for 12 h. The reaction mixture was then filtered through a pad of Celite and the solvent was removed under reduced pressure to give the crude product, which was then purified by

column chromatography over silica-gel using petroleum ether/EtOAc (8:2) as eluent to give **139** as a pale yellow oil.

Yield	(0.608g, 96%)
$[\alpha]_D^{25}$	-2.3^o (*c* 1.6, $CHCl_3$)
IR ($CHCl_3$, υ_{max})	3400, 3019, 2926, 1519, 1031, 909, 758, 669, 625 cm^{-1}.
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.82 (t, *J* = 6.9 Hz, 3H), 1.19 (br s, 24H), 1.54-1.59 (m, 2H), 2.10 (br s, 1H), 3.32 (br s, 6H), 3.37 (s, 3H), 3.56-3.60 (m, 2H), 3.64-3.69 (m, 2H), 3.88-3.93 (m, 1H), 4.61 (d, *J*= 5.2 Hz, 2H), 4.64-4.75 (m, 3H), 4.82 (d, *J*= 6.5 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.7, 29.3, 29.6 (several overlapping peaks), 29.7, 30.6, 31.9, 55.4, 55.9, 56.2, 69.7, 70.0, 78.3, 80.1, 96.6, 97.0, 98.4
Elemental Analysis	Anal. Calcd for $C_{24}H_{50}O_7$: C, 63.96; H, 11.18%. Found: C, 63.96; H, 11.18%.
LC-MS (ESI-TOF)	*m/z*: 473.21 (M+Na)

Synthesis of (5*S*,6*S*,7*S*)-7-azido-6-(methoxymethoxy)-5-tetradecyl-2,4,9,11-tetraoxadodecane (140).

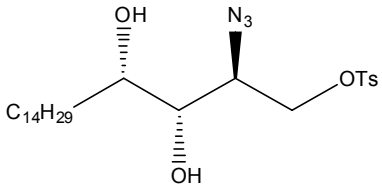


To a solution of **139** (0.550 g, 1.22 mmol) in dry CH_2Cl_2 (4 mL) at 0 ^oC Et_3N (0.2 mL, 1.47 mmol), *p*-tosyl chloride (254 mg, 1.33 mmol), and DMAP (3 mg, 2 mol %) were added. The reaction mixture was stirred at room temperature for 3 h and then poured into DCM/H_2O mixture. The organic phase was separated and the aqueous phase was extracted with DCM (3 X 10 mL). The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to a white solid, which was dissolved in dry DMF (3 mL). To this, NaN_3 (0.099 g, 1.52 mmol) was added and the reaction mixture was heated to 95 ^oC under argon atmosphere for about 14 h, and then cooled to room temperature. The reaction mixture was concentrated to half of its volume *in vacuo*. The residue obtained was dissolved in 8 mL of EtOAc and washed with brine solution. The organic solvent was separated, dried over Na_2SO_4 and

concentrated in *vacuo* to furnish crude azide **140**, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) as eluent to give the azide **140** as a yellow oil.

Yield	(0.482 g, 83%)
$[\alpha]_D^{25}$	$+7^{o}$ (*c* 0.5, $CHCl_3$)
IR ($CHCl_3$, υ_{max})	2927, 2103, 1519, 1030, 910, 756, 669, 625 cm^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.19 (br s, 24H), 1.52-1.61 (m, 2H), 3.32 (s, 6H), 3.37 (s, 3H), 3.60-3.92 (m, 5H), 4.60-4.75 (m, 6H)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.7, 29.3, 29.6 (several overlapping peaks), 29.7, 30.6, 31.9, 55.4, 55.9, 56.2, 67.1, 69.7, 78.3, 80.1, 96.6, 97.0, 98.4.
Elemental Analysis	Anal. Calcd for $C_{24}H_{49}N_3O_6$: C, 60.60; H, 10.38; N, 8.83%; Found C, 60.52; H, 10.44; N, 8.90%

Synthesis of (2S,3S,4S)-2-azido-3,4-dihydroxyoctadecyl 4-methylbenzenesulfonate (142).



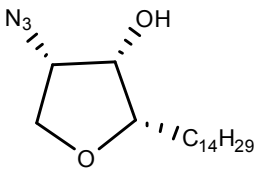
To a solution of **140** (0.236 g, 0.50 mmol) in THF (3 mL) was added 10% aq. HCl (2 mL) at 10 °C and stirred at room temperature for 5 h. The reaction mixture was quenched by the addition of a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3X10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in *vacuo* to afford the crude azidotriol **141** as a residue. The residue obtained was used as such without further purification in the next step.

To a solution of the above crude azidotriol **141** in CH_2Cl_2 (3 mL) was added Et_3N (0.15 mL) and *p*-toluenesulphonyl chloride (0.094 g, 0.50 mmol) at 0 °C and stirred at room temperature for 4 h. The reaction mixture was quenched by addition of water (3 mL), extracted with ethyl acetate (3X10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the product, which was then purified by silica gel column chromatography using EtOAc/petroleum ether (3.5:6.5) to afford pure tosylated derivative

142 as a white solid. The spectral and analytical data were in good agreement with that of reported in literature.[21]

Yield	(0.197 g, 80% for two steps)
mp (^{o}C)	64-65 °C (Lit.[21] 63-64 ^{o}C).
$[\alpha]_D^{25}$	+14.1^o (*c* 0.45, $CHCl_3$) {Lit.[21] = +14^o (*c* 0.4, $CHCl_3$)}.
IR ($CHCl_3$, υ_{max})	3373, 2925, 2103, 1469, 1192, 1185, 1030, 910, 756, 669, 625 cm^{-1}.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.42 (dd, *J* =11.0, 3.1 Hz, 1H), 4.30-4.20 (m, 1H), 3.79-3.72 (m, 2H), 3.35 (m, 1H), 2.45 (s, 3H), 1.57-1.18 (m, 26H), 0.88 (t, *J* = 7.2 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 14.1, 21.7, 22.7, 25.6, 29.3, 29.4, 29.5, 29.6 (several overlapping peaks), 29.7, 31.9, 34.0, 61.6, 69.8, 70.0, 71.6, 128.0, 130.0, 132.4, 145.3.
Elemental Analysis	Anal. Calcd for $C_{25}H_{43}N_3O_5S$: C, 60.33; H, 8.71; N, 8.44; S, 6.44%; Found C, 60.28; H, 8.77; N, 8.49; S, 6.35%.

(2*S*,3*S*,4*S*)-4-azido-2-tetradecyltetrahydrofuran-3-ol (143).

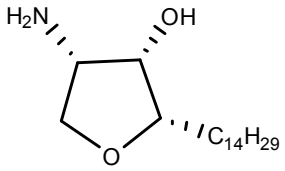


To a solution of **142** (0.180 g, 0.36 mmol) in MeOH (5 mL) was added K_2CO_3 (0.105 g, 0.75 mmol) at 0 ^{o}C and the reaction mixture was stirred at RT for 6 h. The volatiles were removed under reduced pressure. Diethyl ether (20 mL) was added to the residue and filtered through a short bed of Celite and washed with diethyl ether (10 mL). Evaporation of the solvent followed by a silica gel column chromatography (5:1) gave pure azido alchol **143** as a colorless solid.

Yield	(0.117 g, 92%).
M. Pt (^{o}C)	99.6-100.2 °C [lit.[23]: 99.4-100.1 ^{o}C].
$[\alpha]_D^{25}$	+16.4^o (*c* 1.0, $CHCl_3$) [lit.: +16.7 (*c* 1.0, $CHCl_3$)].
IR ($CHCl_3$, υ_{max})	3335, 2917, 2850, 2104, 1467, 1215, 1017, 722, 625 cm^{-1}.
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.23-1.44 (m, 24H), 1.57-1.65 (m, 2H), 2.11 (brs, 1H), 3.74-3.79 (m, 1H), 3.84 (dd, *J* =

	9.0, 7.0 Hz, 1H), 3.95 (dd, *J* = 9.0, 7.5 Hz, 1H), 4.00-4.15 (m, 1H), 4.18-4.22 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$)	δ 14.1, 22.7, 25.7, 29.4, 29.6 (several overlapping peaks), 29.7, 31.9, 63.7, 68.5, 72.5, 82.1.
Elemental Analysis	Anal. Calcd. for $C_{18}H_{35}N_3O_2$: C, 66.42; H, 10.84; N, 12.91%. Found: C, 66.36; H, 10.77; N, 12.99%.

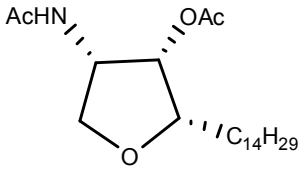
Synthesis of 4-amino-2-tetradecyltetrahydrofuran-3-ol (jaspine B or Pachastrissamine) I.



To a solution of **143** (0.049 g, 0.15 mmol) in MeOH (2 mL) and CH_2Cl_2 (1 mL) was added a catalytic amount of 5% Pd/C and the reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm. balloon pressure) for 7 h. The reaction mixture was then filtered through a pad of Celite and washed with CH_2Cl_2/MeOH (1:1, 10 mL). The solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography over silica gel using CH_2Cl_2/MeOH (9:1) containing 1% NH_4OH as eluent to give Pachastrissamine (Jaspine B) as an amorphous solid. The spectral and analytical data of jaspine B **I** are in good conformity with the reported values.[18]

Yield	(41 mg, 90%).
$[\alpha]_D^{25}$	+17.7 ^{o} (*c* 0.40, EtOH) {lit.[18] $[\alpha]_D^{25}$ = +18 (c 0.1, EtOH)}
IR ($CHCl_3$, υ_{max})	3350, 2926, 1469, 1030, 726 cm^{-1}.
^{1}H-NMR (200 MHz, CD_3OD+$CDCl_3$)	δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.25-1.39 (m, 24H), 1.57-1.66 (m, 2H), 2.10 (brs, 3H), 3.49-3.53 (m, 1H), 3.63-3.67 (m, 1H), 3.69-3.75 (m, 1H), 3.84-3.88 (m, 1H), 3.89-3.94 (m, 1H).
^{13}C NMR (100 MHz, CD_3OD)	δ 14.1, 22.7, 25.7, 29.3, 29.6 (several overlapping peaks), 29.7, 30.6, 31.9, 54.4, 71.8, 72.3, 83.2.
Elemental Analysis	Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68%; Found C, 72.26; H, 12.51; N, 4.62%.

Synthesis of 4-acetamido-2-tetradecyltetrahydrofuran-3-yl acetate, II.



To a solution of jaspine B **I** (0.030 g, 0.10 mmol) in pyridine (2 mL) was added acetic anhydride (0.5 mL, 6 mmol, excess) at 15 ^{o}C. Then, the reaction mixture was stirred at RT for 24 h. The volatiles were removed in *vacuo* and to the residue EtOAc (15 mL) was added and the organic layer was washed with aq. NaCl solution, dried over Na_2SO_4 and concentrated in *vacuo*. Silica-gel column chromatography of the residue using toluene/EtOAc (3:1, v/v) as an eluent gave diacetyl derivative of jaspine B **II** as a white solid.

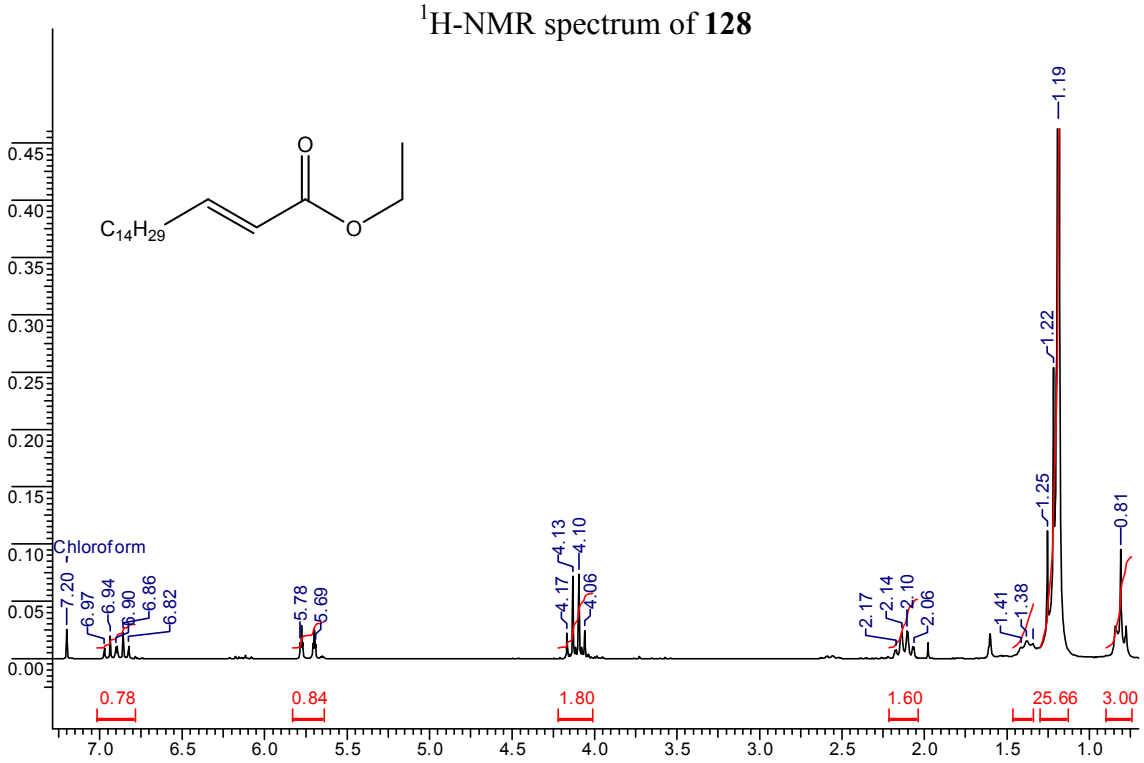
Yield	(0.036 g, 95%)
mp	96-98 ^{o}C [lit.[25]: 95-98 ^{o}C].
$[\alpha]_D^{25}$	–28.1 ^{o} (*c* 1.2, $CHCl_3$) [lit.[18]: –28.4 (*c* 1.0, $CHCl_3$)].
IR ($CHCl_3$, υ_{max})	2918, 2850, 1739, 1651, 1549, 1469, 1375, 1236, 1215, 1082, 1052, 948, 719 cm^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 0.87 (t, *J* = 7.1 Hz, 3H), 1.24 (br s, 24H), 1.44-1.51 (m, 2H), 1.98 (s, 3H), 2.16 (s, 3H), 3.54-3.62 (m, 1H), 3.85-3.93 (m, 1H), 4.02-4.10 (m, 1H), 4.75 (ddd, *J* = 8.1, 8.2, 5.2, 7.9 Hz, 1H), 5.34 (dd, *J* = 5.4, 3.3 Hz, 1H), 5.59 (d, *J* = 7.8 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	δ 14.1, 20.6, 22.6, 23.1, 25.9, 29.26, 29.3, 29.4, 29.5, 29.55, 29.61, 29.64, 31.9, 51.3, 69.9, 73.5, 81.2, 169.8
Elemental Analysis	Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65%; Found: C, 68.81; H, 10.70; N, 3.72%.

Table 2

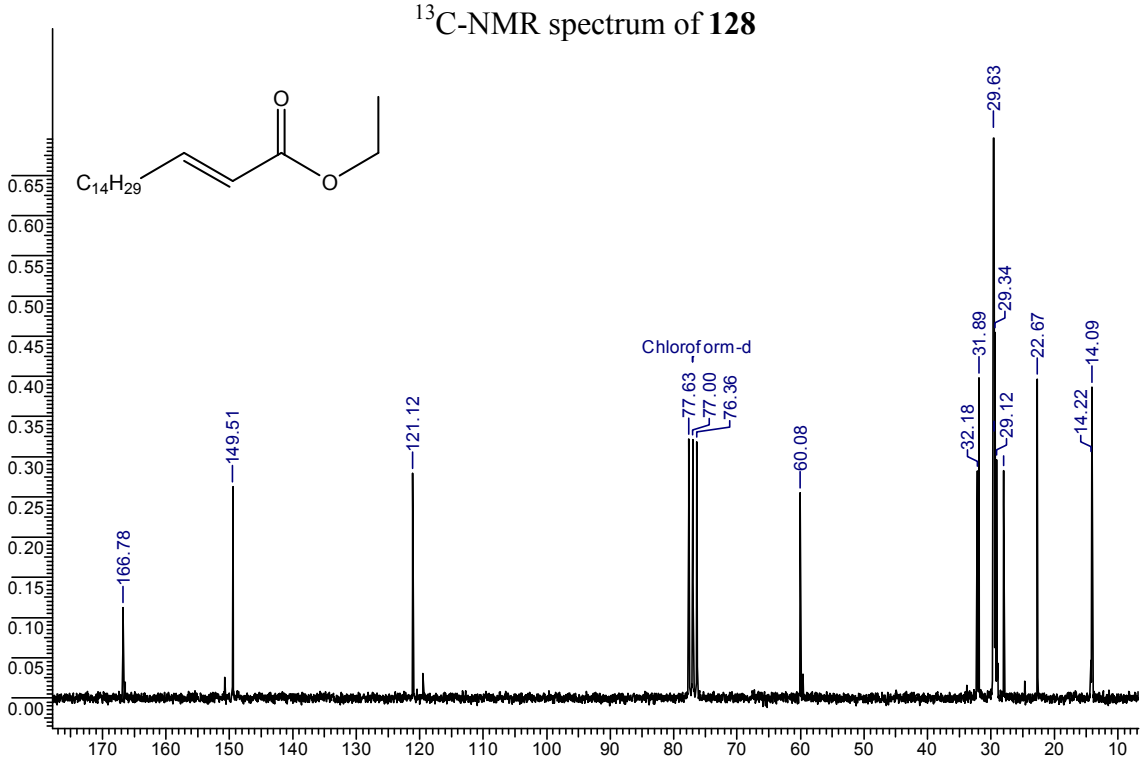
^{1}H & ^{13}C spectra of some selected compounds are given below:

S No.	Spectra
1	^{1}H & ^{13}C spectra of **128**
2	^{1}H & ^{13}C spectra of **129**
3	^{1}H & ^{13}C spectra of **130**
4	^{1}H & ^{13}C spectra of **136**
5	^{1}H & ^{13}C spectra of **137**
6	^{1}H & ^{13}C spectra of **138**
7	^{1}H & ^{13}C spectra of **139**
8	^{1}H & ^{13}C spectra of jaspine B **(I)**
9	^{1}H & ^{13}C spectra of jaspine B diacetate**(II)**

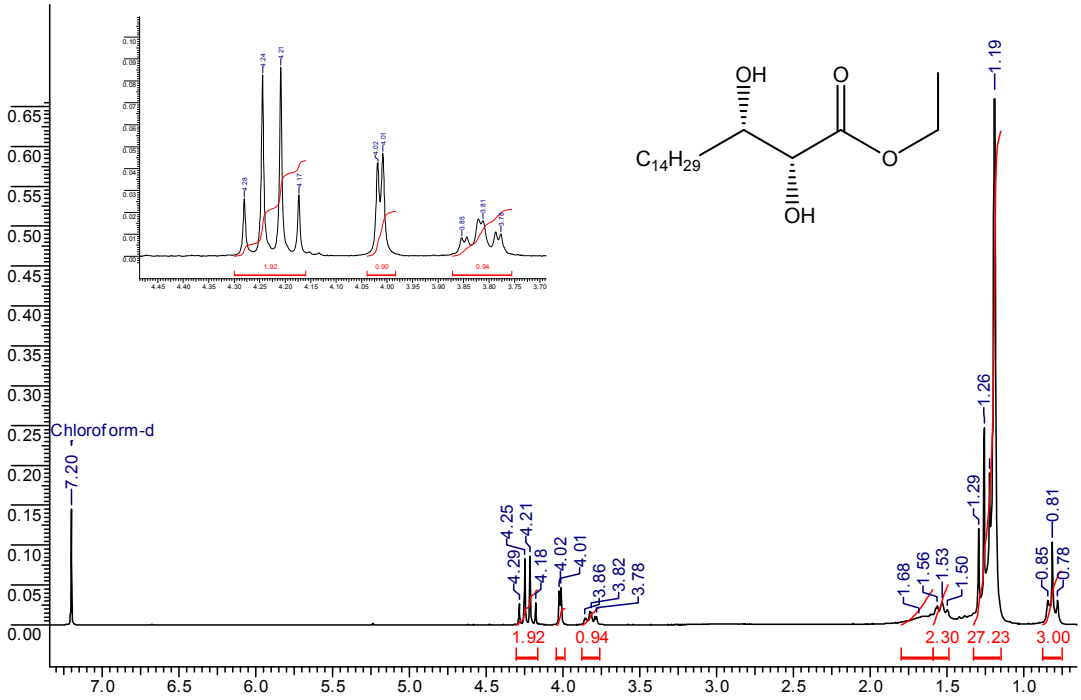
^{1}H-NMR spectrum of **128**



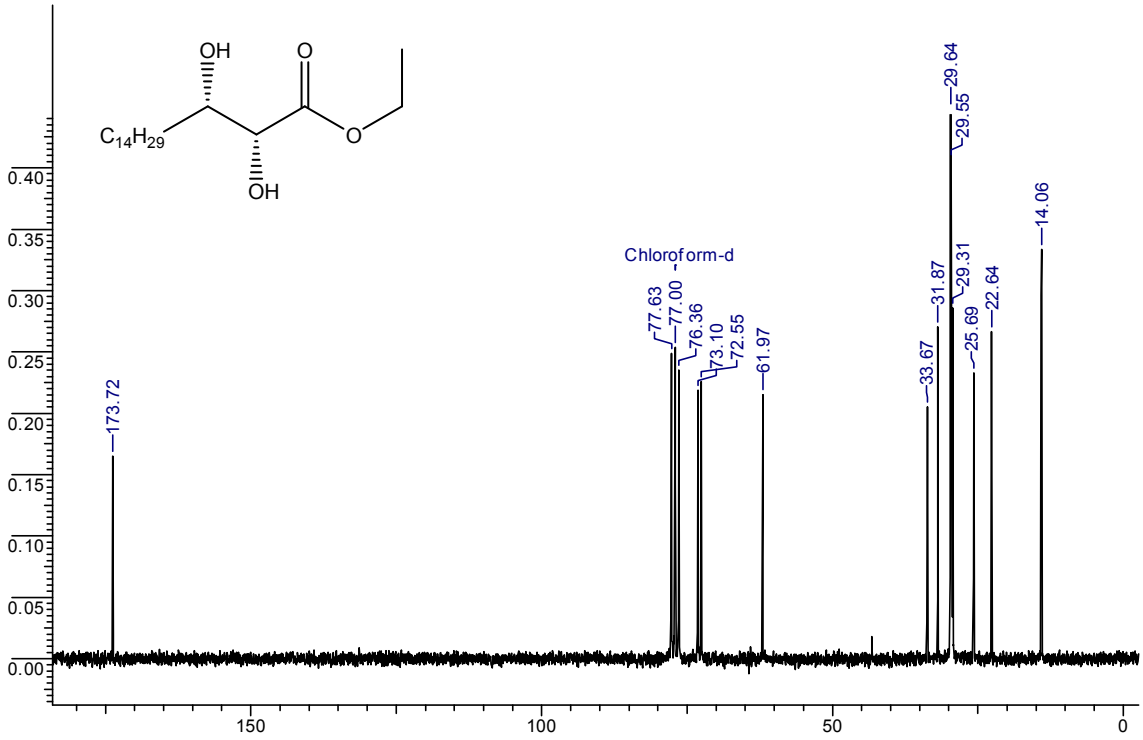
^{13}C-NMR spectrum of **128**



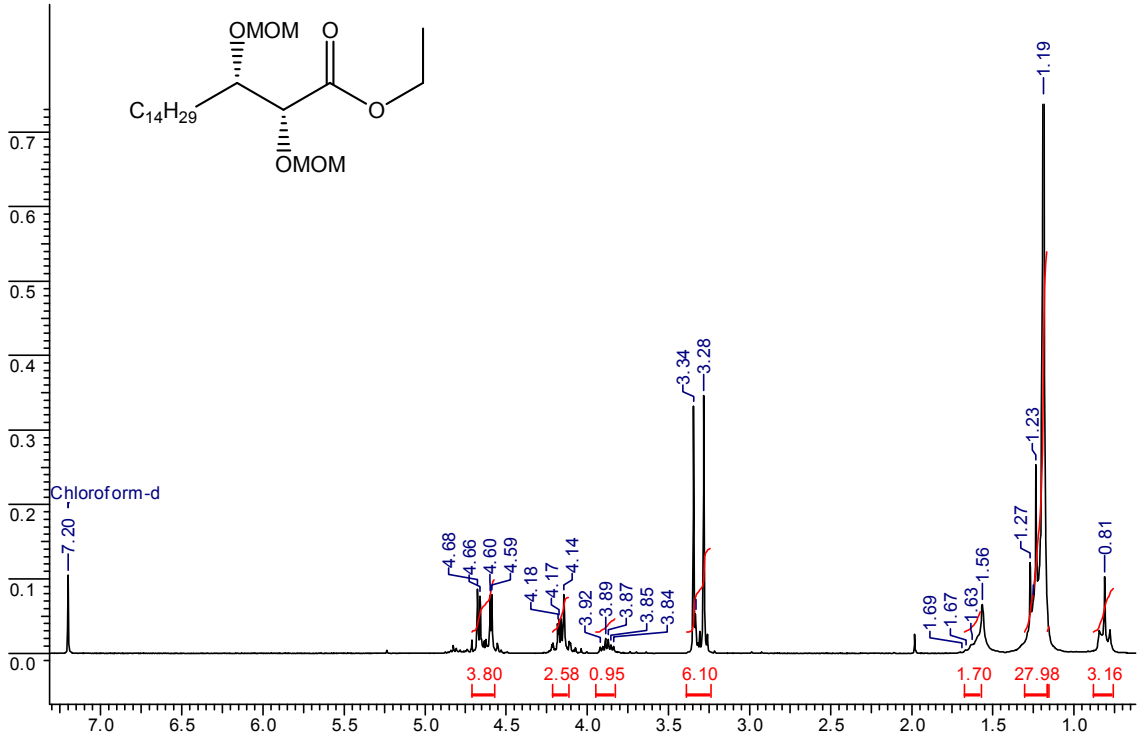
^{1}H-NMR spectrum of **129**



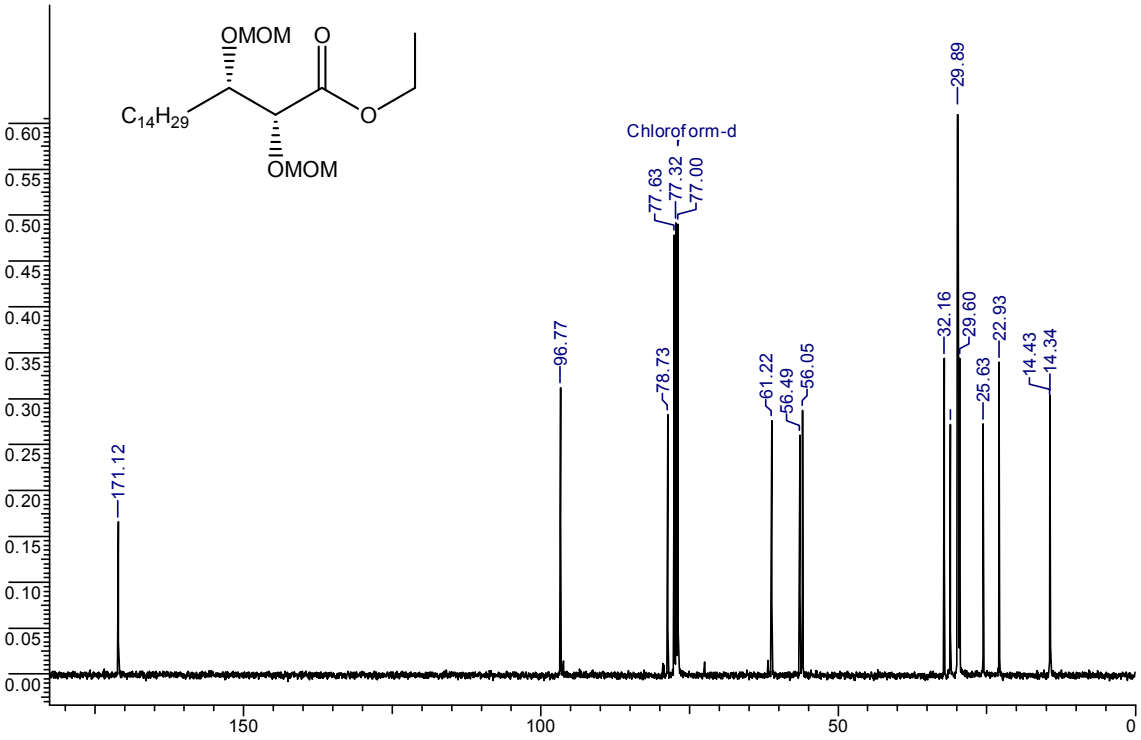
^{13}C-NMR spectrum of **129**



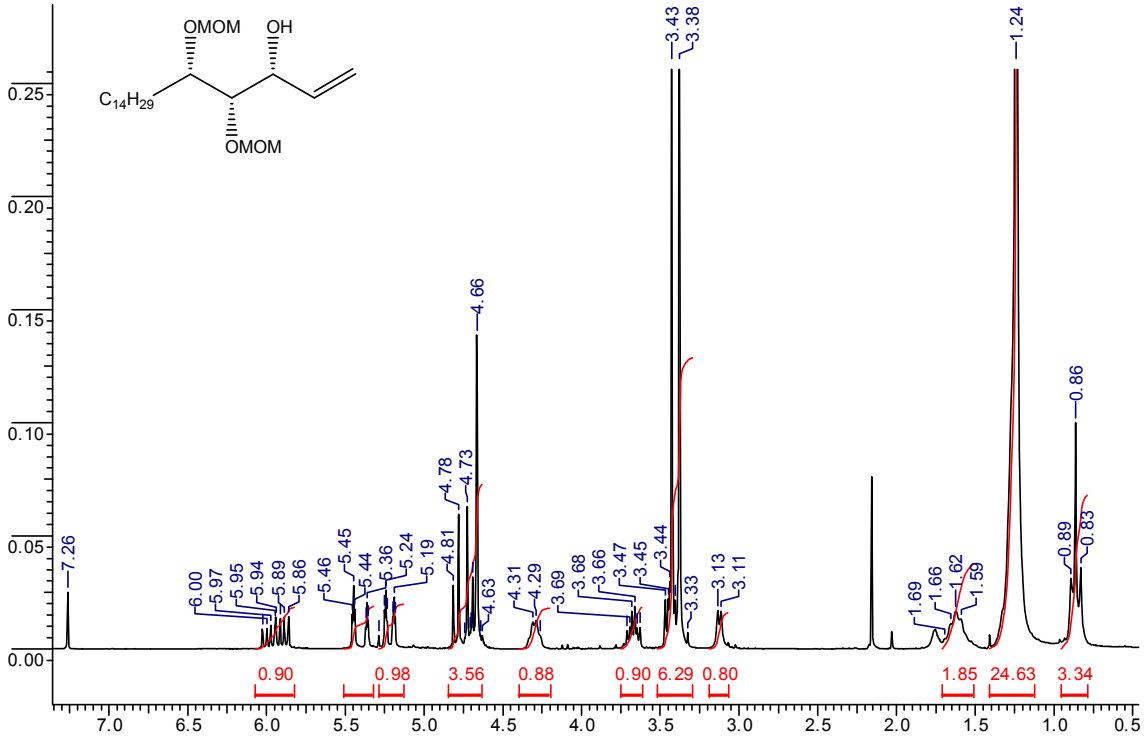
^{1}H-NMR spectrum of **130**



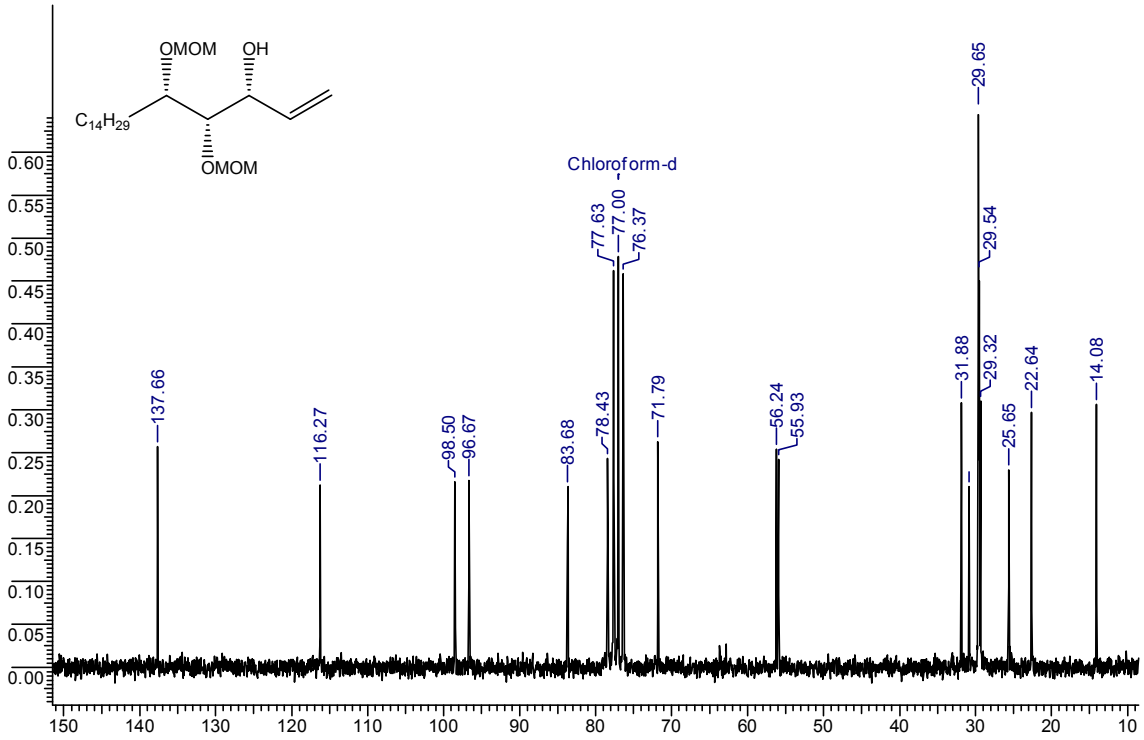
^{13}C-NMR spectrum of **130**



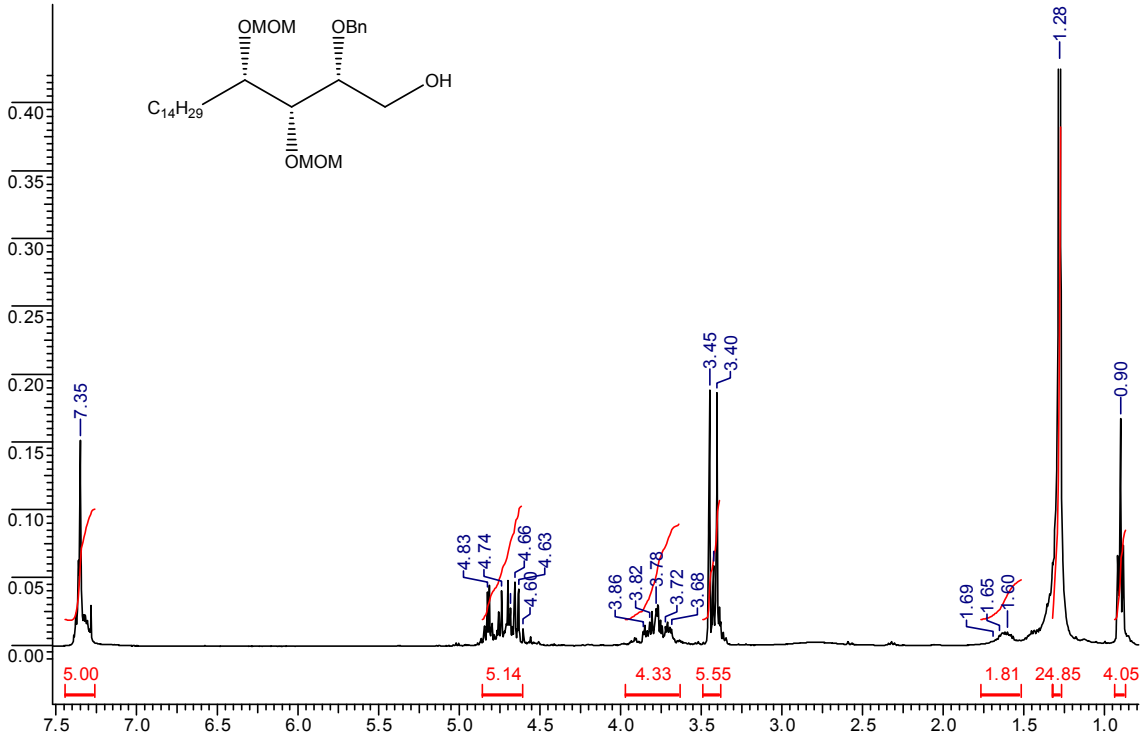
^{1}H-NMR spectrum of **136**



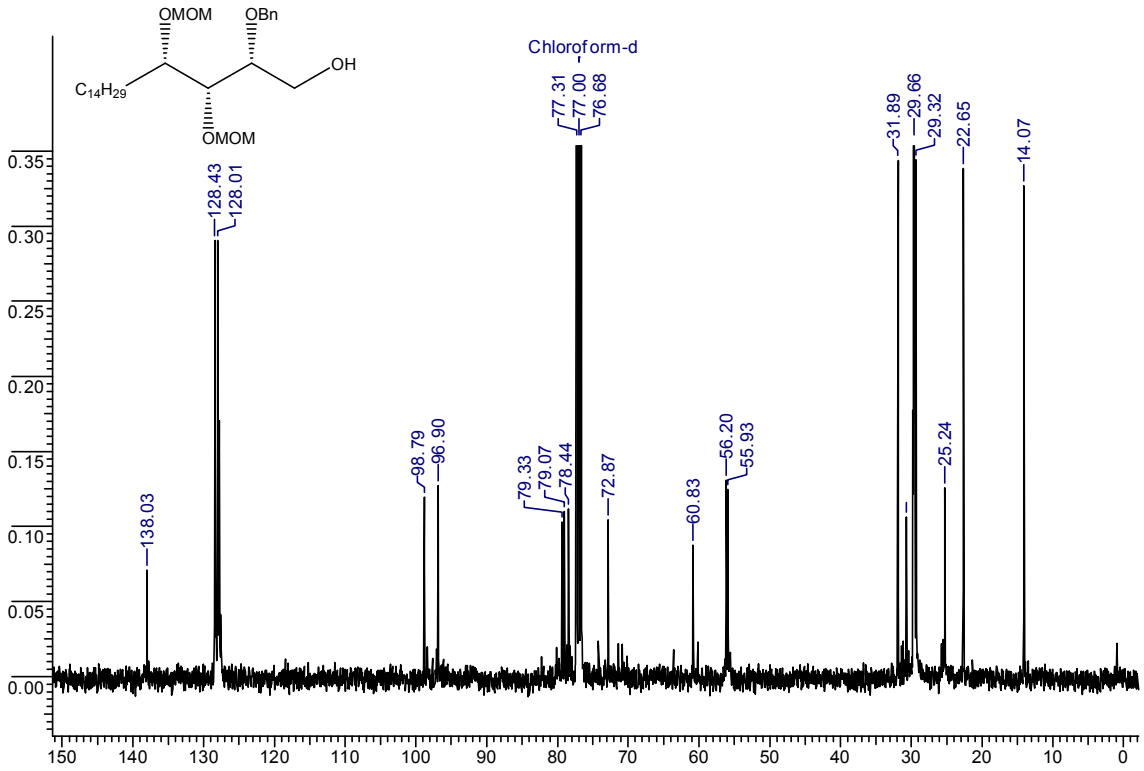
^{13}C-NMR spectrum of **136**



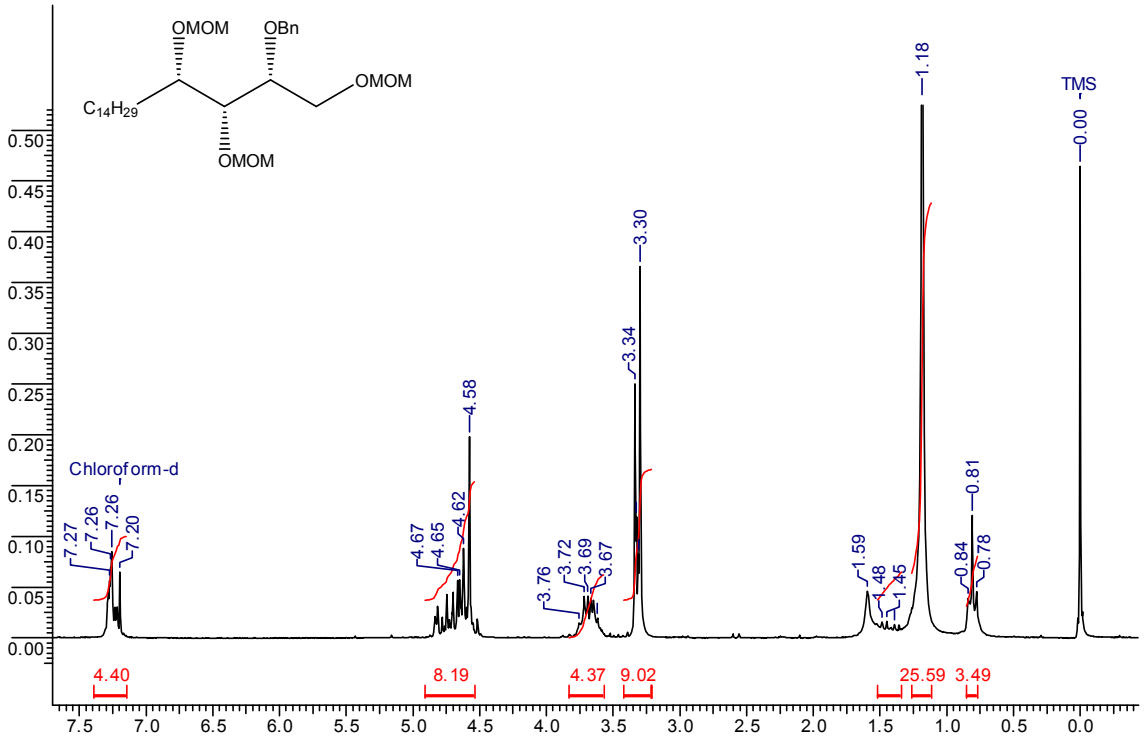
^{1}H-NMR of spectrum of **137**



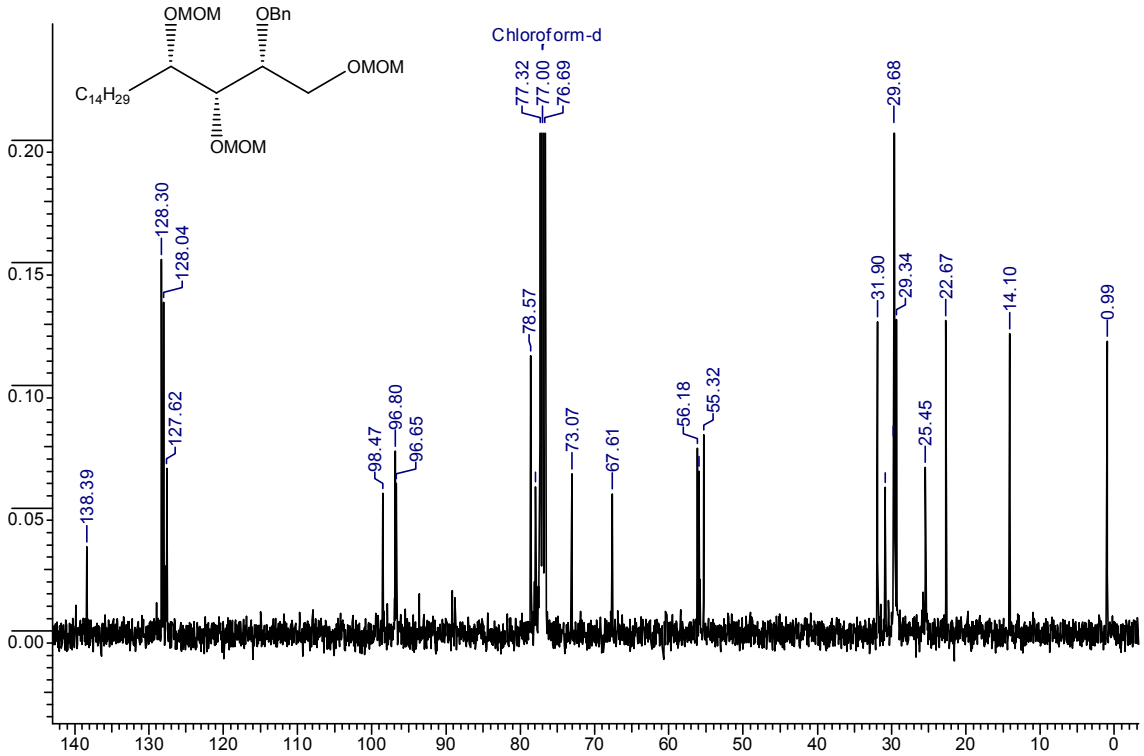
^{13}C-NMR spectrum of **137**



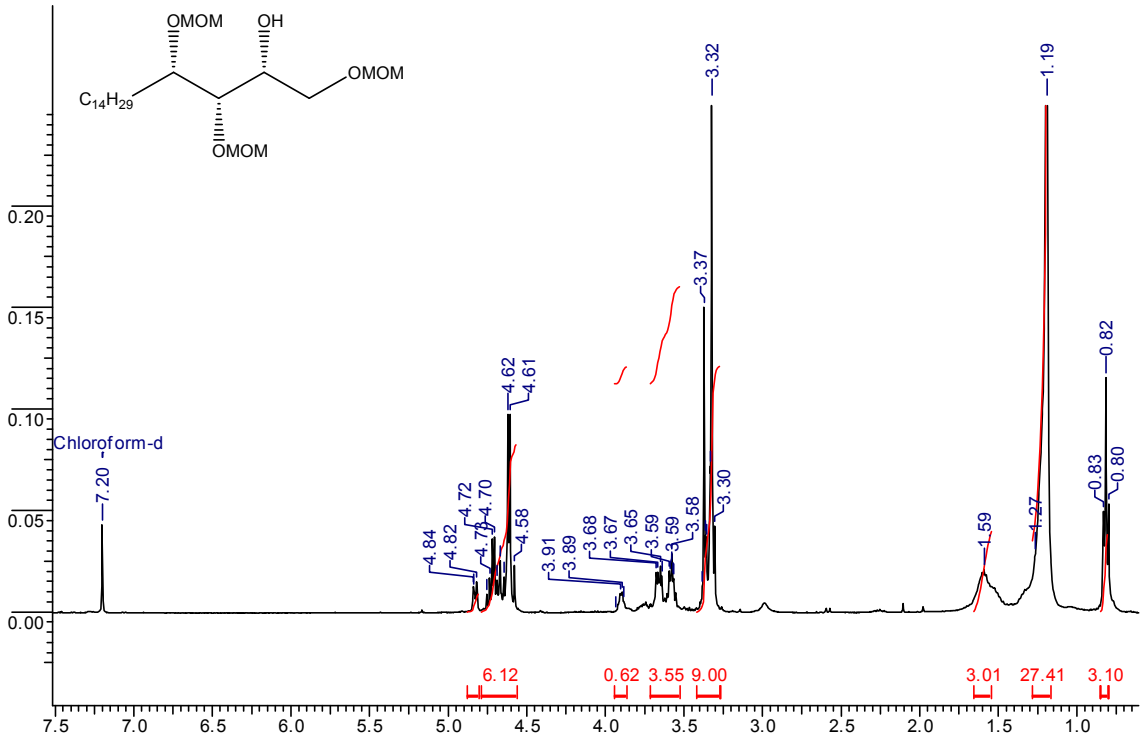
^{1}H-NMR spectrum of **138**



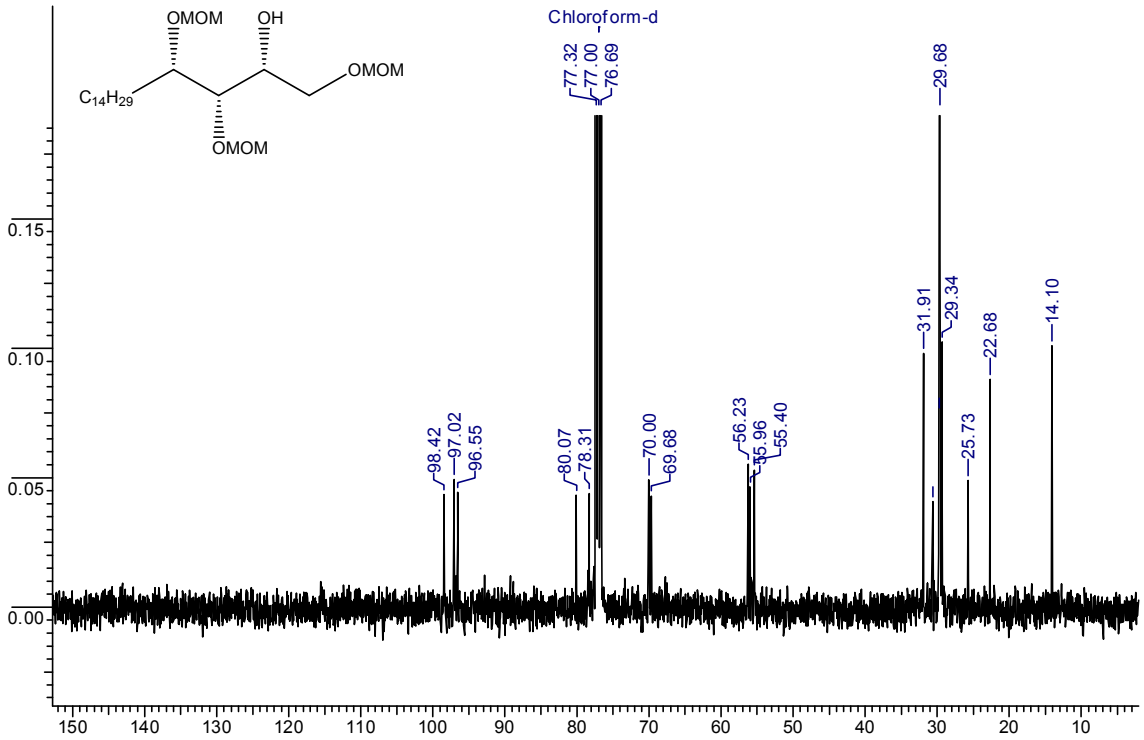
^{13}C-NMR spectrum of **138**



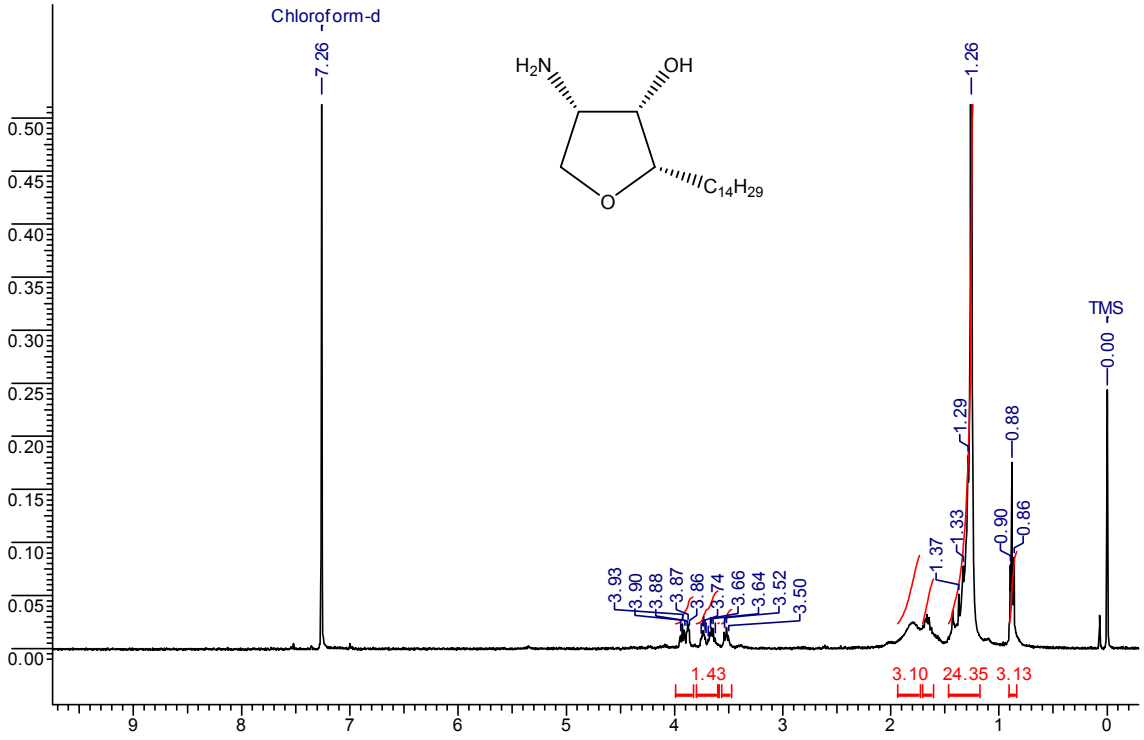
^{1}H-NMR spectrum of **139**



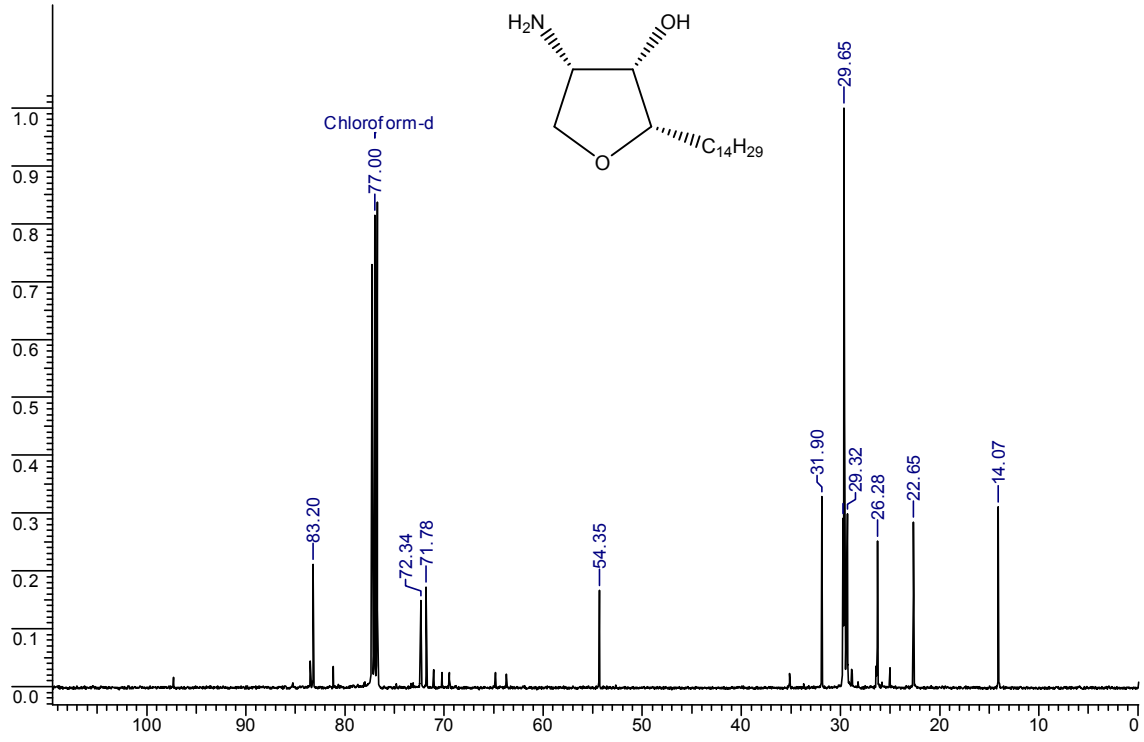
^{13}C-NMR spectrum of **139**



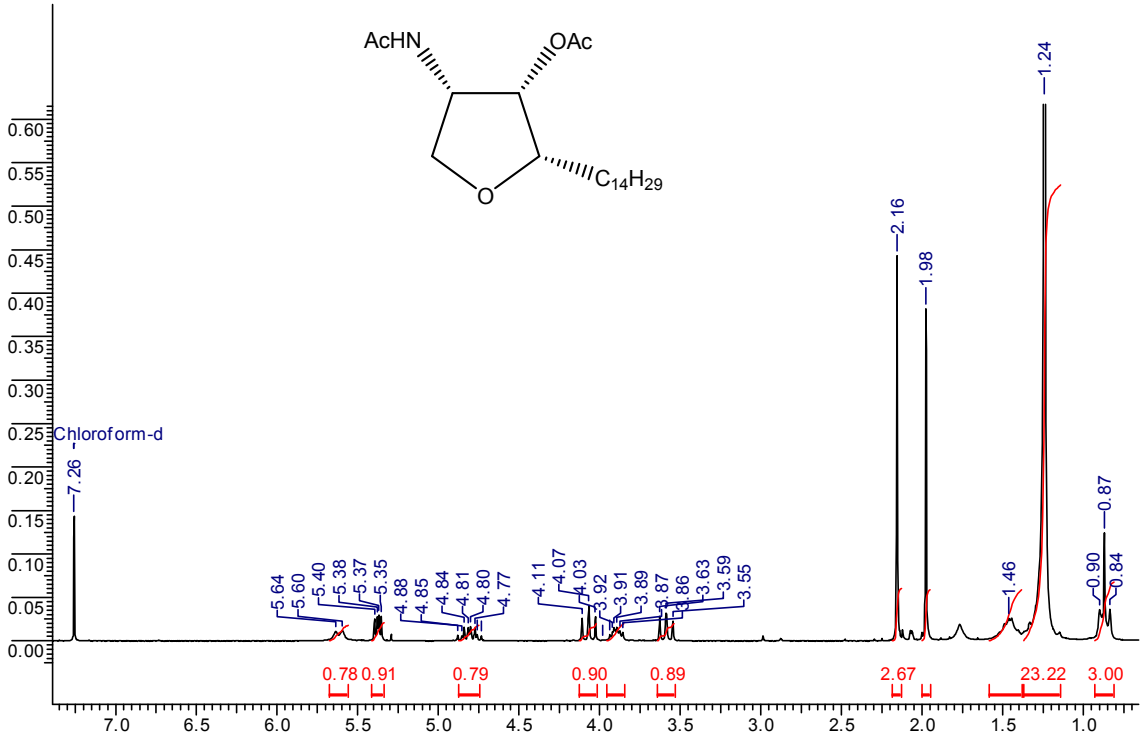
^{1}H-NMR spectrum of jaspine B (**I**)



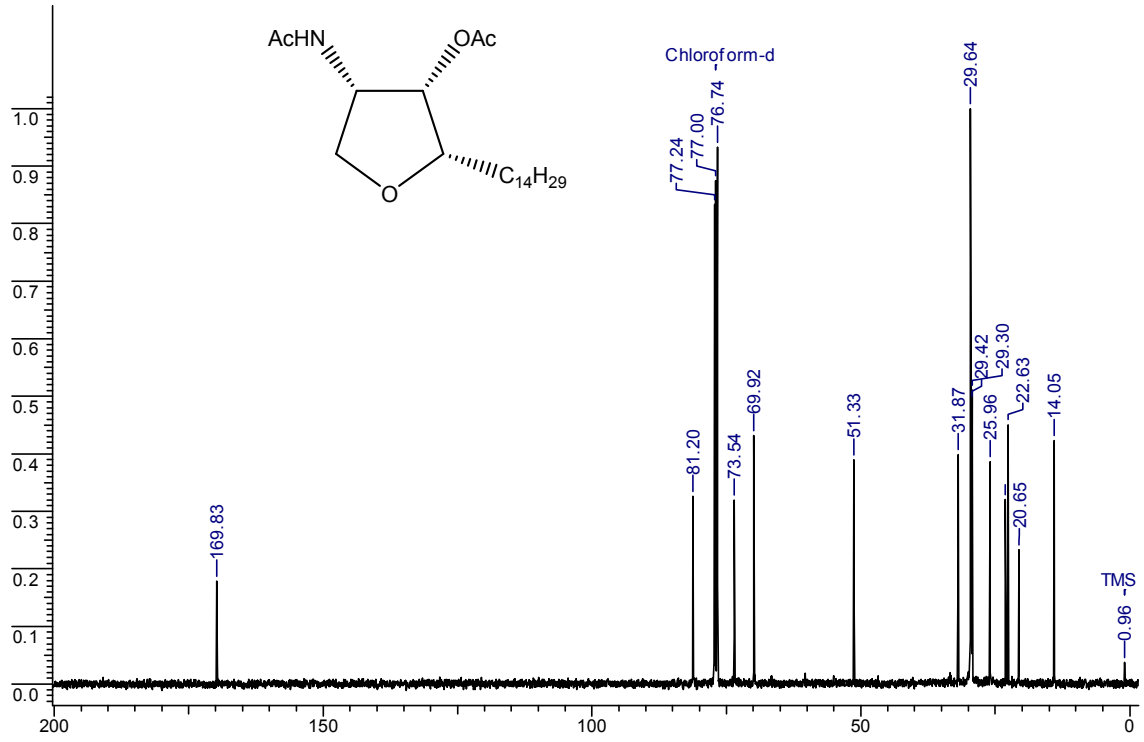
^{13}C-NMR spectrum of jaspine B (**I**)



^{1}H-NMR spectrum of diacetyl derivative of jaspine B (**II**)



^{13}C-NMR spectrum of diacetyl derivative of jaspine B (**II**)



3.2.7 References

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31. For the measurement of ee, the diol **130** was converted into dibenzoate by the reaction with benzoyl chloride (conditions: benzoyl chloride, pyridine, 0 °C-RT, 6 h, 91% yield). The enantiomeric purity of the dibenzoate was estimated to be 97% by chiral HPLC analysis using Lichrocart 250-4 (4 mm I.D. × 25 cm) HPLC-Cartridge (R.R.-Whelk-01), 1% ^{i}PrOH in hexane, 1mL/min (λ = 240 nm).

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SECTION-C

Enantioselective synthesis of

(S) - Dapoxetine

3.3.0 Introduction

Depression is a common psychiatric disorder and one of the most frequent illnesses in the world-affecting people of all gender, ages and backgrounds. Depression has major effects on economic productivity, individual well being and social functioning, around the globe. It is a huge burden on individuals, families, and society.[1a] Nearly 121 million people worldwide suffer from depression. Depressive disorders are the 4th leading cause, worldwide, of life years lost due to disability (behind infectious diseases, heart disease and respiratory infections, and before HIV/AIDS), depressive disorders are expected to rank 2nd in global diseases by 2020 (after heart disease). Antidepressant medications are widely used effective treatments for depression. Existing antidepressant drugs are known to influence the functioning of certain neurotransmitters (chemicals used by brain cells to communicate), primarily serotonin, norepinephrine, and dopamine, known as monoamines.

It has recently been suggested that (Premature ejaculation) PE might be associated with perturbations in serotonergic 5-hydroxytryptamine (5-HT) neurotransmission[1b,2] It has been proposed that premature ejaculation may be caused by decreased central serotonergic signaling, hyposensitivity of the 5-HT_{2C} receptor, or hypersensitivity of the 5-HT_{1A} receptor, all of which have been shown to decrease ejaculatory latency time in animal model systems.[3,4] PE is a common problem, which may be associated with considerable anxiety, frustration, and negative impact on affected men and their sexual partners. No pharmaceutical agents have been approved for this indication. However, therapies that target 5-HT neurotransmission, such as SSRI (selective serotonin reuptake inhibitor) *anti*-depressants, have been used in this setting with varying efficacy and tolerability. Dapoxetine is the first agent to be developed specifically to treat PE. This agent significantly prolongs IELT (intravaginal ejaculation latency time) and increases the sense of control and sexual satisfaction for men with PE and their partners. Dapoxetine is well tolerated, with a favorable pharmacokinetic profile that allows for on-demand use. Dapoxetine hydrochloride is an SSRI with a short half-life developed specifically for the treatment of men with PE,[5-8] but is slightly different from the SSRIs (such as Zoloft, Paxil, and Prozac) (Fig. **1**) widely prescribed for depression and other psychiatric disorders such as bulimia or anxiety. The American Urological Association as well as the International

Consultation on Sexual Dysfunctions now recommends the off-label use of the selective SSRIs, which increase 5-HT neurotransmission, for the management of PE.[1b,9,10] Although the off-label use of antidepressant SSRIs such as fluoxetine, sertraline, and paroxetine may increase ejaculatory latency time[11-13] these SSRIs do not reach peak plasma concentrations for several hours after administration; many require a long lead-in dosing period for efficacy[1b] and the typically long half-lives of these drugs can result in significant drug accumulation in the body, increased exposure to medication and, consequently, an increased likelihood of adverse events.[6,14] In addition, men taking antidepressant SSRIs daily have reported sexual side effects such as decreased libido and erectile dysfunction after prolonged treatment with these drugs.[6]

The asymmetric synthesis of individual enantiomers is extremely important because the (*S*) and (*R*)-isomers usually display very different pharmacological or physiological properties.[8] For example, the enantiomer (*S*)-(+)-*N,N*-dimethyl-α-[2-(1-naphthalenyloxy) ethyl]benzenemethanamine [(*S*)-dapoxetine] is a potent serotonin re-uptake inhibitor for treating depression and other disorders as bulimia or anxiety. Dapoxetine is the D-enantiomer of LY 243917 and found to be 3.5 times more potent as a serotonin reuptake inhibitor than the L-enantiomer of LY 243917.

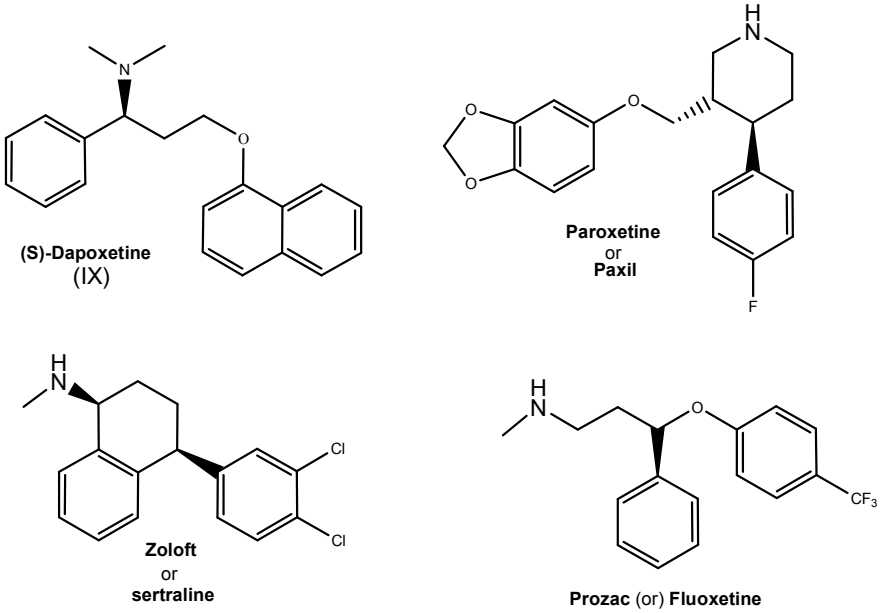


Fig. **1** Structure of (S)-Dapoxetine and various SSRI *anti*-depressants

3.3.1 Dapoxetine and Pharmacology

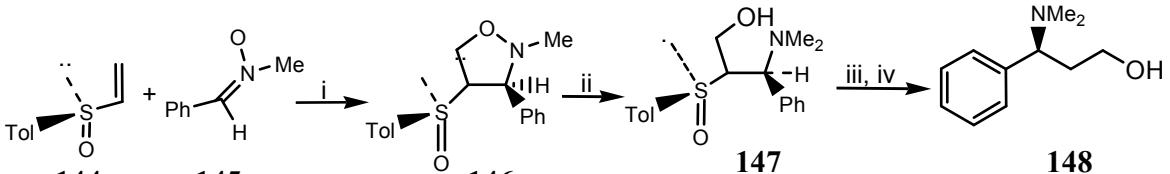
Dapoxetine hydrochloride was originally an antidepressant and one of the side effects of several antidepressants is retarded ejaculation (an inability to reach orgasm), inability to sustain an erection and/or impotence. It was pharmacologist Thor Karl who spotted the repositioning potential of Dapoxetine hydrochloride and suggested its indication for premature ejaculation treatment. Considering there are now last minute regulatory problems, it is assumed that the new drug will be granted a license for this indication in the nearest future. Many drug companies have seen the potential benefits of reprofiling old drugs rather than starting from research with each new disease or disorder.

If approved by the Food and Drug Administration (FDA), this would make Dapoxetine join the ranks of erectile dysfunction drugs such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®), and some dopamine agonists such as cabergoline (Dostinex®) and pramipexole, as drugs which can be used to improve male sexual health.[15]

3.3.2 Review of literature

Koizumi *et al* approach (1982)[16a]

Koizumi and co-workers synthesized (*S*)-(3)-*N,N*-dimethyl amino-3-phenylpropan-1-ol **122** foremost intermediate of target molecule (S)-dapoxetine starting from (*R*)-(+)-*p*-tolyl vinyl sulfoxide **118**.

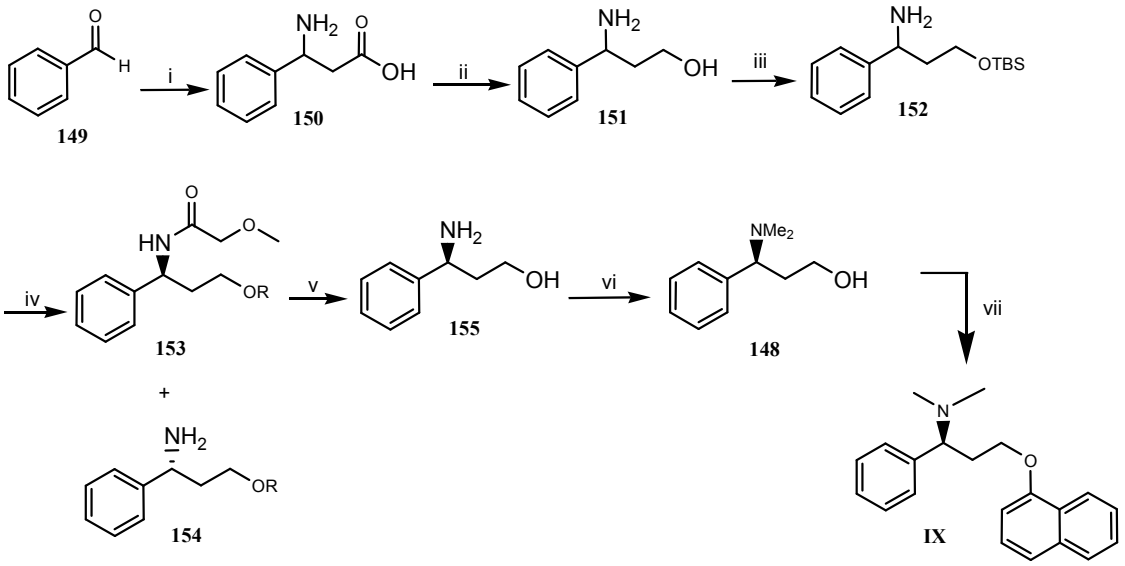


144 **145** **146** **147** **148**

Scheme 36. Reaction conditions: (i) benzene, reflux, 20 h, 40%. (ii) (a) MeI; (b) Zn-AcOH, rt. (iii) $TiCl_4$-AcOH-AcONa, rt. (iv) Raney Ni-EtOH, rt.

Gotor *et al* approach (2006)[17a]

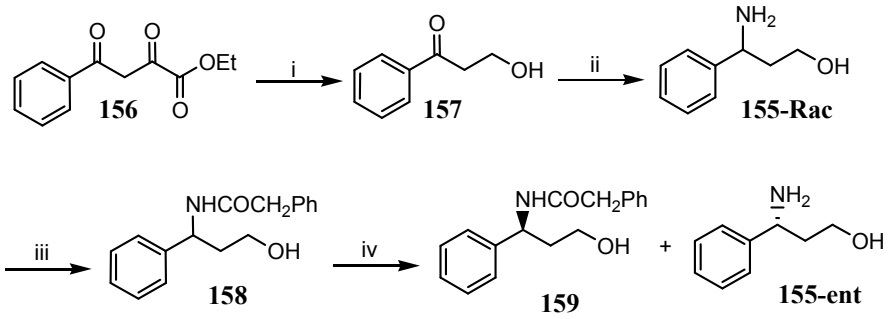
Very recently Gotor and co-workers reported lipase catalyzed resolution of chiral 1, 3-amino alcohols, and its application in the asymmetric synthesis of (*S*)-dapoxetine.



Scheme **37**. Reaction conditions: (i) $CH_2(COOH)_2$, NH_4OAc, EtOH, 80 ^oC,12 h. (ii) $LiAlH_4$, THF, 65 ^oC, 3 h. (iii) TBDMSCl, imidazole, CH_2Cl_2, rt. (iv) Acyl donor, enzyme, solvent, 30 ^oC. (v) HCl 6M, 50 ^oC. (vi) *p*-formaldehyde, HCOOH, rt, 83%. (vii) PPh_3, DEAD, 1-napthol, THF, rt, 72%.

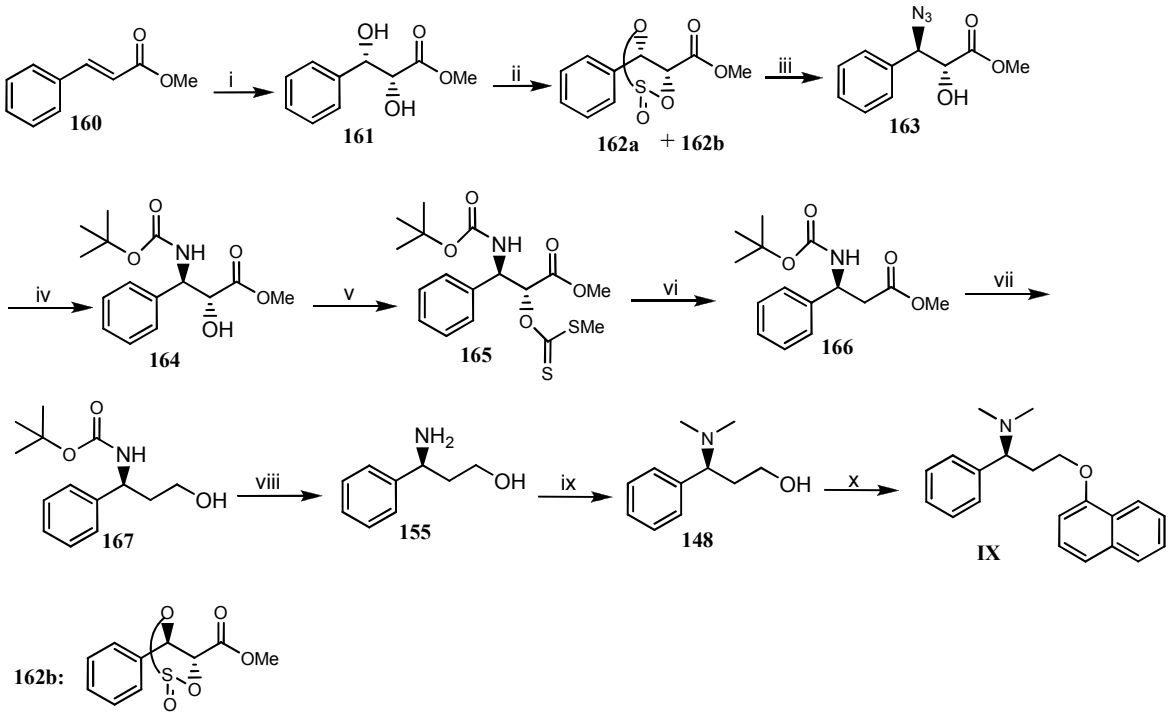
Fadnavis *et.al* approach (2006)[18]

Fadnavis *et al.* reported synthesis of enantiomerically pure (*R*) and (*S*)-3-amino-3-phenyl-1-propanol prominent intermediate in the synthesis of the (*S*)-dapoxetine *via* the resolution with immobilized penicillin G acylase.



Scheme 38. Reaction conditions: (i) Bakers yeast, diisopropyl ether, 48 h, 90%. (ii) NH_4OAc, $NaBH_3CN$, EtOH, rt, 36 h, 65%. (iii) $PhCH_2COCl$, NaOH, rt, 4 h, 80%. (iv) *penicillin G acylase*, 4 h, water, 47.5% (**159**).

Shafi *et al.* approach (2007)[17b]



Scheme 39. Reaction conditions: (i) $(DHQ)_2PHAL$ (1 mol%), OsO_4 (0.1 mol%), $K_3Fe(CN)_6$ (3 eq.), K_2CO_3 (3 eq.), $MeSO_2NH_2$ (1eq.), H_2O:*t*-BuOH (1:1), rt, 24 h, 83%, 96% ee. (ii) CH_2Cl_2, Et_3N, $SOCl_2$, 0 ^oC to rt, 1 h, 90% (1:1 ratio of **162**a and **162**b); (iii) NaN_3, DMF, rt, 78%; (iv) H_2/Pd-C, EtOAC, rt, $(Boc)_2O$, Et_3N, 80%. (v) MeI, CS_2, Et_3N, CH_2Cl_2, 0 ^oC to rt, 12 h; (vi) *n*-$(Bu)_3SnH$, AIBN, toluene, reflux.(vii) $LiAlH_4$, THF, rt, 12 h; (viii) TFA, DCM, rt; (ix) HCHO, HCOOH; (x) Ph_3P, DEAD, 1-napthol, THF, rt, 72%.

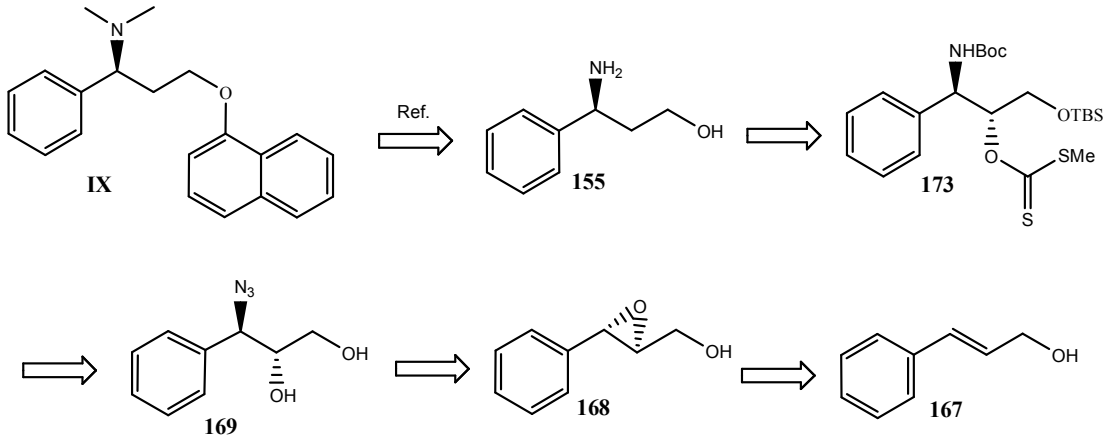
3.3.3 Present work

3.3.3.1 Objectives

Very few methods are currently available for the synthesis of pharmaceutically important and potent (S)-dapoxetine. Toru Koizumi *et al.* reported the synthesis of intermediate **8** (see Scheme **1**) by employing asymmetric induction in the 1,3-dipolar cyclo-addition of (R)-(+)-*p*-tolylvinyl sulfoxide with acyclic nitrones in high enantiomeric excess.[16a] Another method described in the literature to synthesize (S)-dapoxetine is a radiochemical synthesis from (S)-(+)-N-methyl-α-[2-(1-naphthalenyloxy)ethyl]benzenemethanamine hydrochloride using $^{11}CH_3I$.[16b] Recently, two asymmetric synthetic approaches are reported for the synthesis of (*S*)-Dapoxetine starting from achiral starting materials.[17] Herein, we report a novel asymmetric synthetic route for the synthesis of (*S*)-Dapoxetine (**I**), starting from the commercially available and inexpensive achiral starting material *trans*-cinnamyl alcohol (**1**), for the first time.

3.3.3.2 The retro synthetic strategy for (*S*)-Dapoxetine

The Sharpless asymmetric epoxidation can be envisioned as a powerful tool offering considerable opportunities for synthetic manipulations,[19] which has been employed as a key step in our synthetic strategy as shown in Scheme **40**.

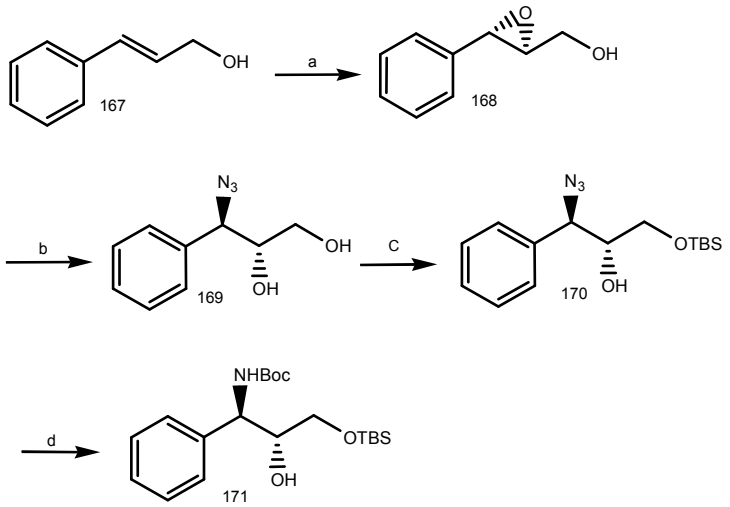


Scheme **40.** Retrosynthetic approach for (*S*)-Dapoxetine (**I**).

We envisioned that the amino alcohol **155** could be prepared from the xanthate ester **173,** which in turn could be prepared from the azido diol **169**. The azido diol **169** itself could be prepared from the epoxide **168** which in turn could be synthesized by Sharpless asymmetric epoxidation of the commercially available *trans*-cinnamyl alcohol **167**.

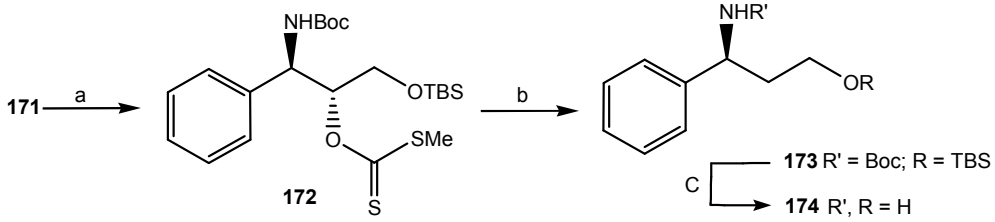
3.3.4 Results and discussions

Trans-cinnamyl alcohol **167** was subjected to SAE (Sharpless asymmetric epoxidation) conditions[20] to give the epoxide **168** in 88% yield with 98% ee. Regioselective opening of the epoxide **168** with NaN_3 gave the azido diol **169** as the single product in 97% yield. The formation of azido alcohol **169**, was confirmed by its IR spectrum showing strong absorption at 2106 and 3450 cm^{-1} which can be assigned to N_3 and OH groups respectively. The azido diol **169** was converted in to the mono-protected azido alchol **170** in 96% yield, which on treatment with Pd(C) in the presence of $(BOC)_2O$ in EtOAc afforded the *N*-Boc protected alcohol **171** in 88% yield (Scheme **41**).



Scheme **41**. Synthesis of intermediate **171** (Sharpless epoxidation method as a key step). Reagents and conditions: (a) (*R,R*)-(+)-DET, $Ti(O^iPr)_4$, ^{t}-BuOOH, MS 4 Å, –20 ^oC, 8 h, 88%; (b) NaN_3, MeOH:H_2O (5:1), 65 ^oC, 4 h, 97%; (c) TBSCl, dry DCM, imidazole, 0 ^oC-RT, 6 h, 96%; (d) H_2, Pd(C), EtOAc, RT, 12 h, 88%.

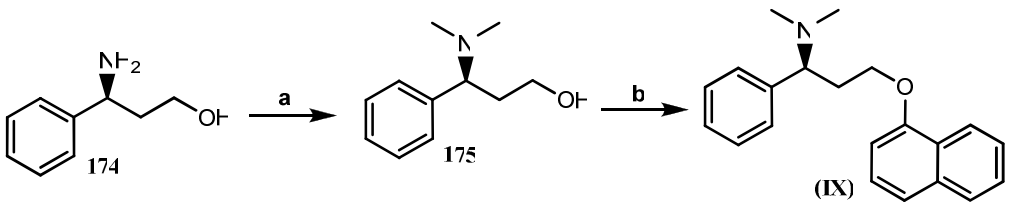
The alcohol **171** on treatment with CS_2 and methyl iodide in the presence of TEA in DCM gave **172** in 84% isolated yield. The IR spectrum of **172** showed disappearance of hydroxyl group. ^{1}H-NMR spectrum of **172** showing singlet for the three protons at δ 2.35 for the *S*-methyl confirmed the presence of O-C(=S)SMe group. The intermediate **172** on reaction with hydride source (tri-*n*-butyl tinhydride) using catalytic amount of AIBN (as radical initiator) and imidazole in refluxing toluene under inert atmosphere gave the deprotected compound **173** (Barton-McCombie[21] protocol), which was further treated with TFA in THF to give the amino alcohol **174** in 81% isolated yield in two steps (Scheme **42**).



Scheme **42**. Synthesis of intermediate **174.** Reagents and conditions: (a) CS_2, NaH, THF, MeI, 0 ^oC-RT, over night, 84%; (b) n-Bu_3SnH, AIBN, toluene, reflux, 6 h; (c) TFA, THF, 10 ^oC-RT, 5 h, 81% (for two steps).

Enantio-selective synthesis of (*S*)-Dapoxetine from intermediate 174

The amino alcohol **174** was converted in to (S)-Dapoxetine (IX) by employing the literature procedure[17a] (Scheme **43**).



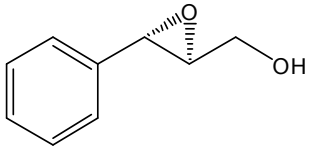
Scheme 43. synthesis of (S)-Dapoxetine (IX)**.** Reaction conditions: (a) HCHO, HCOOH, Reflux, 9h, 84%; (b) Ph_3P, DEAD, α-naphthol, THF, rt, 72%.

3.3.5 Conclusion

In conclusion, a novel total synthesis of (*S*)-Dapoxetine with high enantioselectivity starting from an achiral starting material has been developed in which the chiral center was established by Sharpless asymmetric epoxidation to afford (*S*)-Dapoxetine (**IX**) with the required stereochemistry. In conclusion, we have developed a stereoselective total synthesis of (*S*)-(+)-dapoxetine starting from *trans*-cinnamyl alcohol comprising of 8 isolated steps with an overall yield of 20% in 97% ee.

3.3.6 Experimental

4.1.1 Synthesis of (2*S*,3*S*)-(3-phenyl-oxiranyl)-methanol (168)

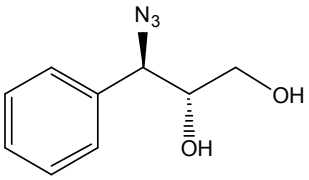


To a stirred solution of (*R*,*R*)-(+)-diisopropyl tartrate (0.83 mL, 0.92 g, 3.91 mmol) in CH_2C1_2 (450 mL) at −20 °C, 2.8 g activated powdered 4 Å molecular sieves, $Ti(OPr^i)_4$ (0.78 mL, 0.74 g, 2.61 mmol) and 3.0 M solution of TBHP in toluene (34.78 mL, 104.34 mmol) were added sequentially. The mixture was allowed to stir at −20 °C for 1 h and then a solution of freshly distilled (*E*)-3-phenyl-2-propenol (*trans*-cinnamyl alcohol) (7.0 g, 52.17 mmol) in 10 mL of CH_2C1_2 was added drop wise over 30 min. After 3 h at −20 °C, the reaction was quenched at −20 °C with 10% aqueous solution of NaOH saturated with NaCl (4.2 mL). After diethyl ether (60 mL) was added the cold bath was allowed to warm to 10 °C with stirring. Maintaining the temperature at 10 °C, $MgSO_4$ (5 g) and Celite (500 mg) were added. After another 15 min of stirring, the mixture was allowed to settle and the clear upper solution was filtered through a pad of Celite and washed with diethyl ether. Azeotropic removal of TBHP with toluene at reduced pressure gave **168** as pale yellow oil. Recrystallization from petroleum

ether/diethyl ether gave yellow crystals of **168** (98% 'ee' determined by spectroscopic analysis of the ester derived from (+)-MTPA chloride).

Yield	(6.89 g, 88%); M.P.: 53.6-54.2 °C.
$[\alpha]_D^{25}$	–49.1 (c 2.45, $CHCl_3$) {lit.[20] $[\alpha]_D^{25}$ = –49.6 (c 2.4, $CHCl_3$)}
IR($CHCl_3$, υ_{max})	3435, 3019, 2927, 1384, 1216, 1069, 1025, 929, 757, 669 cm^{-1}
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 2.74 (br s, 1H), 3.21-3.25 (m, 1H), 3.74 (dd, *J* = 4.4, 12.8 Hz, 1H), 3.92 (d, *J* = 2.2 Hz, 1H), 4.02 (dd, *J* = 2.4, 12.7 Hz, 1H), 7.22-7.41 (m, 5H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ 55.6, 61.2, 62.5, 125.7, 128.3, 128.4, 136.6.
Elemental Analysis	Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75%. Found: C, 55.89; H, 5.79; N, 21.67%.

4.1.2 Synthesis of (2R,3R)-3-azido-3-phenylpropane-1,2-diol (169)

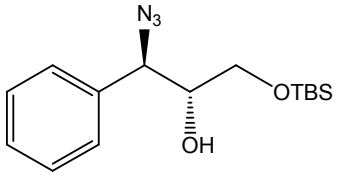


The epoxy alcohol **168** (2.0 g, 13.32 mmol), NaN_3 (1.73 g, 26.63 mmol) and NH_4Cl (1.42 g, 26.63 mmol) in a solvent mixture of methanol (12 mL) and water (1.5 mL) were warmed at 65 °C for 6 h. The reaction mixture was cooled to RT and the solid was filtered. The filtrate was concentrated to a residue, which was taken in to ethyl acetate, washed with brine and water, dried and concentrated to give a syrup, which was purified by column chromatography (eluent: petroleum ether/EtOAc 7:3) to afford the azido diol **169** as a yellow oily liquid.

Yield	(2.50 g, 97%).
$[\alpha]_D^{25}$	–165.1 (*c* 1.1, $CHCl_3$).
IR($CHCl_3$, υ_{max})	3402, 3055, 2926, 2855, 2106, 1602, 1493, 1454, 1384, 1265, 1093, 1041, 741 cm^{-1}.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 2.90 (br s, 2H), 3.47-3.67 (m, 2H), 3.69-3.82 (m, 1H), 4.43-4.59 (d, *J* = 7.1 Hz, 1H), 7.2-7.47 (m, 5H).
^{13}C-NMR (100 MHz, $CDCl_3$)	δ 62.8, 67.0, 73.9, 127.7, 128.8, 128.9, 136.0.

Elemental Analysis Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75%. Found: C, 55.99; H, 5.78; N, 21.81%.

4.1.3 Synthesis of (1*R*,2*R*)-1-azido-3-(*tert*-butyldimethylsilyloxy)-1-phenylpropan-2-ol (170)



To a stirred solution of azido diol **169** (0.421 g, 2.18 mmol) in CH_2Cl_2 (15 mL), imidazole (0.180 g, 2.62 mmol) was added. To this solution, *t*-butylchlorodimethylsilane (0.329 g, 2.18 mmol) was added at 0 ^oC and the reaction mixture was stirred at RT for 5 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3X10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Silica gel column chromatography of the crude product using Pet ether/EtOAc (10:0.3) as eluent provided mono-TBS protected azido alcohol **170** as a colorless liquid.

Yield (0.643 g, 96%).

$[\alpha]_D^{25}$ -33^o (*c* 1.0, $CHCl_3$).

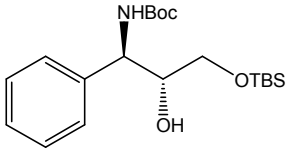
IR($CHCl_3$, υ_{max}) 3339, 3015, 2955, 2930, 2105, 1463, 1389, 1255, 1117, 837, 759 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$) δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 2.10 (br s, 1H), 3.55-3.80 (m, 3H), 4.48 (d, *J* = 7.0 Hz, 1H), 7.25-7.32 (m, 5H).

^{13}C-NMR (50 MHz, $CDCl_3$) δ -5.5, 18.3, 25.6, 25.8, 63.2, 66.7, 73.7, 127.77, 127.8, 128.5, 128.7, 128.9, 129.1, 136.3.

Elemental Analysis Anal. Calcd for $C_{15}H_{25}N_3O_2Si$: C, 58.60; H, 8.20; N, 13.67%. Found: C, 58.68; H, 8.12; N, 13.76%.

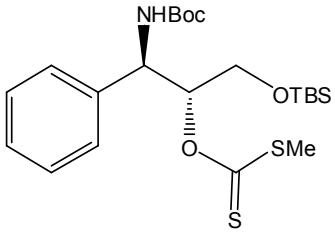
4.1.4 Synthesis of *tert*-butyl (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1-phenylpropylcarbamate (171)



To a solution of **170** (0.310 g, 1.008 mmol) in EtOAc (12 mL) was added a catalytic amount of 5% Pd/C and the reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm. balloon pressure) for 12 h. The reaction mixture was then filtered through a pad of Celite and the solvent was removed under reduced pressure to give the crude product, which was then purified by column chromatography over silica-gel using petroleum ether/EtOAc (60:40) as eluent to afford **171** as a pale yellow oil.

Yield	(0.338 g, 88%).
$[\alpha]_D^{25}$	-12.6^o (*c* 0.55, $CHCl_3$).
IR($CHCl_3$, υ_{max})	2955, 2930, 2451, 2210, 1678, 1479, 1447, 1372, 1165, 837, 759 cm^{-1}.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 1.40 (s, 9H), 2.10 (br s, 1H), 3.55-3.80 (m, 3H), 4.48 (d, *J* = 7.0 Hz, 1H), 7.25-7.32 (m, 5H).
^{13}C-NMR (50 MHz, $CDCl_3$)	δ –5.6, 18.1, 25.8, 28.3, 58.1, 63.95, 72.9, 79.4, 126.8, 127.4, 128.4, 139.5, 155.6.
Elemental Analysis	Anal. Calcd for $C_{20}H_{35}NO_4Si$: C, 62.95; H, 9.25; N, 3.67%. Found: C, 62.88; H, 9.29; N, 3.75%.
LC-MS (ESI-TOF) *m*/*z*:	[M+23] = 404.30.

***tert*-butyl (1*R*,2*R*)-2-(methoxycarbonyl)-2-O-(*S*-methyldithiocarbonate)-1-phenylethylcarbamate (172)**

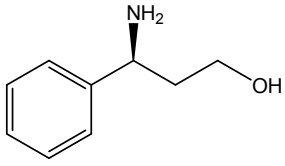


To a solution of **171** (0.404 g, 1.06 mmol) in THF (10 mL) at 0 ^oC was added sodium hydride (50% assay, 0.056 g, 1.17 mmol). Vigorous gas evolution was observed. After the reaction mixture was stirred for 20 min carbon disulfide (0.100 mL, 1.64 mmol) was added in one portion. Stirring was continued for the next 30 min after which methyl iodide (0.20 mL, 3.18 mmol) was added in a single portion. The reaction mixture was stirred for another 2 h (progress of reaction mixture was monitored by TLC) and the reaction was quenched by the addition of ice-cold

water (2 mL). The solution was filtered, concentrated in *vacuo* and the residue was extracted with ethyl acetate (3 X 5 mL). The combined organic extracts were washed with saturated sodium bicarbonate (5 mL) solution. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using 12% ethyl acetate in petroleum ether as eluent, to give **172** as a pale yellow solid.

Yield and MP	(0.418 g, 84%); MP = 107-109 ^oC
$[\alpha]_D^{25}$	-12.6^o (*c* 1.0, Acetone)
IR($CHCl_3$, υ_{max})	3398, 3064, 3031, 2976, 1693, 1513, 1435, 1310, 1215, 837, 759 cm^{-1}.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 1.40 (s, 9H), 2.35 (s, 3H), 5.37 (d, *J*= 7.1 Hz,1H), 6.12-6.14 (d, *J*= 7.0 Hz, 1H), 7.30-7.40 (m, 5H).
Elemental Analysis	Anal. Calcd for $C_{22}H_{37}NO_4S_2Si$: C, 56.01; H, 7.91; N, 2.97; S, 13.59%. Found: C, 56.09; H, 7.99; N, 2.90; S, 13.44%.

(*S*)-3-amino-3-phenylpropan-1-ol (174)

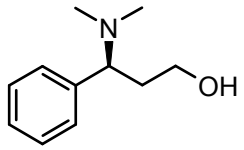


To a solution of the xanthate ester **136** (0.250 g, 0.53 mmol) in toluene (15 mL) tri-*n*-butyltin hydride (0.462g, 1.59 mmol) and catalytic amount of AIBN (0.1 mol% w/w based on **173**) were added at room temperature under inert atmosphere. The reaction mixture was heated at reflux till completion of reaction (progress of reaction was monitored by TLC). After the completion of the reaction (as shown by TLC), toluene was removed under reduced pressure to give a thick viscous residue. This residue was dissolved in 15 mL of THF and 1.0 mL of TFA was added to the solution at 10 ^oC under nitrogen atmosphere. The reaction mixture was stirred at RT for 5 h. 20 mL of 1.0 M NaOH solution was slowly added at 0 ^oC and the mixture was extracted with EtOAc/MeOH (95:5) (2X15 mL). The organic extracts were combined dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The separated crude product was

purified by silica-gel column chromatography with $CHCl_3$/MeOH (9:1) to afford **174** as a colorless solid.

Yield	0.065 g (81% for two steps)
$[\alpha]_D^{25}$	-11.6^o (*c* 0.6, $CHCl_3$). {lit.[17a] $[\alpha]_D^{25}$ = –11.2 (c 0.5, $CHCl_3$)}.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 2.10 (m, 2H), 3.55 (t, 2H), 3.96 (m, 1H), 7.09-7.24 (m, 5H).
^{13}C NMR (50 MHz, $CDCl_3$)	δ 39.4, 57.4, 56.4, 126.1, 128.2, 128.9, 139.9.
Elemental Analysis	Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%. Found: C, 71.40; H, 8.60; N, 9.36%.

(*S*)-3-(*N, N*-dimethylamino)-3-phenylpropan-1-ol (175)



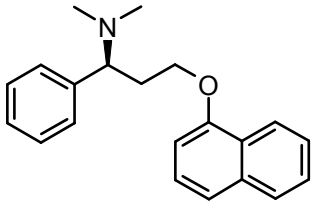
To a solution of amino alcohol **174** (0.030 g, 0.198 mmol) in formic acid (25 μL), was added a 30% aqueous solution of formaldehyde (79 μL, 1.05 mmol) and the mixture refluxed over 9 h. The completion of the reaction was monitored by TLC.

After completion of the reaction, the solution was acidified with conc. HCl to pH = 1 and basified with 3 N NaOH. The organic phases were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give **175** as a residue. The crude product was purified by flash column chromatography. The spectral and analytical data of **175** are in good agreement with the literature values.[17a]

Yield	0.017 g (84%)
$[\alpha]_D^{25}$	$+37.1^o$ (*c* 0.6, $CHCl_3$). {lit.[17a] $[\alpha]_D^{25}$ = +38.0 (c 0.6, $CHCl_3$)}.
IR($CHCl_3$, υ_{max})	3412, 2446, 2311, 1345, 1265, 1215, 1168, 1048, 915, 848, 759, 733 cm^{-1}.
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 1.64-1.76 (m, 1H), 2.15 (s, 6H), 2.52-2.69 (m, 1H), 3.38-3.65 (m, 1H), 3.88-3.94 (m, 1H), 7.30-7.42 (m, 5H).
^{13}C NMR (50 MHz, $CDCl_3$)	δ 32.1, 36.4, 63.1, 67.5, 127.1, 127.8, 128.3, 128.8, 128.9, 136.1.

Elemental Analysis Anal. Calcd for $C_9H_{13}NO$: C, 73.70; H, 9.56; N, 7.81%. Found: C, 73.77; H, 9.53; N, 7.89%.

(*S*)-*N, N*-dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine (IX)



To a solution of **175** (15 mg, 0.17 mmol) in dry THF (2 mL) was added 1-naphthol (25 mg, 0.17 mmol) maintaining a nitrogen atmosphere The mixture was cooled to 0 ^oC and PPh_3 (45 mg, 0.17 mmol) and DEAD (27 μL, 0.17 mmol) were successively added.

The solution was allowed to warm to room temperature (28 ^oC) and stirred at RT for 16 h. After completion of the reaction (as shown by TLC), THF was evaporated and the crude product was purified by flash silica-gel column chromatography using EtOAc/MeOH mixture which afforded (*S*)-dapoxetine as a colorless oil.

Yield 0.019 g (73%)

$[\alpha]_D^{25}$ +61.7 (*c* 0.3, $CHCl_3$). {lit.[17a] $[\alpha]_D^{20}$ = +62.5 (c 0.3, $CHCl_3$)}.

IR($CHCl_3$, υ_{max}) 2962, 2950, 2311, 2103, 1922, 1728, 1346, 1265, 1168, 1046, 914, 848, 733 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.34-2.45 (m, 1H), 2.59-2.71 (m, 1H), 3.55-3.63 (m, 1H), 3.93-4.12 (m, 2H), 7.19-7.52 (m, 9H), 7.70-7.74 (m, 1H), 7.95-8.21 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 32.0, 36.4, 63.1, 67.5, 104.5, 120.1, 127.1, 127.4, 127.8, 128.3, 128.9, 136.0, 138.1, 155.2.

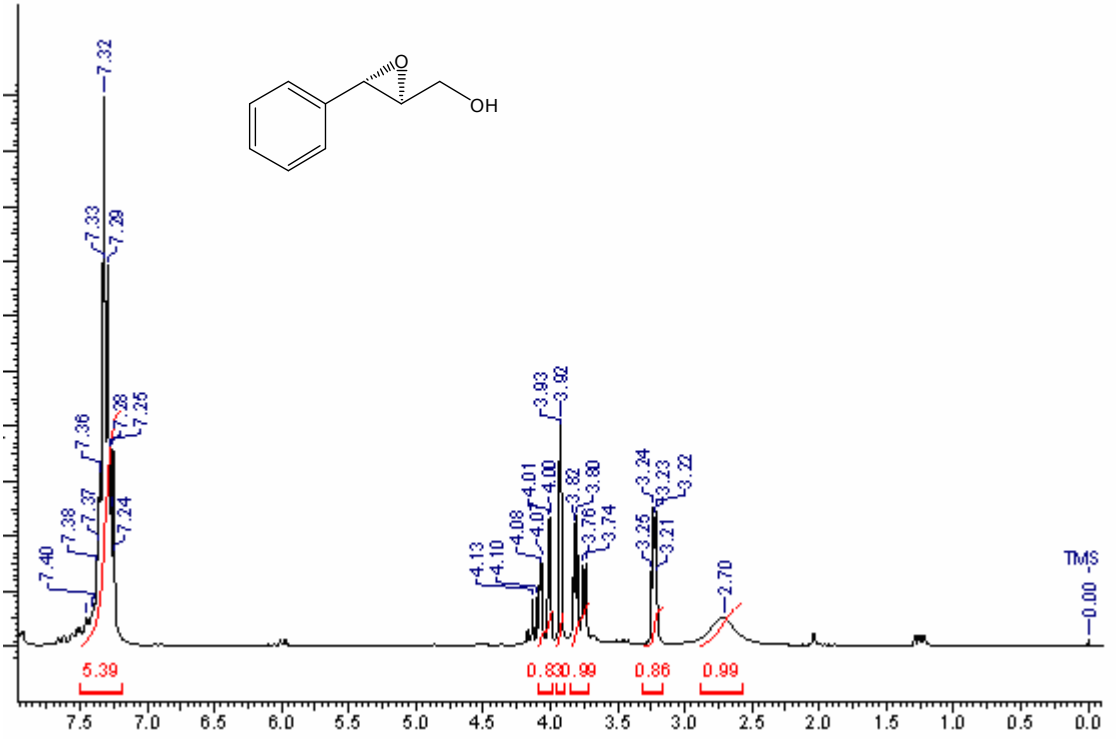
Elemental Analysis Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59%. Found: C, 82.50; H, 7.50; N, 4.65%.

3.3.7 Spectra

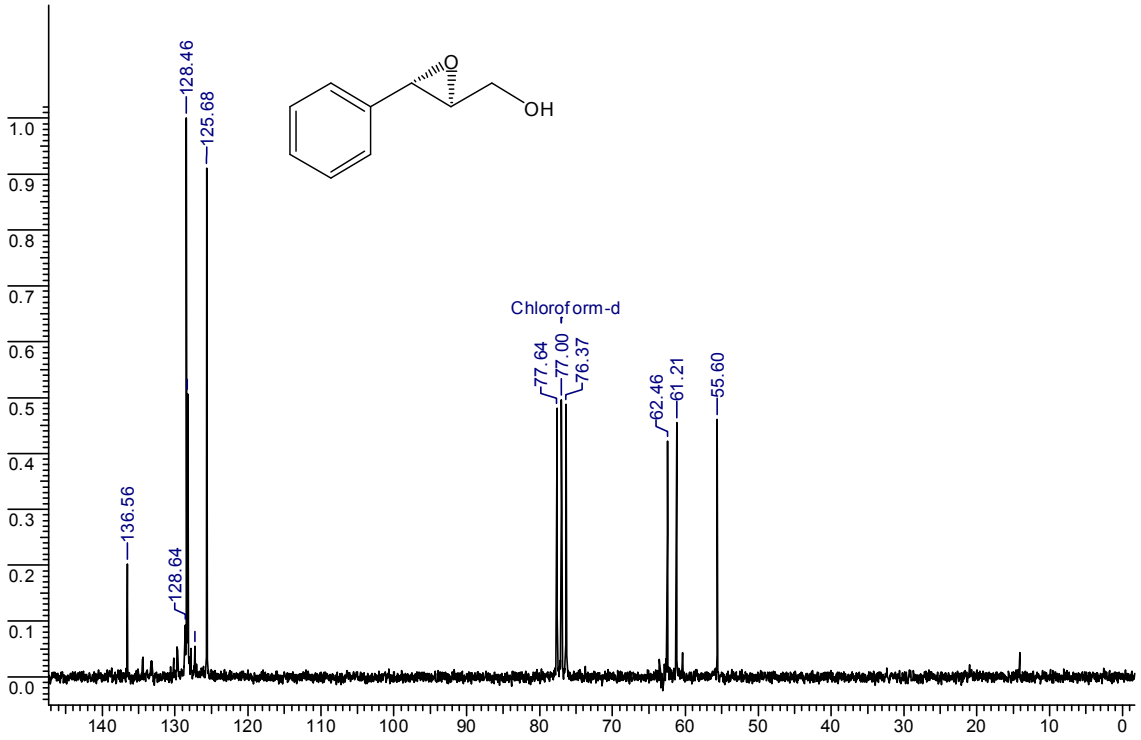
Table 3 ^{1}H & ^{13}C spectra of some the selected compounds are given below:

S No.	Spectra
1	^{1}H & ^{13}C spectra of **168**
2	^{1}H & ^{13}C spectra of **169**
3	^{1}H & ^{13}C spectra of **170**
4	^{1}H spectrum of **173**
5	^{1}H & ^{13}C spectra of **175**
6	^{1}H & ^{13}C spectra of (*S*)-Dapoxetine **IX**

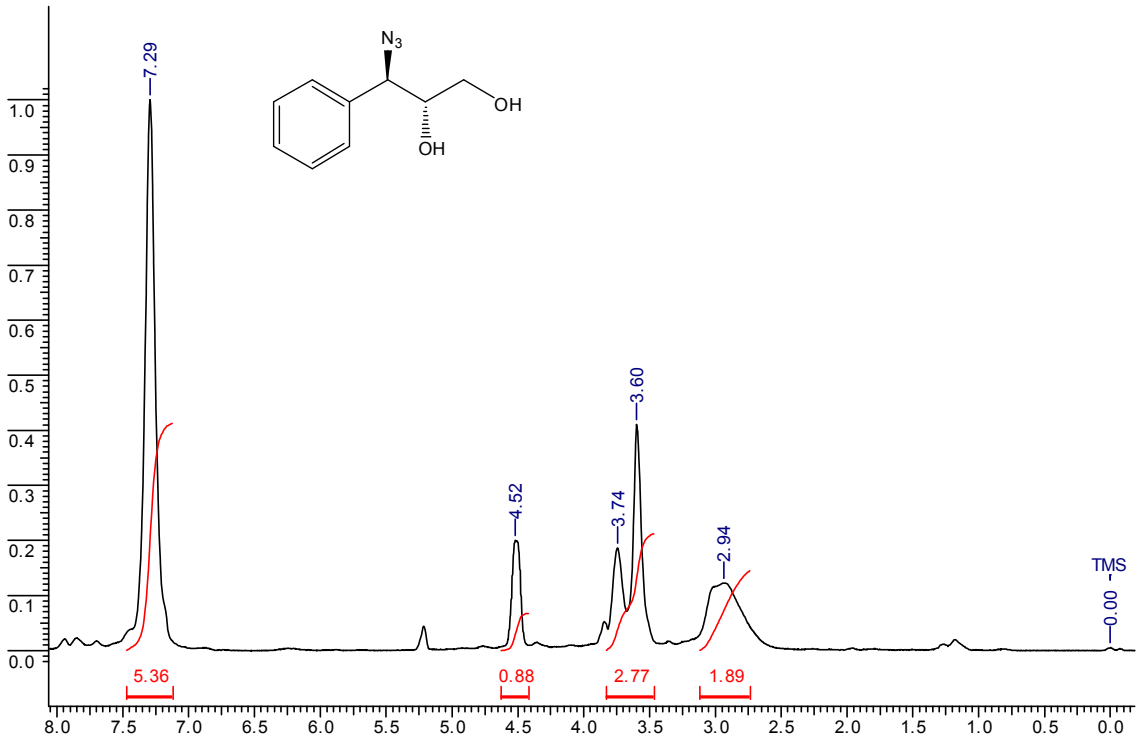
^{1}H-NMR spectrum of **168**



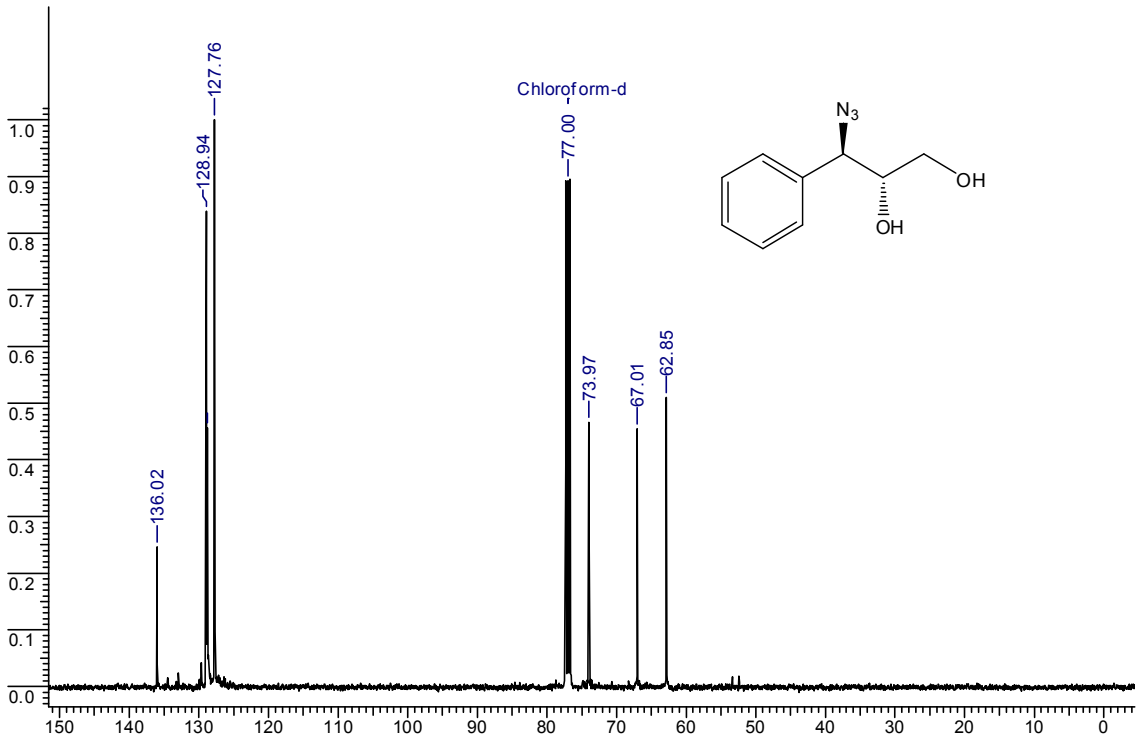
^{13}C-NMR spectrum of **168**



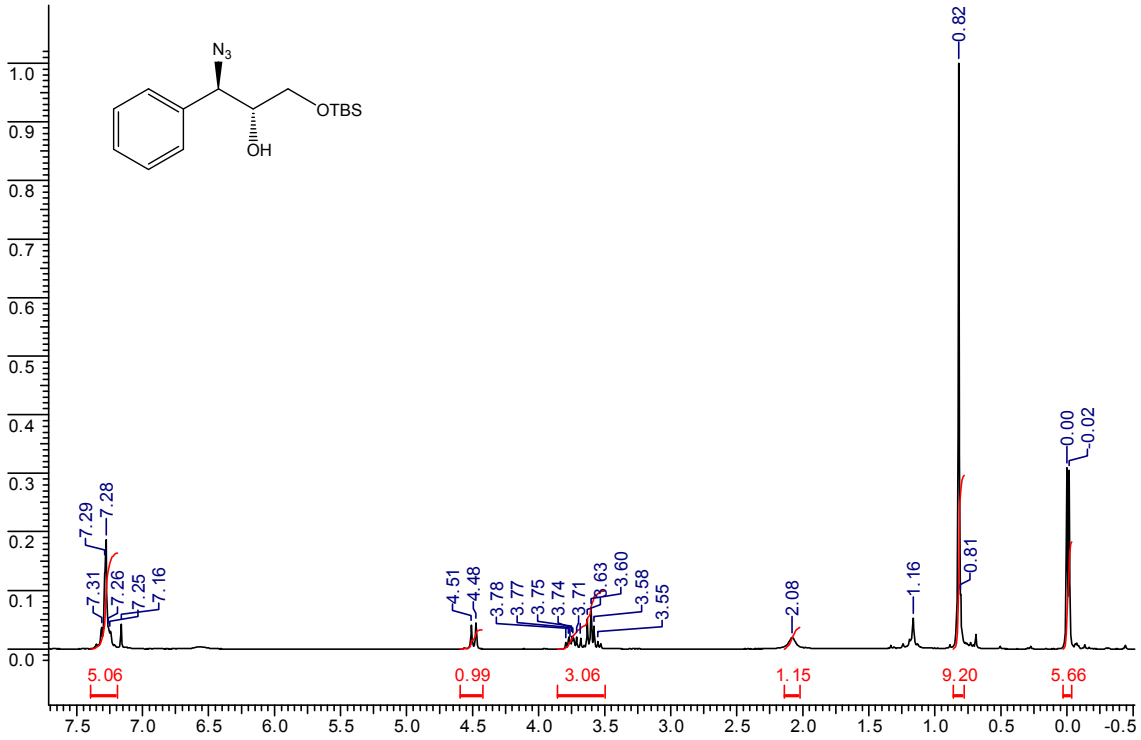
^{1}H-NMR spectrum of **169**



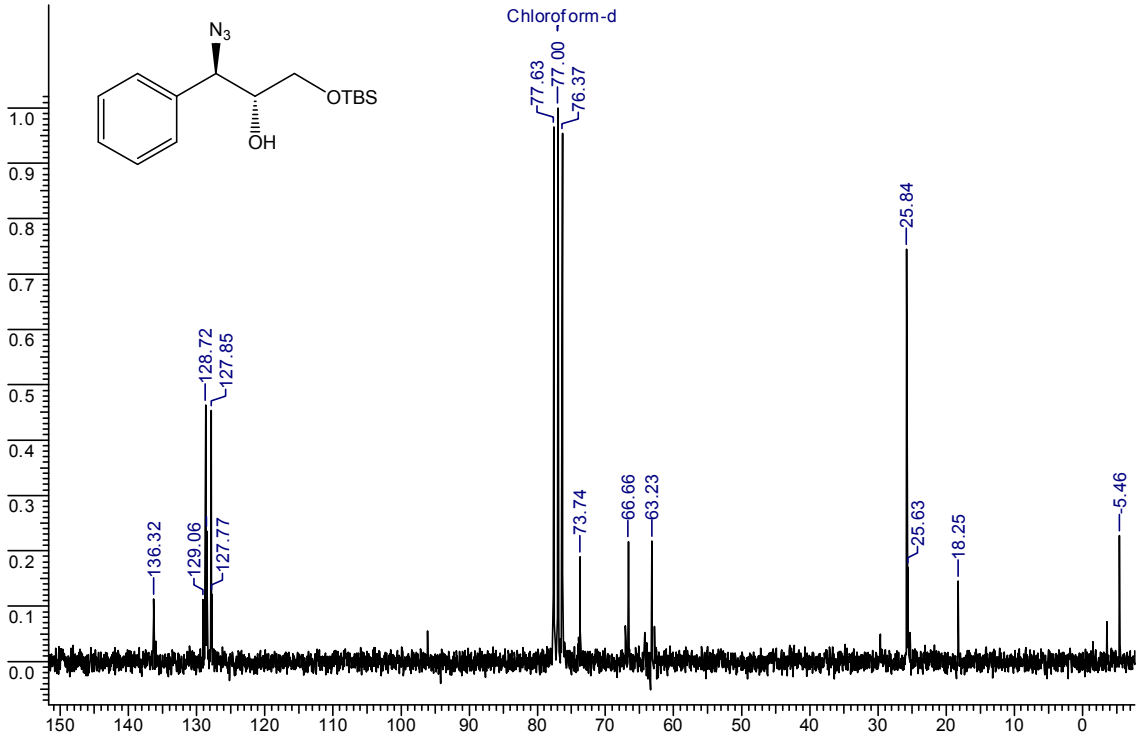
^{13}C-NMR spectrum of **169**



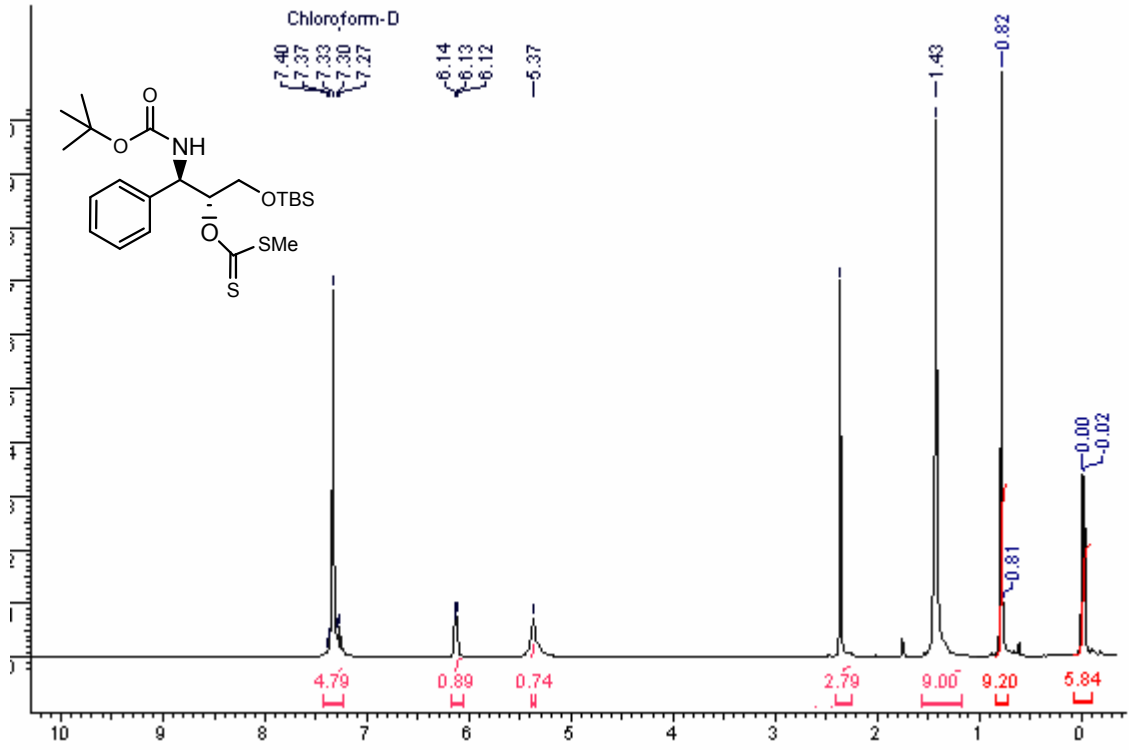
^{1}H-NMR spectrum of **170**



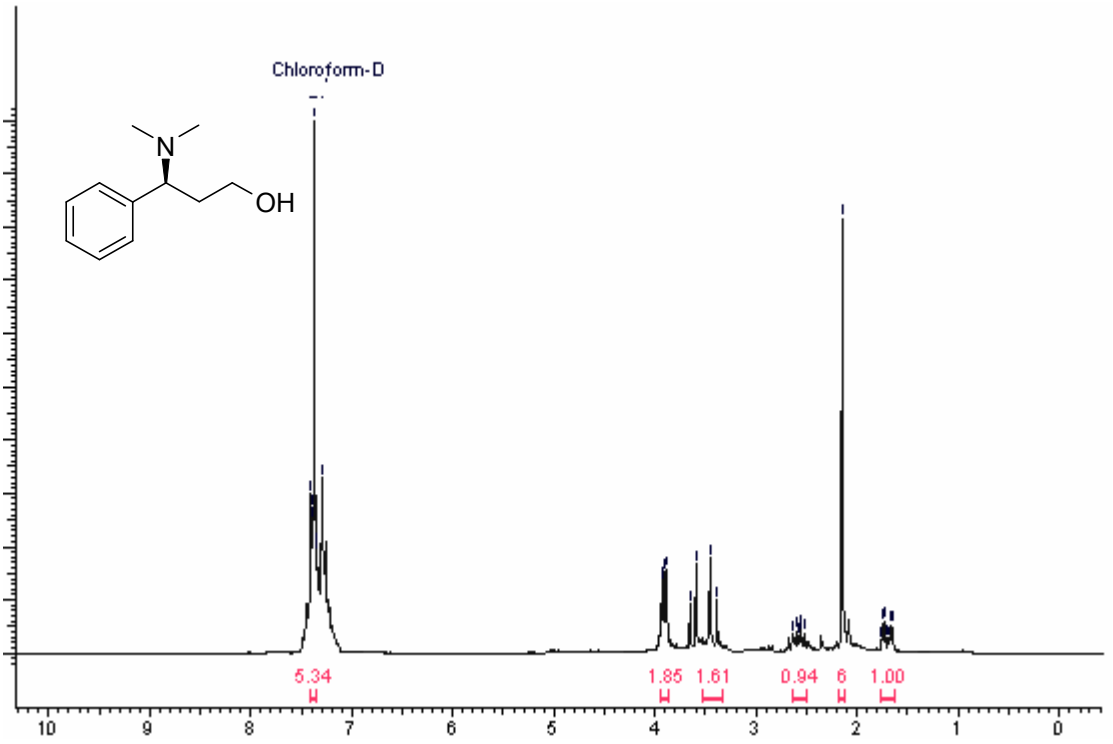
^{13}C-NMR spectrum of **170**



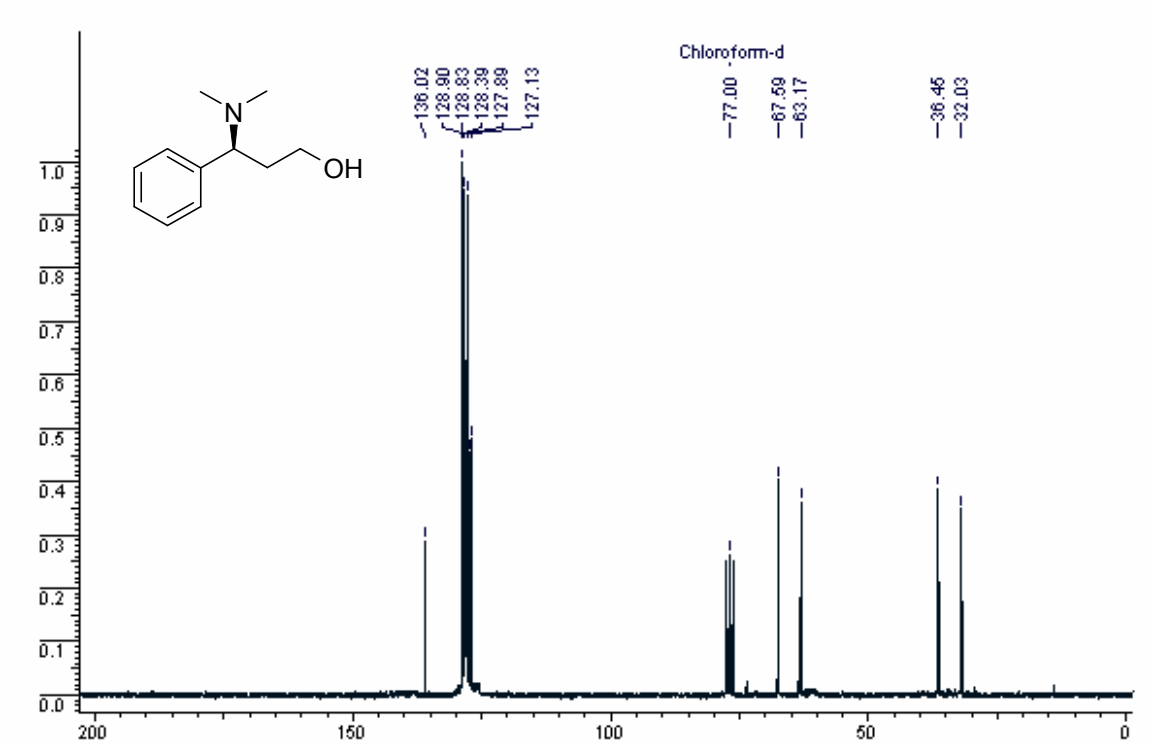
^{1}H NMR spectra of 173



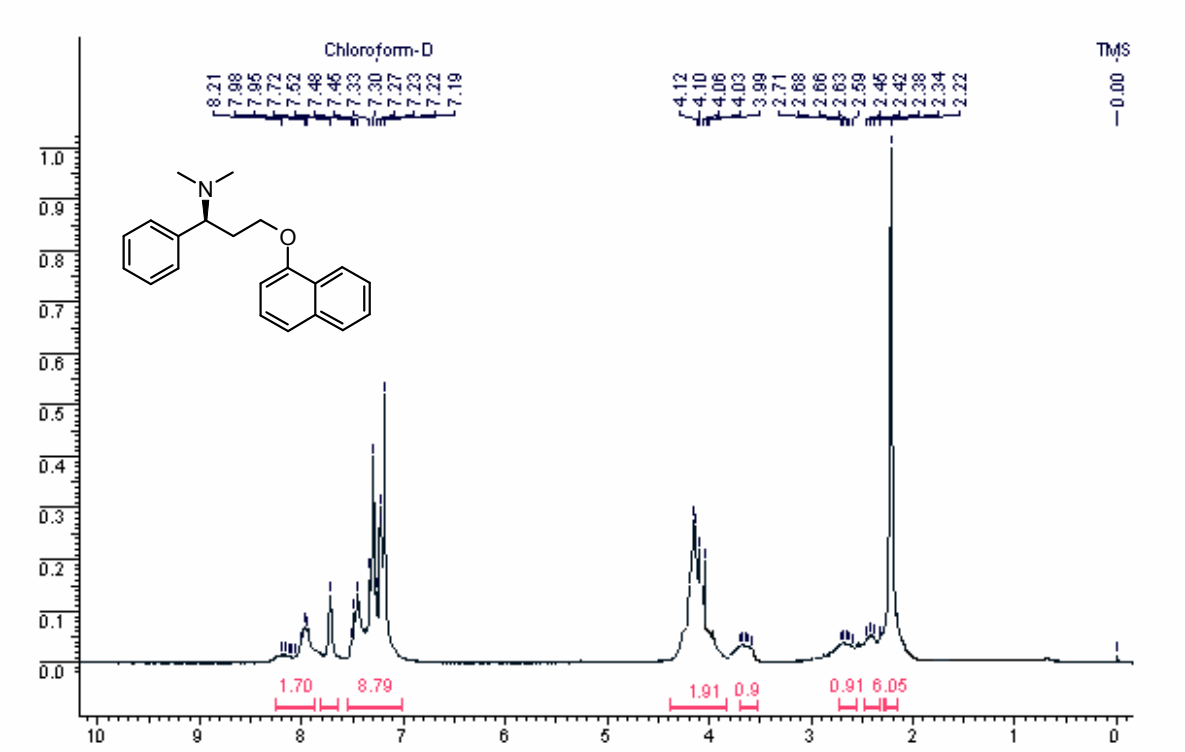
^{1}H-NMR spectrum of 175



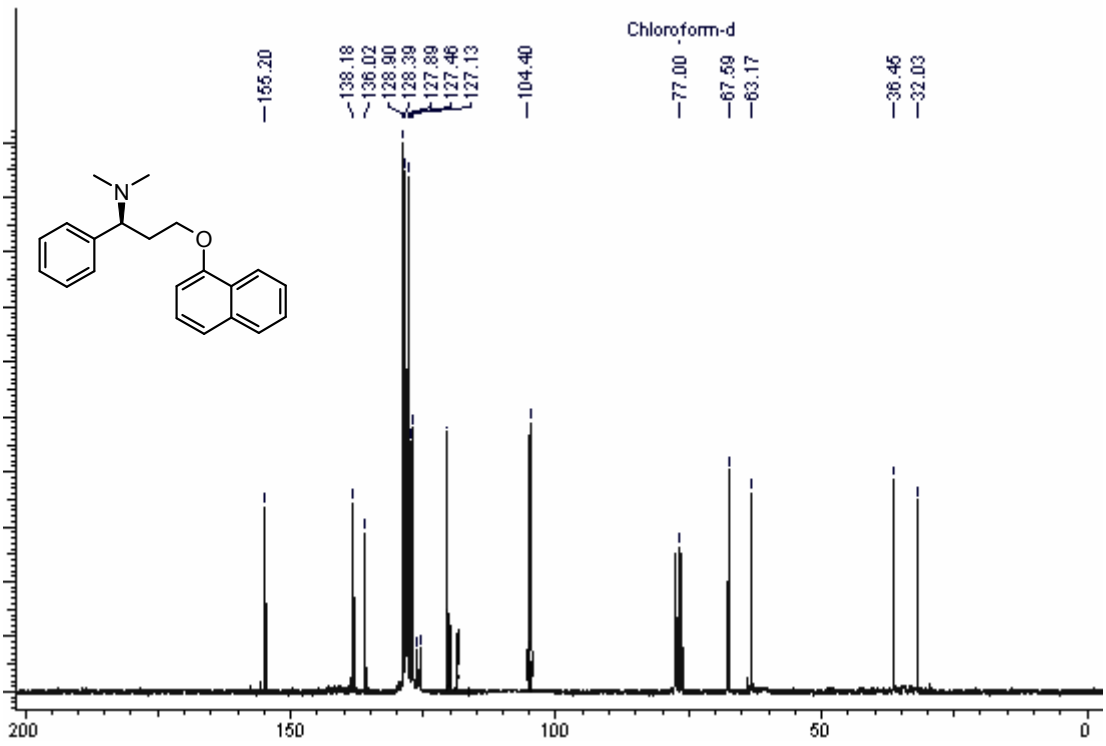
^{13}C NMR spectrum of 175



^{1}H NMR spectrum of (*S*)-Dapoxetine (IX)



^{13}C NMR spectrum of (*S*)-Dapoxetine (IX)



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List of Publications

1. Ultrasound promoted acetylation of alcohols in room temperature ionic liquid under ambient conditions, Atul R. Gholap, **K. Venkatesan**, Thomas Daniel, R. J. Lahoti and K. V. Srinivasan, *Green chem.*, **2003**, *5*, 693-696.

2. An efficient synthesis of 1,8-dioxo-octahydro-xanthene derivatives promoted by a Room Temperature Ionic Liquid at ambient conditions under ultrasound irradiation, **K. Venkatesan**, Suresh S. Pujari, R.J. Lahoti and K.V. Srinivasan, *Ultrasonics Sonochemistry*, **2008**, *15*, 548.

3. Stereoselective selective synthesis of Pachastrissamine (Jaspine B) starting from 1-pentadecanol, **K. Venkatesan** and K.V. Srinivasan, *Tetrahedron: Asymmetry*, **2008,** *19*, 209.

4. Proline catalyzed simple and efficient synthesis of 1,8-dioxo-decahydroacridines in aqueous ethanol medium, **K. Venkatesan**, Suresh S. Pujari and K.V. Srinivasan, accepted for publication in *Synthetic communicaitons*.

5. Concise stereoselective synthesis of (S)-Dapoxetine starting from cinnamyl alcohol, **K. Venkatesan** and K.V. Srinivasan, Communicated to *Tetrahedron: Asymmetry*.

6. PEG-400 promoted one-pot synthesis of benzo[b]pyrans at ambient temperature, **K. Venkatesan** and K.V. Srinivasan, Communicated to *ARKIVOC*.

7. Ligand free Suzuki/ Suzuki-Miyaura coupling reactions catalyzed by Pd(0) nanoparticles at ambient conditions under ultrasound irradiation, **K. Venkatesan**, Harish Kumar and K. V. Srinivasan (manuscript under preparation**).**