Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles

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Doctor of Philosophy in Chemistry

Submitted by

Upasana Borthakur

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India
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Dedicated
To
My Parents and Sister

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles**" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Anil K. Saikia.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Date: Upasana Borthakur

IIT Guwahati

Indian Institute of Technology Guwahati
Department of Chemistry
North Guwahati, Guwahati-781039, India
Phone: +91 (361) 2582316; Fax: +91 (361) 2690762
Dr. Anil K. Saikia e-mail: asaikia@iitg.ernet.in
Professor

CERTIFICATE

This is to certify that **Miss Upasana Borthakur** has been working under my supervision since July 2014 as a regular registered Ph. D. student. I am forwarding her thesis entitled "**Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Date: Prof. Anil K. Saikia
IIT Guwahati Supervisor

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Upasana Borthakur

LIST OF ABBREVIATIONS

Ac	acetyl	LA	Lewis acid
Ar	aryl	LDA	lithium diisopropyl amide
Boc	*tert*-butoxycarbonyl	*m*-CPBA	*meta*-chloroperoxybenzoic acid
Bn	benzyl	mp	melting point
Bu	buytl	m/z	mass to charge ratio
CCDC	cambridge crystallographic data centre	NMR	nuclear magnetic resonance
COSY	correlated Spectroscopy	NOE	nuclear Overhauser effect
CSA	camphorsulfonic acid	NOESY	nuclear overhauser enhancement spectroscopy
Me	methyl	ORTEP	oak ridge thermal ellipsoid plot
DCE	1,2-dichloroethane	Ph	phenyl
DCM	dichloromethane	ppm	parts per million
DIAD	diisopropyl azodicarboxylate	Pr	propyl
DMAP	4-dimethylaminopyridine	*p*-TSA	*p*-toluenesulfonic acid
DMF	*N*, *N*-dimethylformamide	rt	room temperature
DMSO	dimethyl sulfoxide	TEA	triethyl amine
de	diastereomeric excess	Tf	trifluoromethanesulfonyl
dr	diastereomeric ratio	TFA	trifluoroacetic acid
ee	enantiomeric excess	THF	tetrahydrofuran
Et	ethyl	TLC	thin layer chromatography
HMQC	Heteronuclear Multiple-Quantum Correlation	TMS	trimethylsilyl
IR	infrared	Tol	*p*-Toluyl
KBr	potassium bromide	Ts	*p*-toluenesulfonyl

Abbreviations for intensities of ^{1}H-NMR signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	brs	broad signal
dddd	doublet of doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet	MHz	Mega-Hertz

Abstract

The contents of this thesis have been divided into five chapters based on the results gathered by various experiment work performed during the complete course of the research period. The chapter **1** presents an introduction to oxygen, nitrogen and sulfur containing heterocyclic compounds, their biological importance and different literature methods for their synthesis. Chapter **2** describes synthesis of tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* cascade cyclization and Friedel-Crafts reaction. In Chapter **3**, use of vinylsilanes in diastereo- and regio-selective synthesis of dihydropyrans *via* oxonium-ene cyclization reaction has been reported. Chapter **4** is about the use of vinylsilanes in highly diastereo- and regio-selective synthesis of 1,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one *via* iminium–ene cyclization reaction. Chapter **5** deals with bismuth triflate catalyzed highly diastereoselective synthesis of substituted tetrahydrothiophene *via* tandem isomerization, Michael and aldol reactions.

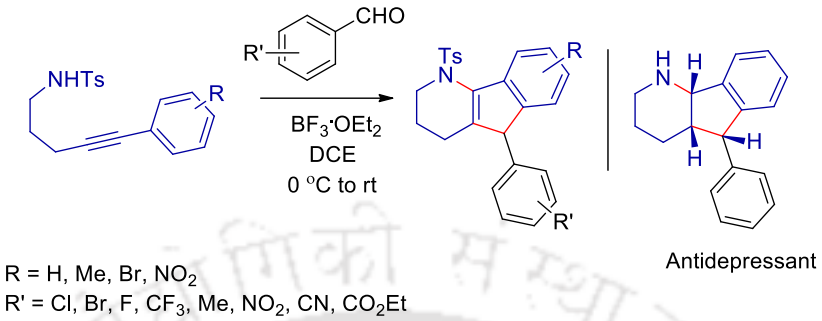
Chapter 1: An introduction to oxygen, nitrogen and sulfur containing heterocyclic compounds

Oxygen, nitrogen and sulfur containing heterocyclic compounds are widely encountered in almost all natural products, bioactive molecules and are also important synthetic intermediates. They are the core units of pharmaceutical chemistry and hence play a key role in designing of new drugs. For the synthesis of these heterocycles, various methods have been developed such as 1,*n*-enyne rearrangement, Prins cyclization, hetero-Diels–Alder cyclization, intramolecular ene cyclization, transition metal salts catalyzed cyclization reactions, ring-closing metathesis and cascade reactions. Among various above methods stated, this thesis mainly discusses about cascade reactions and ene cyclization reactions.

Chapter 2: Synthesis of Tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* Cascade Cyclization and Friedel-Crafts Reaction

Indenopyridine framework is one of the most privileged heterocyclic scaffolds since it appears in 4-aza-fluorenone group of alkaloids. Cascade reactions are gaining importance in organic synthesis due to its ability to form complex molecular framework. Similarly, Friedel-Crafts reaction is one of the important reaction in organic synthesis for C-C bond formation. Hereby, we present an efficient method for the synthesis of tetrahydro-1*H*-indeno[1,2-*b*]pyridine framework from the reaction of 4-methyl-*N*-(pent-4-yn-1-

yl)benzenesulfonamides and aldehydes following cascade reaction. The above strategy has been successfully applied to the synthesis of (±)-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno-[1,2-*b*]pyridine, which shows some amount of antidepressant activity.



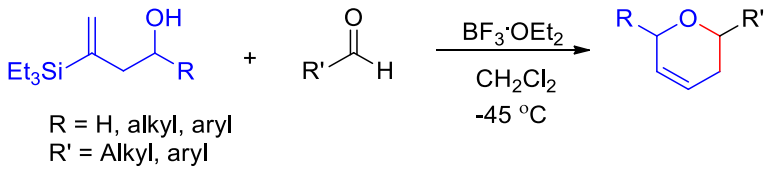
Scheme 1

To determine the optimal condition, various Lewis and Bronsted acids were screened in different solvent. Metal triflates and salts were also examined. It was observed that boron trifluoride etherate ($BF_3{\cdot}OEt_2$) (2.0 equiv) in 1,2-dichloroethane (DCE) solvent gave the most optimized condition With this optimized condition, substrate scope of the reaction was explored with various alkynes and aldehydes and corresponding indenopyridines were obtained with 53-87% yield.

In conclusion, a mild and efficient method has been developed for the synthesis of tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* cascade cyclization of alkyne tosylamides and aryl aldehydes in good yields and further used the methodology for the synthesis of biologically active molecule (±)-5-Phenyl-2,3,4,4*a*,5,9*b*-hexahydro-1*H*-indeno[1,2-*b*]pyridine.

Chapter 3: Vinylsilanes in Highly Diastereo- and Regio-selective Synthesis of Dihydropyrans

Oxonium-ene reaction is gaining importance in organic synthesis due to its ability to form carbon-carbon, carbon-heteoatom bonds in a single step and its diastereoselectivity. In this chapter, an efficient method for the synthesis of diastereo- and regio-selective synthesis of dihydropyrans *via* oxonium-ene cyclization reaction using vinylsilanes and aldehydes as substrates has been described.

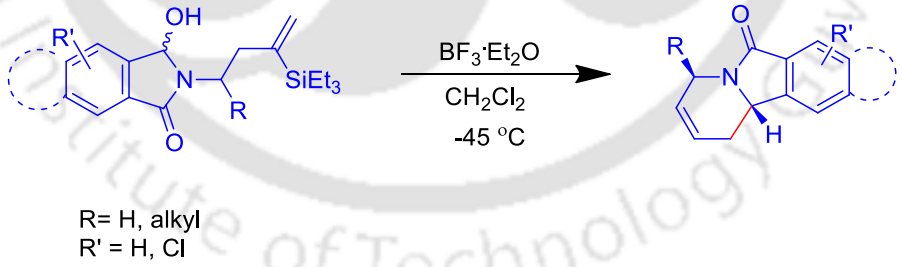


The reaction was optimized with various Lewis and Brønsted acids as well as metal salts and triflate, but boron trifluoride etherate ($BF_3{\cdot}OEt_2$) (1.2 equiv) in dichloromethane at -45 ^oC is found to be the best condition. Using this optimized condition, a variety of aldehydes and alcohols were evaluated as substrates and dihydropyrans were obtained as single diastereoisomer as well as single regioisomer. However, the reaction with aliphatic aldehydes and reaction of arylated secondary silylated alcohol with aldehyde gave the regioisomeric mixture. The formation of regioisomeric compounds could also be explained by considering stepwise oxonium-ene reaction.

To conclude, dihydropyrans were synthesized from aldehydes and silyl-homoallylic alcohols in moderate to good yields. The reaction proceeds *via* concerted oxonium-ene and stepwise oxonium-ene reactions. The oxonium-ene cyclization process provides single regioisomeric products whereas stepwise oxonium-ene reaction gives mixture of regioisomers. The reaction is also diastereo-selective.

Chapter 4: Vinylsilanes in highly Diastereo- and Regio-selective Synthesis of 1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one *via* Iminium–ene Cyclization Reaction.

The iminium–ene reaction is considered as an efficient method for the synthesis of nitrogen-containing heterocycles where the imine moiety behaves as an enophile. In this chapter a methodology for the synthesis of isoindolone following iminium–ene cyclization *via* the formation of *N*- acyliminium ion has been described**.**



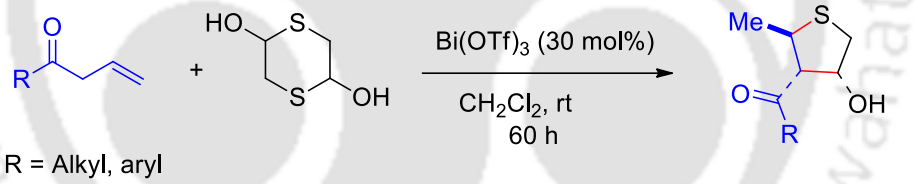
Out of various reagents examined, boron trifluoride etherate ($BF_3{\cdot}OEt_2$) (2.0 equiv) in dichloromethane at -45 ^oC was found to be the best condition for this reaction. With this optimized condition, substrate scope was studied with both primary and secondary *N*-substituted homoallylic vinylsilanes and the reaction gave the desired products as a single diastereoisomer as well as single regioisomer. However, regioisomeric mixture was

obtained in case of succinimide derivative, which can be explained by considering stepwise iminium-ene reaction.

In conclusion, we have demonstrated a simple methodology for the synthesis of isoindolones from *N*- homoallylic amido alcohols in presence of Lewis acid in good to high yields. The reaction proceeds *via* concerted iminium-ene reaction to provide single regioisomeric products as well as single diastereomer. It also proceeds *via* stepwise manner to give regioisomeric mixture in case of succinimide derivative.

Chapter 5: Bismuth(III) Triflate Catalyzed Highly Diastereoselective Synthesis of Substituted Tetrahydrothiophene *via* Tandem Isomerization, Michael and Aldol Reactions.

Domino reactions are gaining importance in recent times because of formation of several C-C and C-X (heteroatom) bonds in a single step, ease of operation, atom economic and minimization of waste. In this chapter a bismuth(III) trifluoromethanesulfonate ($Bi(OTf)_3$) catalyzed reaction of *β,γ*-unsaturated ketone and 1,4-dithiane-2,5-diol affording highly substituted tetrahydrothiophenes *via* sequential rearrangement, Michael and aldol reactions has been disclosed.



The reaction was performed with various Lewis/Bronsted acids as well as different metal salts and triflates and it was found that Bismuth(III) Triflate ($Bi(OTf)_3$) (0.3 equiv) at room temperature gives the most optimized condition The reaction was extended to various ketones and corresponding tetrahydrothiophenes were obtained in 53-82% yield with a diastreomeric ratio up to >98:2

In conclusion we have demonstrated a methodology for the construction of substituted tetrahydrothiophenes in good yields *via* domino double bond rearrangement, Michael and aldol reactions with high diastereoselectivity. The major advantages of the reaction are that three reactions can be performed with a single catalyst in one pot thereby reducing time, reagents, solvents, waste and cost.

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CHAPTER 1

Introduction to Oxygen, Nitrogen and Sulfur Heterocyclic Compounds

1.1 Introduction to Heterocyclic Compounds

Cyclic compounds containing at least two different atoms as a member of the ring are referred to as heterocyclic compounds. Most of the known organic compounds include at least one heterocyclic ring. Generally, nitrogen, oxygen and sulfur are the most common heteroatoms but rings containing other heteroatoms, such as boron, silicon, phosphorus and selenium are also known. Many of them occur naturally and are active members of our biological system, e.g. heme, chlorophyll, nucleic acid (purine and pyrimidine bases), vitamins (thiamine, riboflavin) etc.[1] Because of their applications in medicine, agriculture, photodiodes and other fields they have covered a vast and expanding area of chemistry. Heterocyclic compounds can be classified as aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic analogues of amines, ethers and thioethers. The most common aliphatic heterocyclic compounds are oxirane (**1**), aziridine (**2**), thiirane (**3**), oxetane (**4**), azetidine (**5**), thietane (**6**) tetrahydrofuran (**7**), pyrrolidine (**8**), tetrahydrothiophene (**9**), tetrahydropyran (**10**), piperidine (**11**) and tetrahydothiopyran (**12**).

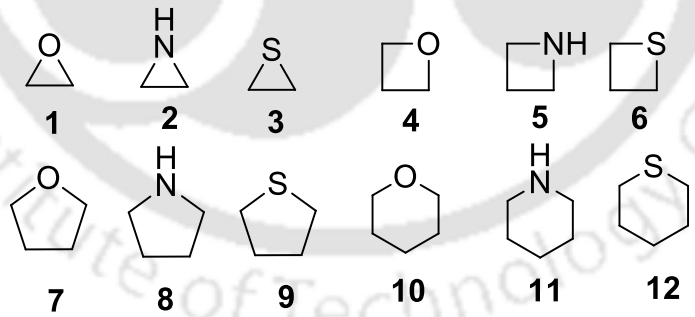


Figure 1.1.1. *Some common three to six membered saturated heterocycle.*

On the other hand, aromatic heterocycles are those who follow the Hückel rule for aromaticity, i.e., having cyclic, conjugated and planar systems and have (4n+2) π electron system. Furthermore, some of their properties resemble those of the benzene. The well-known simple aromatic heterocyclic compounds are furan (**13**), pyrrole (**14**), pyridine (**15**) and thiophene (**16**).

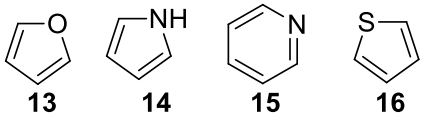


Figure 1.1.2. *Some common aromatic heterocycles.*

Apart from monocycles, fused heterocyclic ring systems are also encountered frequently. They are formed by the fusion of heterocycles with other rings, either carbocyclic or heterocyclic. Some common oxygen, nitrogen and sulfur containing fused heterocycles are indole (**17**), isoindolone (**18**), chroman (**19**), thiochroman (**20**) and quinoline (**21**)

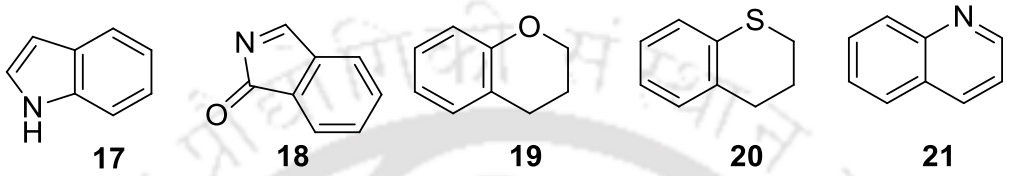


Figure 1.1.3. *Some common fused heterocycles.*

This introductory chapter is designed to highlight the importance of some oxygen, nitrogen and sulfur containing heterocyclic compounds such as dihydropyrans, tetrahydrothiophenes, indenopyridines, and isoindolones, and also manifest in the various methodologies for their synthesis.

1.2. Importance of pyridine derivatives like indenopyridines and isoindolones.

The indenopyridines are the class of nitrogen heterocycles containing a pyridine ring fused to indene moiety. Indenopyridine skeleton is present in a wide range of natural products and pharmaceutical drugs. Many of these molecules possess biological activity, like other nitrogen-containing alkaloids. For example, hexahydroindenopyridine (**22**) is a part of the new class of compounds known for their antidepressant action.[2] Other examples comprising of this structural unit, such as NSC314622 (**23**), MJIII- 65 (**24**), shows anticancer activities.[3] On the other hand, the 2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridine ring system is found in natural products such as haouamines A (**25**) and B (**26**), which are two metabolites isolated from the ascidian *Aplidium haouarianum*. *(Figure 1.2.1*).[4]

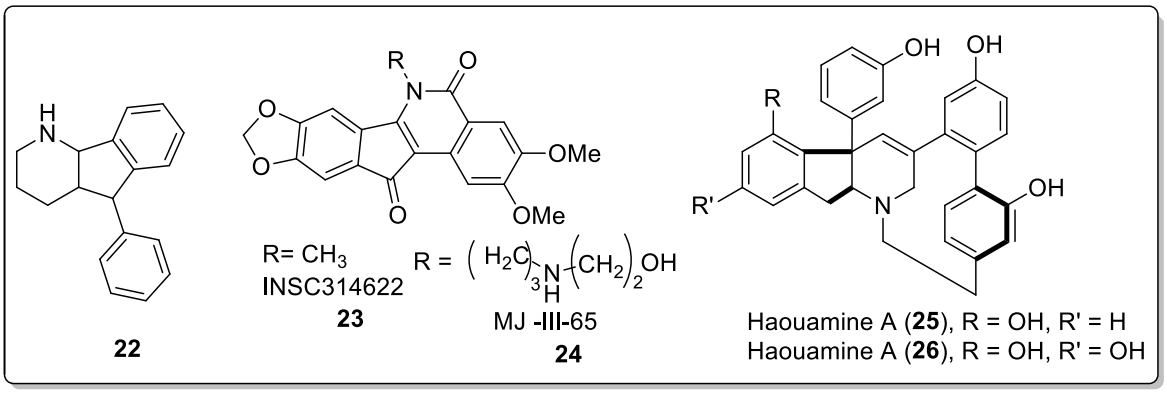


Figure 1.2.1. *Some bioactive molecules containing indenopyridines*

Another important class of fused nitrogen heterocycles is isoindolones. This scaffold is present in many biologically active compounds. Natural alkaloids, lennoxamine (**27**) and magallanesine (**28**) isolated from Berberis, contain isoindolone moiety.[5] Similarly, *N*-[(9*bS*)-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]-isoindol-9-yl]-*N*′-[5-({[(2*S*)-5-chloro-2,3-dihydro-1*H*-inden-2-yl]amino}-methyl)-1*H*-pyrazol-3-yl]urea (**29**) shows selective Cdk4/6 inhibitors activity.[6] Besides these, the isoindolone scaffold shows a series of other biological activities such as non-nucleoside HIV-1 reverse transcriptase inhibitors,[7] inhibitors of tubulin polymerization,[8] antiobesity agents,[9] TNF-α inhibitors,[10] and urotensin-II receptor antagonists (*Figure 1.2.2*).[11]

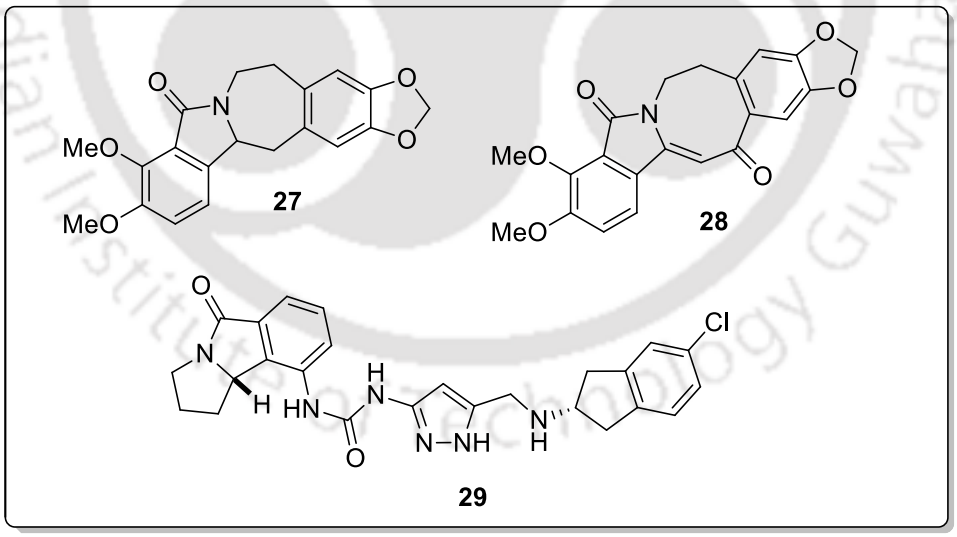


Figure 1.2.2. *Some bioactive molecules containing isoindolones*

1.3. Importance of dihydropyrans.

In organic chemistry, dihydropyrans refer to two heterocyclic compounds namely 3,4-dihydro-2*H*-pyran and 3,6-dihydro-2*H*-pyran. The double bond of dihydropyran is very reactive which can be added to various groups such as hydrogen, water, chlorine, hydrogen chloride, alkyl hypochlorites, phosgene, alcohols, glycols, and organic acids. Consequently,

dihydropyrans act as an important intermediate for a large number of organic syntheses.[12] They are the subunits of the various biologically active molecules. For example, 3,6-dihydro-2*H*-pyran unit containing molecule laulimalide (**30**) known for its potent activity as an antimitotic agent like taxol.[13] Unlike taxol, it is active against multi-drug cell lines. Similarly, soranginin A (**31**) isolated from *Sorangium cellulosum* acts as a broad spectrum antibiotic.[14] Okadaic acid (**32**), is a toxin produced by several species of dinoflagellates, and is known to accumulate in both marine sponges and shellfish.[15] The dimeric 42 carbon-ring polyketides, swinholide (**33**) found mostly in the marine sponge *Theonella* shows cytotoxic and antifungal activities *via* disruption of the actin skeleton (*Figure 1.3.1*).[16]

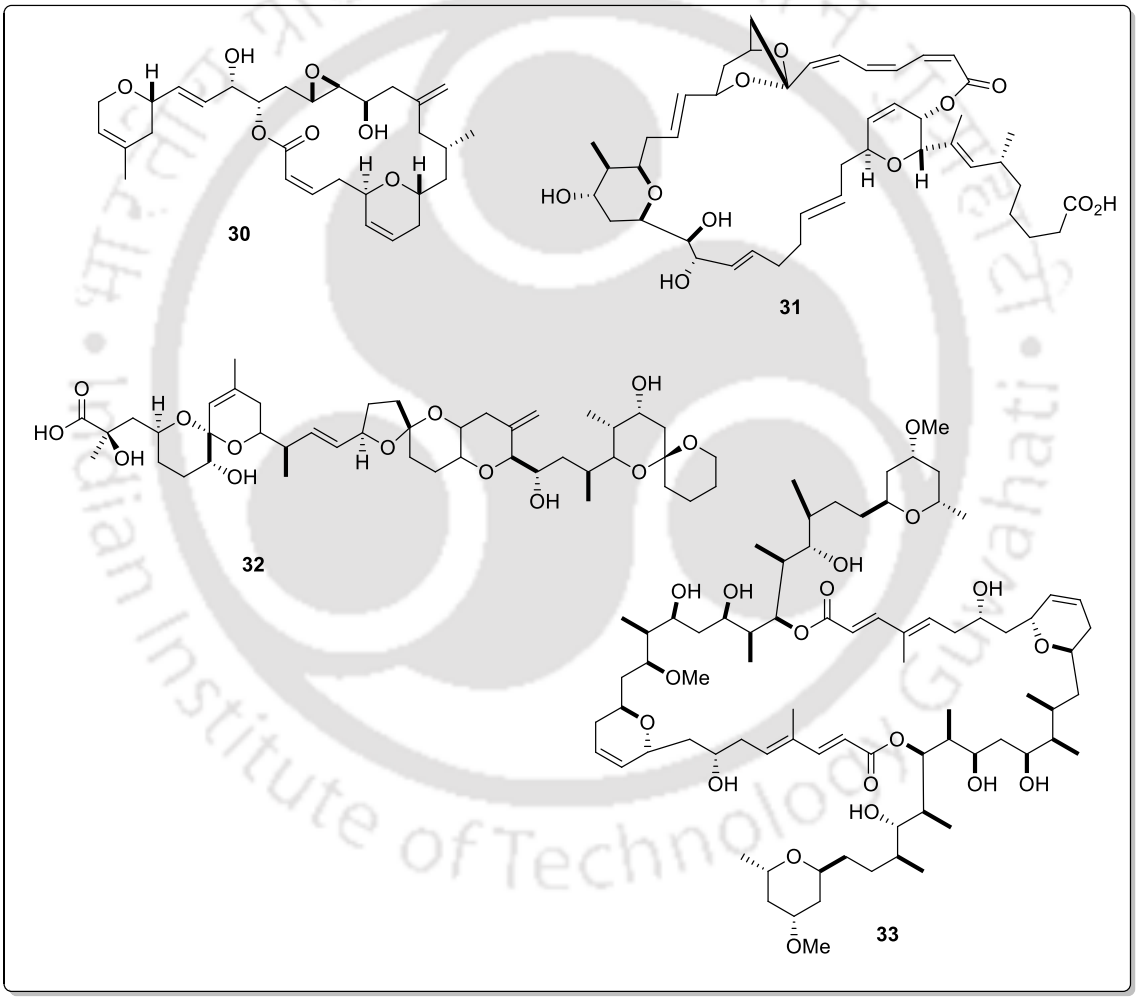


Figure 1.3.1. *Some bioactive molecules containing dihydropyran*

1.4. Importance of tetrahydrothiophenes.

The tetrahydrothiophene is the core structural unit of many natural products and pharmaceutical agents. For example, biotin (**34**), a water-soluble B vitamin, required for normal cellular functions and growth, possess tetrahydrothiophene moiety.[17] Similarly,

bioactive molecule breynin A (**35**) isolated from Taiwanese woody shrub *Breynia officinalis* Hemsl. acts as potent hypocholesterolemic glycosides in rats.[18] Apart from these, other bioactive compounds containing tetrahydrothiophene moiety are the anti-HIV nucleoside **36**,[19] and the analogues of penicillin (**37**)[20] (*Figure 1.4.1*). Moreover, tetrahydrothiophenes also act as anti-oxidative agents,[21] hypercholesterolemic agents,[22] and plant growth regulators.[23]

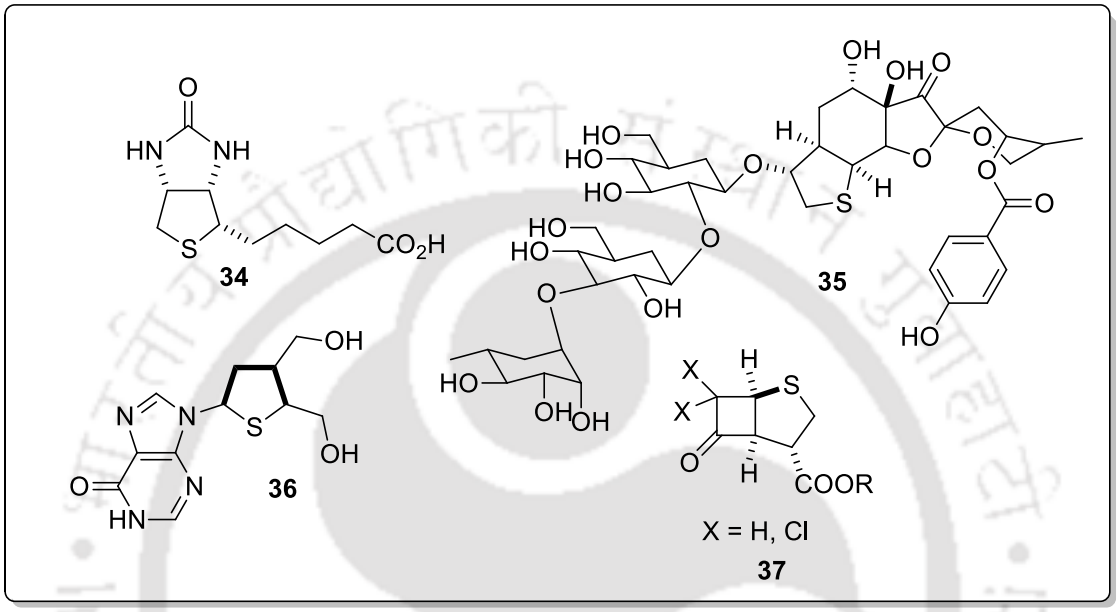


Figure 1.4.1. *Some bioactive molecules containing tetrahydrothiophenes*

1.5. An overview for the synthesis of oxygen, nitrogen and sulphur heterocycles

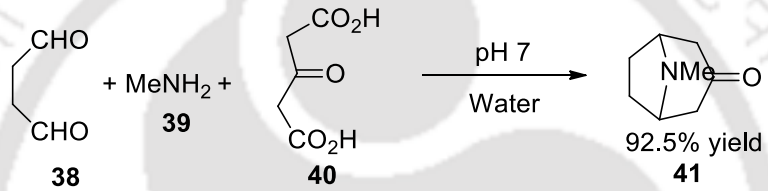
Due to the immense presence of oxygen, nitrogen and sulfur heterocycles in natural products and bioactive compounds, development of efficient methods for the synthesis of these heterocycles have been a subject of great interest for organic researchers. Over the years, many strategies have been developed to build these compounds, among the most widely used methods are the 1,*n*-enyne rearrangement, ring-closing metathesis, cascade reaction, Prins cyclization reaction, transition metal salts catalyzed cyclization reactions, ene reactions, and hetero-Diels-Alder cyclization. Out of the above stated methods, this thesis will focus mainly on the cascade and ene reaction in details.

1.5.1. Cascade reaction

A cascade reaction also called domino reaction or tandem reaction can be defined as the chemical process, consisting of at least two consecutive reactions such that each step occurs only in virtue of the chemical functionality formed in the previous step. Cascade reactions nowadays have become a subject of intense research. Its immense growing

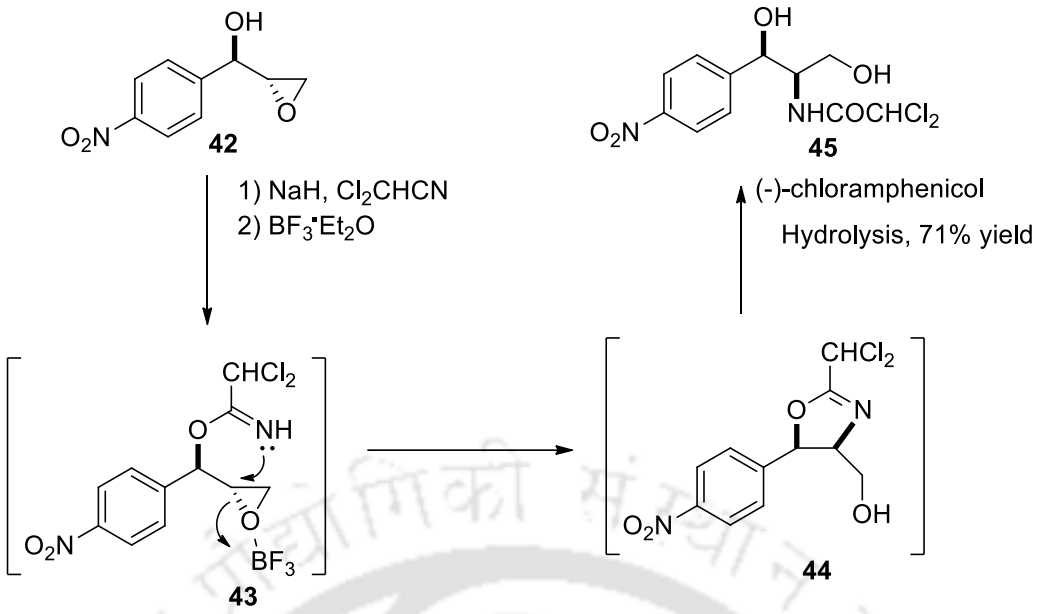
popularity is due to its undeniable benefits over others which includes atom economy, reduction in quantities of chemicals, solvent used and eventually decrease in waste generated by them as well as time and effort to carry them out. Based on the mechanism involved, K. C. Nicolaou labels the cascades as nucleophilic/electrophilic, radical, pericyclic or transition-metal-catalyzed cascade reaction.[24] Herein, we have given a summary of different cascade reactions involved in the synthesis of heterocycles from literature and will particularly study in details about cascade or domino Michael and aldol reaction.

One of the earliest examples of cascade reaction in literature is the synthesis of tropinone (**41**) in 1917 by Robert Robinson. An intramolecular double Mannich reaction was carried out between succinaldehyde (**38**), methylamine (**39**) and acetonedicarboxylic acid (**40**) at pH 7 in water to afford tropinone (**41**) in 92.5% yield (*Scheme 1.5.1.1)* **.**[25]



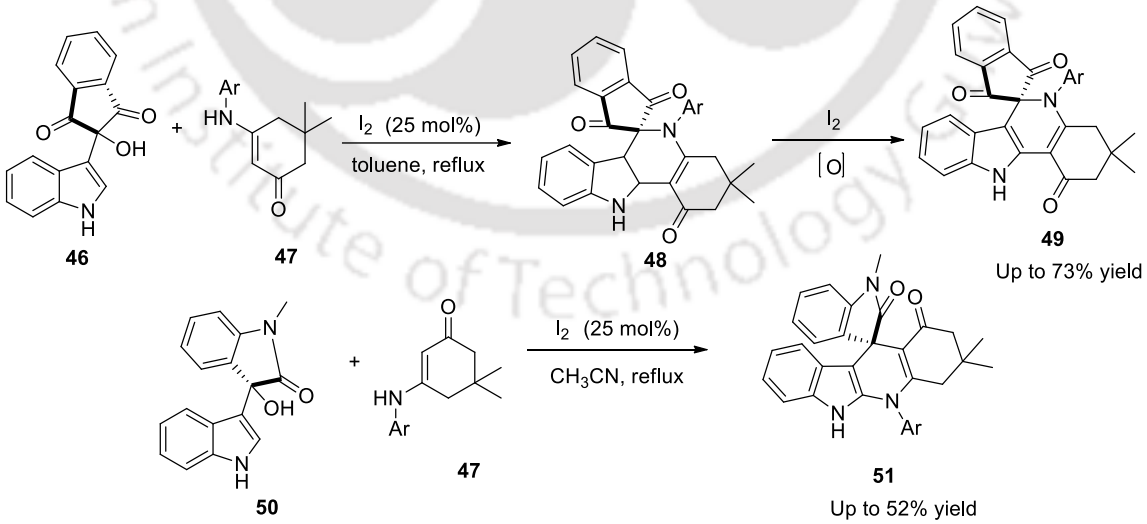
Scheme 1.5.1.1

Rao and coworkers have described a strategy for the synthesis of the broad-spectrum antibiotic (–)-chloramphenicol. The chiral epoxy alcohol **42** upon treatment with dichloroacetonitrile in the presence of NaH formed intermediate **43**, which is followed by $BF_3.OEt_2$ mediated cascade reaction involving the intramolecular opening of epoxy dichloroimidates to give intermediate **44**, which after an *in situ* hydrolysis facilitated by excess $BF_3 \cdot OEt_2$, afforded (–)-chloramphenicol (**45**) in 71% overall yield (*Scheme 1.5.1.2)***.**[26]



Scheme 1.5.1.2

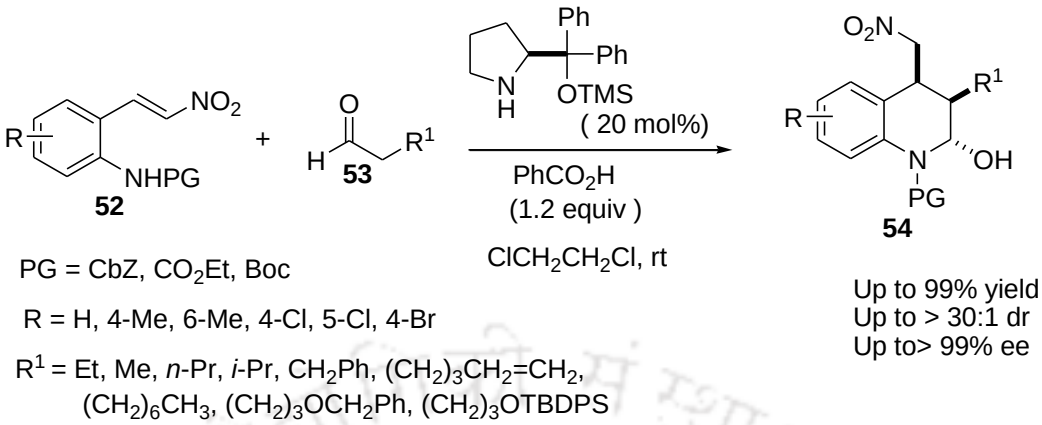
Hao *et al*. had developed a simple method for the synthesis of spiro-dihydro carboline derivatives *via* an iodine-catalyzed cascade formal [3+3] cyclo-addition reaction. In the presence of iodine, 2-hydroxy-2-(1*H*-indol-3-yl)-2*H*-indene-1,3-dione (**46**) reacts with enaminones **47** following 1,4 then 1,2 addition to afford the [3+3] cyclized tetrahydrogen carboline intermediate **48** which is then easily oxidized to give the spirodihydro-γ-carboline **49** derivatives. However, when 3-hydroxy-3-(1H-indol-3-yl)-1-methylindolin-2- one (**50**) was subjected to the reaction with enaminones, α-carboline derivatives **51** were obtained in moderate yields in CH_3CN instead of γ-carboline (*Scheme 1.5.1.3*)**.**[27]



Scheme 1.5.1.3

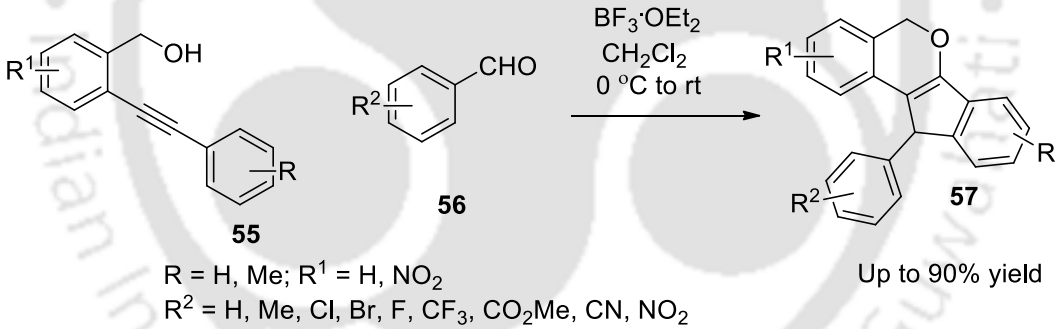
In 2014, Lee *et al*. have reported a highly enantioselective synthesis of chiral tetrahydroquinolines **54** by a Michael addition/aza-cyclization cascade reaction of aldehydes **53** with 2-amino-β- nitrostyrenes **52.** The reaction is catalysed by

diphenylprolinol TMS to give the desired tetrahydroquinolines in good to high yield with excellent diastereo- and enantioselectivities (*Scheme 1.5.1.4*)**.**[28]



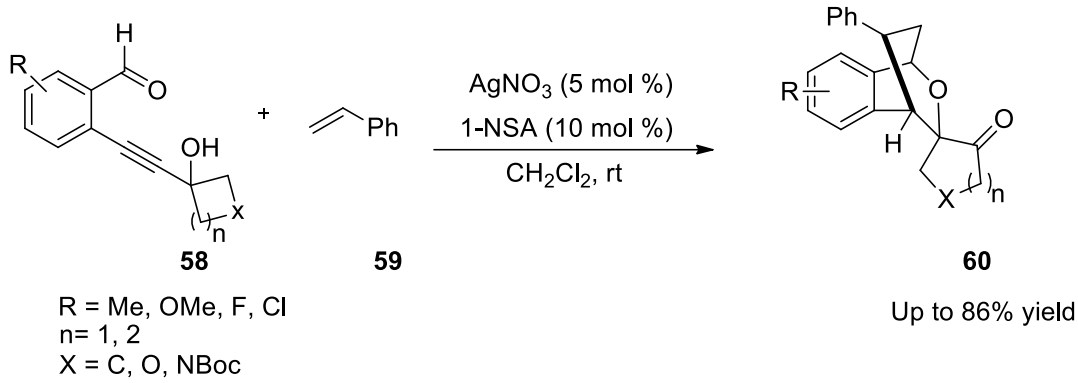
Scheme 1.5.1.4

In 2016, Saikia and coworkers have reported a $BF_3.OEt_2$ mediated intermolecular cascade cyclization and Friedal-Craft reaction between alkynol **55** and aromatic aldehydes **56** to form four-membered dihydroindeno[1,2-*c*]isochromene **57** in a good to excellent yields. The aspect of this reaction is that it produces dihydroindeno[1,2-*c*]isochromene regioselectively (*Scheme 1.5.1.5*)**.**[29]



Scheme 1.5.1.5

Recently, Li and coworkers, reported a highly stereoselective synthesis of spirocineole scaffolds from 2-alkynylbenzaldehydes **58** and styrenes **59** under very mild reaction condition. The reaction proceeds *via* Ag(I)-catalyzed alkyne cyclo-isomerization and oxa-[4+2]-cycloaddition to give an oxonium intermediate followed by 1,2-alkyl migration to provide spiro-2-oxabicyclo[2.2.2]octanes **60** in high yields with excellent stereoselectivities (*Scheme 1.5.1.6*) **.**[30]

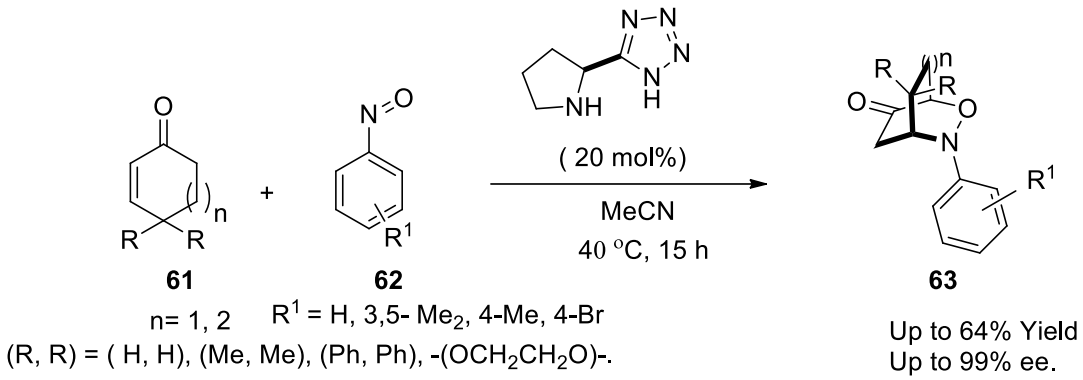


Scheme 1.5.1.6

1.5.1.1 Domino Michael and aldol reactions

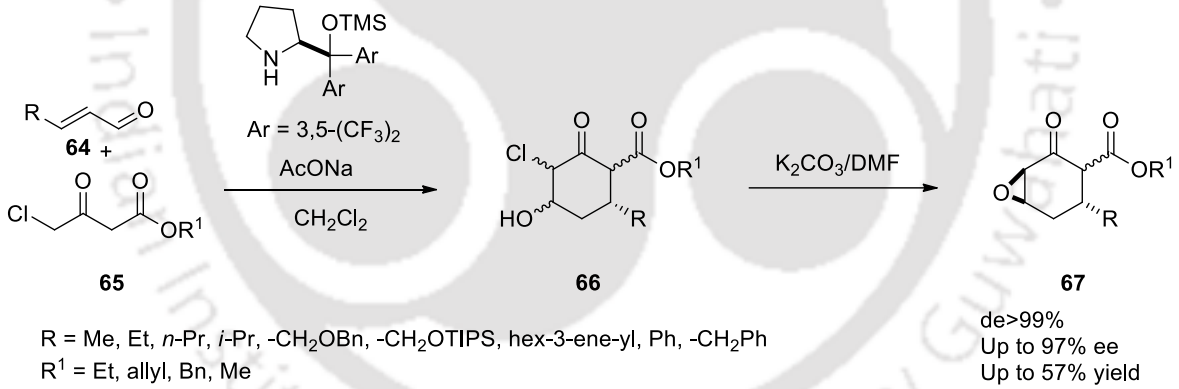
The aldol condensation reaction is a classical reaction for C-C bond formation[31] and is used for the synthesis of biologically active molecules and natural products.[32] Similarly, Michael reactions are considered as a tool for C-C bond formation reactions and has been used for construction of complex molecules in organic synthesis.[33] Domino (cascade or tandem) Michael-aldol are the consecutive series of reactions involving Michael and aldol reactions. Domino reactions are gaining importance in recent times because of formation of several C-C and C-X (heteroatom) bonds in a single step, ease of operation, atom economic and minimization of waste. One of the classic reaction is Robinson annulation which involves a Michael addition followed by an aldol condensation.[34] Gary Posner *et al*. were the first to report the construction of macrolide structures *via* multiple Michael/aldol reactions.[35] Some of the recent methodologies for synthesizing heterocycles *via* domino Michael and aldol reactions are discussed below.

In 2004, Yamamoto and coworkers reported a domino *O*-nitroso aldol/Michael reaction to produce nitroso Diels-Alder adducts **63**. The reaction proceeds *via* an *O*-nitroso aldol reaction between various enones **61** and nitrosobenzenes **62** in the presence of 20 mol% of pyrrolidine based tetrazoles catalyst followed by Michael reaction at 40 °C in MeCN as the solvent to afford the Diels-Alder adducts with yield up to 64% and 99% ee. (*Scheme 1.5.1.1.1).*[36]



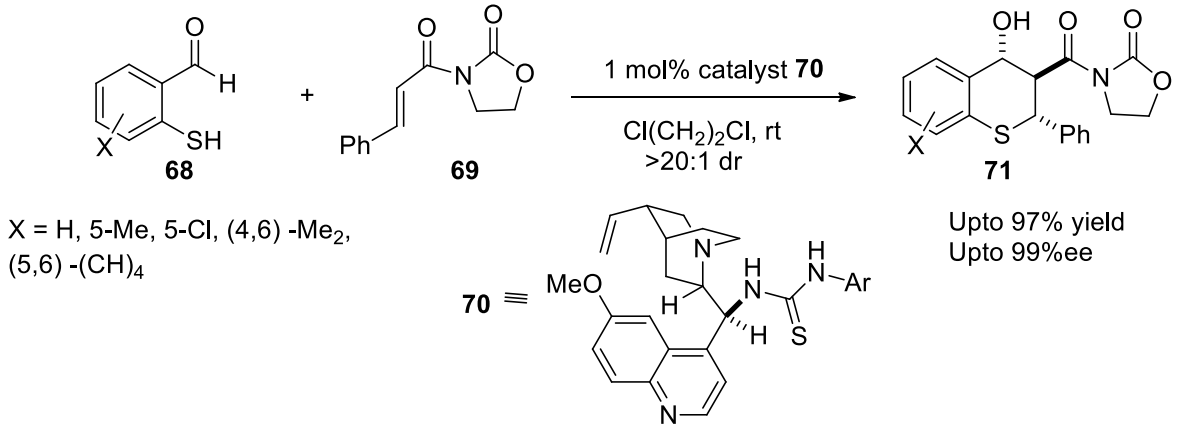
Scheme 1.5.1.1.1

Jørgensen and coworkers, reported the synthesis of highly functionalized complex epoxycyclohexanone derivatives **67** with up to four chiral centers. The reaction proceeds *via* Michael reaction followed by aldol reaction between aldehydes **64** and diketones **65** in the presence of 2[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine and AcONa as an additive in CH_2Cl_2 to give intermediate **66**. Finally, K_2CO_3 deprotonates the alcohol followed by intramolecular S_N2 reaction to form various highly functionalized products **67** with very good enantiomeric excess and high diastereomeric ratio (*Scheme 1.5.1.1.2*).[37]



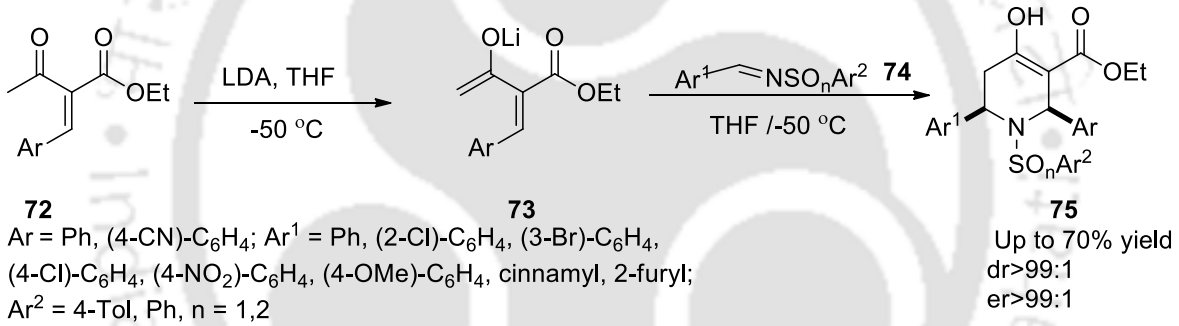
Scheme 1.5.1.1.2

Zu *et al.* had reported a tandem Michael-aldol approach for the synthesis of chiral benzothiopyrans **71** in the presence of 1 mol% of chiral bifunctional thiourea catalyst **70**. The reaction proceeds *via* cascade Michael and aldol reaction between 2-mercaptobenzaldehydes **68** and *α,β*-unsaturated oxazolidinone **69** with excellent enantioselectivity. The reaction is promoted by the noncovalent hydrogen bonding interactions between the bifunctional amine thiourea unit in **70**, which synergistically activates both the Michael donor and acceptor (*Scheme 1.5.1.1.3*).[38]



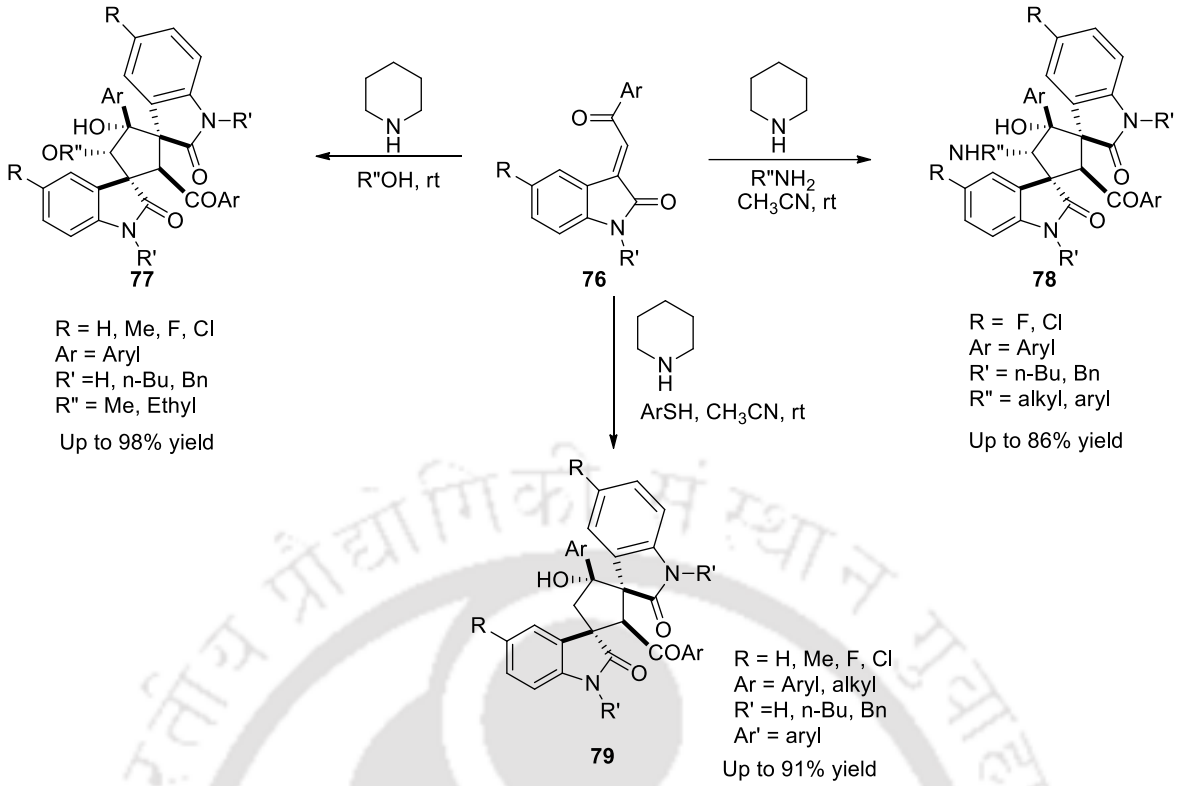
Scheme 1.5.1.1.3

Ghorai and coworkers had demonstrated the synthesis of substituted one-pot diastereo- and enantioselective substituted piperidines. The enolates **73** generated from *α*-arylmethylidene-*β*-keto esters **72** were reacted with various *N*-activated aldimines **74** at low temperature in a domino imino-aldol aza-Michael fashion to produce substituted piperidines **75** as a single diastereomer with 2,6-*cis* configuration (*Scheme 1.5.1.1.4*).[39]



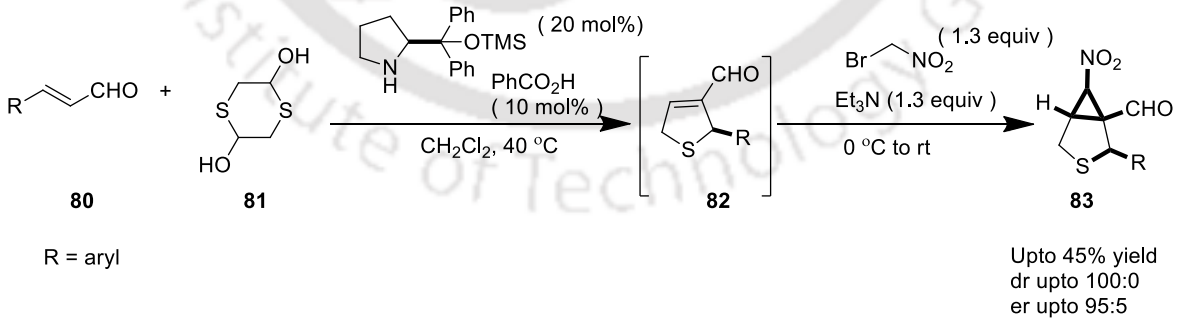
Scheme 1.5.1.1.4

Yan and coworkers had reported the base (piperidine) promoted domino reactions between two molecules of 3-phenacylideneoxindoles **76** for the construction of novel dispirocyclopentanebisoxindoles. The reaction is believed to proceed *via* domino Michael addition, aldol condensation, and nucleophilic substitution as well as the reduction reaction. The alkoxy group acts as a nucleophile for the reaction of **76** with piperidine in alcohol to furnish product **77**, whereas solution of various amine in acetonitrile generates **78**. On the other hand, no nucleophilic substitution was observed in case of using acetonitrile solution of thiophenol, and leads to the product **79** (*Scheme 1.5.1.1.5*).[40]



Scheme 1.5.1.1.5

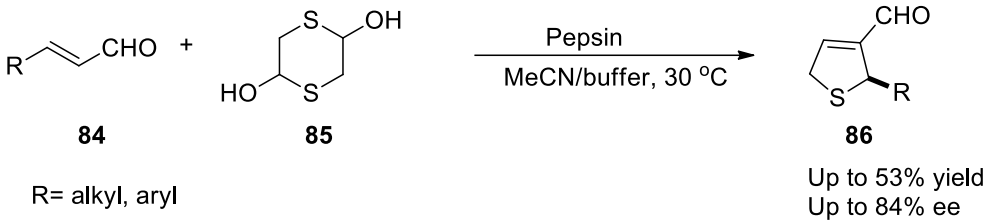
Zaghi *et al.* have synthesized functionalized nitrocyclopropanes **83** following a one-pot, four-step method catalyzed by (*S*)-diphenylprolinol TMS ether. The *α,β*-unsaturated aldehydes **80** and 1,4-dithiane-2,5-diol (**81**) underwent a domino sulfa Michael/aldol condensation to generate chiral dihydrothiophene adducts **82** followed by domino Michael/*α*-alkylation reaction with bromonitromethane to obtained **83** with moderate yield but with high diastereo- and enantioselectivity (*Scheme 1.5.1.1.6).*[41]



Scheme 1.5.1.1.6

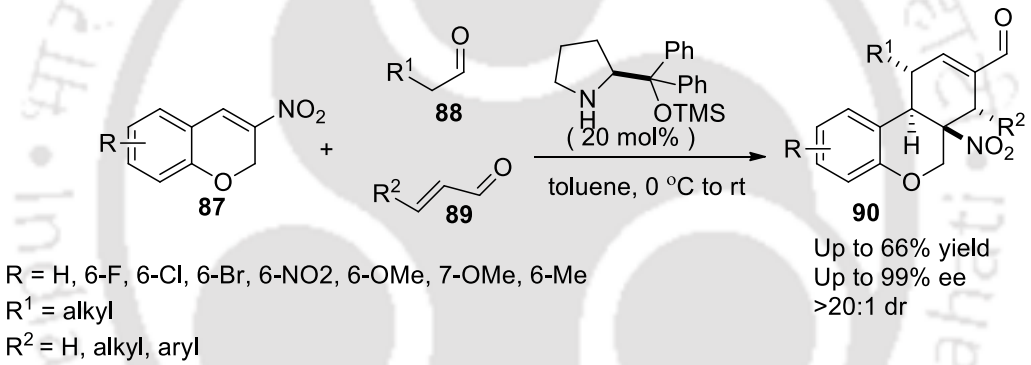
In 2016, He and coworkers had reported the pepsin (from porcine gastric mucosa) catalysed domino thia-Michael/aldol condensation reaction of aldehydes **84** with 1,4-dithiane-2,5-diol (**85**) in MeCN using phosphate buffer (NaH_2PO_4/Na_2HPO_4, 0.067 M, pH 6.5, 0.30 mL) to obtain corresponding functionalized chiral dihydrothiophenes **86** without an additive with enantioselectivities up to 84% ee. The active sites of pepsin consist of two

aspartate residue, Asp32 and Asp215, one has to be in its protonated form and other is to be in deprotonated form for the activity of the catalyst (*Scheme 1.5.1.1.7).)*[42]



Scheme 1.5.1.1.7

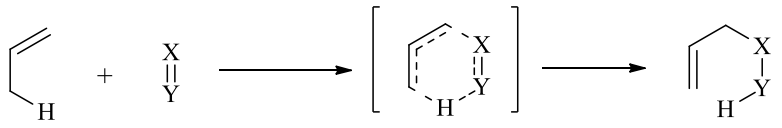
In 2017, Enders and coworkers developed a triple domino reaction methodology for the synthesis of functionalized tricyclic chromanes **90** using (*S*)-TMS-diarylprolinol catalyst. The reaction proceeds *via* Michael/Michael/aldol condensation reaction between aliphatic aldehydes **88**, nitro-chromenes **87**, and *α,β*-unsaturated aldehydes **89** to provide chromanes with four contiguous stereogenic centers in good yields and excellent stereoselectivities (*Scheme 1.5.1.1.8).*[43]



Scheme 1.5.1.1.8

1.5.2. Ene reaction

Ene reaction was discovered by Alder in 1943.[44] The process can be defined as the group transfer pericyclic reaction between electrophilic carbon-carbon and carbon-hetero atom multiple bonds which acts as a enophile and an alkene with a allylic hydrogen (the ene). The allylic hydrogen migrates to the enophile to form two new σ- and a π-bond. The reaction is also known as Alder-Ene reaction and is one of the simplest ways for carbon-carbon, carbon–hetero atom bond formations (*Scheme 1.5.2.1)* and has been extensively used for the natural product synthesis.[45]



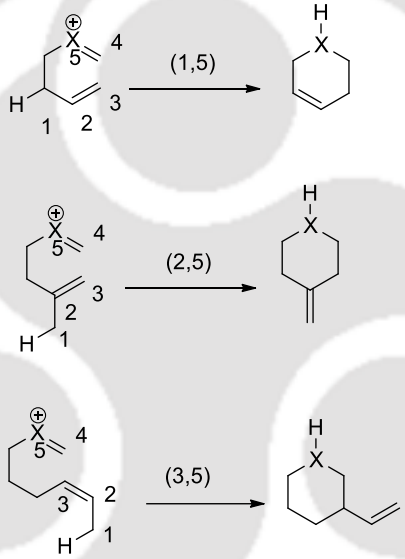
X=Y : C=C, C≡C, C=N, C=O, C=S, N=N, N=O

Scheme 1.5.2.1 Ene reaction

The ene (alkene) component of the ene reaction can react with a quite broad range of enophiles. Enophiles may contain carbon, carbon multiple bonds as well as carbon-heteroatom multiple bond such as carbonyls, imines, aza double bonds, oxonium ion, iminium ion and thionium ion and hence are termed as carbonyl-ene,[46] imino-ene,[47] aza-ene,[48] oxonium-ene, iminium-ene and thionium-ene[49] respectively. Out of the above stated ene reactions, we are going to discuss in details about oxonium-ene and iminium-ene reactions.

1.5.2.1 Oxonium ene reaction

Ene reaction having oxonium ion as enophile is known as oxonium ene reaction. The intramolecular addition between an oxonium ion and an alkene provides a convenient source

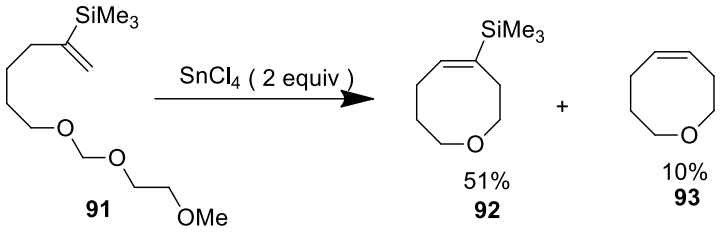


Scheme 1.5.2.1.1 Classification of oxonium-ene cyclization reaction

to various cyclic ethers known as oxonium-ene cyclization. Based on Mikami's terminology, most popular oxonium-ene type cyclization are of three types (1,5), (2,5), and (3,5) depending upon the connectivity between enophile to the ene (*scheme 1.5.2.1.1*).[50]

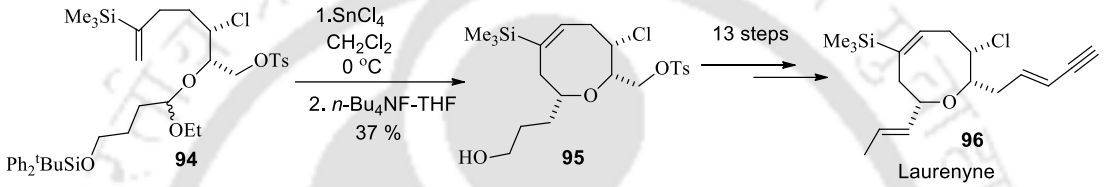
(1, 5)-Oxonium-Ene reaction

(1,5)-Oxonium-ene reaction has been well studied by Overman and co-workers. In 1986, they utilized this protocol for the synthesis of eight-membered oxacycles. For example, treatment of vinylsilane acetal **91** with 2 equiv of $SnCl_4$ (-15 °C, 9h) provided the silyl oxocene **92** in 51% yield, together with 10% of **93** (*Scheme 1.5.2.1.2*).[51a]



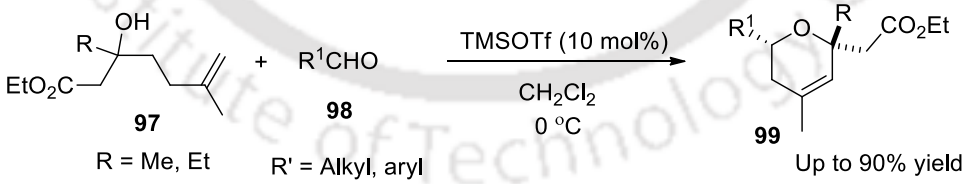
Scheme 1.5.2.1.2

Later in 1988, the same group reported the first total synthesis of Laurenyne (**96**), a C15 nonisoprenoid containing the laurenan skeleton. The key step of the reaction is (1,5)-oxonium-ene cyclization of acetal **94** in the presence of stannic chloride in CH_2Cl_2 at 0 °C followed by *O*-desilylation with $(n\text{-}Bu)_4NF$. The oxocene **95** formed was then converted to Laurenyne **96** in 13 steps (*Scheme 1.5.2.1.3*).[51b]



Scheme 1.5.2.1.3

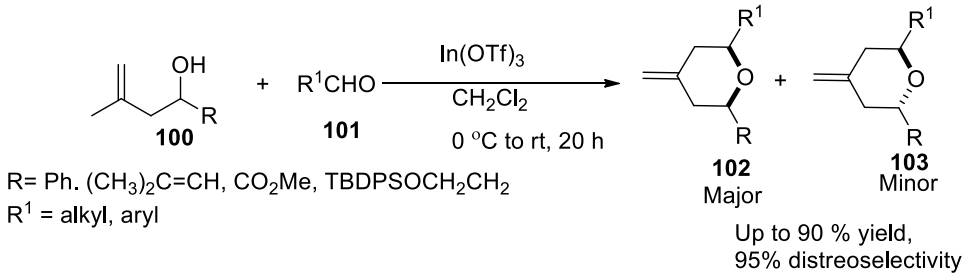
Saikia and coworkers had reported a diastreo- and regioselective synthesis of dihydropyrans following a (1,5)-Oxonium-ene reaction mechanism. In presence of catalytic amount of TMSOTf, tertiary alcohols **97** react with different aldehydes **98** to form a six membered chair like transition state where the bulkier ester group occupies the equatorial position to minimize the 1,3-diaxial interaction leading to the high distereoselectivity of the reaction and furnish the corresponding substituted dihydropyrans **99** up to 90% yield(*Scheme 1.5.2.1.4).*[52]



Scheme 1.5.2.1.4

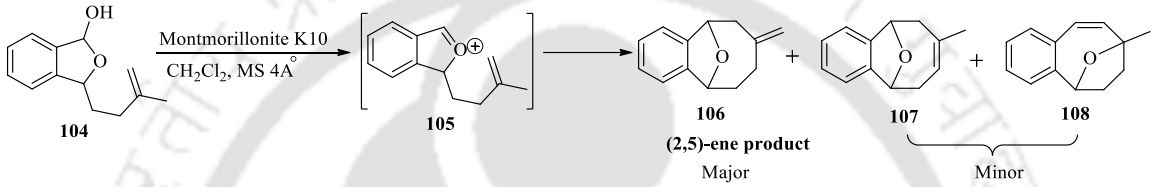
(2,5)-Oxonium-Ene reaction

In 2002, Loh and group have reported a $In(OTf)_3$ mediated synthesis of exocyclic double bond containing *cis*-2,6-disubstituted tetrahydropyrans which are important core units of natural products such as (+)-dactylolide and (+)-zampanolide. The reaction proceeds *via* (2,5)-oxonium ene cyclization between homoallylic alcohols **100** and aldehydes **101** giving a seies of tetrahydropyrans (**102**, **103**) in good to high yield with excellent diastereoselectivity. (*Scheme 1.5.2.1.5*)[53]



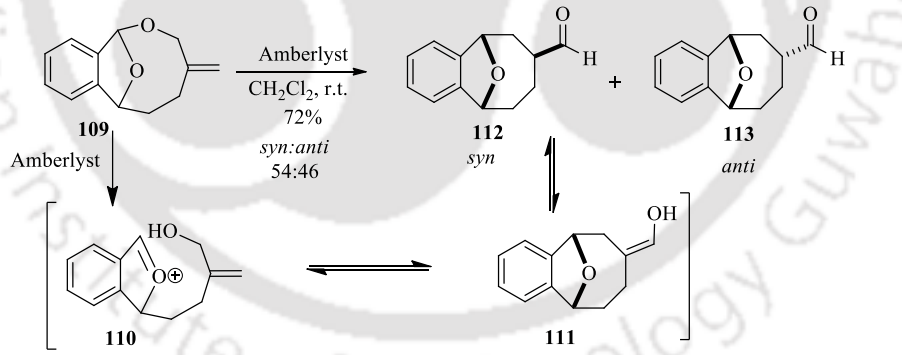
Scheme 1.5.2.1.5

Mikami and coworkers studies have shown that, lactol **104** on treating with mesoporous solid acids such as montmorillonite K-10 produces a tricyclic compound with exocyclic double bond **106** as the major product *via* (2,5)-oxonium-ene reaction and its endo cyclic regioisomers (**107**, **108**) as minor products (*Scheme 1.5.2.1.6*)[54a]



Scheme 1.5.2.1.6

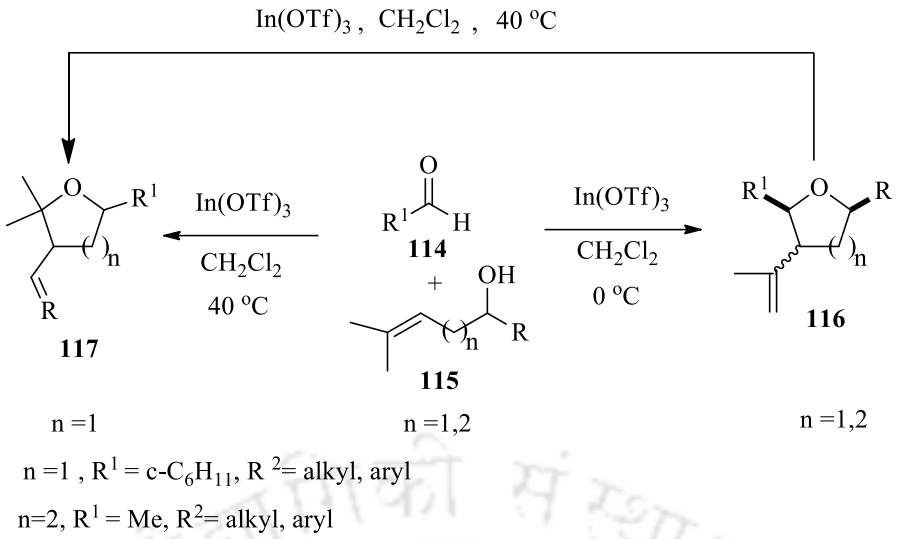
In order to study the mechanism of the reaction, Mikami trapped enol form of the ene product **111**, which immediately tautomerized to the corresponding aldehydic forms (**112**,**113**) to restrict the regioisomerization to its endo cyclic isomers (*Scheme 1.5.2.1.7*)[54b]



Scheme 1.5.2.1.7

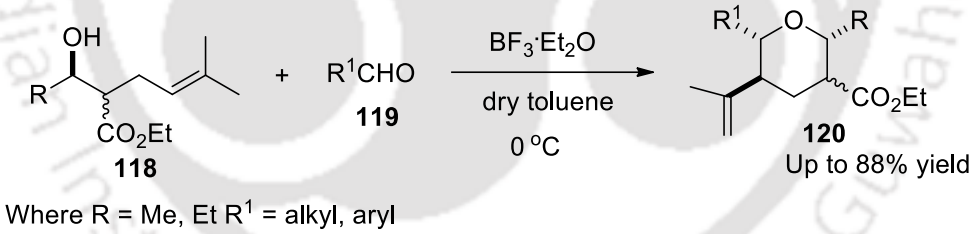
(3,5)-Oxonium-Ene reaction

Loh and coworkers had shown a $In(OTf)_3$ mediated synthesis of tetrahydrofurans and tetrahydropyrans **116** from the reaction of aldehyde **114** and unsaturated alkenes **115** having γ and δ hydroxyl groups *via* intramolecular (3,5)-oxonium-ene cyclization at 0 °C (*Scheme 1.5.2.3.8*).[55] On increasing the temperature to 40 °C thermodynamic isomer **117** was observed. However, this rearrangement was limited to tetrahydrofuran skeleton only.



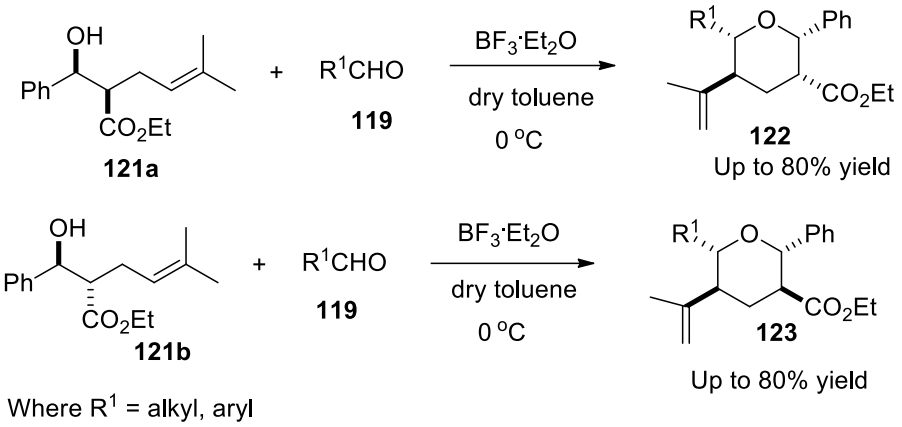
Scheme 1.5.2.1.8

Saikia and coworkers have investigated the stereochemistry of 2,3,5,6-tetrasubstituted tetrahydropyrans formed by the reaction of different *β*-keto esters with various aldehydes. The methyl and ethyl substituted *β*-keto esters **118** which was prepared as inseparable diastereomers, when reacted with different aldehydes **119** in dry toluene in presence of boron trifluoride etherate afforded a mixture of diastereomeric products **120** with a distreomeric ratio of 1:1 which could be separated by column chromatography (*Scheme 1.5.2.1.9*).[56]



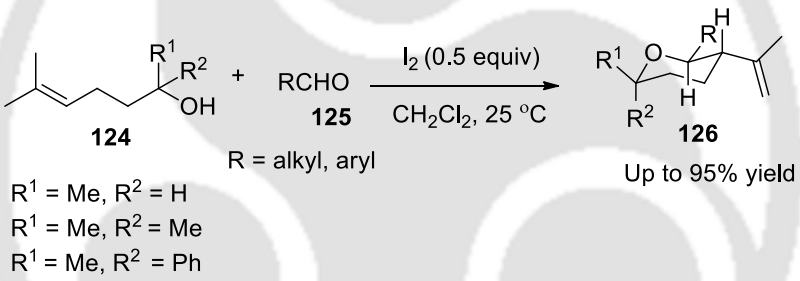
Scheme 1.5.2.1.9

Whereas phenyl substituted *β*-ketoester **121** was prepared as two separable *anti*- and *syn*-diastereomers. The *syn* alcohol **121a** reacted with aldehydes **119** in the presence of boron trifluoride etherate to give tetrahydropyrans **122** via (3,5)-oxonium-ene reaction. On the other hand, the reaction of *anti* alcohol **121b** with aldehydes **119** gave tetrahydropyran **123** (*Scheme 1.5.2.1.10*).[56]



Scheme 1.5.2.1.10

Subba Reddy and co-workers had reported a metal-free protocol for the synthesis of 2,3,6-trisubstituted tetrahydropyrans **126** *via* (3,5)-oxonium-ene cyclization. The reaction of 6-methylhept-5-en-2-ol derivatives **124** with different aldehydes **125**, using molecular iodine under mild reaction condition afford the corresponding tetrahydropyrans in good yields with excellent stereoselectivity (*Scheme 1.5.2.1.11*).[57]

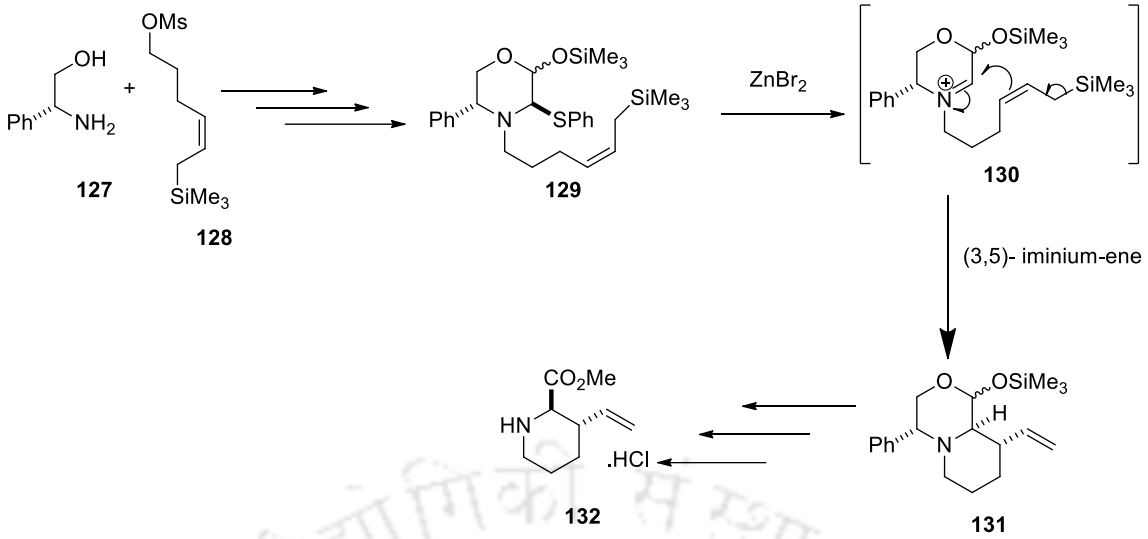


Scheme 1.5.2.1.11

1.5.2.2 Iminium ene reaction

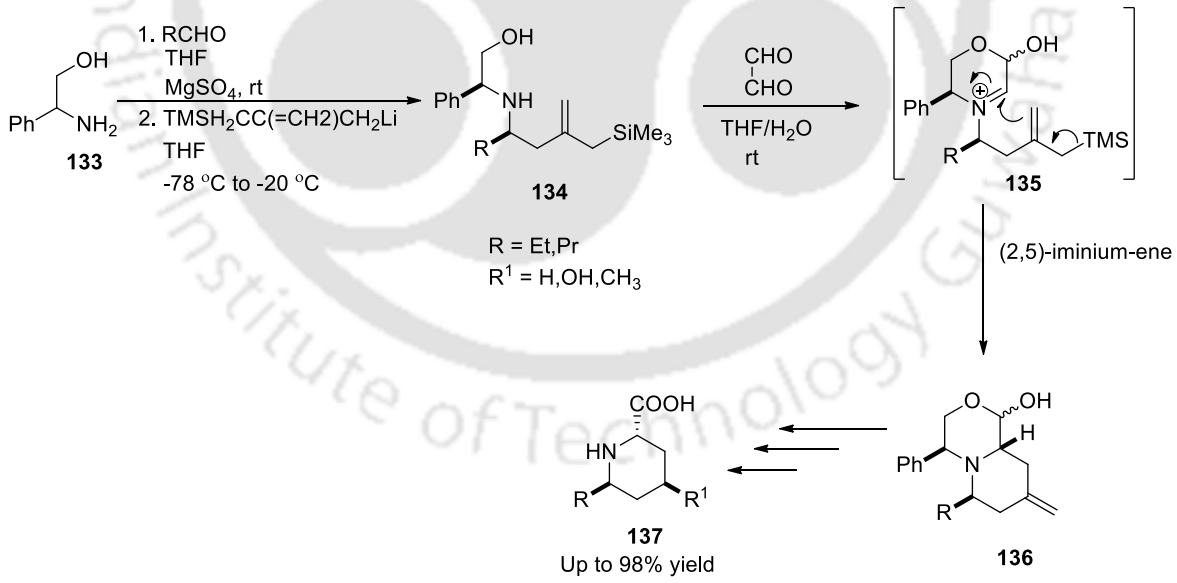
The iminium–ene reaction is a powerful method for the synthesis of nitrogen-containing heterocycles, analogous to oxonium ene reaction, here iminium ion acts as an enophile instead of oxonium ion. The intermolecular iminium ene leads to the synthesis of homoallylic amines through the formation of a new carbon-carbon bond between an alkene (ene) and an imine (enophile). However, the intramolecular iminium ene reaction affords cyclic amines.

Puchot-Kadouri and coworkers reported the synthesis of enantiopure 3-vinyl pipecolic acid starting from (*R*)-phenylglycinol **127** and mesyloxyallylsilane **128** where iminium–ene cyclization is the most important key step. Following a series of steps, trimethylsilyloxy **129** derivatives were obtained, which was then transformed to an iminium ion **130** by treating with $ZnBr_2$, followed by (3,5)-iminium–ene cyclization reaction to form bicyclic compound **131** which after a series of reaction generates (2*R*,3*S*)-3-vinyl pipecolic acid methyl ester **132** as its hydrochloride (*Scheme 1.5.2.2.1*).[58]



Scheme 1.5.2.2.1

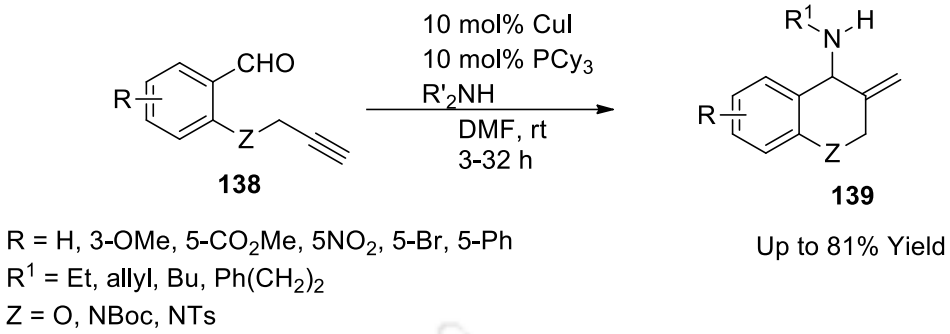
The same group in 2000 had reported the synthesis of biologically important 6-alkyl and 4,6-disubstituted derivatives of pipecolic acid **137**. The synthesis starts with the reaction of (*S*)-phenylglycinol (**133**) with aldehydes followed by reaction with [2-((trimethylsilyl)methyl)prop-2-enyl]lithium to produce the *β*-amino alcohols **137** which on reaction with glyoxal gave bicyclic intermediates **136** *via* (2,5)- iminium–ene which after series of reaction generates the corresponding pipecolic acids (*Scheme 1.5.2.2.2*).[59]



Scheme 1.5.2.2.2

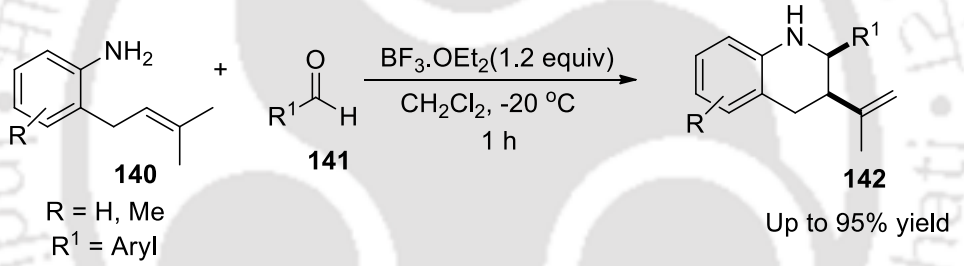
Ohkuma and coworkers had reported the synthesis of various oxygens and nitrogen heterocycles by the reaction of propargyl salicylaldehyde **138** and related compounds with dialkylamines *via* iminium ene cyclization with reverse electron demand. Initially copper(I) acetylide was formed by treatment of terminal alkyne with CuI and base, which is in equilibrium with iminium ion generated in situ from aldehydes and dialkyl amine. The

iminium salts converted to the cyclized product *via* the iminium-alkyne ene-type reaction, followed by hydrolysis to give **139** up to 81% yield (*Scheme 1.5.2.2.3*).[60]



Scheme 1.5.2.2.3

Our group in 2013 had reported the synthesis of tetrahydroquinolines *via* (3,5)-iminium–ene reaction between 2-allylic anilines **140** and aromatic aldehydes **141**. Aldehydes and amines form imines, which was activated by $BF_3 \cdot OEt_2$ to undergo cyclization following an iminium ene pathway to generate a carbocation intermediate which finally eliminates a proton to give tetrahydroquinolines **142** up to 95% yield (*Scheme 1.5.2.2.4*).[61]



Scheme 1.5.2.2.4

1.6. References:

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CHAPTER 2

Synthesis of Tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* Cascade Cyclization and Friedel-Crafts Reaction

2.1. Importance and applications

Indenopyridine framework is one of the most privileged heterocyclic scaffolds since it appears in the 4-aza-fluorenone group of alkaloids. 4-Aza-fluorenone (5*H*-Indeno[1,2-*b*]pyridin-5-ones) isolated from the root of the plant *Polyalthia debilis* are the core structural units of a wide range of natural products. One of its simplest member is onychnine (**1)** and others include 7-methoxy onychine (**2**), cyathocaline (**3**) and isoursuline (**4)**. Azafluorenone derivatives have been reported to possess aldose reductase inhibition activity and cytotoxic activity.[1] Similarly, another indenopyridine containing moiety phenindamine (**5**) is a potential antihistamine drug. It was developed by Hoffman-La Roche in the late 1940s and used to treat symptoms of the common cold and allergies, such as sneezing, itching, rashes, and hives. Phenindamine appears to compete with histamine for histamine H1- receptor sites on effector cells and thereby reduce the intensity of allergic reactions and tissue injury responses of histamine release.[2] Apart from this, drug CDB-4022 (**6**), an indenopyridine, exhibits antispermatogenic activity in various animals (*Figure 2.1.1*).[3]

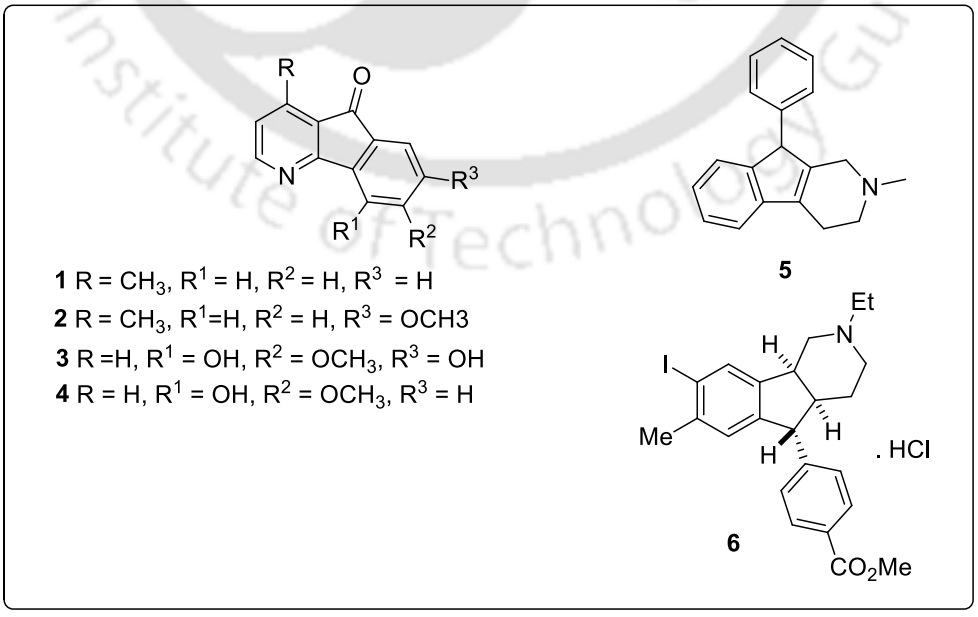
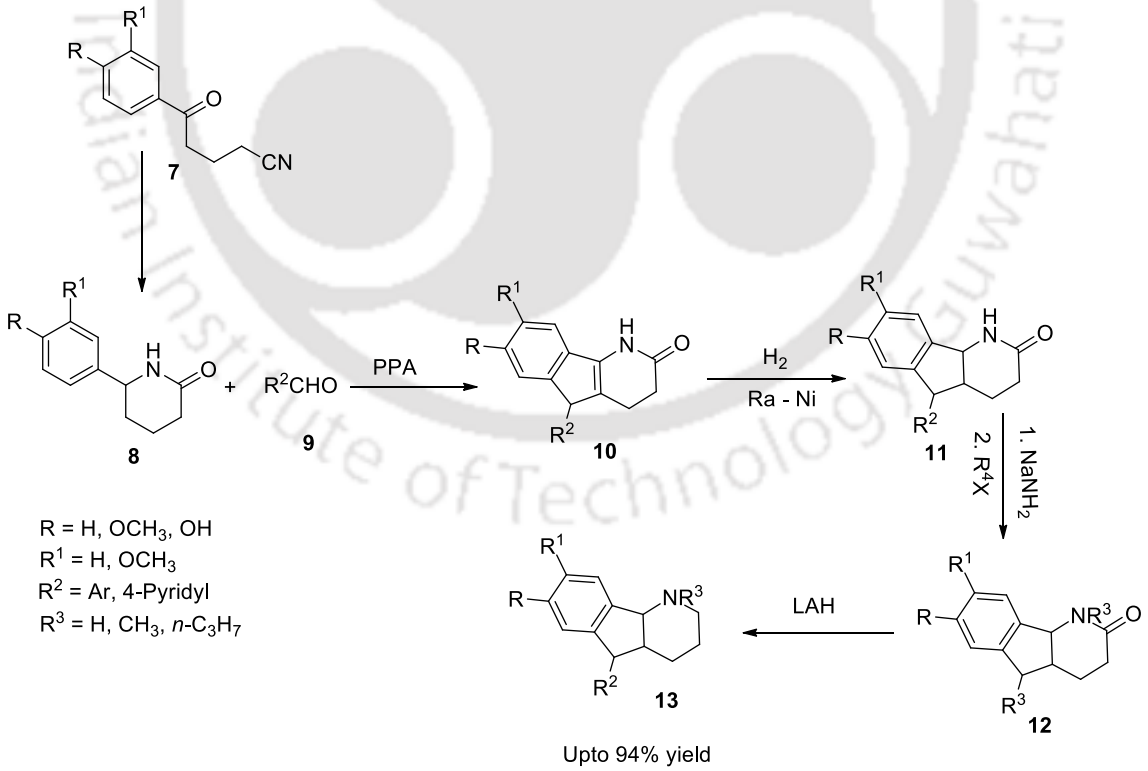


Figure 2.1.1. *Some bioactive molecules containing Indenopyridine framework.*

2.2. An overview of relevant synthetic methods

According to the literature, there are several synthetic methods for the construction of these types of fused indenopyridine moieties, most popular being the one-pot multicomponent reactions under different conditions.[1-8] Apart from this, other methods includes [2+4] cycloaddition/annulation reaction,[9] Pd(0)-catalyzed cross-coupling reaction,[10] Pummerer reaction of imidosulfoxides,[11] cyclization using diynes.[12] Several indenopyridine synthesis are also reported following multisteps procedures.[13] Some of the methodologies for synthesizing indenopyridine derivatives are discussed below.

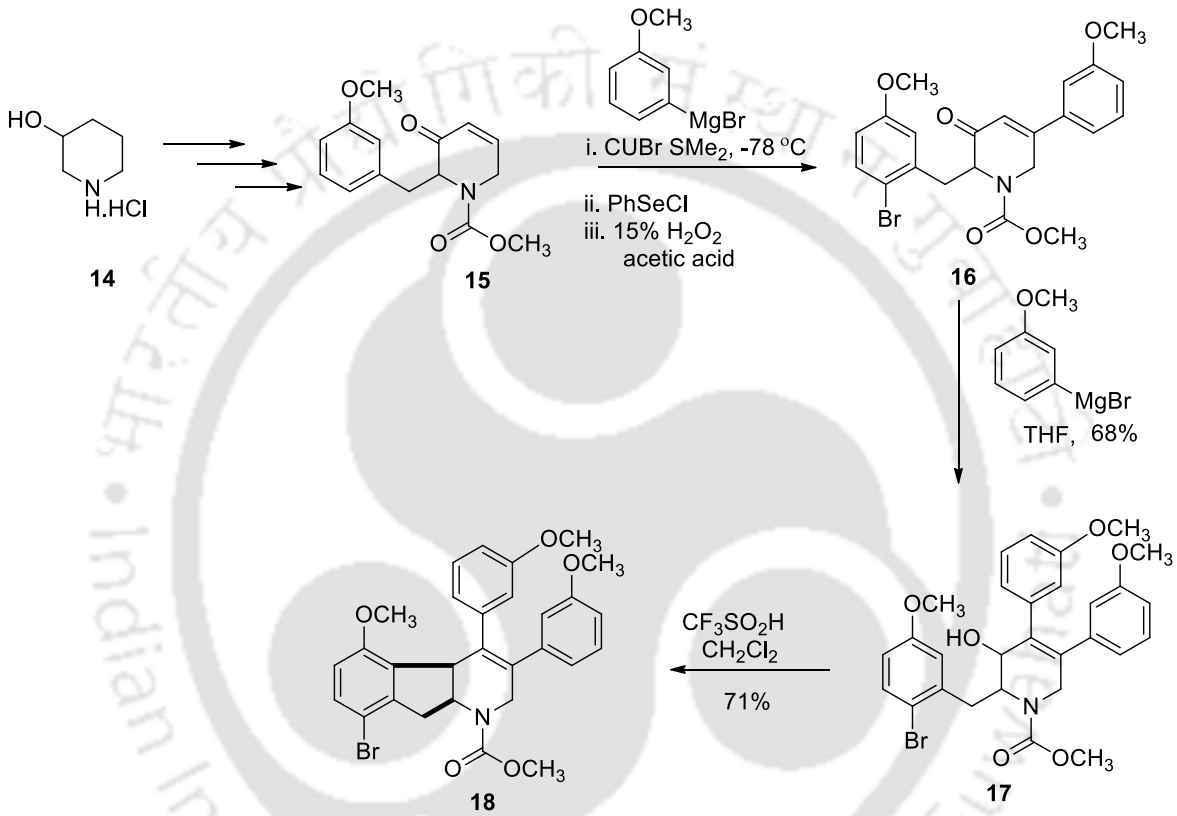
In 1984, Kunstmann and coworkers had described the synthesis of various 2,3,4,4a,5,9b-hexa-hydro-indeno[l,2-*b*]pyridines **13**. 5-Oxo-5-phenylvaleronitriles **7** readily undergo cyclization to give 6-phenyl-3,4-dihydropyridin-2-ones **7**, which then condensed with aldehydes **9** in the presence of polyphosphoricacid to yield l,2,3,4-tetrahydro-5*H*-indeno[l,2-*b*]pyridin-2-ones **10**. Catalytic hydrogenation followed by alkylation at the nitrogen and subsequent reduction by $LiAlH_4$ afforded the desired substituted indenopyridines up to 94% yield (*Scheme 2.2.1*).[13a]



Scheme 2.2.1

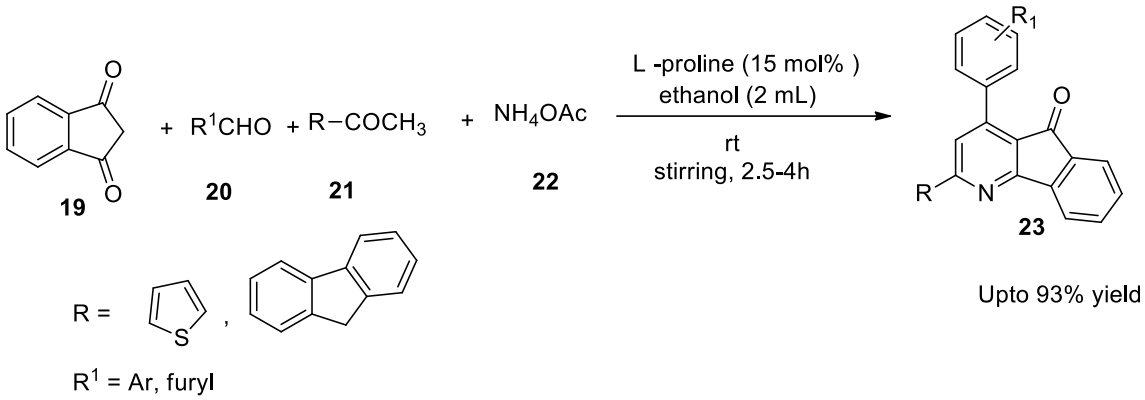
Rawal and coworkers had reported the synthesis of the tricyclic indeno-tetrahydropyridine core of natural product haouamine A by featuring an acid-catalyzed Friedel−Crafts ring

closure reaction as the key step. The *α,β*-unsaturated ketone 1**5** synthesized using commercially available HCl salt of 3-hydroxypiperidine **14** following a series of steps, was treated with CuBr followed by trapping of enolate with phenylselenyl chloride, then oxidation using H_2O_2 accompanied by selenoxide elimination to produce the substituted *α,β*-unsaturated ketone **16** . Further addition of 3-methoxyphenylmagnesium bromide followed by the treatment of triflic acid directs an acid-catalyzed Friedel−Crafts ring closure to produce the indenotetrahydropyridine **18** in 71% yield (*Scheme 2.2.2*).[13c]



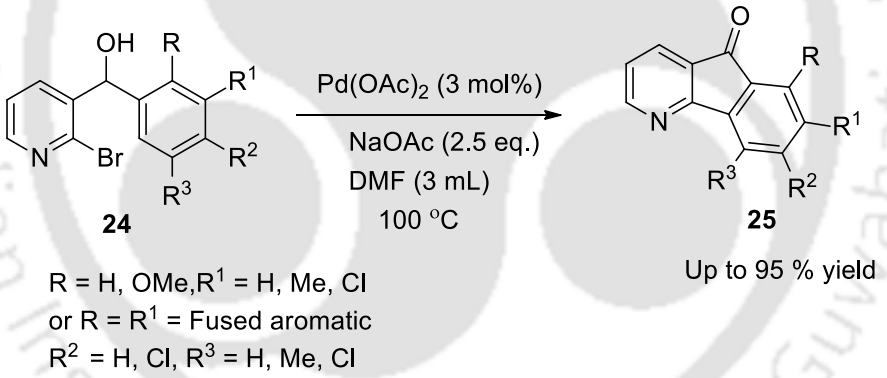
Scheme 2.2.2

In 2010, Mukhopadhyay and coworkers had shown the synthesis of indenopyridine derivative *via* one-pot four-component reaction employing L-proline as an organocatalyst (*Scheme 2.2.3*). The aldehyde **20**, indan-1,3-dione **19**, 2-acetyl thiophene or 2-acetyl fluorene **21** and ammonium acetate **22** were stirred in the presence of 15 mol% of L-proline in ethanol (2 mL) at room temperature for the stipulated time and afforded the indenopyridine derivatives **23** up to 93% yield.[5]



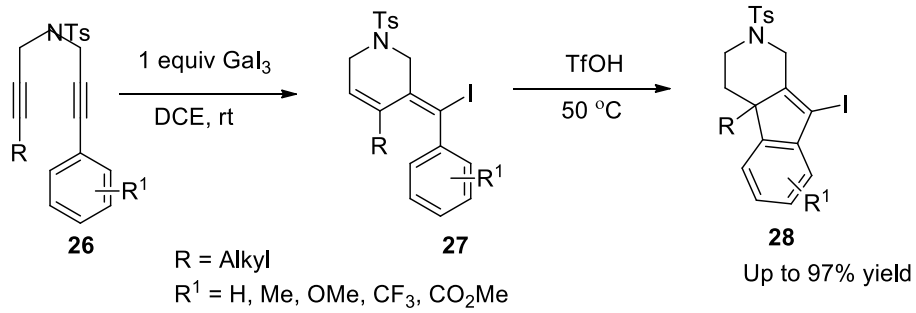
Scheme 2.2.3

In 2013, Ray and coworkers reported a short and highly efficient one step protocol for the synthesis of azafluorenone *via* oxidative intramolecular Heck cyclization. In the presence of Pd(0), precursor alcohols **24** undergoes simultaneous oxidation and cyclization to afford indenopyridines **25** in excellent yield. One remarkable feature of the reaction is that no ligand is required for the catalytic cycle. It is believed that the compound itself could play the ligand's role to reduce Pd(II) to Pd(0) (*Scheme 2.2.4*).[10]



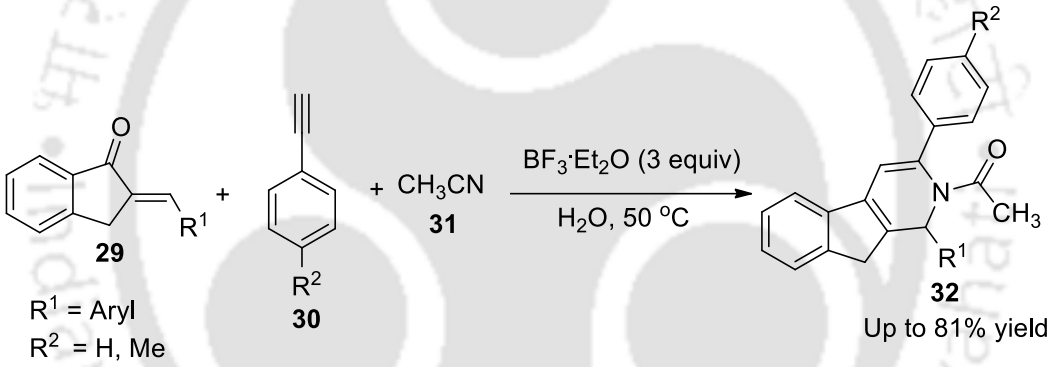
Scheme 2.2.4

Snyder and group have developed an efficient protocol for the synthesis of iodoindenopyridines. In the presence of stoichiometric amount of gallium(III) halide, the 1,6-diynes **26** endure cyclization to form vinyl halides **27**. Under acidic condition the generated iodocyclization products undergo Friedel−Crafts cyclization, affording iodoindenopyridines **28**, which was further explored for cross-coupling reactions (*Scheme 2.2.5*).[12a]



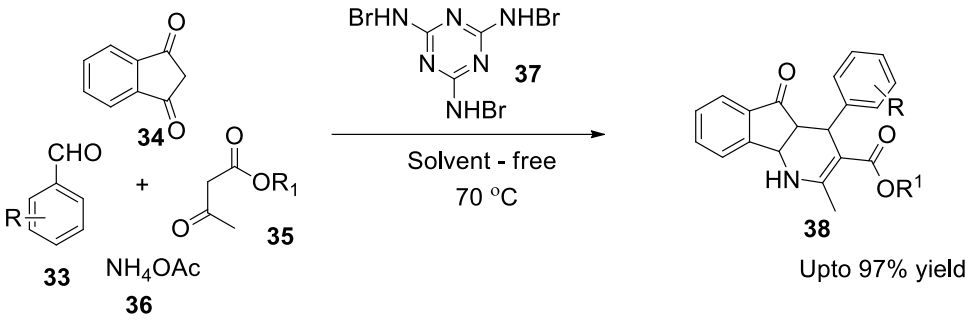
Scheme 2.2.5

Sasidhar and coworkers reported a $BF_3{\cdot}OEt_2$ mediated one-step synthesis of indenopyridines **32** from readily available arylidene ketones **29**, phenyl acetylenes **30** and nitrile **31** in presence of 2.0 equivalents of water. This annulation provides access to complex polycyclic frameworks with excellent substrate scope without dry solvents or an inert atmosphere. (*Scheme 2.2.6*).[6]



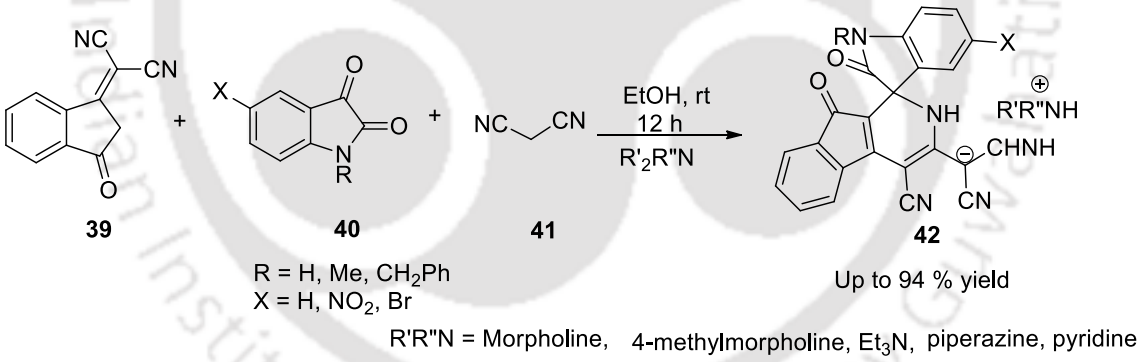
Scheme 2.2.6

Mansoor and coworkers reported an efficient one-pot methodology for the synthesis of 4-aryl-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridine derivatives **38** *via* four-component cyclocondensation of aromatic aldehydes **33**, 1,3-indanedione **34**, *β*-ketoesters **35** and ammonium acetate **36** in the presence of 10 mol% of tribromomelamine **37** as the catalyst at 70 °C under solvent free condition. The indenopyridines were obtained up to 97% yield (*Scheme 2.2.7*).[1]



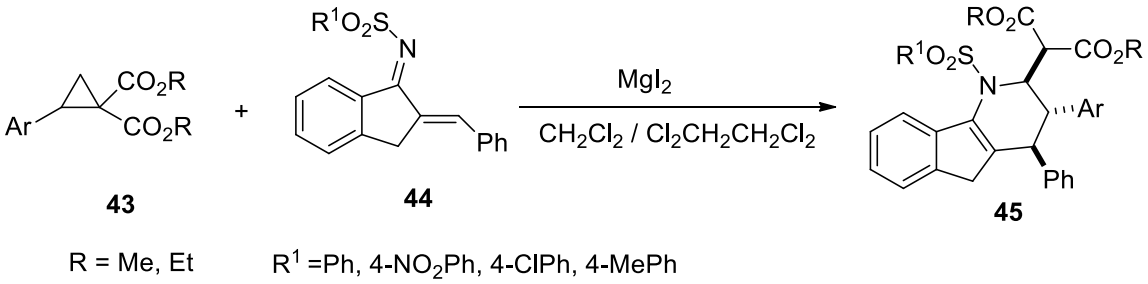
Scheme 2.2.7

Bazgir and group had described an environmentally friendly one-pot synthesis of indenopyridine-fused spirocyclic systems **42** using 1,1-dicyanomethylene-3-indanone **39**, isatins **40**, and malononitrile **41** in the presence of amines in ethanol medium. The reaction is believed to takes place *via* domino mechanism through Knoevenagle/Micheal/elimination/[5 + 1] cyclisation sequence to formed spirooxindole-fused indenopyridine salts, which was later neutralized by dilute hydrochloric acid (*Scheme 2.2.8*).[2]



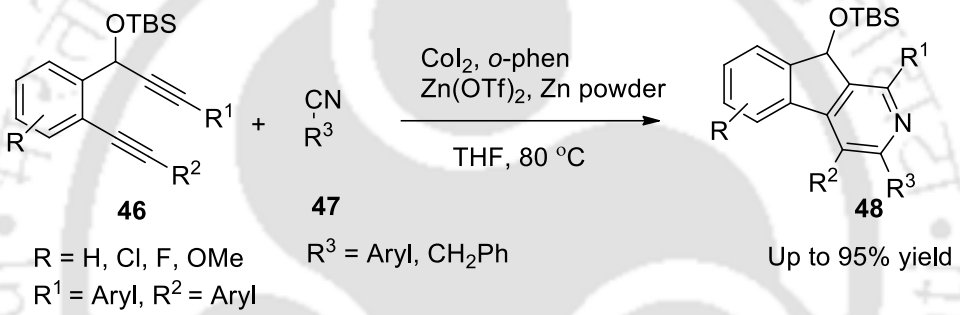
Scheme 2.2.8

Banerjee and coworkers reported the synthesis of highly functionalized indenopyridine derivatives *via* [2+4] cycloaddition reaction of DACs (donor acceptor Cyclopropanes) **43** which is a source of 2-styrylmalonate, and chalconimine **44** in presence of MgI_2 in CH_2Cl_2 /$Cl_2CH_2CH_2Cl_2$. Various substituted indenopyridine **45** were obtained up to 86% yield (*Scheme 2.2.9*).[9b]



Scheme 2.2.9

Yanzhong and coworkers described a regioselective synthesis of indeno[2,1-*c*]pyridine derivatives **48** by the cycloaddition reaction of diynes **46** bearing TBS protected propargylic alcohol fragments with nitriles **47** in presense of catalyst CoI_2, Zn powder as the reducing agent, *o*-phenanthroline as the ligand, and Zn(OTf)$_2$ as the additive in THF solvent at 80 ^oC (*Scheme 2.2.10*).[12b]



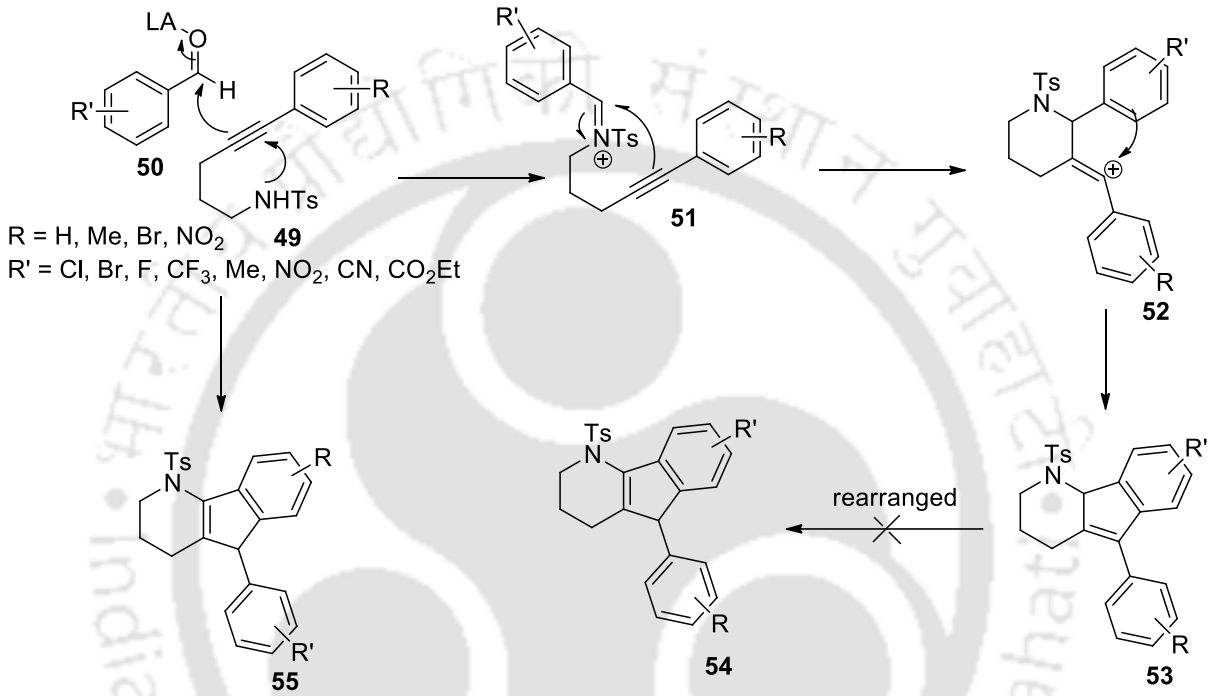
Scheme 2.2.10

2.3. Present strategy and objective

The tetrahydro-1*H*-indeno[1,2-*b*]pyridines are a class of nitrogen heterocycles containing a piperidine ring fused to 2,3-dihydro-1*H*-indene. 2,4*a*,9,9*a*-tetrahydro-1*H*-indeno[2,1-*b*]pyridine ring system are core units of biologically active molecules.[13c] There are only a few methods for the synthesis of 1*H*-indeno[1,2-*b*]pyridines.[9,13a,c,d,e] The major drawback of most of these methods is the requirement of multistep procedures. Therefore, the development of highly efficient methods for the synthesis of 1*H*-indeno[1,2-*b*]pyridines are still in demand. In continuation of our interest for the synthesis of nitrogen heterocycles we are in search of a methodology for the synthesis of these nitrogen heterocycles.[14]

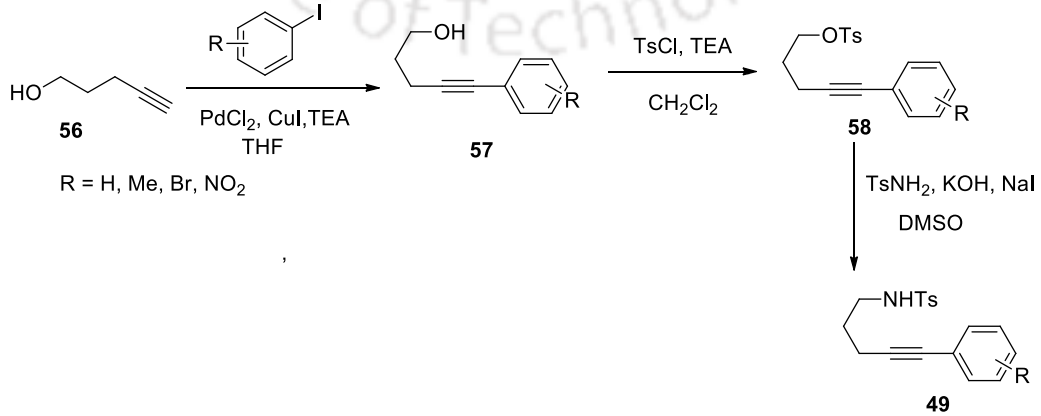
Cascade reactions are gaining importance in organic synthesis due to its ability to form complex molecular framework.[15] Similarly, Friedel-Crafts reaction is one of the important reaction in organic synthesis for C-C bond formation.[13c,16] On the other hand, tandem Prins-Friedel-Crafts[17] and aza-Prins-Friedel-Crafts[18] reactions are considered as an efficient methodology for the synthesis of variously substituted heterocyclic compounds. Jin and

coworkers have reported the triflic acid catalyzed cascade cyclization of arenyl enynes *via* acetylene-cation cyclization and Fridel-Crafts type reaction.[19] On the basis of these facts, we envisioned that the reaction of α-sulfonamido-alkynes **49** with aldehydes **50** under Lewis acidic conditions would provide intermediate **51**. Tandem aza-Prins cyclization and Friedel-Crafts type reaction may provide product **53**. The product **53** may rearrange to give more stable enamide **54**. However, in contrast product **55** was obtained, which was confirmed by X-ray crystallographic analysis of **55d** (*Scheme 2.3.1*).



Scheme 2.3.1

The benzenesulfonamides **49** were synthesized from tosylated alcohol **58** and sulphonamide in presence of potassium hydroxide and sodium iodide in DMSO solvent.



Scheme 2.3.2

The tosylated alcohol **58** were prepared by sonagashira reaction of alcohol **56** with phenyliodides in presence of palladium catalyst, copper iodide, triethylamine in

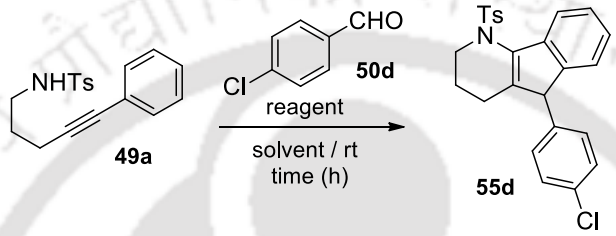
tetrahydrofuran solvent which was followed by tosylation with tosyl chloride using triethylamine in dichloromethane (*Scheme 2.3.2*).

2.4. Results and discussion

2.4.1. Optimization studies

To start with, 4-methyl-*N*-(5-phenylpent-4-yn-1-yl)benzenesulfonamide (**49a)** was reacted with *p*-chlorobenzaldehyde (**50d**) in dichloromethane with 2.0 equivalents of boron trifluoride etherate and 5-(4-chlorophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-

Table 2.4.1.1. Optimization of the reaction condition



entry	reagent (mmol)	solvent	time/h	yield (%)[a]
1	$BF_3{\cdot}OEt_2$ (2)	CH_2Cl_2	12	45
2	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	12	38
3	$BF_3{\cdot}OEt_2$ (2)	DCE	12	70
4	$BF_3{\cdot}OEt_2$ (2)	toluene	12	30
5	$Zn(OTf)_2$ (1)	CH_2Cl_2	24	13
6	$Cu(OTf)_2$ (1)	CH_2Cl_2	24	9
7	$In(OTf)_3$ (1)	CH_2Cl_2	24	25
8	Ag(OTf) (1)	CH_2Cl_2	24	--[b]
9	$InCl_3$ (1)	CH_2Cl_2	24	18
10	$FeCl_3$ (1.2)	CH_2Cl_2	24	20
11	CSA (1.2)	CH_2Cl_2	24	--[b]
12	TfOH (1.2)	CH_2Cl_2	24	20

[a]Yield refers to isolated yield. Compounds are characterised by ^1H, ^{13}C NMR, IR spectroscopy and Mass spectrometry. [b]No reaction, starting material was recovered.

indeno[1,2-*b*]pyridine (**55d**) was obtained in 45% yield in 12 h (Table 2.4.1.1, entry 1). To optimize the reaction condition different reagents and solvents were screened and the results are summarized in Table **2.4.1.1**. The reaction with 1.0 equivalent of $BF_3{\cdot}OEt_2$ gave 38% yield (Table 2.4.1.1, entry 2). The same reaction with 2.0 equivalents of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane (DCE) gave 70% yield (Table 2.4.1.1, entry 3), but in toluene it produced only 30% of the product (Table 2.4.1.1, entry 4). Metal triflates such as zinc,

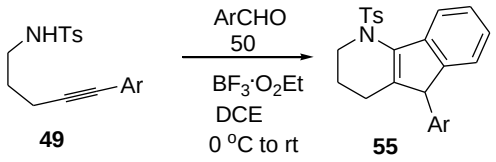
copper, indium and silver triflates were also screened for the reaction. Out of these, only zinc, copper and indium triflates gave 13%, 9% and 25% yields, respectively (Table 2.4.1.1, entries 5-7). In the case of AgOTf starting material was recovered in 98% yield (Table 2.4.1.1, entry 8). Similarly, metal salts $InCl_3$ and $FeCl_3$ gave 18% and 20% yields, respectively (Table 2.4.1.1, entries 9-10). Brønsted acids such as camphor sulfonic acid (CSA) failed to give the desired product but starting material was recovered in 96% yield (Table 2.4.1.1, entry 11). On the other hand, triflic acid (TfOH) gave 20% yield (Table 2.4.1.1, entry 12).

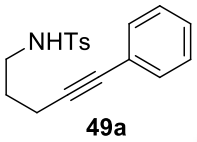
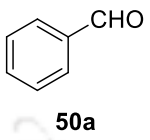
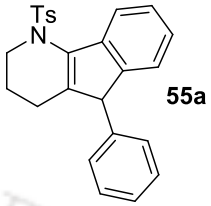
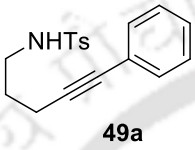
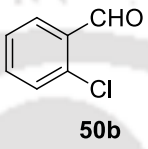
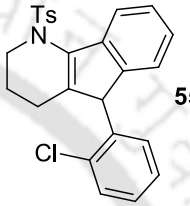
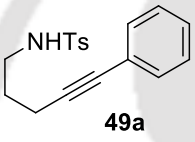
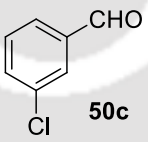
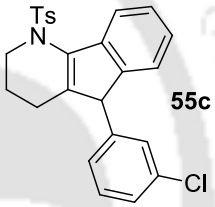
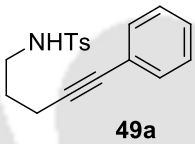
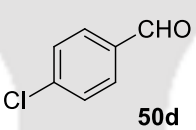
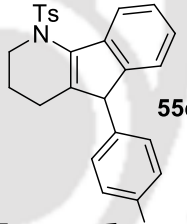
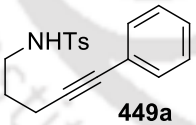
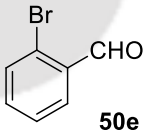
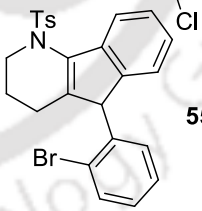
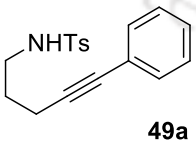
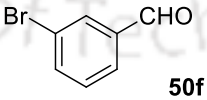
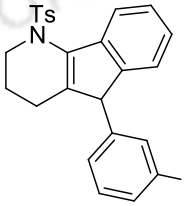
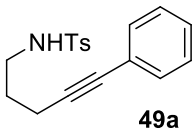
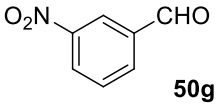
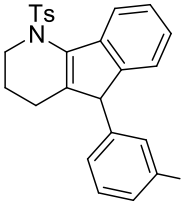
2.4.2. Substrate scope of the reaction

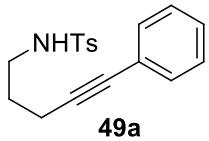
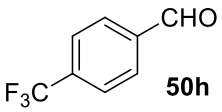
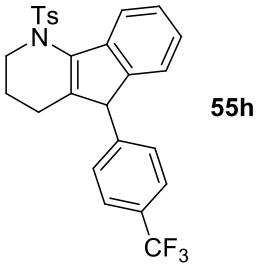
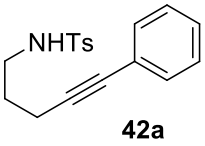
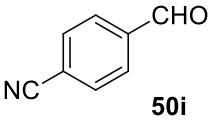
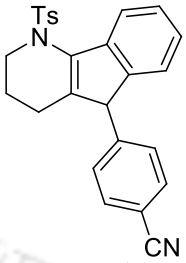
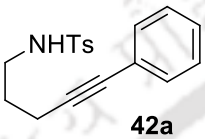
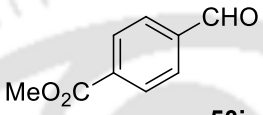
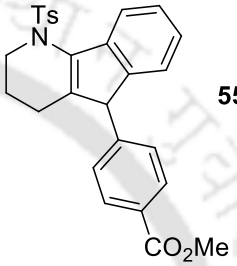
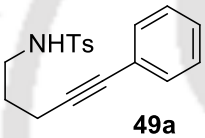
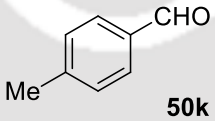
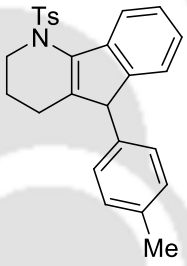
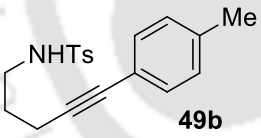
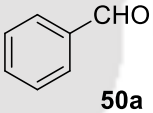
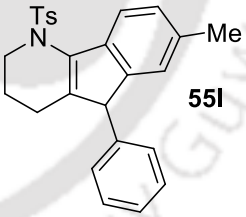
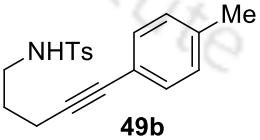
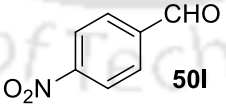
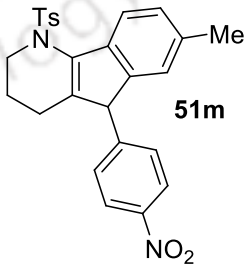
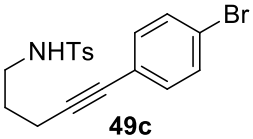
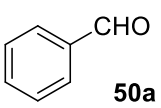
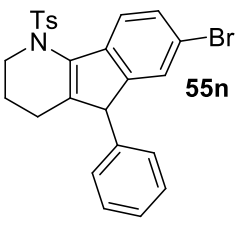
With these optimized conditions in hand, we further examined the scope of the reaction with a variety of substrates (Table 2.4.2.1.). It was observed from Table 2.4.2.1, that alkynes having aryl substituents (Table 2.4.2.1, entries 1−14, 16, and 18) gave the desired product in good yields. Both electron-withdrawing and electron-donating groups in the aromatic ring of the aldehydes gave moderate to high yields. However, an aldehyde having a highly electron donating methoxy group on the aromatic ring (Table 2.4.2.1, entry 17) decomposed under these reaction conditions. Similarly, methyl- and bromide-substituted aryl groups (Table 2.4.2.1, entries 12−14) in the alkyne side chain gave moderate yields. In this case, a mixture of unidentified byproducts was observed. In contrast, a substrate (Table 2.4.2.1, entry 15) having an electron-withdrawing nitro group on the aromatic ring failed to give the product. This is due to the destabilization of carbocation **57** formed during the reaction (*Scheme 2.4.5.1*). The structures of the products were determined by ^{1}H and ^{13}C NMR and X-ray analysis. The sharp downfield shift of the C-5H proton of compounds **55b,e** (δ 5.04 ppm) is due to the electron-withdrawing effect of *o*-substituted chloride and bromide groups on the aromatic ring.

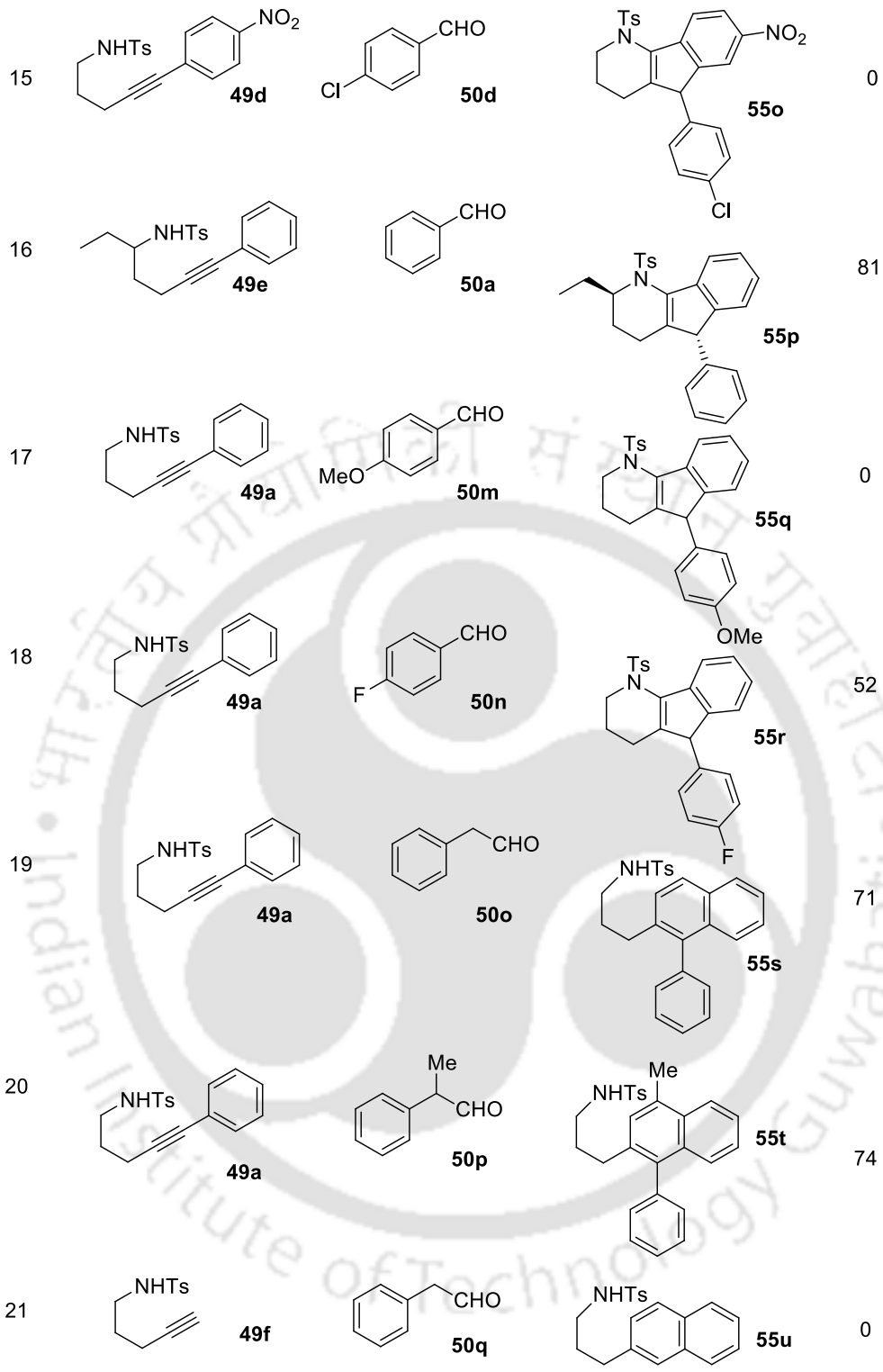
There is an unexpected result in the reaction of alkyne **49a** with phenylacetaldehyde (**50o**) and 2-phenylpropanal (**50p**) (Table 2.4.2.1, entries 19 and 20), where sulfonamide-substituted aromatized products **55s,t** were obtained in 71% and 74% yields, respectively. It was observed from Table 2.4.2.1 that alkynes having aryl substituents (entries 19 and 20) gave the desired product but terminal alkyne **49f** (Table 2.4.2.1, entry 21) failed to produce the same.

Table 2.4.2.1. Synthesis of Tetrahydro-1*H*-indeno[1,2-*b*]pyridine



Sl.No.	amide **49**	aldehyde **50**	product	yield (%)[a]
1	 **49a**	 **50a**	 **55a**	57
2	 **49a**	 **50b**	 **55b**	62
3	 **49a**	 **50c**	 **55c**	65
4	 **49a**	 **50d**	 **55d**	70
5	 **449a**	 **50e**	 **55e**	53
6	 **49a**	 **50f**	 **55f**	59
7	 **49a**	 **50g**	 **55g**	54

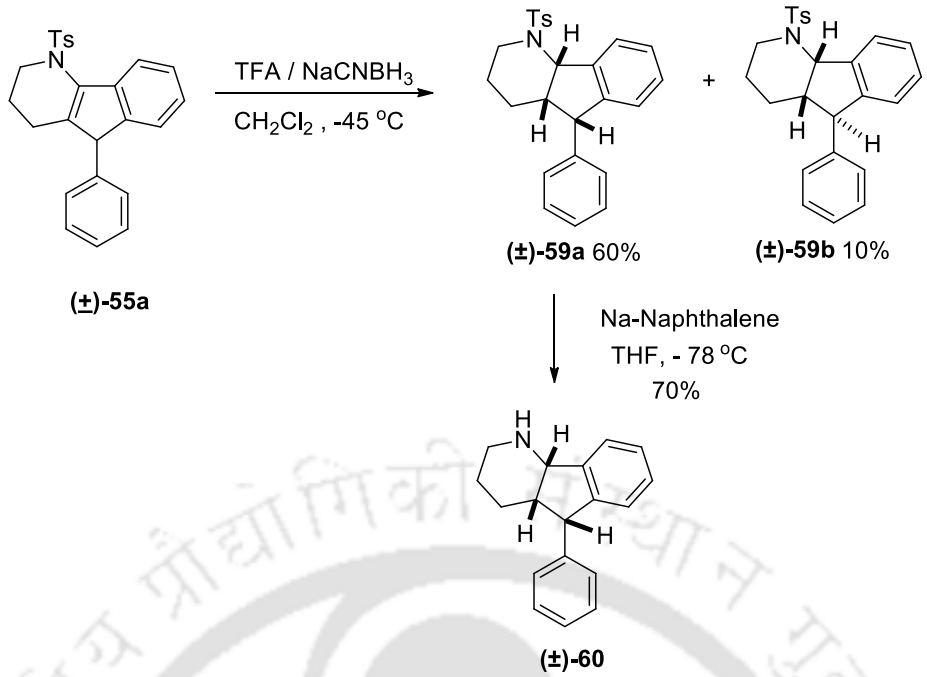
8	 **49a**	 **50h**	 **55h**		61
9	 **42a**	 **50i**	 **55i**		78
10	 **42a**	 **50j**	 **55j**		75
11	 **49a**	 **50k**	 **55k**		87
12	 **49b**	 **50a**	 **55l**		57
13	 **49b**	 **50l**	 **51m**		56
14	 **49c**	 **50a**	 **55n**		52



[a]Yields refer to isolated yield. Compounds are characterized by ^{1}H, ^{13}C NMR, IR and mass spectrometry.

2.4.3 Total synthesis of (±)-5-phenyl-2,3,4,4*a*,5,9*b*-hexahydro-1*H*-indeno[1,2-*b*]pyridine (60).

The former strategy has been successfully applied to the synthesis of (±)-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno- [1,2-*b*]pyridine (**60**). The compound **60** shows some amount of antidepressant activity.[13a,20] The synthesis started with the reduction of (±)-**55a** with sodium cyanoborohydride and trifluoroacetic acid in dichloromethane to give



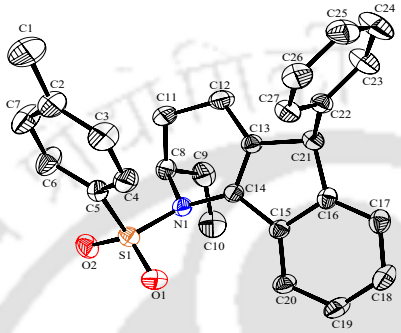
Scheme 2.4.3.1 Total synthesis of (±)-5-phenyl-2,3,4,4*a*,5,9*b*-hexahydro-1*H*-indeno[1,2-*b*]pyridine.

diastereomeric mixtures of cis-(±)-**59a** and trans-(±)-**59b**, in 60% and 10% yields, respectively (*Scheme 2.4.3.1*). Compound (±)-**59a** after deprotection of the tosyl group with sodium naphthalenide provides the final product (±)-**60**.

2.4.4 Structural determination and stereochemistry of the compounds

The structures of the products **55** was determined by X-ray crystallographic analysis of **55d,e**.[21] An ethyl-substituted alkyne (Table 2.4.2.1, entry 16) gave trans product **55p** with respect to ethyl and phenyl at the 2- and 5- positions, the stereochemistry of which was confirmed by X-ray crystallographic analysis.[21] The structures of compounds **55s,t** were determined from ^{1}H and ^{13}C NMR, COSY, and HMQC analysis of compound **55s**. Compound **55s** shows a broad singlet at δ 4.44 ppm in ^{1}H NMR and 18 signals in the aromatic region of ^{13}C NMR. Moreover, the proton at δ 4.44 ppm does not correlate with carbon in an HMQC analysis (*Section 2.8*). This indicates that this peak belongs to the −NH− proton of the −NHTs group.

55d **55e**



55p

Figure 2.4.4.1. *ORTEP diagram of* **55d**, **55e and 55p**

The *cis* and *trans* stereochemistry of compounds (±)-**59a** and (±)-**59b** were determined by coupling constants and NOE experiments. The vicinal coupling constant of proton C-9bH of (±)-**59a**, resonating at 5.47 ppm, was found to be 5.6 Hz. Similarly, the vicinal coupling constant of proton C-9bH of (±)-**59b**, resonating at 5.10 ppm, was also found to be 5.6 Hz. This indicates that in both compounds the configuration of the ring junction is same (*Figure 2.4.4.2*). On the other hand, the vicinal coupling constants of proton C-5H of **(±)-59a**,

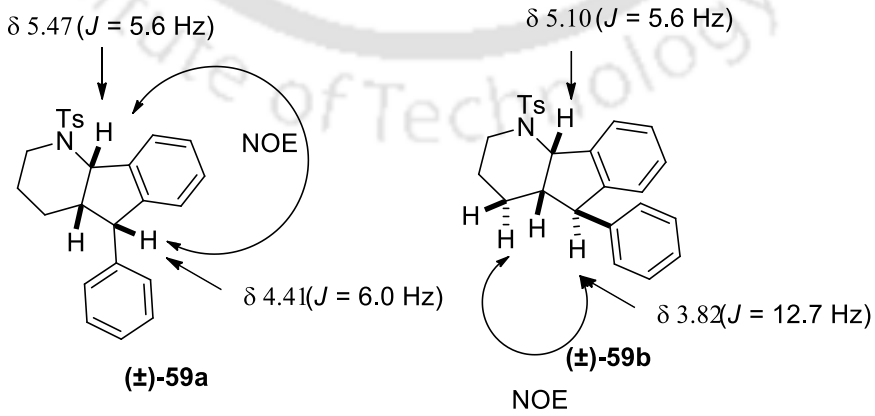


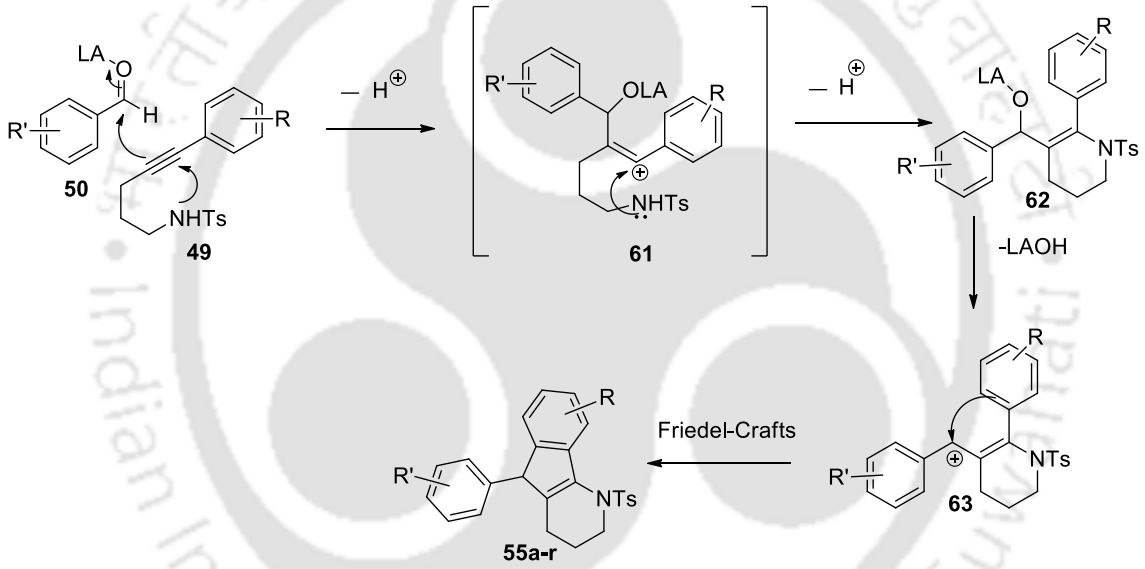
Figure 2.4.4.2. Coupling constants and NOE of compounds (±)-**59a** and (±)-**59b**.

resonating at 4.41 ppm, and **(±)-59b**, resonating at 3.82 ppm, were found to be 6.0 and 12.7 Hz, respectively. Compound (±)-**59a** showed a clear characteristic NOE correlation

between the hydrogens C-9bH and C-5H, which clearly indicates that the two hydrogens are *cis* to each other (*Figure 2.4.4.2*). However, there was no such NOE correlation between the hydrogens C-9bH and C-5H in compound (±)-**59b**. Therefore, the configuration of the C-9bH and C-5H protons of compound (±)-**59b** is *trans*.

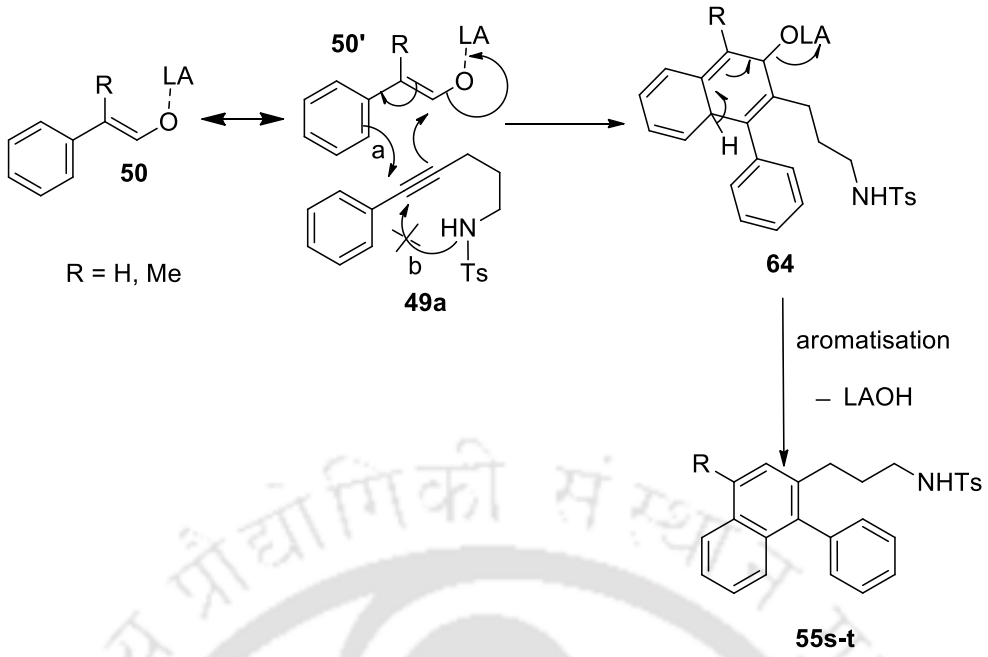
2.4.5. Plausible mechanism of the reaction

A plausible mechanism for the formation of compounds **55a-r** is shown below (*Scheme 2.4.5.1*). The boron trifluoride etherate activates the carbonyl group of the aldehyde for the nucleophilic attack by alkyne group which is subsequently attacked by tosylamide group to form intermediate **62**, which after decomposition generates carbocation **63**. The carbocation **63** is attacked by aryl group to give the Friedel-Crafts products **55a-r**.



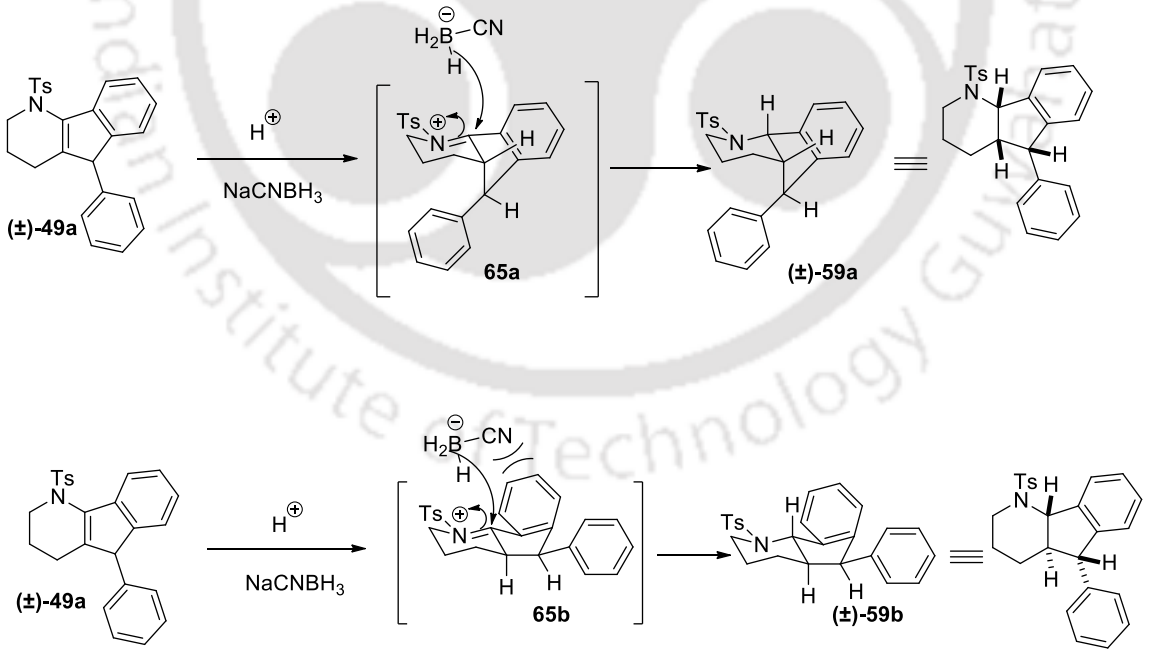
Scheme 2.4.5.1 Mechanism for the formation of tetrahydro-1*H*-indeno[1,2-*b*]pyridine

The formation of **55r** and **55s** is shown in *Scheme 2.4.5.2*. In this case, aldehyde **50** enolized under Lewis acidic conditions to form **50'**, and subsequently reacts with alkyne **49** to form the Diels−Alder adduct **64**, which after aromatization give naphthalene derivatives **55s,t**.



Scheme 2.4.5.2 Mechanism for the Formation of Naphthalene Derivatives

The mechanism of formation of **(±)-59a** and **(±)-59b** from **(±)-49a** after protonation and subsequent addition of hydride can be explained as follows *(Scheme 2.4.5.3*). Out of the



Scheme 2.4.5.3 Mechanism of formation of Hexahydro-1*H*-indeno[1,2-*b*]pyridine

two possible transition states **65a,b**, in their chair conformation, transition state **65a** is more favored than **65b** due to the repulsion between the phenyl group and incoming cyanoborohydride in the latter leads to the formation *cis*- isomer as the major one.

2.5. Conclusion:

In conclusion, we have developed a mild and efficient method for the synthesis of tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* cascade cyclization of alkyne tosylamides and aryl aldehydes in good yields. The reaction is compatible with a wide range of functional groups such as ester, nitro, nitrile and halides. The methodology is used for the synthesis of biologically active molecule (±)-5-Phenyl-2,3,4,4*a*,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine.

2.6. Experimental section

2.6.1. Instrumentation and characterization

General Information: All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

General Procedure for Formation of compounds 49

Synthesis of sulphonamide 49: A round-bottomed flask fitted with a reflux condenser was charged with 4-methylbenzenesulfonamide (393 mg, 2.3 mmol), finely powdered potassium hydroxide (72 mg, 1.30 mmol.) and dimethylsulfoxide (2 mL). The resulting suspension was heated to 50 °C and stirred for 2 hours. The resulting solution was cooled to room temperature and compound **58** (1 mmol) in dimethylsulfoxide (1 mL) was added dropwise, followed by sodium iodide (44 mg, 0.30 mmol.) in one portion. The mixture was heated to 50 °C and stirred until TLC showed full consumption of starting material. The mixture was cooled to room temperature, ice-cold water (30 mL) added and the aqueous layer extracted with ethyl acetate (40 mL) .The organic layer was washed with brine dried over Na_2SO_4 and concentrated in vacuum followed by purification by column chromatography to give sulphonamides **49**. Compound **49a** and **49e** are known and their spectroscopic data agreed well with the reported data.[22]

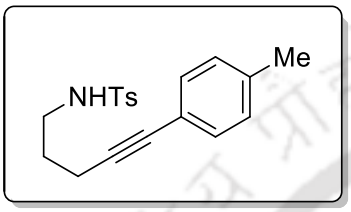
General Procedure for Formation of compounds 55 :

To a solution of *N*-tosylated alkyne amine **49** (0.3 mmol) in dry 1,2-dichloroethane (2 mL) was added aldehyde **50** (35 mg, 0.33 mmol) at 0 °C, followed by $BF_3{\cdot}OEt_2$ (87 mg, 0.6

mmol). The reaction mixture was brought to room temperature and kept for 12 h. After completion of the reaction, as determined by TLC, dichloroethane was added to the reaction mixture, washed with saturated sodium bicarbonate and brine solutions, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatography using ethyl acetate and hexane as eluents.

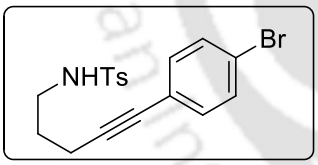
2.7. Spectral data

4-Methyl-*N*-(5-(*p*-tolyl)pent-4-yn-1-yl)benzenesulfonamide (49b):



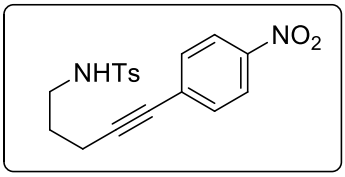
colorless solid; mp 99−101 °C; R_f (hexane/EtOAc 4/2) 0.58; yield 229 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.72−1.77 (m, 2 H), 2.33 (s, 3 H), 2.39 (s, 3 H), 2.41 (t, J = 7.2 Hz, 2 H), 3.10−3.12 (m, 2 H), 5.01 (brs, 1 H), 7.07 (d, J = 7.8 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.9, 21.6, 21.7, 28.5, 42.5, 81.9, 87.7, 127.3, 128.3, 129.1, 129.9, 131.5, 137.0, 138.0, 143.5; IR (KBr, neat) 3276, 3052, 2925, 2851, 1912, 1892, 1599, 1429, 1326, 1159, 1093, 958, 815, 665 cm^{-1} ; HRMS (ESI) calcd for $C_{19}H_{22}NO_2S$ $(M + H)^+$)$^+$: *m/z* 328.1366, found 328.1384.

***N*-(5-(4-Bromophenyl)pent-4-yn-1-yl)-4-methylbenzenesulfonamide (49c):**



colorless solid; mp 114−116 °C; R_f (hexane/EtOAc 4/2) 0.6; yield 262 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73−1.80 (m, 2 H), 2.41 (s, 3 H), 2.43 (t, J = 7.2 Hz, 2 H), 3.09−3.14 (m, 2 H), 4.78 (brs, 1 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 21.8, 28.4, 42.4, 80.9, 89.8, 122.1, 122.6, 127.3, 129.9, 131.6, 133.2, 137.0, 143.7; IR (KBr, neat) 3275, 3059, 2927, 2855, 1644, 1583, 1487, 1325, 1160, 1071, 1010, 817, 737, 663 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}BrNO_2S$ $(M + H)^+$)$^+$: *m/z* 394.0294, found 394.0313.

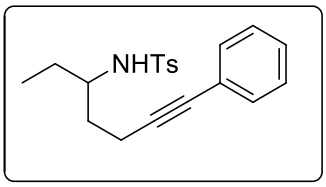
4Methyl-*N*-(5-(4-nitrophenyl)pent-4-yn-1-yl)benzenesulfonamide (49d):



Colorless solid; mp 126−128 °C; R_f (hexane/EtOAc 2/1) 0.33; yield 250 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77−1.85 (m, 2 H), 2.42 (s, 3 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 3.11−3.16 (m, 2 H), 4.52 (brs, 1 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 8.15 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.9, 21.7, 28.3, 42.3, 80.3, 94.8, 123.6,

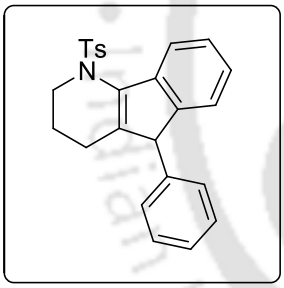
127.2, 129.9, 130.8, 132.4, 136.9, 143.7, 146.9; IR (KBr, neat) 3298, 2925, 2228, 1593, 1515, 1342, 1158, 1094, 854, 750, 688 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_4S$ $(M + H)^+$ $)^+$: *m/z* 359.1060, found 359.1086.

4-Methyl-*N*-(7-phenylhept-6-yn-3-yl)benzenesulfonamide (49e):



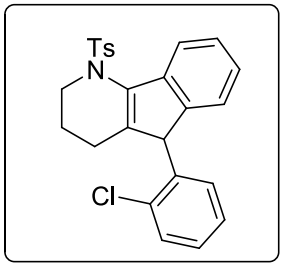
Colorless solid; mp 65−67°C; R_f (hexane/EtOAc 9/1) 0.33; yield 249 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3 H), 1.38−1.47 (m, 1 H), 1.49−1.57 (m, 1 H), 1.58−1.66 (m, 1 H), 1.69−1.74 (m, 1 H), 2.30−2.36 (m, 2 H), 2.38 (s, 3 H), 3.30−3.39 (m, 1 H), 4.83 (brs, 1 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.28−7.30 (m, 3 H), 7.35−7.38 (m, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 16.0, 21.6, 27.8, 33.4, 54.8, 81.3, 89.3, 123.8, 127.1, 127.8, 128.3, 129.7, 131.6, 138.2, 143.3; IR (KBr, neat) 3282, 3059, 2966, 2876, 2236, 1953, 1599, 1491, 1307, 1161, 1093, 1008, 912, 758, 664 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}NO_2S$ $(M + H)^+$ $)^+$: *m/z* 342.1522, found 342.1530.

5-Phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55a):



Colorless solid; mp 150−152 °C; R_f (hexane/EtOAc 9/1) 0.49; yield 73 mg, 57%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21−1.27 (m, 1 H), 1.37−1.41 (m, 1 H), 1.87 (dt, *J* = 18.6 and 6.6 Hz, 1 H), 2.08 (dt, *J* = 18.6 and 7.2 Hz, 1 H), 2.41 (s, 3 H), 3.54 (ddd, *J* = 12.6, 7.2, and 3.0 Hz, 1 H), 3.81 (ddd, *J* = 14.4, 6.6, and 3.0 Hz, 1 H), 4.29 (s, 1 H), 6.95 (d, *J* = 7.2 Hz, 2 H), 7.13−7.16 (m, 2 H), 7.21−7.28 (m, 5 H), 7.31−7.34 (m, 1 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 8.01 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.8, 22.1, 47.9, 55.9, 122.5, 123.7, 125.6, 127.0, 127.2, 128.1, 128.3, 128.9, 129.8, 136.1, 136.7, 138.8, 139.8, 141.1, 144.1, 146.6; IR (KBr, neat) 3060, 2926, 2856, 1600, 1493, 1454, 1353, 1166, 1092, 985, 811, 662 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}NO_2S$ $(M + H)^+$ $)^+$: *m/z* 402.1522, found 402.1521.

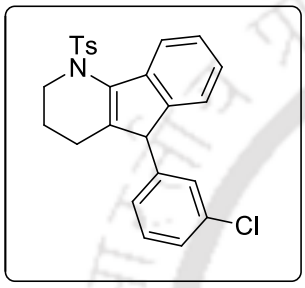
5-(2-Chlorophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55b):



Colorless solid; mp 162−164 °C; R_f (hexane/EtOAc 9/1) 0.53; yield 86 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26− 1.29 (m, 1 H), 1.37−1.41 (m, 1 H), 1.85 (ddd, *J* = 10.8, 6.6, and 4.2 Hz, 1 H), 2.18 (ddd, *J* = 18.0, 11.4, and 6.6 Hz, 1 H), 2.41 (s, 3 H), 3.55

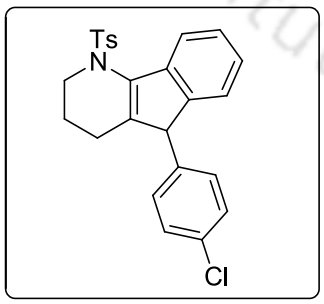
(ddd, J = 13.8, 9.6, and 4.2 Hz, 1 H), 3.81 (ddd, *J* = 15.0, 9.6, and 5.4 Hz, 1 H), 5.04 (s, 1 H), 6.47 (d, J = 7.6 Hz, 1 H), 7.04 (t, *J* = 9.6 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.21 (s, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 8.01 (d, *J* = 8.0 Hz, 1 H); 13C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.8, 22.0, 47.9, 51.4, 122.7, 123.7, 125.7, 127.2, 127.4, 128.1, 128.4, 128.5, 129.9, 135.2, 136.1, 137.1, 137.8, 141.2, 144.1, 146.1; IR (KBr, neat) 3063, 2928, 2855, 1597, 1490, 1456, 1354, 1164, 1091, 986, 813, 740 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}ClNO_2S$ $(M + H)^+$ $)^+$: *m/z* 436.1133, found 436.1118.

5-(3-Chlorophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]- pyridine (55c):



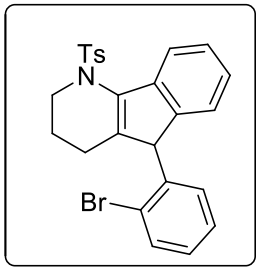
Colorless solid; mp 156−158 °C; R_f (hexane/EtOAc 9/1) 0.48; yield 90 mg, 65%; ^{1}H NMR (600 MHz, CDCl3) δ 1.17− 1.21 (m, 1 H), 1.39−1.43 (m, 1 H), 1.85 (ddd, *J* = 18.6, 6.6, and 4.2 Hz, 1 H), 2.01 (ddd, *J* = 18.6, 9.6, and 7.8 Hz, 1 H), 2.41 (s, 3 H), 3.49 (ddd, *J* = 13.2, 10.2, and 3.0 Hz, 1 H), 3.90 (ddd, *J* = 14.4, 5.4, and 3.0 Hz, 1 H), 4.24 (s, 1 H), 6.88 (s, 1 H), 6.94 (d, J = 7.2 Hz, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 7.20−7.22 (m, 2 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 8.03 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, CDCl3) δ 19.0, 21.9, 22.1, 48.0, 55.4, 122.8, 123.7, 125.8, 126.9, 127.3, 127.5, 127.9, 128.1, 130.0, 130.2, 134.7, 137.3, 141.0, 142.0, 144.2, 145.9; IR (KBr, neat) 3059, 2926, 2856, 1596, 1457, 1352, 1164, 1093, 987, 811, 688 cm−1; HRMS (ESI) calcd for $C_{25}H_{23}ClNO_2S$ $(M + H)^+$ $)^+$: *m/z* 436.1133, found 436.1135.

5-(4-Chlorophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55d):



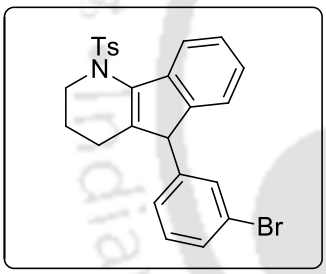
Colorless solid; mp 159−161 °C; R_f (hexane/EtOAc 9/1) 0.58; yield 97 mg, 70%; ^{1}H NMR (600 MHz, CDCl3) δ 1.23− 1.29 (m, 1 H), 1.39−1.42 (m, 1 H), 1.84 (ddd, *J* = 18.6, 7.2, and 5.4 Hz, 1 H), 2.08 (ddd, *J* = 15.0, 7.8, and 4.2 Hz, 1 H), 2.42 (s, 3 H), 3.54 (ddd, *J* = 16.8, 9.6, and 3.0 Hz, 1 H), 3.79 (ddd, *J* = 14.4, 6.6, and 3.6 Hz, 1 H), 4.26 (s, 1 H), 6.88 (d, *J* = 7.8 Hz, 2 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 7.21−7.26 (m, 4 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 8.00 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, CDCl3) δ 19.1, 21.8, 22.0, 47.8, 55.1, 122.6, 123.6, 125.7, 127.2, 128.0, 129.1, 129.6, 129.8, 132.9, 136.0, 136.9, 138.2, 138.3, 141.0, 144.1, 146.1; IR (KBr, neat) 3063, 2927, 2856, 1618, 1597, 1490, 1354, 1164, 1091, 1017, 986, 813, 766 $^{cm-1}$; HRMS (ESI) calcd for $C_{25}H_{23}ClNO_2S$ $(M + H)^+$ $)^+$: *m/z* 436.1133, found 436.1135.

5-(2-Bromophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55e):



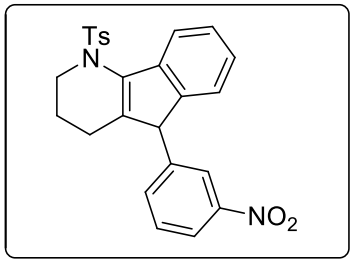
Colorless solid; mp 182−184 °C; Rf (hexane/EtOAc 9/1) 0.53; yield 81 mg, 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22− 1.30 (m, 1 H), 1.36−1.42 (m, 1 H), 1.86 (ddd, *J* = 19.2, 7.2, and 4.8 Hz, 1 H), 2.20 (ddd, *J* = 19.2, 7.6, and 4.0 Hz, 1 H), 2.42 (s, 3 H), 3.55 (ddd, *J* = 14.4, 6.4, and 3.2 Hz, 1 H), 3.80 (ddd, J = 14.0, 6.4, and 3.2 Hz, 1 H), 5.04 (s, 1 H), 6.43−6.46 (m, 1 H), 7.06− 7.10 (m, 2 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 7.21−7.25 (m, 3 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.61−7.63 (m, 1 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 8.01 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.8, 22.0, 47.9, 54.2, 122.7, 123.6, 125.7, 127.2, 128.0, 128.1, 128.6, 128.7, 129.9, 133.1, 137.1, 138.5, 139.6, 141.1, 144.1, 146.2; IR (KBr, neat) 2959, 2927, 2854, 1594, 1466, 1353, 1164, 1093, 1026, 987, 811, 765 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}BrNO_2S$ $(M + H)^+$ $)^+$: *m/z* 480.0627, found 480.0608.

5-(3-Bromophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55f):



Colorless solid; mp 178−180 °C; R_f (hexane/EtOAc 9/1) 0.54; yield 90 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10− 1.21 (m, 1 H), 1.37−1.44 (m, 1 H), 1.84 (ddd, J = 18.8, 6.8, and 3.6 Hz, 1 H), 2.09 (ddd, *J* = 19.2, 8.0, and 4.0 Hz, 1 H), 2.41 (s, 3 H), 3.46 (ddd, *J* = 17.2, 7.2, and 3.2 Hz, 1 H), 3.89 (ddd, *J* = 14.4, 5.6, and 3.6 Hz, 1 H), 4.23 (s, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 7.06 (s, 1 H), 7.13 (d, *J* = 7.8 Hz, 1 H), 7.15−7.18 (m, 2 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.35 (t, *J* = 7.8 Hz, 2 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 8.03 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.0, 21.9, 22.0, 47.9, 55.3, 122.7, 123.6, 125.7, 127.2, 127.3, 128.0, 129.9, 130.4, 130.5, 130.7, 137.1, 137.9, 140.9, 142.1, 144.2, 145.8; IR (KBr, neat) 2925, 2854, 1594, 1467, 1352, 1297, 1164, 1093, 1025, 988, 812, 765 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}BrNO_2S$ $(M + H)^+$ $)^+$: *m/z* 480.0627, found 480.0625.

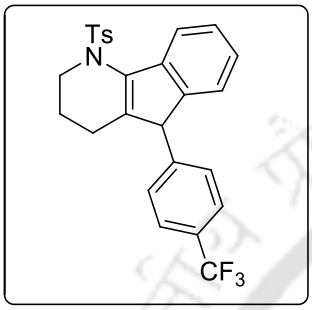
5-(3-Nitrophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]- pyridine (55g):



Colorless solid; mp 115−117 °C; R_f (hexane/EtOAc 9/1) 0.28; yield 77 mg, 54%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18− 1.22 (m, 1 H), 1.41−1.45 (m, 1 H), 1.83 (dt, *J* = 18.6 and 4.8 Hz, 1 H), 2.14 (dt, *J* = 18.6 and 7.8 Hz, 1 H), 2.42 (s, 3 H), 3.49−3.54 (m, 1 H), 3.86 (dt, *J* = 14.4 and 4.8 Hz, 1 H), 4.39 (s, 1 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.37 (t, *J* = 7.2 Hz, 1 H),

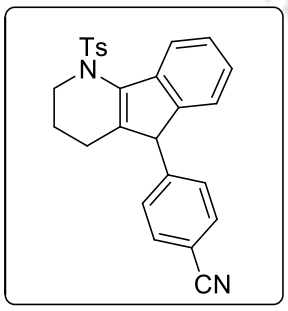
7.46 (t, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 2 H), 7.85 (s, 1 H), 8.04 (d, *J* = 7.8 Hz, 1 H), 8.10 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.8, 22.1, 47.8, 55.2, 122.5, 123.1, 123.6, 126.0, 127.6, 128.0, 130.0, 134.6, 135.8, 136.9, 137.9, 141.0, 142.2, 144.4, 145.4, 148.9; IR (KBr, neat) 3065, 2926, 2854, 1620, 1599, 1500, 1455, 1352, 1163, 1092, 987, 810, 740 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}N_2O_4S$ $(M + H)^+$ $)^+$: *m/z* 447.1373, found 447.1370.

1-Tosyl-5-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55h):



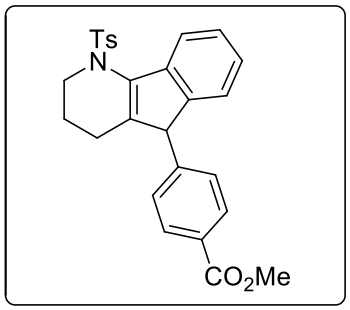
Colorless solid; mp 166−168 °C; R_f (hexane/EtOAc 9/1) 0.45; yield 91 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25−1.33 (m, 1 H), 1.39−1.43 (m, 1 H), 1.83 (dt, *J* = 18.0 and 6.4 Hz, 1 H), 2.10 (dt, *J* = 19.2 and 7.2 Hz, 1 H), 2.42 (s, 3 H), 3.55 (ddd, *J* = 14.0, 6.8, and 3.2 Hz, 1 H), 3.80 (ddd, *J* = 14.0, 6.0, and 2.8 Hz, 1 H), 4.35 (s, 1 H), 7.06−7.11 (m, 3 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 8.01(d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.8, 22.0, 47.8, 55.4, 122.8, 123.7, 124.3 (q, *J* = 270.5 Hz), 125.8, 125.9 (q, *J* = 3.6 Hz), 125.9, 127.4, 128.1, 128.7, 129.5 (q, *J* = 32.3 Hz), 130.0, 136.0, 137.3, 137.8, 141.1, 144.3, 145.8; 19F NMR (376 MHz, CDCl3/C6F6) δ 99.27; IR (KBr, neat) 3065, 2926, 2853, 1617, 1459, 1326, 1164, 1123, 1066, 1018, 817, 733 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{23}F_3NO_2S$ $(M + H)^+$ $)^+$: *m/z* 470.1396, found 470.1392.

4-(1-Tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridin-5-yl)benzonitrile (55i):



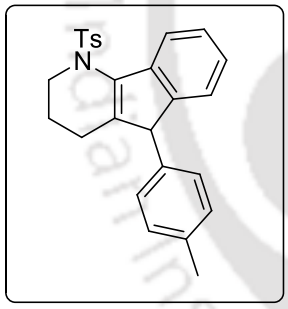
Colorless solid; mp 154−156 °C; R_f (hexane/ EtOAc 4/1) 0.4; yield 106 mg, 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25−1.31 (m, 1 H), 1.40−1.44 (m, 1 H), 1.81 (dt, *J* = 15.0 and 6.6 Hz, 1 H), 2.11 (dt, *J* = 18.6 and 7.2 Hz, 1 H), 2.43 (s, 3 H), 3.55 (ddd, *J* = 14.4, 9.6, and 3.6 Hz, 1 H), 3.78 (ddd, *J* = 14.4, 7.2, and 3.0 Hz, 1 H), 4.34 (s, 1 H), 7.06−7.09 (m, 3 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 7.8 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, CDCl3) δ 19.2, 21.9, 22.0, 47.8, 55.6, 111.2, 118.9, 122.9, 123.6, 125.9, 127.6, 128.1, 129.1, 129.9, 132.8, 136.0, 137.2, 137.7, 141.0, 144.3, 145.4, 145.9; IR (KBr, neat) 3064, 2925, 2855, 2228, 1604, 1499, 1458, 1352, 1298, 1164, 1092, 1022, 987, 816, 737 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{23}N_2O_2S$ $(M + H)^+$ $)^+$: *m/z* 427.1475, found 427.1474.

Methyl 4-(1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridin-5-yl)benzoate (55j):



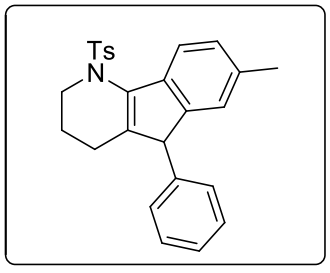
Colorless solid; mp 120−122 °C; R_f (hexane/ EtOAc 9/1) 0.37; yield 110 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20−1.30 (m, 1 H), 1.35−1.45 (m, 1 H), 1.81 (dt, *J* = 18.6 and 5.4 Hz, 1 H), 2.10 (dt, *J* = 18.6 and 7.8 Hz, 1 H), 2.42 (s, 3 H), 3.52−3.57 (m, 1 H), 3.78−3.84 (m, 1 H), 3.91 (s, 3 H), 4.34 (s, 1 H), 7.03 (d, *J* = 7.8 Hz, 2 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 2 H), 7.93 (d, *J* = 7.8 Hz, 2 H), 8.02 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.8, 22.0, 47.8, 52.3, 55.6, 122.7, 123.6, 125.7, 127.3, 128.0, 128.3, 129.2, 129.9, 130.3, 135.9, 137.2, 137.9, 141.0, 144.2, 145.4, 145.9, 167.0; IR (KBr, neat) 3063, 2956, 2852, 1925, 1729, 1606, 1494, 1459, 1352, 1275, 1159, 1106, 1020, 987, 814, 765 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{26}NO_4S$ $(M + H)^+$)$^+$: *m/z* 460.1577, found 460.1580.

5-(p-Tolyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55k):



Colorless solid; mp 125−127 °C; R_f (hexane/EtOAc 9/1) 0.50; yield 114 mg, 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20−1.30 (m, 1 H), 1.32−1.45 (m, 1 H), 1.87 (dt, *J* = 19.2 and 5.4 Hz, 1 H), 2.07 (dt, *J* = 19.2 and 7.2 Hz, 1 H), 2.32 (s, 3 H), 2.41 (s, 3 H), 3.52−3.57 (m, 1 H), 3.78−3.82 (m, 1 H), 4.25 (s, 1 H), 6.85 (d, *J* = 7.2 Hz, 2 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 7.11−7.15 (m, 2 H), 7.23 (d, *J* = 7.2 Hz, 2 H), 7.30−7.34 (m, 1 H), 7.66 (d, *J* = 7.2 Hz, 2 H), 8.00 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.3, 21.8, 22.1, 47.9, 55.5, 122.4, 123.6, 125.5, 126.9, 128.1, 128.2, 129.6, 129.8, 136.1, 136.5, 136.6, 136.7, 138.8, 141.0, 144.0, 146.8; IR (KBr, neat) 3061, 2927, 2853, 1606, 1458, 1352, 1298, 1165, 1092, 1022, 986, 765 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{26}NO_2S$ $(M + H)^+$: *m/z* 416.1679, found 416.1678.

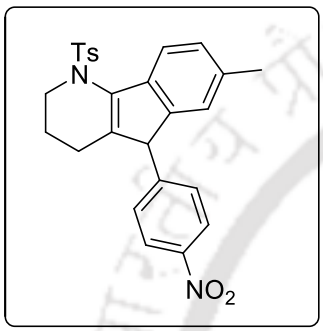
7-Methyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]- pyridine (55l):



Colorless solid; mp 127−129 °C; R_f (hexane/EtOAc 9/1) 0.45; yield 72 mg, 57%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20− 1.28 (m, 1 H), 1.34−1.40 (m, 1 H), 1.84 (dt, *J* = 19.2 and 6.0 Hz, 1 H), 2.06 (dt, *J* = 19.2 and 7.2 Hz, 1 H), 2.31 (s, 3 H), 2.41 (s, 3 H), 3.51−3.56 (m, 1 H), 3.80−3.84 (m, 1 H), 4.24 (s, 1 H),

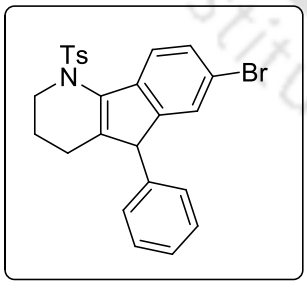
6.95− 6.96 (m, 3 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 7.19−7.38 (m, 5 H), 7.66 (t, *J* = 7.8 Hz, 2 H), 7.89 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 21.5, 21.8, 22.0, 47.9, 55.7, 122.2, 124.5, 127.1, 127.7, 128.1, 128.3, 128.9, 129.8, 135.3, 136.1, 136.6, 137.6, 138.3, 140.0, 144.0, 146.9; IR (KBr, neat) 2924, 2855, 1603, 1493, 1451, 1347, 1164, 1091, 985, 817, 737 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{26}NO_2S$ $(M + H)^+$: *m/z* 416.1679, found 416.1683.

7-Methyl-5-(4-nitrophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno- [1,2-*b*]pyridine (55m):



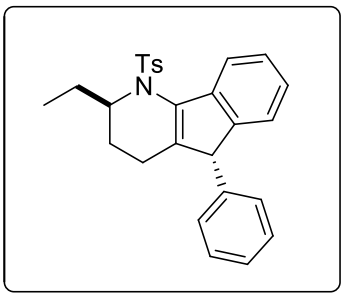
Colorless solid; mp 130−132 °C; R_f (hexane/ EtOAc 9/1) 0.35; yield 79 mg, 56%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25−1.30 (m, 1 H), 1.40−1.45 (m, 1 H), 1.80 (dt, *J* = 18.6 and 6.0 Hz, 1 H), 2.11 (dt, *J* = 18.6 and 7.2 Hz, 1 H), 2.31 (s, 3 H), 2.43 (s, 3 H), 3.53−3.57 (m, 1 H), 3.80 (dt, *J* = 11.4 and 3.0 Hz, 1 H), 4.36 (s, 1 H), 6.90 (s, 1 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 8.12 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 21.5, 21.8, 22.0, 47.8, 55.1, 122.6, 124.2, 124.5, 128.0, 128.3, 129.1, 129.9, 130.7, 135.8, 136.0, 137.6, 138.2, 144.3, 145.6, 147.2, 148.3; IR (KBr, neat) 2925, 2855, 1600, 1523, 1347, 1164, 1091, 814, 777 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{25}N_2O_4S$ $(M + H)^+$: *m/z* 461.1530, found 461.1529.

7-Bromo-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine (55n):



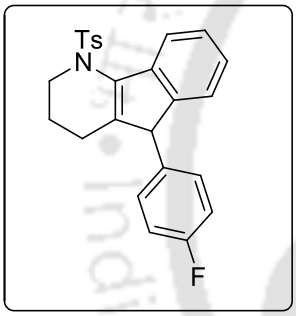
Colorless solid; mp 180−182 °C; R_f (hexane/EtOAc 9/1) 0.42; yield 64 mg, 52%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18− 1.27 (m, 1 H), 1.35−1.39 (m, 1 H), 1.84 (dt, *J* = 19.2 and 6.0 Hz, 1 H), 2.06 (dt, *J* = 19.2 and 7.2 Hz, 1 H), 2.42 (s, 3 H), 3.51−3.56 (m, 1 H), 3.81 (ddd, *J* = 14.4, 6.0, and 3.0 Hz, 1 H), 4.26 (s, 1 H), 6.93 (d, *J* = 7.2 Hz, 2 H), 7.24−7.30 (m, 6 H), 7.45 (d, *J* = 8.4 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.88 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.0, 21.8, 22.0, 47.9, 55.8, 119.7, 124.0, 126.9, 127.5, 128.1, 128.2, 129.1, 129.9, 130.1, 135.9, 136.3, 138.8, 139.0, 140.0, 144.2, 148.6; IR (KBr, neat) 2924, 2855, 1603, 1451, 1347, 1164, 1091, 985, 816, 737 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}BrNO_2S$ $(M + H)^+$: *m/z* 480.0627, found 480.0626.

2-Ethyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]- pyridine (55p):



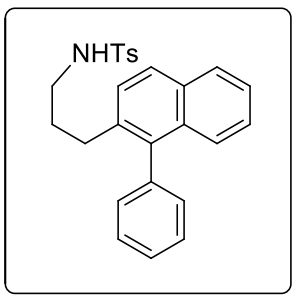
Crystalline solid; mp 169−171 °C; R_f (hexane/EtOAc 9/1) 0.60; yield 102 mg, 81%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 3 H), 1.03−1.07 (m, 1 H), 1.24−1.29 (m, 1 H), 1.34 (dd, *J* = 13.8 and 7.2 Hz, 1 H), 1.49−1.55 (m, 1 H), 1.78 (dd, *J* = 19.2 and 6.6 Hz, 1 H), 2.12 (dt, *J* = 19.2 and 8.4 Hz, 1 H), 2.38 (s, 3 H), 4.06−4.09 (m, 1 H), 4.20 (s, 1 H), 7.01 (d, *J* = 7.8 Hz, 2 H), 7.15 (s, 2 H), 7.19 (d, *J* = 7.2 Hz, 2 H), 7.23−7.29 (m, 3 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 2 H), 8.04 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.2, 19.1, 21.8, 22.2, 24.4, 55.8, 57.8, 122.6, 123.5, 125.4, 127.0, 127.1, 128.1, 128.2, 128.8, 129.7, 134.2, 135.6, 137.7, 139.7, 141.8, 143.9, 146.5; IR (KBr, neat) 3062, 2966, 2870, 1674, 1598, 1493, 1457, 1347, 1169, 1092, 1024, 949, 763 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{28}NO_2S$ $(M + H)^+$: *m/z* 430.1835, found 430.1833.

5-(4-Fluorophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]- pyridine (55r):



Colorless gum; R_f (hexane/EtOAc 9:13) 0.58; yield 70 mg, 52%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24−1.30 (m, 1 H), 1.38−1.42 (m, 1 H), 1.85 (dt, *J* = 18.6 and 6.6 Hz, 1 H), 2.08 (dt, *J* = 18.6 and 7.2 Hz, 1 H), 2.42 (s, 3 H), 3.55 (ddd, *J* = 12.0, 9.0, and 2.4 Hz, 1 H), 3.79 (ddd, *J* = 14.4, 6.6, and 3.6 Hz, 1 H), 4.27 (s, 1 H), 6.90−6.96 (m, 4 H), 7.11 (d, *J* = 7.2 Hz, 1 H), 7.16 (d, *J* = 7.2 Hz, 1 H), 7.20−7.25 (m, 2 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 8.00 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2, 21.8, 22.0, 47.9, 55.1, 115.7 (d, *J* = 21.0 Hz), 122.6, 123.6, 125.7, 127.2, 128.1, 129.7 (d, *J* = 7.5 Hz), 129.8, 135.5, 136.1, 136.8, 138.4, 140.9, 144.1, 146.4, 162.1 (d, *J* = 244.5 Hz); ^{19}F NMR (376 MHz, CDCl3/C6F6) δ 39.16; IR (KBr, neat) 2924, 2854, 1601, 1507, 1459, 1352, 1161, 1093, 815, 735 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}FNO2S$ $(M + H)^+$: *m/z* 420.1428, found 420.1430.

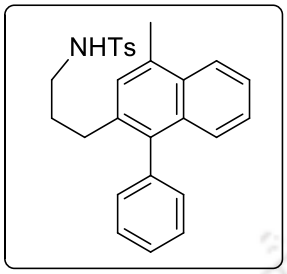
4-Methyl-N-(3-(1-phenylnaphthalen-2-yl)propyl)benzenesulfonamide (55s):



Colorless solid; mp 183−185 °C; R_f (hexane/EtOAc 4/ 1) 0.43; yield 94 mg, 71%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.57− 1.60 (m, 2 H), 2.33 (s, 3 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 2.72−2.76 (m, 2 H), 4.44 (brs, 1 H), 7.12 (d, *J* = 7.2 Hz, 2 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 7.24−7.27 (m, 3 H), 7.33−7.36 (m, 1 H), 7.38−7.42 (m, 3 H), 7.60 (d, *J* = 7.8 Hz, 2 H), 7.71 (d, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 30.7, 31.3, 42.8, 125.3, 126.1, 126.6, 127.2, 127.5, 127.9, 128.5, 128.6, 129.8, 130.4, 130.5, 132.2, 133.1, 136.2, 137.9, 138.2,

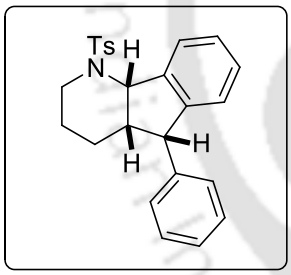
139.2, 143.4; IR (KBr, neat) 3060, 2960, 2855, 1597, 1490, 1454, 1328, 1160, 1094, 1023, 817, 750 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{26}NO_2S$ $(M + H)^+$: *m/z* 416.1679, found 416.1675.

4-Methyl-N-(3-(4-methyl-1-phenylnaphthalen-2-yl)propyl)benzenesulfonamide (55t):



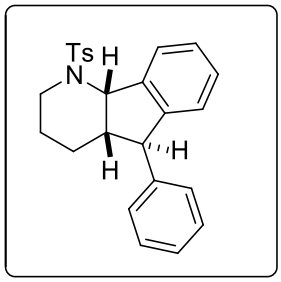
Colorless solid; mp 108−110 °C; R_f (hexane/EtOAc 4/1) 0.41; yield 101 mg, 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.60−1.66 (m, 2 H), 2.41 (s, 3 H), 2.45 (t, *J* = 7.2 Hz, 2 H), 2.70 (s, 3 H), 2.77−2.81 (m, 2 H), 4.37 (brs, 1 H), 7.17−7.19 (m, 3 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.33−7.35 (m, 2 H), 7.41−7.47 (m, 4 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.6, 21.7, 30.7, 31.3, 42.9, 124.0, 125.1, 125.8, 127.2, 127.3, 128.2, 128.5, 129.8, 130.6, 130.7, 131.3, 133.2, 134.0, 135.8, 136.6, 137.1, 139.5, 143.4; IR (KBr, neat) 3063, 2925, 2854, 1598, 1494, 1442, 1326, 1160, 1095, 1032, 760 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{28}NO_2S$ $(M + H)^+$: *m/z* 430.1835, found 430.1834.

5-Phenyl-1-tosyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]- pyridine (59a):



Colorless solid; mp 74−76 °C; R_f (hexane/EtOAc 9/ 1) 0.5; yield 60 mg, 60%; ^{1}H NMR (400 MHz, CDCl3) δ 0.91− 1.00 (m, 2 H), 125−1.28 (m, 2 H), 2.44 (s, 3 H), 2.46−2.50 (m, 1 H), 2.86 (t, *J* = 12.8 Hz, 1 H), 3.86 (d, *J* = 14.0 Hz, 1 H), 4.41 (d, *J* = 6.0 Hz, 1 H), 5.47 (d, *J* = 5.6 Hz, 1 H), 7.19−7.25 (m, 6 H), 7.27−7.34 (m, 5 H), 7.84 (d, *J* = 8.0 Hz, 2 H); 13C NMR (150 MHz, $CDCl_3$) δ 21.8, 22.4, 23.2, 42.0, 44.9, 52.7, 60.5, 124.1, 125.8, 127.1, 127.2, 127.4, 127.7, 128.4, 129.6, 130.0, 138.1, 138.7, 141.1, 142.2, 143.4; IR (KBr, neat) 3028, 2926, 2856, 1598, 1495, 1452, 1332, 1162, 1022, 719 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}NO_2S$ $(M + H)^+$: *m/z* 404.1679, found 404.1678.

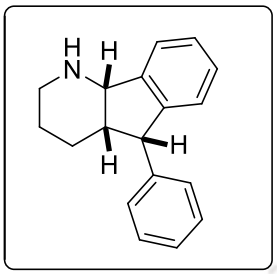
5-Phenyl-1-tosyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*] pyridine (59b):



Colorless solid; mp 69−71 °C; R_f (hexane/EtOAc 9/ 1) 0.21; yield 10 mg, 10%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.57− 1.61 (m, 2 H), 182−1.85 (m, 1 H), 1.97 (dd, *J* = 13.2 and 9.2 Hz, 1 H), 2.21−2.28 (m, 1 H), 2.31 (s, 3 H), 2.42−2.47 (m, 1 H), 3.12 (dt, *J* = 12.8 and 3.6 Hz, 1 H), 3.82 (d, *J* = 12.7 Hz, 1 H), 5.10 (d, *J* = 5.6 Hz, 1 H), 6.98 (d, *J* = 7.2 Hz, 3 H), 7.16−7.26 (m, 10 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 24.0, 25.3, 40.1, 41.8, 42.0, 60.6, 126.3, 127.2, 127.7, 128.3, 128.4,

128.5, 129.2, 129.3, 129.6, 130.1, 136.9, 138.1, 139.7, 142.5; IR (KBr, neat) 3027, 2924, 1600, 1492, 1449, 1336, 1159, 1099, 701 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}NO_2S$ $(M + H)^+$: *m/z* 404.1679, found 404.1681.

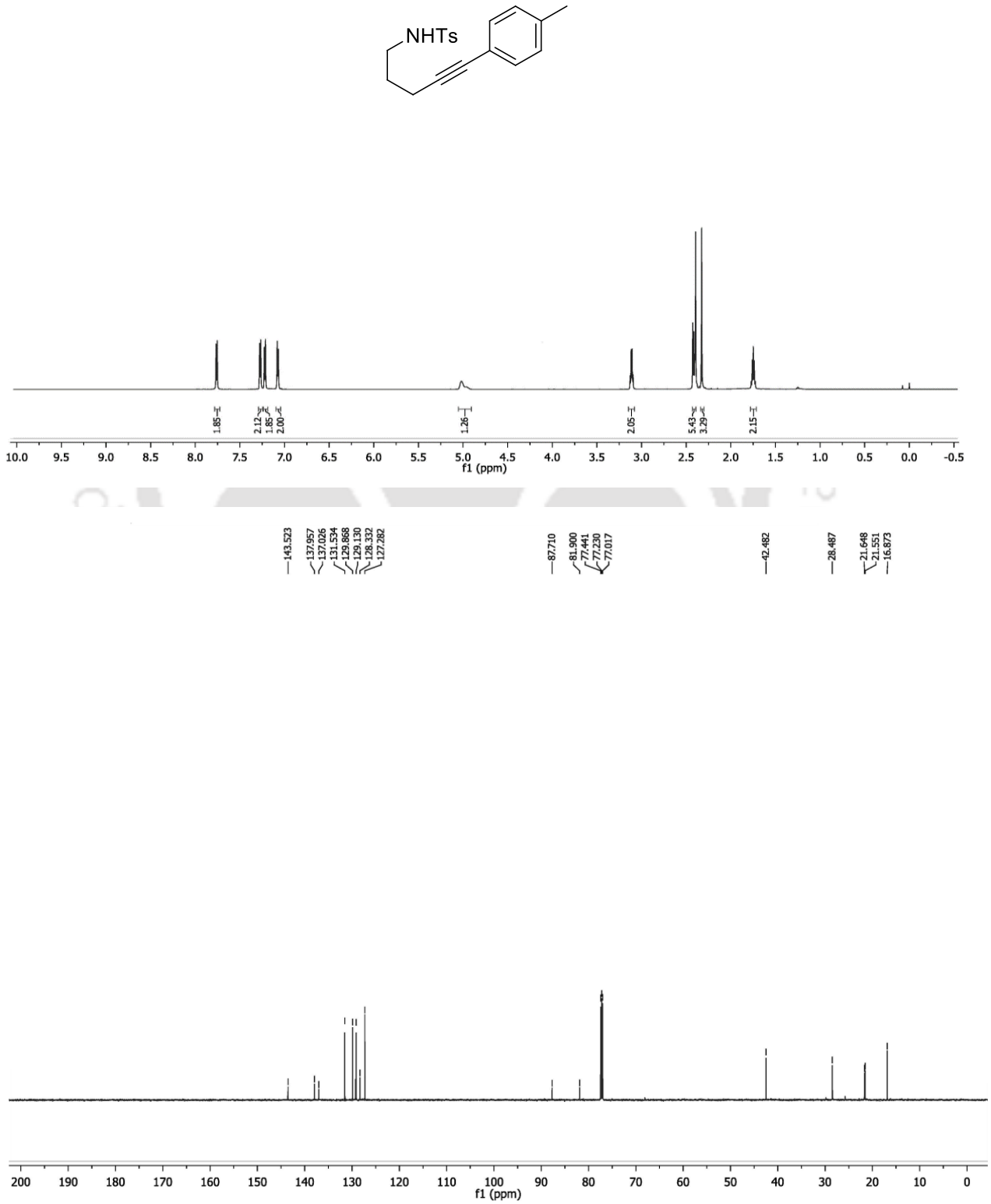
5-Phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (60):



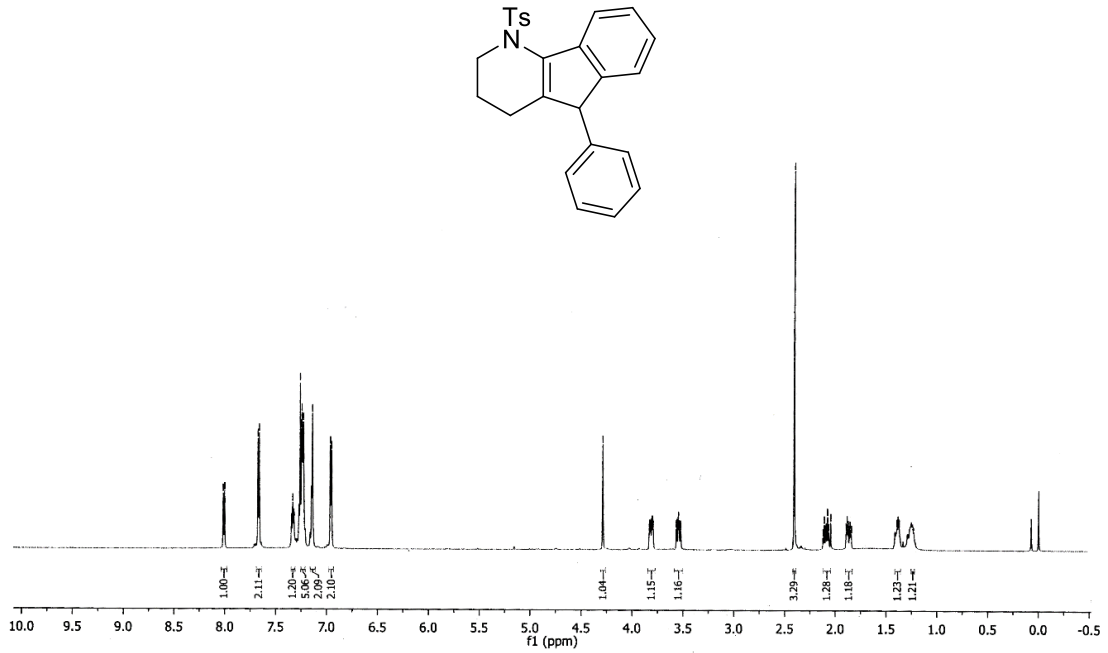
Colorless solid; mp 85−87 °C; R*f* (DCM/MeOH 9/1) 0.33; yield 43 mg, 70%; 1 H NMR (400 MHz, $CDCl_3$) δ 0.98−1.12 (m, 2 H), 122−1.43 (m, 2 H), 2.57−2.66 (m, 2 H), 2.87 (d, *J* = 12.4 Hz, 1 H), 4.39 (d, *J* = 6.0 Hz, 1 H), 4.55 (d, *J* = 5. Hz, 1 H), 7.22−7.28 (m, 5 H), 7.29−7.36 (m, 3 H), 7.49 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.9, 25.2, 41.5, 46.0, 53.2, 61.0, 123.7, 126.1, 126.8, 127.1, 127.3, 128.4, 129.7, 139.2, 143.5, 143.9; IR (KBr, neat) 3440, 2926, 2853, 1641, 1453, 1154, 1076, 1031, 775, 703 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}N$ $(M + H)^+$: *m/z* 250.1590, found 250.1589

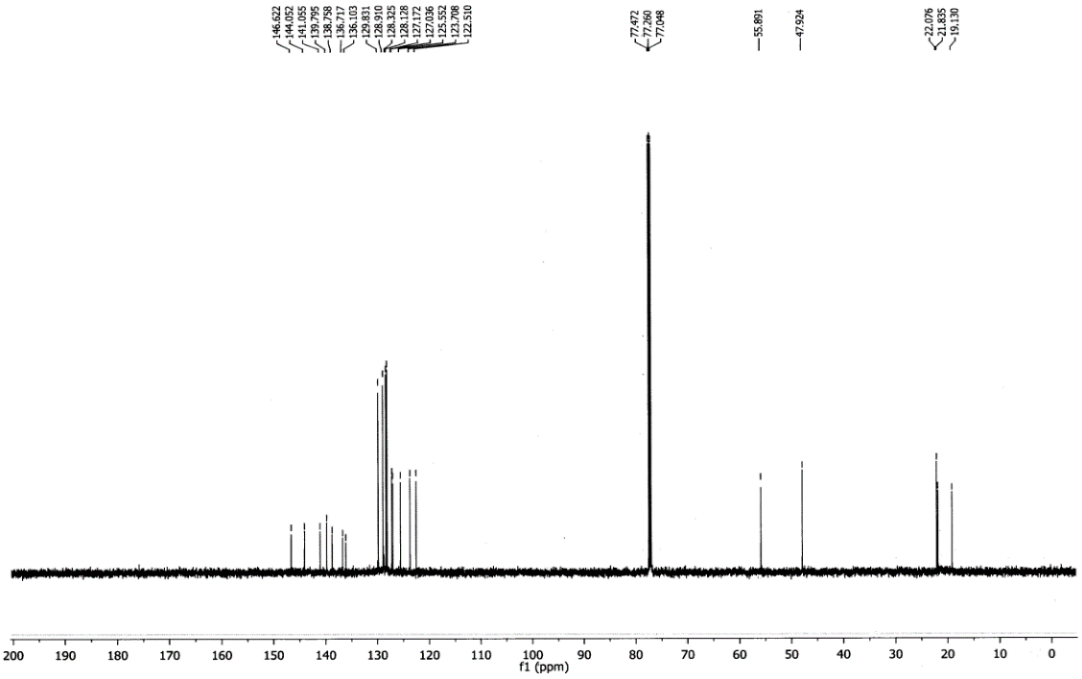
2.8. Selected spectra

^{1}H and ^{13}C Spectra of compound **49b**

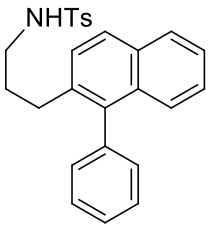


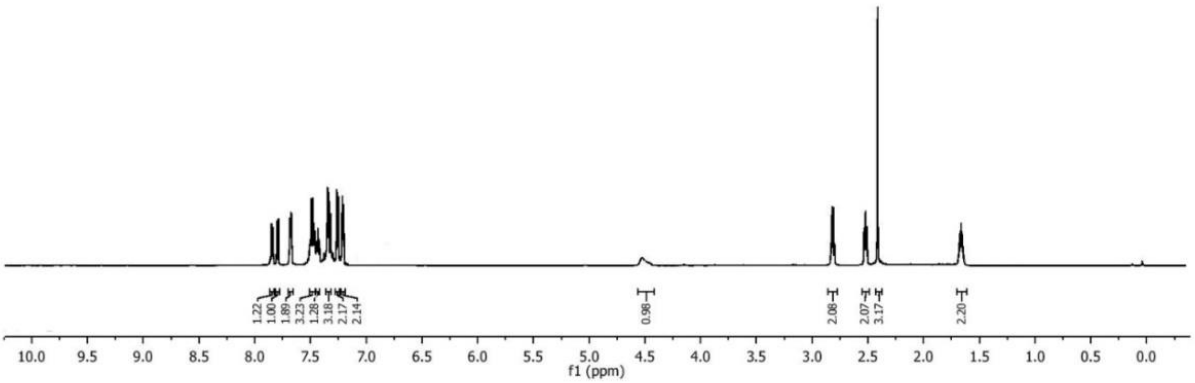
^{1}H and ^{13}C Spectra of compound **55a**

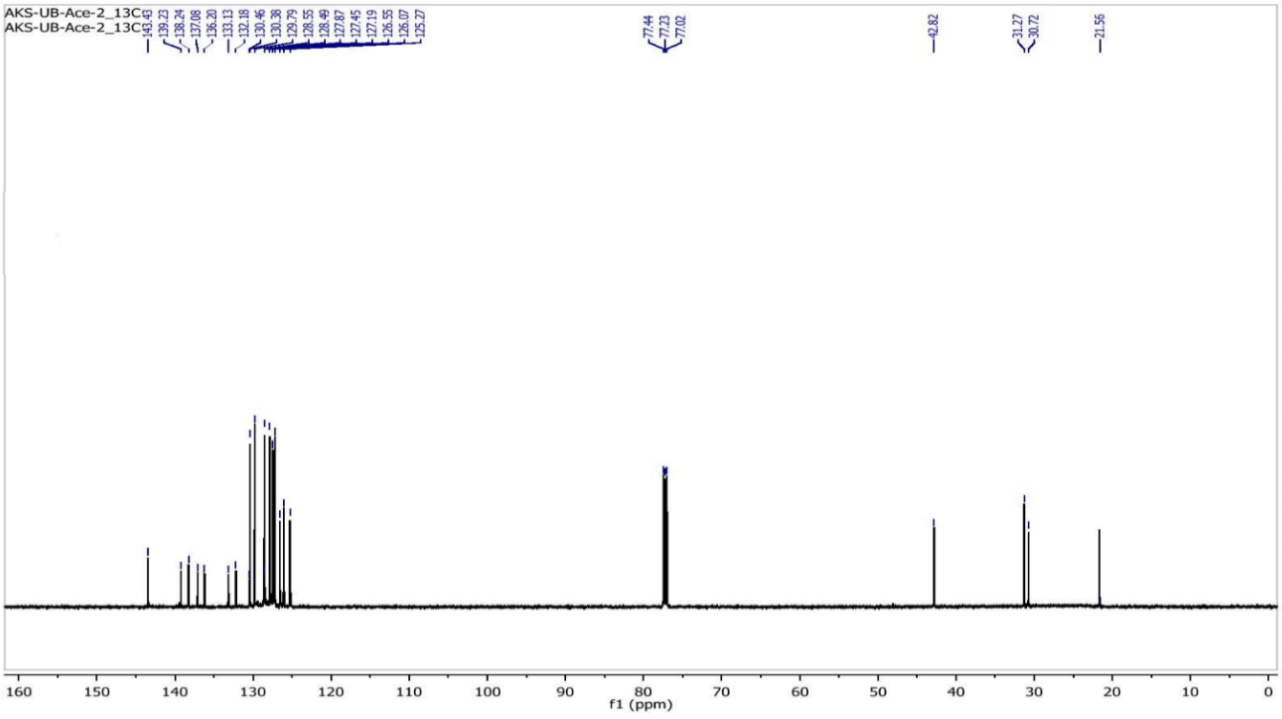




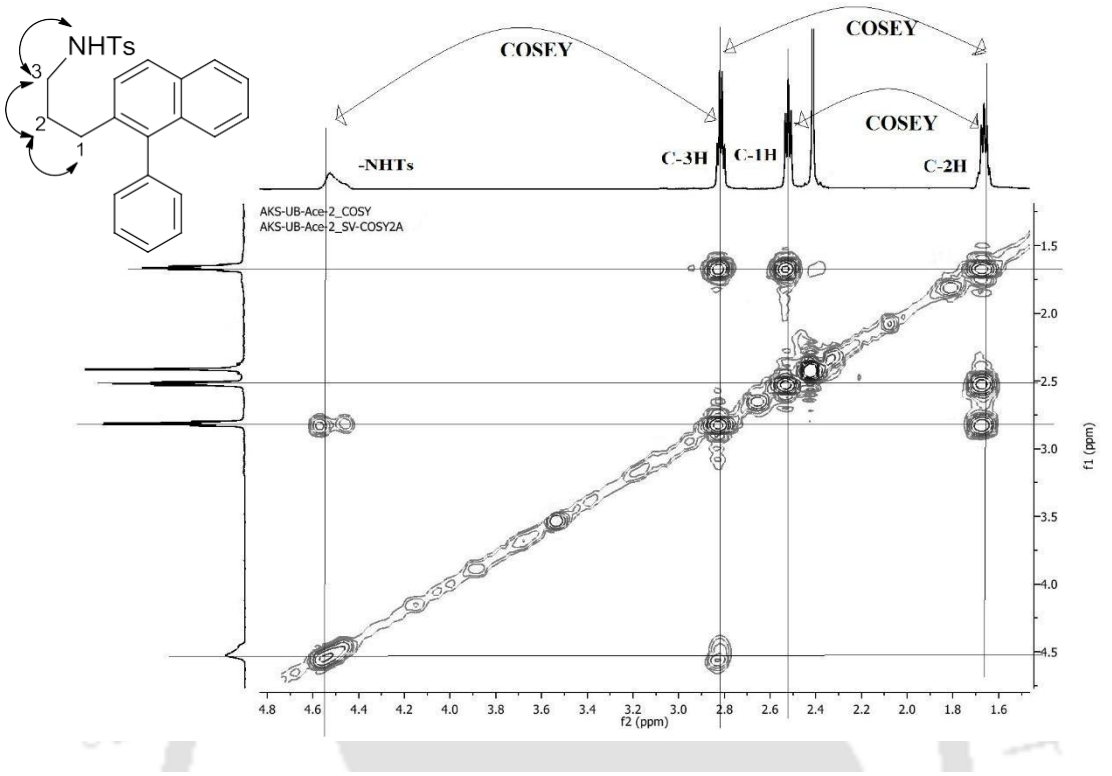
^{1}H and ^{13}C Spectra of compound **51s**

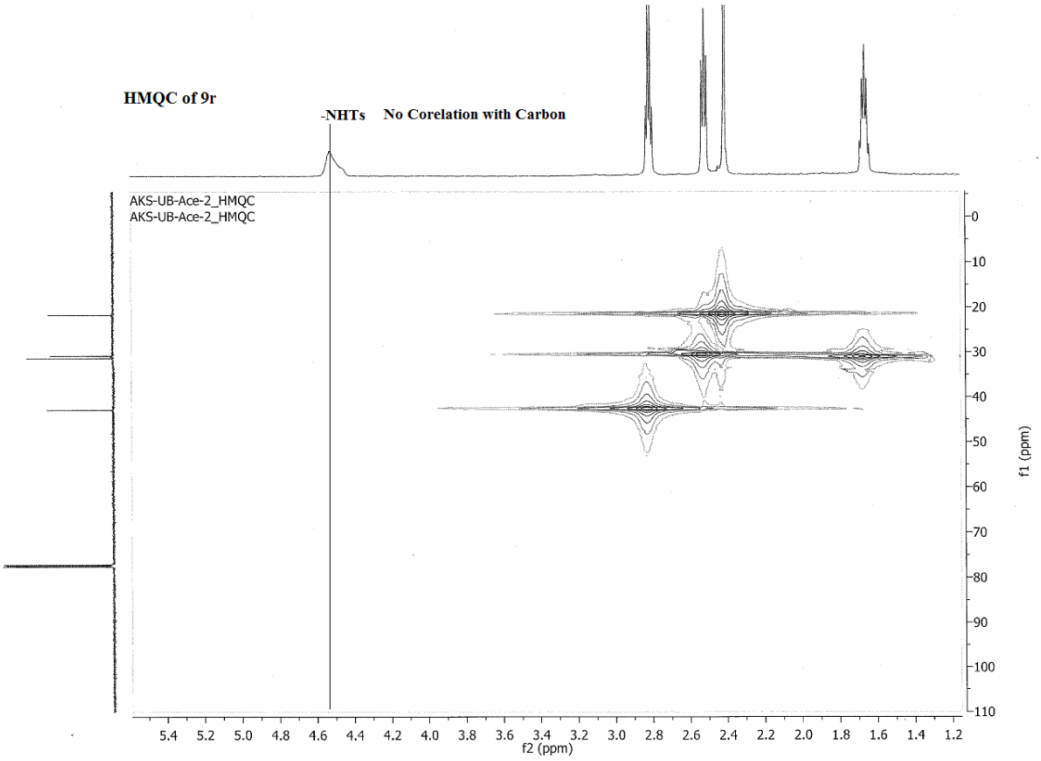




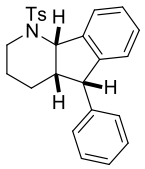


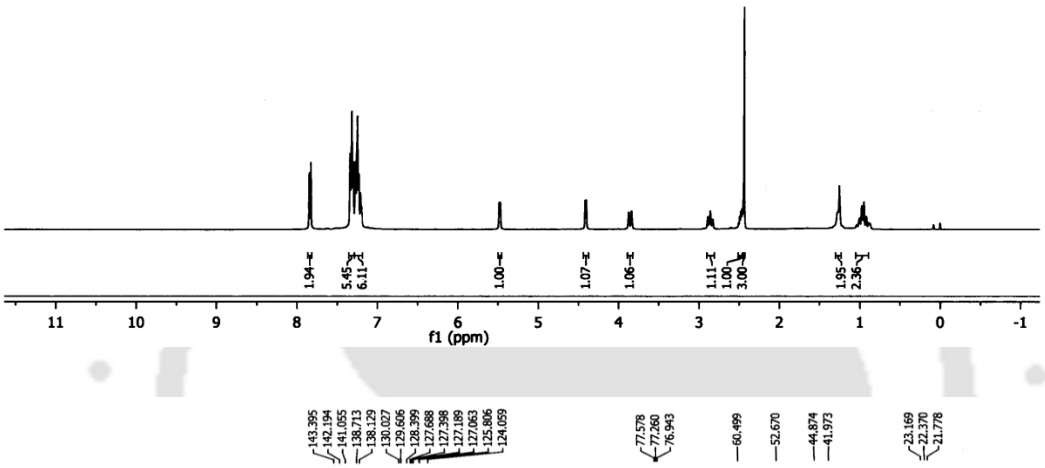
COSYand HMQC spectra of compound 55s

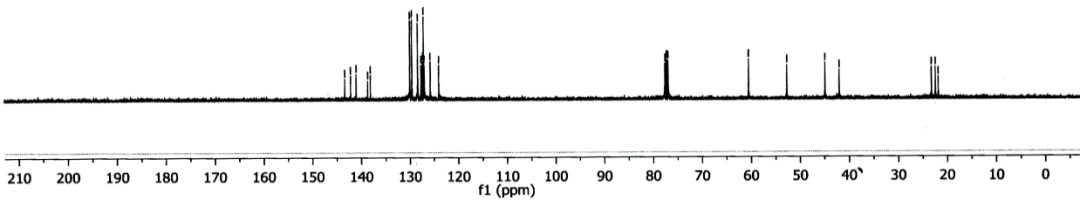




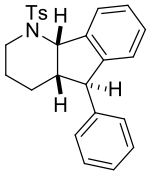
^{1}H and ^{13}C Spectra of compound **59a**

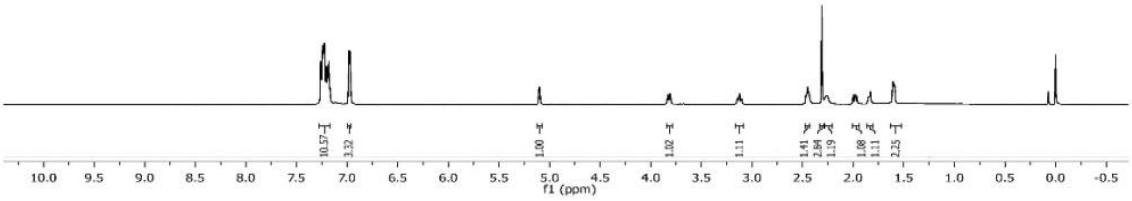


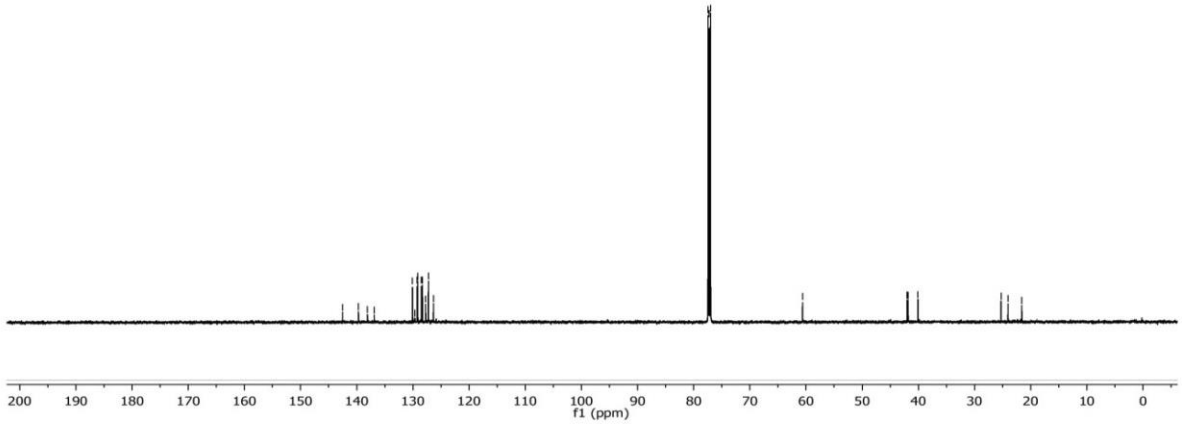




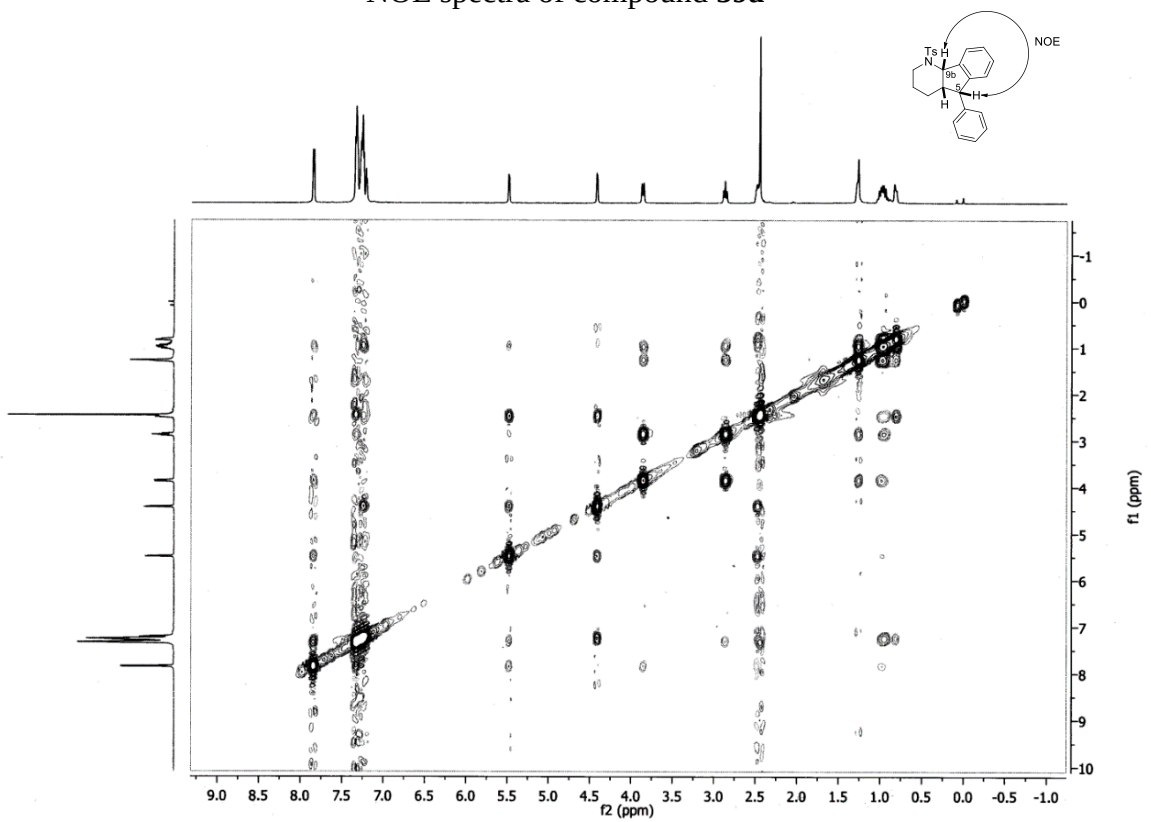
^{1}H and ^{13}C Spectra of compound **59b**

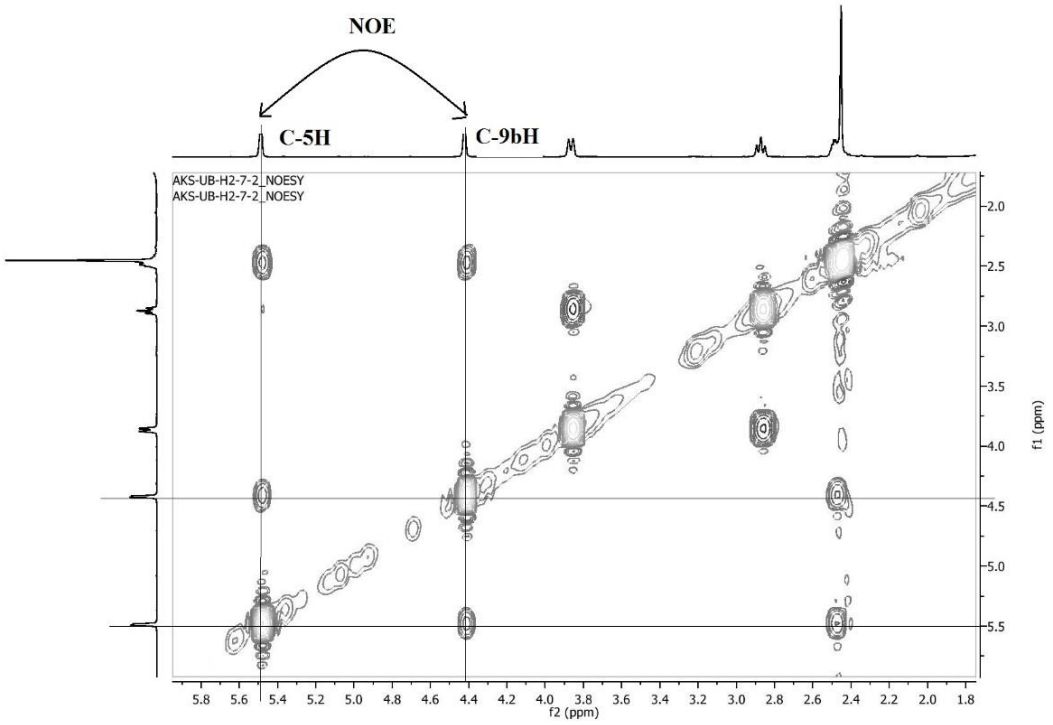




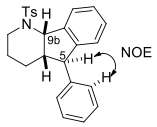


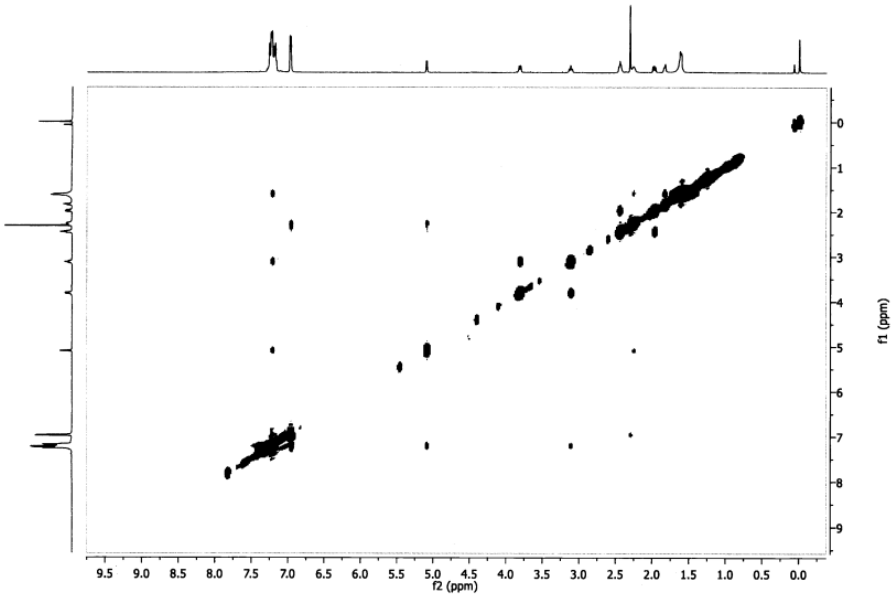
NOE spectra of compound **59a**

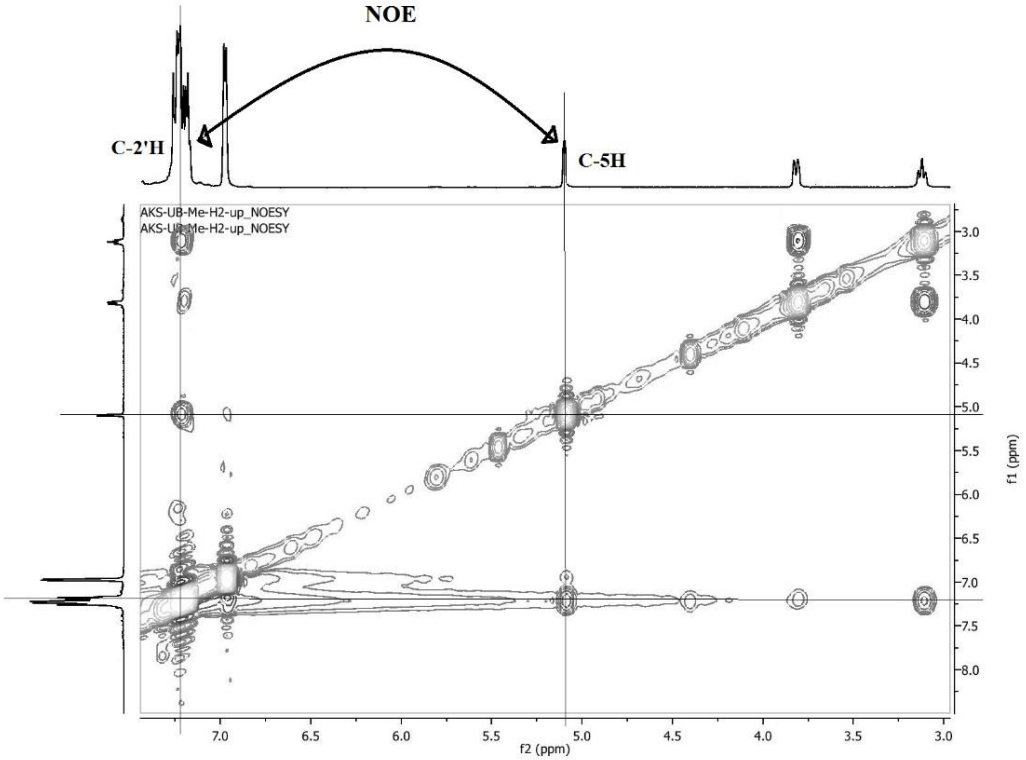




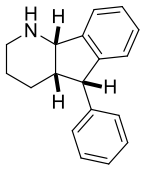
NOE spectra of compound **59b**

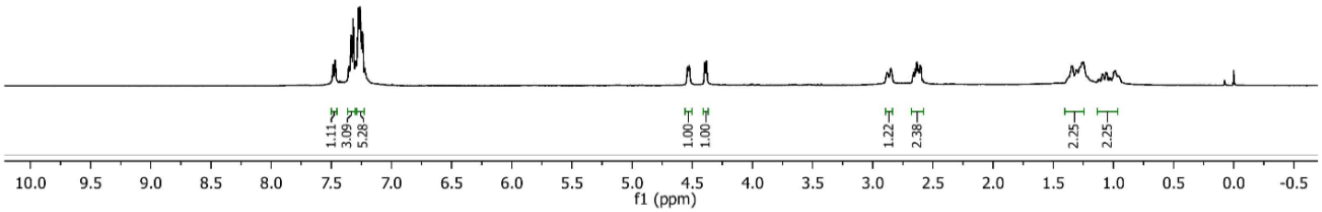


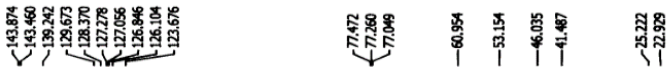


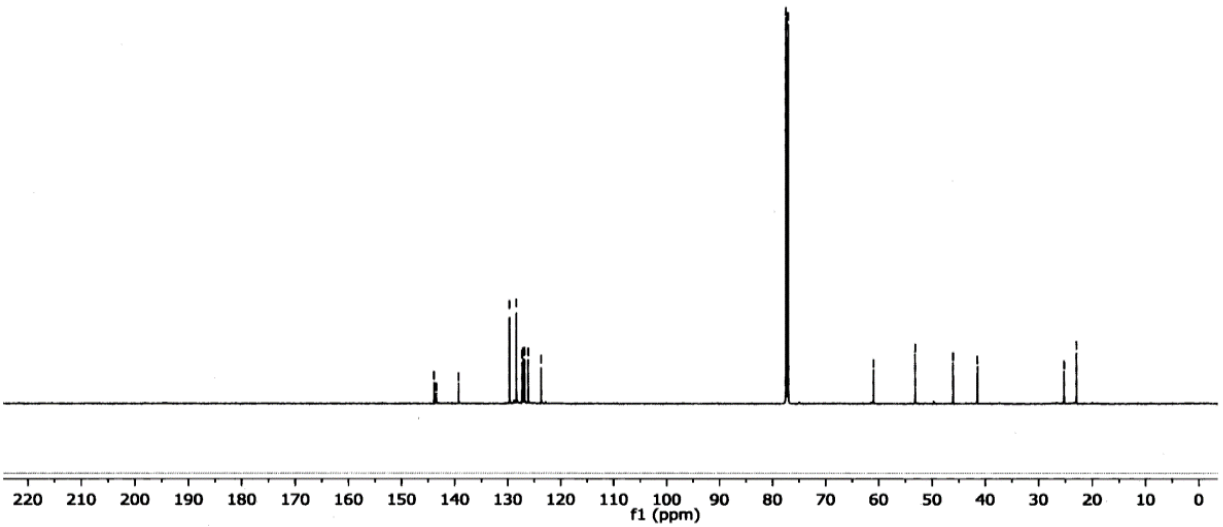


^{1}H and ^{13}C Spectra of compound **60**









2.9. Crystal parameters

The crystal parameters of compound **55d**

	CCDC 1488115
Formula	$C_{25}H_{22}ClNO_2S$
Formula weight	435.95
T/K	296(2)
Crystal system	Monoclinic
Space group	P21/n
a/Å	15.8893(11)
b/Å	8.6895(6)
c/Å	16.3849(14)
α/°	90.00
β/°	102.646(8)
γ/°	90.00
V/Å^3	2207.4(3)
Z	4
Abs. Coeff./mm^{-1}	0.289
Abs. Correction	None
GOF on F^2	1.093
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0695
	wR2 = 0.1147
R indices [all data]	*R1* = 0.1220
	wR2 =0.1445

The crystal parameters of compound **55e**

	CCDC 1488152
Formula	$C_{25}H_{22}BrNO_2S$
Formula weight	480.40
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	8.8934(5)
b/Å	10.6507(5)
c/Å	12.7350(7)
α/°	87.351(4)
β/°	71.155(4)
γ/°	71.657(3)
V/Å^3	1081.54(10)
Z	2
Abs. Coeff./mm^{-1}	2.019
Abs. Correction	multi-scan
GOF on F^2	1.100
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0384
	wR2 = 0.0683
R indices [all data]	*R1* = 0.0569
	wR2 = 0.0739

The crystal parameters of compound **55p**

	CCDC 1432405
Formula	$C_{27}H_{27}NO_2S$
Formula weight	429.56
T/K	296(2)
Crystal system	Triclinic
Space group	P1
a/Å	10.3833(9)
b/Å	10.4789(10)
c/Å	10.8297(9)
α/º	103.353(4)
β/º	96.832(4)
γ/º	90.812(5)
V/Å^3	1137.28(17)
Z	2
Abs. Coeff./mm^{-1}	0.166
Abs. Correction	multi-scan
GOF on F^2	1.058
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0387
	wR2 = 0.0525
R indices [all data]	*R1* = 0.0971
	wR2 =0.1069

2.10. References

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CHAPTER 3

Vinylsilanes in Highly Diastereo- and Regio-selective Synthesis of Dihydropyrans

3.1. Importance and applications

Dihydropyrans are important structural units found in many biologically active natural products.[1] Aspergillides C (**1**), a secondary metabolite, isolated from the marine-derived fungus *Aspergillus ostianus* containing bicyclic, 14-membered macrolide with 2,6-*cis*-dihydropyran ring, shows cytotoxic activity against mouse lymphocytic leukemia cells (L1210) with LD_{50} value of 2.0 µg/mL.[2] Similarly, another secondary metabolite, jerangolid A (**2**), a polyketide isolated from myxobacterium *Sorangium cellulosum* So ce 307 shows potent antifungal activity against a range of pathogens, such as *Hansenula anomala* and *Mucor hiemalis* (MIC 0.07 µg/mL), *Debaryomyces hansenii* and *Trisporo terrestre* (0.1 - 0.4 µg/mL), and *Candida albicans* (4.2 µg/ mL)[3] (*Figure 3.1.1*).

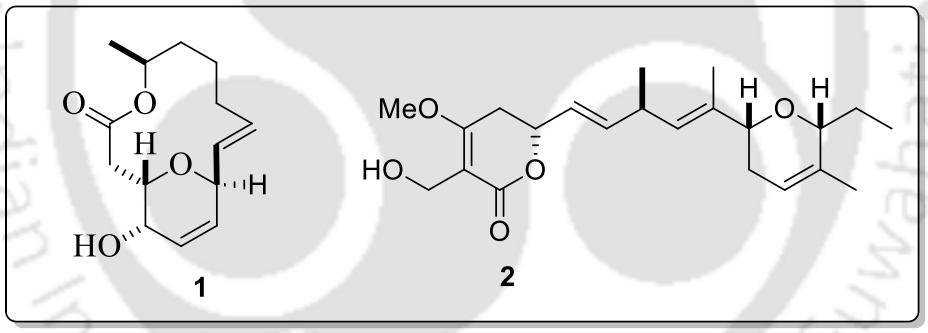


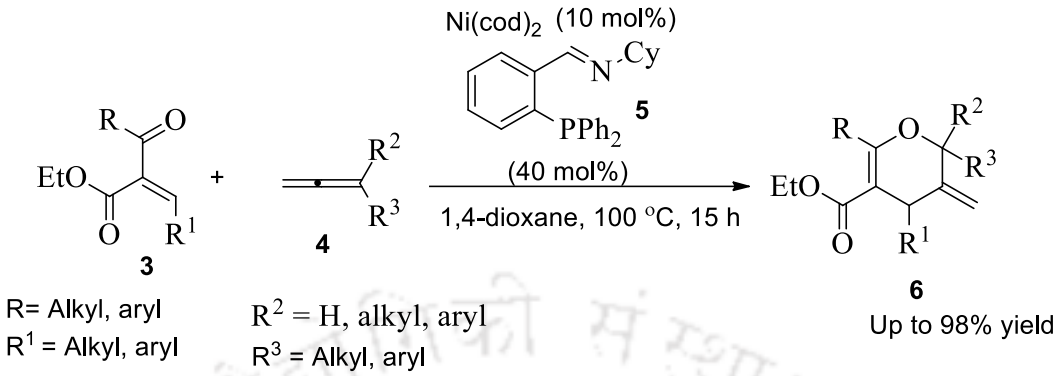
Figure 3.1.1. *Some bioactive molecules containing dihydropyran*

3.2. An overview of relevant synthetic methods

Over the years, several synthetic approaches have been developed for the preparation of dihydropyrans such as hetero Diels−Alder cycloaddition,[4] ring-closing metathesis,[5] base promoted cyclizations of sulfenyl dienols,[6] [4+2] annulations,[7] gold-catalyzed cyclization of allenic alcohols,[8] Prins cyclization,[9] silyl-Prins cyclization,[10] stannyl-Prins cyclization,[11] oxonium-ene cyclization reactions,[12] and intramolecular C-C bond formation of alkyne-epoxide.[13]

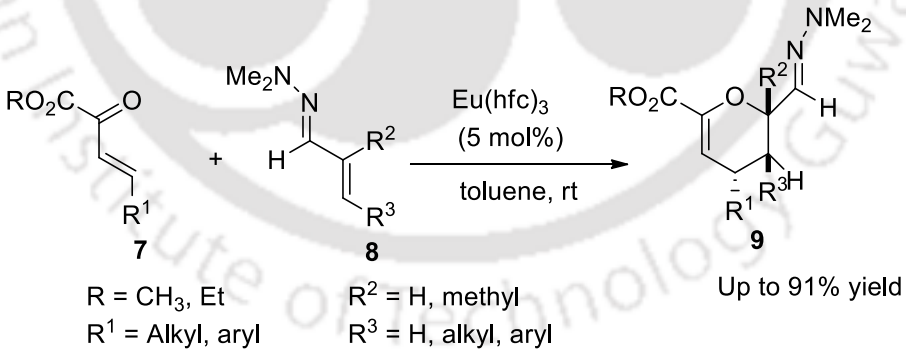
Matsubara and coworkers reported the synthesis of highly substituted dihydropyran **6** *via* [4+2] cycloaddition of enones **3** with allenes **4**. The reaction was mediated by nickel catalyst at 100 ^{0}C in presence of highly active iminophosphine **5** ligand in 1,4- dioxane

solvent. Enones are susceptible to oxidative cyclization of nickel(0) in the presence of an iminophosphine ligand, which allow intermolecular cycloaddition with allenes to afford corresponding dihydropyrans with high yields (*Scheme 3.2.1*).[4a]



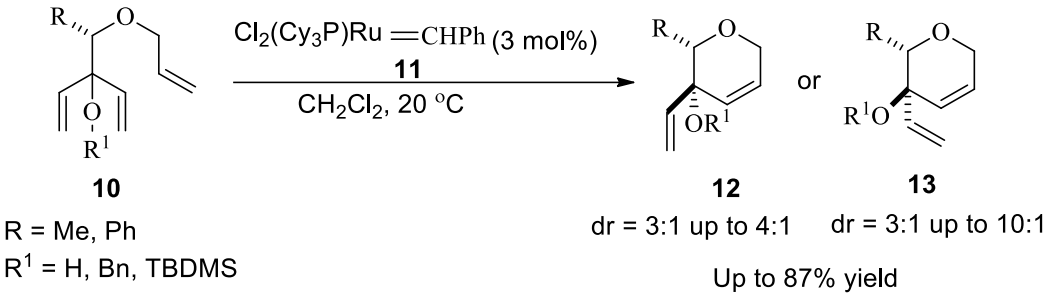
Scheme 3.2.1

Tamaru and coworkers developed an economical method for the synthesis of highly functionalized dihydropyrans **9** using inverse-electron-demand oxa-Diels−Alder reaction of *α*-keto-*β,γ*-unsaturated esters **7** (i.e. oxa-diene) with electron-rich *α,β*-unsaturated hydrazones **8** (i.e., dienophile) in the presence of $Eu(hfc)_3$ as the catalyst. An umpolung strategy is used, where hydrazone has been developed to convert the electrophilic character of carbonyl compounds to nucleophilic character, which afforded the highly endo selective dihydropyrans with high yields (*Scheme 3.2.2*).[4e]



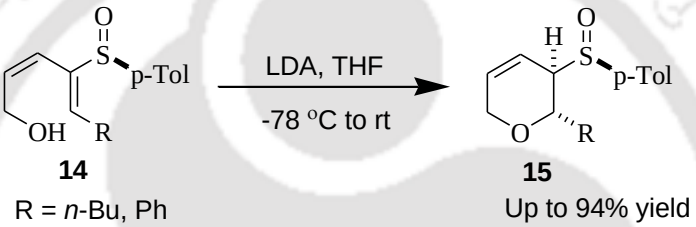
Scheme 3.2.2

In 2000, Schmidt *et al*. had shown the synthesis of dihydropyrans *via* diastereoselective ring-closing metathesis. Divinyl carbinols **10** containing two diastereotopic vinyl moieties derived from α-hydroxy carboxylic acid esters were treated with 3 mol% of Grubbs' catalyst **11** to obtain dihydropyrans **12**,**13** with high diastereomeric ratio. Different diastereomers were obtained depending on the steric demand of the oxo substituent of the divinyl carbinol moiety (unprotected OH, TBDMS, or benzyl ether) (*Scheme 3.2.3*).[5a]



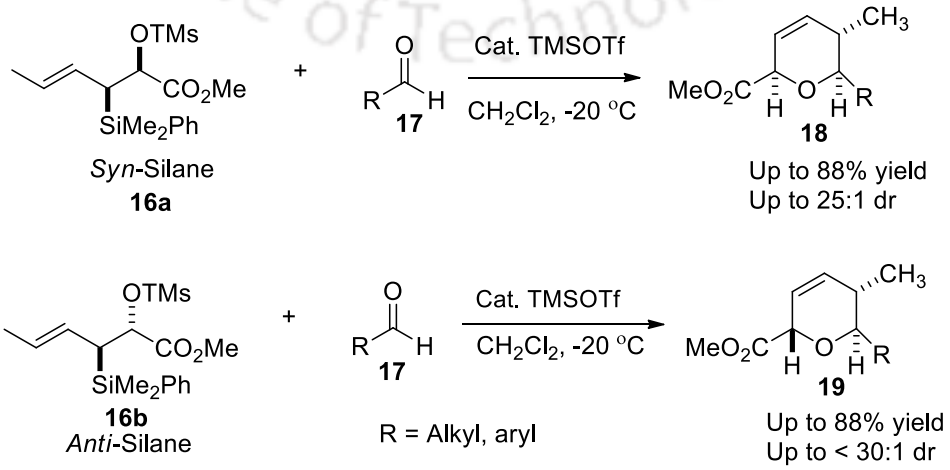
Scheme 3.2.3

Pradilla and his group reported a base promoted intramolecular cyclization of enantiopure sulfinyl dienols **14** to afford sulfinyl dihydropyrans **15**. Sulfinyl dienols on treatment with LDA at -78 °C in THF produced the dihydropyrans in excellent yield with a single isomer. This strategy leads to the creation of two asymmetric centers (*Scheme 3.2.4*).[6a]



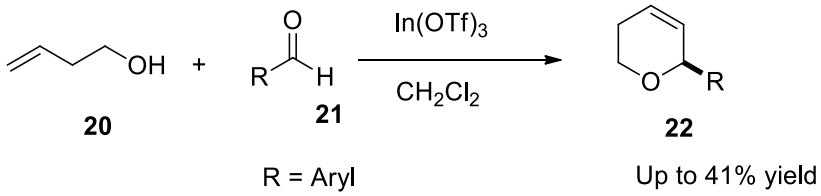
Scheme 3.2.4

Panek and coworkers had demonstrated a highly stereoselective synthesis of dihydropyrans *via* [4+2]-annulation of chiral crotylsilanes **16**. In the presence of a catalytic amount of TMSOTf, chiral silanes **16a** and **16b** directly coupled with aldehydes **17**, affording functionalized dihydropyrans up to 98% ee. The configuration of the silanes decides the stereochemical course of the reaction, leading to the high diastereoselectivity of the dihydropyrans **18** and **19**. (*Scheme 3.2.5*).[7a]



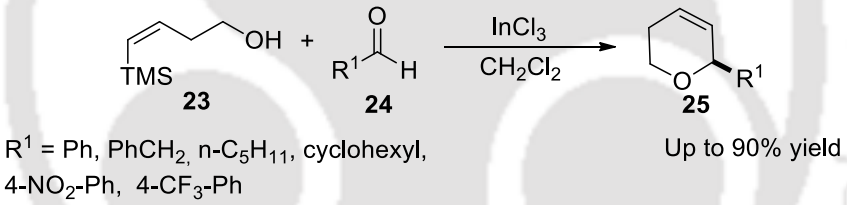
Scheme 3.2.5

In 2011, Dobbs and coworkers reported the synthesis of 3,6-dihydro-2H-pyrans **22**. In the presence of indium triflate, homoallylic alcohol **20** reacts with aromatic aldehydes **21** following a Prins type of cyclization, and the product was obtained as single isomer but with low yield (*Scheme 3.2.6*).[9h]



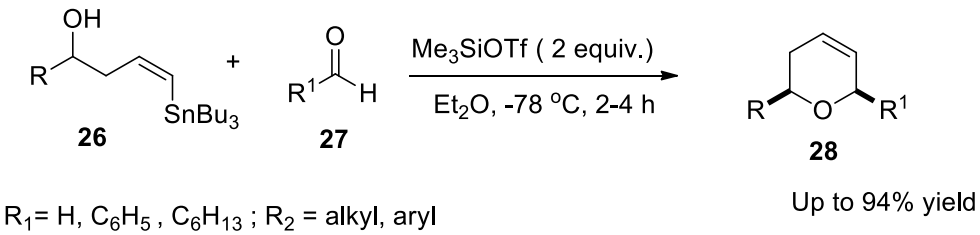
Scheme 3.2.6

Dobbs and his group in 2002, reported a methodology for the synthesis of 2,6 *cis*-substituted dihydropyran **25** mediated by indium chloride *via* silyl-Prins cyclization between 4-trimethylsilyl-3-buten-1-ol (**23**) with different aldehydes **24**. The reaction is believed to proceed *via* β-silicon stabilization of carbocation formed by cationic cyclization after nucleophilic attack from alcohol to the lewis acid-activated aldehyde (*Scheme 3.2.7*).[10b]



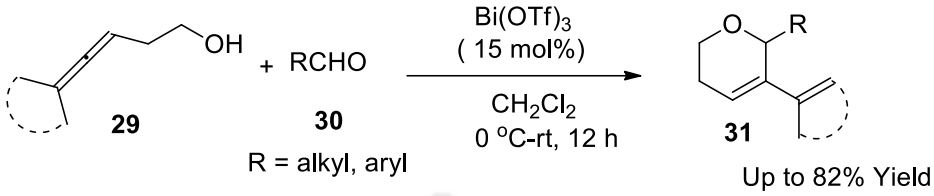
Scheme 3.2.7

Furman and coworkers had shown a stereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans **28** *via* stannyl-Prins cyclization. In the presence of TMSOTf, the reaction of vinylstannanes **26** with aldehydes **27** afforded *cis*-2,6-disubstituted dihydropyrans **25** in good yields with excellent stereoselectivity (*Scheme 3.2.8*). The dihydropyrans are obtained in the racemic form but on using optically pure vinylstannane, optically pure 2,6-disubstituted dihydropyrans were obtained.[11]



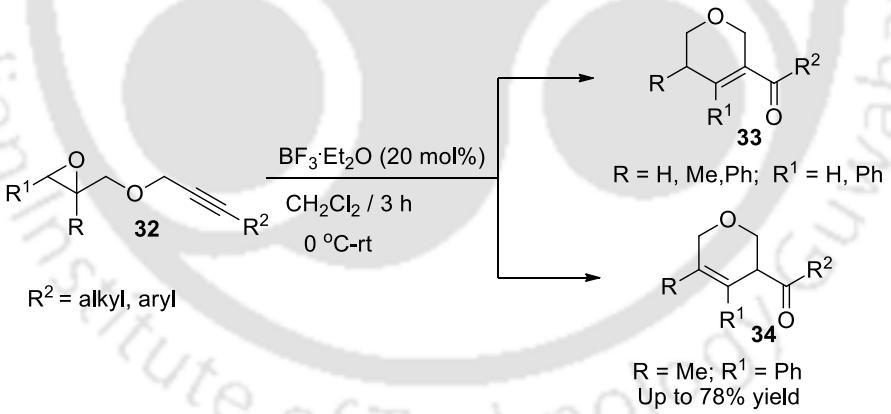
Scheme 3.2.8

Recently our group had reported the synthesis of dihydropyrans **31** from *β*-allenols **29** and aldehydes **30** using catalytic amount of bismuth trifluoromethanesulfonate in dichloromethane. The reaction proceeds *via* oxonium ene cyclization to gives various dihydropyrans in good yield with high regioselectivity. (*Scheme 3.2.9*).[12g]



Scheme 3.2.9

In 2014, our group had reported a BF_3•OEt_2 mediated intramolecular C−C bond formation of oxygen tethered alkyne and epoxide **32**. The carbocation formed after the opening of epoxide in the presence of Lewis acid undergoes stabilisation *via* rearrangement followed by 6-exo-trig cyclization and finally trapping of water. Depending upon the substituents in the epoxide ring of **32**, the carbocation formed is stabilized following different rearrangement pathways leading to the formation of two different dihydropyrans units i.e., 3,6- and 5,6-dihydropyrans **33** and **34**. (*Scheme 3.2.10*).[13]

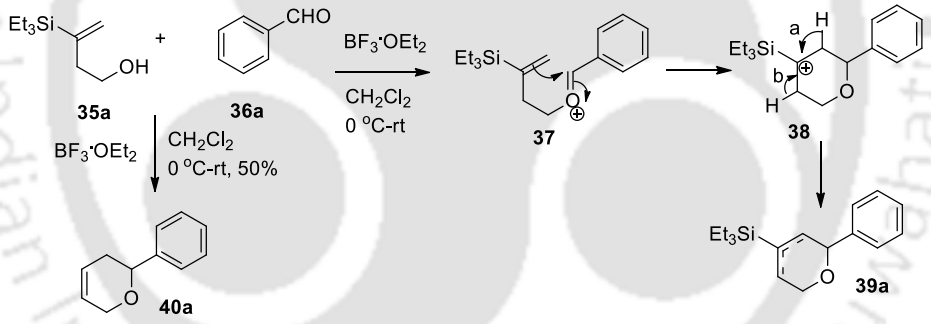


Scheme 3.2.10

3.3. Present strategy and objective

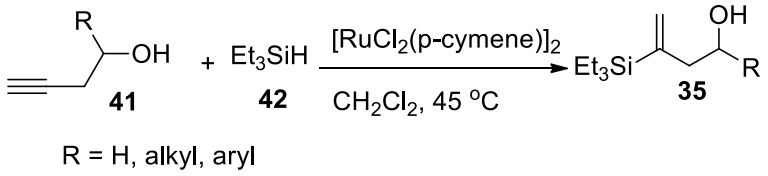
Vinylsilanes are considered as critical building blocks in organic synthesis. Owing to their *α*-, *β*- and *γ*-silicon effects they stabilize the carbocation much more than the unsilylated analogues.[14] They have been utilized in the construction of five, six, seven, eight and nine membered oxacycles using various methodologies, among them oxonium-ene cyclization[15] and Prins cyclization[10b,c] are notable. They are also used in the synthesis of various carbocycles.[16] Interestingly these heterocyclic ring systems are core units of many

biologically active molecules[17] and natural products.[18] Overman and coworkers demonstrated the use of vinylsilanes for the regioselective synthesis of five, six, seven,[19] eight and nine membered oxacycles *via* oxonium-ene cyclization reaction.[15] Dobbs and coworkers studied the applicability of vinylsilanes towards the synthesis of indolizidine and quinolizidine derivatives.[20] They have also developed methodologies for the regioselective synthesis of dihydropyrans using vinylsilanes *via* Prins cyclization reactions.[10b,c] Other methods for the generation of dihydropyrans using vinylsilane includes Hinkle's Lewis acid initiated addition/silyl-Prins cyclization,[10d,e] and Speckamp's vinylsilane-terminated cyclization of ester substituted oxycarbenium ion intermediates.[10f] The formation of regioselective dihydropyrans is believed to be due to the *β*-silicon effect.[10b,c] The drawback of the existing methods are the formation of silylated oxacycles which needs to be removed in subsequent steps[15] and formation of diastereomers.[10d,f] Therefore, there is an urgent need for the development of highly regio- and diastereo-selective methodologies for the synthesis of oxacycles. In this chapter, we report a synthesis of dihydropyrans *via* oxonium-ene cyclization using vinylsilanes and aldehydes mediated by borontrifluoride etherate ($BF_3{\cdot}OEt_2$) in good yields with excellent regio- and diastereoselectivity.



Scheme 3.3.1

We envisioned that Prins cyclization of silyl-homoallyl alcohol **35a** and aldehyde **36a** would give intermediate carbocation **38**, which after subsequent elimination of *α*-proton will generate regioisomeric silylated dihydropyrans **39a** (*Scheme 3.3.1*). But in contrast dihydropyran **40a** was obtained as a single regioisomer in 50% yield.



Scheme 3.3.2

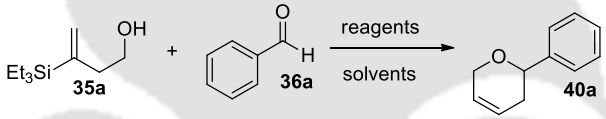
The vinylsilane **35** were synthesized from homopropagylalcohols **41** and triethylsilane **42** in presence of $[RuCl_2(p\text{-cymene})]_2$ (*Scheme 3.3.2*).[21]

3.4. Results and discussion

3.4.1. Optimization studies

In an intial investigation, 3-(triethylsilyl)but-3-en-1-ol (**35a)** and benzaldehyde (**36a**) was treated with 1.2 equivalent of BF_3•OEt_2 (Table 3.4.1.1, entry 1) and corresponding 2-Phenyl-3,6-dihydro-2*H*-pyran (**40a**) was obtained in 50% yield, when the reaction was performed at -45 ^oC the yield increased to 72% (Table 3.4.1.1, entry 2). $InCl_3$ in dichloromethane and dichloroethane gave 50% and 45% yields, respectively (Table 3.4.1.1, entries 3-4). On the other hand, $In(OTf)_3$ produced 65% yield (Table 3.4.1.1, entry 5). $FeCl_3$ furnished only 40% yield (Table 3.4.1.1, entry 6) whereas $CeCl_3$•H_2O at 80 ^oC in CH_3CN gave decomposed

Table 3.4.1.1.Optimization of the reaction



S. No.	Reagent (equiv)	Solvent	Temp./ ^oC	Time/h	(%) yield[a]
1	BF_3·OEt_2 (1.2)	DCM	0-rt	12	50
2	BF_3·OEt_2 (1.2)	DCM	-45	4	72
3	$InCl_3$ (1.0)	DCM	rt	12	50
4	$InCl_3$ (1.0)	DCE	rt	12	45
5	$In(OTf)_3$ (0.3)	DCM	rt	5	65
6	$FeCl_3$ (1.2)	DCM	0-rt	12	40
7	$CeCl_3$·H_2O (1.1)	CH_3CN	80	24	0[b]
8	TfOH (0.2)	DCE	rt	12	0[c]
9	*p*-TsOH (0.2)	DCE	80	24	0[c]
10	$SnCl_4$ (0.1)	DCM	-45	4	45[d]

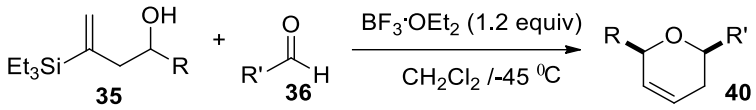
[a]Yields are isolated yield. [b]Starting material recovered. [c]Decomposed products. [d]mixture of **40a** and **39a** with a ratio of 3:2.

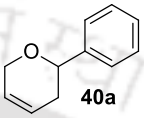
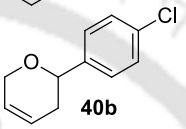
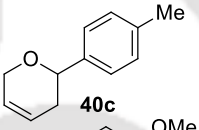
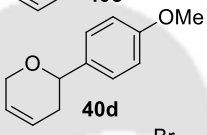
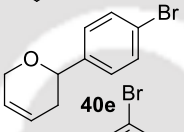
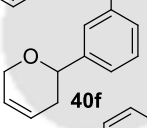
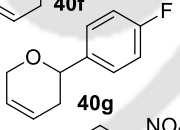
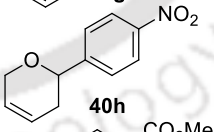
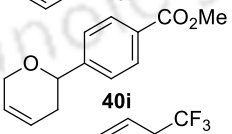
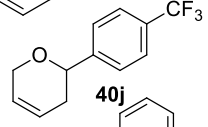
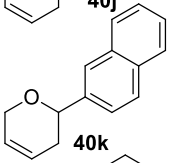
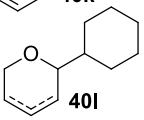
products (Table 3.4.1.1, entry 7). Brønsted acids such as TfOH and *p*-TSA were proved to be inappropriate for the reaction (Table 3.4.1.1, entries 8-9). Whereas, 10 mol% $SnCl_4$ gave only 45% yield along with silylated product **39a** (Table 3.4.1.1, entry 10).

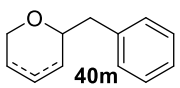
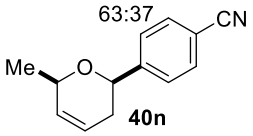
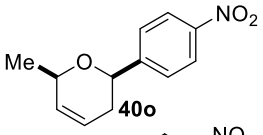
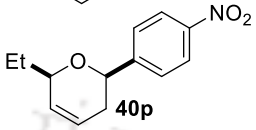
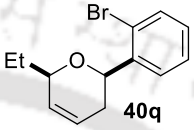
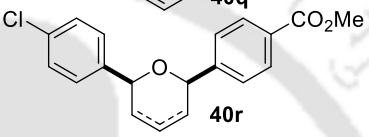
3.4.2. Substrate scope of the reaction

With these optimized reaction conditions the scope of the reaction was further tested using primary alcohol **35a** and aldehydes **36a-k** as substrates and the results are summarized in

Table 3.4.2.1 Synthesis of dihydropyrans



entry	alcohol **35**	aldehyde **36**	product **40**	% yield[a]
1	**35a**, R = H	**36a**, R' = Ph	 **40a**	72
2	**35a**	**36b**, R' = 4Cl-Ph	 **40b**	75
3	**35a**	**36c**, R' = 4Me-Ph	 **40c**	76
4	**35a**	**36d**, R' = 4OMe-Ph	 **40d**	76
5	**35a**	**36e**, R' = 4Br-Ph	 **40e**	78
6	**35a**	**36f**, R' = 3Br-Ph	 **40f**	67
7	**35a**	**36g**, R' = 4F-Ph	 **40g**	65
8	**35a**	**36h**, R' = 4NO_2-Ph	 **40h**	83
9	**35a**	**36i**, R' = 4CO_2Me-Ph	 **40i**	80
10	**35a**	**36j**, R' = 4-CF_3-Ph	 **40j**	65
11	**35a**	**36k**, R' = napth	 **40k**	65
12	**35a**	**36l**, R' = Cyclohexyl	 **40l** 62:38	65[b]

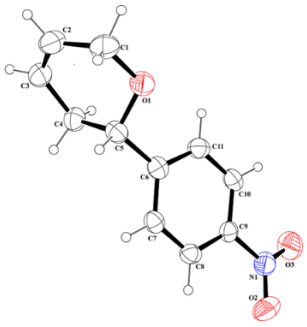
13	**35a**	**36m**, R' = CH_2Ph	 **40m**	68[b]
14	**35b**, R = Me	**36n**, R' = 4-CN-Ph	 **40n** 63:37	77
15	**35b**	**36h**	 **40o**	78
16	**35c**, R = Et	**36h**	 **40p**	76
17	**35c**	**36o**, R' = 2Br-Ph	 **40q**	65
18	**35d**, R = 4Cl-Ph	**36i**	 **40r** 80:20	60[b]

[a]Yields refer to isolated yield. [b]Ratio is determined from ^{1}H NMR.

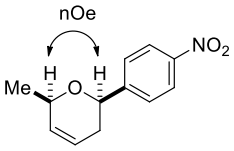
Table 3.4.2.1. As seen from the Table 3.4.2.1, the reaction shows wide applicability to various aldehydes including aryl aldehydes having electron-donating (Table 3.4.2.1, entries 3 and 4) and electron-withdrawing groups (Table 3.4.2.1, entries 2 and 5-10) on the aromatic ring. 2-Naphthaldehyde was also found to be effective for this reaction (Table 3.4.2.1, entry 11). The reaction with aliphatic aldehydes (Table 3.4.2.1, entries 12,13) gave regioisomeric mixture with a ratio of 62:38 and 63:37, respectively, in moderate yields. Alkyl substituted secondary silylated alcohols **35b-c** also gave good yields with high diastereoselectivity (Table 3.4.2.1, entries 14-17), whereas reaction of arylated secondary silylated alcohol **35d** with aldehyde **36i** gave a mixture of two regioisomers **40r** with a ratio of 80:20 and 60% overall yield (Table 3.4.2.1, entry 18).

3.4.3. Stereochemistry of the dihydropyrans

The structures of the dihydropyrans formed were determined *via* X-Ray crystallographic analysis of compound **40h**.[22] Crude ^{1}H NMR spectra of compounds **40h** and **40o** proves the high regio- and distreoselectivity of the reaction. The *cis*-configuration of the 2,6-disubstituted compounds was determined by the 2-D nuclear Overhauser effect (nOe) experiment of compound **40o**. It may be noted that the structure and stereochemistry of the products are in contrast to the product obtained by Overman from $SnCl_4$ mediated cyclization of acetal-vinylsilanes[15,19] where silylated



40h



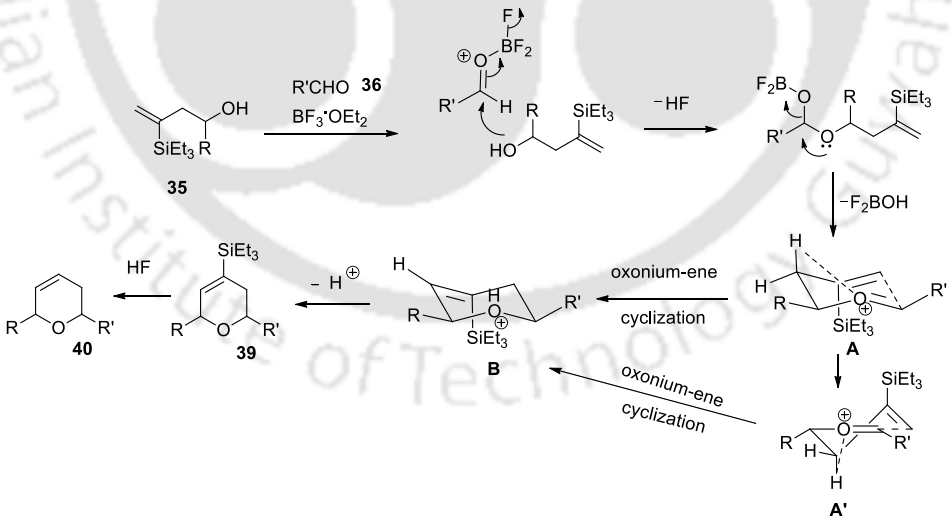
40o

Figure 3.4.3.1. *ORTEP diagram of* **40h** and nOe of **40o**

oxacycles and oxacycles having exocyclic double bond were formed. The position of the double bond of the present reaction is also different from the products of Dobbs as well.[10b,c] The remarkable feature of this reaction is the configurational control of the vinylsilane for the exclusive formation of 3,6-dihydro-2*H*-pyran in most of the cases.

3.4.4. Plausible mechanism for the formation of dihydropyrans.

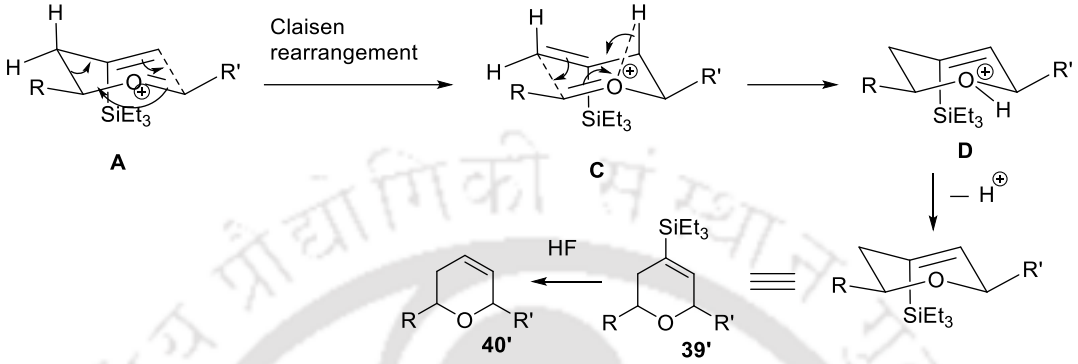
The reaction is believed to proceed *via* oxonium-ene cyclization reaction. Lewis acid activates the carbonyl group of aldehyde for the nucleophilic attack by alcohol to generate oxocarbenium ion **A** which forms six membered transition state with hydrogen



Scheme 3.4.4.1a

at C-3. The species **A** after oxonium-ene cyclization reaction followed by elimination of proton gives silylated dihydropyrans **B**. Finally the removal of silyl group by in situ generated HF acid gives the final product **40** (*Scheme 3.4.4.1a*). The formation of mixture of regioisomer in case of **40l-m** and **40r** can be explained with the help of Claisen rearrangement of intermediate **A**. Here intermediate **A** undergoes Claisen rearrangement to

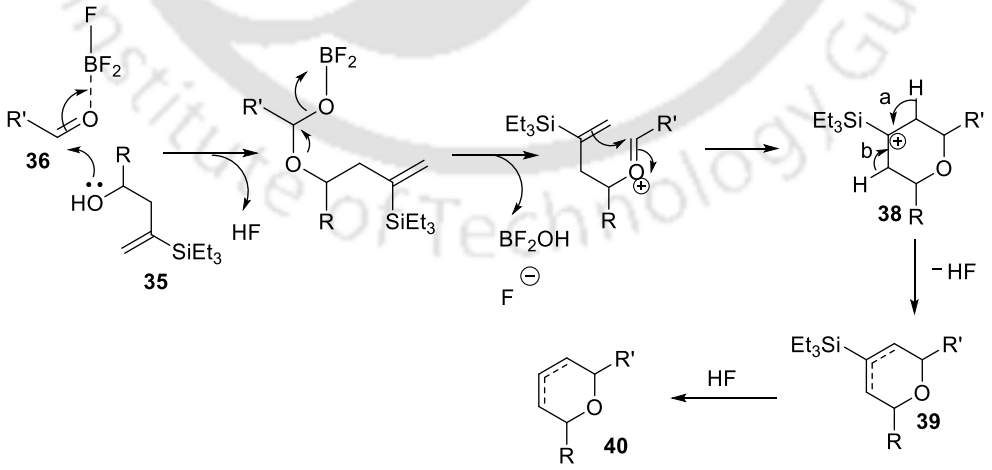
give intermediate **C**, which after oxonium-ene cyclization reaction gives intermediate **D**. The **D** eliminates a proton to give silylated dihydropyrans **39′** which after desilylation with HF produce the dihydropyran **40′** *(Scheme 3.4.4.1b*).This mechanism is less probable as the newly formed oxocarbenium ion **C** is less stabilized by H (Table 3.4.2.1, entries 1-13) group compared to Me and Et groups (Table 3.4.2.1, entries 14-17).



Scheme 3.4.4.1b

Scheme 3.4.4.1 *Proposed mechanism of the reaction*

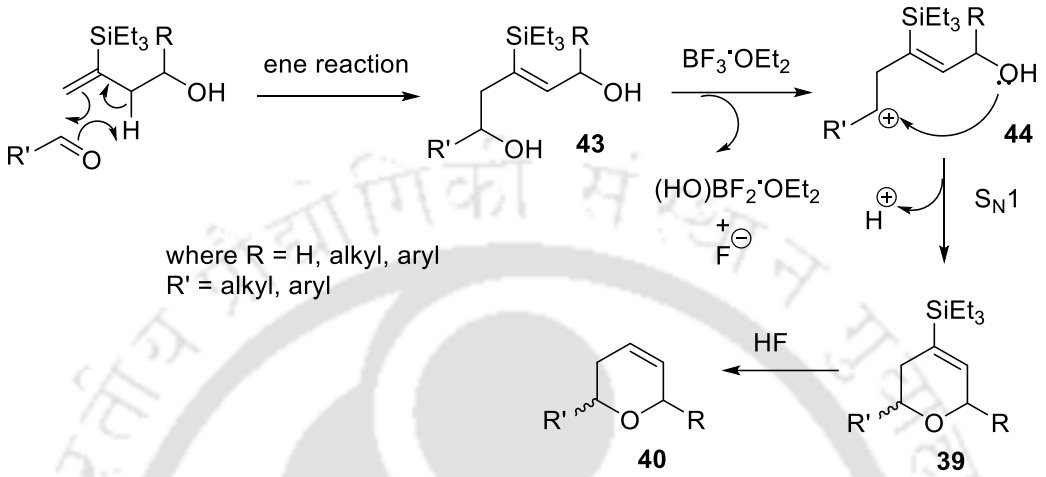
The formation of regioisomeric compounds **40l-m** and **40r** could also be explained by considering stepwise oxonium ene reaction. The carbocation **38** formed after cyclization may eliminate protons *via* pathways ‘a’ and ‘b’ to give silylated intermediate **39** as a regioisomeric mixture, which after desilylation by HF acid gives regioisomeric compounds **40** (*Scheme 3.4.4.2*).



Scheme 3.4.4.2 *Stepwise mechanism for the formation of regioisomeric mixture*

The reaction is not proceeded *via* classical Prins cyclization reaction because the carbenium ion **38** (*Scheme 3.3.1*), formed during the reaction, is destabilized due to the *α*-silicon effect, which is attributed to poor ability of Si-C bond to undergo

hyperconjugation.[23,24] Therefore, it proceeded via oxonium-ene cyclization reaction. Another possibility of formation of dihydropyran is *via* acyclic ene reaction as shown in *Scheme 3.4.4.3*. The ene reaction between aldehyde and triethylsilyl homoallylic alcohol generates diol **43**, which after reaction with BF_3•OEt_2 forms carbenium ion **44**. The nucleophilic attack of carbenium ion **44** by alcoholic group *via* S_N1 type reaction will

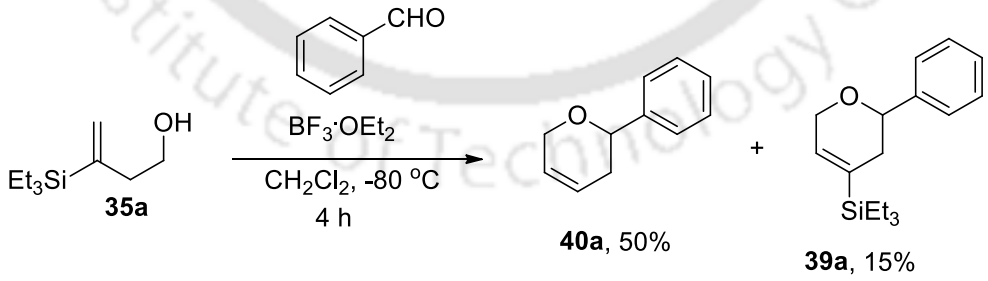


Scheme 3.4.4.3 *Acyclic-ene mechanism*

produce **40** as a diastereomeric mixture. Therefore, this mechanism is ruled out although it supports the formation of single regioisomer.

3.4.5. Controlled experiment

In order to prove that the reaction proceeds *via* a silylated dihydropyran intermediate, a controlled reaction was performed. Thus, the alcohol **35a** (1.0 mmol) was reacted with



Scheme 3.4.5.1 *Controlled reaction of **35a** and benzaldehyde*

benzaldehyde (1.0 mmol) in presence of BF_3·OEt_2 (1.2 mmol) at -80 °C for 4 h. It was observed that 15% of silylated compound **39a** was obtained along with 50% of **40a** (*Scheme 3.4.5.1*).

3.5. Conclusion:

In summary we have developed a methodology for the synthesis dihydropyrans from silyl-homoallylic alcohols and aldehydes in moderate to good yields. The reaction proceeds *via* concerted oxonium-ene and stepwise oxonium-ene reactions. The oxonium-ene cyclization process provides single regioisomeric products whereas stepwise oxonium-ene reaction gives a mixture of regioisomers. The reaction is also diastereo-selective. The drawback of the reaction is that it gives regioisomeric mixture with aliphatic aldehydes and aromatic substituted secondary homoallylic alcohols.

3.6. Experimental section

3.6.1. Instrumentation and characterization

As described in chapter 2 section 2.6.1.

3.6.2. General Procedure for the synthesis of starting material (35a-35d):

To a solution of $[RuCl_2(p\text{-cymene})]_2$ (30 mg, 5 mol%) in CH_2Cl_2 (3 mL) was added triethylsilane (151 mg, 1.3 mmol), and the mixture was stirred for 15 min at 45 ^oC before addition of homopropargyl derivatives (70 mg, 1.0 mmol). The reaction mixture was stirred at the same temperature for 2.5 h under N_2 atmosphere. After evaporation of the solvent under reduced pressure, the crude mixture was chromatographed on silica gel using ethyl acetate and hexane as eluents to afford the desired compounds.[21]

3.6.3. General Procedure for the synthesis of dihydropyrans (40a-40r):

To a solution of vinylsilane (0.5 mmol) in CH_2Cl_2 (3 mL) was added aldehyde (0.55 mmol), followed by $BF_3{\cdot}OEt_2$ (85 mg, 0.6 mmol) at -45 ^oC under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for around 4-5 h. After completion of the reaction, as determined by TLC, reaction mixture was brought to room temperature, diluted with CH_2Cl_2 (10 mL), washed with saturated sodium bicarbonate and brine solutions, and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was purified by column chromatography using ethyl acetate and hexane as eluents.

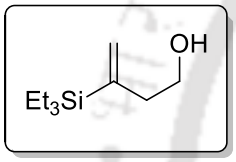
3.6.4. Procedure for controlled reaction:

To a mixture of benzaldehyde (**36a)** (63 mg, 0.59 mmol) and 3-(triethylsilyl)but-3-en-1-ol (**35a**) (100 mg, 0.54 mmol) in dry CH_2Cl_2 (2 mL) at -80 °C was added $BF_3{\cdot}OEt_2$ (91 mg,

0.65 mmol). The reaction mixture was strirred at -80 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was warmed to room temperature, CH_2Cl_2 was added to the mixture, which was then washed with saturated sodium bicarbonate and brine solutions and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was purified by column chromatography using ethyl acetate and hexane (Hexane : EtOAC; 99:1) as eluents to give triethyl(2-phenyl-3,6-dihydro-2*H*-pyran-4-yl)silane (**39a**) with 15% yield and 2-phenyl-3,6-dihydro-2*H*-pyran (**40a**) with 50% yield.

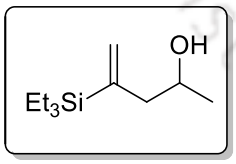
3.8. Spectral data

3-(Triethylsilyl)but-3-en-1-ol (35a):



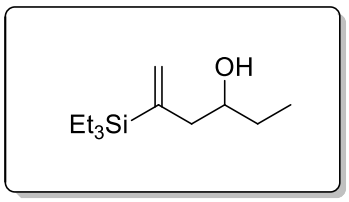
Colourless oil; R_f (hexane/EtOAc 19:1) 0.53; yield 119 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8.0 Hz, 6 H), 0.93 (t, *J* = 8.0 Hz, 9 H), 2.40 (t, *J* = 6.4 Hz, 2 H), 3.67 (t, *J* = 6.4 Hz, 2 H), 5.44 (d, *J* = 2.8 Hz, 1 H), 5.72-5.73 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.1, 7.5, 39.6, 61.5, 128.4, 145.6; IR (KBr, neat) 3397, 2955, 2878, 1461, 1238, 1098, 1011, 730 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{23}OSi$ $(M + H)^+$: *m/z* 187.1513, found 187.1507.

4-(Triethylsilyl)pent-4-en-2-ol (35b):



Colourless oil; R_f (hexane/EtOAc 19:1) 0.55yield 115 mg, 48%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.61 (q, *J* = 7.8 Hz, 6 H), 0.93 (t, *J* = 7.8 Hz, 9 H), 1.20 (d,*J* = 6.6 Hz, 3 H),1.71 (bs, 1 H) 2.16 (dd, *J* = 13.8 and 9.0 Hz, 1 H), 2.35 (dd, *J* = 13.8 and 3.0 Hz, 1 H), 3.82-3.85 (m, 1 H), 5.47 (d, *J* = 2.4 Hz, 1 H), 5.74-5.76 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.2, 7.5, 23.1, 47.2, 65.9, 129.2, 146.6; IR (KBr, neat) 3378, 2956, 2877, 1461, 1417, 1237, 1118, 1012, 930, 722 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{25}OSi$ $(M + H)^+$: *m/z* 201.1669, found 201.1663

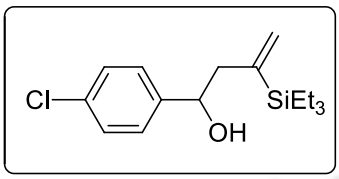
5-(Triethylsilyl)hex-5-en-3-ol (35c):



Colourless oil; R_f (hexane/EtOAc 19:1) 0.56; yield 113mg, 52%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.60 (q, *J* = 7.8 Hz, 6 H), 0.93 (t, *J* = 7.8 Hz, 9 H), 0.95 (t, *J* = 7.2 Hz, 3 H), 1.48-1.50 (m, 2 H), 1.80 (bs, 1 H), 2.08 (dd, *J* = 13.8 and 9.6 Hz, 1 H), 2.40 (dd, *J* = 13.8 and 3.0 Hz, 1 H), 3.54-3.57 (m, 1 H),

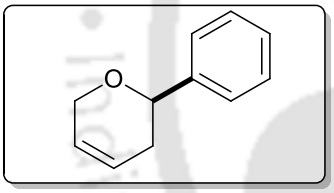
5.47 (d, *J* = 3.0 Hz, 1 H), 5.73-5.75 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.2, 7.5, 10.3, 30.0, 44.9, 71.0, 129.2, 146.6; IR (KBr, neat) 3446, 2953, 2820, 1655, 1453, 1275, 1179, 1091, 1023, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{27}OSi$ $(M + H)^+$: *m/z* 215.1826, found 215.1824.

1-(4-Chlorophenyl)-3-(triethylsilyl)but-3-en-1-ol (35d):



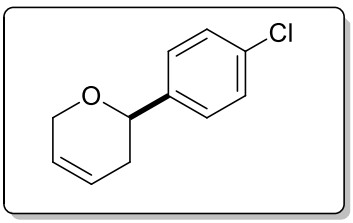
Colourless oil; R_f (hexane/EtOAc 19:1) 0.48; yield, 90mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (q, *J* = 8.0 Hz, 6 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 2.18 (bs, 1 H), 2.36 (dd, *J* = 14.0 and 10.0 Hz, 1 H), 2.57 (d, *J* = 14.0 Hz, 1 H), 4.70 (dd, *J* = 10.0 and 3.2 Hz, 1 H), 5.55 (d, *J* = 2.0 Hz, 1 H), 5.82 (s, 1 H), 7.32 (s, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.2, 7.6, 47.5, 71.6, 127.4, 128.7, 130.0, 133.2, 142.8, 146.1; IR (KBr, neat) 3435, 2954, 2876, 1639, 1492, 1413, 1091, 1012, 738 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{26}ClOSi$ $(M + H)^+$: *m/z* 297.1436, found 297.1439.

2-Phenyl-3,6-dihydro-2*H*-pyran (40a):



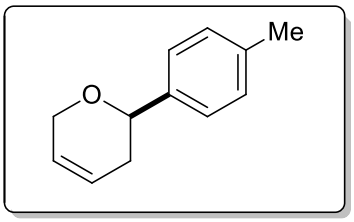
Colourless oil; R_f (hexane) 0.58; yield 62 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22-2.30 (m, 1 H), 2.32-2.42 (m, 1 H), 4.32-4.43 (m, 2 H), 4.56 (dd, *J* = 10.4 and 3.6 Hz, 1 H), 5.80-5.84 (m, 1 H), 5.90-5.93 (m, 1 H), 7.25-7.29 (m, 1 H), 7.33-7.40 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 66.8, 75.9, 124.7, 126.1, 126.7, 127.7, 128.6, 142.8; IR (KBr, neat) 2926, 2828, 1602, 1492, 1178, 1089, 822, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{13}O$ $(M + H)^+$: *m/z* 161.0961, found 161.0942.

2-(4-Chlorophenyl)-3,6-dihydro-2*H*-pyran (40b):



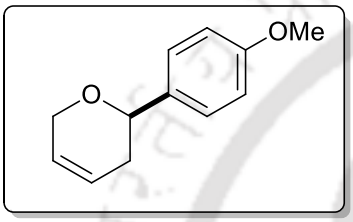
Colourless oil; R_f (hexane) 0.58; yield 78 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.23-2.28 (m, 1 H), 2.28-2.34 (m, 1 H), 4.32-4.39 (m, 2 H), 4.53 (dd, *J* = 10.2 and 3.6 Hz, 1 H), 5.81 (d, *J* = 10.2 Hz, 1 H), 5.89-5.92 (m, 1 H), 7.32 (s, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1, 66.8, 75.1, 124.4, 126.7, 127.5, 128.7, 133.3, 141.4; IR (KBr, neat) 2926, 2828, 1602, 1492, 1178, 1089, 822, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}ClO$ $(M + H)^+$: *m/z* 195.0571, found 195.0559.

.(2-(p-Tolyl)-3,6-dihydro-2*H*-pyran (40c):



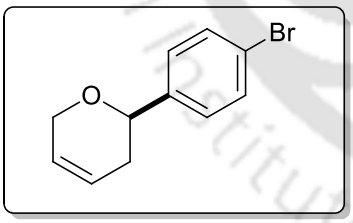
Colourless oil; R_f (hexane) 0.51; yield 71 mg, 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.22-2.27 (m, 1 H), 2.35 (s, 3 H), 2.36-2.41 (m, 1 H), 4.35-4.37 (m, 2 H), 4.53 (dd, *J* = 10.2 and 3.0 Hz, 1 H), 5.81 (dt, *J* = 10.2 and 1.2 Hz, 1 H), 5.91-5.93 (m, 1 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 7.27 (d, *J* = 7.8Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 33.1, 66.8, 75.8, 124.8, 126.1, 126.7, 129.3, 137.4, 139.8; IR (KBr, neat) 2925, 2822, 1450, 1386, 1179, 1091, 812, 733 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}O$ $(M + H)^+$: *m/z* 175.1117, found 175.1115.

2-(4-Methoxyphenyl)-3,6-dihydro-2*H*-pyran (40d):



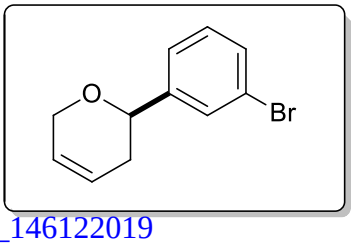
Colourless oil; R_f (hexane/EtOAc 49:1) 0.43; yield 68 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18-2.26 (m, 1 H), 2.33-2.43 (m, 1 H), 3.80 (s, 3 H), 4.28-4.41 (m, 2 H), 4.51 (dd, *J* = 10.0 and 3.2 Hz, 1 H), 5.78-5.82 (m, 1 H), 5.89-5.94 (m, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.0, 55.5, 66.8, 75.5, 114.0, 124.8, 126.7, 127.5, 135.0, 159.3; IR (KBr, neat) 2925, 2852, 1617, 1461, 1247, 1176, 1035, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}O_2$ $(M + H)^+$: *m/z* 191.1067, found 191.1072.

2-(4-Bromophenyl)-3,6-dihydro-2*H*-pyran (40e):



Colourless oil; R_f (hexane) 0.73; 0.50; yield 100 mg, 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.24-2.26 (m, 1 H), 2.27-2.32 (m, 1 H), 4.32-4.39 (m, 2 H), 4.52 (dd, *J* = 10.2 and 3.6 Hz, 1 H), 5.81 (d, *J* = 10.2 Hz, 1 H), 5.89-5.92 (m, 1 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.47 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.0, 66.7, 75.1, 121.5, 124.4, 126.6, 127.8, 131.7, 141.9; IR (KBr, neat) 2923, 1588, 1489, 1401, 1264, 1070, 1032, 817, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}BrO$ $(M + H)^+$: *m/z* 239.0066 found 241.0052 (^{81}Br).

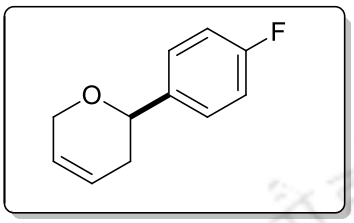
2-(3-Bromophenyl)-3,6-dihydro-2*H*-pyran (40f):



Colourless oil; R_f (hexane/EtOAc 99:1) 0.53; yield 85 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.24-2.35 (m, 2 H), 4.33-4.39 (m, 2 H), 4.53 (dd, *J* = 10.2 and 3.6 Hz, 1 H), 5.81 (dd, *J* = 10.2 and 2.4 Hz, 1 H), 5.89-5.91 (m, 1 H), 7.22 (t, *J*

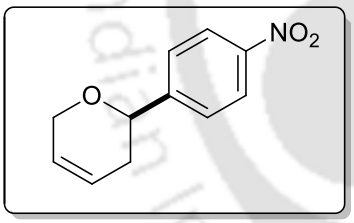
= 7.8 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.55 (s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.0, 66.7, 75.0, 122.7, 124.3, 124.6, 126.6, 129.2, 130.1, 130.7, 145.1; IR (KBr, neat) 2926, 2827, 1650, 1597, 1425, 1181, 1091, 1023, 774 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}BrO$ $(M + H)^+$: *m/z* 241.0046, found 241.0038 (^{81}Br).

2-(4-Fluorophenyl)-3,6-dihydro-2*H*-pyran (40g):



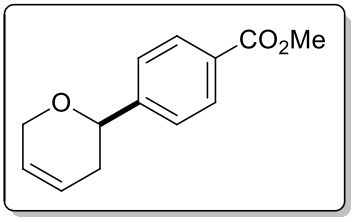
Colourless oil; R_f (hexane) 0.58; yield 62 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20-2.38 (m, 2 H), 4.31-4.42 (m, 2 H), 4.53 (dd, *J* = 10.0 and 3.6 Hz, 1 H), 5.78-5.84 (m, 1 H), 5.88-5.94 (m, 1 H), 7.01-7.06 (m, 2 H), 7.33-7.37 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1, 66.8, 75.2, 115.4 (d, *J* = 21.2 Hz), 124.5, 126.6, 127.8 (d, *J* = 8.0 Hz), 138.6 (d, *J* = 3.2 Hz), 162.4 (d, *J* = 243.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 46.47 (s, 1F); IR (KBr, neat) 2924, 2852, 1641, 1463, 1262, 1020, 798, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}FO$ $(M + H)^+$: *m/z* 179.0867, found 179.0902.

2-(4-Nitrophenyl)-3,6-dihydro-2*H*-pyran (40h):



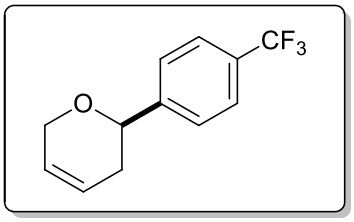
Colourless solid; mp 70-72 ^{o}C; R_f (hexane/EtOAc 95:5) 0.58; yield 91 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22-2.35 (m, 2 H), 4.38-4.40 (m, 2 H), 4.65 (dd, *J* = 9.6 and 4.2 Hz, 1 H), 5.83-5.90 (m, 1 H), 5.91-5.95 (m, 1 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 8.20 (dd, *J* = 8.5 and 1.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1, 66.7, 74.7, 123.9, 124.0, 126.3, 126.7, 147.5, 150.2; IR (KBr, neat) 2932, 2830, 1661, 1518, 1347, 1180, 1090, 1019, 850, 746, 667 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}NO_3$ $(M + H)^+$: *m/z* 206.0812, found 206.0814.

Methyl 4-(3,6-dihydro-2*H*-pyran-2-yl)benzoate (40i):



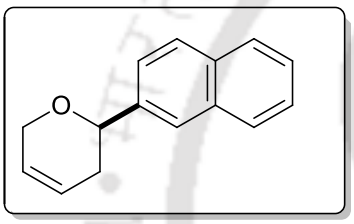
Colourless gum; R_f (hexane/EtOAc 49:1) 0.50; yield 93 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28-2.30 (m, 2 H), 3.90 (s, 3 H), 4.37-4.40 (m, 2 H), 4.61 (dd, *J* = 8.4 and 5.4 Hz, 1 H), 5.81-5.83 (m, 1 H), 5.90-5.92 (m, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1, 52.3, 66.7, 75.3, 124.3, 125.9, 126.7, 129.4, 130.0, 148.0, 167.2; IR (KBr, neat) 2963, 1724, 1612, 1437, 1339, 1181, 1095, 1020, 799 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{15}O_3$ $(M + H)^+$: *m/z* 219.1016 found 219.1013.

2-(4-(Trifluoromethyl)phenyl)-3,6-dihydro-2*H*-pyran (40j):



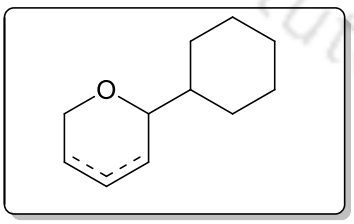
Colourless oil; R_f (hexane) 0.34; yield 80 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.29-2.31 (m, 2 H), 4.35-4.42 (m, 2 H), 4.62 (dd, *J* = 7.6 and 6.0 Hz, 1 H), 5.82-5.85 (m, 1 H), 5.90-5.94 (m, 1 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1, 66.7, 75.1, 123.5, 124.2, 124.4 (q, *J* = 270.3 Hz), 125.5 (q, *J* = 3.8 Hz), 126.2, 126.7, 129.8 (q, 32.3 Hz);^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$)δ 99.26 (s, 1F); IR (KBr, neat) 2928. 2851, 1623, 1418, 1327, 1127, 1067, 835, 746, 663 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{12}F_3O$ $(M + NH^4)^+$: *m/z* 246.1100, found 246.1108.

2-(Naphthalen-2-yl)-3,6-dihydro-2*H*-pyran (40k):



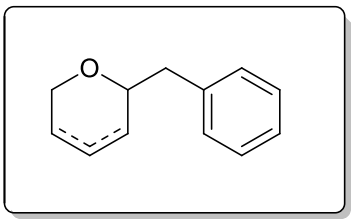
Colourless solid; mp 56-58 ^{o}C; R_f (hexane) 0.40; yield 73 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34-2.39 (m, 1 H), 2.42-2.50 (m, 1 H), 4.39-4.49 (m, 2 H), 4.75 (dd, *J* = 10.0 and 3.6 Hz, 1 H), 5.85-5.88 (m, 1 H), 5.96-6.00 (m, 1 H), 7.46-7.53 (m, 3 H), 7.83-7.87 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.1, 66.8, 75.9, 124.4, 124.64, 125.9, 126.2, 126.6, 127.8,128.2, 128.3, 133.1, 133.5, 140.2; IR (KBr, neat) 2926, 2825, 1603, 1448, 1387, 1186, 1090, 1022, 818, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{15}O$ $(M + H)^+$: *m/z* 211.1117 found 211.1127.

2-Cyclohexyl-3,6-dihydro-2*H*-pyran and 6-cyclohexyl-3,6-dihydro-2*H*-pyran (40l, regioisomeric mixture, 62:38):



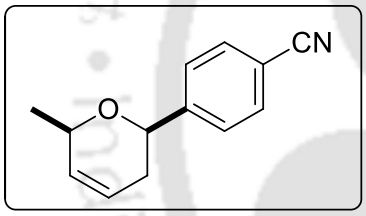
Colourless gum; R_f (hexane) 0.5; yield 58 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92-1.32 (m, 6 H), 1.34-1.46 (m, 1 H), 1.64-1.78 (m, 5 H), 1.84-2.10 (m, 2 H), 2.00-2.10 (m, 1 H), 2.21-2.30 (m, 1 H, major), 3.17-3.23 (m, 1 H, major), 3.59-3.66 (m, 1 H, minor), 3.83-3.88 (m, 1 H, minor), 3.94-3.97 (m, 2 H, minor), 4.10-4.22 (m, 2 H, major), 5.64-5.73 (m, 1 H), 5.78-5.87 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.3, 26.4, 26.6, 26.8, 26.9, 28.4, 28.5, 28.6, 28.9, 29.4, 29.9, 43.0, 43.1, 64.0, 66.5, 78.3, 78.5, 124.8, 125.3, 126.6, 129.3; IR (KBr, neat) 2935, 2853, 1642, 1401, 1184, 1090, 785 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{19}O$ $(M + H)^+$: *m/z* 167.1430, found 167.1449.

2-Benzyl-3,6-dihydro-2*H*-pyran and 6-benzyl-3,6-dihydro-2*H*-pyran (40m, regioisomeric mixture, 63:37):



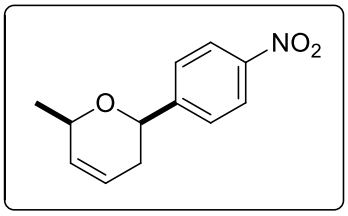
Colourless gum; R_f (hexane) 0.48; yield 63 mg, 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.91-1.96 (m, 1 H), 2.05-2.07 (m, 1 H, major), 2.24-2.29 (m, 1 H, minor), 2.71-2.75 (m, 1 H), 2.90-2.96 (m, 1 H), 3.63-3.67 (m, 1 H, minor), 3.73-3.77 (m, 1 H, major), 3.96-3.99 (m, 2 H, minor), 4.15-4.33 (m, 2 H, major), 5.62-5.65 (m, 1 H, minor) 5.69-5.71 (m, 1 H, major), 5.76-5.79 (m, 1 H, major), 5.83-5.86 (m, 1 H, minor), 7.19-7.24 (m, 3 H), 7.27-7.30 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.4, 30.9, 42.0, 42.6, 63.6, 66.2, 74.7, 75.0, 124.3, 125.3, 126.4, 126.5, 128.5, 129.5, 129.6, 129.7, 138.5, 138.7; IR (KBr, neat) 2926, 2784, 1636, 1400, 1086, 743, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}O$ $(M + H)^+$: *m/z* 175.1117, found 175.1132.

4-((2*R,6*R**)-6-Methyl-3,6-dihydro-2*H*-pyran-2-yl)benzonitrile (40n):**



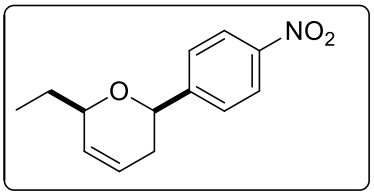
Colourless gum; R_f (hexane/EtOAc 98:2) 0.48; yield 76 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.8 Hz, 3 H), 2.20-2.24 (m, 2 H), 4.41-4.45 (m, 1 H), 4.67 (dd, *J* = 10.0 and 4.4 Hz, 1 H), 5.71-5.74 (m, 1 H), 5.84-5.86 (m, 1 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 33.0, 72.0, 75.2, 111.3, 119.2, 123.8, 126.6, 131.9, 132.5, 148.4; IR (KBr, neat) 2926, 2854, 2230, 1741, 1611, 1464, 1373, 1243, 1094, 1046, 840, 785 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}NO$ $(M + H)^+$: *m/z* 200.1070 found 200.1073.

(2*R,6*R**)-6-Methyl-2-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran (40o):**



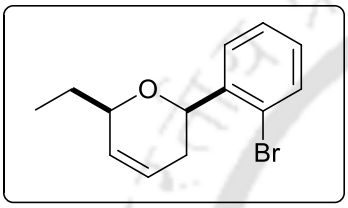
White solid; mp 74-76 ^{o}C; R_f (hexane/EtOAc 19:1) 0.50; yield 85 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.8 Hz, 3 H), 2.22-2.32 (m, 2 H), 4.43-4.48 (m, 1 H), 4.72 (dd, *J* = 10.4 and 4.0 Hz, 1 H), 5.71-5.75 (m, 1 H), 5.84-5.90 (m, 1 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 8.20 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 33.1, 72.0, 75.0, 123.7, 123.9, 126.7, 131.9, 147.4, 150.4; IR (KBr, neat) 2978, 2831, 1603, 1520, 1459, 1348, 1213, 1106, 1073, 851, 745 cm^{-1}; HRMS (ESI) calcd. for$C_{12}H_{14}NO_3$ $(M + H)^+$: *m/z* 220.0968, found 220.0957.

(2*R,6*R**)-6-Ethyl-2-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran (40p):**



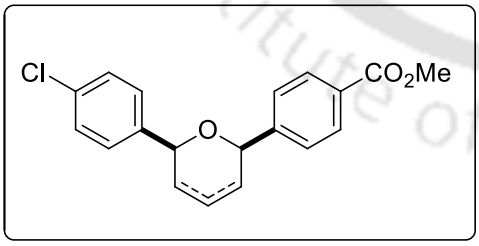
Colourless gum; R_f (hexane/EtOAc 19:1) 0.59; yield 82 mg, 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.2 Hz, 3 H), 1.64-1.70 (m, 2 H), 2.12-2.21 (m, 1 H), 2.26-2.31 (m, 1 H), 4.27-4.28(m, 1 H), 4.72 (dd, *J* = 10.8 and 3. 6 Hz, 1 H), 5.73-5.76 (m, 1 H), 5.88-5.93 (m, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 8.20 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.5, 28.6, 33.3, 74.7, 76.6, 123.8, 124.3, 126.5, 130.5, 147.3, 150.7; IR (KBr, neat) 2966, 2853, 1606, 1520, 1348, 1183, 1078, 867, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}NO_3$ $(M + Na)^+$: *m/z* 256.0944, found 256.0940.

(2*R,6*R**)-2-(2-Bromophenyl)-6-ethyl-3,6-dihydro-2*H*-pyran (40q):**



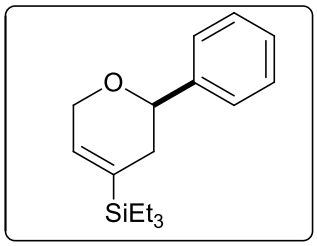
Colourless oil; R_f (hexane/EtOAc 99:1) 0.50; yield 81 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.2 Hz, 3 H), 1.62-1.70 (m, 2 H), 2.01-2.10 (m, 1 H), 2.41-2.48 (m, 1 H), 4.28-4.32 (m, 1 H), 4.90 (dd, *J* = 10.4 and 3.2 Hz, 1 H), 5.69-5.73 (m, 1 H), 5.88-5.94 (m, 1 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.5, 28.6, 31.9, 74.9, 76.6, 121.8, 125.0, 127.7, 128.0, 128.8, 130.2, 132.6, 142.6; IR (KBr, neat) 2966, 2810, 1568, 1435, 1344, 1182, 1071, 719, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}BrO$ $(M + H)^+$: *m/z* 269.0359, found 269.0351 (^{79}Br).

Methyl 4-((2*R,6*S**)-6-(4-chlorophenyl)-5,6-dihydro-2*H*-pyran-2-yl)benzoate and methyl 4-((2*R**,6*S**)-6-(4-chlorophenyl)-3,6-dihydro-2*H*-pyran-2-yl)benzoate (40r, regioisomeric mixture, 80:20):**



Colourless oil; R_f (hexane/EtOAc 99:1) 0.50; yield 106mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29-2.44 (m, 2 H), 3.90 (s, 3 H, major), 3.91 (s, 3 H, minor), 4.58 (dd, *J* = 7.8 and 5.8 Hz, 1 H, minor), 4.78-4.88 (m, 1 H, major), 5.34-5.44 (m, 1 H), 5.78-5.83 (m, 1 H, major), 5.98-6.02 (m, 1 H, major), 6.07-6.11 (m, 1 H, minor), 6.12-6.117 (m, 1 H, minor), 7.31-7.42 (m, 4 H), 7.46-7.51 (m, 2 H), 7.98-8.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 33.1, 52.3, 69.4, 74.1, 75.7, 75.9, 77.7, 78.0, 124.9, 125.1, 125.9, 126.2, 126.3, 127.1, 127.4, 128.7, 128.8, 128.9, 129.5, 129.6, 129.8, 129.9, 130.1, 133.5, 133.8, 140.0, 141.1, 146.6, 147.5, 147.7, 167.2; IR (KBr, neat) 2924, 2850, 1722, 1615, 1434, 1281, 1108, 1017, 766, 706 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}ClO_3$ $(M + H)^+$: *m/z* 329.0959, found 329.0959.

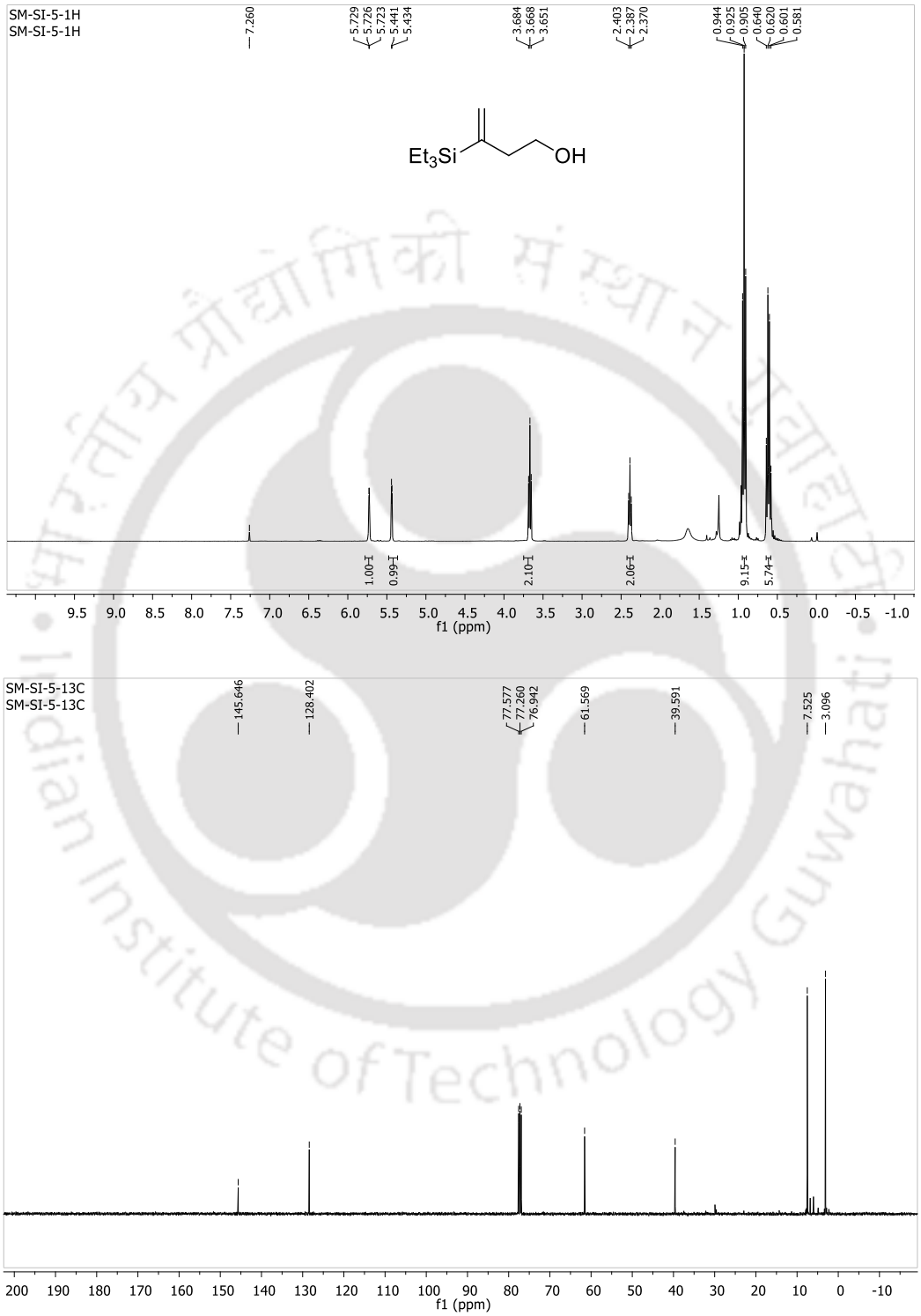
Triethyl(2-phenyl-3,6-dihydro-2*H*-pyran-4-yl)silane (39a):



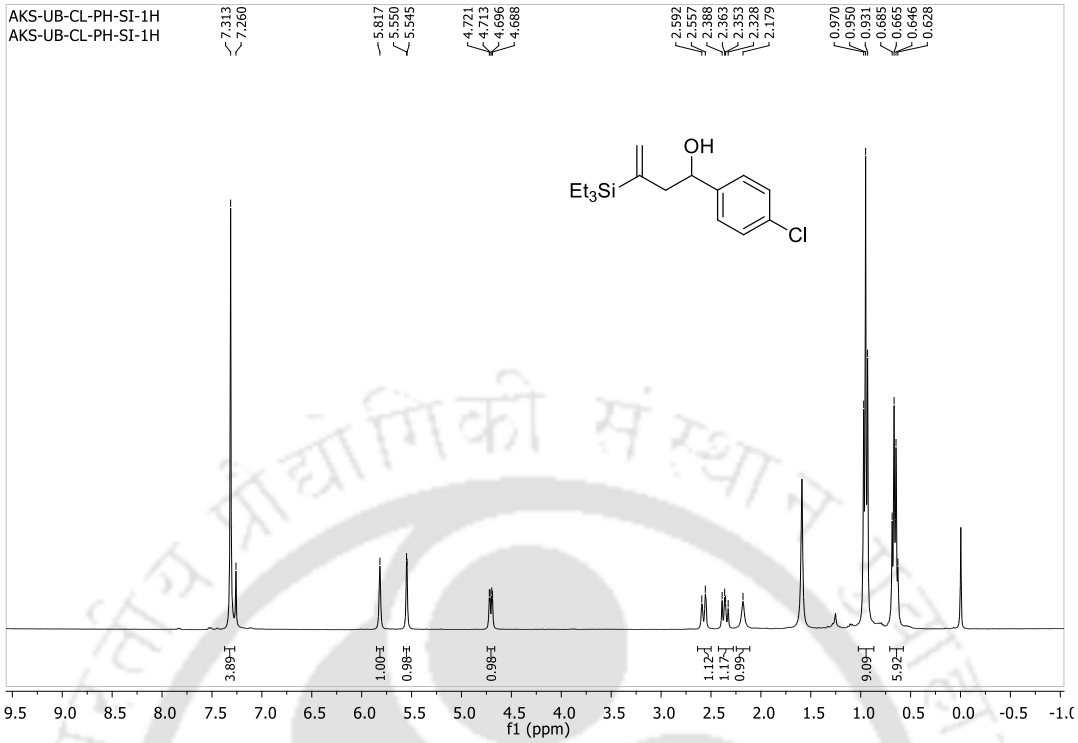
Colourless oil; R_f (hexane) 0.6; yield 22 mg, 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (q, *J* = 7.6 Hz, 6 H), 0.95 (t, *J* = 7.6 Hz, 9 H), 2.20-2.29 (m, 1 H), 2.30-2.37 (m, 1 H), 4.40-4.42 (m, 2 H), 4.48 (dd, *J* = 10.0 and 3.2 Hz, 1 H), 6.03-6.04 (m, 1 H), 5.89-5.95 (m, 1 H), 7.25-7.30 (m, 1 H), 7.33-7.40 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.6, 7.6, 35.5, 68.0, 76.0, 126.1, 127.7, 128.6, 134.2, 135.7, 143.2; IR (KBr, neat) 2926, 2828, 1634, 1399, 1125, 1026, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{27}OSi$ $(M + H)^+$: *m/z* 275.1826, found 275.1815.

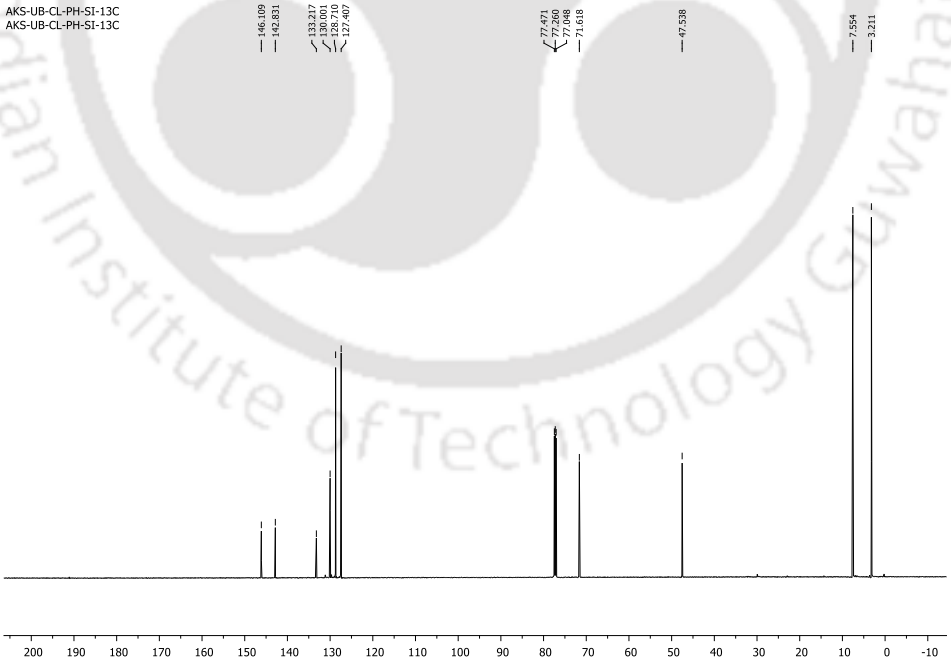
3.8. Selected spectra

^{1}H and ^{13}C Spectra of compound **35a**

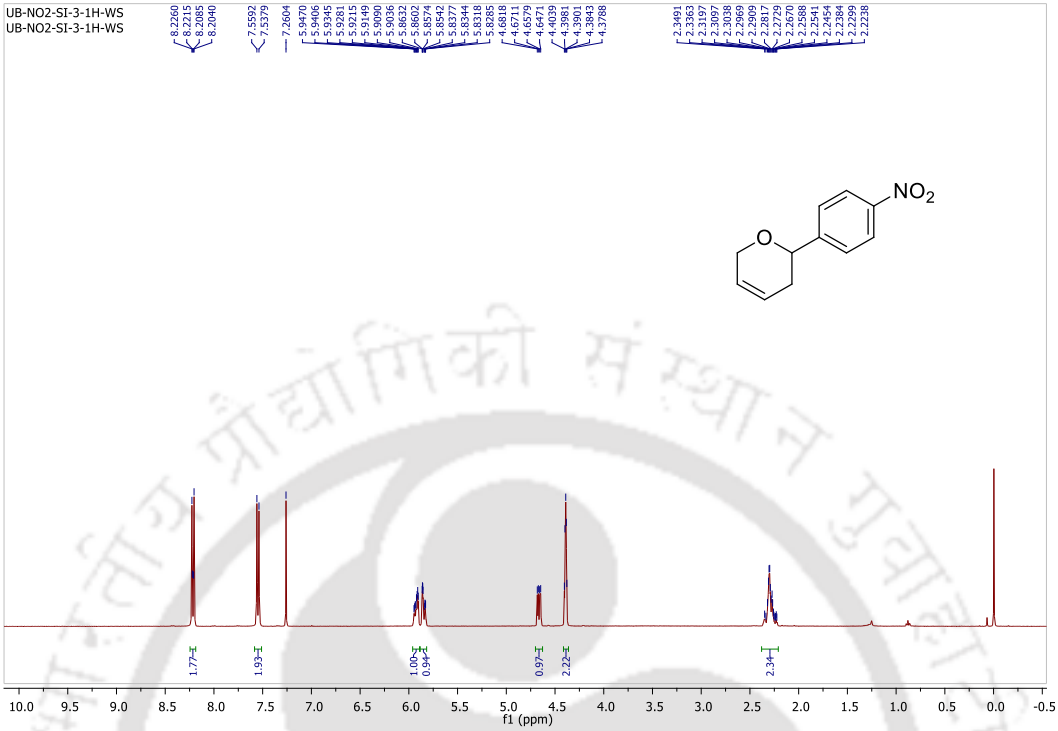


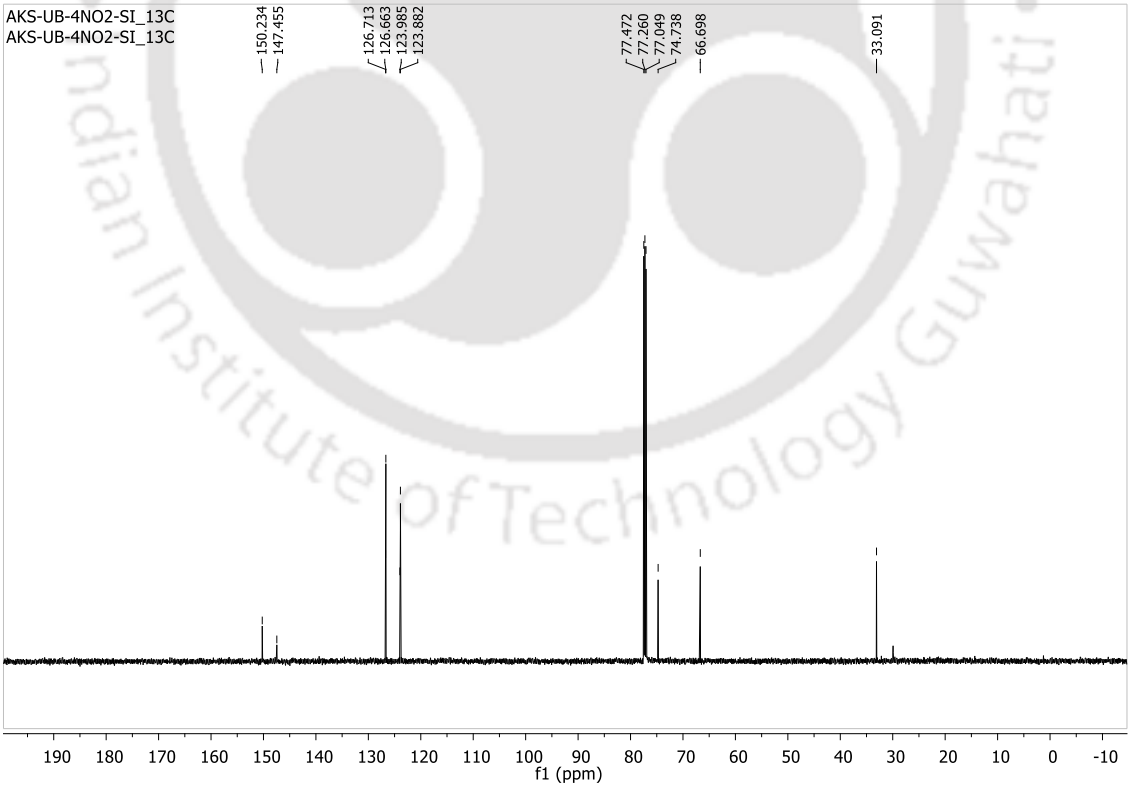
^{1}H and ^{13}C Spectra of compound **35d**



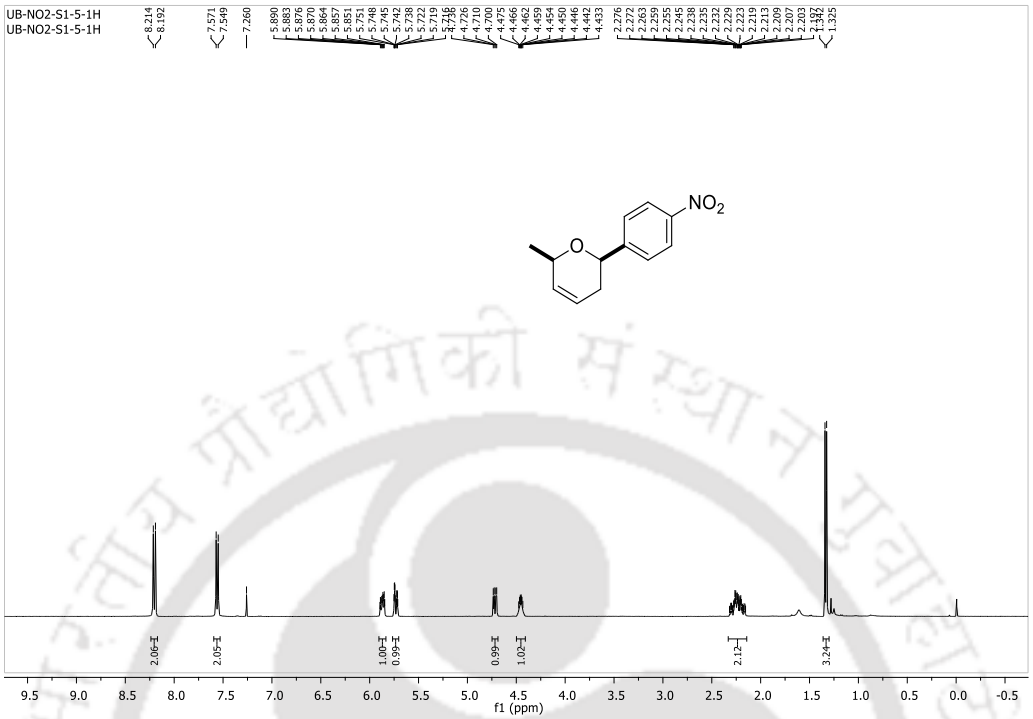


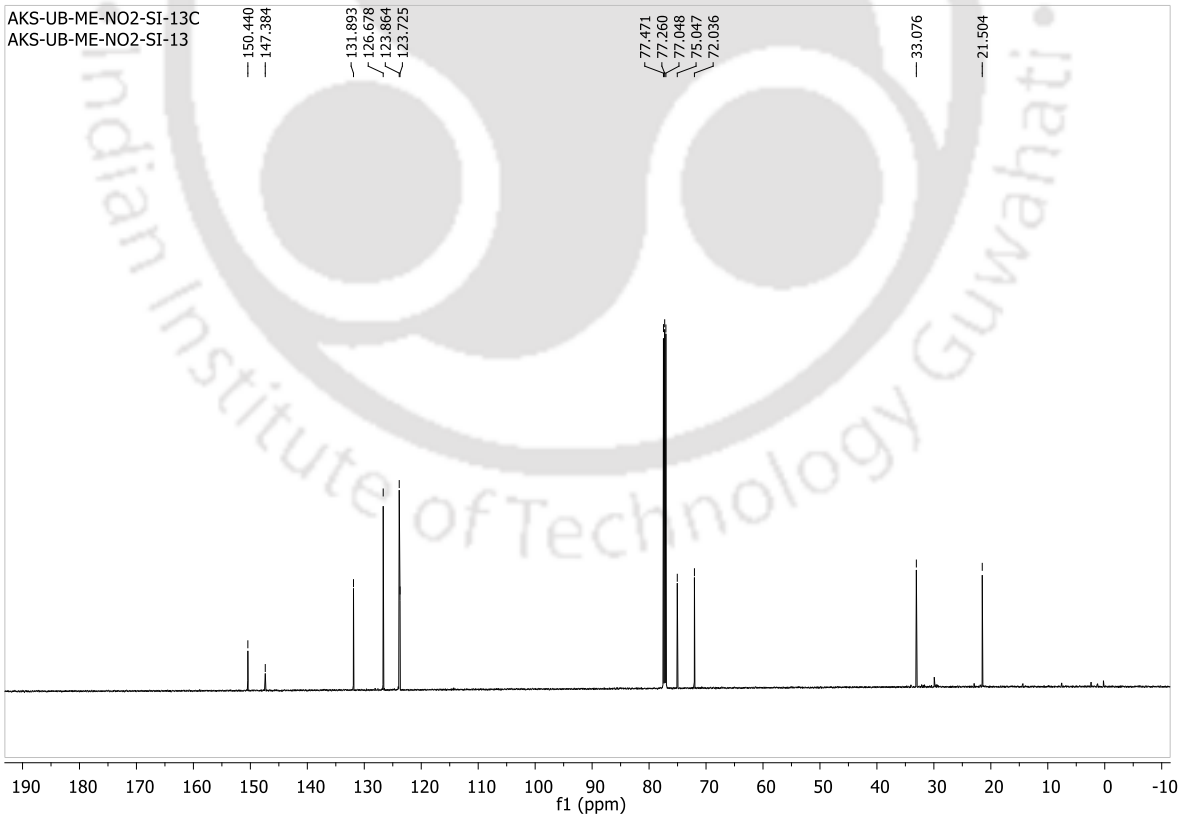
^{1}H and ^{13}CSpectra of compound **40h**



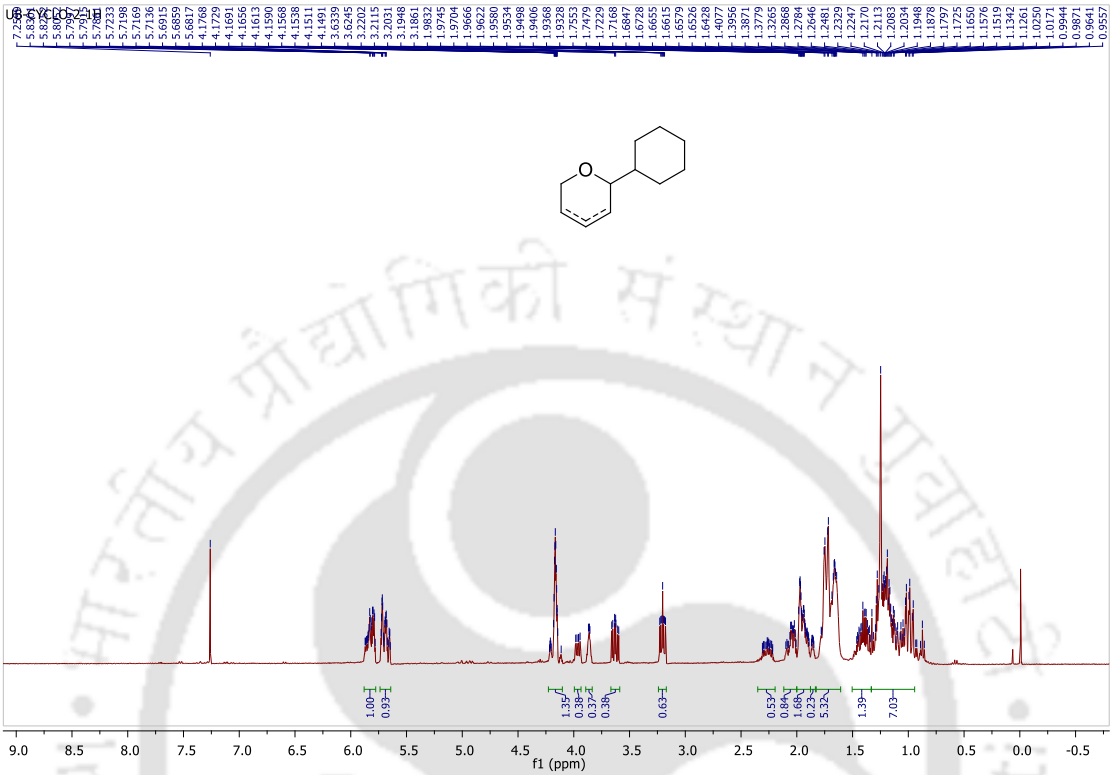


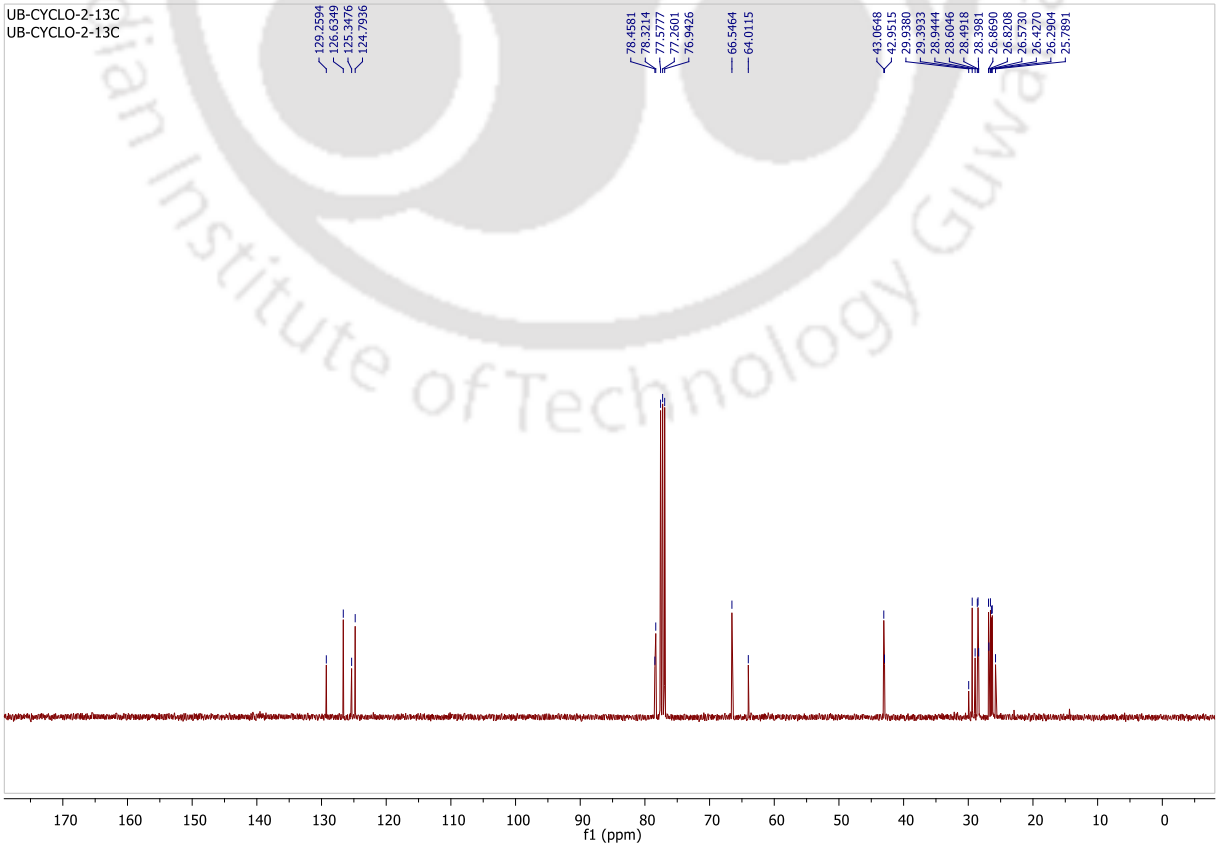
^{1}H and ^{13}CSpectra of compound **40o**



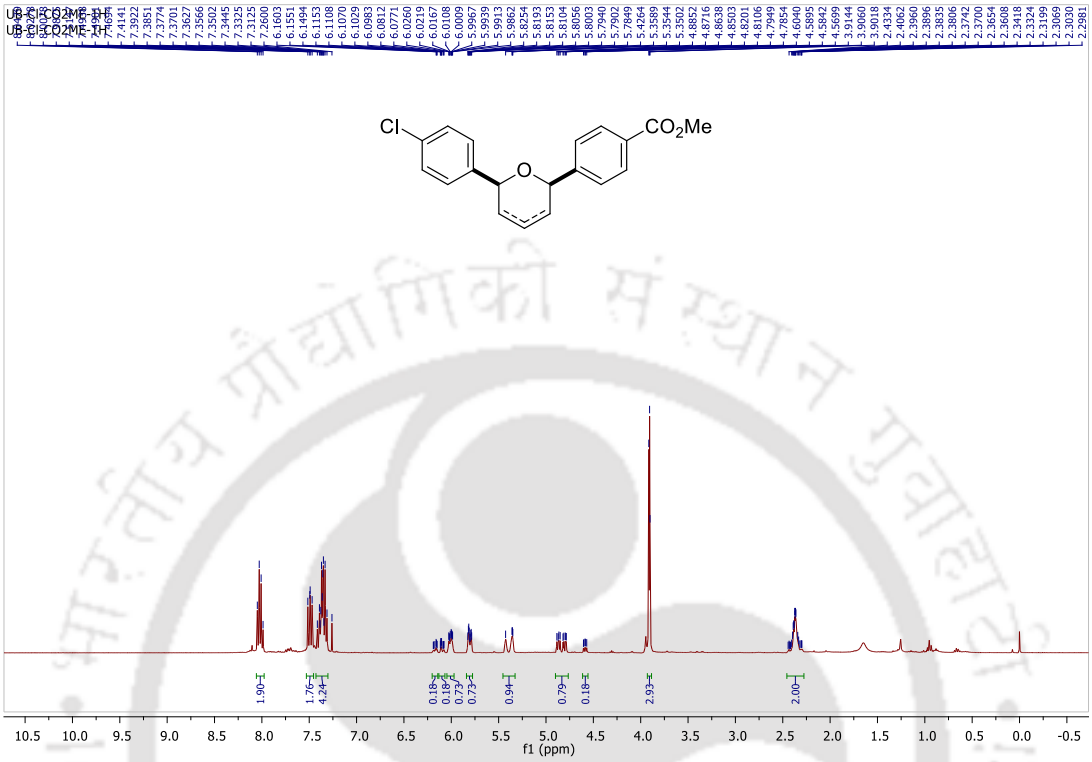


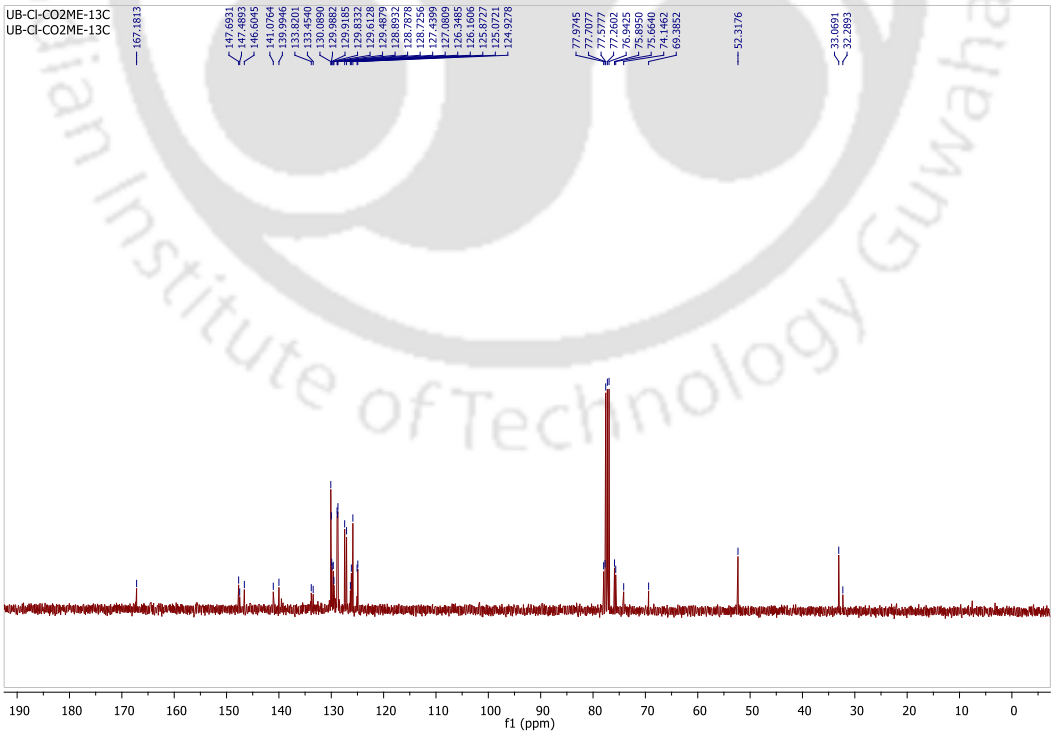
^{1}H and ^{13}CSpectra of compound **40l**



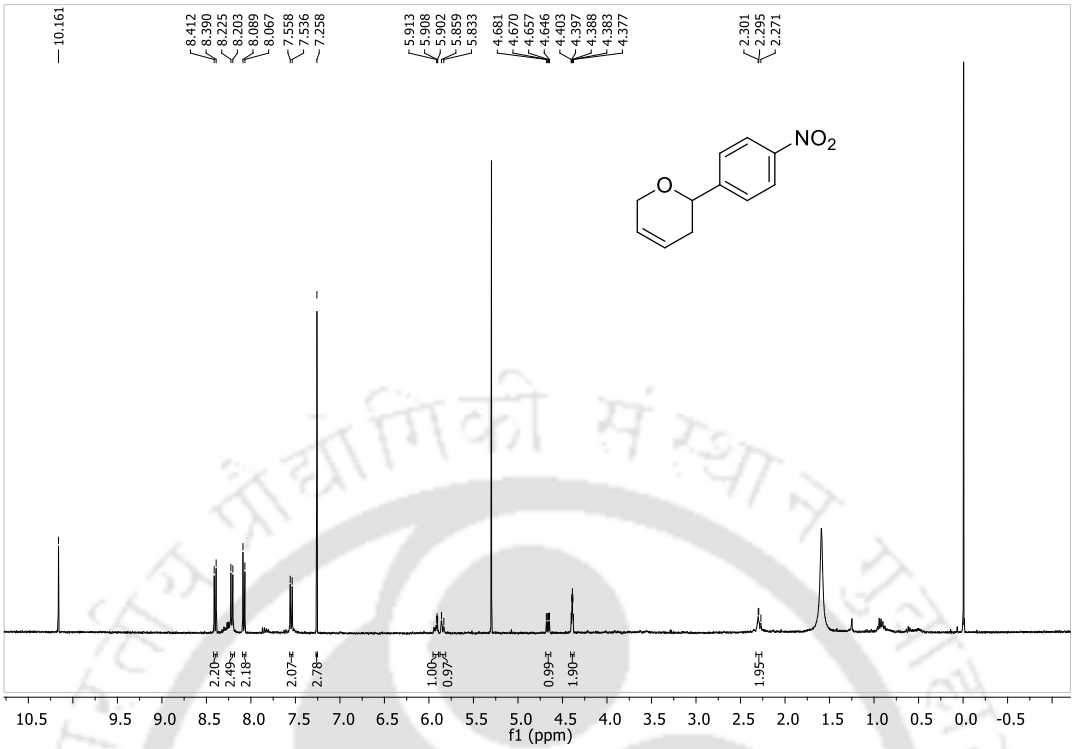


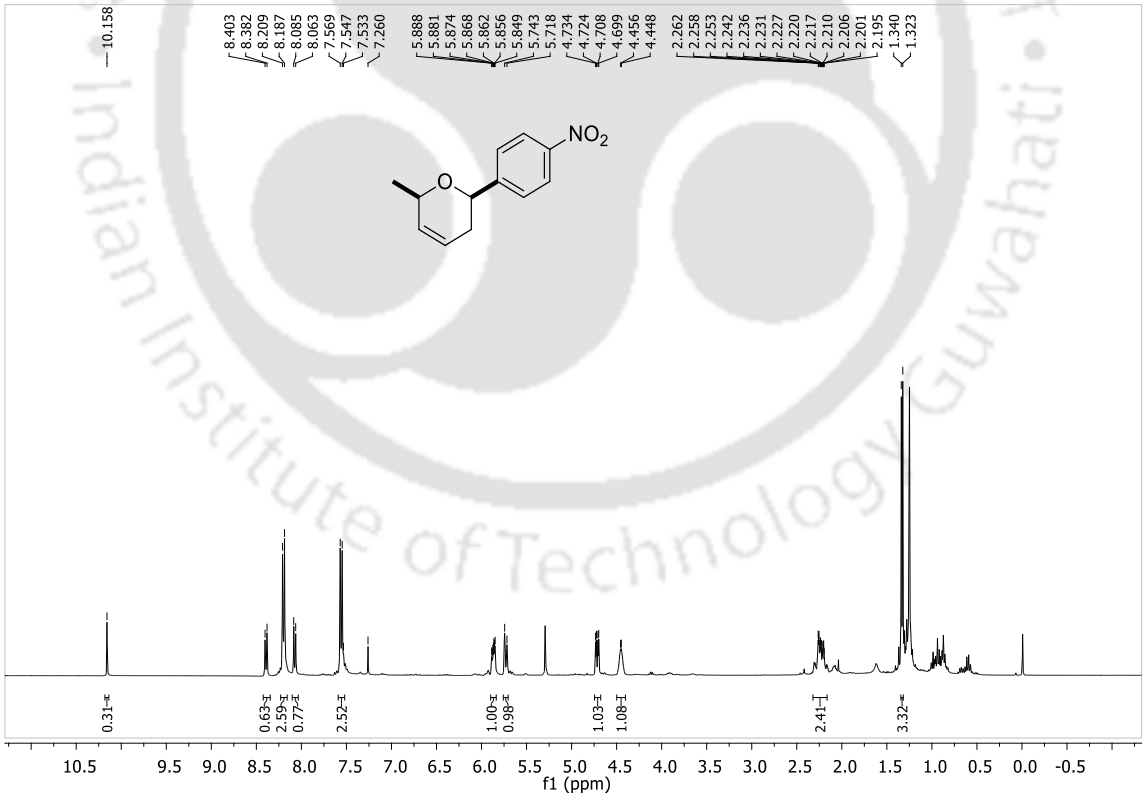
^{1}H and ^{13}CSpectra of compound **40r**



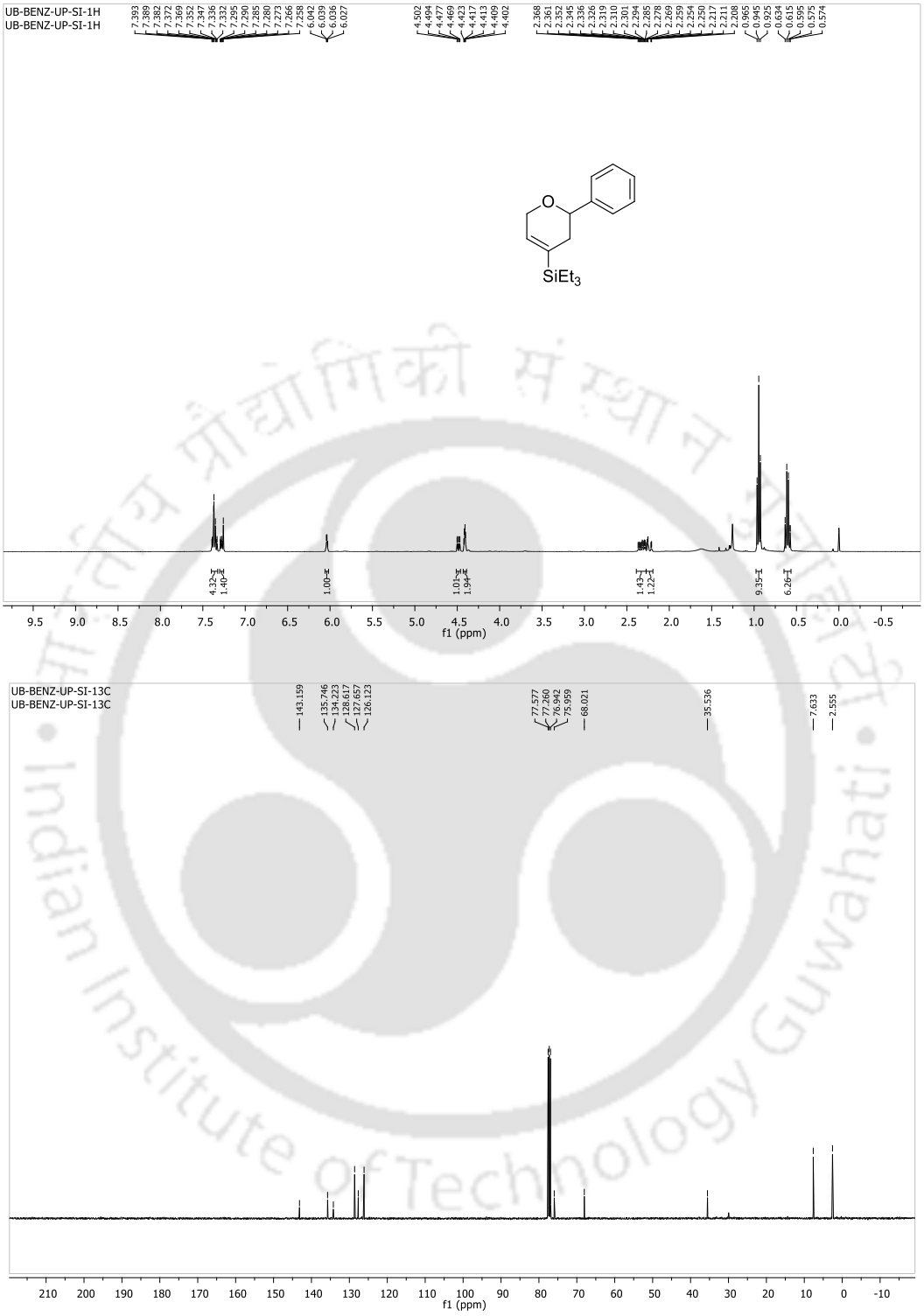


Crude ^{1}H Spectra of compound **40h** and **40o**

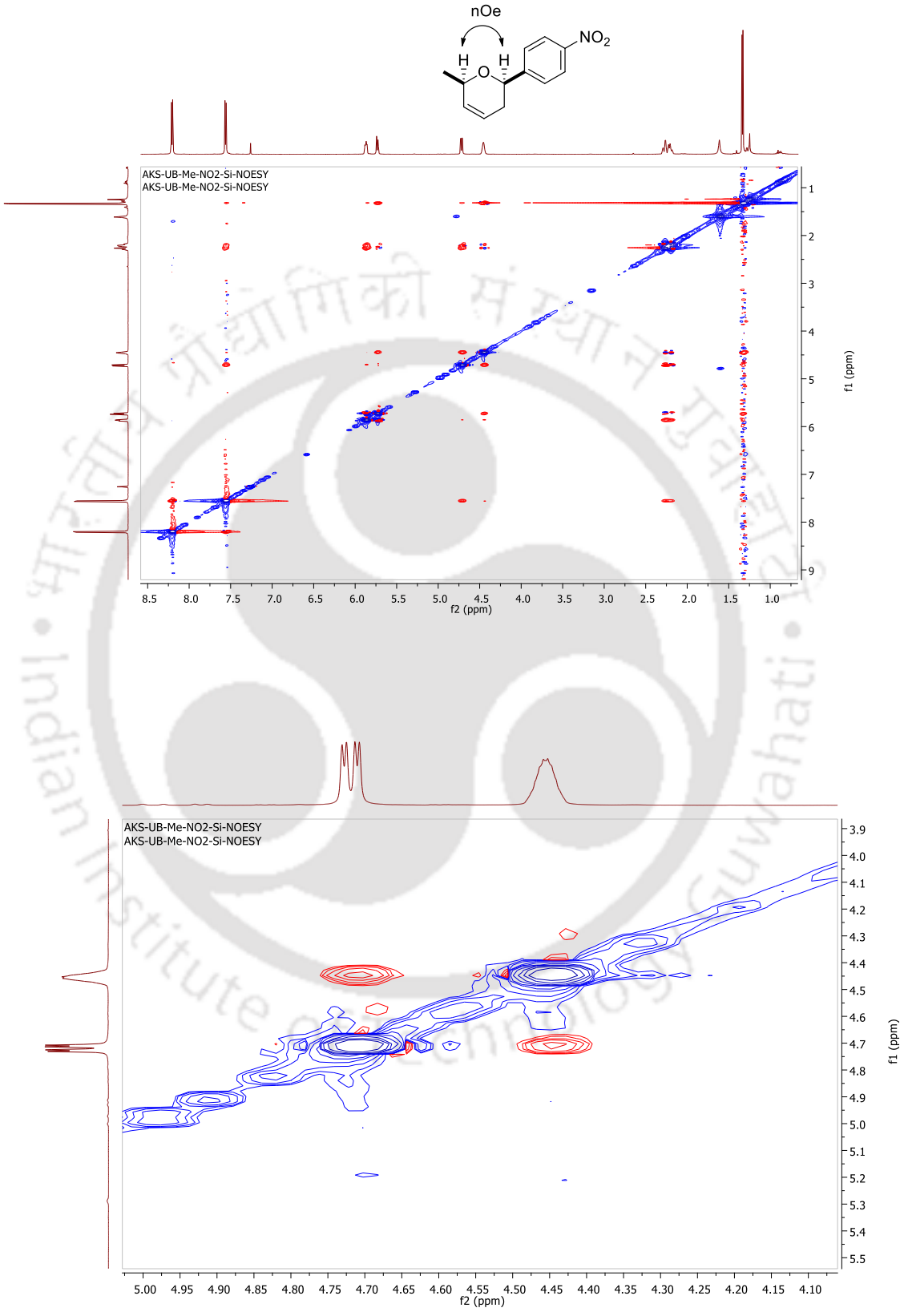




^{1}H and ^{13}C Spectra of compound **39a**



NOE corelation of 40o



3.9. Crystal parameters

The crystal parameters of compound 40h

	CCDC 1588747
Formula	$C_{11}H_{11}NO_3$
Formula weight	205.21
T/K	293(2)
Crystal system	Orthorhombic
Space group	P n a 21
a/Å	6.8236(6)
b/Å	18.8561(17)
c/Å	7.8450(6)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	1009.39(15)
Z	4
Abs. Coeff./mm^{-1}	0.099
Abs. Correction	Multi-scan
GOF on F^2	1.083
Final *R* indices [*I*> 2σ(I)]	*R1* = 0.0524 *wR2* = 0.1482
R indices [all data]	*R1* = 0.0687 *wR2*=0.1650

3.10. References

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CHAPTER 4

Vinylsilanes in Highly Diastereo- and Regio-selective Synthesis of 1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one *via* Iminium–ene Cyclization Reaction.

4.1. Importance and applications

Nitrogen containing fused heterocycles are a privileged structural moiety present in many biologically active molecules. Among them, isoindolones, have gained much attention due to its widespread applications in various drugs. For example, valmerins (**1**), a new family containing the tetrahydropyrido[1,2-*a*]isoindone core, shows cyclin-dependent kinase/glycogen synthase kinase inhibitory activities and also exhibit antitumor activities.[1] Similarly, pyridoisoindolone **2** and azapinoisoindolone **3** compounds inhibits potent U-II receptor antagonist activity.[2] 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (**4**) acts as non-nucleoside HIV-1 reverse transcriptase inhibitor.[3] Apart from their presence in biologically active molecules, these skeletons also found in various natural products (*Figure 4.1.1*).[4]

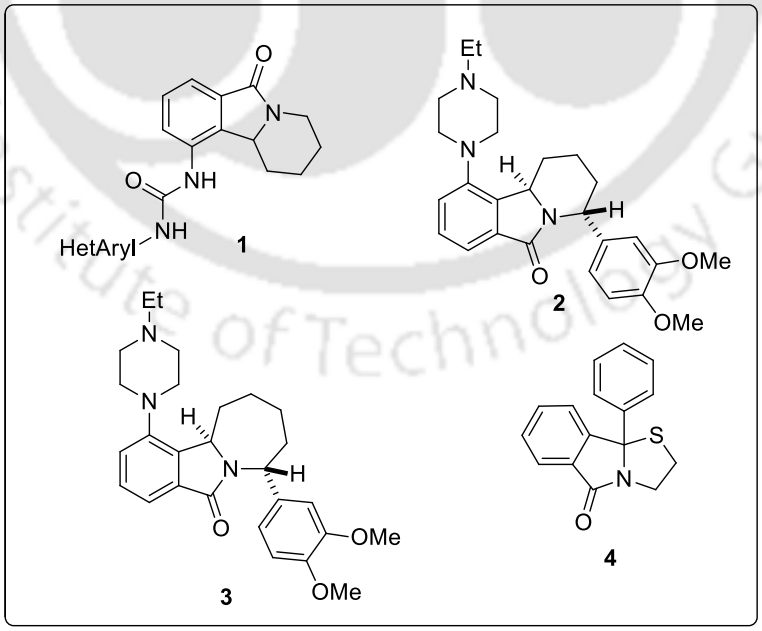
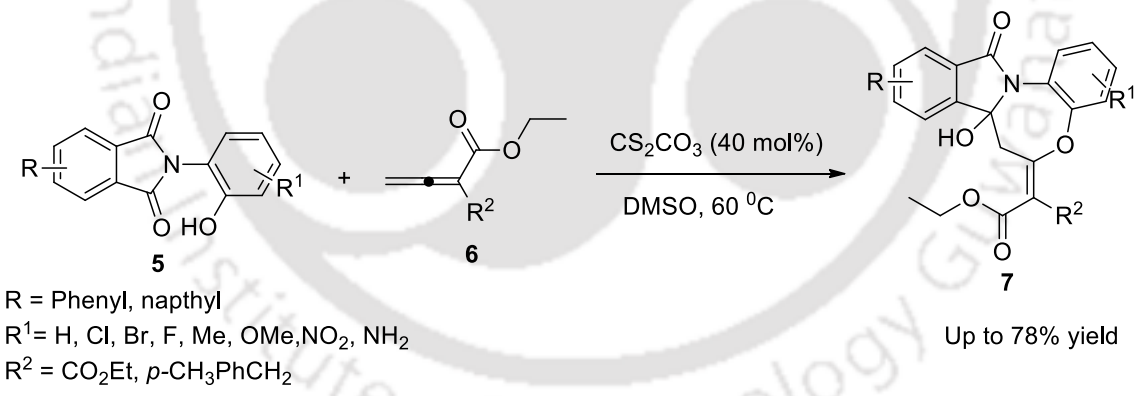


Figure 4.1.1. *Some bioactive molecules containing isoindolones*

4.2. An overview of relevant synthetic methods

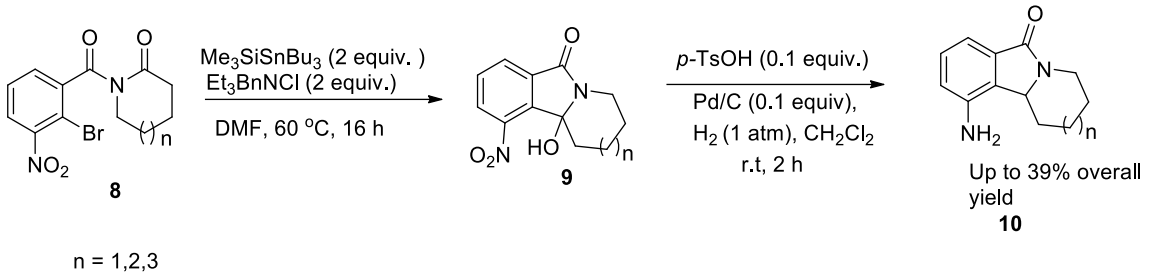
Over the years, several synthetic methods have been developed for the construction of isoindolones, such as synthesis of pyridoisoindolones either using 2-formylbenzoic acid and esters or from *β*-hydroxy lactones *via* acyl iminium ions;[5] from carboxybenzaldehyde,[6] allenoate,[7] aza-Nazarov cyclization,[8] aza-Prins cyclization,[9] vinyl sulfides,[10] and nitrophthalimide[1]. Beside these, formation of *γ*-lactam ring under Shibasaki's conditions,[4] *N*-acyliminium ion cyclization of trimethylsilylmethylallenes,[11] palladium catalyzed cross-coupling reaction,[12] formation of ketenimine intermediate,[13] synthesis of thiazino isoindolones[14] and formation of diazocinoisoindolone from isobenzofuranones and amine[15] are also reported. Some of the recent methods for the synthesis of isoindolone derivatives are summarised below.

Zhou and coworkers reported a domino *β*-addition and *γ*-aldol reaction of 2-(2-hydroxyphenyl)-isoindoline-1,3-dione **5** derivatives with allenoate **6** catalyzed by Cs_2CO_3. The reaction provides a channel for the combination of structural unity between benzooxazepine and isoindolone units which afford stereoselective functionalized benzooxazepino[5,4- *a*]isoindolone derivatives **7** up to 78% yield (*Scheme 4.2.1*).[7]



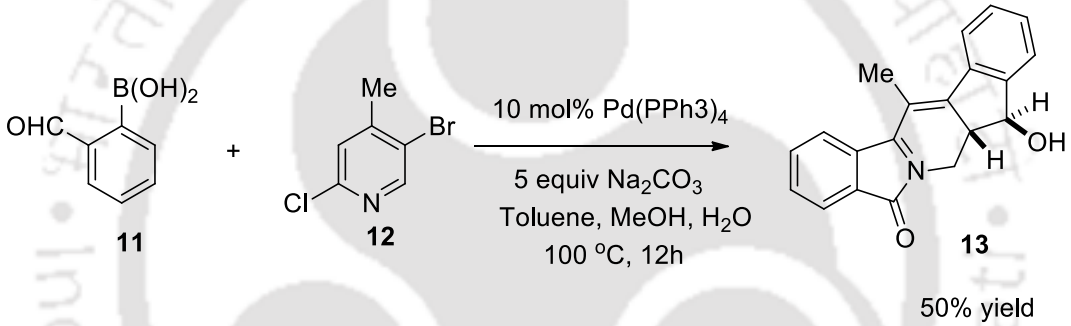
Scheme 4.2.1

Renard and group described a shorter and more efficient synthesis of tetrahydropyrido[2,1-*a*]isoindolone and higher analogues such as hexahydroazepino[2,1-*a*]isoindolone and hexahydroazocino[2,1-*a*]isoindolone **10**. The key step of this pathway is the formation of *γ*-lactam ring **9** under Shibasaki's conditions. i.e. cyclization of imide **8** using a stannyl aryl anion generated on aryl halide from $Me_3SiSnBu_3$ and halide ion, followed by one-pot, three-step procedure i.e. elimination of tertiary alcohol, reduction of the resulting alkene followed by reduction of the nitro group to form isoindolones **10**, which can be used for the preparation of bioactive valmerins generations (*Scheme 4.2.2*).[4]



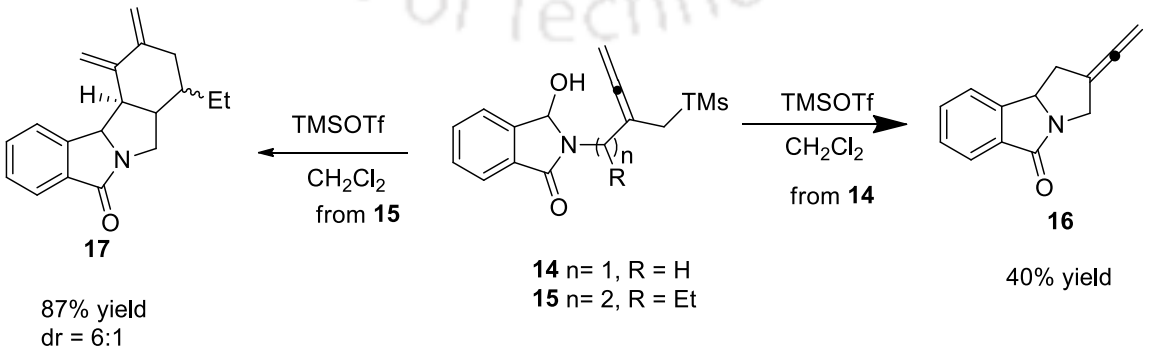
Scheme 4.2.2

Mamane and group reported the one-pot formation of pyrido[2,1-*a*]isoindolones in the presence of palladium catalyst. The pyridine **12** and 2-formylphenylboronic acid (**11**), undergo palladium catalyzed cross-coupling reaction, followed by two consecutive nucleophilic cyclizations to afford π-conjugated pentacyclic product, isoindolone **13** in 50% yield (*Scheme 4.2.3*).[12]



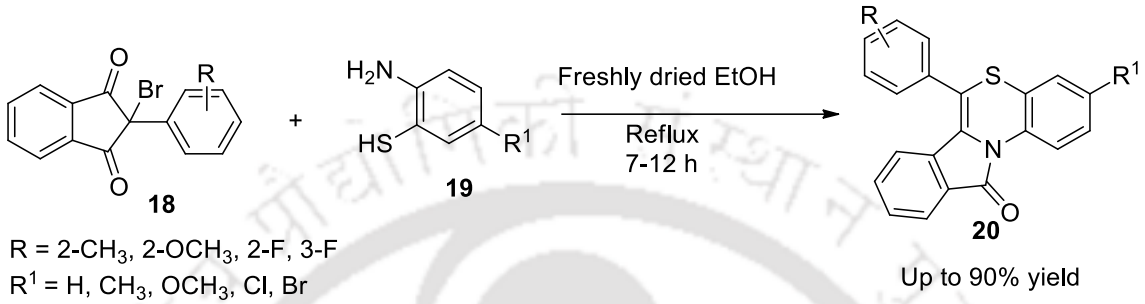
Scheme 4.2.3

Kim *et al*. have studied the *N*-acyliminum ion cyclizations using allenylmethylsilanes. In the presence of TMSOTf, allene **14** furnish five-membered exo-allene products **16** by direct substitution at the α-carbon of TMS group. 6-Endo cyclization of allene **15** however, provides six-membered exo-1,3-diene **17** (*Scheme 4.2.4*).[11]



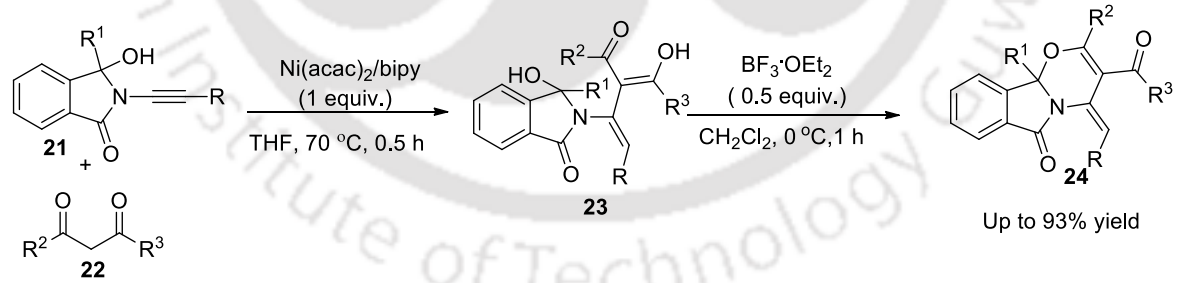
Scheme 4.2.4

Sindhu and coworkers reported a simple and efficient method for the synthesis of novel heterocyclic frameworks, *i.e.* 11*H*-benzo[5,6][1,4]thiazino[3,4-*a*]isoindol-11-ones **20**, *via* one-step reaction of substituted 2-aminobenzenethiols **19** and 2-bromo-(2/3-substitutedphenyl)-1*H* indene-1,3(2*H*)-diones **18**. The above methodology provides several advantages like short reaction time, high atom economy and easy workup. (*Scheme 4.2.5*).[14]



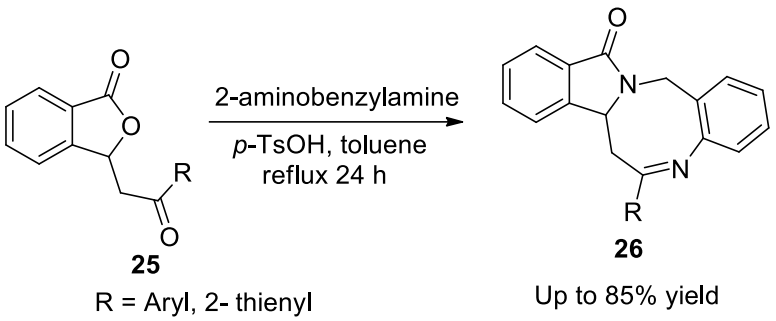
Scheme 4.2.5

Sueda and group described a methodology for the formation of tricyclic isoindolones **24**. In the presence of nickel-catalyst, 1,3-dicarbonyl compounds **22** undergo regio-selective addition to *α*-hydroxyynamides **21** *via* a tandem decyclization–addition–cyclization, where a ketenimine intermediate is formed to afford the α-hydroxy enamide **23**, which is then subjected to intramolecular dehydrative condensation in the presence of $BF_3{\cdot}OEt_2$, to provide the corresponding isoindolones in good yields (*Scheme 4.2.6*).[13]



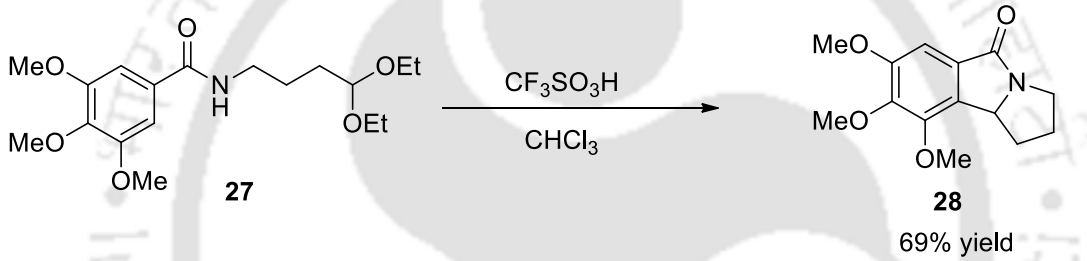
Scheme 4.2.6

Gerhard and coworkers had described an efficient method for the synthesis of benzo[6,7][1,5]diazocino[2,1- *a*]isoindol-12(14*H*)-one **26** ring system from 3-(2-oxo-2-phenylethyl) isobenzofuran1(3*H*)-ones **25** and 2-amino benzylamine catalysed by *p*-toluenesulfonic acid (*Scheme 4.2.7*).[15]



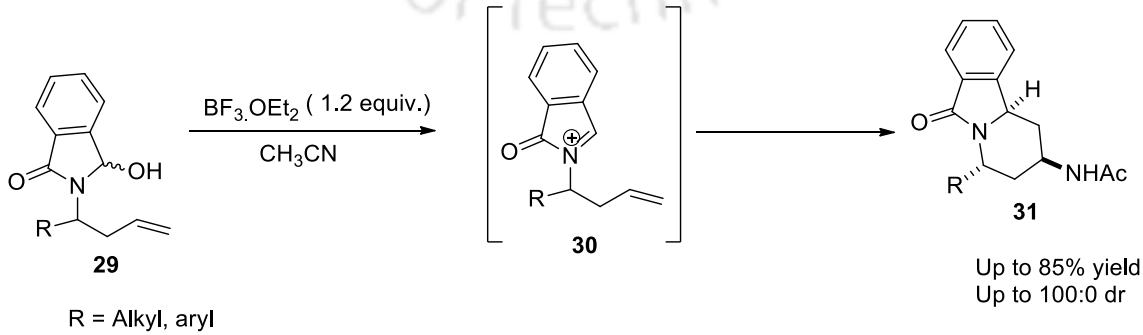
Scheme 4.2.7

Klumpp and group described a method for the synthesis of ring-fused isoindolone **28**. The tethered acetal **27** on treatment with excess of triflic acid, undergoes cyclization, through the formation of *N*-acyliminium ion, which then give isoindolinone by the aza-Nazarov reaction (*Scheme 4.2.8*).[8]



Scheme 4.2.8

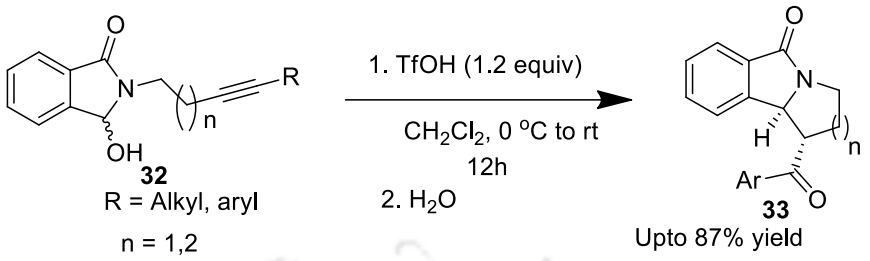
In 2014, our group had reported a simple protocol for the synthesis of 1,3,4,10*b*-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one **31** derivatives. In presence of $BF_3.OEt_2$, the *N*-homoallyl amido alcohols **29** form *N*-acyliminium ions **30**, which undergoes tandem endo-trig cyclization (aza-Prins) followed by an intermolecular Ritter reaction to form **31** with high diastereoselectivity (*Scheme 4.2.9*).[9a]



Scheme 4.2.9

Recently, our group also described a simple methodology for the synthesis of pyrroloisoindolone and pyridoisoindolone. Treatment of regioselectively reduced *N*-

homopropargyl imides **32** with triflic acid generates endocyclic *N*-acyliminium ion which undergoes aza-Prins cyclization to afford isoindolones **33** as single diastereomer (*Scheme 4.2.10*).[9b]

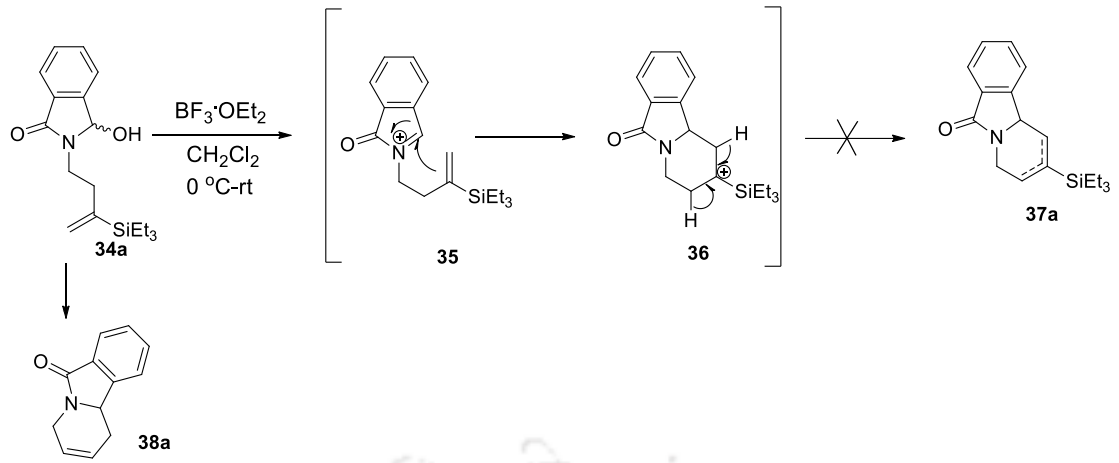


Scheme 4.2.10

4.3. Present strategy and objective

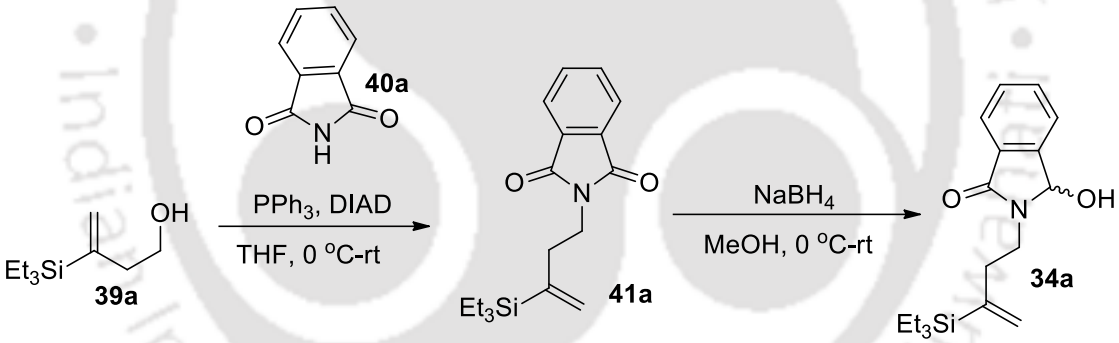
Vinylsilanes are considered as one of the most important building blocks in organic synthesis. There are various reports on the synthesis of nitrogen fused heterocycles using vinylsilanes as precursors,[16-18] and most notable among them is aza-silyl-Prins cyclization.[17] *N*-acylium ion cyclization has always been a popular strategy for synthesis of fused nitrogen ring systems.[8,9,11,16,17a] Overman and coworkers have reported the regio-controlled synthesis of indolizidinones and quinolizidinones *via N*-acylium ion-vinylsilane cyclizations.[16a,b] Dobbs and coworkers studied the applicability of acyliminium ion-vinylsilane cyclization towards the synthesis of *N*- fused heterocycles *via* aza-Prins reactions.[17a] One of the powerful method for the synthesis of nitrogen-containing heterocycles is iminium–ene reaction. The most important aspect of iminium-ene reaction is its ability to form carbon-carbon, carbon-heteoatom bonds in a single step and its streoselectivity.[18,19] As part of our research interest in the synthesis of fused nitrogen heterocycles,[9] herein we have reported a methodology for the synthesis of 1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one using vinylsilanes *via* iminium ene cyclization of *N*-acyliminium ion, mediated by borontrifluoride etherate in high yields with excellent regio- and diastereo-selectivity (*Scheme 4.3.1*).

We envisioned that aza silyl Prins cyclization of *N*-homoallyl amido alcohol **34a** would give intermediate carbocation **36**, which after subsequent elimination of α-proton will generate regioisomeric silylated isoindolones **37a** (*Scheme 4.3.1*). But in contrast isoindolone **38a** was obtained as a single regioisomer. It may be noted that the position of the double bond of the azabicyclic compounds (**38a-h**) in the present case is different from the products of Overmann[16a,b] and Dobbs[17a].



Scheme 4.3.1

.The *N*-homoallyl amido alcohol **34a** was prepared from the Mitsonobou reaction of vinylsilane homoallylic alcohol **39a** with pthalimide **40a**, followed by selective reduction with sodium borohydride (*Scheme 4.3.2*).The vinylsilane **39a** was prepared as per chapter 2, section 3.6.2.



Scheme 4.3.2

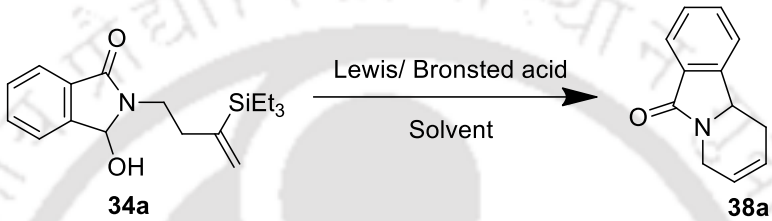
4.4. Results and discussion

4.4.1. Optimization studies

In an initial investigation, 3-hydroxy-2-(3-(triethylsilyl)but-3-enyl)isoindolin-1-one (**34a**) was treated with one equiv. of $BF_3{\cdot}OEt_2$ in dichloromethane, and the corresponding product 1,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (**38a**) was obtained with 65% yield in 12h (Table 4.4.1.1, entry 1). The reaction was examined with Brønsted acids like TfOH and TFA and product **38a** was obtained with 55% and 45% yields, respectively (Table 4.4.1.1, entries 2-3). Metal triflates such as $In(OTf)_3$, $Bi(OTf)_3$, $Sc(OTf)_3$ were also screened and the product was formed with 55%, 10% and 52% yields, respectively, in 24h (Table 4.4.1.1, entries 4-6). The reaction was also screened with metal salts like $FeCl_3$, and $InCl_3$ which gave **38a** with 50% and 45% yields, respectively (Table 4.4.1.1, entries 7-8). So,

from the above investigation on various reagents, $BF_3{\cdot}OEt_2$ found to deliver the product with highest yield. In order to increase the yield, we further performed the reaction at -40 ^oC with $BF_3{\cdot}OEt_2$, where an increment up to 72% yield was observed (Table 4.4.1.1, entry 9). To further improve the yield, the catalyst loading was increased from one equivalent to two equivalents which resulted in 86% yield (Table 4.4.1.1, entry 10). Other solvents like toluene and dichloroethane furnished the product with lower yield (Table 4.4.1.1, entries 11-12).

Table 4.4.1.1. Optimization of the reaction



34a **38a**

Entry	Reagent(equiv.)	Solvent	Temp/ ^0C	Time/h	Yield(%)[a]
1	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	0 to rt	12	65
2	TfOH (1)	CH_2Cl_2	0 to rt	12	55
3	TFA (1)	CH_2Cl_2	0 to rt	12	45
4	$In(OTf)_3$ (1)	CH_2Cl_2	0 to rt	24	55[b]
5	$Bi(OTf)_3$ (1)	CH_2Cl_2	0 to rt	24	10[b]
6	$Sc(OTf)_3$ (1)	CH_2Cl_2	0 to rt	24	52[b]
7	$FeCl_3$(1)	CH_2Cl_2	0 to rt	24	50[b]
8	$InCl_3$(1)	CH_2Cl_2	0 to rt	24	45[b]
9	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	-45	12	72
10	$BF_3{\cdot}OEt_2$ (2)	CH_2Cl_2	-45	12	86
11	$BF_3{\cdot}OEt_2$ (1)	DCE	0 to rt	12	52[b]
12	$BF_3{\cdot}OEt_2$ (1)	Toluene	0 to rt	24	55[b]

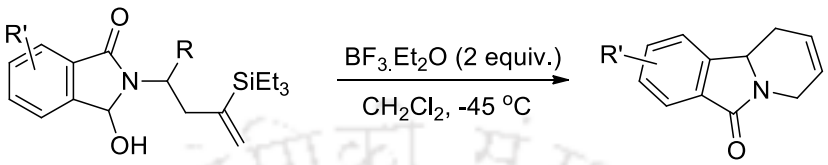
[a]Yields are isolated yield. [b]Starting material recovered

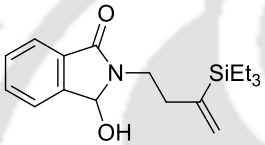
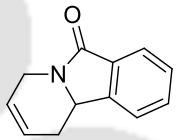
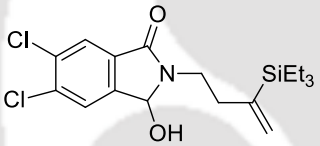
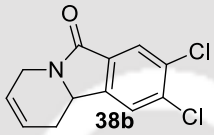
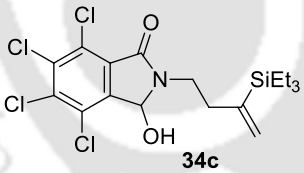
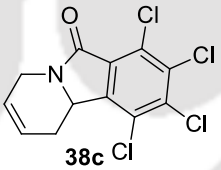
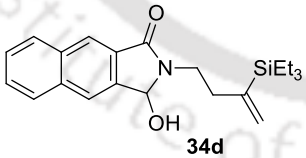
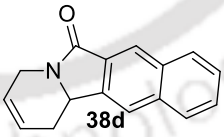
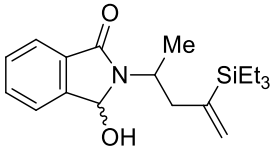
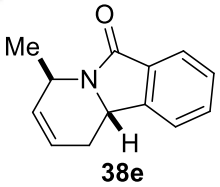
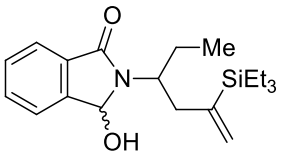
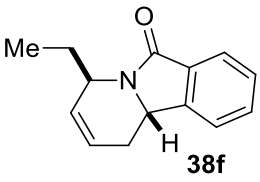
4.4.2. Substrate scope of the reaction

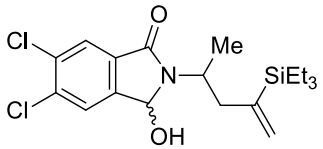
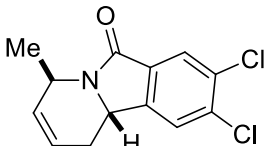
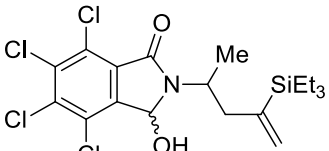
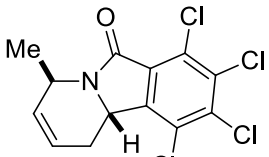
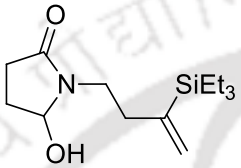
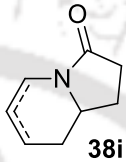
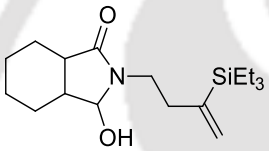
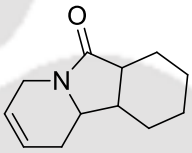
With this optimized reaction condition, we further examined the scope of the reaction with variety of substrates and results are outlined in Table 4.4.2.1. As seen from the Table 4.4.2.1, various substituted pthalimides containing primary *N*-homoallylamido alcohols yielded the product with very high yield (Table 4.4.2.1, entries1-3). However, naphthalene substituted pthalimide gave moderate yield (Table 4.4.1.1, entry 4). The scope of the reaction was further extended to alkyl substituted secondary *N*-reducedhomoallyl alcohols, and corresponding products were obtained with good to moderate yields (Table 4.4.2.1,

entries 5-8). However, on using succinimide substituted *N*-reducedhomoallyl alcohol instead of pthalimide, regioisomeric mixture of azabicyclic product with a ratio of 69:31 was obtained (Table 4.4.1.1, entry 9). The reaction of hexahydro pthalimide could give only decomposed product (Table 4.4.1.1, entry 10).

Table 4.4.2.1. Synthesis of isoindolones



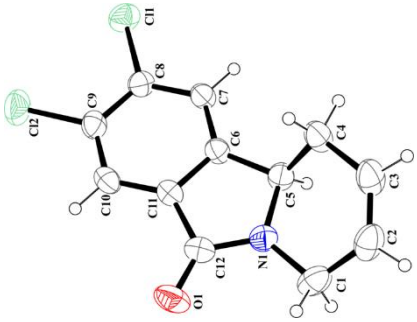
Entry	**34**	**38**	Yield(%)[a]
1	 **34a**	 **38a**	86
2	 **34b**	 **38b**	90
3	 **34c**	 **38c**	88
4	 **34d**	 **38d**	65
5	 **34e** 93:7[b]	 **38e**	77
6	 **34f** 92:8[b]	 **38f**	75

7	 **34g** 82:18[b]	 **38g**	78
8	 **34h** 98:2[b]	 **38h**	72
9	 **34i**	 **38i** 58: 42[c]	80
10	 **34j**	 **38j**	0[d]

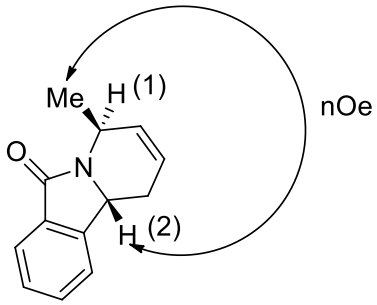
[a]Yield refers to isolated yield. [b]Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c]Regioisomeric ratio determined by ^{1}H NMR spectroscopy. [d]Decomposed product.

4.4.3 Stereochemistry of the compounds

The stereochemistry of the compounds were determined by X-ray crystallographic analysis of compound **38b**, and 2-D nuclear Overhauser effect (nOe) experiment of compound **38e**. There was a correlation between bridgehead proton H(2) and methyl protons in **38e**, which clearly indicates that they are *cis* to each other.



38b

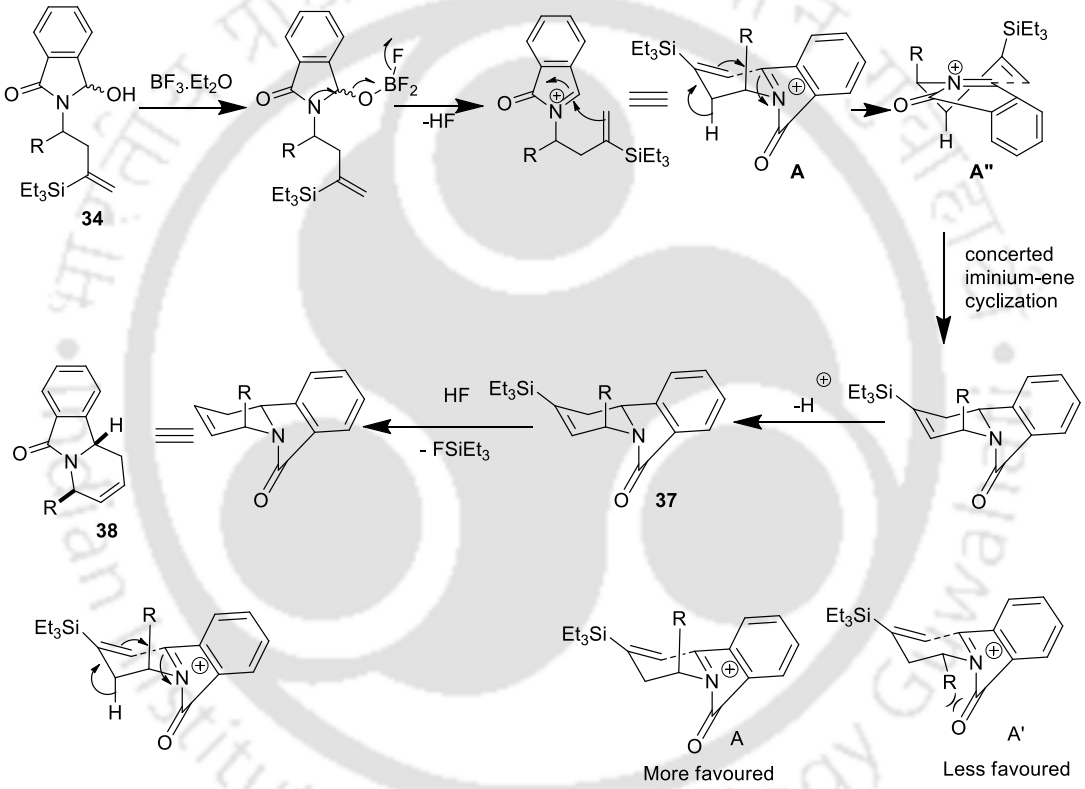


38e

Figure 4.4.3.1. *ORTEP diagram of* **38b** and nOe of **38e**

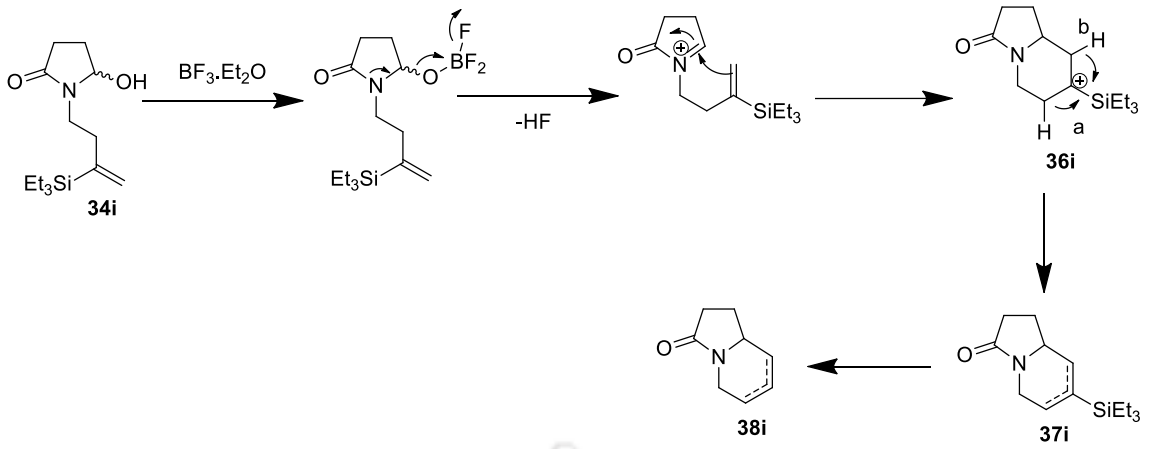
4.4.4. Plausible mechanism for the synthesis of isoindolones

In presence of Lewis acid, *N*- homoallyl amido alcohol **34** generates *N*-acyliminium ion to form six membered transition state **A**, which undergoes concerted iminium-ene cyclization to give silylated isoindolones **37**. The insitu generated HF removes the silyl group to give final compound **38**. It should be noted that transition state **A**, where R substitution is at axial position is favored over transition state **A′**, where R group is at equatorial position due to less steric hindrance experienced between R and the carbonyl group of the *N*-acyliminium ion in case of **A** compared to **A′**, which leads to the high distreoselectivity of the reaction (*Scheme 4.4.4.1*).



Scheme 4.4.4.1.*Plausible mechanism of the reaction*

The formation of regioisomeric mixture in case of **38i** can be explained by considering the stepwise iminium-ene cyclization. The carbocation **36i** formed after cyclization can eliminate protons *via* pathways ‘a’ and ‘b’ to give silylated intermediate **37i**, which after desilylation by HF acid gives regioisomeric compounds **38i** (*Scheme 4.4.4.2*).



Scheme 4.4.4.2. *Stepwise mechanism for the formation of regioisomeric mixture*

4.5. Conclusion:

We have reported a simple methodology for the synthesis of isoindolones from *N*-homoallylic amido alcohols in presence of Lewis acid in good yields. The reaction proceeds *via* concerted iminium-ene reaction to provide single regioisomeric products as well as single diastereomer. It also proceeds *via* step wise manner to give diastereomeric mixture in case of succinimide derivative.

4.6. Experimental section

4.6.1. Instrumentation and characterization

As described in chapter 2 section 2.6.1.

4.6.2. General procedure for preparation of starting material (34a-j).

$NaBH_4$ (111-148 mg, 3-4 mmol) was added to a solution of homoallyl imides **41** (1 mmol) in methanol at 0 ^oC. The reaction mixture was brought to room temperature and monitored by TLC for full conversion. After completion of starting material the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2C1_2 (3 x 5mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography to give reduced homoallylalcohols **34**.

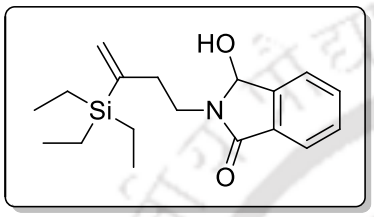
4.6.3. General procedure for preparation of products (38a-i).

To a solution of vinylsilane **34** (1 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}OEt_2$ (282 mg, 2 mmol) at -45 ^oC under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for around 12 h. After completion of the reaction, as determined by TLC, reaction mixture was brought to room temperature, diluted with CH_2Cl_2 (10 mL), washed

with saturated sodium bicarbonate and brine solutions, and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was purified by column chromatography using ethyl acetate and hexane as eluents.

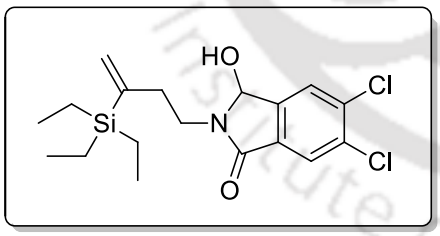
4.7. Spectral data

3-Hydroxy-2-(3-(triethylsilyl)but-3-enyl)isoindolin-1-one (34a):



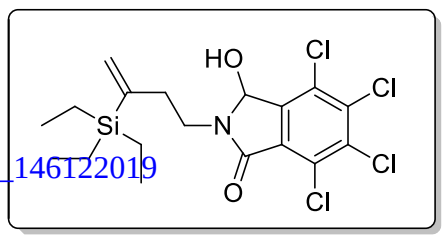
Yellowish gum; R_f (hexane/EtOAc 4:1) 0.46; yield 176 mg, 95%;^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, *J* = 7.6 Hz, 6 H), 0.91 (t, *J* = 7.6 Hz, 9 H), 2.24-2.38 (m, 2 H), 3.21-3.25 (m, 1 H), 3.37-3.40 (m, 1 H), 4.07 (br, 1 H), 5.36 (d, *J* = 2.4 Hz, 1 H), 5.65-5.66 (d, *J* = 1.2 Hz, 1 H), 5.72 (d, *J* = 10.8 Hz, 1 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 7.48-7.56 (m, 2 H), 7.60 (d, *J* = 7.6 Hz, 1 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.0, 7.6, 34.2, 38.8, 81.9, 123.3, 123.5, 127.4, 129.8, 131.6, 132.3, 144.3, 145.9, 167.6; IR (KBr, neat) 3329, 2952, 2873, 1678, 1448, 1421, 1111, 1060, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{28}NO_2Si$ $(M+H)^+$: *m/z* 318.1884, found 318.1889.

5,6-Dichloro-3-hydroxy-2-(3-(triethylsilyl)but-3-en-1-yl)isoindolin-1-one (34b):



Colourless solid; mp 128-130 ºC; R_f (hexane/EtOAc 9:1) 0.54; yield 327 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (q, *J* = 7.6 Hz, 6 H), 0.92 (t, *J* = 7.6 Hz, 9 H), 2.29-2.42 (m, 2 H), 3.31-3.38 (m, 1 H), 3.56-3.63 (m, 1 H), 3.61 (br, 1 H), 5.39 (d, *J* = 2.4 Hz, 1 H), 5.67-5.68 (m, 1 H), 5.71(d, *J* = 11.2 Hz, 1 H), 7.52(s, 1H), 7.7 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.0, 7.6, 34.1, 39.3, 81.2, 125.1, 125.9, 127.7, 131.4, 135.0, 137.2, 143.3, 145.9, 165.5; IR (KBr, neat) 3249, 2954, 2878, 1682, 1422, 1070, 1098, 1011, 724, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{26}Cl_2NO_2Si$ $(M + H)^+$: *m/z* 386.1104, found 386.1123.

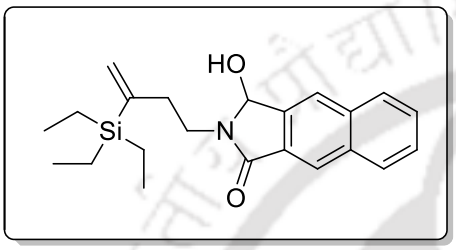
4,5,6,7-Tetrachloro-3-hydroxy-2-(3-(triethylsilyl)but-3-en-1-yl)isoindolin-1-on (21c):



Colourless solid; mp 125-127 ºC; R_f (hexane/EtOAc 9:1) 0.60; yield 339 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (q, *J* = 7.6 Hz, 6 H), 0.92 (t, *J* = 7.6 Hz,

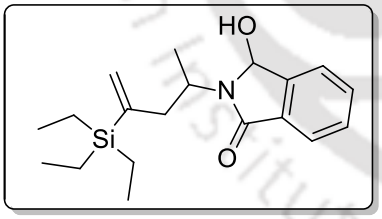
9 H), 2.32-2.44 (m, 2 H), 3.38-3.42 (m, 1 H), 3.76-3.78 (m, 1 H), 4.37 (d, *J* = 11.6 Hz, 1 H), 5.40 (d, *J* = 2.0 Hz, 1 H), 5.70-5.77 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.0, 7.6, 33.9, 39.3, 80.1, 127.6, 127.9, 128.7, 129.6, 136.0, 137.6, 141.6, 145.5, 163.6; IR (KBr, neat) 3361, 2953, 2878, 1696 1423, 1376, 1228, 1078, 1012, 732 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{24}Cl_4NO_2Si$ $(M + H)^+$: *m/z* 454.0319, found 454.0320.

3-Hydroxy-2-(3-(triethylsilyl)but-3-en-1-yl)-2,3-dihydro-1H-benzo[f]isoindol-1-one (34d):



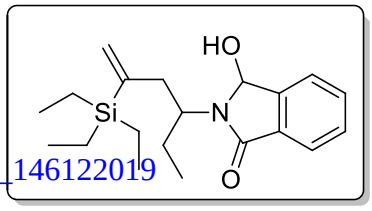
Yellowish gum; R_f (hexane/EtOAc 4:1) 0.60; yield 201 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.6 Hz, 6 H), 0.90 (t, *J* = 7.6 Hz, 9 H), 2.28-2.41 (m, 2 H), 3.30-3.35 (m, 1 H), 3.50-3.54 (m, 1 H), 4.42 (d, *J* = 9.2 Hz, 1 H), 5.39 (d, *J* = 2.4 Hz, 1 H), 5.57-5.68 (m, 1 H), 5.84 (d, *J* = 11.6Hz, 1 H), 7.38 (t, 7.2 Hz, 1H), 7.50-7.55 (m, 2 H), 7.68 (s, 1H), 7.86 (d, *J* = 8 Hz, 1 H), 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.9, 7.6, 33.9, 39.0, 81.9, 123.0, 123.5, 127.0, 127.3, 128.0, 128.6, 128.9, 129.6, 133.6, 135.4, 139.3, 145.8, 167.5; IR (KBr, neat) 3330, 2952, 2878, 1696, 1423, 1376, 1228, 1078, 1022, 731 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{30}NO_2Si$ $(M + H)^+$: *m/z* 368.2040, found 368.2062.

3-Hydroxy-2-(4-(triethylsilyl)pent-4-en-2-yl)isoindolin-1-one (34e):



Colourless gum; R_f (hexane/EtOAc 4:1) 0.50; yield 215 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (q, *J* = 7.6 Hz, 6 H), 0.92 (t, *J* = 7.6 Hz, 9 H), 1.39 (d, *J* = 7.2 Hz, 3 H), 2.43-2.48 (m, 1 H), 2.76-2.81 (m, 1 H), 3.00-3.16 (m, 1 H), 4.29-4.34 (m, 1 H), 5.37 (d, *J* = 2.8 Hz, 1 H), 5.71 (d, *J* = 1.2 Hz, 1 H), 5.84 (d, *J* = 11.2 Hz, 1 H), 7.43-7.46 (m, 1 H), 7.49-7.52 (m, 2 H), 7.67(d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.1, 7.6, 18.4, 42.3, 47.4, 82.0, 123.2, 123.5, 128.2, 130.1, 132.3, 132.4,144.0, 146.4, 167.2; IR (KBr, neat) 3338, 2958, 2873, 1680, 1448, 1421, 1111, 1060, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{30}Cl_2NO_2Si$ $(M + H)^+$: *m/z* 332.2040, found 332.2042.

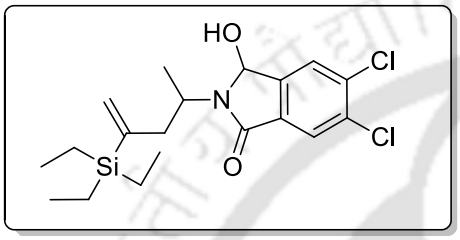
3-Hydroxy-2-(5-(triethylsilyl)hex-5-en-3-yl)isoindolin-1-one (34f):



Colourless solid; mp 85-87 ^{o}C; R_f (hexane/EtOAc 4:1) 0.53; yield 207 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (q, *J* = 7.6 Hz, 6 H), 0.84 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.6

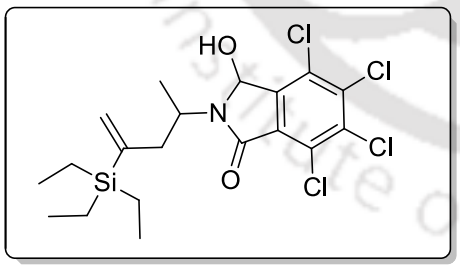
Hz, 9 H), 1.75-1.85 (m, 1 H), 1.87-1.93 (m, 1 H), 2.50 (q, *J* = 7.2 Hz, 1 H), 2.77 (q, *J* = 7.6 Hz, 1 H), 2.89-3.02 (br, 1 H), 4.05-4.13 (m, 1 H), 5.35 (d, *J* = 2.8 Hz, 1 H), 5.71 (d, *J* = 1.2 Hz, 1 H), 5.76 (s, *J* = 1 H), 746-7.49 (m, 1 H), 7.53-7.54 (m, 2 H), 7.73 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.1, 7.6, 11.6, 25.2, 40.5, 53.7, 82.2, 123.2, 123.5, 128.1, 130.0, 132.2, 144.1, 146.5, 167.8; IR (KBr, neat) 3348, 2960, 2873, 1680, 1448, 1421, 1111, 1060, 745cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{32}NO_2Si$ $(M + H)^+$: *m/z* 346.2202, found 346.2215.

5,6-Dichloro-3-hydroxy-2-(4-(triethylsilyl)pent-4-en-2-yl)isoindolin-1-one (34g):



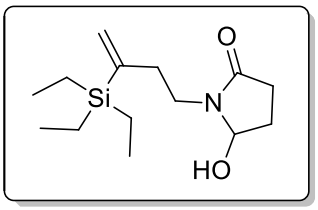
Colourless solid; mp 123-125 ^{o}C; R_f (hexane/EtOAc, 9:1) 0.62; yield 247 mg, 62%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.65 (q, *J* = 7.2 Hz, 6 H), 0.93 (t, *J* = 7.8 Hz, 9 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 2.43 (q, *J* = 8.4 Hz, 1 H), 2.75 (q, *J* = 6.6 Hz, 1 H), 3.80-4.10 (m, 1 H), 4.20-4.23 (m, 1 H), 5.38 (s,1 H), 5.76 (s,1 H), 5.80 (s,1 H), 7.62 (d, *J* = 3Hz, 1 H), 7.68 (d, *J* = 8.4Hz, 1 H); ^{13}C NMR (150MHz, $CDCl_3$) δ 3.1, 7.6, 18.3, 41.8, 48.3, 81.6, 125.1, 125.6, 128.4, 132.0, 134.7, 136.7, 143.3, 146.1, 165.3; IR (KBr, neat) 3269, 2958, 2880, 1690, 1450, 1070, 1098, 1011, 730, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{28}Cl_2NO_2Si$ $(M + H)^+$: *m/z* 400.1255, found 400.1269.

4,5,6,7-Tetrachloro-3-hydroxy-2-(4-(triethylsilyl)pent-4-en-2-yl)isoindolin-1-one (34h):



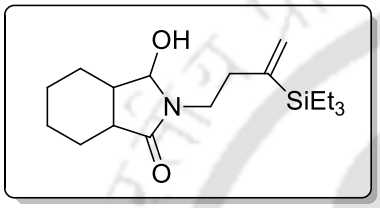
Colourless solid; mp 120-122 ^{o}C; R_f (hexane/EtOAc 9:1) 0.68; yield 271 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (q, *J* = 7.6 Hz, 6 H), 0.92 (t, *J* = 7.6 Hz, 9 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 2.41-2.47 (m, 1 H), 2.73-2.78 (m, 1 H), 3.24-3.35 (m, 1 H), 4.24-4.29 (m, 1 H), 5.33 (d, *J* = 2.4 Hz, 1 H), 5.68 (s,1 H), 5.85(d, *J* = 9.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.1, 7.6, 18.1, 41.8, 48.6, 80.1, 128.4, 128.5, 128.6, 129.5, 136.1, 137.0, 141.4,146.1, 162.8; IR (KBr, neat) 3365, 2957, 2878, 1696, 1461, 1376, 1238, 1098, 1011, 734 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{26}Cl_4NO_2Si$ $(M + H)^+$: *m/z* 468.0476, found 468.0487.

5-Hydroxy-1-(3-(triethylsilyl)but-3-enyl)pyrrolidin-2-one (34i):



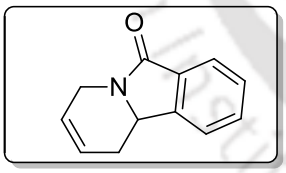
Colourless liquid; R_f (hexane/EtOAc 7:3) 0.30; yield 121 mg, 45%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.61 (q, *J* = 7.8 Hz, 6 H), 0.91 (t, *J* = 7.8 Hz, 9 H), 1.87-1.92 (m, 1 H), 2.26-2.33 (m, 4 H), 2.50-2.56 (m, 1 H), 3.12-3.23 (m,1 H), 3.53-3.58 (m, 1 H), 5.19 (d, *J* = 5.4 Hz,1 H), 5.37 (s,1 H), 5.69 (s,1 H); ^{13}C NMR (150MHz, $CDCl_3$) δ 2.9, 7.5, 28.5, 29.1, 33.5, 39.7, 83.5, 127.2, 146.1, 175.1; IR (KBr, neat) 3407, 2953, 2877, 1668, 1460, 1423, 1283, 1161, 1071, 1009, 928, 733 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{28}NO_2Si$ $(M + H)^+$: *m/z* 270.1884, found 270.1897.

3-Hydroxy-2-(3-(triethylsilyl)but-3-en-1-yl)octahydro-1*H*-isoindol-1-one (34j):



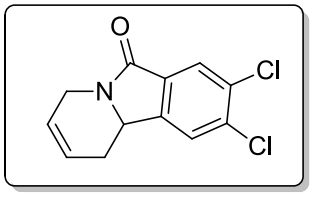
Colourless liquid; R_f (hexane/EtOAc 3:1) 0.56; yield 145 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8 Hz, 6 H), 0.91 (t, *J* = 8 Hz, 9 H), 1.25-1.35 (m, 4 H), 1.39-1.46 (m, 1 H), 1.63-1.66 (m, 2 H), 1.89-1.93 (m,1 H), 2.23-2.37 (m, 4 H), 3.06-3.25 (m, 2 H), 3.48-3.55 (m, 1 H), 5.14 (dd, *J* = 7.2, 4.8 Hz,1 H), 5.36 (d, *J* = 2.4 Hz,1 H), 5.36 (d, *J* = 1.2 Hz,1 H); ^{13}C NMR (400MHz, $CDCl_3$) δ 3.0, 7.6, 22.2, 23.3, 23.5, 24.3, 33.9, 37.5, 39.5, 41.2, 84.5, 127.3, 146.3, 175; IR (KBr, neat) 3335, 2953, 2883, 1688, 1458, 1113, 1060, 822, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{34}NO_2Si$ $(M + H)^+$: *m/z* 324.2353, found 324.2331.

1,10*b*-Dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38a):



Colourless gum; R_f (hexane/EtOAc, 7:3) 0.53; yield 47 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95-2.03 (m, 1 H), 2.72-2.78 (m, 1 H), 3.81-3.87 (m, 1 H), 4.36 (dd, *J* = 10.8 and 4.3Hz, 1 H), 4.60-4.65 (m, 1 H), 5.85-5.93 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.52-7.56 (m, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 40.0, 54.9, 122.0, 123.1, 123.9, 124.1, 128.4, 131.5, 132.7, 146.2, 167.2; IR (KBr, neat) 2966, 2924, 1671, 1645, 1418, 1256, 1087, 763, 721cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{12}NO$ $(M + H)^+$: *m/z* 186.0913, found 186.0932

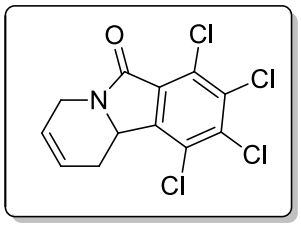
.8,9-Dichloro-1,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38b):



White solid; mp 195-197 ^oC; R_f (hexane/EtOAc 4:1) 0.43; yield 56 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97-2.05 (m, 1 H), 2.70-2.77 (m, 1 H), 3.82-3.79 (m, 1 H), 4.44 (dd, *J* = 10.8 and 4.8Hz, 1 H), 4.59-4.65 (m, 1 H), 5.87-5.93 (m, 2 H), 7.57 (s, 1 H), 7.95 (s, 1 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0,

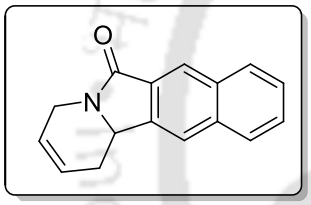
40.1, 54.4, 122.8, 123.9, 124.4, 125.8, 132.6, 133.3, 136.0, 145.3, 165.0; IR (KBr, neat) 2921, 2849, 2329, 1689, 1591, 1428, 1023, 746, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{10}Cl_2NO$ $(M + H)^+$: *m/z* 254.0134, found 254.0154

7,8,9,10-Tetrachloro-1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38c):



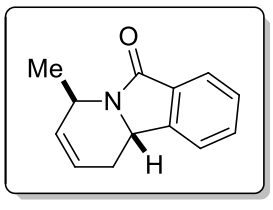
White solid; mp 182-184 ^oC; R_f (hexane/EtOAc 4:1) 0.50; yield 62 mg, 88%;^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91-1.99 (m, 1 H), 3.10-3.19 (m, 1 H), 3.80-3.86 (m, 1 H), 4.50 (dd, *J* = 10.8 and 4.8Hz, 1 H), 4.65-4.70 (m, 1 H), 5.85-5.93 (m, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 40.2, 54.1, 122.8, 123.6, 127.7, 129.4, 130.2, 134.6, 136.2, 144.3, 162.9; IR (KBr, neat) 2970, 2925, 2375, 1642, 1417, 1382, 1056, 1032, 756, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_8Cl_4NO$ $(M + H)^+$: *m/z* 321.9355, found 321.9354

1,12*b*-Dihydrobenzo[*f*]pyrido[2,1-*a*]isoindol-6(4*H*)-one (38d):



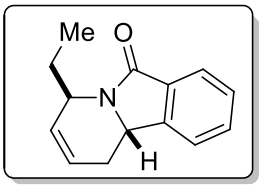
Colourless gum; R_f (hexane/EtOAc, 3:7) 0.44; yield 41 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04-2.12 (m, 1 H), 2.82-2.89 (m, 1 H), 3.88-3.94 (m, 1 H), 4.63 (dd, *J* = 10.8 and 4.8Hz, 1 H), 4.67-4.73 (m, 1 H), 5.89-5.99 (m, 2 H), 7.53-7.61 (m, 2 H), 7.87 (s, 1 H), 7.92 (d, *J* = 8 Hz,1 H), 8.00-8.02 (m, 1H), 8.40 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 40.2, 54.9, 121.0, 123.4, 124.1, 126.6, 127.8, 128.3, 129.9, 130.6, 133.3, 135.2, 141.3, 167.0; IR (KBr, neat) 2966, 2924, 2855, 1670, 1655, 1418, 1256, 1098, 763, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{14}NO$ $(M + H)^+$: *m/z* 236.1064, found 236.1072.

4-Methyl-1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38e):



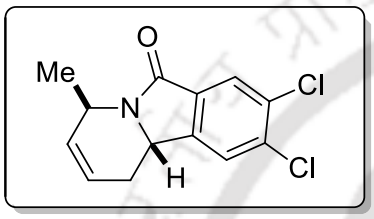
Colourless gum; R_f (hexane/EtOAc 3:7) 0.57; yield 46 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 7.2 Hz, 3 H), 1.89-1.97 (m, 1 H), 2.67-2.74 (m, 1 H), 4.47 (dd, *J* = 10.8 and 4.8Hz, 1 H), 4.77-4.79 (m, 1 H), 5.78-5.87 (m, 2 H), 7.43-7.47 (m, 2 H), 7.50-7.54 (m, 1 H), 7.50-7.54 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 30.2, 45.7, 52.5, 122.2, 122.6, 123.9, 128.4, 130.0, 131.4, 133.0, 146.3, 166.8; IR (KBr, neat) 2966, 2924, 1671, 1645, 1418, 1256, 763, 721 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}NO$ $(M + H)^+$: *m/z* 200.1070, found 200.1088.

4-Ethyl-1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38f):



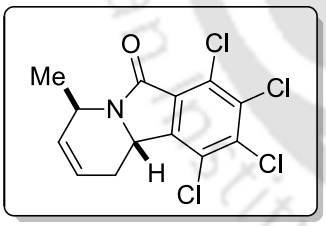
Colourless gum; R_f (hexane/EtOAc 7:3) 0.60; yield 46 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.6 Hz, 3 H), 1.65-1.72(m, 1 H), 1.76-1.85 (m, 1 H), 1.87-1.96 (m, 1H), 2.70-2.74 (m, 1 H), 4.50 (dd, *J* = 10.8 and 5.2 Hz, 1 H), 4.65-4.69 (m, 1 H), 5.84-5.91 (m, 2 H), 7.44-7.49 (m, 2 H), 7.52-7.54 (m, 1H), 7.87-7.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 30.0, 30.5, 50.9, 53.3, 122.1, 123.1, 124.0, 128.4, 128.6, 131.4, 132.9, 146.5, 167.2; IR (KBr, neat) 2966, 2928, 2875, 1679, 1467, 1417, 1237, 1101, 763, 715 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO$ $(M + H)^+$: *m/z* 214.1226, found 214. 1249

8,9-Dichloro-4-methyl-1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38g):



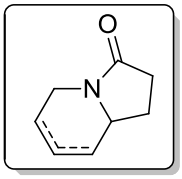
White solid; mp 195-197 °C; R_f (hexane/EtOAc 4:1) 0.50; yield 52 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.8 Hz, 3 H), 1.91-1.99 (m, 1 H), 2.65-2.72 (m, 1 H), 4.45 (dd, *J* = 11.2 and 4.8Hz, 1 H), 4.74-4.76 (m, 1 H), 5.80-5.88 (m, 2 H), 7.56 (s, 1 H), 7.94 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 30.0, 46.0, 52.0, 122.2, 124.5, 125.8, 130.2, 133.0, 133.3, 136.0, 145.3, 164.6; IR (KBr, neat) 2972, 2926, 1687, 1649, 1419, 1213, 1104, 960, 722, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{12}Cl_2NO$ $(M + H)^+$: *m/z* 268.0292, found 268.0297.

7,8,9,10-Tetrachloro-4-methyl-1,10*b*-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one (38h):



White solid; mp 180-182 °C; R_f (hexane/EtOAc 4:1) 0.53; yield 51 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.8 Hz, 3 H), 1.86-1.94 (m, 1 H), 3.08-3.15 (m, 1 H), 4.52 (dd, *J* = 10.8 and 4.4Hz, 1 H), 4.81-4.83 (m, 1 H), 5.80-5.87 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 28.5, 46.1, 51.8, 122.2, 127.7, 129.7, 130.2, 134.6, 136.2, 144.3, 162.4; IR (KBr, neat) 2980, 2957, 2898, 1641, 1417, 1338, 1032, 760, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{10}Cl_4NO$ $(M + H)^+$: *m/z* 335.9511, found 335.9517.

8,8a-Dihydroindolizin-3(1*H*,2*H*,5*H*)-one (38i, regioisomeric mixture, 58:42):

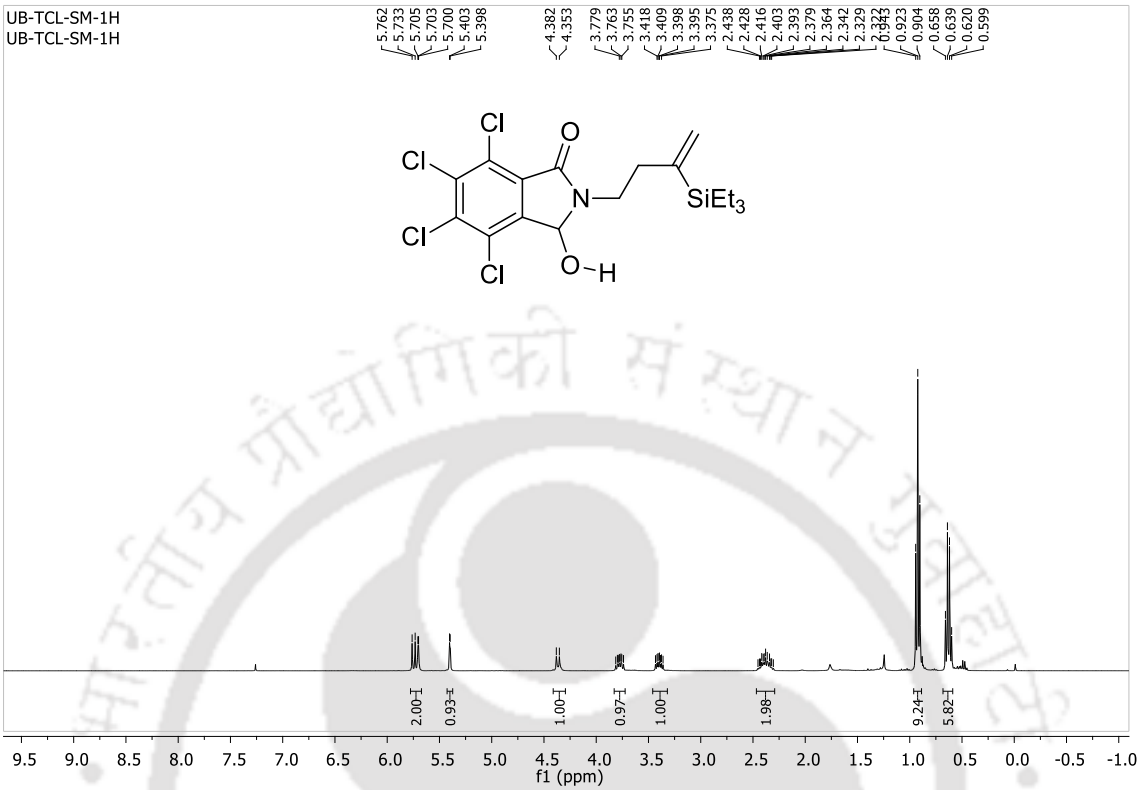


Colourless gum; R_f (hexane/EtOAc 1:1) 0.44; yield 41 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-1.63 (m, 1 H, minor), 1.64-1.73 (m, 1 H, major), 1.99-2.09 (m, 2 H, major), 2.21-2.27 (m, 1 H), 2.29-2.31 (m, 1 H, major), 2.31-2.36 (m, 1 H), 2.38 (t, 2 H, major), 2.46-2.52 (m, 1 H, minor), 2.85 (dt, *J* = 12 and 4.8Hz, 1 H, minor), 3.55 (d, *J* = 18 Hz, 1 H, major), 3.61-3.65 (m, 1 H, major), 4.14-4.29 (m, 2 H, major), 5.67-5.79 (m, 1 H), 5.79-5.83 (m, 1 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.7, 26.4, 30.1, 31.8, 32.6, 36.4, 40.5, 53.2,

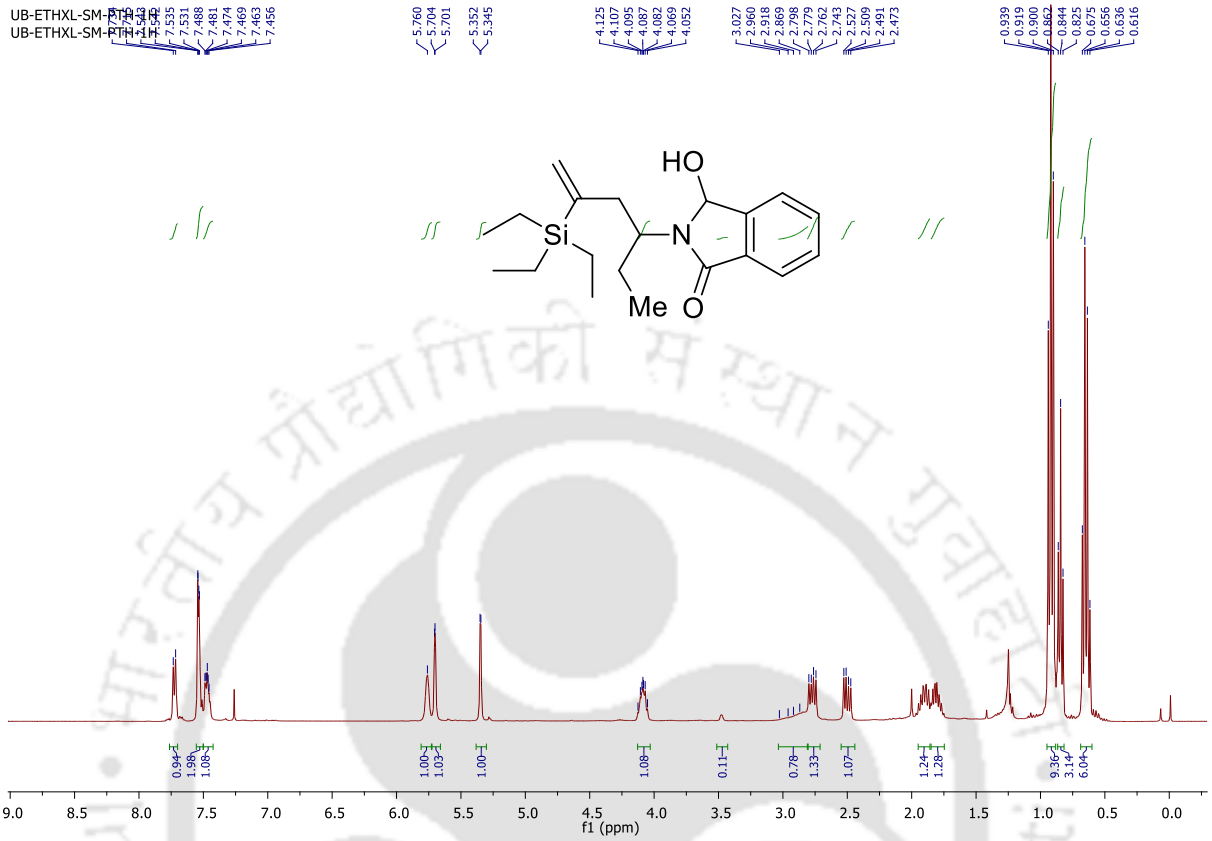
55.1, 123.6, 124.4, 125.2, 128.4, 173.3, 174.5; IR (KBr, neat) 2924, 2849, 1667, 1641, 1464, 1267, 1072, 749, 670 cm^{-1}; HRMS (ESI) calcd. for $C_8H_{12}NO$ $(M + H)^+$: *m/z* 138.0913, found 138.0933.

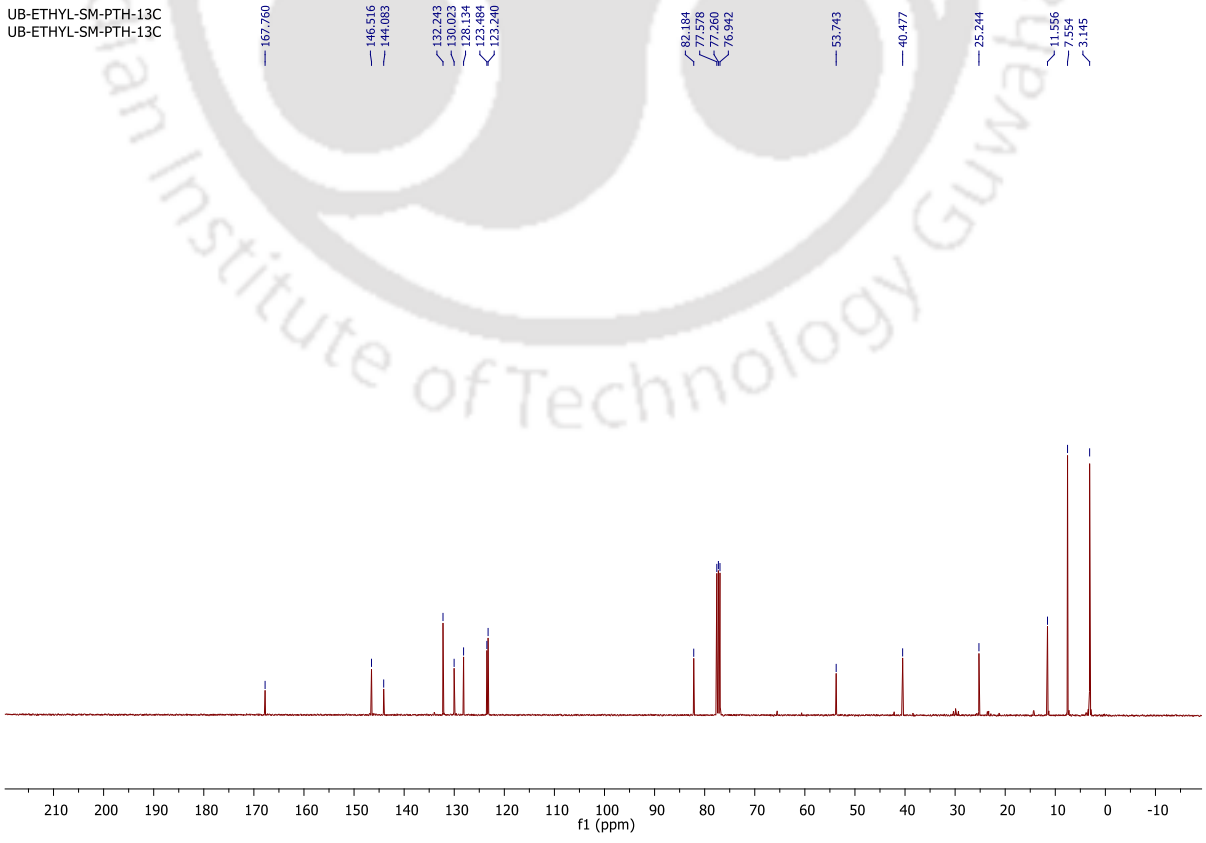
4.8. Selected spectra

^{1}H and ^{13}C Spectra of compound **34c**

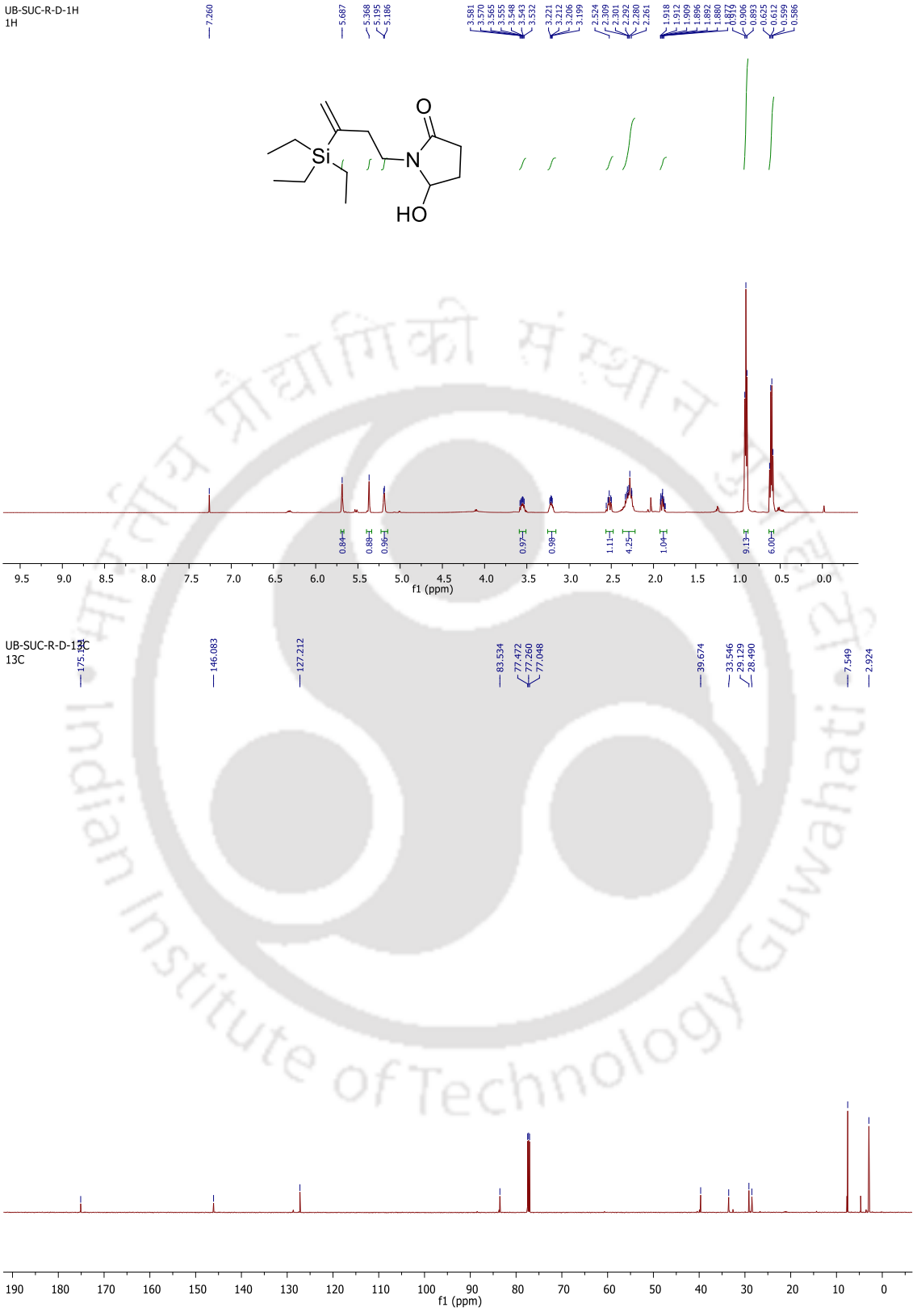


^{1}H and ^{13}C Spectra of compound **34f**

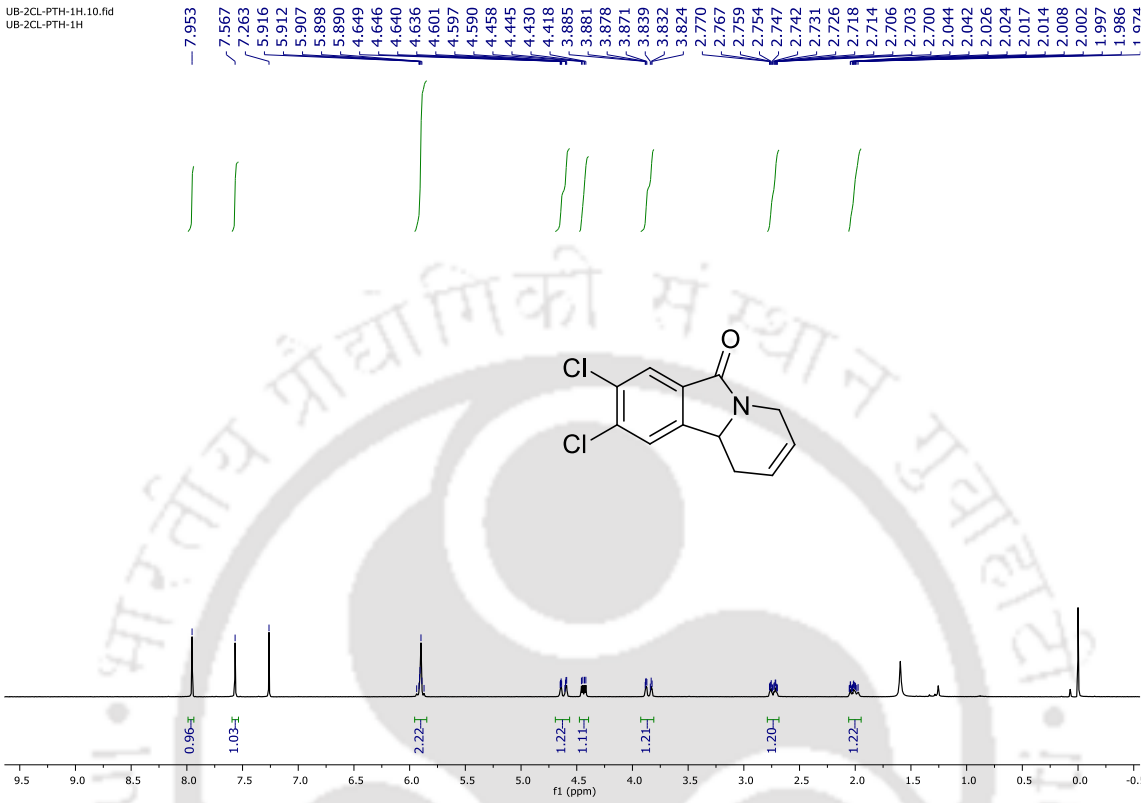


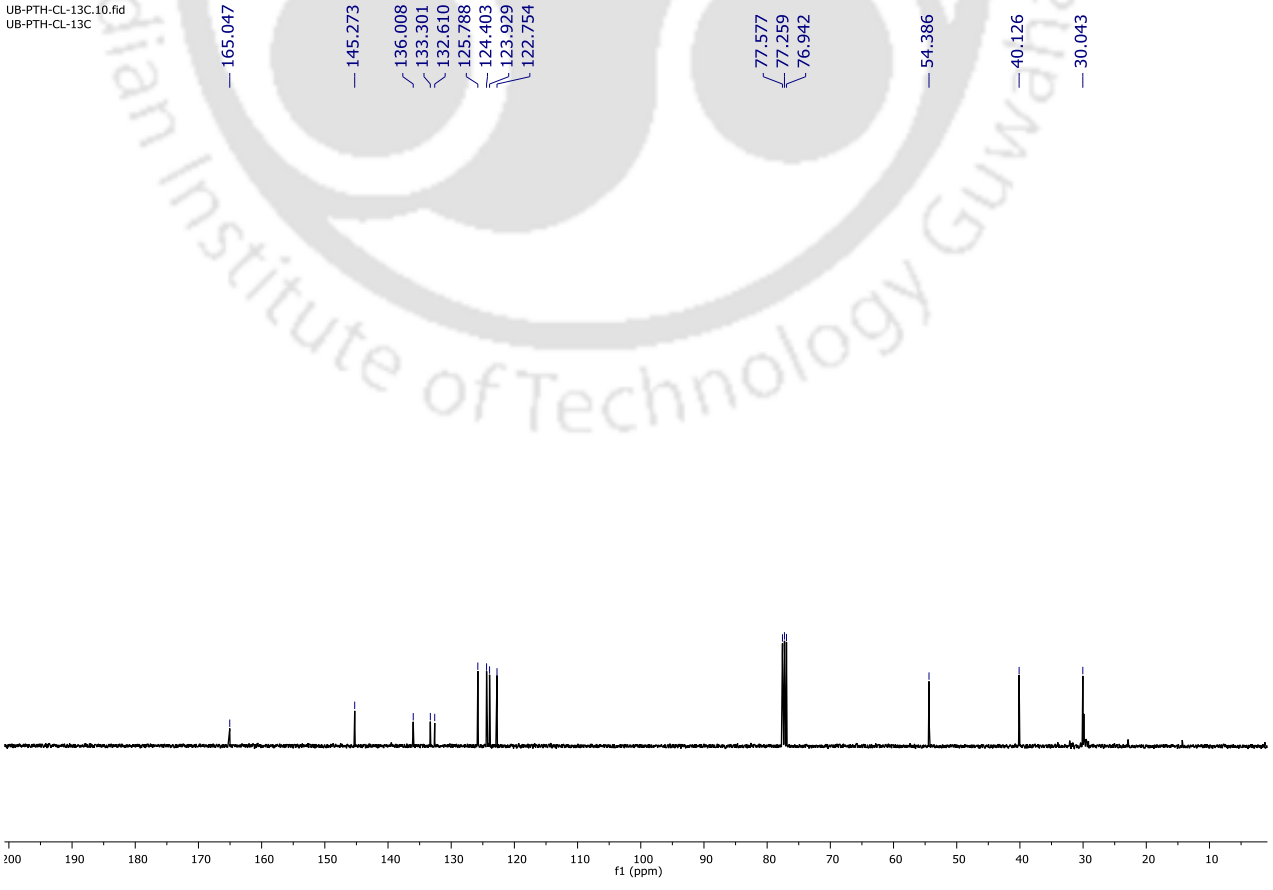


^{1}H and ^{13}C Spectra of compound **34i**

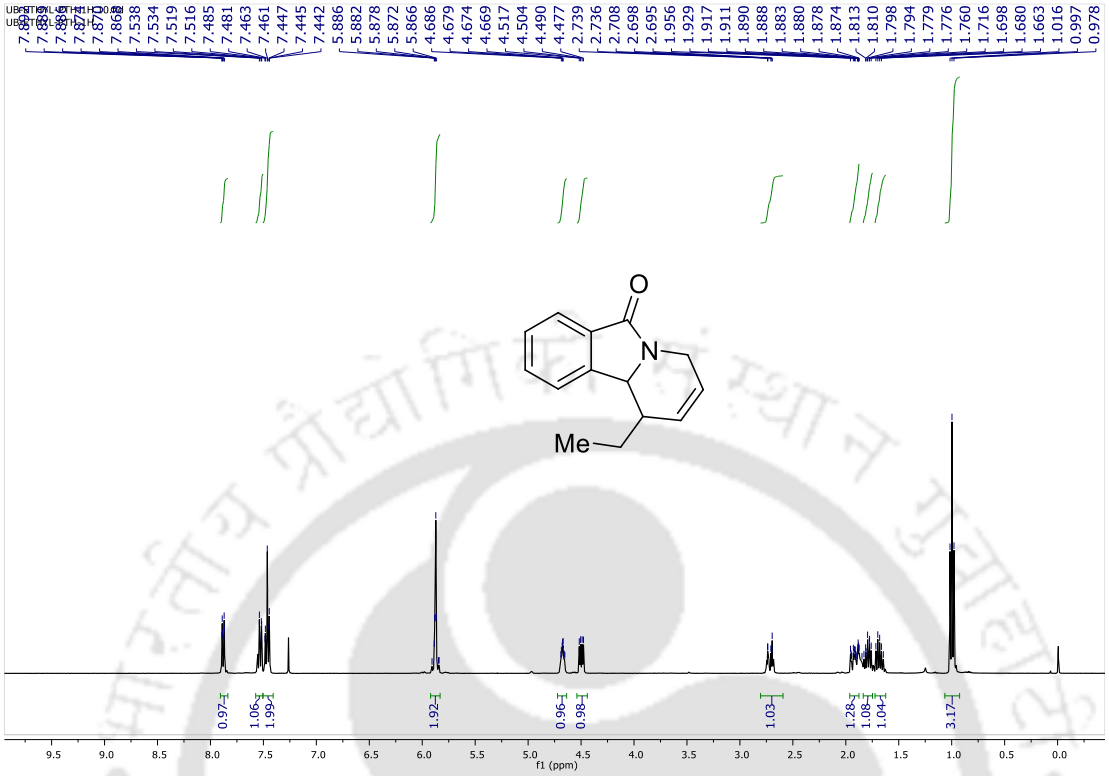


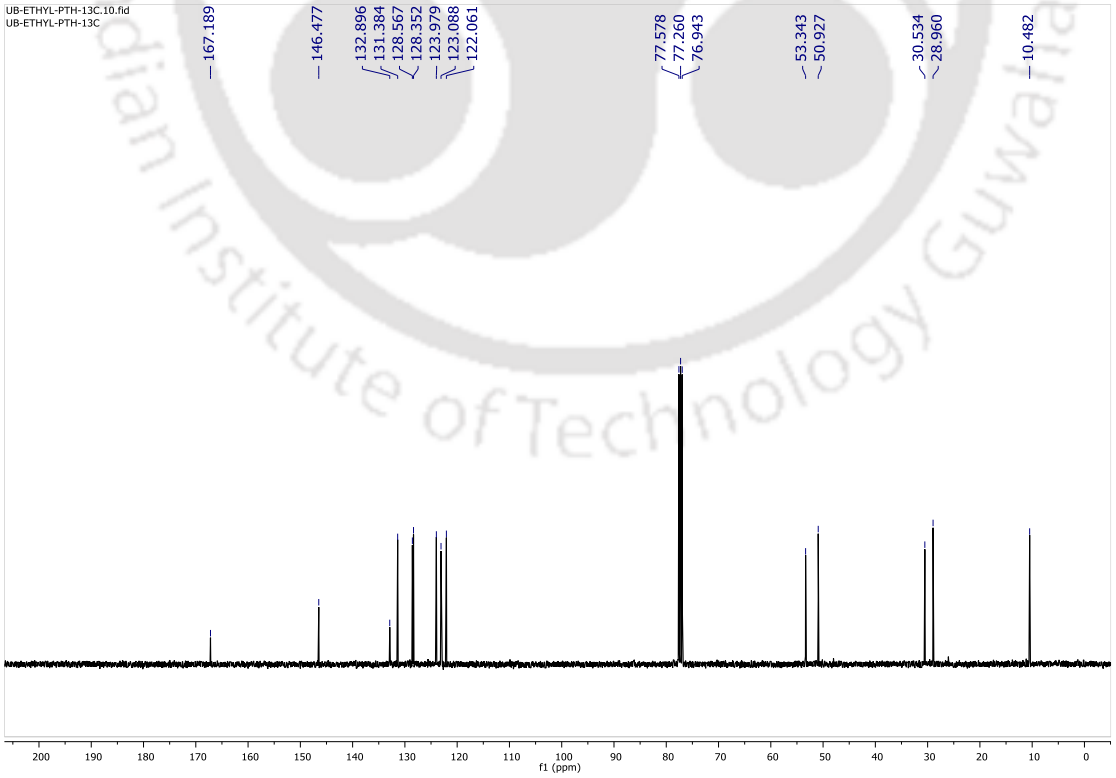
^{1}H and ^{13}C Spectra of compound **38b**



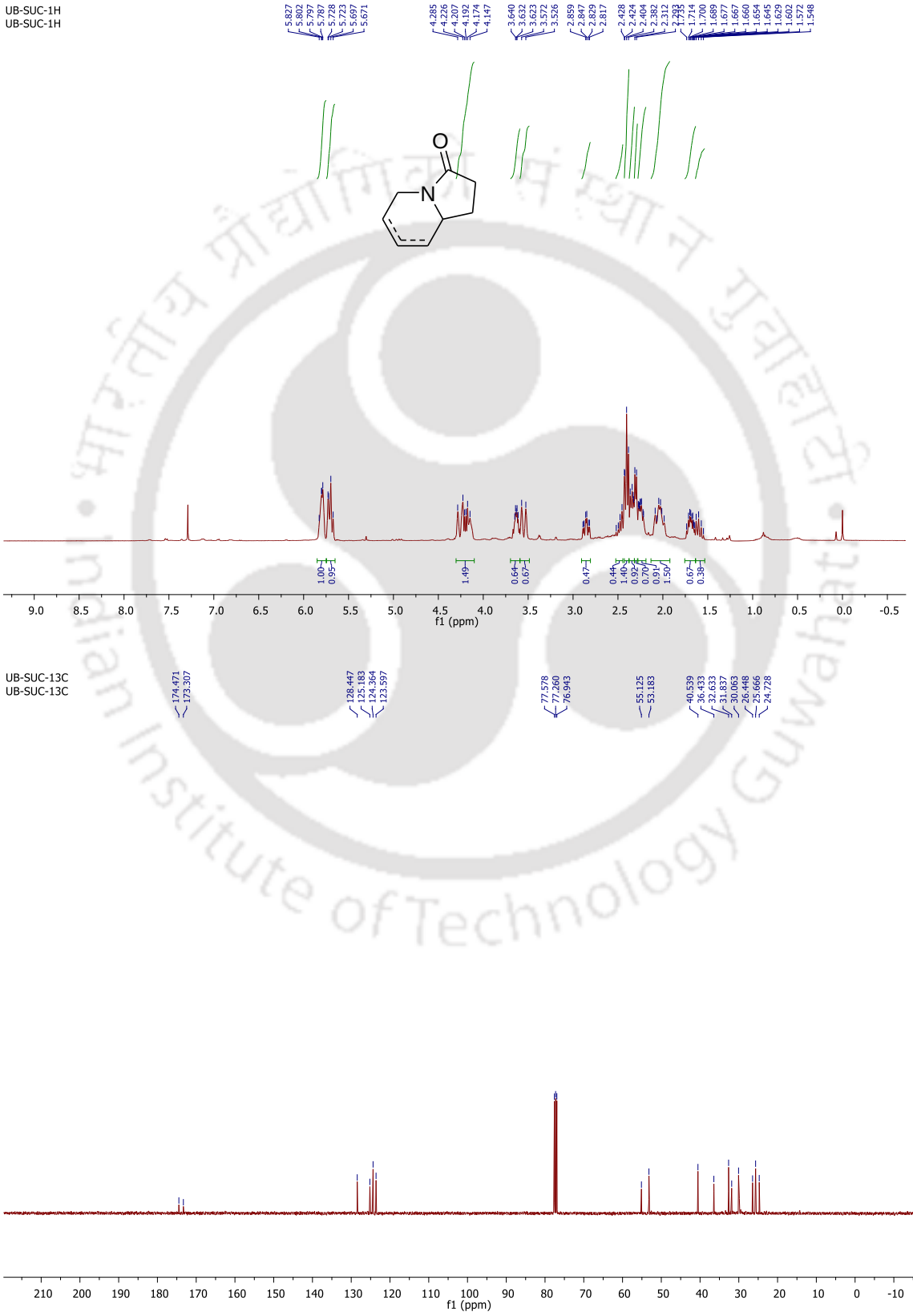


^{1}H and ^{13}C Spectra of compound **38f**

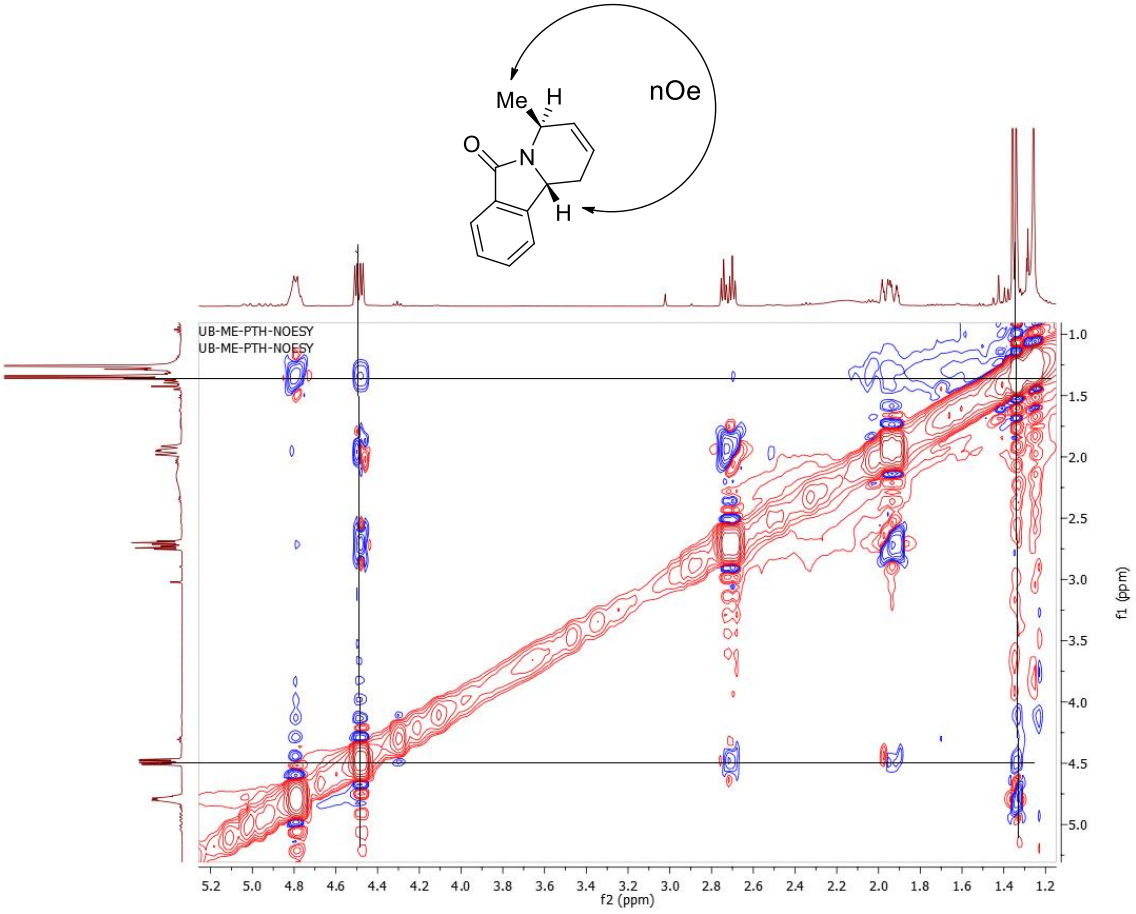




^{1}H and ^{13}C Spectra of compound **38i**



NOE corelation of 38e



4.9. Crystal parameters

The crystal parameters of compound 38b

	CCDC 1950378
Formula	C12H9Cl2NO
Formula weight	254.10
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	7.1311(7)
b/Å	21.300(2)
c/Å	7.8897(8)
α/°	90.00
β/°	114.039(3)
γ/°	90.00
V/Å^3	1094.42(19)
Z	4
Abs. Coeff./mm^{-1}	0.567
Abs. Correction	Multi-scan
GOF on F^2	1.014
Final *R* indices [*I*> 2σ(I)]	*R1* = 0.0410 *wR2* = 0.1406
R indices [all data]	*R1* = 0.0562 *wR2*=0.1262

4.10. References

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17. (a) Chio, F. K. I.; Guesné, S. J. J.; Hassall, L.; McGuire, T.; Dobbs, A.P. *J. Org. Chem*. **2015**, *80*, 9868. (b) Mittapalli, R. R.; Guesne,́ S. J. J.; Parker, R. J.; Klooster, W. T.; Coles, S. J.; Skidmore, J.; Dobbs, A. P. *Org. Lett*. **2019**, *21*, 350.
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20. The crystallographic data for the compound **38b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1950378.

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CHAPTER 5

Bismuth(III) Triflate Catalyzed Highly Diastereoselective Synthesis of Substituted Tetrahydrothiophene *via* Tandem Isomerization, Michael and Aldol Reactions

5.1. Importance and applications

The tetrahydrothiophene framework is considered as one of the core units of many biologically important molecules. For example, sulfonium salt of tetrahydrothiophene, salacinol (**1**), isolated from aqueous extracts of *Salacia reticulata* shows potent *α*-glucosidase inhibitory action.[1] Similarly, a 19-membered ring with an alpha-acyltetronic acid and tetrahydrothiophene moiety, tetronothiodin (**2**), isolated from the fermentation broth of *Streptomyces sp*. NR0489 is considered as a novel nonpeptide cholecystokinin type-B receptor antagonist.[2] Another example, such as nucleoside **3** shows a potent activity against human cytomegalovirus.[3] Tetrahydrothiophene containing compounds also act as antioxidative agents,[4] hypercholesterolemic agents,[5] and plant growth regulators.[6] Apart from these, they are also considered as a good coordinating metal complex ligands[7] and substrates for carbon-carbon bond forming reactions.[8]

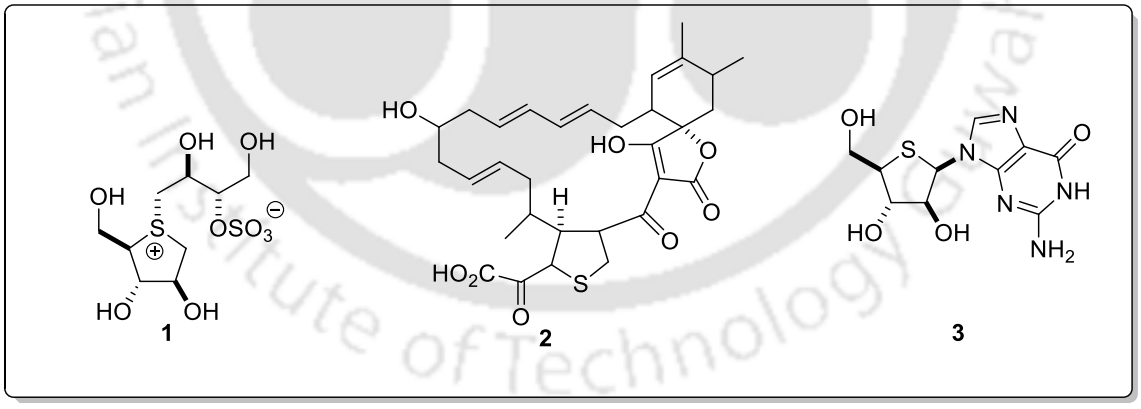


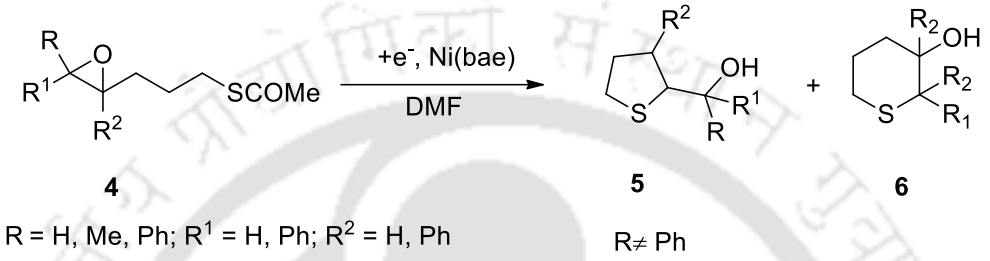
Figure 5.1.1. *Bioactive molecules containing tetrahydrothiophenes.*

5.2. An overview of relevant synthetic methods

There are numerous methods for the synthesis of tetrahydrothiophenes, namely, intramolecular ring opening of epoxides by thiolates,[9] thia-Prins cyclization reaction,[10] double Michael,[11] domino Michael-aldol,[12] Baylis-Hillman reaction,[13] rhodium catalyzed denitrogenative rearrangement of 1-sulfonyl-1,2,3-triazoles,[14] metal-free nucleophilic thiyl radical intramolecular cycloaddition cascade reactions,[15] hydrothiolation of nonactivated

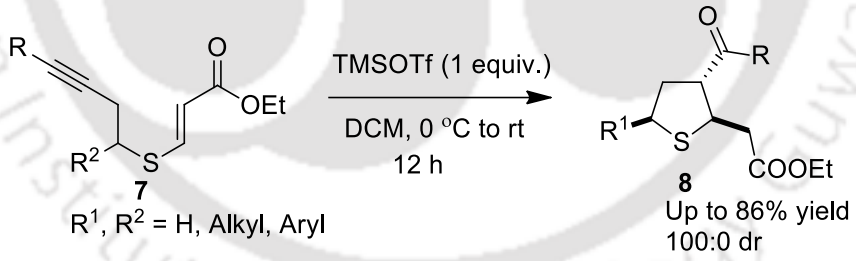
olefins,[16] and photolysis of diazo compounds.[17] Some of the recent synthetic methodologies have been discussed below.

Kitagawa and coworkers reported the synthesis of tetrahydrothiophene using thiolate generated by catalytic electroreduction of thioacetates containing an epoxide ring **4** in the presence of nickel complex, Ni(bae). The reaction proceeds *via* intramolecular ring-opening of the epoxides by thiolate followed by 5-exo-ring closure to generate corresponding tetrahydrothiophene **5**. Depending on the substituents in the epoxide ring, endo-cyclization products **6** were also obtained in some cases (*Scheme 5.2.1*).[9]



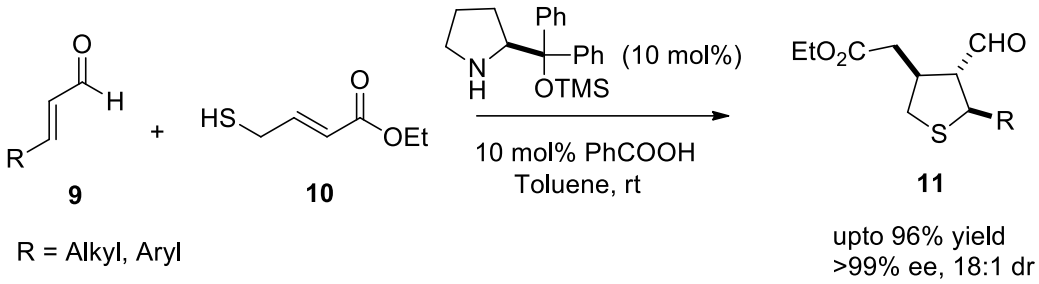
Scheme 5.2.1

Our group in 2015 has reported the diastereoselective synthesis of tetrahydrothiophenes from thioacrylates **7** *via* thia-Prins cyclization mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf). The reaction follows a 5-endo-trig cyclization which is against Baldwin's rules to generate the corresponding substituted tetrahydrothiophene **8** up to 86% yield (*Scheme 5.2.2*).[10]



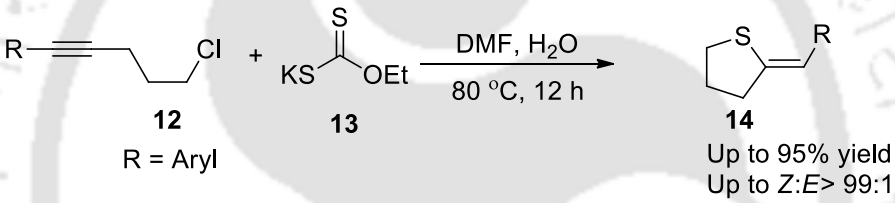
Scheme 5.2.2

Wang and coworkers have reported a novel organocatalytic, enantioselective domino double Michael addition reaction between a variety of *α,β*-unsaturated aldehydes **9** and trans-ethyl 4-mercapto-2-butenoate (**10**). The process, efficiently catalyzed by readily available (*S*)-diphenylprolinol TMS ether, generates highly functionalized chiral tetrahydrothiophenes **11** with three new stereogenic centers in high and excellent enantioselectivities and high stereoselectivities (*Scheme 5.2.3*).[11]



Scheme 5.2.3

Li and coworkers had developed a metal-free environmentally friendly protocol for the synthesis of (*Z*)-tetrahydrothiophene **14** using (5-chloropent-1-yn-1-yl)benzene **12** derivatives, and odorless, stable and cheap $EtOCS_2K$ **13** as the sulfur source. The reaction believes to proceed *via* a cycloaddition cascade process of the nucleophilic thiyl radicals generated by nucleophilic substitution of $EtOCS_2K$ to alkynyl halide components which leads to the formation of tetrahydrothiophenes with broad substrate scope, good functional group tolerance, and excellent stereoselectivity (*Z/E* ratios up to 99/1) (*Scheme 5.2.4*).[15]

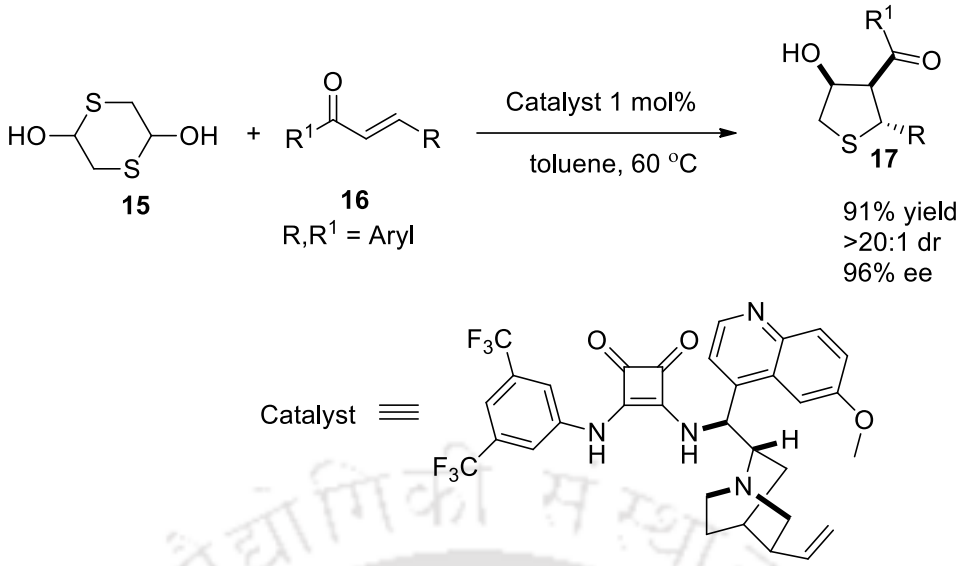


Scheme 5.2.4

5.2.1 Synthesis of tetrahydrothiophene *via* domino Michael and Aldol reaction.

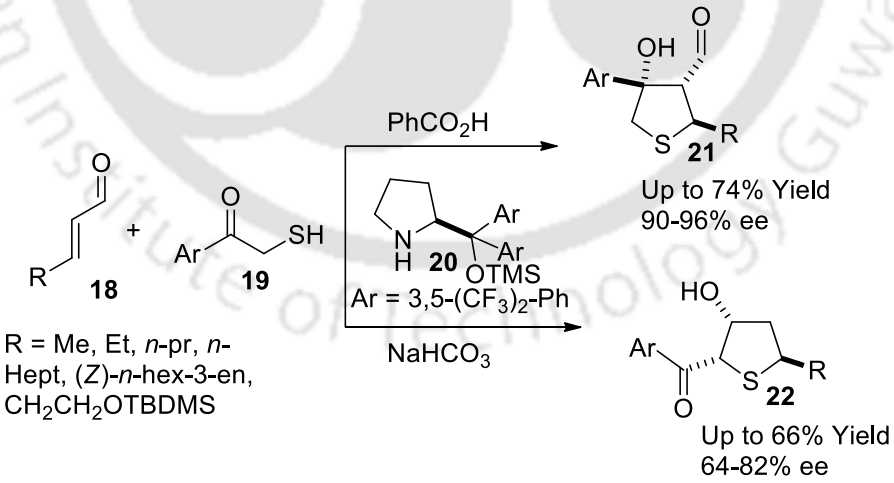
The aldol condensation and Michael reactions are considered as a tool for C-C bond formation reactions.[18,19] Out of various method stated above, domino Michael and aldol reactions are frequently used now a days for the synthesis of tetrahydrothiophenes as it leads to the formation of several C-C and C-S bonds in a single step hence, minimizing time, waste and cost.[12] Herein we have shown some recent methodologies for the construction of tetrahydrothiophene *via* domino Michael and aldol reactions.

In 2011, Xu and his group had reported a sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol (**15**) and chalcones **16** in the presence of a bifunctional squaramide catalyst. The reaction is believed to proceed *via* the synergistic activation of both mercaptoacetaldehyde and enone by bifunctional squaramide to allow Michael followed by aldol reaction to generate tetrahydrothiophenes **17** with three contiguous chiral centers in good yield with high diastereo- and enantio-selectivity (*Scheme 5.2.1.1*).[12a]



Scheme 5.2.1.1

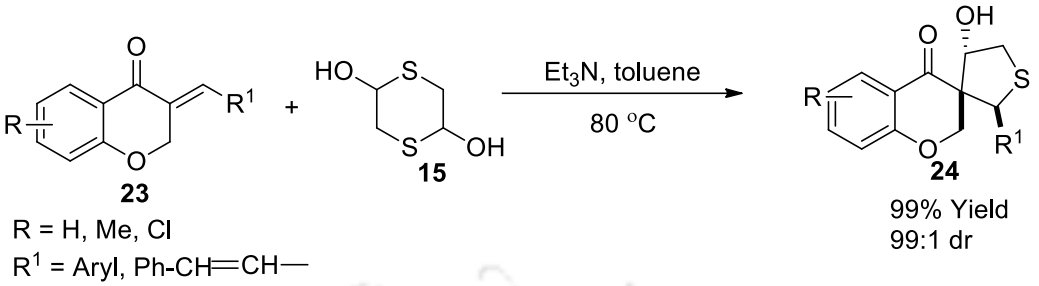
Jørgensen and group had developed a methodology for the synthesis of optically active highly functionalized tetrahydrothiophenes *via* Michael-aldol domino reactions between thiol **19** and α,β-unsaturated aldehydes **18** in presence of chiral L-proline derivative (*S*)- 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]-pyrrolidine (S)-6 **20** as catalyst. The outcome of the reaction depends on the additive used. In the presence of benzoic acid as an additive, tetrahydrothiophene carbaldehydes **21** were obtained whereas on using sodium bicarbonate as an additive, the reaction gave (tetrahydrothiophen-2-yl)phenyl methanones **22** (*Scheme 5.2.1.2*).[12b]



Scheme 5.2.1.2

Kong and co-workers had described a new and facile approach towards the synthesis of spiro chromanone-tetrahydrothiophenes *via* sulfa-Michael/aldol cascade reaction of (*E*)-3-arylidenechroman-4-ones **23** with 1,4-dithiane-2,5-diol (**15**) in the presence of 20 mol% Et_3N at 80 °C in toluene. 2-Mercaptoacetaldehyde generates from1,4-dithiane-2,5-diol undergoes intramolecular sulfa-Michael addition to 3-benzylidenechroman-4-one followed

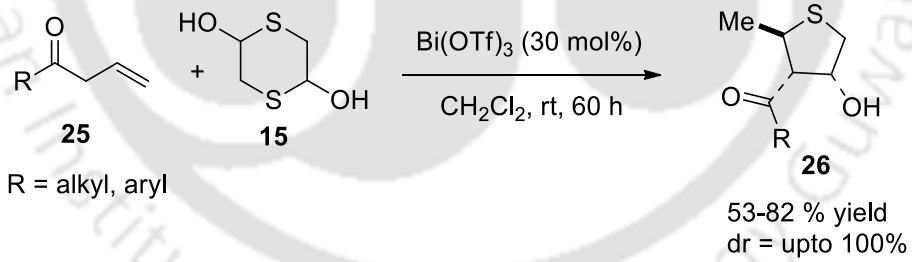
by intramolecular aldol reaction to deliver the final 4′-hydroxy-2′-aryl-4′,5′-dihydro-2′H-spiro[chroman-3,3′-thiophen]-4-ones **24** with three stereocenters in high yields with good to excellent diastereoselectivities (*Scheme 5.2.1.3*).[12c]



Scheme 5.2.1.3

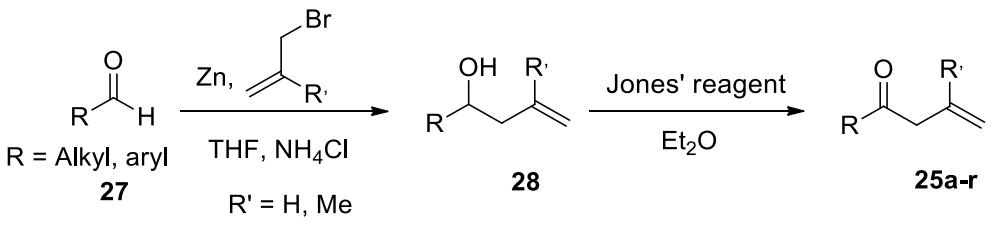
5.3. Present strategy and objective

Olefin isomerization is an important transformation in organic synthesis[20] particularly in isomerization of *β,γ*-unsaturated to *α,β*-unsaturated carbonyl compounds, which is usually carried out by acids[21]or bases.[22] Bismuth(III) salts have been found to be an efficient catalyst in many organic transformations.[23] It has been realized that $Bi(OTf)_3$ can take part in Friedel-Crafts alkylation reaction.[24] In this communication, we report $Bi(OTf)_3$ catalyzed domino alkene isomerization, Michael and Aldol reactions starting with *β,γ*-unsaturated carbonyl compounds and marcaptoaldehyde to give highly functionalized tetrahydrothiophene with high diastereoselectivity in a single pot (*Scheme 5.3.1*).



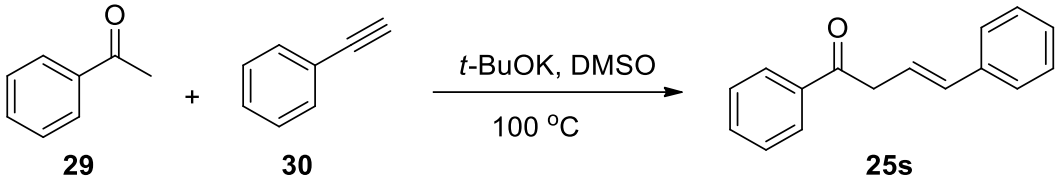
Scheme 5.3.1

The *β,γ*-unsaturated carbonyl compounds **25a-r** were synthesized from aldehydes **27** by performing Barbier reaction with allyl bromide derivatives in presence of zinc to form secondary homoallylic alcohols **28** followed by oxidation using Jones reagent (*Scheme 5.3.2*).[25a]



Scheme 5.3.2

The *β,γ*-unsaturated carbonyl compound **25s** was prepared by adding *t*-BuOK to the solution of acetophenone (**29**) and phenyl acetylene (**30**) in DMSO followed by reflux at 100 °C (*Scheme 5.3.3*).[25b]

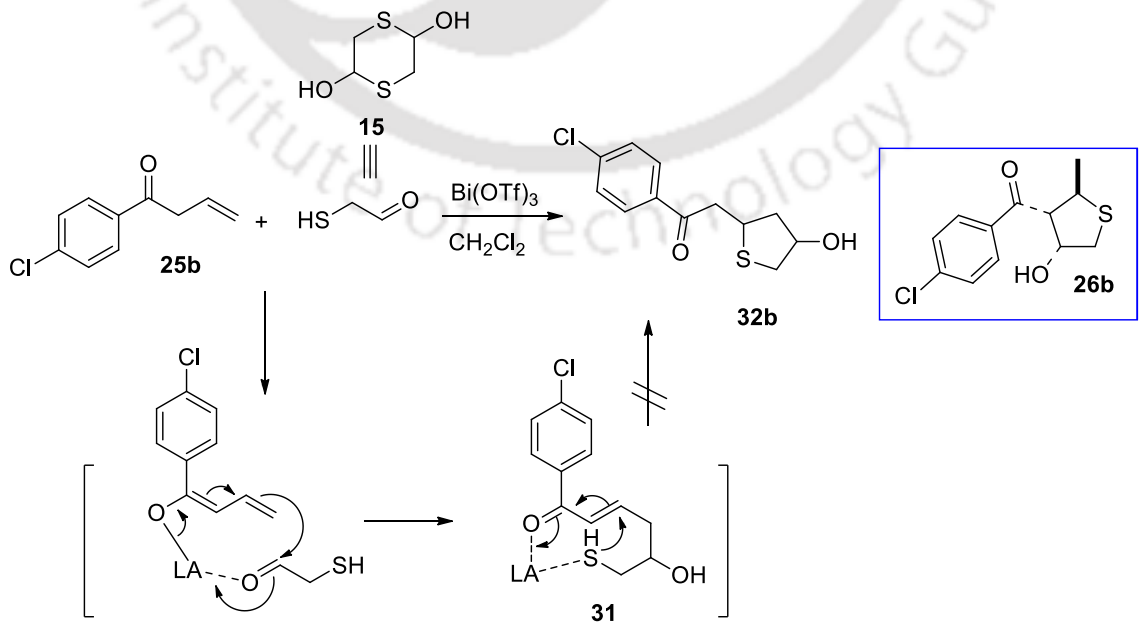


Scheme 5.3.3

5.4. Results and discussion

5.4.1. Optimization studies

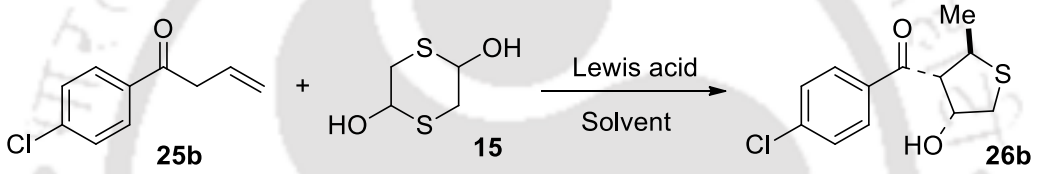
In continuation of our interest in the synthesis of sulfur heterocyclic compounds,[10, 26] we envisioned that *β,γ*-unsaturated ketone, 1-(4-chlorophenyl)but-3-en-1-one (**25b**) under Lewis acidic conditions would generate enolate which will react with 1,4-dithiane-2,5-diol (**15**) in an aldol type fashion to give intermediate hydroxy ketone **30**, which after Michael reaction will give tetrahydrothiophene **31b** (*Scheme 5.4.1.1*). However, in contrast, when the reaction was performed with 10 mol% of $Bi(OTf)_3$ in dichloromethane (DCM), compound **26b** was obtained as a single diastereomer in 25% yield after 60 h. With this unprecedented result in hand the reaction was optimized using different reaction conditions. Increasing the amount of $Bi(OTf)_3$ to 30 mol% gave 60% yield (entry 2, Table 5.4.1.1), and further increase of $Bi(OTf)_3$ to one equivalent could



Scheme 5.4.1.1

not enhance the yield even after 60 h, (entry 4, Table 5.4.1.1). In order to reduce the time span, reaction was performed at 40 ^{0}C, but compound **26b** was obtained as a diastereomeric mixture with a ratio of 80:20 with 45% overall yield (entry 7, Table 5.4.1.1). Other solvents like toluene and dichloroethane were not suitable for the reaction (entries 5-6, Table 5.4.1.1). Increasing the molar concentration of dithiane **15** to 1.5 equivalents (entry 3, Table 5.4.1.1), did not make a better yield. Similarly, indium(III) triflate ($In(OTf)_3$) and silver(I) triflate (AgOTf) in DCM at room temperature gave 42% and 12% yields, respectively (entries 8-9, Table 5.4.1.1). Copper(II) triflate, on the other hand, was considered inappropriate since no conversion was noted throughout the reaction period (entry 10, Table 5.4.1.1). Lewis acid such as boron trifluoride etherate as well as Brønsted acid trifluoroacetic acid gave decomposed products (entries 11-12, Table 5.4.1.1). Triflic

Table 5.4.1.1.Optimization of the reaction



Entry	Acids	Reagent Ratio (**1b**:**2**:Catalyst)(equiv)	Solvent	Temp/ ^{o}C	Time/h	(%) yield[a]
1	$Bi(OTf)_3$	(1:1:0.1)	DCM	rt	60	25
2	$Bi(OTf)_3$	(1:1:0.3)	DCM	rt	60	60
3	$Bi(OTf)_3$	(1:1.5:0.3)	DCM	rt	60	50
4	$Bi(OTf)_3$	(1:1:1)	DCM	rt	60	63
5	$Bi(OTf)_3$	(1:1:0.3)	DCE	rt	60	32
6	$Bi(OTf)_3$	(1:1:0.3)	Toluene	rt	60	40
7	$Bi(OTf)_3$	(1:1:0.3)	DCM	40	12	45[b]
8	$In(OTf)_3$	(1:1:0.3)	DCM	rt	60	42
9	AgOTf	(1:1:0.3)	DCM	rt	60	12
10	$Cu(OTf)_2$	(1:1:0.3)	DCM	rt	60	0[c]
11	$BF_3{\cdot}OEt_2$	(1:1:1.2)	DCM	0-rt	12	0[d]
12	TFA	(1:1:1.2)	DCM	0-rt	12	0[d]
13	TfOH	(1:1:1.2)	DCM	0-rt	12	0[e]
14	TfOH	(1:1:0.05)	DCM	0-rt	12	0[e]

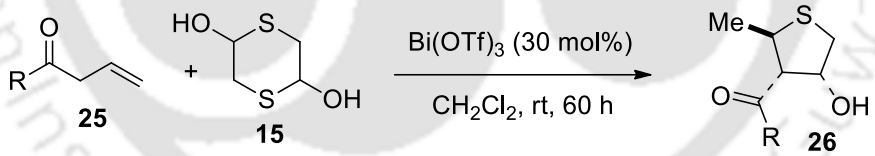
[a]Yields refer to isolated yield. [b]Diastereomeric ratio: 80:20. [c]Starting material recovered. [d]Decomposed products.[e]Unidentified mixture

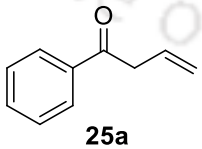
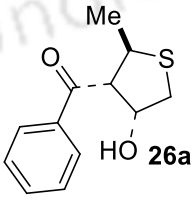
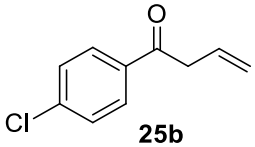
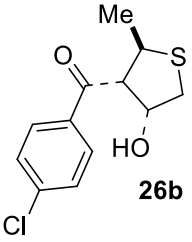
acid with 1.2 equivalents and 5 mol% gave unidentified mixture (entries 13-14, Table 1). It was concluded that 30 mol% $Bi(OTf)_3$ in DCM at room temperature is the optimized reaction condition (entry 2, Table 5.4.1.1).

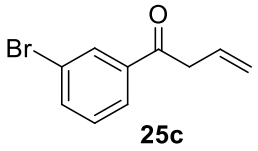
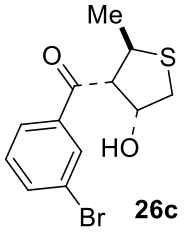
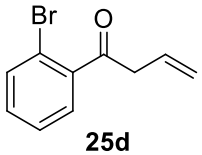
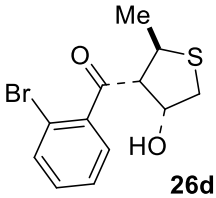
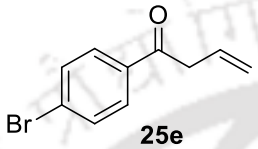
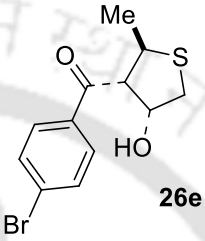
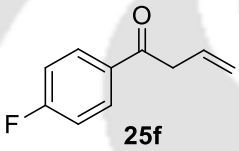
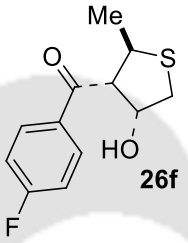
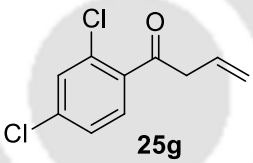
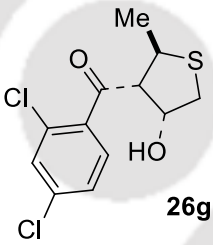
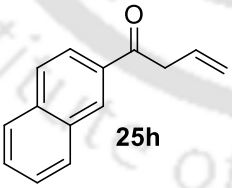
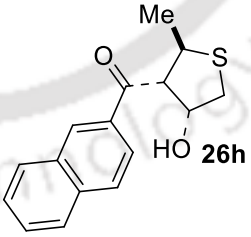
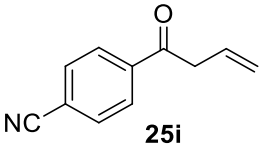
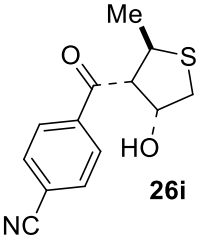
5.4.2. Substrate scope of the reaction

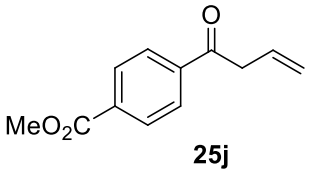
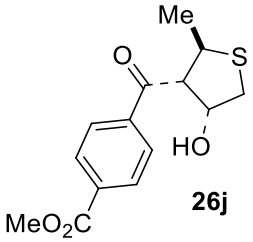
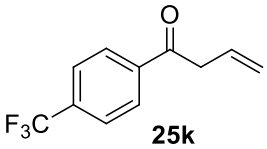
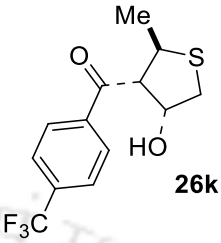
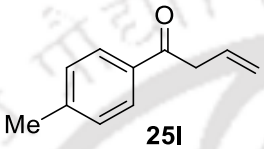
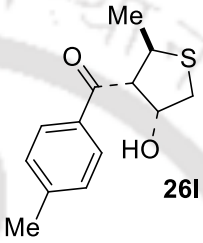
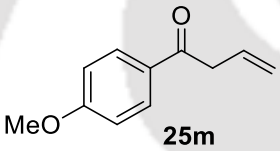
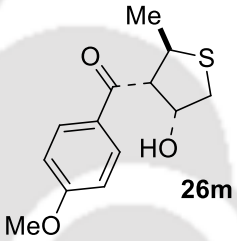
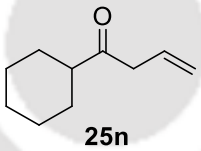
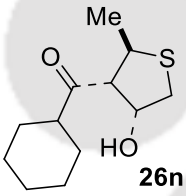
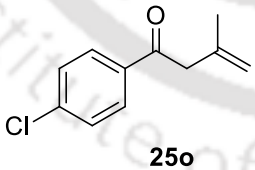
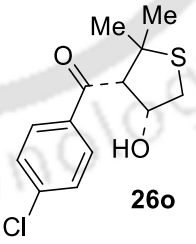
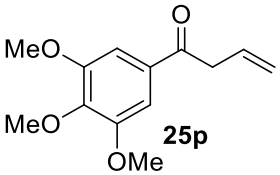
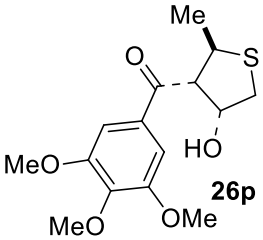
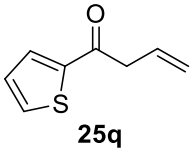
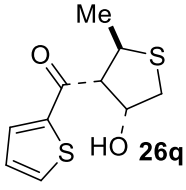
With this optimized condition in hand, the reaction was extended to various ketones and the results are shown in Table 5.4.2.1. Both aliphatic (Table 5.4.2.1. entries 14, 18) and aromatic (Table 5.4.2.1, entries 1-13, 15-17) ketones react well under the reaction condition with good yields and high diastereoselectivity. There is no role of substituents on the aromatic ring of the ketone in determining the yield of the reaction. However, the electron-donating groups in the aromatic ring produced slightly higher yields (Table 5.4.2.1, entries 12-13, 16). The substrate having substituents at 2-position of the olefin **25o** gave 2,2-dimethyl tetrahydrothiphene **26o** in good yield. A ketone with heteroaromatic ring (Table 5.4.2.1, entry 17) also worked well under the reaction conditions. On the other hand, internal olefin **25s** (Table 5.4.2.1, entry 19) with a phenyl ring in 1-position of the olefin failed to give the desired product which might be due to the stability of the conjugated system which restricted the rearrangement of the double bond. The structure and configuration of the products were confirmed by the X-ray crystallographic analysis of the sulfone derivative **26e′** of compound **26e**.[27]

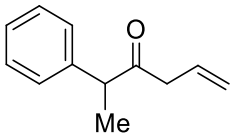
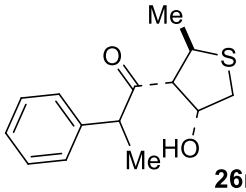
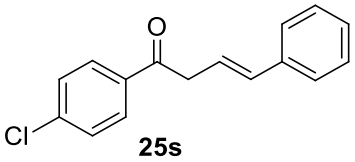
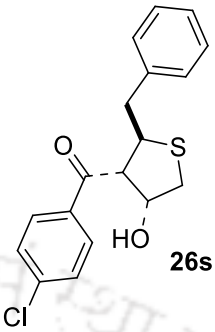
Table 5.4.2.1. Synthesis of substituted tetrahydrothiophenes



Entry	Ketones **25**	Products **26**	dr[a]	Yield (%)[b]
1	 **25a**	 **26a**	96:4	69
2	 **25b**	 **26b**	>98:2	60

3	 **25c**	 **26c**	90:10	53
4	 **25d**	 **26d**	>98:2	56
5	 **25e**	 **26e**	>98:2	58
6	 **25f**	 **26f**	93:7	61
7	 **25g**	 **26g**	>98:2	63
8	 **25h**	 **26h**	96:4	68
9	 **25i**	 **26i**	>98:2	62

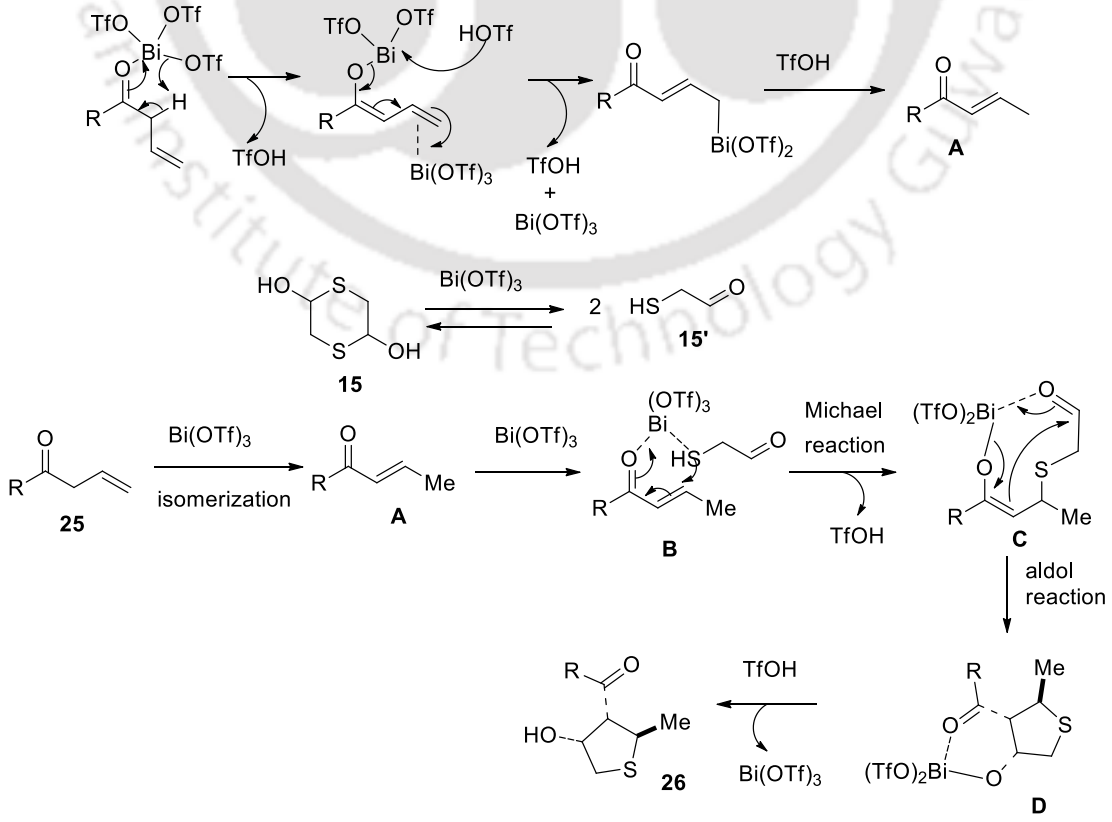
10	 **25j**	 **26j**	>98:2	65
11	 **25k**	 **26k**	90:10	56
12	 **25l**	 **26l**	>98:2	68
13	 **25m**	 **26m**	96:4	d
14	 **25n**	 **26n**	91:9	69
15	 **25o**	 **26o**	93:7	68
16	 **25p**	 **26p**	>98:2	62
17	 **25q**	 **26q**	93:7	65

18	 **25r**	 **26r**	98:2	82
19	 **25s**	 **26s**	-----	

[a]The ratio of dr is determined by ^{1}H NMR spectroscopy. [b]Yields refer to isolated yields.

5.4.3. Plausible mechanism for the synthesis of tetrahydrothiophenes

The proposed mechanism is shown in *Scheme 5.4.3.1*. Bismuth(III) trilflate isomerizes the *β,γ*-ketone **25** to *α,β*-ketone **A**. Under the Lewis acidic condition 1,4-dithiane-2,5-diol **15** opens up its ring to form mercaptoacetaldehyde **15′.** Ketone **A** and mercaptoacetaldehyde **15′** undergo Michael reaction where both carbonyl and thiol groups are coordinated to $Bi(OTf)_3$ which facilitate the



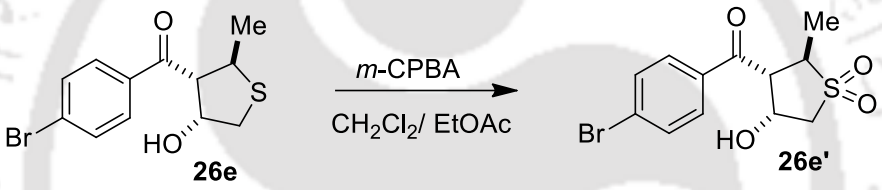
Scheme 5.4.3.1

attack by thiol group of mercaptoacetaldehyde to give intermediate **C**. The intermediate **C** after intramolecular aldol reaction gives intermediate **D** which after reaction with TfOH gives final product **26** and regenerates $Bi(OTf)_3$. The formation of a coordinate bond between bismuth enolate and aldehyde group is responsible for high diastereoselectivity of the reaction.

5.5 Streochemistry of tetrahydrothiophenes

5.5.1 Synthesis of (4-bromophenyl)(4-hydroxy-2-methyl-1,1-dioxidotetrahydrothiophen-3-yl)methanone

The stereochemistry of the tetrahydrothiophenes were determined by X-ray crystallographic analysis of the sulfone derivative **26e′** of compound **26e,** which was prepared by treating (4-bromophenyl)(4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone **26e** with *m*-chloroperbenzoic acid (*Scheme 5.5.1.1*).



Scheme 5.5.1.1

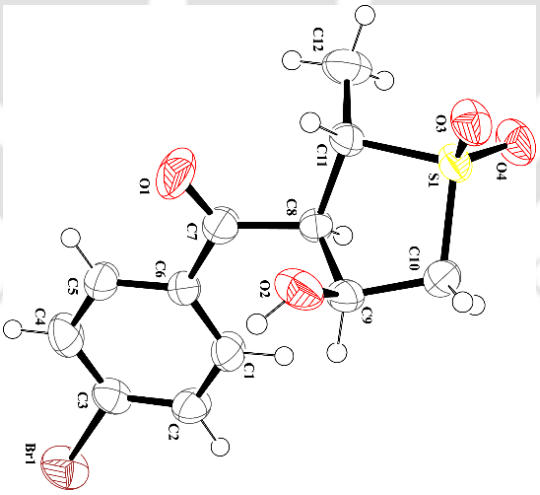


Figure 5.5.1.1. ORTEP Diagram of **26e′** with 50% probability ellipsoid

5.6. Conclusion

In conclusion, we have demonstrated a methodology for the construction of substituted tetrahydrothiophenes in good yields via domino double bond rearrangement, Michael and aldol reactions with very high diastereoselectivity. The major advantage of the reaction is

the usage of a single Lewis acid catalyst to perform three consecutive reactions in one pot thereby reducing time, solvent, reagent, waste and cost. The reaction is also atom economic. Therefore, the work falls within the purview of green chemistry.

5.7. Experimental section

5.7.1. Instrumentation and characterization

As described in chapter 2 section 2.6.1.

5.7.2. Synthesis of starting materials

The *β,γ*-unsaturated carbonyl compounds **25a-s** were synthesized as per literature procedure[26] and the structure and purity of known compounds **25a-b**, **25f**, **25h**, **25l-n** and **25s** were confirmed by comparison of their spectral data (^{1}H NMR and ^{13}C NMR) with those reported in literature.[28]

*Purification of Compounds **25c**, **25d**, **25g**, **25k** was not done and used as such for next step.

5.7.3. General procedure for the synthesis of tetrahydrothiophene (26a-r):

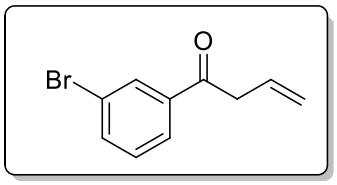
To a solution of $Bi(OTf)_3$ (197 mg, 0.3 mmol) and dithianediol (151mg, 1 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of *β,γ*-unsaturated carbonyl compounds **25a-s** (1 mmol) in dry CH_2Cl_2 (1 mL) dropwise under nitrogen atmosphere. The reaction mixture was then stirred at room temperature. The reaction was continued for a specified time at the same temperature and monitored by TLC. After completion of reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to obtain the crude product. The crude product was further purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the compound **25a-r**.

5.7.4. Preperation of (4-bromophenyl)(4-hydroxy-2-methyl-1,1-dioxidotetrahydrothiophen-3-yl)methanone (26e′):

A solution of *m*-chloroperbenzoic acid (86 mg, 0.50 mmol) in ethylacetate (1.0 mL) was added to a solution of (4-bromophenyl)(4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone (48 mg, 0.16 mmol) in dichloromethane (3 mL) drop wise at 5 ^{o}C and stirred at this temperature until TLC shows complete conversion. The resulting solution was diluted with dichloromethane and washed with saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated under vacuum to give (4-bromophenyl)(4-hydroxy-2-methyl-1,1-dioxidotetrahydrothiophen-3-yl)methanone (35mg, 66%).

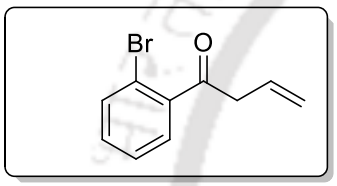
5.8. Spectral data

1-(3-Bromophenyl)but-3-en-1-one (25c)



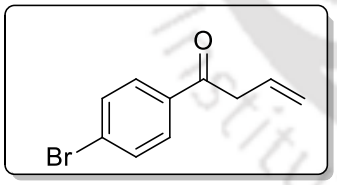
Green oil; R_f (hexane/EtOAc 49:1) 0.50; yield 196 mg, 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (d, *J* = 5.8 Hz, 2 H), 5.19-5.26 (m, 2 H), 6.02-6.08 (m, 1 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.68 (d, *J* = 7.4 Hz, 1 H), 7.88 (d, *J* = 7.4 Hz, 1 H), 8.08 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 119.4, 123.2, 127.0, 130.5, 130.7, 131.6, 136.3, 138.5, 196.8; IR (KBr, neat) 2878, 1673, 1622, 1401, 1071, 808, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}BrO$ $(M + H)^+$: *m/z* 224.9910, found 224.9900.

1-(2-Bromophenyl)but-3-en-1-one (25d):



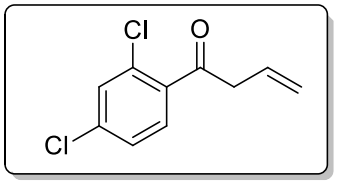
Green oil; R_f (hexane/EtOAc 49:1) 0.50; yield 187 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (d, *J* = 6.5 Hz, 2 H), 5.18-5.26 (m, 2 H), 6.00-6.02 (m, 1 H), 7.30-7.39 (m, 3 H), 7.61 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.5, 118.9, 119.5, 127.6, 128.8, 130.3, 131.9, 133.9, 141.6, 202.2; IR (KBr, neat) 2924, 2853, 1672, 1620, 1396, 1295, 1070, 804, 734 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}BrO$ $(M + H)^+$: *m/z* 224.9910, found 224.9923.

.1-(4-Bromophenyl)but-3-en-1-one (25e):



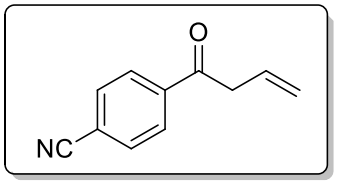
Colourless solid; R_f (hexane/EtOAc 49:1) 0.50; mp 65-68 °C; yield 139 mg, 63%; ^{1}H NMR (400MHz, $CDCl_3$) δ 3.71 (d, *J* = 4.2 Hz, 2 H), 5.18-5.30 (m, 2 H), 6.00-6.11 (m, 1 H), 7.60 (d, *J* = 8.6Hz, 2 H), 7.82 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.3, 119.1, 128.4, 129.9, 130.8, 132.0, 135.3, 197.0; IR (KBr, neat) 2925, 2853, 1672, 1620, 1397, 1218, 1007, 804, 734 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}BrO$ $(M + H)^+$: *m/z* 224.9910, found 224.9909.

1-(2,4-Dichlorophenyl)but-3-en-1-one (25g):



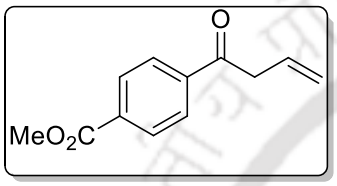
Colourless gum; R_f (hexane/EtOAc 49:1) 0.62; yield 147 mg, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, *J* = 6.8 Hz, 2 H), 5.19-5.27 (m, 2 H), 5.96-6.06 (m, 1 H), 7.34 (dd, *J* = 8.4 and 1.9 Hz, 1 H), 7.46-7.49 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.6, 119.6, 127.6, 130.1, 130.5, 130.6, 132.3, 137.3, 137.7, 199.9; IR (KBr, neat) 2966, 2928, 1699, 1583, 1374, 1297, 1016, 877, 788 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_9Cl_2O$ $(M + H)^+$: *m/z* 215.0025, found 215.0054.

4-(But-3-enoyl)benzonitrile(25i):



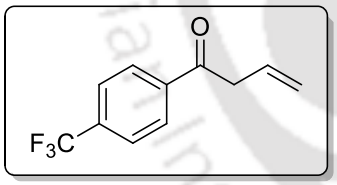
Colourless oil; R_f (hexane/EtOAc 19:1) 0.50; yield 129 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79(m, 2 H), 5.21-5.29 (m, 2 H), 6.01-6.10 (m, 1 H), 7.78 (d, *J* = 8.6 Hz, 2 H), 8.06 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 116.6, 118.1, 119.7, 128.9, 130.2, 132.7, 139.6, 196.8; IR (KBr, neat) 2879, 2231, 1692, 1626, 1400, 1209, 1009, 832, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{10}NO$ $(M + H)^+$: *m/z* 172.0757, found 172.0786.

.Methyl 4-(but-3-enoyl)benzoate(25j):



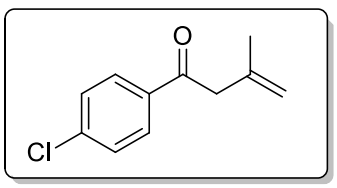
Colourless solid; R_f (hexane/EtOAc 19:1) 0.48; mp 68-70 ºC; yield 143 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, *J* = 6.6 Hz, 2 H), 3.95 (s, 3 H), 5.21-5.28 (m, 2 H), 6.03-6.13 (m, 1 H), 8.00 (d, *J* = 8.4Hz, 2 H),8.13 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 52.7, 119.4, 128.4, 128.6, 130.1, 130.7, 134.2, 140.0, 146.5, 166.4, 197.8; IR (KBr, neat) 3018, 1724, 1679, 1620, 1401, 1284, 1111, 1011, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{13}O_3$ $(M + H)^+$: *m/z* 205.0859, found 205.0883.

1-(4-(Trifluoromethyl)phenyl)but-3-en-1-one (25k):



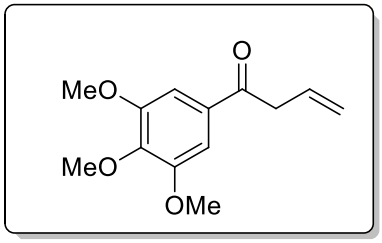
Green oil; R_f (hexane/EtOAc 49:1) 0.40; yield 171 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (d, *J* = 6.2 Hz, 2 H), 5.20-5.23 (m, 2 H), 6.02-6.10 (m, 1 H), 7.71 (d, *J* = 7.6 Hz, 2 H),8.07 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5, 119.1, 123.5 (q, *J* = 180.6 Hz), 125.6, 126.3 (q, *J* = 1.8 Hz), 128.5, 130.3, 134.2 (q, *J* = 22.4 Hz), 139.1, 197.1; IR (KBr, neat) 3010, 2870, 1673, 1627, 1401, 1324, 1131, 1067, 813, 769 cm^{-1};HRMS (ESI) calcd. for $C_{11}H_{10}F_3O$ $(M + H)^+$: *m/z* 215.0678, found 215.0696.

1-(4-Chlorophenyl)-3-methylbut-3-en-1-one (25o):



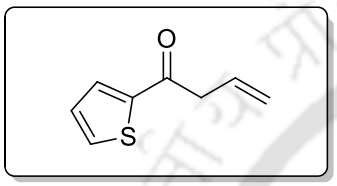
Colourlessgum; R_f (hexane/EtOAc 49:1) 0.58; yield 139 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3 H), 3.66 (s, 2 H), 4.84 (s, 1 H), 4.99 (s, 1 H), 7.42 (d, *J* = 8.6 Hz, 2 H),7.91 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 47.9, 115.4, 129.1, 130.0, 135.2, 139.7, 139.8, 197.1; IR (KBr, neat) 2975, 2920, 1686, 1590, 1485, 1400, 1208, 1093, 1008, 817, 779 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}ClO$ $(M + H)^+$: *m/z* 195.0571, found 195.0558.

1-(3,4,5-Trimethoxyphenyl)but-3-en-1-one (25p):



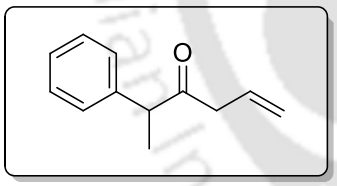
Colourless solid; R_f (hexane/EtOAc 4:1) 0.50; mp 88-90 ^oC; yield 165 mg, 70%; ^1H NMR (600 MHz, $CDCl_3$) δ3.75 (d, *J*= 6.7 Hz, 2 H), 3.93 (s, 9 H), 5.21-5.26 (m, 2 H), 6.05-6.13 (m, 1 H), 7.24 (s, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 43.6, 56.5, 61.2, 105.9, 118.9, 131.4, 132.0, 142.8,153.2, 197.0; IR (KBr, neat) 2938, 2835, 1672, 1642, 1588, 1452, 1336, 1126, 1003, 823, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{17}O_4$ $(M + H)^+$: *m/z* 237.1121, found 237.1134.

1-(Thiophen-2-yl)but-3-en-1-one (25q):



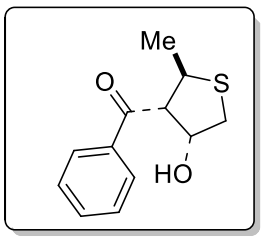
Green oil; R_f (hexane/EtOAc 49:1) 0.40; yield 98 mg, 65%;^1H NMR (400 MHz, $CDCl_3$) δ 3.69 3.68-3.70 (m, 2 H), 5.21-5.26 (m, 2 H), 6.01-6.10 (m, 1 H), 7.13 (dd, *J* = 4.8 and 3.8 Hz, 1 H), 7.65 (dd, *J* = 4.8 and 1.0 Hz, 1 H), 7.74 (dd, *J* = 4.8 and 3.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.4, 119.1, 128.3, 130.9, 132.5, 134.0, 143.9, 191.0; IR (KBr, neat) 3060, 2936, 2292, 2253, 1633, 1420, 1270, 1038, 913, 743 cm^{-1}; HRMS (ESI) calcd. for C_8H_9OS $(M + H)^+$: *m/z* 153.0369, found 153.0385.

2-Phenylhex-5-en-3-one (25r):



Colourless oil; R_f (hexane/EtOAc 49:1) 0.50; yield 139 mg, 80%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38(d, *J* = 7.0 Hz, 3 H), 3.10-3.12 (m, 2 H), 3.80 (q, *J* = 7.0 Hz, 1 H), 4.96-5.11 (m, 2 H), 5.77-5.87 (m, 1 H), 7.19-7.26 (m, 3 H), 7.30-7.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 45.9, 52.5, 118.6, 127.3, 128.0, 129.1, 130.9, 140.4, 208.6; IR (KBr, neat) 2978, 2933, 1713, 1635, 1452, 1267, 1071, 992, 761, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}O$ $(M + H)^+$: *m/z* 175.1117, found 175.1137.

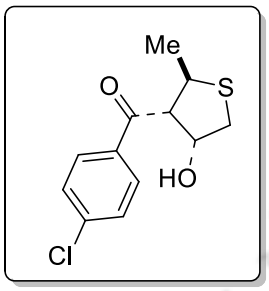
((2R*,3R*,4R*)-4-Hydroxy-2-methyltetrahydrothiophen-3-yl)(phenyl)methanone (26a):



Colourless gum; R_f (hexane/EtOAc 19:3) 0.50; yield 104 mg, 69%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.5 Hz, 3 H), 3.02 (d, *J* = 11.7 Hz, 1 H), 3.36 (dd, *J* = 11.7 and 4.0 Hz, 1 H), 3.46 (brs, 1 H), 3.65 (dd, *J* = 10.2 and 3.0 Hz, 1 H), 4.05-4.10 (m, 1 H), 4.80 (brs, 1 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* =

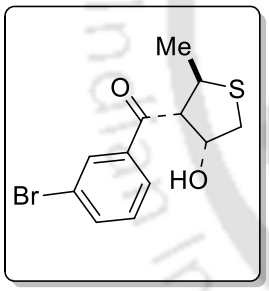
7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 40.6, 43.1, 61.4, 77.5, 128.6, 129.2, 134.3, 137.2, 200.8; IR (KBr, neat) 3120, 2878, 1673, 1631, 1400, 1201, 1018, 877, 769 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}O_2S$ $(M + H)^+$: *m/z* 223.0787, found 223.0791.

4-Chlorophenyl)((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone (26b):**



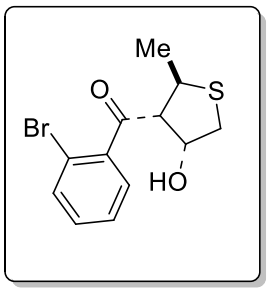
Colourless solid; R_f (hexane/EtOAc 19:3) 0.53; mp 84-86 ºC; yield 84 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.4 Hz, 3 H), 2.98 (d, *J* = 11.6 Hz, 1 H), 3.35 (dd, *J* = 11.7 and 4.0 Hz, 1 H), 3.58 (dd, *J* = 10.0 and 3.2 Hz, 1 H), 4.04-4.11 (m, 1 H), 4.80 (t, *J* = 2.8 Hz, 1 H), 7.48 (dd, *J* = 6.8 and 1.8 Hz, 2 H), 7.90 (dd, *J* = 6.8 and 1.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ20.3, 40.3, 42.5, 61.6, 76.8, 129.3, 129.8, 135.3, 140.6, 198.9; IR (KBr, neat) 3449, 2931, 1969, 1623, 1447, 1279, 1021, 920, 757, 693 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}ClO_2S$ $(M + H)^+$: *m/z* 257.0398, found 257.0411.

(3-Bromophenyl)((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone (26c):**



Colourless solid; R_f (hexane/EtOAc 19:3) 0.54; mp 88-90ºC; yield 71 mg, 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.6 Hz, 3 H), 3.00 (d, *J* = 11.6 Hz, 1 H), 3.10 (brs, 1 H), 3.38 (dd, *J* = 11.6 and 4.0 Hz, 1 H), 3.58 (dd, *J* = 11.6 and 3.2 Hz, 1 H), 4.06-4.13 (m, 1 H), 4.80 (brs, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 8.08 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 40.6, 42.5, 62.1, 76.9, 123.6, 127.1, 130.7, 131.6, 137.0, 139.0, 198.9; IR (KBr, neat) 3125,3026, 1659, 1401, 1235, 1072, 1016, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}BrO_2S$ $(M + H)^+$: *m/z* 300.9892, found 300.9897.

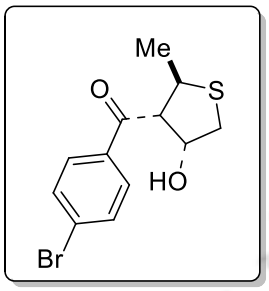
(2-Bromophenyl)((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone (26d):**



Colourless gum; R_f (hexane/EtOAc 19:3) 0.53; yield 75 mg, 56%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.4 Hz, 3 H), 2.90 (d, *J* = 11.8 Hz, 1 H), 3.28 (dd, *J* = 11.8 and 3.6 Hz, 1 H), 3.57 (dd, *J* = 11.8 and 3.0 Hz, 1 H), 4.07-4.13 (m, 1 H), 4.72 (brs, 1 H), 7.32-7.34 (m,1 H), 7.39-7.40 (m,2 H), 7.60 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 40.4, 41.1, 67.1, 77.4, 118.4, 128.0,

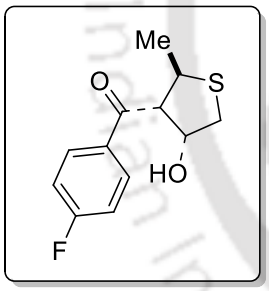
128.7, 132.1, 133.7, 141.9, 203.2; IR (KBr, neat) 3128, 3015, 1698, 1627, 1401, 1275, 1097, 1022, 751 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}BrO_2S$ $(M + H)^+$: *m/z* 300.9892, found 300.9875.

(4-Bromophenyl)((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone (26e):**



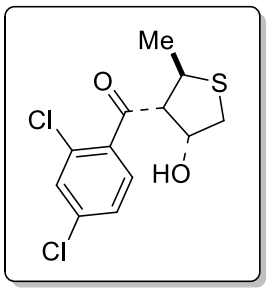
Colourless solid; R_f (hexane/EtOAc 19:3) 0.55; mp 98-100 ^oC; yield 78 mg, 58%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.5 Hz, 3 H), 2.98 (d, *J* = 11.6 Hz, 1 H), 3.35 (dd, *J* = 11.6 and 3.8 Hz, 2 H), 3.56 (dd, *J* = 10.0 and 3.2 Hz, 1 H), 4.02-4.09 (m, 1 H), 4.78 (brs, 1 H), 7.63 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.6, 40.7, 42.9, 61.6, 77.0, 129.7, 130.1, 130.3, 132.5, 132.7, 135.9, 199.5; IR (KBr, neat) 3442, 2927, 2855, 1680, 1584, 1397, 1265, 1072, 1009, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}BrO_2S$ $(M + H)^+$: *m/z* 300.9892, found 300.9906.

(4-Fluorophenyl)((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone (26f):**



Colourless gum; R_f (hexane/EtOAc 19:3) 0.53; yield 89 mg, 61%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.5 Hz, 3 H), 3.03 (d, *J* = 11.8 Hz, 1 H), 3.36 (dd, *J* = 11.8 and 4.0 Hz, 1 H), 3.60 (dd, *J* = 11.8 and 3.0 Hz, 1 H), 4.06-4.10 (m, 1 H), 4.80 (brs, 1 H), 7.19 (t,*J* = 8.4 Hz, 2 H), 7.99-8.03 (m,2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 40.6, 43.0, 61.4, 77.5, 116.3 (d, *J* = 21.9 Hz), 131.4 (d, *J* = 9.5 Hz), 133.6 (d, *J* = 3.0 Hz), 166.5 (d, *J* = 255.3 Hz), 199.0; IR (KBr, neat) 3121, 3015, 1672, 1633, 1401, 1233, 1018, 864, 596 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}FO_2S$ $(M + H)^+$: *m/z* 241.0693,found 241.0664.

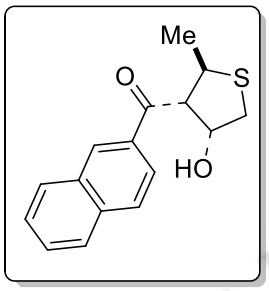
(2,4-Dichlorophenyl)((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophen-3-yl)methanone(26g):**



Colourless gum; R_f (hexane/EtOAc 19:3) 0.60; yield 86 mg, 63%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, *J* = 6.5 Hz, 3 H), 2.81 (brs, 1 H), 2.90 (d, *J* = 11.8 Hz, 1 H), 3.30 (dd, *J* = 11.8 and 3.8 Hz, 1 H), 3.55 (dd, *J* = 9.6 and 3.0 Hz, 1 H), 4.02-4.10 (m, 1 H), 4.70 (brs, 1 H), 7.33 (d, *J* = 8.2 Hz, 1 H), 7.40 (d, *J* = 2.2 Hz, 1 H), 7.43 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 40.5, 41.2, 67.2, 76.9,

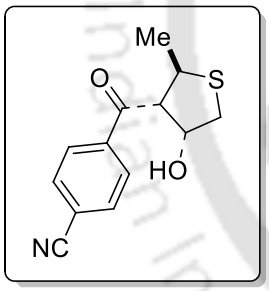
127.9, 130.1, 130.4, 131.5, 137.7, 138.1, 201.1; IR (KBr, neat) 3296, 2920, 2851, 1662, 1585, 1440, 1291, 1103, 1034, 816, 778 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{13}Cl_2O_2S$ $(M + H)^+$: *m/z* 291.0008, found 291.0037.

((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)(naphthalen-2-yl)methanone (26h):**



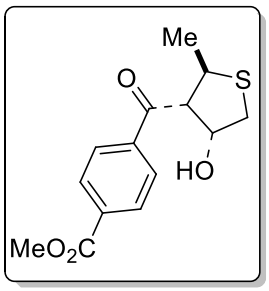
Brown solid; R_f (hexane/EtOAc 19:3) 0.51; mp 90-92 ^oC; yield 97 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.5 Hz, 3 H), 3.06 (d, *J* = 11.8 Hz, 1 H), 3.42 (dd, *J* = 11.8 and 4.0 Hz, 1 H), 3.82 (dd, *J* = 11.8 and 3.0 Hz, 1 H), 3.58 (brs, 1 H), 4.10-4.18 (m, 1 H), 4.88 (brs, 1 H), 7.57-7.67 (m,2 H), 7.89-7.95 (m, 2 H), 7.99-8.01 (m,2 H), 8.48 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 40.7, 43.4, 61.3, 77.6, 123.9 127.4, 128.1, 129.2, 129.4, 130.0, 130.7, 132.6, 134.6, 136.2, 200.9; IR (KBr, neat) 3128, 1673, 1400, 1215, 1023, 748 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{17}KO_2S$ $(M + K)^+$: *m/z* 311.0503,found 311.0492.

4-((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydro-thiophene-3-carbonyl)benzonitrile (26i):**



Colourless solid; R_f (hexane/EtOAc 3:1) 0.50; mp 150-152 ^oC; yield 89 mg, 62%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.5 Hz, 3 H), 2.88 (brs, 1 H), 3.00 (d, *J* = 11.8 Hz, 1 H), 3.39 (dd, *J* = 11.8 and 4.0 Hz, 1 H), 3.60 (dd, *J* = 11.8 and 3.4 Hz, 1 H), 4.09-4.17 (m, 1 H), 4.81 (brs, 1 H), 7.82 (d,*J* = 8.6 Hz,2 H),8.04 (d,*J* = 8.6 Hz,2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 40.6, 41.9, 62.8, 77.6, 117.2, 117.9, 128.9, 133.0, 140.2, 198.4; IR (KBr, neat) 3425, 2926, 2231, 1687, 1405, 1296, 1017, 869, 740, 630 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}NO_2S$ $(M + H)^+$: *m/z* 248.0740, found 248.0711.

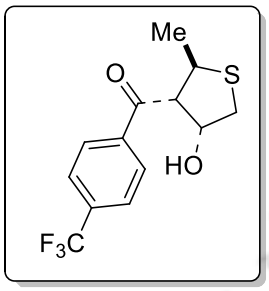
Methyl 4-((2*R,3*R**,4*R**)-4-hydroxy-2-methyltetrahydrothiophene-3-carbonyl)benzoate (26j):**



Colourless solid; R_f (hexane/EtOAc 19:3) 0.37; mp 95-97 ^oC; yield 89 mg, 65%; ^1H NMR (400MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.5 Hz, 3 H), 3.00 (d, *J* = 11.8 Hz, 1 H), 3.39 (dd, *J* = 11.8 and 4.0 Hz, 1 H), 3.67 (dd, *J* = 11.8 and 3.2 Hz, 1 H), 3.96 (s, 3 H), 4.09-4.14 (m, 1 H), 4.82 (t, *J* = 2.8 Hz, 1 H), 8.00 (d,*J* = 8.4 Hz,2 H),8.15 (d,*J* = 8.4 Hz,2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 40.5, 42.3, 52.8,

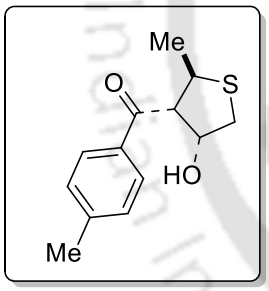
62.5, 77.6, 128.4, 130.3, 134.7, 140.4, 166.2, 199.6; IR (KBr, neat) 3120, 1723, 1684, 1401, 1283, 1110, 1014, 783 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NaO_4S$ $(M + Na)^+$: *m/z* 303.0662, found 303.0683.

((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)(4-(trifluoromethyl)phenyl)-methanone (26k):**



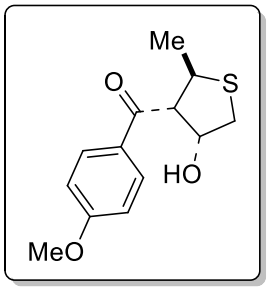
Green solid; Rf (hexane/EtOAc 19:3) 0.45; mp 68-70 ºC; yield 76 mg, 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.6 Hz, 3 H), 3.05 (d, *J* = 11.8 Hz, 1 H), 3.10 (brs, 1 H), 3.42 (dd, *J* = 11.8 and 4.0 Hz, 1 H), 3.67 (dd, *J* = 10.0 and 3.3 Hz, 1 H), 4.07-4.12 (m, 1 H), 4.84 (s, 1 H), 7.78 (q, *J* = 8.2 Hz, 2 H), 8.06 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 40.1, 42.9, 62.4, 77.6, 123.6 (q, *J* = 271.2 Hz), 126.3 (q, *J* = 3.6 Hz), 128.9, 129.2, 135.4 (q, *J* = 32.8 Hz), 139.8, 199.0; IR (KBr, neat) 3427, 2928, 1685, 1410, 1327, 1130, 1067, 827, 629 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}F_3O_2S$ $(M + H)^+$: *m/z* 291.0661, found 291.0680.

((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)(p-tolyl)methanone(26l):**



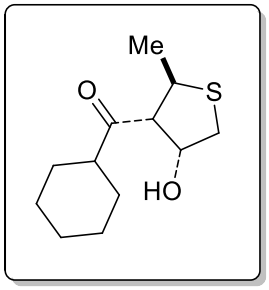
Colourless gum; R_f (hexane/EtOAc 19:3) 0.53; yield 106 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.5 Hz, 3 H), 2.44 (s, 3 H), 3.00 (dd, *J* = 11.6 and 0.8 Hz, 1 H), 3.34 (dd, *J* = 11.6 and 4.0 Hz, 1 H), 3.62 (dd, *J* = 11.6 and 3.0 Hz, 1 H), 4.02-4.12 (m, 1 H), 4.78 (brs, 1 H), 7.30 (d,*J* = 8.0 Hz,2 H),7.87 (d,*J* = 8.0 Hz,2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.9, 40.3, 43.1, 61.0, 76.9, 128.7, 129.8, 134.7, 145.4, 200.5; IR (KBr, neat) 3127, 3017, 1674, 1401, 1183, 1020, 879, 594 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}NaO_2S$ $(M + Na)^+$: *m/z* 259.0763, found 259.0794.

((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)(4-methoxyphenyl)methanone(26m):**



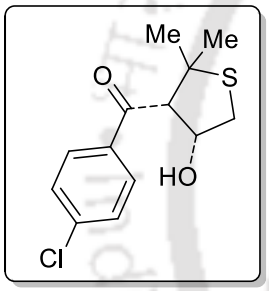
Colourless gum; R_f (hexane/EtOAc 3:1) 0.47; yield 111 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.5 Hz, 3 H), 3.00 (dd, *J* = 11.6 and 0.8 Hz, 1 H), 3.32 (dd, *J* = 11.6 and 4.0 Hz, 1 H), 3.61 (dd, *J* = 11.6 and 3.0 Hz, 1 H), 3.88 (s, 3 H), 4.00-4.08 (m, 1 H), 4.76-4.78 (m, 1 H), 6.96 (d,*J* = 8.8 Hz,2 H),7.87 (d,*J* = 8.8 Hz,2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 40.6, 43.6, 55.8, 60.5, 77.4, 114.4, 130.1, 131.2, 164.7, 199.6; IR (KBr, neat) 3122, 1635, 1600, 1401, 1267, 1174, 1027, 604 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{17}O_3S$ $(M + Na)^+$: *m/z* 275.0712, found 275.0693.

Cyclohexyl((2*R,3*R**,4*R**)-4-hydroxy-2-methyl-tetrahydrothiophen-3-yl)methanone (26n):**



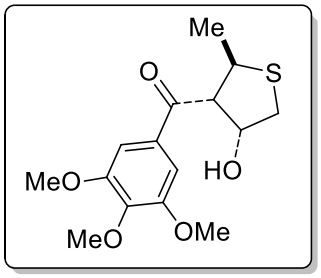
Colourless solid; R_f (hexane/EtOAc 19:3) 0.43; mp 75-77 ^oC; yield 120 mg, 80%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16-1.43 (m, 5 H), 1.32 (d, *J* = 6.5 Hz, 3 H), 1.67-1.72 (m, 1 H), 1.80-1.89 (m, 4 H), 2.45-2.52 (m, 1 H), 2.92-2.96 (m, 2 H), 3.10 (brs, 1 H), 3.26 (dd, *J* = 11.6 and 3.8 Hz, 1 H), 3.88-3.96 (m, 1 H), 4.71 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 25.6, 25.8, 25.9, 28.0, 28.3, 40.7, 42.2, 52.0, 65.3, 77.6, 214.0; IR (KBr, neat) 3117, 2855, 1698, 1631, 1400, 1145, 1023, 686 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{21}O_2S$ $(M + H)^+$: *m/z* 229.1257, found 229.1283.

(4-Chlorophenyl)((3*R,4*R**)-4-hydroxy-2,2-dimethyl-tetrahydrothiophen-3-yl)methanone (26o):**



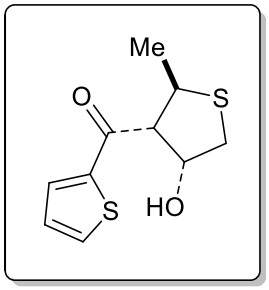
Colourless gum; R_f (hexane/EtOAc 19:3) 0.58; yield 80 mg, 58%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 1.51 (s, 3 H), 3.19 (dd, *J* = 9.8 and 3.5 Hz, 1 H), 2.90 (dd, *J* = 11.6 and 2.2 Hz, 1 H), 3.31 (dd, *J* = 11.6 and 4.6 Hz, 1 H), 3.80 (d, *J* = 3.5 Hz, 1 H), 4.92-4.95 (m, 1 H), 7.50 (d, *J* = 8.6 Hz, 2 H), 7.88 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 33.9, 39.7, 54.7, 60.1, 60.2, 79.1, 129.5, 130.4, 136.4, 141.1, 202.3; IR (KBr, neat) 3415, 2957, 2857, 1658, 1587, 1401, 1221, 1090, 1008, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}ClO_2S$ $(M + H)^+$: *m/z* 271.0554, found 271.0573.

((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)(3,4,5-trimethoxyphenyl)-methanone (26p):**



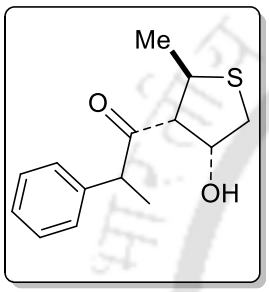
Colourless solid; Rf (hexane/EtOAc 13:7) 0.50; mp 112-114 ^oC; yield 245 mg, 62%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.5 Hz, 3 H), 3.03 (d, *J* = 11.6 Hz, 1 H), 3.37 (dd, *J* = 11.6 and 4.0 Hz, 1 H), 3.58 (dd, *J* = 10.2 and 3.0 Hz, 1 H), 3.91 (dd,*J*= 4.3 Hz, 1 H), 3.93 (s, 6 H), 3.94 (s, 3 H), 4.02-4.08 (m, 1 H), 4.80-4.82 (m, 1 H), 7.22 (s, 2 H); ^{13}C NMR (100 MHz, CDCl3) δ 20.3, 40.5, 43.4, 56.6, 60.8, 61.2, 77.5, 106.3, 132.2, 143.8, 153.4, 199.6; IR (KBr, neat) 3460, 2936, 1674, 1584, 1460, 1414, 1330, 1266, 1129, 1024, 1000, 742 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}O_5S$ $(M + H)^+$: *m/z* 313.1104, found 313.1122.

((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)(thiophen-2-yl)methanone (26q):**



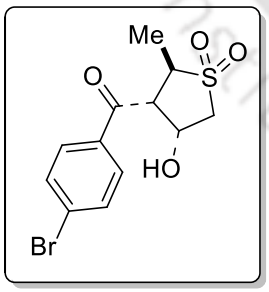
Colourless gum; Rf (hexane/EtOAc 19:3) 0.49; yield 97 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.5 Hz, 3 H), 3.03 (d, *J* = 11.6 Hz, 1 H), 3.32 (dd, *J* = 11.6 and 3.8 Hz, 1 H), 3.41 (dd, *J* = 10.4 and 3.0 Hz, 1 H), 3.68 (brs, 1 H), 4.02-4.10 (m, 1 H), 4.80-4.82 (m, 1 H), 7.18-7.21 (m, 1 H), 7.75-7.79 (m, 2 H); ^{13}C NMR (100 MHz, CDCl3) δ 20.3, 40.4, 43.4, 62.7, 77.7, 128.9, 133.4, 136.0, 144.6, 193.6; IR (KBr, neat) 3423, 2924, 2850, 1654, 1413, 1244, 1029, 801, 729 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{13}O_2S_2$ $(M + H)^+$: *m/z* 229.0351, found 229.0364.

1-((2*R,3*R**,4*R**)-4-Hydroxy-2-methyltetrahydro-thiophen-3-yl)-2-phenylpropan-1-one (26r):**



Colourless solid; R_f (hexane/EtOAc 19:3) 0.48; mp 98-100 ºC; yield 118 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.5 Hz, 3 H), 1.43 (d, *J* = 6.8 Hz, 3 H), 2.67 (brs, 1 H), 2.80 (dd, *J* = 9.8and 3.5 Hz, 1 H), 2.90 (d, *J* = 11.2 Hz, 1 H), 3.19 (dd, *J* = 11.2 and 7.8 Hz, 1 H), 3.88-3.96 (m, 2 H), 4.75 (brs, 1 H), 7.19-7.21 (m, 2 H), 7.26-7.30 (m, 1 H), 7.33-7.37 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 20.5, 40.9, 41.1, 53.7, 53.8, 65.8, 77.2, 127.9, 128.3, 129.4, 139.5, 208.5; IR (KBr, neat) 3335, 2970, 2866, 1705, 1601, 1452, 1410, 1332, 1279, 1023, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{19}O_2S$ $(M + H)^+$: *m/z* 251.1100, found 251.1120.

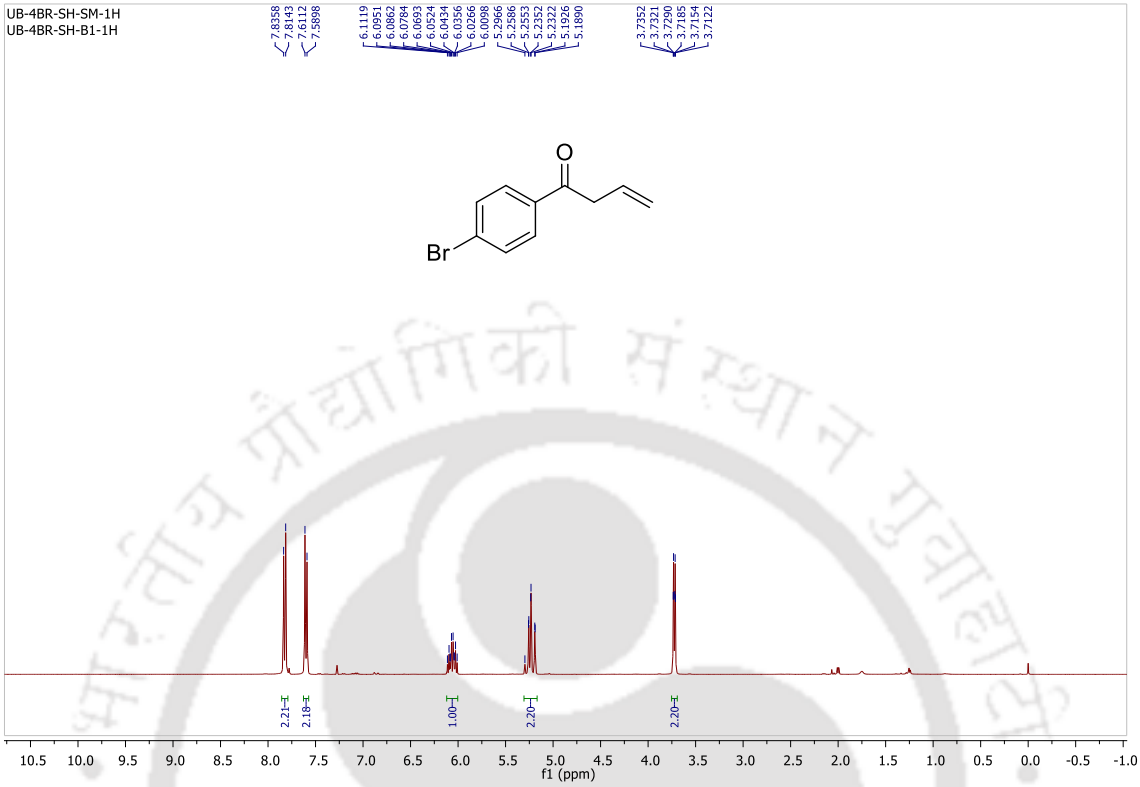
(4-bromophenyl)(4-hydroxy-2-methyl-1,1-dioxidotetrahydrothiophen-3-yl)methanone (26e′):

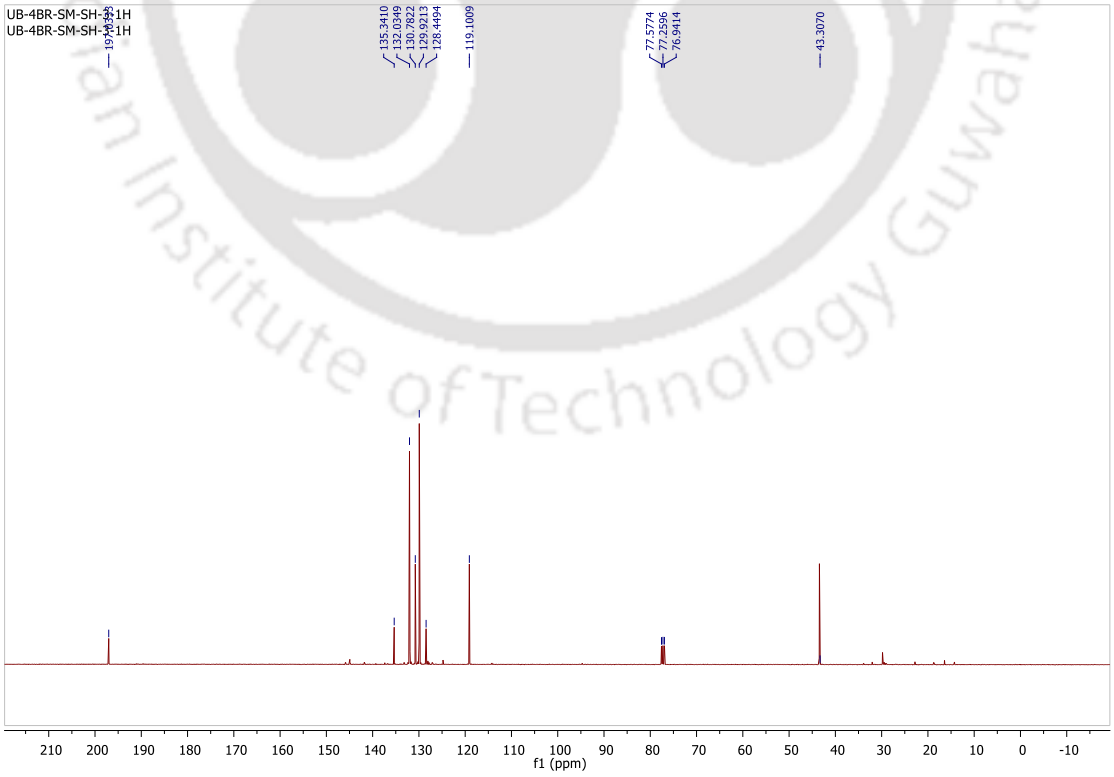


Colourless solid; R_f (hexane/EtOAc 1:1) 0.70; mp 160-164 ºC; yield 35 mg, 66%;^{1}H NMR (400 MHz, Acetone-d6) δ 1.24 (d, *J* = 6.4 Hz, 3 H), 3.25 (d, *J* = 14.0 Hz, 1 H), 3.52 (dd, *J* = 14.0and 5.2 Hz, 1 H), 3.80-3.86 (m, 1 H), 4.11 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 4.88 (d, *J* = 4.0 Hz, 1 H), 5.00-5.05 (m, 1 H), 7.70 (dd, *J* = 6.8 and 1.6 Hz, 2 H), 8.00 (dd, *J* = 6.8 and 1.6 Hz, 2 H); ^{13}C NMR (100 MHz, Acetone-d6) δ 10.8, 54.9, 57.3, 61.7, 68.9, 128.7, 131.2, 132.9, 136.1, 195.2; IR (KBr, neat) 3298, 2921, 2852, 1678, 1635, 1584, 1461, 1396, 1294, 1121, 1070, 1015, 867, 829, 731 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}BrO_4S$ $(M + H)^+$: *m/z* 332.9791, found 332.9801.

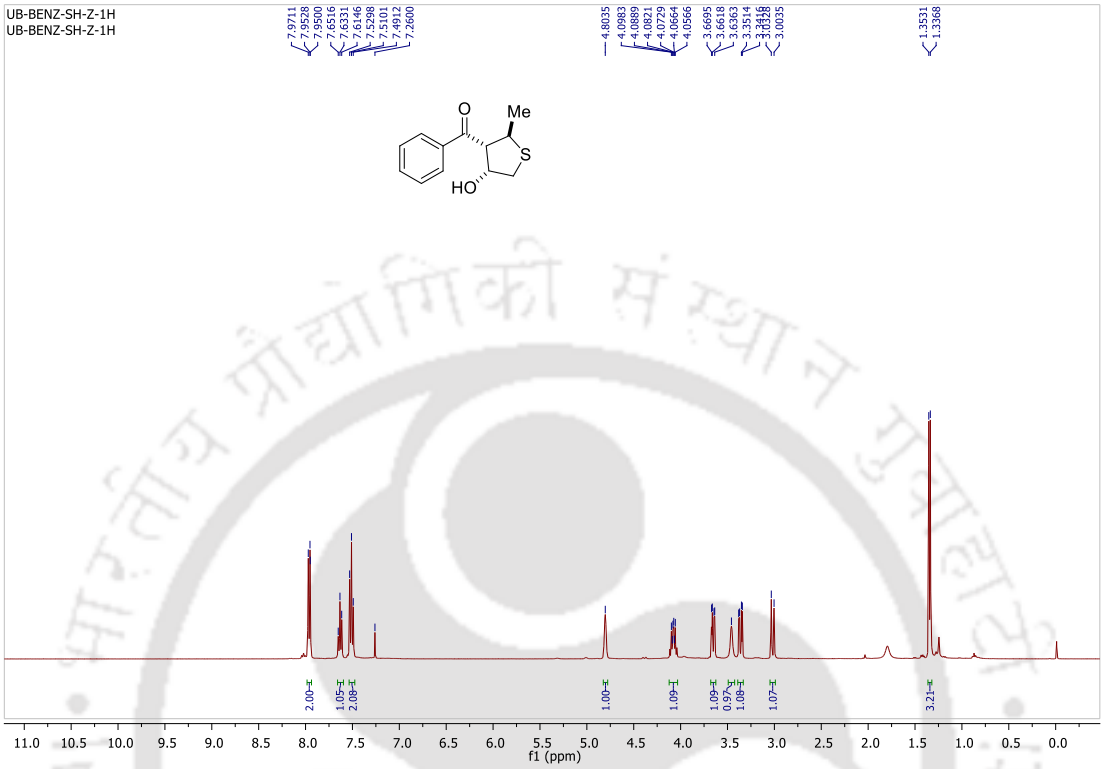
5.9. Selected spectra

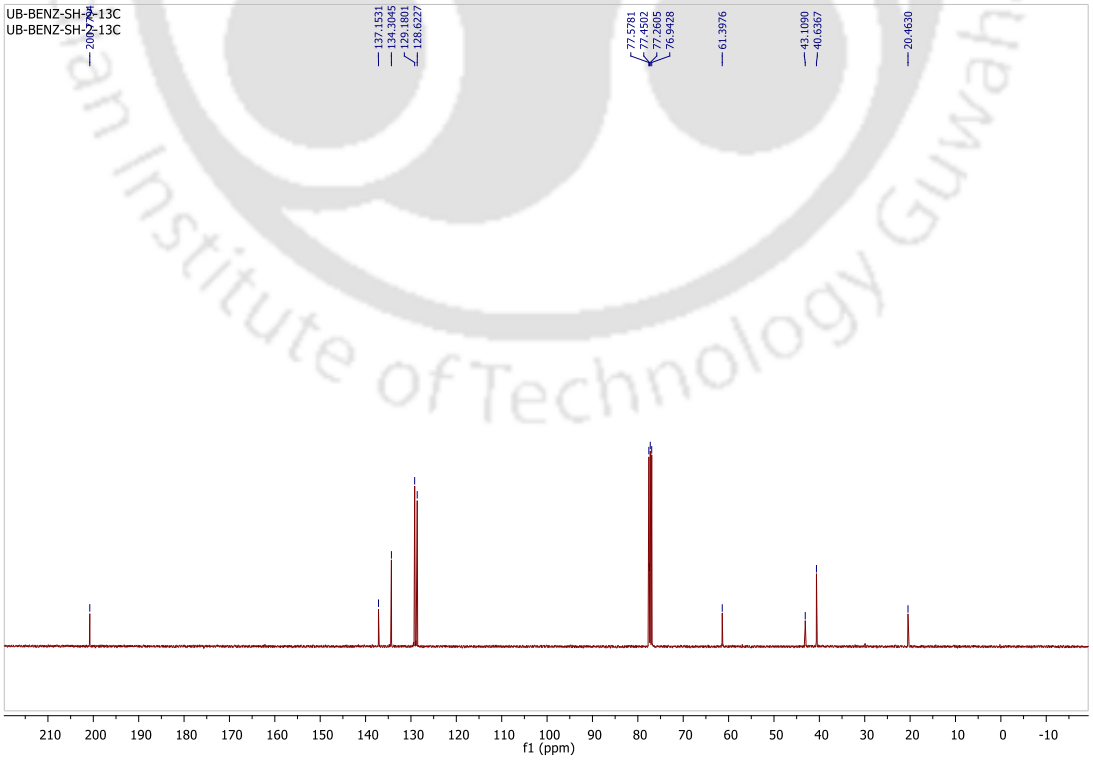
^{1}H and ^{13}C Spectra of compound (25e):



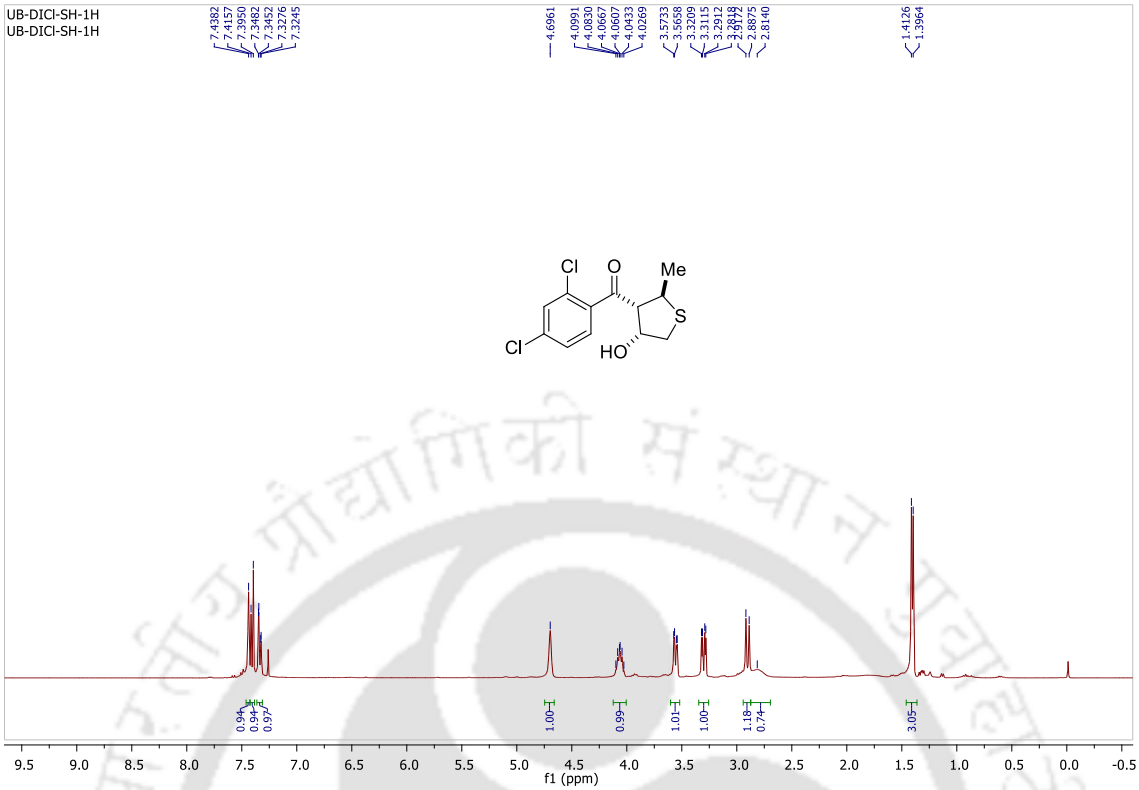


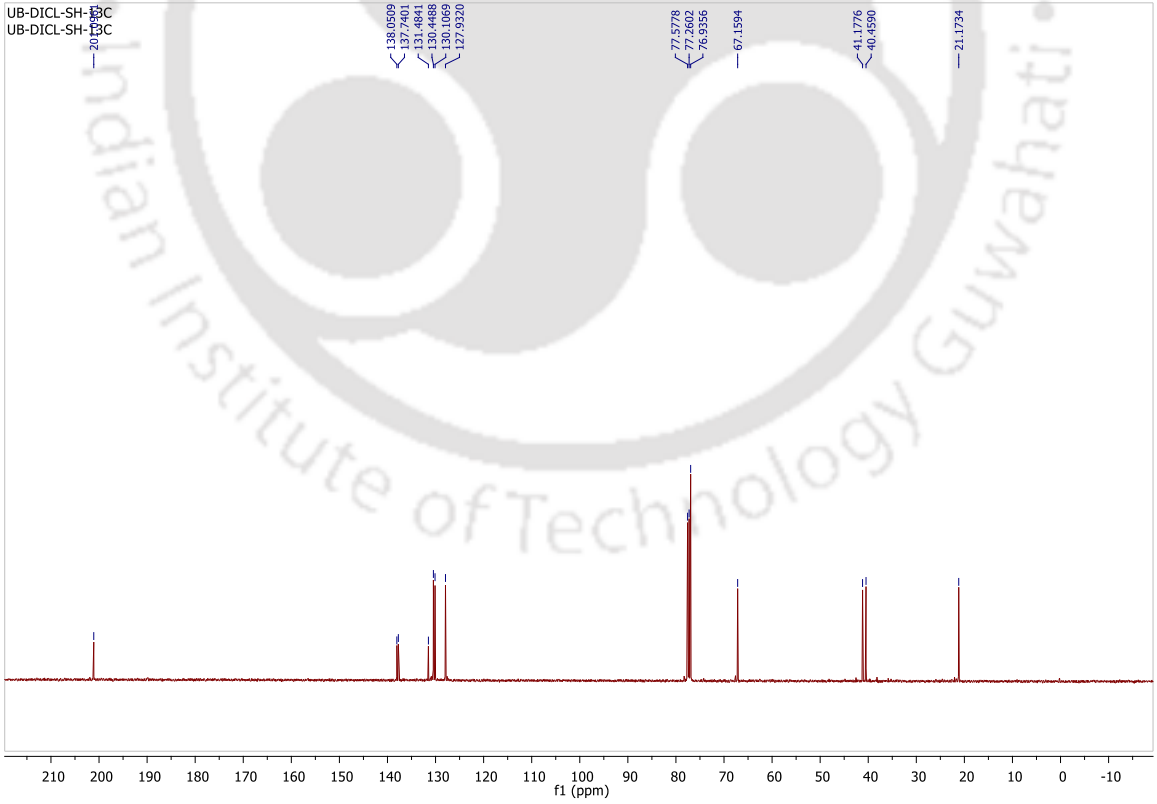
^{1}H and ^{13}C Spectra of compound (26a)



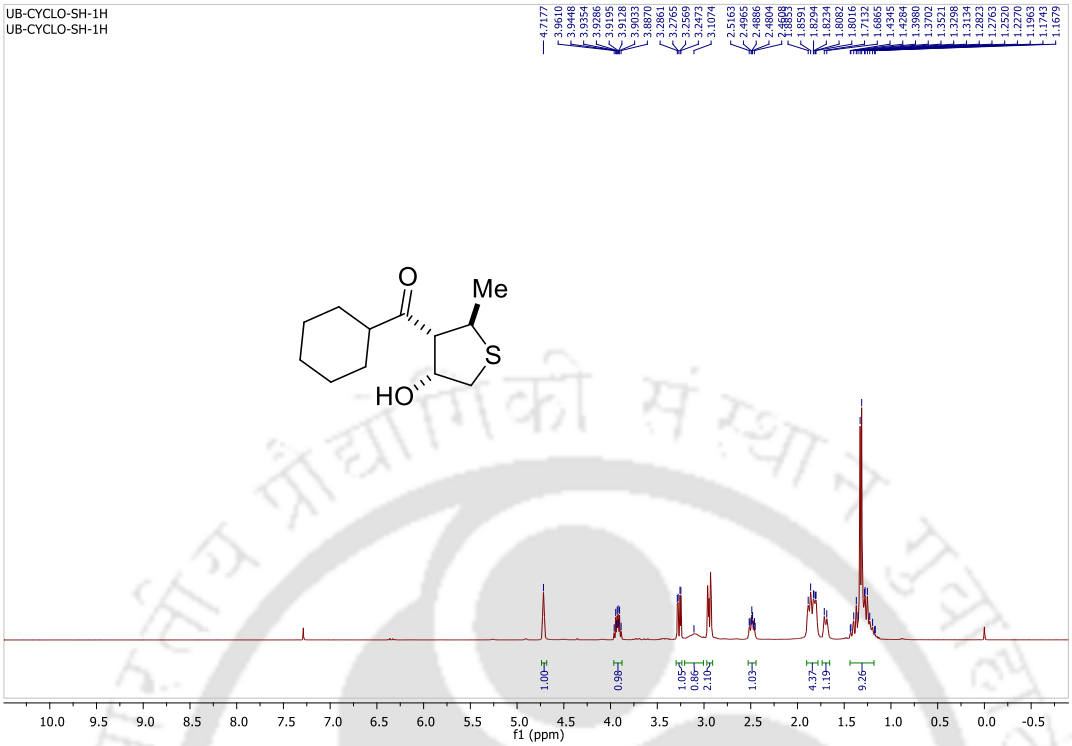


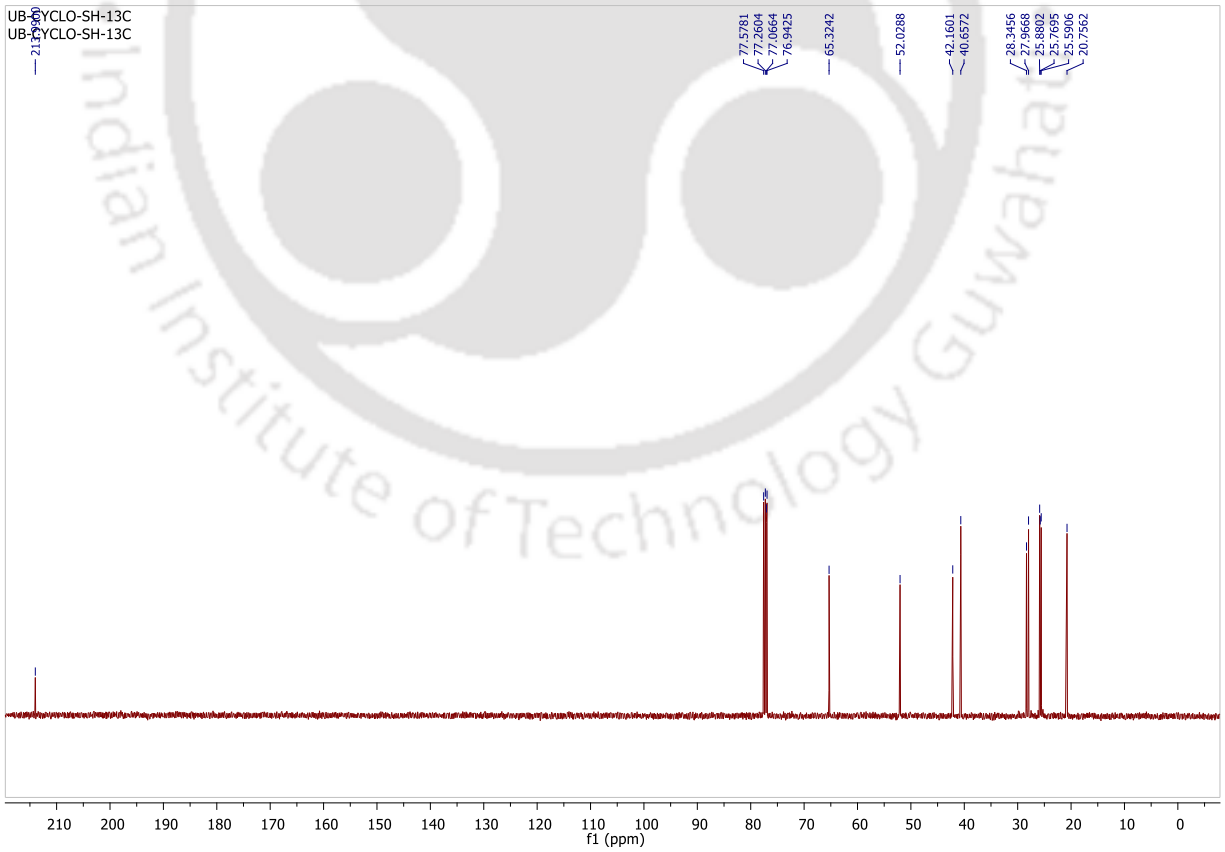
^{1}H and ^{13}C NMR spectra of compound **26g**



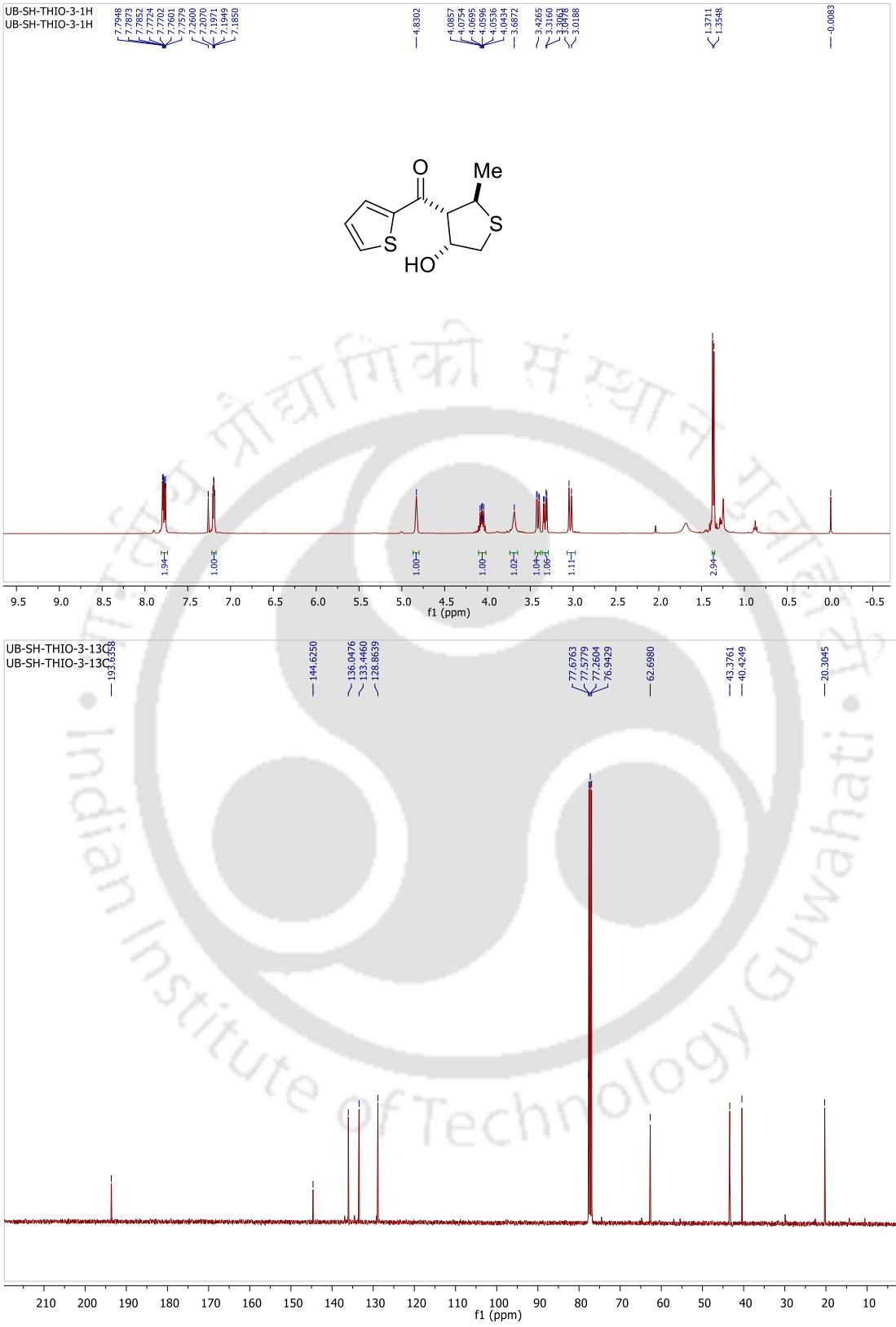


^{1}H and ^{13}C NMR spectraof compound **26n**

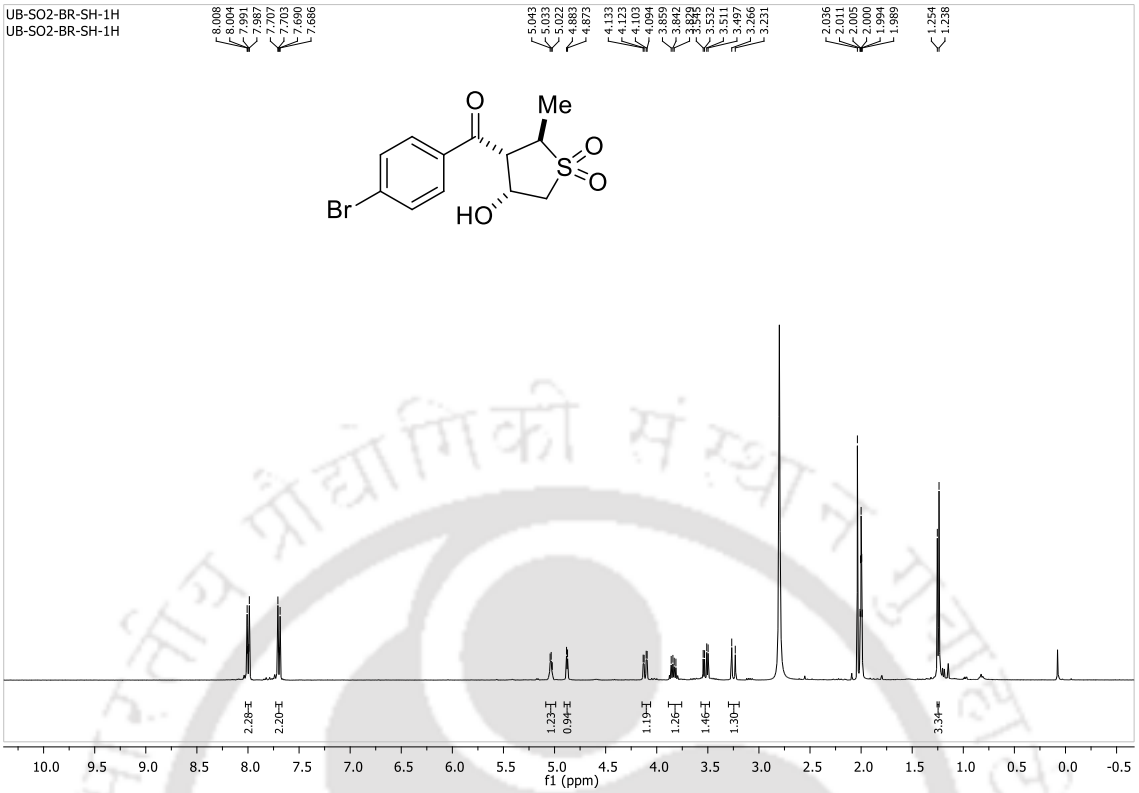


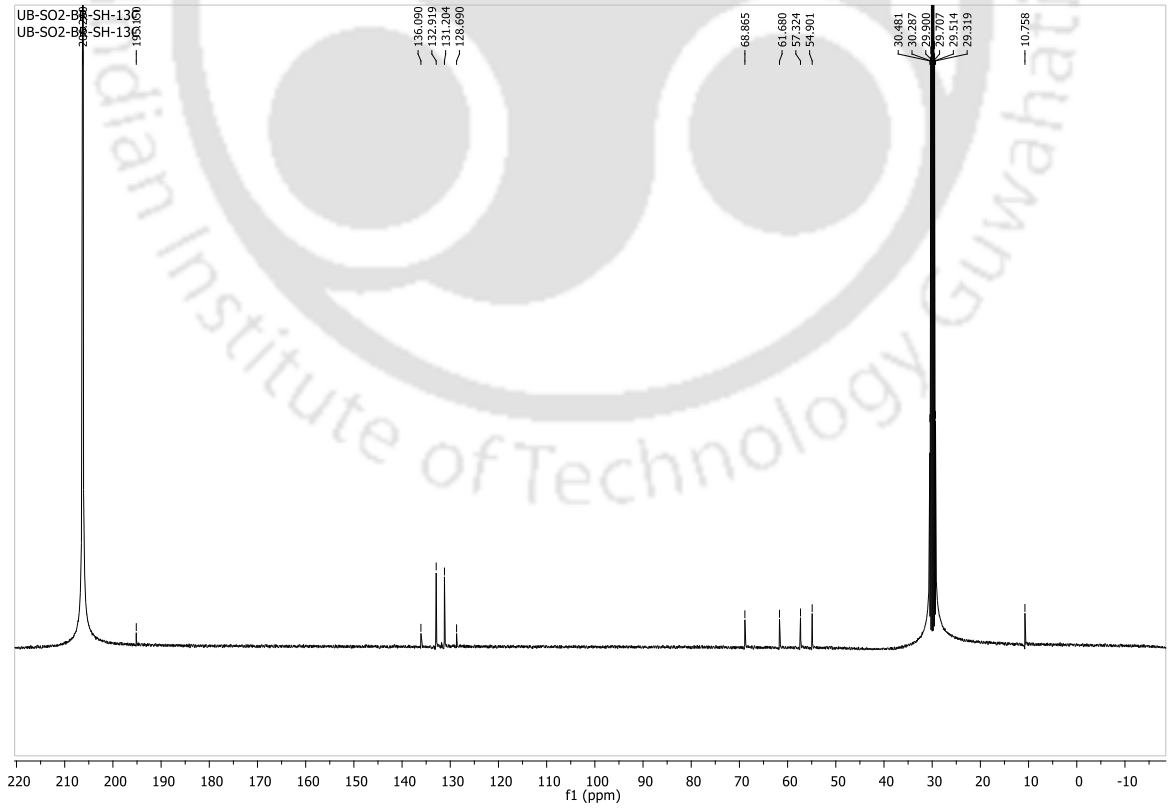


^{1}H and ^{13}C NMR spectra of compound **26q**



^{1}H and ^{13}C Spectra of compound (26e′):





5.9. Crystal parameters

The crystal parameters of compound **26e′**

	CCDC 1907356
Formula	C12H13BrO4S
Formula weight	333.19
T/K	293(2)
Crystal system	Monoclinic
Space group	C2/c
a/Å	22.2577(16)
b/Å	7.9662(4)
c/Å	15.8255(16)
α/°	90.00
β/°	109.144(10)
γ/°	90.00
V/Å^3	2650.8(4)
Z	8
Abs. Coeff./mm^{-1}	3.262
Abs. Correction	none
GOF on F^2	1.013
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0392
	wR2 = 0.0558
R indices [all data]	*R1* = 0.0772
	wR2=0.0882

5.10. References

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List of Publications

1. Synthesis of Tetrahydro-1*H*-indeno[1,2-*b*]pyridine *via* Cascade Cyclization and Friedel-Crafts Reaction" **Borthakur**, **U**.; Borah, M.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2016**, 81, 8736.
2. **"**Vinylsilanes in Highly Diastereo- and Regio-selective Synthesis of Dihydropyrans**"** **Borthakur**, **U**.; Biswas, S.; Saikia, A. K. *ACS Omega* **2019**, *4*, 2630.
3. "Bismuth Triflate Catalyzed Highly Diastereoselective Synthesis of Substituted Tetrahydrothiophene*via* Tandem Isomerization, Michael and Aldol Reactions" **Borthakur**, **U**.; Saikia, A. K. *ChemistrySelect **2019**, 4, 11136*.
4. "Diastereoselective Synthesis of Substituted Morpholines from *N*-Tethered Alkenols: Total Synthesis of (±)-Chelonin A" Borah, M.; **Borthakur**, **U**.; Saikia, A. K. *J. Org. Chem.* **2017,** *82*, 1330.
5. "Highly regioselective Synthesis of 4-tosylthiomorpholine *via* Intramolecular Cyclization of N-tethered Thioalkenol" Saikia, A. K.; Deka, M. J.; **Borthakur**, **U**. *Org. Biomol. Chem*. **2016**, *14*, 10489.
6. "Vinylsilanes in highly Diastereo- and Regio-selective Synthesis of 1,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one via Iminium–ene cyclization reaction" **Borthakur**, **U**.; Saikia, A. K. **2019** (*manuscript under preparation*).