Synthesis of Nitrogen and Oxygen Heterocyclic Compounds

A Dissertation Submitted to the
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as Partial Fulfillment for the Degree of

Doctor of Philosophy in Chemistry

Submitted by

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Dedicated

To

My Parents, Brother and Sisters

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled “**Synthesis of Nitrogen and Oxygen Heterocyclic Compounds**” 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 acknowledgement had been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Ms. **Ngangbam Renubala Devi** has been working under my supervision since July 2014 as a regular registered Ph. D. student. I am forwarding her thesis entitled “**Synthesis of Nitrogen and Oxygen Heterocyclic Compounds**” 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 her thesis and this work has not been submitted elsewhere for a degree.

th September, 2019
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Ngangbam Renubala Devi

LIST OF ABBREVIATIONS

Ac	*acetyl*	LAH	*lithium aluminium hydride*
Ar	*aryl*	LDA	*lithiumdiisopropyl amine*
($Bi(OTf)_3$)	*bismuth trifluoromethanesulfonate*	mp	*melting point*
Bn	*benzyl*	MS	*molecular sieves*
Bu	*butyl*	m/z	*mass to charge ratio*
CCDC	*cambridge crystallographic data centre*	NMO	*N-methylmorpholine N-oxide*
Cy	*cyclohexyl*	NMR	*nuclear magnetic resonance*
DCE	*1,2-dichloroethane*	NOESY	*nuclear overhauser enhancement spectroscopy*
DCM	*dichloromethane*	ORTEP	*oak ridge thermal ellipsoid plot*
DFT	*density function theory*	Ph	*phenyl*
DIAD	*diisopropylazodicarboxylate*	ppm	*parts per million*
DMAP	*4-dimethylaminopyridine*	Pr	*propyl*
DMF	*N, N-dimethylformamide*	*p*-TSA	*p-toluenesulfonic acid*
DMSO	*dimethylsulfoxide*	rt	*room temperature*
de	*diastereomeric excess*	THF	*tetrahydrofuran*
dr	*diastereomeric ratio*	TMSOTf	*trimethylsilyl trifluoromethanesulfonate*
EDDA	*Ethylenediamine acetic acid*		
ee	*enantiomeric excess*	TFA	*trifluoroacetic acid*
HRMS	*high resolution mass spectrometry*	TLC	*thin layer chromatography*
IR	*infrared*	TMS	*trimethylsilyl*
LA	*lewis acid*	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 research work presented in this thesis has been divided into four chapters based on the results of experimental work performed during the complete course of the research period. The chapter **1** of the thesis presents introduction to nitrogen and oxygen containing heterocyclic compounds, their biological significance and literature methods for their synthesis. Chapter **2** has been divided into two sub-sections, section **2A** and **2B**. Section **2A** describes regioselective synthesis of dihydropyran derivatives *via* oxonium-ene cyclization reaction catalyzed by bismuth(III) trifluoromethanesulfate ($Bi(OTf)_3$). Section **2B** represents trimethylsilyltrifluoromethanesulfonate (TMSOTf) catalyzed diastereoselective synthesis of substituted pyranopyrans from β-allenols and aldehydes. Chapter **3** deals with stereo- and regio-selective synthesis of substituted pyrollidines mediated by Indium (III) chloride. Chapter **4** is about regioselective synthesis of 4-vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-tethered benzyl-alkenols catalyzed by Indium (III) Chloride. The methodology is exemplified with the formal synthesis of (±)-isocyclocelabenzine.

Chapter 1: Introduction to nitrogen and oxygen containing heterocyclic compounds

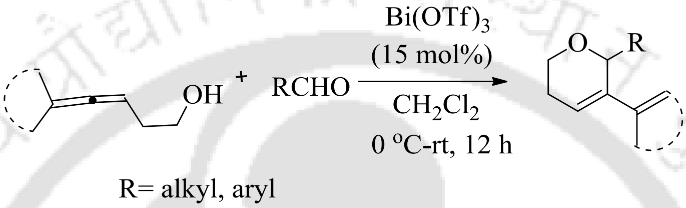
Five and six membered nitrogen and oxygen heterocyclic compounds are the core structural units found in a broad array of natural products, bioactive compounds as well as in important synthetic intermediates. Wide range of biological activities and the synthetic usefulness, give nitrogen and oxygen heterocyclic compounds provides a valuable asset to the organic synthetic community. Heterocycles *e.g.* dihydropyrans, tetrahydropyrans, pyranopyrans, pyrrolidines and piperidines, to name a few, are important structural motifs in many natural and biologically active compounds.

Over the years, many synthetic strategies have been developed in order to mimic all these naturally available compounds or to build a part of these complicated systems. The most widely used methods are the 1,*n*-enyne rearrangement, ring-closing metathesis, Prins cyclization reactions, oxonium-ene reactions and transition metal salts catalyzed cyclization reactions etc. Among these methods transition metal catalyzed cyclization of 1,*n*-enynes provides several advantages over the traditional strategies because various new functional groups are easily introduced into the ring systems as well as the method acts as a powerful tool for the synthesis of nitrogen and oxygen heterocycles. Oxonium-ene reactions also attracted attention due to the formation of exclusive single isomers, generation of olefin functional groups and application in natural product synthesis.

Chapter 2:

Section A: Regioselective synthesis of dihydropyrans *via* oxonium-ene reaction of *β*-allenols and aldehydes

Allenols are considered as a versatile intermediate in organic synthesis due to their high reactivity. They can undergo self-cyclization reaction or intermolecular reaction easily. Therefore, in this chapter, we described a $Bi(OTf)_3$ catalyzed oxonium-ene cyclization reaction of allenic alcohols with aldehydes for the synthesis of 3,6-dihydro-2*H*-pyrans in good yields. The reaction conditions are very mild and pleasant (*Scheme 1*).



Scheme 1. *Synthesis of dihydro-2H-pyrans and the scope of the reaction*

The reaction is highly regioselective as the two olefinic bonds are *trans* to each other. In NOE spectra of compound 5-(cyclopent-1-en-1-yl)-6-(2-nitrophenyl)-3,6-dihydro-2*H*-pyran, irradiation of peak at 6.01ppm showed enhancement of peaks at 2.53 ppm and also irradiation of peak at 5.31 ppm showed enhancement of peaks at aromatic peak at 7.28 ppm as well as aliphatic peak at 6.21 ppm. The structure is finally concurred by X-ray crystallography of the same compound.

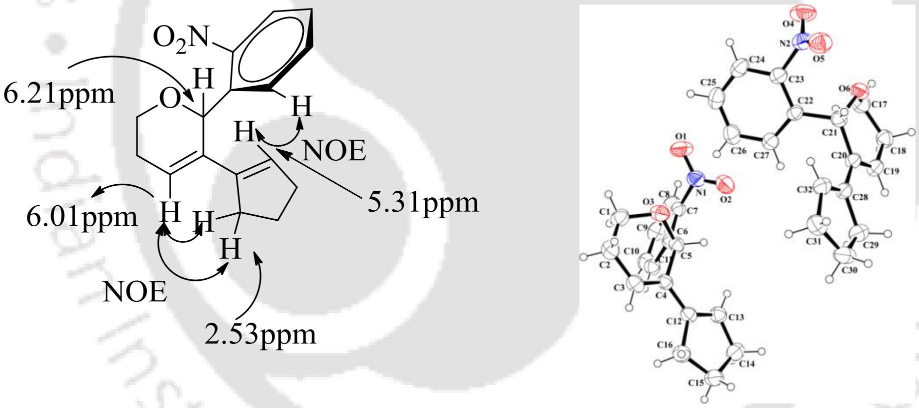
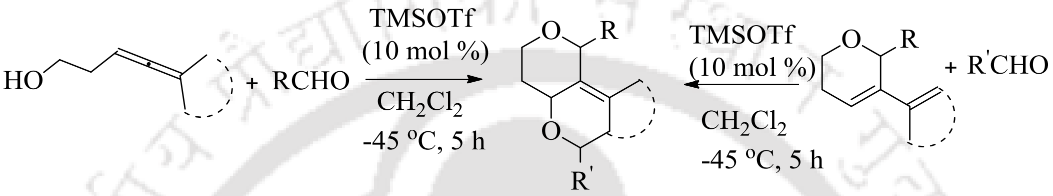


Figure 1*. NOE and X-ray cryatallography structure of 5-(cyclopent-1-en-1-yl)-6-(2-nitrophenyl)-3,6-dihydro-2H-pyran*

In conclusion, we have developed a mild, efficient, and general method for the synthesis of dihydropyrans *via* oxonium-ene reaction from *β*–allenols and aldehydes in good yields. The method is highly regioselective.

Section B: TMSOTf catalyzed diastereoselective synthesis of pyranopyrans using *β*-allenols and aldehydes

This section briefly discusses about an efficient method for the diastereoselective synthesis of pyranopyrans using *β*-allenols and aldehydes catalysed by TMSOTf at - 40 °C for 5 h. The reaction is achieved *via* oxonium-ene reaction of *β*-allenols and aldehydes followed by [4+2] hetero Diels-Alder type cyclization with another aldehyde molecule (*Scheme 2*). The pyranopyrans can also be directly obtained from the reaction of dihydropyrans (*as synthesized in Section A*) and aldehydes under similar reaction conditions.



Scheme 2. *Synthesis of pyranopyrans and scope of the reaction.*

The structure and stereochemistry of pyranopyrans are determined from NMR spectroscopy and 2D- nuclear Overhauser effect as well as X-ray crystallographic analysis of compound Dimethyl 4,4'-((1S*,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-*c*]isochromene-1,6-diyl)dibenzoate (*Figure 2*).

In conclusion, we have developed an efficient method for the synthesis of substituted hexahydropyrano[4,3-*b*]pyran skeletons in moderate yields *via* oxonium-ene reaction followed by [4+2] cycloaddition reaction. The reaction is highly regioselective as well as diastereoselective. The strategy is compatible with a wide range of functional groups.

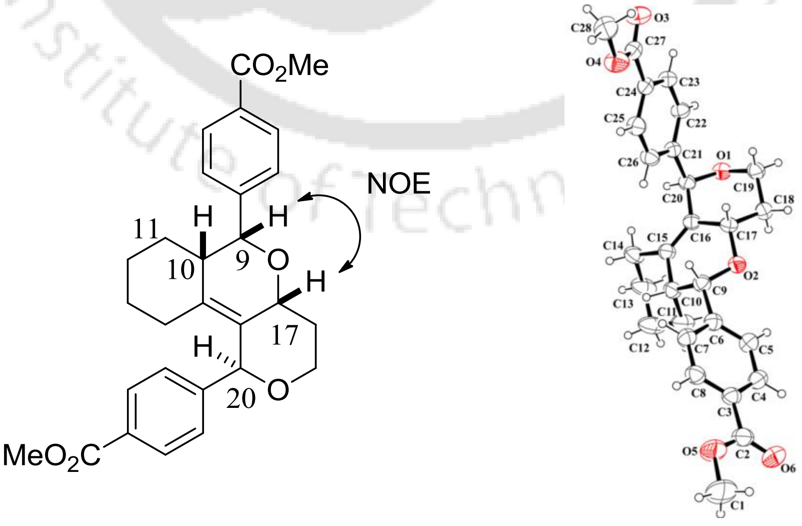
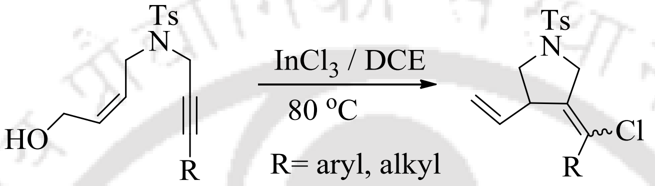


Figure 2. *NOE and X-ray crystallographic structure of Dimethyl 4,4'-((1S*,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene-1,6-diyl)dibenzoate*

Chapter 3: Stereo- and regio-selective synthesis of 4-vinylpyrrolidine from *N*-tethered alkyne-alkenol

Lewis acids such as $FeCl_3$ and $InCl_3$ have long been used in organic synthesis for different transformations. The utility of indium trichloride as Lewis acids are encouraged by their unique π-acidity, alkynophilicity, relatively low toxicity, air, moisture compatibility and recyclability. We now present a methodology for the synthesis of pyrrolidine derivatives using intramolecular C−C bond formation from *N*-tethered alkyne-alkenol mediated by $InCl_3$ in moderate to good yields with good regio- and stereo-selectivity. (*Scheme 3*)

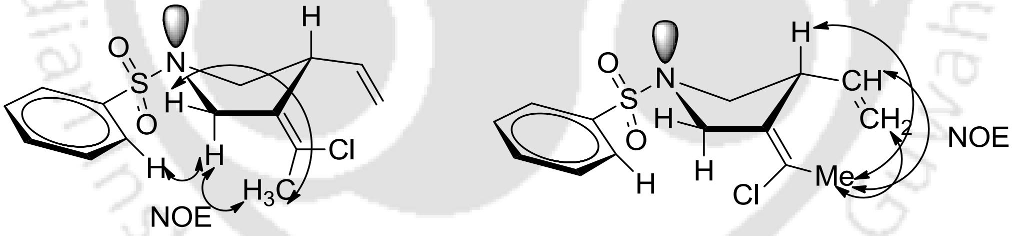


E:***Z*** selectivity upto **6:94**

Yield upto **90%**

Scheme 3. *Synthesis of N-vinyl pyrrolidines and scope of the reaction.*

The reaction is highly regio- and stereo-selective giving *Z* selectivity as major products in all substrates. The stereochemistry of the pyrrolidine products was confirmed by nOe of compounds *E* and *Z* 3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine (*Figure 3*).



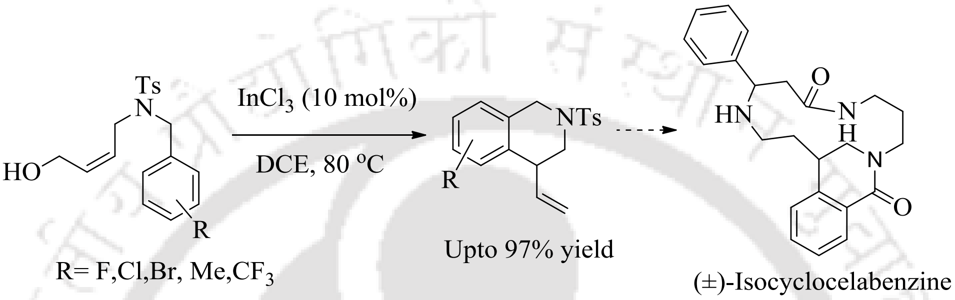
***E*-(minor)** *Z*-**(major)**

Figure 3. *NOE of E and Z 3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine.*

In conclusion, we have developed an efficient reaction condition for the synthesis of substituted vinyl pyrrolidine derivatives with exocyclic vinyl chloride at 3-position as well as vinylic group at 4-position of the pyrrolidine rings *via* indium(III) chloride mediated intramolecular cyclization reaction of *N*-tethered alkyne-alkenols in good yields. One of the important aspects of the reaction is the dual role exhibited by indium(III) chloride as Lewis acid as well as chloride source.

Chapter 4: Synthesis of tetrahydroisoquinolines from *N*-tethered benzyl-alkenol mediated by Indium(III) chloride: Formal synthesis of (±)-Isocyclocelabenzine

In this chapter, we briefly discuss a general methodology for the synthesis of tetrahydroisoquinoline derivatives (*Scheme 4*). The methodology was further extended for the formal synthesis of (±)-isocyclocelabenzine, a type of spermidine alkaloids, first isolated from *Maytenus mossmbicensis*.



Scheme 4. *Synthesis of 2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline and formal synthesis of (±)-isocyclocelabenzine.*

In conclusion, we have developed a mild and efficient method for the synthesis of vinyl substituted tetrahydroisoquinoloine derivatives *via* intramolecular cyclization of *N*-tethered benzyl-alkenol in high yields. The methodology is compatible with a wide range of functional groups. The advantage of the reaction is the generation of vinyl functionality regioselectively at such a position which can be used for the formal synthesis of (±)-isocyclocelabenzine alkaloids.

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CHAPTER 1

Introduction to Nitrogen and Oxygen Heterocyclic Compounds

1.1. Background:

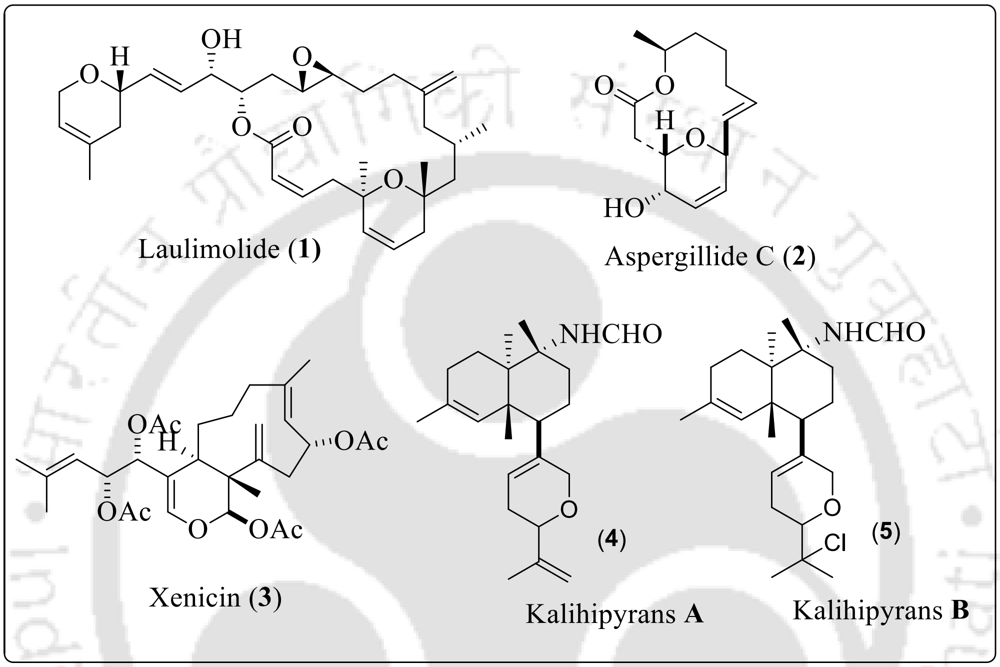
Cyclic compounds can be broadly classified into two types; carbocycles, those cyclic structures having only carbons in the ring system and heterocycles, those cyclic structures having another element in addition to carbons. The other elements can be nitrogen, oxygen, sulfur or any other elements. Heterocycles containing above elements are widely known because of their higher abundancy in naturally occurring bioactive molecules. Various cyclic bio-active molecules are well known but five-, six-, and seven-membered cyclic structures are more common in nature. In our contribution we tried to mimic these naturally occurring bioactive molecules by using various known reactions. In this chapter we will discuss a short history of *N*- and *O*-heterocycles.

Nitrogen heterocycles such as pyrrolidines, piperidines and isoquinolines are more abundant in nature. As such five- and six-membered saturated oxygen heterocycles *e.g.* dihydropyrans, tetrahydropyrans, tetrahydrofurans, pyranopyrans and isochromanes are also important structural motifs in many natural and biologically active compounds.[1] It is well explored that fused pyran derivatives showed numerous types of a pharmacological and biological properties, such as fungicidal, insecticidal, acaricidal activity, antiviral, anticonvulsant and antileishmanial activity. Moreover, they have been introduced as non-peptide human immunodeficiency virus (HIV) protease inhibitors. Despite their wide range of pharmacological, industrial, and synthetic applications, the synthesis of pyranopyrans has received little attention. In this chapter we will discuss a brief history, importance, applications and synthesis of dihydropyrans, pyranopyrans, pyrrolidines and tetrahydroisoquinoline derivatives.

1.2. Importance and applications of *O*-hetercycles:

1.2.1. Dihydropyrans:

Various oxygen containing heterocycles are abundantly found in nature. Most of the pharmacological activities are attributed to the substitution pattern on the heterocyclic rings. Five- and six-membered oxygen containing heterocycles possess significant biological properties among them dihydropyrans are widely spread in natural products or biologically active molecules (*Figure 1.2.1.1*). For example, dihydropyrans such as laulimalide (**1**) is a cancer therapeutic lead recently isolated from pacific marine sponges.[2] Aspergillide C (**2**) is a 14-membered macrolide which has a property of cytotoxity, firstly derived from the marine fungus *Aspergillus ostianus* also contains dihydropyran ring.[3] Xenicin (**3**) is a diterpenoid having a nine membered carbocyclic ring. It is a marine natural product obtained from the soft coral *Xenia elongate* and has significant cytotoxic and antibacterial properties.[4] Similarly, diterpenes kalihipyrans **A** (**4**) and **B** (**5**) derived from marine sponge *Acanthella carvernosa*, are also used in antifouling activity.[5]



Laulimolide (**1**)

Aspergillide C (**2**)

Xenicin (**3**)

(**4**)

Kalihipyrans **A**

(**5**)

Kalihipyrans **B**

Figure 1.2.1.1: Bioactive molecules containing dihydropyrans.

1.2.2. Pyranopyrans:

Pyranopyrans are the class of bicyclic compounds containing oxygen on both rings. They also possess many medicinal values (*Figure 1.2.2.1*). The glycofused benzopyran **6** was recently identified as a novel ligand for amyloid *β*-peptidase in the development of novel therapeutics for Alzheimer's disease.[6a] Martiriol (**7**) which has both dihydropyran and pyranopyran rings is isolated from the red algae of the genus *Laurencia* and shows potent activity against various tumor cells.[7] Compound **8** is a natural product produced by a rare bacterial strain *Actinoalloteichus nanshanensis sp. Nov*. Salinomycin (**9**) is an antibiotic that has recently been found to activate cell death in a variety of human cancer cells.[6b] Salinomycin is a polyether made by a strain of *streptomyces albus*. Streptomyces is a type of bacteria, usually found in soil but sometimes on plants and animals.[8]

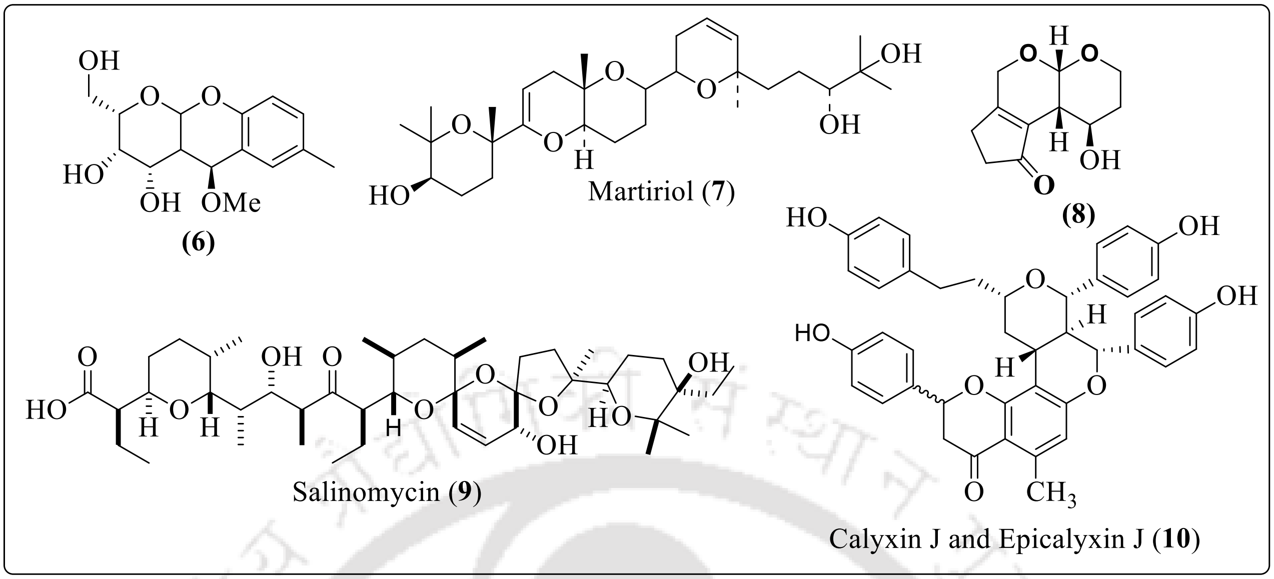


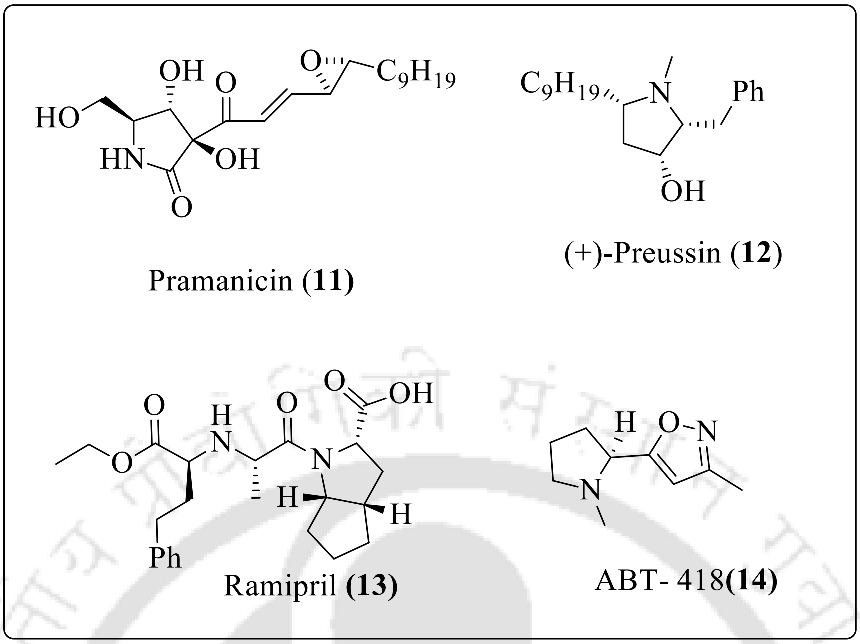
Figure 1.2.2.1: Biologically active compounds containing pyranopyran rings.

Calyxin J and epicalyxin J (**10**) are also pyranopyran containing heterocyclic biomolecules which show antitumor activity.[9]

1.3. Importance and applications of *N*-heterocycles:

1.3.1. Pyrrolidines:

Pyrrolidines are the class of 5-membered saturated nitrogen heterocyclic compounds. They can be found in various natural sources (*Figure 1.3.1.1*). Five-membered nitrogen containing heterocyclic compounds possesses varieties of biological and pharmacological importance such as pramanicin (**11**), an inhibitor of *Cryptococcus neoformans*, was isolated from a sterile fungus which has subsequently been identified as a species of *Stagonospora*.[10] (+)-Preussin (**12**) has a significantly broader spectrum of antifungal activity, it is isolated from fermentation of *Aspergillus ochraceus* ATCC 22947 and *Preussia* sp.[11] Ramipril (**13**) is an angiotensin-converting enzyme (ACE) inhibitor, used for the treatment of high blood pressure and congestive heart failure.[12] Likewise, ABT-418 (**14**) is a cholinergic channel activator which is also used for treatment of both Alzheimer's disease and ADHD.[13]



Pramanicin (**11**)

(+)-Preussin (**12**)

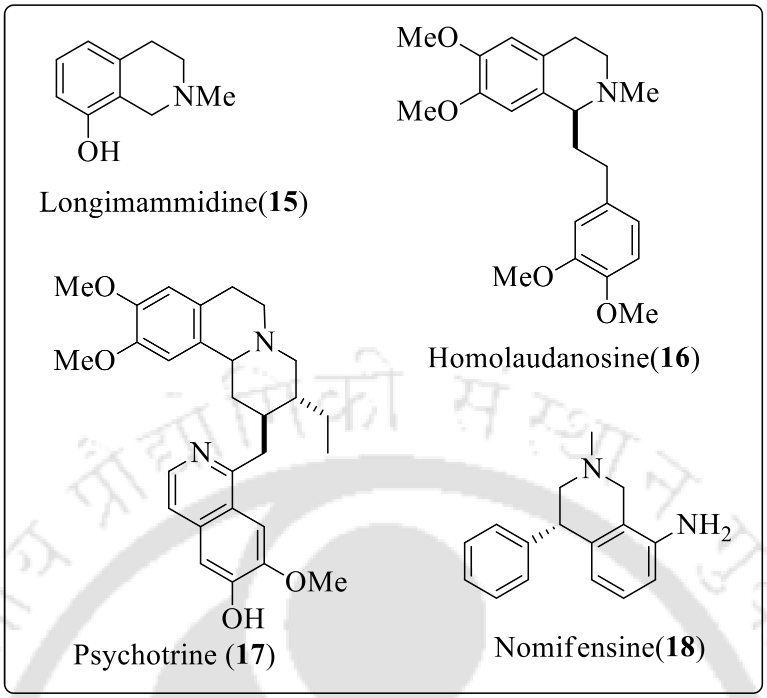
Ramipril **(13)**

ABT- 418**(14)**

Figure 1.3.1.1: Biologically active compounds containing pyrrolidine rings.

1.3.2. Tetrahydroisoquinolines (THIQ):

Saturated alkaloids such as tetrahydroisoquinolines (THIQ) are abundantly found in nature. They are very much part of the naturally rich bioactive molecules (*Figure 1.3.2.1*). For example, hydroxyl substituted THIQ derivative Longmammidine (**15**), also known as cactus alkaloids, is extracted from the Mexican cactus *Dolichothele longimamma*.[14] This alkaloid tends to cause psychotic effects. Another THIQ derivative homolaudanosine (**16**) is isolated from the plant *Dysoxylum lenticellare* shows cardio active properties on rat cardiac tissues.[15] Psychotrine (**17**), a type of THIQ derivative is found to be a potent inhibitor of DNA polymerase activity of human immunodefiency virus-1 reverse transcriptase.[16] Nomifensine (**18**) is used as anti-depressant drug by increasing the amount of synaptic norepinephrine and dopamine availability to receptors by blocking the dopamine and norepinephrine reuptake transporters.[17]



Longimammidine(**15**)

Homolaudanosine(**16**)

Psychotrine (**17**)

Nomifensine(**18**)

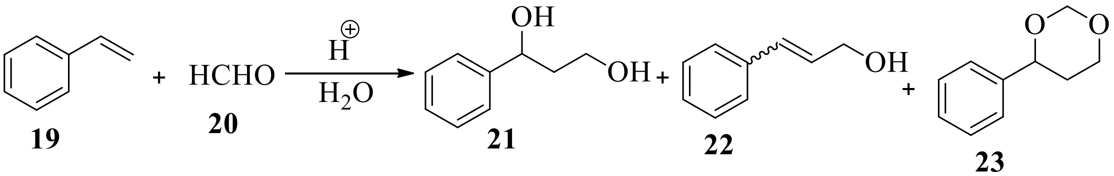
Figure 1.3.2.1: Biologically active compounds containing THIQs.

1.4. A brief reviews and discussions on the synthesis of nitrogen and oxygen containing heterocyclic compounds:

Various methodologies for the synthesis of these heterocyclic compounds are known but modern and lesser time consuming synthetic methods are still preferred. Over the years, many synthetic strategies have been developed in order to mimic all these naturally available compounds or to build a part of these complicated systems. The most widely used method for oxygen heterocycles are the Prins cyclization, oxa-Pictet-Spengler, hetero-Diels-Alder, oxonium-ene cyclization, 1,*n*-enyne rearrangement and transition metal salts catalyzed cyclization etc. Transition metal-catalyzed oxidative cyclization of 1,*n*-enynes, provides an efficient mechanism for the synthesis of nitrogen and oxygen heterocyclic compounds. Metal catalyzed cyclization of *N*-tethered alkyne-alkenol[18a]/alkanol[18b]/epoxide[18c] also provides a new pathway for the synthesis of *N*-heterocycles to give almost single product diastereoselectively.

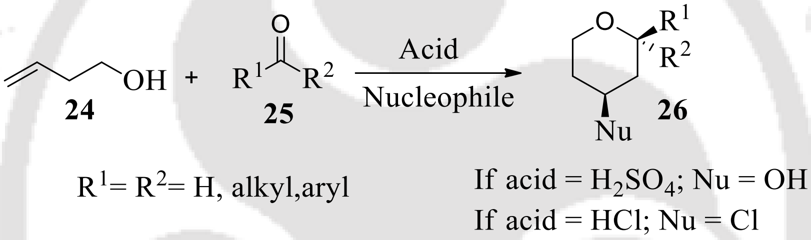
1.4.1. Prins cyclization:

In 1919 Dutch chemist H. J. Prins first reported a reaction between simple styrene (**19**) and formaldehyde (**20**) in aqueous acidic medium, which resulted in a mixture of products such as diol **21**, unsaturated alcohol **22** and 1,3-dioxane **23** (*Scheme 1.4.1.1*).[19]



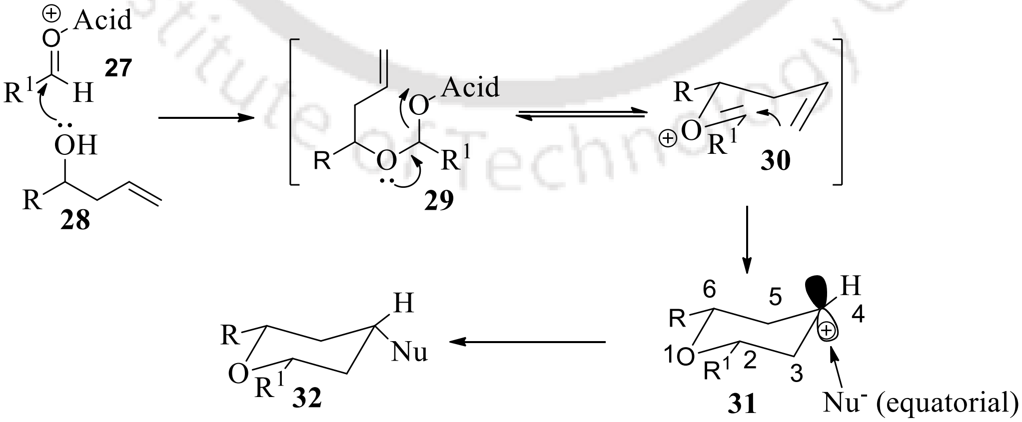
Scheme 1.4.1.1

In 1955, Hanschke has further developed Prins reaction for the selective synthesis of tetrahydropyran (THP) rings **26** by reacting 3-buten-1-ol (**24**) with various aldehydes or ketones **25** in the presence of acid, called Prins cyclization reaction (*Scheme 1.4.1.2*).[20]



Scheme 1.4.1.2

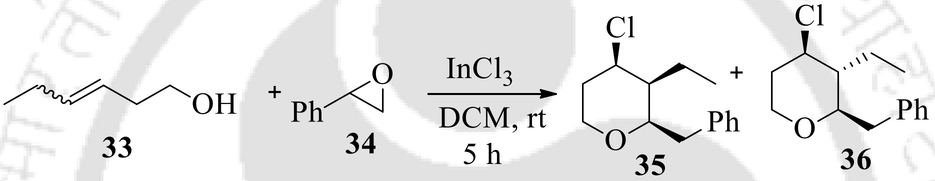
In most of the cases the Prins cyclization reaction is highly diastereoselective and give 2,4,6-substituted tetrahydropyrans with all equatorial substitutions. The diastereoselectivity can be



Scheme 1.4.1.3. Mechanism of the Prins cyclization reaction.

explained by considering the mechanism of the reaction.[21]The lone pair of the homoallylic alcohol **28** attacks the carbonyl centre of the aldehyde **27** in the presence of acid to generate an oxocarbenium ion **30** as a key intermediate, which undergoes 6-*endo*-trig-cyclization to give more stable tetrahydropyranyl cation **31**. According to Alder's DFT calculations, carbocation **30** in its chair conformation is stabilized by stereoelectronic effects. The C2- C3 and C5-C6 σ* and σ orbital overlap both the equatorial lone pair of the oxygen atom and the vacant p orbital at C4. Optimal overlap is reached when the hydrogen atom at C4 is pseudo-axial. This stabilization favors equatorial attack by the nucleophile to give tetrahydropyran **32** (*Scheme 1.4.1.3*).

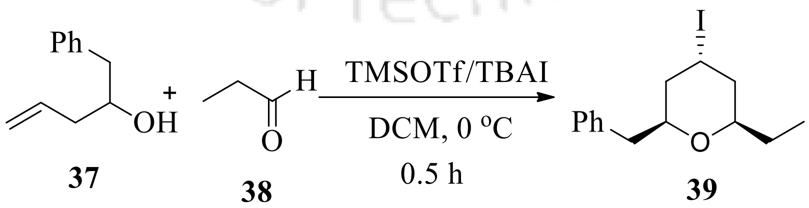
Li and coworkers reported a methodology for the synthesis of 4-chlorotetrahydropyrans **35** and **36** from homoallylic alcohols **33** and epoxides **34** as aldehyde alternative in the presence of $InCl_3$



Alkene	yield	**35**:**36**
E	87%	0:100
Z	96%	100:0

Scheme 1.4.1.4

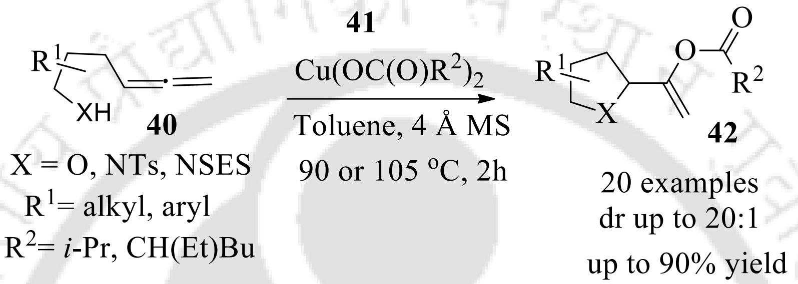
(*Scheme 1.4.1.4*). The stereochemistry depends upon the geometry of olefin, when *cis* unsaturated alcohol was used 2,3,4-trisubstituted tetrahydropyran **35** with *cis* conformation was obtained as the major product. However, when *trans* unsaturated alcohol, such as *trans*-3-hexene-1-ol was used, 2,3,4-trisubstituted tetrahydropyran **36** with a *trans–trans* conformation was obtained as the major product.[22]



Scheme 1.4.1.5

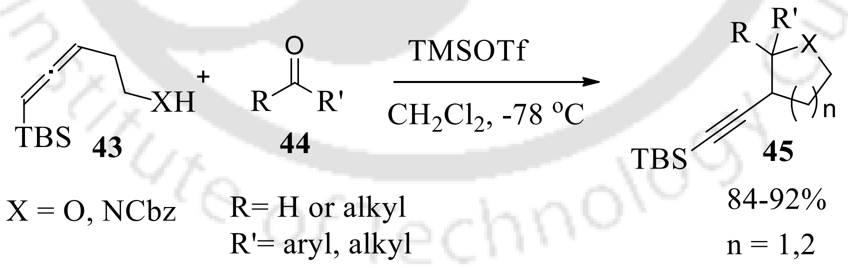
Saikia and coworkers reported an axial selective Prins cyclization reaction for the synthesis of axial-4-iodotetrahydropyran **39** from simple homoallylic alcohol **37** and aldehyde **38** promoted by TMSOTf and tetrabutylammonium iodide (TBAI) (*Scheme 1.4.1.5*).[23]

Chemler and co-workers reported a copper (II) salt **41** promoted intramolecular Prins cyclization reaction of allenols and allenylsufonamides **40** giving a heterocycle-fuctionalized vinyl carboxylate **42** (*Scheme 1.4.1.6*).[24]



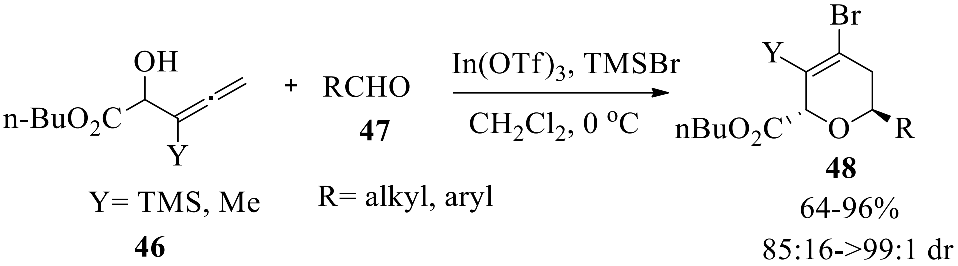
Scheme 1.4.1.6

Allenylsilanes **43** also underwent Prins cyclization reaction with carbonyl compounds **44** to give a highly regio- and stereo-selective di- or tri-substituted tetrahydrofurans, tetrahydropyrans, and pyrrolidines (**45**) with high regio- and stereo-selectivity in the presence of TMSOTf in high yields (*Scheme 1.4.1.7*).[25]



Scheme 1.4.1.7

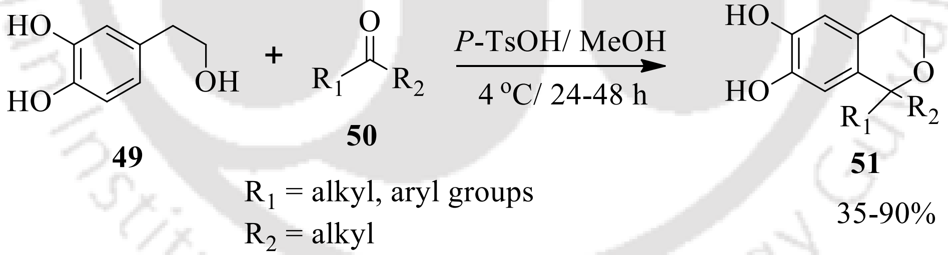
The use of carboalkoxyl allenic alcohol **46** with aldehydes **47** for the efficient synthesis of pyranyl motifs *via* Prins cyclization is described by Loh and co-workers. This method provides an easy access to 2, 6-trans dihydropyrans **48** in good yield with high diastereoselectivity (*Scheme 1.4.1.8*).[26]



Scheme 1.4.1.8

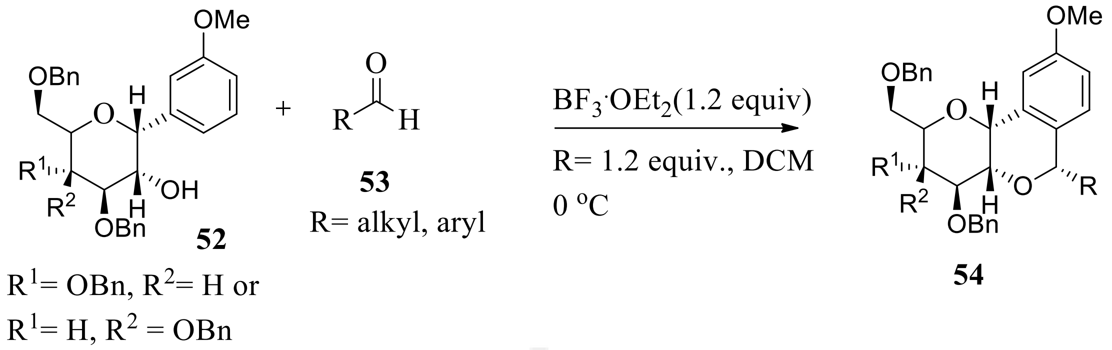
1.4.2. Oxa-Pictet-Spengler reaction:

In 1922, Wünsch and Zott fo the first time reported oxa-Pictet-Spengler reaction. In this reaction, a compound such as a 2-arylethanol reacts with an aldehyde or a ketone, as such or in masked form, to give an aromatic compound with a newly formed pyranic ring. Later, it was modified by many scientists. Guiso and co-workers developed a method for the synthesis of substituted isochromanes **51** *via* oxa-Pictet Spengler reaction between 2-(3,4-dihydroxy) phenylethanol (**49**) and carbonyl compounds **50** using *p*- toluenesulfonic acid as a catalyst at 4 °C (*Scheme 1.4.2.1)*. In this reaction condition, it was found that aldehydes react faster than ketones and aromatic aldehydes gave higher yields than their aliphatic counterparts.[27]



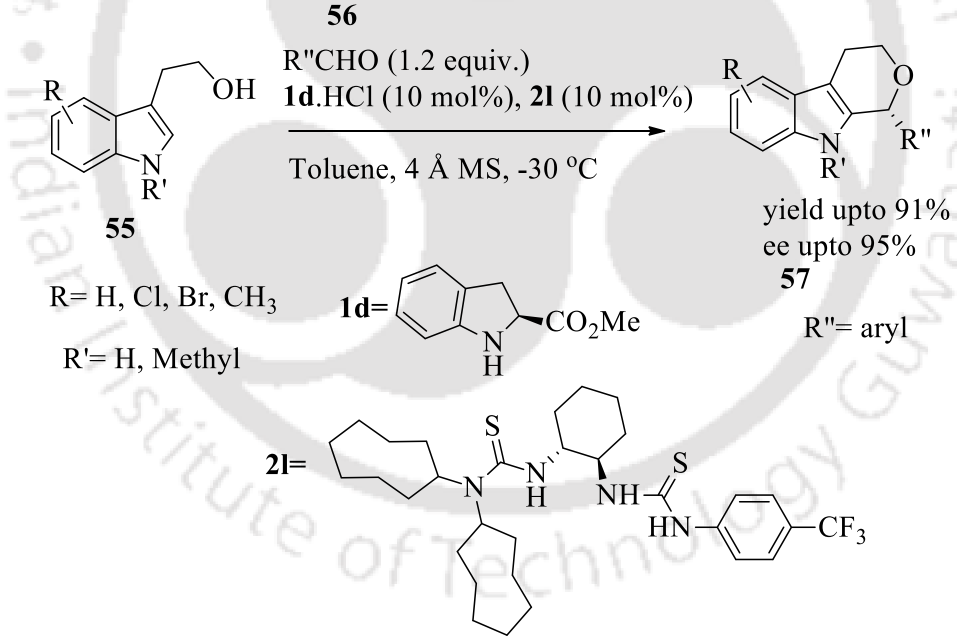
Scheme 1.4.2.1

In 2018, Vankar and co-workers reported a highly stereoselective synthesis of sugar fused 1,2-annulated isochromans **54** *via* oxa-Pictet-Spengler cyclization reaction using C2-hydroxy-*α*-C-arylglycosides **52** and aldehydes **53** in the presence of $BF_3{\cdot}OEt_2$ (*Scheme 1.4.2.2*). This is the first report of the utilization of the oxa-Pictet-Spengler reaction in carbohydrate chemistry. Both glucal and galactal derived C2-hydroxy-*α*-C-aryl glycosides gave the required products in good yields.[28]



Scheme 1.4.2.2

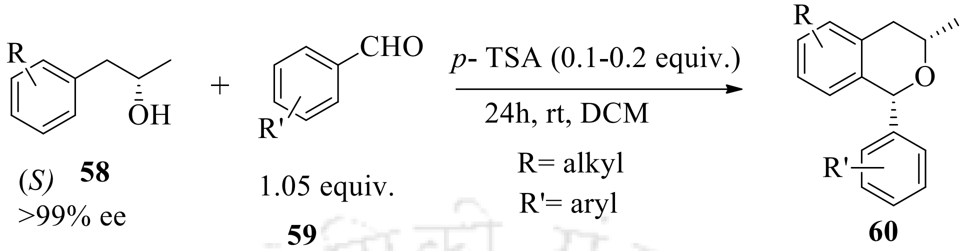
Two catalysts, an amine HCl salt and a bisthiourea, worked in a concerted manner to generate an oxocarbenium ion under mild conditions. This concept was utilized by Seidel and co-workers for the direct catalytic enantioselective oxa-Pictet-Spengler reactions of tryptophol **55** with aldehydes **56** to give tetrahydropyranoindole derivatives **57** (*Scheme 1.4.2.3*).[29]



Scheme 1.4.2.3

A two-step synthesis of various enantiomerically pure 1-aryl- 3-methylisochroman derivatives **60** was reported *via* asymmetric biocatalytic ketone reduction followed by an oxa-Pictet–Spengler reaction of optically pure (> 99% ee) *meta*-methoxyaryl alcohol **58** and various aldehydes **58**

(*Scheme 1.4.2.4*). The compounds were obtained in good yield (47-92%) in favor of the *syn* diastereomers [*dr* (*syn*/*anti*) up to 99:1].[30]



Scheme 1.4.2.4

1.4.3. Oxonium-ene reaction:

Ene reaction was first discovered by Alder in 1943. It involves an alkene (ene) and an enophile in which the σ- bond of allylic hydrogen from alkene suprafacially interacts with the π-bond of the enophile to generate two new σ- bonds and a new π-bond.[31] In the ene cyclization reaction, depending upon the enophile used, it can be divided into an oxonium ion ($X=O^+$), iminium ion ($X=N^+$) or thionium ion ($X=S^+$) ene reactions. Hence, it is regarded as one of the versatile method for the synthesis of hetrocyclic compounds (*Figure 1.4.3.1*)[32]

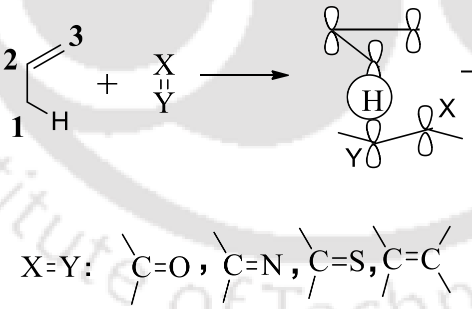
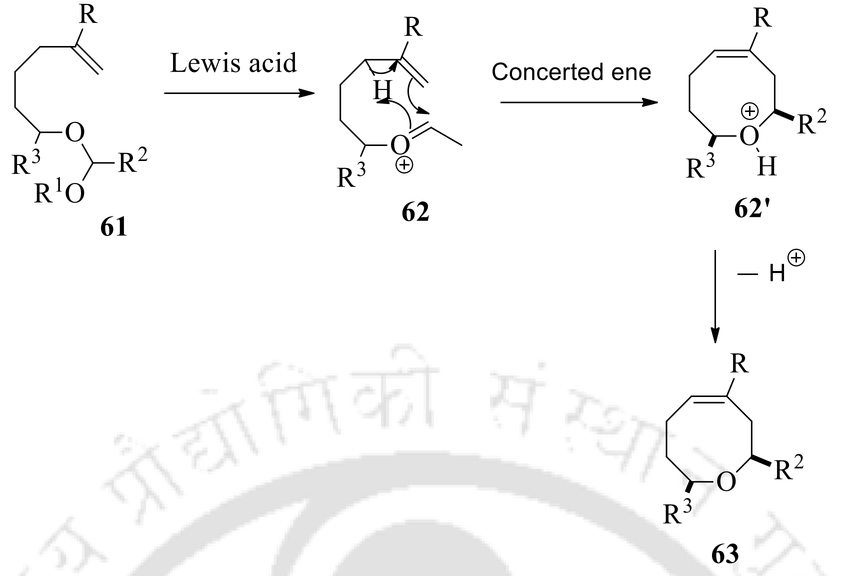


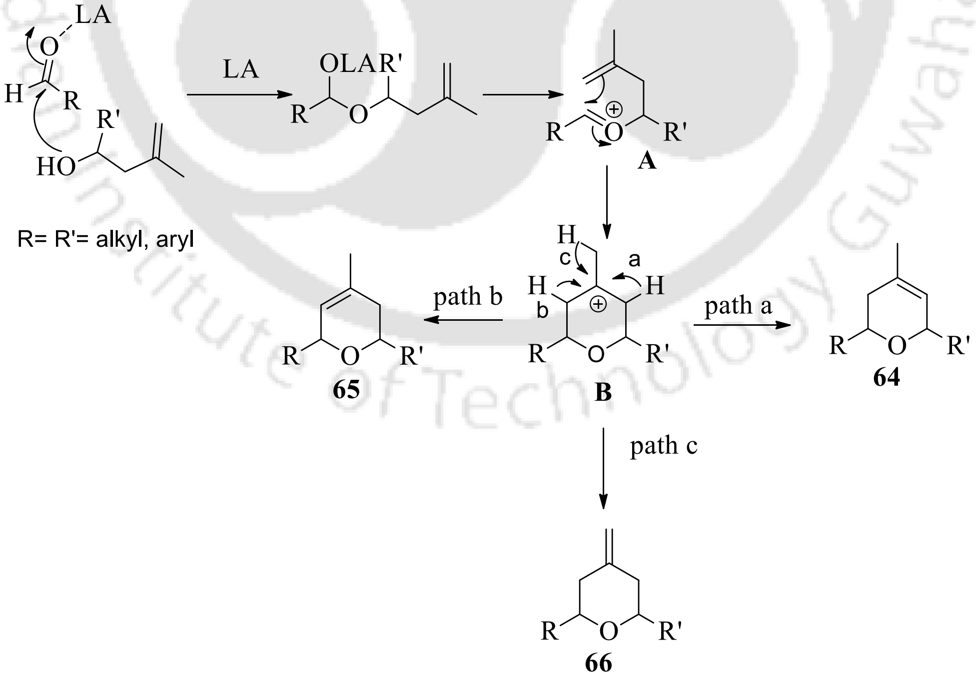
Figure 1.4.3.1. Ene reaction

From a mechanistic perspective, two mechanisms can be proposed for the oxonium-ene



Scheme 1.4.3.1. Concerted mechanism of oxonium-ene cyclization reaction.

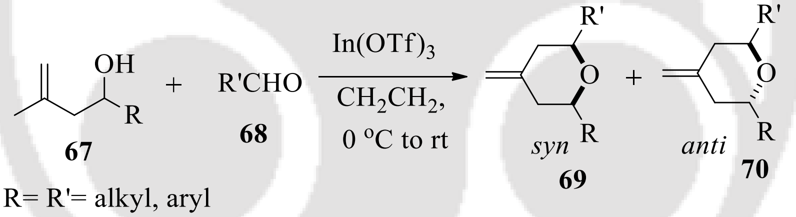
cyclization reaction: concerted and stepwise mechanisms. In the concerted mechanism, it proceeds through a cyclic transition state **62** (*Scheme 1.4.3.1*) and in the stepwise mechanism; there is generation of a carbocation intermediate **B** (*Scheme 1.4.3.*2).



Scheme 1.4.3.2. Stepwise mechanism of oxonium-ene cyclization reaction.

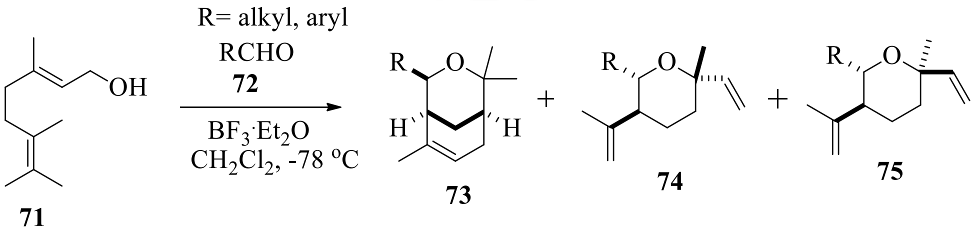
In the Prins reaction, the carbocation intermediate is quenched by a nucleophile to give Prins product whereas elimination of an allylic proton gives an ene-type product. In the case of concerted mechanism, there is simultaneous elimination of a proton and abstraction of that proton by the lone pair of oxygen as well as cyclization occurred at the same time to give intermediate **62’** which after proton elimination gives final product **63** (*Scheme 1.4.3.1*).[33] In the stepwise mechanism, firstly, the Lewis acid activates the carbonyl oxygen, which allows nucleophilic attack by the homoallylic alcohol to form an acetal (*Scheme 1.4.3.1)*. After the decomposition of the acetal, it generates oxonium ion **A**, which then undergoes cyclization reaction to generate carbocation **B**. The carbocation **B** undergoes elimination of a proton to give the oxonium-ene cyclized products **64**, **65** and **66**.[34]

In 2002, Loh and co-workers reported the synthesis of *cis-* and *trans-* 2,6-disubstituted tetrahydropyrans **69** and **70** by oxonium-ene cyclization reaction catalyzed by In(OTf)$_3$ in dichloromethane (*Scheme 1.4.3.3*). The substituted tetrahydropyrans were prepared from the reaction of homoallylic alcohols **67** with different aldehydes **68**.[35]



Scheme 1.4.3.3

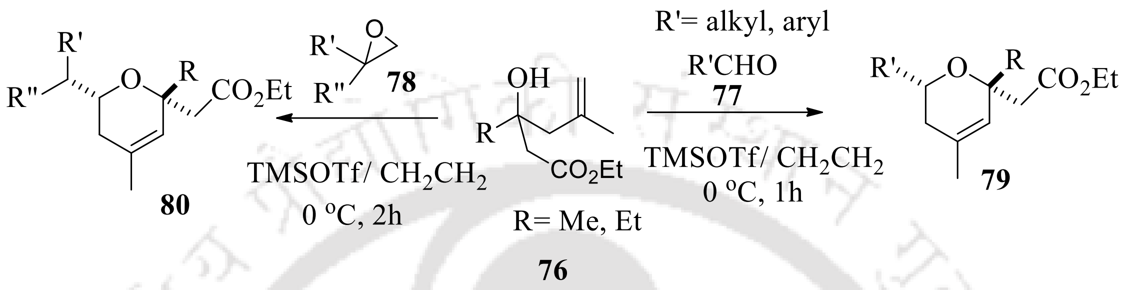
Saikia and co-workers developed a methodology for the synthesis of oxabicyclo[3.3.1] nonenes **73** and substituted tetrahydropyrans **74** and **75** from geraniol **71** with aldehydes **72** mediated by



Scheme 1.4.3.4

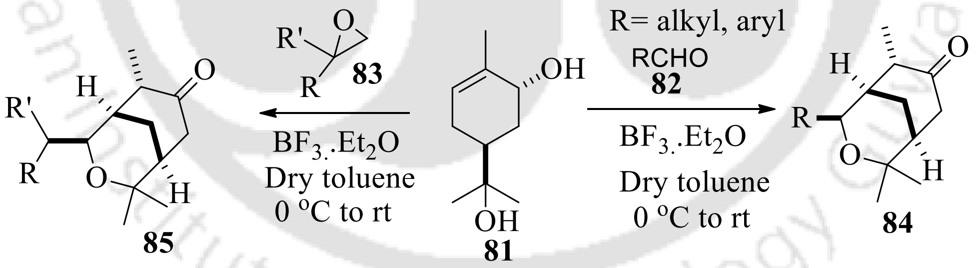
boron trifluoride etherate in dichloromethane at -78 °C as shown in *Scheme 1.4.3.4*.[36]

In 2012, the same group reported the synthesis of tetrasubstituted dihydropyrans **79** and **80** from tertiary alcohols **76** with aldehydes **77** as well epoxides **78**. The reaction was catalyzed by TMSOTf and it was highly regio- and diastereo-selective (*Scheme 1.4.3.5*).[37]



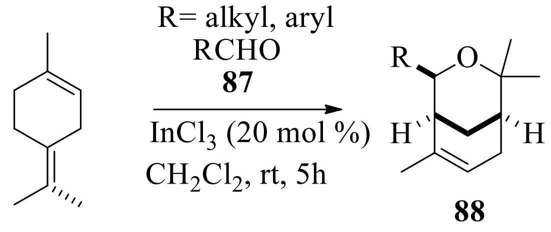
Scheme 1.4.3.5

They also reportedly used commercially available diterpenoid trans-*p*-menth-ene-2,8-diol **81** along with aldehydes **82** and epoxides **83** to synthesize oxabicyclo[3.3.1]nonanones **84** and **85** *via* (3,5)-oxonium-ene reaction (*Scheme 1.4.3.6*). The reaction was diastereoselective and both aliphatic and aromatic aldehydes gave the desired bicyclic compounds.[38]



Scheme 1.4.3.6

In 2016, Marimuthu and co-workers reported an $InCl_3$ catalyzed synthesis of oxabicyclo [3.3.31] nonenes **88** *via* (3,5)- oxonium-ene cyclization reaction from aldehydes **87** and R-(+)-limonene **86** (*Scheme 1.4.3.7*). The reaction conditions are milder and also consumed shorter duration of time as compared to Saikia and co-workers.[39]



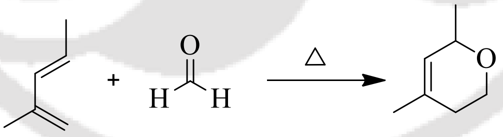
86 **88**

Scheme 1.4.3.7

1.4.4. Hetero Diels-Alder (HDA) reaction:

Hetero Diels-Alder (HDA) reaction is a perfect mechanism for the synthesis of heterocyclic compounds. Many of them used Lewis/Bronsted acid in order to obtain polyheterocyclic compounds. However, many of these synthetic methods suffer from drawbacks in reaction conditions, yields, regio- and diastereo-selectivity. So reactions that can overcome these situations are still preferred.

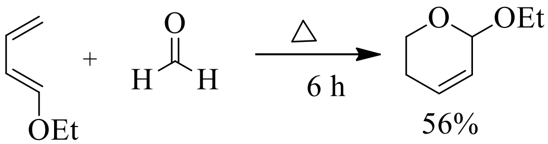
HDA reaction was first reported by Gresham and Steadman in 1951. In their report they have prepared 2,4-dimethyl-5,6-dihydro-1,2-pyran (**91**) by reacting methylpentadiene (**89)** with formaldehyde (**90)** (*Scheme 1.4.4.1*).[40] This was an unusual reaction, as in this case formaldehyde was acting as a dienophile.



89 **90** **91**

Scheme 1.4.4.1

In 1962, Kubler and co-workers reportedly used an electron donating group containing diene

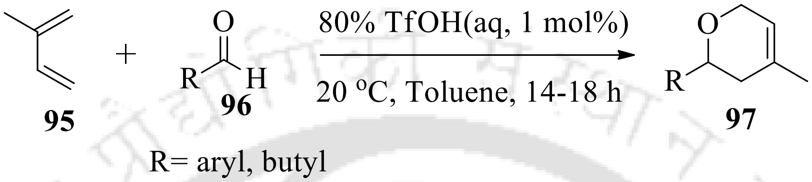


92 **93** **94**

Scheme 1.4.4.2

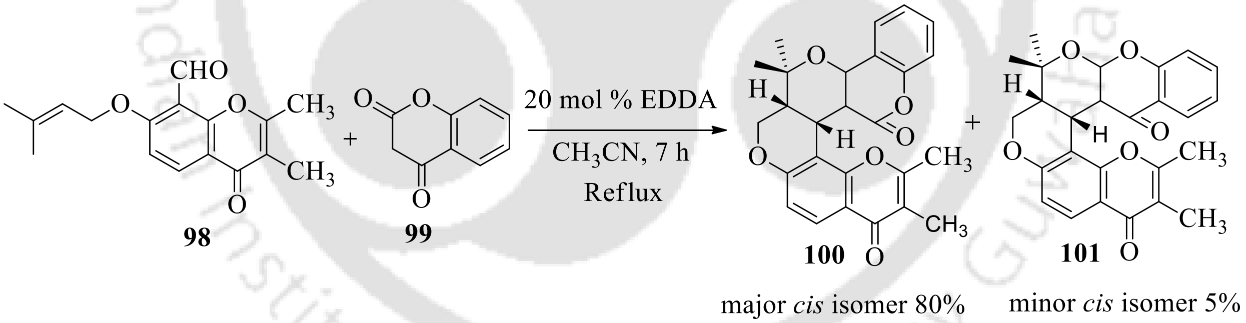
(alkoxy group on the 1-position of a diene) **92** to react with paraformaldehyde (**93**) to give 2-alkoxy-5,6-dihydro-2*H*-pyrans **94** (*Scheme 1.4.4.2*). [41]

V.K. Aggarwal and co-workers reported an efficient method for the hetero Diels-Alder Reaction between aromatic aldehydes **96** and unactivated dienes **95** catalyzed by trifluoromethanesufonic acid (1 mol%) to synthesize 1,3- disubstituted dihydropyrans **97**.[42]



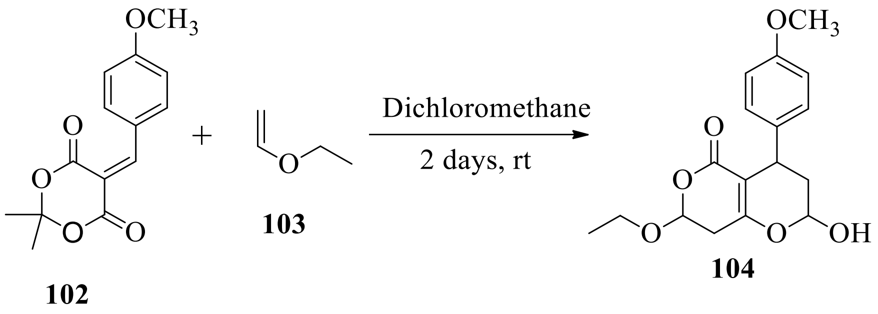
Scheme 1.4.4.3

K. Nagaiah and co-workers developed a series of chromeno-annulated cis-fused pyrano[3,4-*c*] pyran derivatives **100** and **101** by intramolecular [4 + 2] domino Knoevenagel–hetero-Diels-Alder reactions of 1-oxa-1,3-butadienes derived in situ from 1,3-dicarbonyls/active methylenes **99** and 7-O-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones **98** in the presence of 20 mol% ethylene diamine diacetate (EDDA) in acetonitrile under reflux conditions in good to excellent yields (*Scheme 1.4.4.4*).[9]



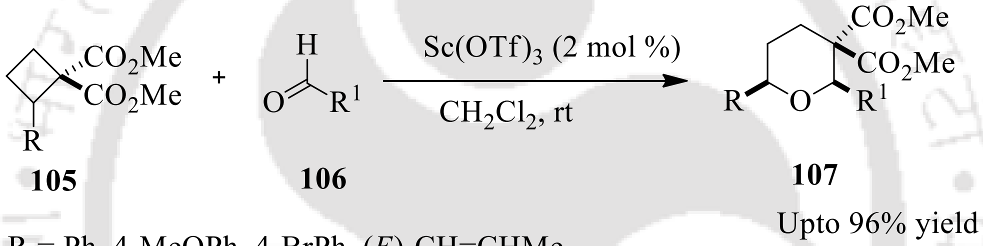
Scheme 1.4.4.4

The reactions of 5-arylidene derivatives of Meldrum's acid **102** with ethyl vinyl ether **103** yielded *trans-trans*-pyrano[4,3-*b*]pyrans, *cis-trans*-pyrano[4,3-*b*]pyrans, or diastereoisomeric mixtures of pyrano[4,3-*b*]pyrans **104**. Therefore, the 5-arylidene derivatives of Meldrum's acid seem to be excellent reagents in pyran synthesis by HDA reaction (*Scheme 1.4.4.5*).[43]



Scheme 1.4.4.5

Johnson and co-workers reported the synthesis of *cis*-2,6-disubstituted tetrahydropyrans **107** *via* HDA reaction between malonate derived cyclobutanes **105** and aldehydes **106** catalyzed by $Sc(OTf)_3$ in dichloromethane at room temperature (*Scheme 1.4.4.6*).[44]



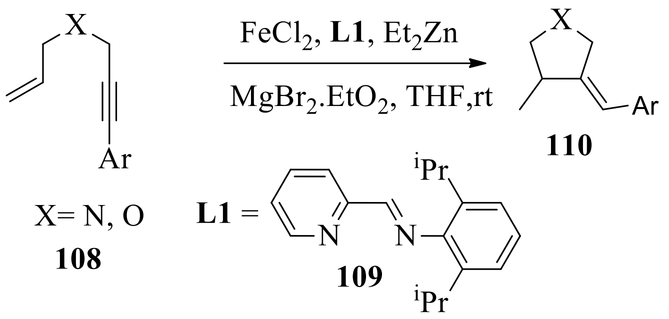
R = Ph, 4-MeOPh, 4-BrPh, (*E*)-CH=CHMe
R^1 = alkyl

Scheme 1.4.4.6

1.4.5. 1,n-Enyne rearrangement reaction:

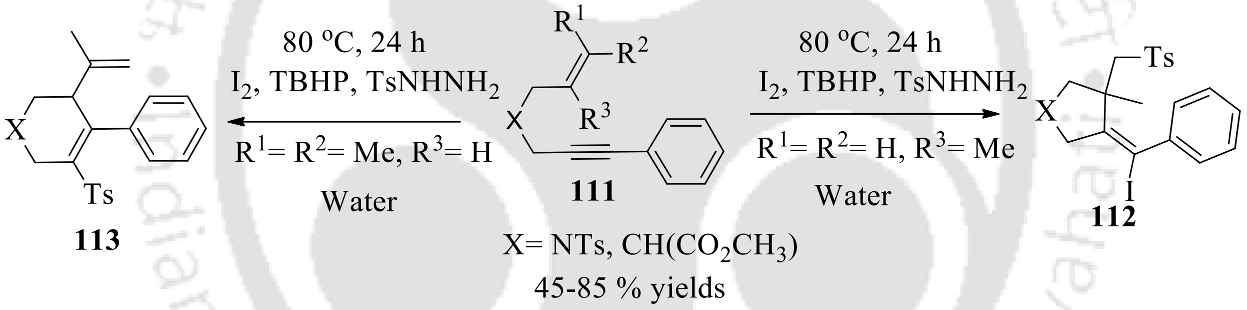
Transition-metal-catalyzed cyclization of 1,*n*-enynes has become an atom-economical and powerful method for building diverse carbo- and hetero-cyclic frameworks. This strategy includes metal-catalyzed oxidative cyclization of 1,*n*-enynes, which offers several advantages over the traditional approaches as numerous new functional groups can be easily introduced into the ring systems and functionalization in the alkene and alkyne moieties occur in both positions of the π bond.

Yang and co-workers synthesized pyrrolidine and tetrahydrofuran derivatives **110** by reductive cyclization of *N*- and *O*-tethered 1,6-enynes **108** in moderate to good yields. A precatalyst of $FeCl_2$ and iminopyridine **109** which was activated in situ by a combination of diethylzinc and magnesium bromide etherate is used as shown in *Scheme 1.4.5.1*.[45]



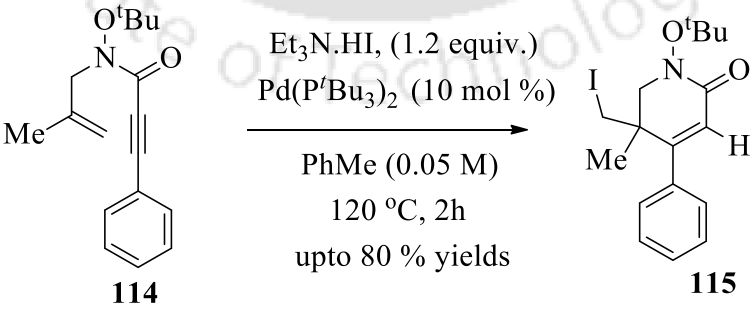
Scheme 1.4.5.1

An iodine-promoted one-pot radical cyclization reaction of 1,6-enynes **111** with sulfonyl hydrazides to provide five-membered **112** and six-membered **113** ring sulfonylated products under the same reaction conditions was established. The reaction proceeded smoothly in water and gave the corresponding products by using I_2/TBHP instead of expensive and toxic catalysts (*Scheme 1.4.5.2*).[46]



Scheme 1.4.5.2

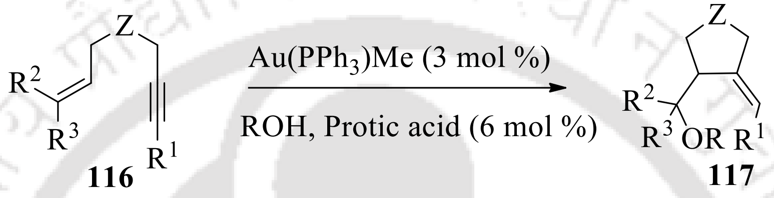
Lautens and group reported a Pd-catalyzed hydrohalogenation of enynes **114** by using



Scheme 1.4.5.3

ammonium iodide as HI surrogates to give dihydropyridinone derivatives **115**. These safe and practical salts avoid many drawbacks associated with traditional HI sources including toxicity and corrosiveness (*Scheme 1.4.5.3*).[47]

In 2006, Echavarren and co-workers proposed a gold (I) catalyzed intramolecular alkoxy- or hydroxycyclization of 1,6-enynes **116**. The gold(I)-catalyzed endocyclic cyclization proceeded by a mechanism different from those followed in the presence of Pd (II), Hg(II), or Rh(I) catalysts to give tetrahydrofuran and pyrrolidine derivatives **117** (*Scheme 1.4.5.4*).[48]

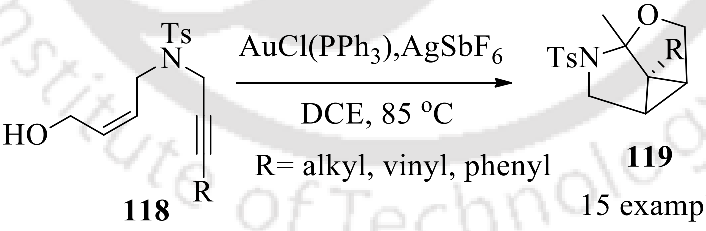


Z= $C(CO_2Me)_2$, $C(SO_2Ph)_2$, NTs

R^1= H, aryl
R^2= R^3= H, alkyl

Scheme 1.4.5.4

The reaction of *N*-tethered alkyne-alkenols **118** in the presence of a cationic gold (I) and $AgSbF_6$ catalysts gave new cycloisomerization products, 4-oxa-6-azatricyclo[3.3.0.0]octanes **119** as reported by Park and co-workers (*Scheme 1.4.5.5*).[49]



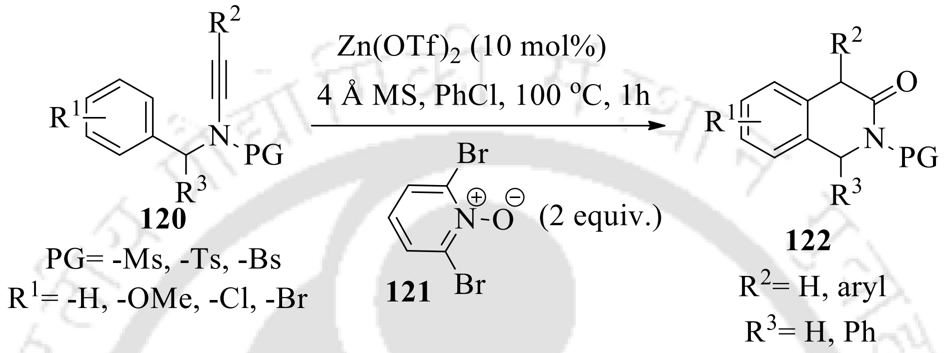
15 examples
upto 72% yields

Scheme 1.4.5.5

1.4.6. Metal salts catalyzed cyclization reaction:

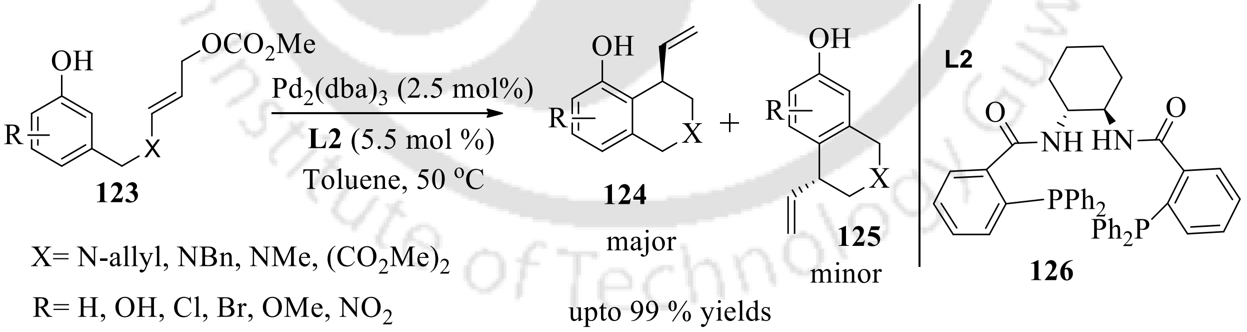
Recently metal salts such as $InCl_3$, $FeCl_3$, $ZnCl_2$, gold and silver salts and other transition metal salts have become a powerful tool for the synthesis of heterocyclic compounds. Some of the examples are briefly discussed below.

In 2015, Ye and co-workers developed an efficient zinc (II)-catalyzed alkyne oxidation/C-H functionalization of ynamide **120** using bromo- substituted pyridine *N*-oxide **121** as the oxidizing agent, thus leading to the synthesis of a highly site-selective variety of isoquinolones and *β*-carbolines **122**.[50]



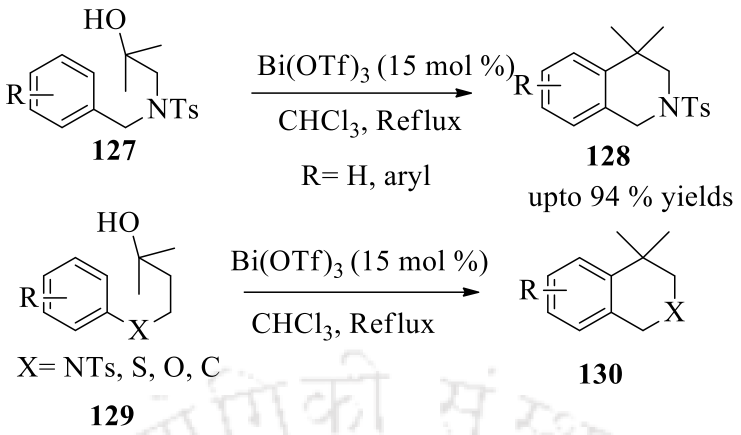
Scheme 1.4.6.1

Zhou and co-workers, in 2015, reported a palladium-catalyzed asymmetric intramolecular Friedel-Crafts type allylic alkylation reaction of phenols **123**. The reaction provides various C4 substituted tetrahydroisoquinolines **124** and **125** with high regio- and enantio-selectivity and moderate to excellent yields, (*Scheme 1.4.6.2*).[51]



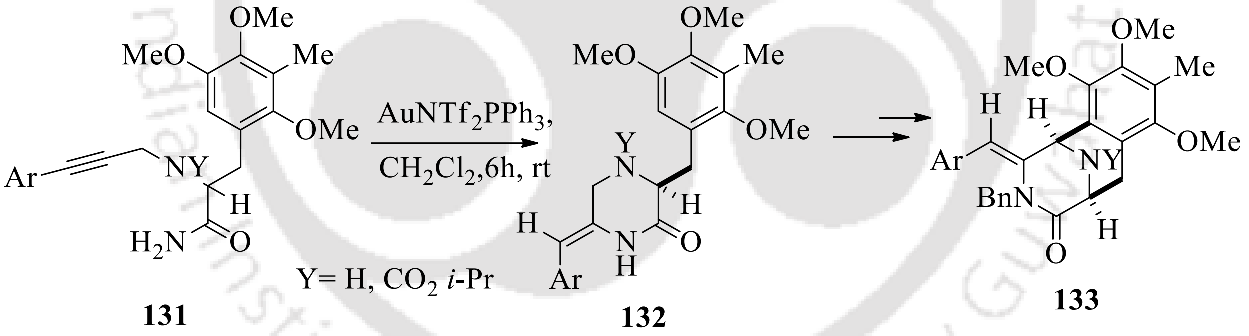
Scheme 1.4.6.2

In 2013, Bunce and co-workers reported a bismuth (III) triflate catalyzed cyclizations of tertiary alcohols **127** and **129** for the synthesis of tetrahydroisoquinolines **128** and disubstituted tetrahydronapthalenes, chromans, thiochromans, tetrahydroquinolines **130,** respectively *via* intramolecular Friedel–Crafts cyclization reaction (*Scheme 1.4.6.3*).[52]



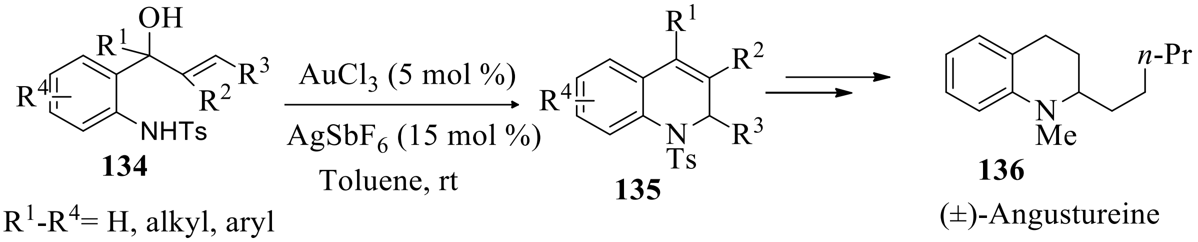
Scheme 1.4.6.3

Takemoto and co-workers developed a gold (I) catalyzed intramolecular hydroamidation of alkynylamide **131** and NBS-mediated oxidative Friedel-Crafts cyclization reaction. The methodology was further extended for the synthesis of **133**, which is a part of the ring system of the tetrahydroisoquinoline antitumor alkaloids such as saframycins, renieramycins and ecteinascidins (*Scheme 1.4.6.4*).[53]



Scheme 1.4.6.4

Chan and co-workers developed an efficient synthetic route towards the synthesis of 1,2-dihydroquinolines **135** *via* $AuCl_3/AgSbF_6$-catalyzed intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols **134** under relatively mild conditions (*Scheme 1.4.6.5*). The synthetic utility of the strategy was further extended towards the synthesis of the natural product (±)-angustureine (**136**).[54]



Scheme 1.4.6.5

In conclusion, five and six membered oxygen and nitrogen heterocyclic compounds are important in synthetic chemistry because of their immense presence in various natural products and pharmaceuticals as discussed above. Therefore, a substantial attention has been paid to develop new and efficient methods to synthesize these heterocycles. In the following chapters IIA-B, III and IV, our main objective is to synthesize and mimic the core structures of these bioactive molecules and to develop better reaction pathways for the organic synthetic community by exploring oxonium-ene, hetero Diels-Alder and metal catalyzed cyclization reaction.

1.5. References:

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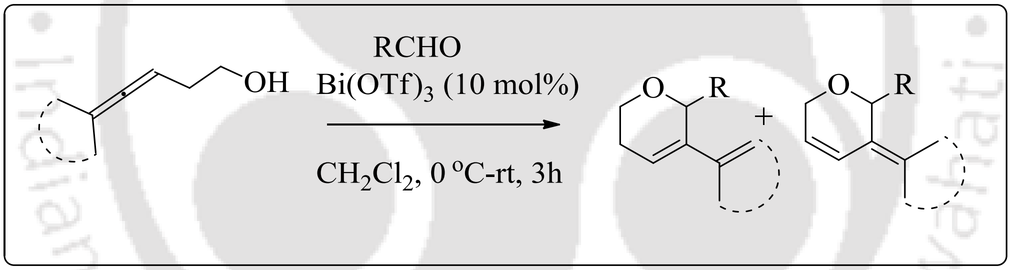
Chapter 2

Section A

Regioselective Synthesis of Dihydropyrans via Oxonium-ene Reaction of β-allenols and Aldehydes



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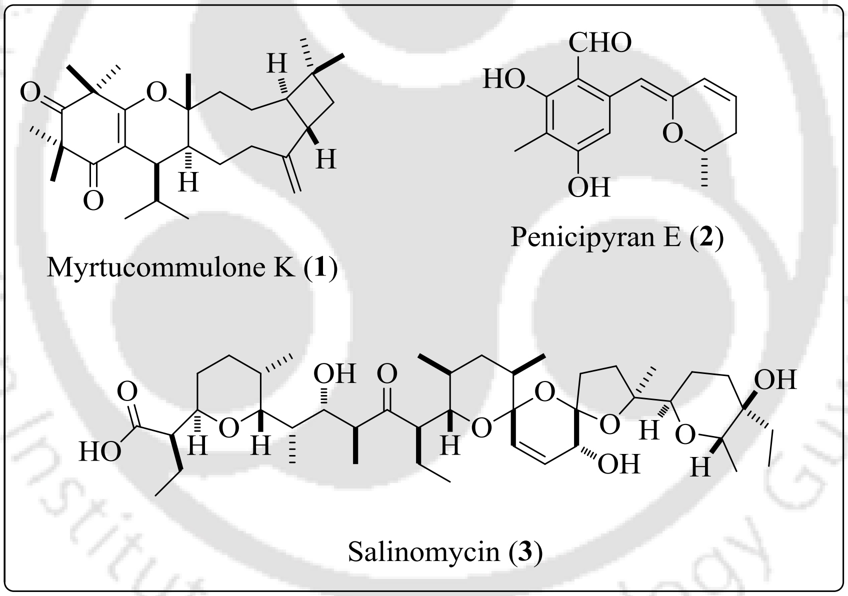
Regioselective Synthesis of Dihydropyrans *via* Oxonium-ene Reaction of *β*-Allenols and Aldehydes

2A.1. Importance and applications:

The dihydro-, tetrahydro-pyrans and furans are core units of many biologically and pharmaceutically active compounds (*Figure 2A.1.1*). For example, myrtucommulone K (**1**) is a meroterpenoids containing dihydropyran ring in its core unit and recently isolated from *Myrtus communis L*. It is used in folk medicine as an antiseptic, disinfectant, and hypoglycemic agent.[1] Penicipyran E (**2**) is also isolated from natural source *Penicillium raistrickii* and it possesses antiproliferative property.[2] Similarly, salinomycin (**3**), a dihydropyran containing polyether isolated from a culture broth of *Streptomyces albus* is shown to possess antibacterial and anticoccidial properties.[3] Importantly, the olefinic bond of the dihydropyran ring can be converted into various polyfunctional tetrahydropyrans.[4] They are also considered as useful starting material for the synthesis of homoallylic alcohols.[5] In addition to these applications, 2, 4-disubstituted dihydropyrans are used as additive for enhancing flavor and aroma of foodstuffs.[6]


Myrtucommulone K (**1**)

Penicipyran E (**2**)

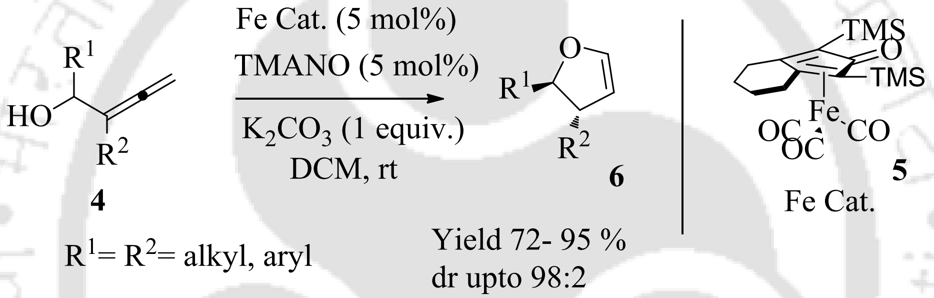
Salinomycin (**3**)

Figure 2A.1.1. *Bioactive molecules containing dihydropyran ring.*

2A.2. Literature Methods:

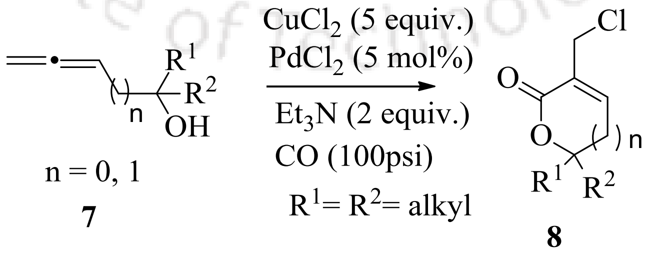
Various synthetic strategies have been reported whereby one can use allenols as starting materials. Several intramolecular as well as intermolecular metal catalysed cyclization reaction involving allenols are known. Some of the methods are analysed below.

Bäckvall and co-workers reported a highly efficient iron-catalyzed intramolecular nucleophilic cyclization of α-allenols **4** to furnish substituted 2,3-dihydrofurans **6** under mild reaction conditions. A highly diastereoselective variant of the reaction was developed as well, giving diastereomeric ratios of up to 98:2. The combination of the iron-catalyzed cycloisomerization with enzymatic resolution afforded the 2,3-dihydrofuran in high ee. (*Scheme 2A.2.1*)[7]



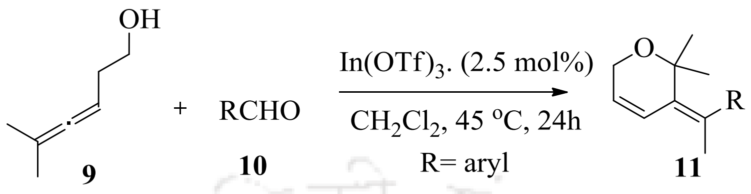
Scheme 2A.2.1

Ma and co-workers extensively studied allene alcohols over the years. They reportedly used $PdCl_2$ and $CuCl_2$ for chlorocyclocarbonylation of 2,3- or 3,4-allenols **7** for the synthesis of 3-chloromethyl-2(5*H*)-furanones and 3-chloromethyl-5,6-dihydropyran-2-ones **8** in a regioselective manner. (*Scheme 2A.2.2*)[8]



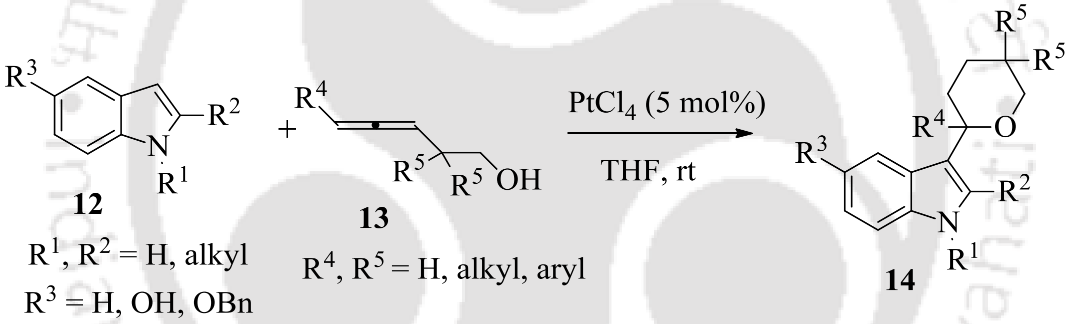
Scheme 2A.2.2

They also recently reported indium(III) triflate catalysed Prins type cyclization of disubstituted *β*-allenols **9** in the presence of aldehydes **10** in dichloromethane affording dihydropyrans **11** at 45 °C. (*Scheme 2A.2.3*)[9]

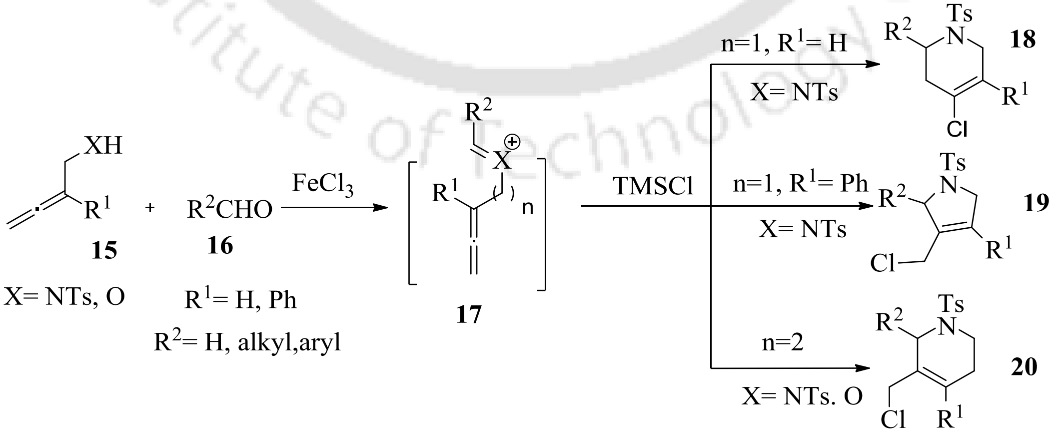


Scheme 2A.2.3

In 2009, Ma and co-workers also used *β*-allenols **13** along with indole **12** to give indole derivatives at C-3 position, containing a six membered ether ring. The reaction is highly regioselective and is catalysed by $PtCl_4$. (*Scheme 2A.2.4*)[10]



Scheme 2A.2.4

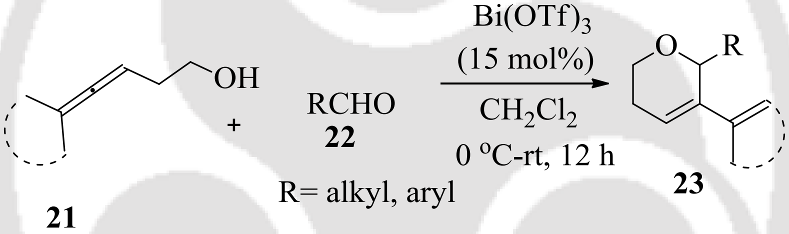


Scheme 2A.2.5

Ma group also reported a $FeCl_3$-catalyzed cyclization of terminal α- or β-sulfonamidoallenes or β-allenols **15** with aldehydes **16** in the presence of TMSCl to form 4-chloro-1,2,3,6-tetrahydropyridines **18** and 3-chloromethyl-2,5-dihydro-1*H*-pyrroles **19**, or 1,2,5,6-tetrehydro-1*H*-pyridines or 5,6-dihydro-2*H*-pyrans **20** (*Scheme 2A.2.5*).[11]

2A.3. Present strategy and objective:

As seen from the previous reports that β-allenols can be used for the synthesis of various heterocyclic compounds using various methods, but oxonium-ene cyclization reaction is not reported for the synthesis of dihydropyrans using β-allenols. In this chapter, we report $Bi(OTf)_3$ catalyzed cyclization reaction of allenic alcohols **21** with aldehydes **22** for the synthesis of 3,6-dihydro-2*H*-pyrans **23** *via* oxonium-ene cyclization reaction in moderate to good yields with high regioselectivity (*Scheme 2A.3.1*).

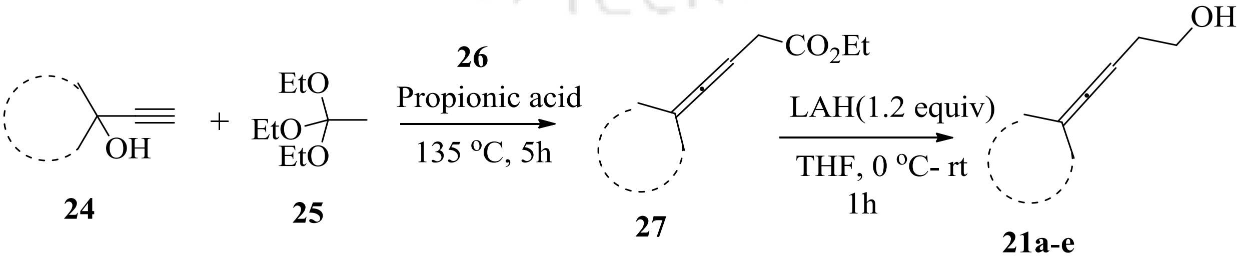


Scheme 2A.3.1

2A.4. Results and Discussions:

2A.4.1. General Procedure for preparation of β-allenols:

The starting material β-allenols can be easily synthesized from tertiary alcohol **24**, triethyl



Scheme 2A.4.1.1

orthoacetate **25** and propionic acid **26** which were heated at 135 ^{o}C for 5h. After the completion of the reaction, the reaction mixture was concentrated and further purified by column chromatography (Hexane:EtOAc:: 9:1) to give allene ester **27**. The allene ester **27** was then reduced to β-allenols **21a-e** by lithium aluminium hydride (LAH). Finally the β-allenols were purified by column chromatography using ethyl acetate and hexane (9: 1:: Hexane: EtOAC) as eluent to give pure compounds **21a-e** (*Scheme 2A.4.1.1*).[12]

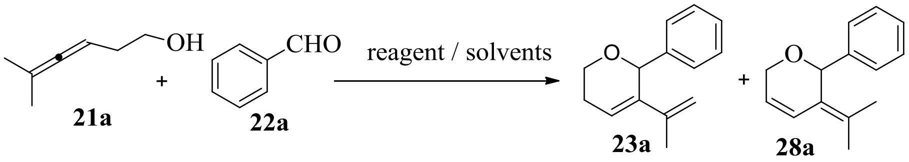
2A.4.2. Optimization Studies:

We started the reaction considering 5-methylhexa-3,4-dien-1-ol (**21a**) (1.0 equiv.) and benzaldehyde (**22a**) (1.0 equiv.) as model substrates and was allowed to react in the presence of borontrifluoride etherate ($BF_3.OEt_2$) (1.2 equiv.) in dichloromethane at 0 ^{o}C to room temperature for 12h. To our dismay the reaction resulted with a complex mixture**.** In continuation to this, the substrates **21a** and **22a** were treated with a variety of reagents and solvents under different reaction conditions**.** The results are summarized in *Table 2A.4.2.1.* As such the reaction failed to provide any products in presence of TfOH (10 mol%) at 0 ^{o}C-room temperature**.** Further screening of the reaction with other reagents such as TMSOTf (10 mol%) in dichloromethane at room temperature provided **28a** with 48% yield**.** Similarly, various Lewis acids such as $In(OTf)_3$, $FeCl_3$, AgOTf, $Sc(OTf)_3$, $Zn(OTf)_2$ and $Bi(OTf)_3$ were next screened, amongst which $Bi(OTf)_3$ (10 mol %) at 0 ^{o}C to room temperature for 12h in dichloromethane gave compound **23a** with 41 % yield (Table 1, entry 9). Further increase in catalytic amount of $Bi(OTf)_3$ from 10 mol% to 15 mol% proved to be fruitful with 75% yield of the desired product. Thus it was observed that **21a** (1.5 equiv.), **22a** (1 equiv.) and $Bi(OTf)_3$ (15 mol %) in dichloromethane at 0 ^{o}C – room temperature for 12h was found to be the most suitable reaction condition.

2A.4.3. Substrate scope of the reaction:

With this established optimum conditions, the utility of the reaction was further investigated with different aldehydes **22a-n** bearing electron-donating and/or withdrawing groups as well as with various β-allenols **21a-e** as shown in *Table 2A.4.3.1*. The reaction of aldehydes **22b-d** bearing moderately electron-withdrawing group such as 4-F, 3-Cl and 4-Br on the benzene ring with **21a** afforded the products **23b-d** in 46-70% yields (*Table 2A.4.3.1, entries 2-4*). The reaction was also found to be feasible with aldehydes **22e-f** having strong electron-withdrawing –NO_2 group

Table 2A.4.2.1. Optimization of the reaction[a]



Entry.	Reagent (equiv)	Solvent	Temp./ °C	Time/h	Product(%) yield[b]
1	$BF_3\cdot OEt_2$ (1.2)	DCM	0 °C -rt	12	c
2	TfOH (0.1)	DCM	0 °C -rt	12	d (80)
3	TMSOTf (0.1)	DCM	rt	12	**28a** (48)
4	$In(OTf)_3$ (0.2)	DCM	0 °C -rt	24	**23a** (27)[d,e]
5	$FeCl_3$ (1.2)	DCM	0 °C -rt	12	d
6	AgOTf (0.2)	DCM	rt	12	c
7	$Sc(OTf)_3$ (0.2)	DCM	rt	12	c
8	$Zn(OTf)_2$ (0.2)	DCM	rt	24	c
9	$Bi(OTf)_3$ (0.10)	DCM	0 °C -rt	12	**23a** (41)
10	$Bi(OTf)_3$ (0.15)	DCM	0 °C -rt	12	**23a** (75)[e]
11	$Bi(OTf)_3$ (0.15)	DCM	-45 °C	12	d (85)[e]
12	$Bi(OTf)_3$ (0.15)	DCE	0 °C -rt	24	d (82)[e]

[a]Reaction conditions: **21a** (1.5 equiv),**22a** (1.0 equiv), solvent (4 mL). [b]Yields are isolated yield. [c]complex mixture. [d]starting material recovered. [e]1.5equivalents of alcohol.

on the benzene ring and afforded the 3-prop-1-en-2-yl substituted dihydropyrans **23e-f** in 78-82% yields (*Table 2A.4.3.1, entries 5-6*). Similarly, treatment of methyl 4-formylbenzoate (**22g**) with **21a** also provided the 3-prop-1-en-2-yl substituted dihydropyran **23g** in 61% yield (*Table 2A.4.3.1, entry 7*). Intrestingly, treatment of 2-phenylpropanal (**22h**) furnished tricyclic compound **23h** in 62 % yield (*Table 2A.4.3.1, entry 8*). Aliphatic aldehyde cyclohexylcarboxaldehyde **22i** (*Table 2A.4.3.1, entry 9*) gave **23i** with 45% yield. Substituents having strong electron donating functional group on the aromatic ring of the aldehyde **22j** surprisingly gave compound **28b** 2-(4-methoxyphenyl)-3-(propan-2-ylidene)-3,6-dihydro-2*H*-pyran instead of 3-prop-1-en-2-yl substituted dihydropyran (*Table 2A.4.3.1, entry 10*). Aliphatic aldehyde isobutyraldehyde **22k,** also reacts with **21d** to give the desired product but with low yield (43 %). To demonstrate the versatility of the reaction, further reactions using various *β*-

allenols and aldehydes were next carried out. Treatment of 4-cyclopentylidenebut-3-en-1-ol (**21b**) with aldehydes **22b** and **22f** produced the product **23j-k** in 46-85% yields (*Table 2.4.3.1*, *entries 11-12*). Reaction of 4-cyclohexylidenebut-3-en-1-ol (**21c**) with aldehydes **22b** and **22j** afforded the corresponding products **23m-l** in 65-73% yields (*Table 2.4.3.1*, *entries 13-14*). Similarly, expansion of the ring of alcohol such as 4-cycloheptylidenebut-3-en-1- ol (**21d**) and 4-cyclooctylidenebut-3-en-1-ol (**21e**) could also react with aldehydes **22k**, **22j** and **22l-n** and provided the corresponding products **23n-r** in 43-72% yields (Table 2A.4.3.1, entries 15-19).

2A.4.4. Stereochemistry of the 3,6-dihydro-2*H*-pyrans:

The structure of the compound was determined from the ^{1}H and ^{13}C NMR analysis. The stereochemistry of compounds was determined from NOE experiment of compounds **23g** and **23k** as well as it was further supported by X-ray crystallographic analysis of **23k** (*Figure 2A.4.4.1*). In the NOE spectra of **23k**, irradiation of peak at 6.01ppm showed enhancement of peaks at 2.53 ppm, it shows a strong correlation of C4 hydrogen and methylene hydrogens of cyclopentenyl ring attached to C5. Also, irradiation of peak at 5.31ppm showed enhancement of

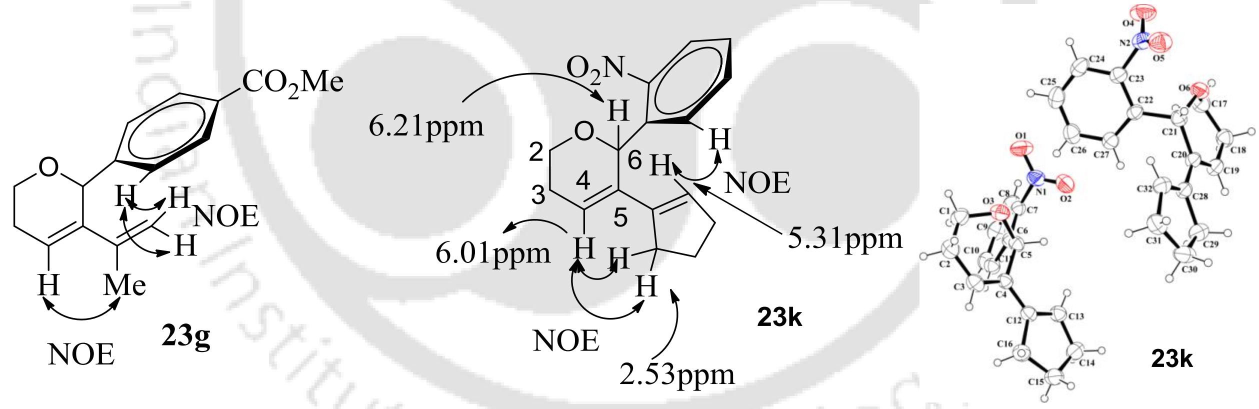
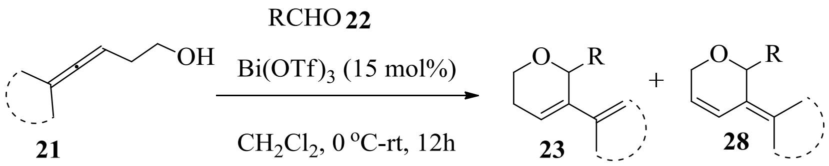
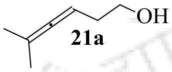
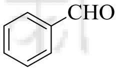
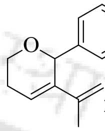
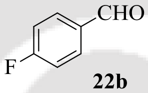
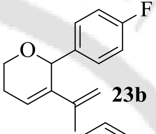
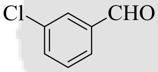
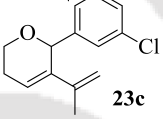
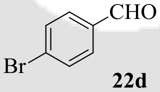
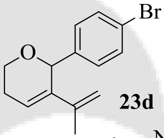
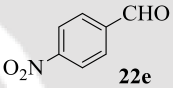
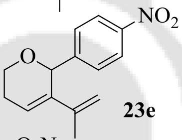
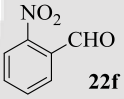
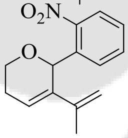
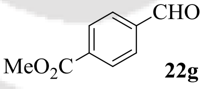
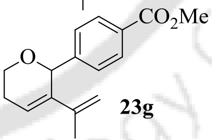
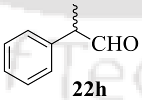
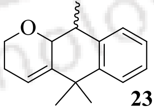
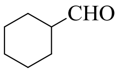
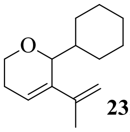
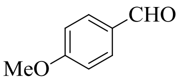
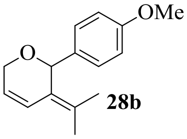
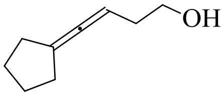
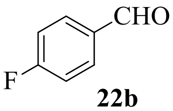
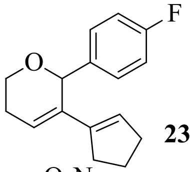
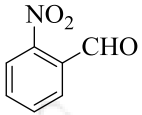
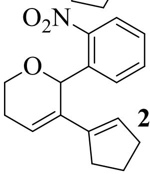
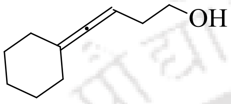
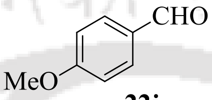
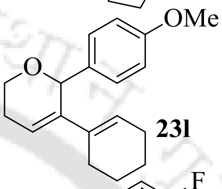
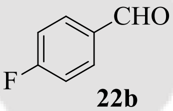
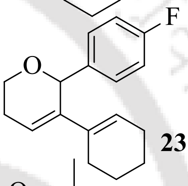
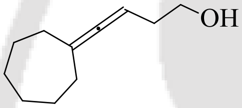
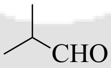
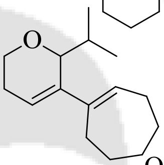
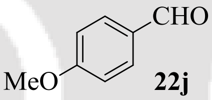
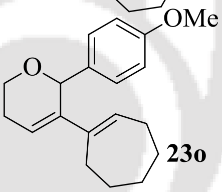
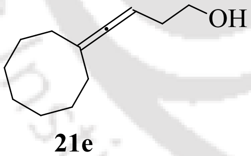
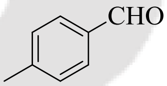
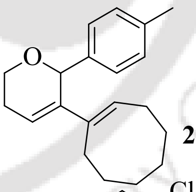
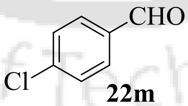
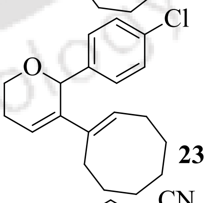
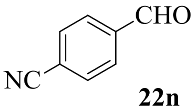
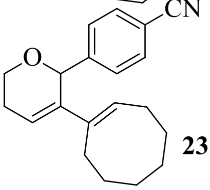


Figure 2A.4.4.1. NOE of compounds **23g**, **23k** and X-ray crystallographic structure of **23k** (35% probability ellipsoid)

Table 2A.4.3.1. Synthesis of dihydropyrans[a]



Entry	Substrates		Product **23**/**28**	Yield (%)[b]
	alcohol **21**	aldehyde **22**		
1	 **21a**	 **22a**	 **23a**	75
2	**21a**	 **22b**	 **23b**	46
3	**21a**	 **22c**	 **23c**	70
4	**21a**	 **22d**	 **23d**	47
5	**21a**	 **22e**	 **23e**	78
6	**21a**	 **22f**	 **23f**	82
7	**21a**	 **22g**	 **23g**	61
8	**21a**	 **22h**	 **23h**	62
9	**21a**	 **22i**	 **23i**	45
10	**21a**	 **22j**	 **28b**	62

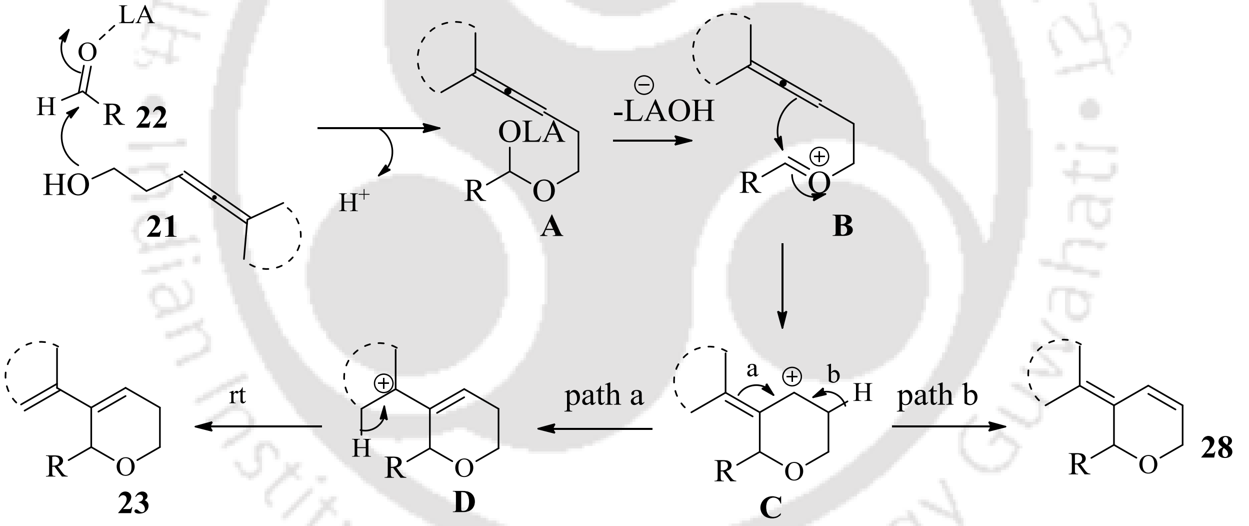
Entry	Substrates Alcohol **21**	Aldehyde**22**	Product **23/28**	Yield (%)[b]
11	 **21b**	 **22b**	 **23j**	46
12	**21b**	 **22f**	 **23k**	85
13	 **21c**	 **22j**	 **23l**	73
14	**21c**	 **22b**	 **23m**	65
15	 **21d**	 **22k**	 **23n**	43
16	**21d**	 **22j**	 **23o**	47
17	 **21e**	 **22l**	 **23p**	66
18	**21e**	 **22m**	 **23q**	72
19	**21e**	 **22n**	 **23r**	46

[a]Reaction conditions: **21** (1.5 equiv), **22**(1.0 equiv), CH_2Cl_2 (4 mL), 0 °C-rt. [b]Isolated yield.

peaks at aromatic peak at 7.28 ppm as well as aliphatic peak at 6.21 ppm. From these perspectives, it is evident that the two olefinic bonds are *trans* to each other and the reaction is highly regioselective.

2A.4.5. Plausible mechanism for the synthesis of 3,6-dihydro-2*H*-pyrans:

A plausible mechanism that accounts for the regioselective synthesis of **23** and **28** is depicted in Scheme *2A.4.5.1*. The Lewis acid activates the carbonyl group of aldehyde **22** for the nucleophilic attack by alcohol **21** to generate acetal **A**. The acetal after cleavage formed oxocarbenium ion **B**, which after cyclization produces intermediate carbocation **C**. The intermediate **C** after rearrangement produces carbocation **D** *via* path a, which after elimination of a proton gives final *S*-trans products **23** at room temperature. On the other hand, carbocation **C** after elimination of a proton *via* pathway b gives compound **28.**



Scheme 2A.4.5.1. Plausible mechanism for the formation of compounds **23** and **28**

2A.5. Conclusion:

In conclusion, an efficient methodology for the synthesis of dihydropyrans starting from *β*-allenols and aldehydes has been developed with moderate to good yields. The reaction is extremely efficient and cost effective as all the starting materials are easily available and can be synthesized readily. On the other hand, $Bi(OTf)_3$ is a very mild, moisture and air insensitive catalyst. The reaction is highly regioselective and provides a methodology for the utilization of β-allenols.

2A.6. Experimental Section:

2A.6.1. Instrumentation and characterization:

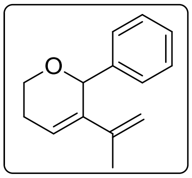
All reagents were purchased from commercial vendors as reagent grade and used without further purification. Column chromatography and TLC were performed using Silica gel (60-120 mesh size) and silica gel GF254 (0.25 mm), respectively. Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded on a Fourier transform-infra red (FT-IR) machine either as neat liquid or KBr pellets. NMR spectra were recorded at 400 MHz (1H, 400 MHz and ^{13}C, 100 MHz) and 600 MHz (^{1}H, 600 MHz and ^{13}C, 150 MHz) machines in $CDCl_3$ using tetramethylsilane as internal standard. Chemical shifts (δ) were reported in parts per million (ppm) and spin-spin coupling constants (J) are given in Hz. High resolution mass (HRMS) were measured using Q-TOF mass analyzer.

2A.6.2. Procedure for the synthesis of 6-phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2*H*-pyran (23a):

To a solution of $Bi(OTf)_3$ (15 mol % 0.050 g) in dichloromethane (3 mL) at 0 ^{o}C was added benzaldehyde (0.5 mmol, 0.053 g) solution in dichloromethane (1 mL) and 5-methylhexa-3,4-dien-1-ol (0.75 mmol, 0.090 g) under N_2 atmosphere. The reaction was stirred for 12h at room temperature. After completion of the reaction as monitored by TLC, dichloromethane was evaporated, washed with saturated brine solution and extracted with EtOAc (2 x 15 mL). The crude product was purified by column chromatography to give 6-phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2*H*-pyran (**23a**) as pale yellow liquid.

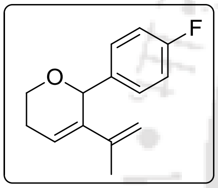
2A.7. Charactererization Data:

*6-Phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**23a**):*



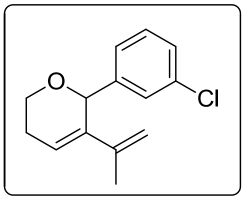
Pale yellow liquid; R_f (hexane/ EtOAc 24:1) 0.50; yield 75 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 2.15-2.24 (m, 1 H), 2.44-2.50 (m, 1 H), 3.54-3.64 (m, 2 H), 4.57 (s, 1 H), 4.78 (s, 1 H), 5.49 (s, 1 H), 6.23 (t, *J* = 4.2 Hz, 1 H) 7.12-7.34 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.9, 58.5, 75.6, 113.0, 124.3, 128.0, 128.4, 129.2, 137.7, 140.6, 140.7; IR (KBr, neat) 2977, 2927, 1606, 1449, 1346, 1150, 1079, 756, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{17}O$ $(M + H)^+$ 201.1274, found 201.1266.

*6-(4-Fluorophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**23b**):*



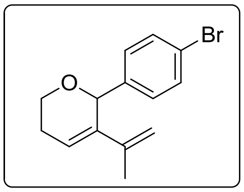
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 52 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 2.16-2.23 (m, 1 H), 2.43-2.52 (m, 1 H), 3.53-3.57 (m, 1 H), 3.59-3.62 (m, 1 H), 4.54 (s, 1 H), 4.79 (s, 1 H), 5.46 (s, 1 H), 6.23 (t, *J* = 4.2 Hz, 1 H), 6.98-7.03 (m, 2 H), 7.28-7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.9, 58.5, 74.8, 113.1, 115.2 (d, *J* =21.2 Hz), 124.5, 130.9 (d, *J* = 8.1 Hz), 136.7 (d, *J* = 3.2 Hz), 137.6, 140.6, 162.6 (d, *J* = 244.6 Hz); IR (KBr, neat) 2956, 2857, 1567, 1467, 1378, 1091, 855, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}FO$ $(M + H)^+$ 219.1180, found 219.1196.

*6-(3-Chlorophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**23c**):*



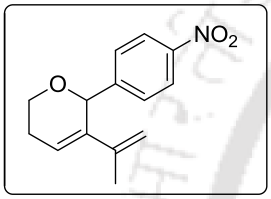
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.46; yield 85 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3 H), 2.20-2.24 (m, 1 H), 2.43-2.52 (m, 1 H), 3.50-3.58 (m, 1 H), 3.60-3.66 (m, 1 H), 4.54 (s, 1 H), 4.81 (s, 1 H), 5.45 (s, 1 H), 6.24 (t, *J* = 4.0 Hz, 1 H), 7.22-7.31 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.8, 58.7, 74.9, 113.2, 124.8, 127.5, 128.2, 129.3, 129.7, 134.3, 137.1, 140.4, 142.9; IR (KBr, neat) 2964, 2925, 2865, 1639, 1595, 1573, 1471, 1427, 1287, 1252, 1184, 1087, 1032, 884, 785, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}ClO$ $(M + H)^+$ 235.0884, found 235.0876.

*6-(4-Bromophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**23d**):*



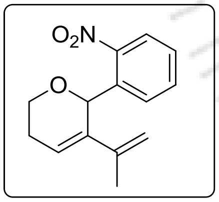
Pale brown oil; R_f (hexane/ EtOAc 23:0.5) 0.48; yield 82 mg, 57%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89 (s, 3 H), 2.15-2.23 (m, 1 H), 2.43-2.48 (m, 1 H), 3.52-3.56 (m, 1 H), 3.59-3.63 (m, 1 H), 4.53 (s, 1 H), 4.79 (s, 1 H), 5.43 (s, 1 H), 6.23 (t, *J* = 4.1 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 25.9, 58.6, 74.8, 113.2, 122.1, 124.7, 131.0, 131.5, 137.3, 139.9, 140.5; IR (KBr, neat) 2925, 2860, 1587, 1481, 1373, 1256, 1118, 1074, 1003, 825, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}BrO$ $(M + H)^+$ 279.0379, found 279.0377.

6-(4-Nitrophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (***23e***)*:*



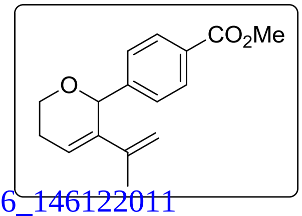
Brown gum; R_f (hexane/ EtOAc 24:1) 0.55; yield 96 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3 H), 2.22-2.28 (m, 1 H), 2.46-2.49 (m, 1 H), 3.50-3.54 (m, 1 H), 3.63-3.67 (m, 1 H), 4.49 (s, 1 H), 4.81 (s, 1 H), 5.54 (s, 1 H), 6.30 (t, *J* = 4.2 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 25.5, 59.0, 74.3, 113.0, 123.4, 125.1, 129.9, 136.5, 140.2, 147.5, 147.9; IR (KBr, neat) 2925, 2854, 1605, 1522, 1347, 1108, 1082, 1015, 854, 771 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1125, found 246.1118.

6-(2-Nitrophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (***23f***)*:*



Brown gum; R_f (hexane/ EtOAc 24:1) 0.57; yield 101 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 3 H), 2.12-2.20 (m, 1 H), 2.42-2.53 (m, 1 H), 3.31-3.38 (m, 1 H), 3.61-3.66 (m, 1 H), 4.67 (s, 1 H), 4.87 (s, 1 H), 6.28-6.31 (m, 2 H), 7.28 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 7.43-7.48 (m, 2 H), 7.80 (dd, *J* = 7.8 and 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 25.8, 58.9, 69.6, 113.4, 124.8, 125.7, 129.0, 131.3, 131.7, 134.5, 136.4, 140.3, 150.2; IR (KBr, neat) 2927, 2858, 1608, 1530, 1463, 1362, 1162, 1088, 1031, 867, 743 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1125, found 246.1128.

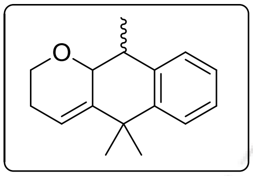
Methyl 4-(3-(prop-1-en-2-yl)-5,6-dihydro-2H-pyran-2-yl)benzoate (***23g***)*:*



Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 79 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3 H), 2.18-2.26 (m, 1 H), 2.44-2.52

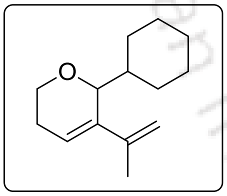
(m, 1 H), 3.51-3.57 (m, 1 H), 3.61-3.72 (m, 1 H), 3.91 (s, 3 H), 4.52 (s, 1 H), 4.79 (s, 1 H), 5.51 (s, 1 H), 6.26 (t, *J* = 4.1 Hz, 1 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 8.00 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.9, 52.3, 59.0, 75.1, 113.2, 124.8, 129.3, 129.8, 129.9, 137.2, 140.6, 145.9, 167.2; IR (KBr, neat) 2925, 1720, 1606, 1435, 1360, 1279, 1108, 1070, 1017, 878, 767 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_3$ $(M + H)^+$ 259.1329, found 259.1323.

5,5,10-Trimethyl-3,5,10,10a-tetrahydro-2H-benzo[g]chromene (***23h***)*:*



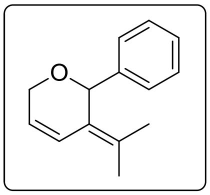
Pale yellow liquid; R$_f$ (hexane/ EtOAc 23:0.5) 0.59; yield 71 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.45 (s, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 2.10-2.18 (m, 1 H), 2.23-2.32 (m, 1 H), 2.91-3.00 (m, 1 H), 3.62-3.68 (m, 1 H), 3.90-3.94 (m, 1 H), 4.00-4.08 (m, 1 H), 5.83 (t, *J* = 3.4 Hz, 1 H), 7.15-7.23 (m, 2 H), 7.30 (dd, *J* = 7.2 and 1.4 Hz, 1 H), 7.34 (dd, *J* = 7.2 and 1.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 26.0, 29.7, 35.0, 39.5, 40.4, 61.8, 75.7, 115.8, 126.2, 126.3, 126.5, 126.7, 138.8, 144.4, 145.5; IR (KBr, neat) 2966, 2924, 2854, 1602, 1488, 1463, 1371, 1263, 1102, 1028, 951, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O$ $(M + H)^+$ 229.1587, found 229.1588.

6-Cyclohexyl-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (***23i***)*:*



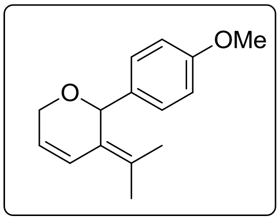
Colourless oil; R$_f$ (hexane/ EtOAc 23:0.5) 0.55; yield 45 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.48 (m, 3H), 1.56-1.69 (m, 6 H), 1.74-1.8 (m, 2 H), 1.85 (s, 3 H), 1.91-1.98 (m, 1 H), 1.24-1.27 (m, 1 H), 3.43-3.49 (m, 1 H), 3.90-3.94 (m, 1H), 4.3 (s, 1 H), 54.78 (s 1H), 4.83 (s, 1H), 5.94-5.96 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 25.7, 25.9, 26.7, 26.8, 27.2, 30.5, 41.1, 62.8, 78.5, 111.5, 123.0, 141.2, 143.3; IR (KBr, neat) 2924, 2851, 1449, 1377, 1250, 1103, 1053, 1012, 845, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{23}O$ $(M + H)^+$ 207.1743, found 207.1759.

2-Phenyl-3-(propan-2-ylidene)-3,6-dihydro-2H-pyran (***28a***)*:*



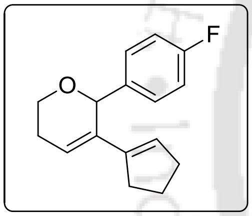
Colorless liquid; R$_f$ (hexane/ EtOAc 24:1) 0.50; yield 97 mg, 48%; 1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 6 H), 4.30 (t, *J* = 2.0 Hz, 2 H) 5.88-5.93 (m, 1 H), 6.43 (s, 1 H), 6.57-6.61 (m, 1 H), 7.20-7.25 (m, 3 H), 7.31-7.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 61.3, 73.9, 122.1, 122.8, 127.0, 128.2, 128.3, 129.6, 137.1, 139.8; IR (KBr, neat) 2977, 2927, 1638, 1492, 1360, 1124, 1078, 1015, 824, 756, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{17}O$ (M + H)$^+$ 201.1274, found 201.1256.

*6-(4-Methoxyphenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**28b**):*



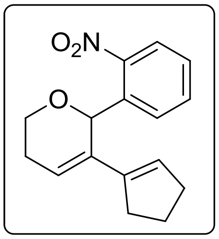
Yellow liquid; R_f (hexane/ EtOAc 24:1) 0.50; yield 70 mg, 62%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.43 (s, 6 H), 3.80 (s, 3H), 4.29 (s, 2 H), 5.88 (d, *J* = 10.2 Hz, 1 H), 6.37 (s, 1 H), 6.60 (d, *J* = 10.8 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.2, 55.4, 61.3., 73.9, 113.7, 122.1, 122.3, 127.6, 129.5, 130.8, 138.4, 158.6; IR (KBr, neat) 3412, 2924, 1722, 1607, 1511, 1370, 1036, 823 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{19}O_2$ (M + H)$^+$ 231.1380, found 231.1378.

*5-(Cyclopent-1-en-1-yl)-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran (**23j**):*



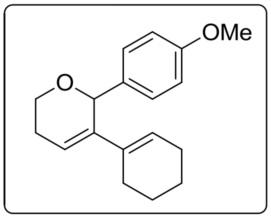
Colourless oil; R_f (hexane/ EtOAc 23:0.5) 0.59; yield 55 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77-1.85 (m, 2 H), 2.16-2.30 (m, 3 H), 2.41-2.53 (m, 3 H), 3.57-3.62 (m, 2 H), 5.15 (s, 1 H), 5.40 (s, 1 H), 6.04 (t, *J* = 4.1 Hz, 1 H), 6.98-7.03 (m, 2 H), 7.25-7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.9, 32.5, 33.6, 58.9, 75.3, 115.2 (d, *J* = 21.2 Hz), 123.9, 127.1, 131.0 (d, *J* = 8.1 Hz), 134.5, 137.0 (d, J = 3.2 Hz), 140.7, 162.6 (d, *J* = 244.5 Hz); IR (KBr, neat) 2923, 1603, 1506, 1224, 1157, 1087, 829 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}FO$ (M + H)$^+$ 245.1336, found 245.1336.

*5-(Cyclopent-1-en-1-yl)-6-(2-nitrophenyl)-3,6-dihydro-2H-pyran (**23k**):*



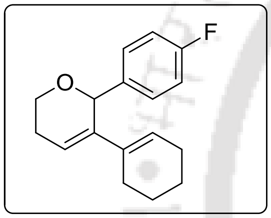
Yellow solid; R_f (hexane/ EtOAc 24:1) 0.48; m. p. 115-119 °C; yield 116 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.89 (m, 2 H), 2.11-2.18 (m, 1 H), 2.25-2.36 (m, 2 H), 2.42-2.59 (m, 3 H), 3.34-3.41 (m, 1 H), 3.60-3.65 (m, 1 H), 5.31 (s, 1 H), 6.10 (t, *J* = 4.0 Hz, 1 H), 6.21 (s, 1 H), 7.29 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 7.40-7.48 (m, 2 H), 7.80 (dd, *J* = 7.8 and 1.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.7, 32.5, 33.6, 59.2, 70.0, 124.6, 124.8, 127.3, 128.9, 131.4, 131.7, 133.3, 134.6, 140.6, 150.4; IR (KBr, neat) 2925, 1528, 1360, 1253, 1180, 1086, 963, 783cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ (M + H)$^+$ 272.1281, found 272.1308.

*5-(Cyclohex-1-en-1-yl)-6-(4-methoxyphenyl)-3,6-dihydro-2H-pyran (**23l**):*



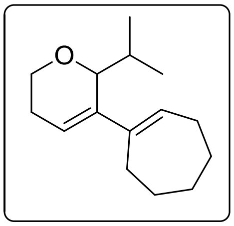
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.58; yield 100 mg, 73%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44-1.48 (m, 2 H), 1.57-1.64 (m, 2 H), 1.86-1.94 (m, 2 H), 2.08-2.14 (m, 2 H), 2.16-2.20 (m, 1 H), 2.42-2.45 (m, 1 H), 3.52-3.58 (m, 2 H), 3.8 (s, 3 H), 5.38(s, 1 H), 5.40 (s, 1H), 6.10 (t, *J* = 4.1 Hz, 1 H), 6.84 (d, *J*= 8.7 Hz, 2 H), 7.24 (d, *J* = 8.6 Hz, 2 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.0, 25.7, 25.8, 25.9, 55.3, 58.4, 74.9, 113.5, 120.5, 124.6, 130.5, 133.3, 134.1, 138.3, 159; IR (KBr, neat) 2927, 1608, 1509, 1461, 1172, 1089, 1035, 819 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}O_2$ $(M + H)^+$ 271.1693, found 271.1690.

*5-(Cyclohex-1-en-1-yl)-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran (**23m**):*



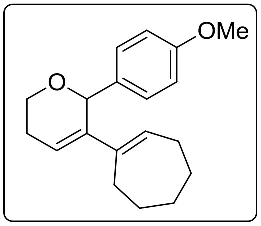
Colourless oil; R_f (hexane/ EtOAc 23:0.5) 0.55; yield 85 mg, 65%; 1H NMR (600 MHz, $CDCl_3$) δ 1.45- 1.5 (m, 2 H), 1.56-1.64 (m, 2 H), 1.86-1.98 (m, 2 H), 2.06-2.11 (m, 1 H), 2.13-2.22 (m, 2 H), 2.42-2.45 (m, 1 H), 3.50-3.54 (m, 1 H), 3.58- 3.62 (m, 1 H), 5.35 (s, 1 H), 5.43 (s, 1 H), 6.07 (t, *J*= 4.08 Hz, 1 H), 6.98-7.01 (m, 2 H), 7.28-7.30 (m, 2 H); 13C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.0, 25.7, 25.8, 25.8, 58.8, 74.7, 115.1 (J= 14.0 Hz), 120.8, 125.0, 130.9 (J = 5.4 Hz), 134.1, 136.9 (J= 5.4 Hz), 138.1, 162 (J= 162 Hz); IR (KBr, neat) 2927, 1602, 1506, 1436, 1223, 1156, 1091, 1056, 924, 823 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}FO$ $(M + H)^+$ 259.1493, found 259.1477.

*5-(Cyclohept-1-en-1-yl)-6-isopropyl-3,6-dihydro-2H-pyran (**23n**):*



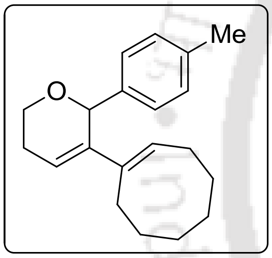
Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.61; yield 48 mg, 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 7.2 Hz, 3 H), 1.45-1.50 (m, 4 H), 1.71-1.76 (m, 2 H), 1.90- 1.94 (m, 2 H), 2.11-2.14 (m, 2 H), 2.19-2.24 (m, 3 H), 3.46-3.52 (dt, *J*= 10.4 Hz, 3.2 Hz, 1 H), 3.92 (dd, *J* = 10.4 Hz and 5.6 Hz, 1 H), 4.25 (s, 1 H), 5.67 (t, *J* = 6.8 Hz , 1 H), 5.74 (d, *J* = 6.4 Hz 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 20.2, 25.9, 27.0, 27.1, 28.7, 30.8, 31.9, 32.8, 63.3, 78.9, 121.0, 127.7, 144.4, 145.0; IR (KBr, neat) 2922, 2848, 1450, 1376, 1263, 1208, 1096, 1043, 941, 847, 786, 751, 476 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{25}O$ $(M + H)^+$ 221.1900, found 221.1898.

*5-(Cyclohept-1-en-1-yl)-6-(4-methoxyphenyl)-3,6-dihydro-2H-pyran (**23o**):*



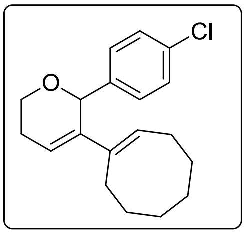
Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.61; yield 65 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27-1.32 (m, 2 H), 1.35-1.41 (m, 1 H), 1.62-1.67 (m, 3 H), 1.99-2.05 (m, 2 H), 2.16-2.22 (m, 1 H), 2.25-2.28 (m, 2 H), 2.33-2.41 (m, 1 H), 3.60-3.63 (m, 2 H), 3.80 (s, 3 H), 5.38 (s, 1 H), 5.61 (t, *J* = 6.8 Hz, 1 H), 6.03 (t, *J* = 4.0 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.4, 26.8, 28.5, 29.9, 32.7, 55.4, 59.3, 75.7, 113.6, 121.0, 129.0, 130.6, 133.2, 140.2, 142.9, 159.3; IR (KBr, neat) 2921, 2849, 1608, 1509, 1460, 1247, 1173, 1035, 825 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{25}O_2$ $(M + H)^+$ 285.1849, found 285.1841.

*(E)-5-(Cyclooct-1-en-1-yl)-6-(p-tolyl)-3,6-dihydro-2H-pyran (**23p**):*



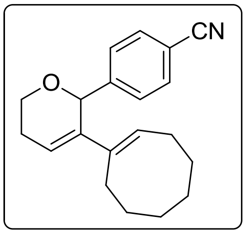
Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.58; yield 92 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.42 (m, 5 H), 1.52-1.55 (m, 3 H), 1.99-2.02 (m, 2 H), 2.12-2.18 (m, 1 H), 2.33 (s, 3 H), 2.34-2.40 (m, 3 H), 3.54-3.59 (m, 2 H), 5.35 (t, *J* = 8 Hz, 1 H), 5.43 (s, 1 H), 6.13 (t, *J* = 4.4 Hz, 1 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.24 (d, *J* = 8 Hz, 2 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 25.4, 26.0, 26.2, 27.2, 27.5, 29.3, 30.4, 58.4, 75.3, 121.5, 127.6, 128.9, 129.4, 137.4, 137.5, 137.6, 138; IR (KBr, neat) 2923, 2853, 1608, 1448, 1258, 1084, 1049, 871, 811, 737, cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{27}O$ $(M + H)^+$ 283.2056 , found 283.2044.

*6-(4-Chlorophenyl)-5-(cyclooct-1-en-1-yl)-3,6-dihydro-2H-pyran (**23q**):*



Pale yellow oil; R_f (hexane/ EtOAc 23:0.5) 0.58; yield 112 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.54 (m, 8 H), 2.02-2.03 (m, 2 H), 2.18-2.20 (m, 1 H), 2.36-2.40 (m, 3 H), 3.49-3.53 (m, 1 H), 3.54-3.63 (m, 1 H), 5.31 (t, *J* = 8.1 Hz, 1 H), 5.43 (s, 1 H), 6.16 (d, *J* = 3.5 Hz, 1 H), 7.28 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.6, 25.9, 26.9, 27.2, 29.0, 30.1, 58.5, 74.5, 121.7, 127.5, 128.1, 130.5, 133.4, 136.7, 137.2, 139.3; IR (KBr, neat) 2922, 2851, 1593, 1486, 1447, 1249, 1089, 1050, 1015, 870, 820, 733 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}ClO$ $(M + H)^+$ 303.1510, found 303.1512.

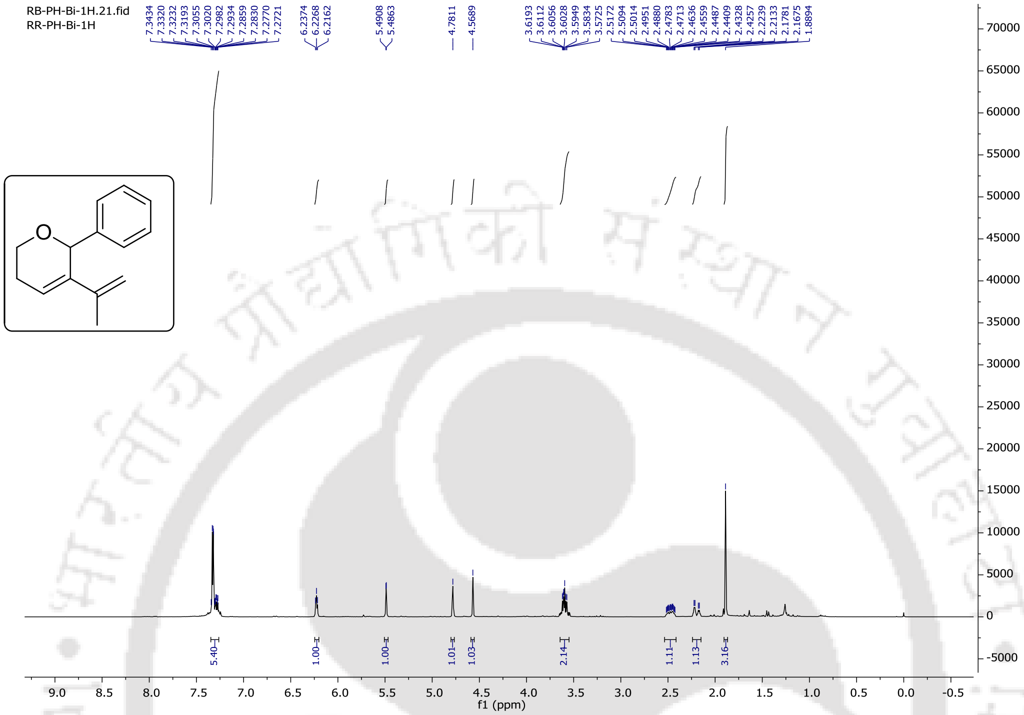
*4-(3-(Cyclooct-1-en-1-yl)-5,6-dihydro-2H-pyran-2-yl)benzonitrile (**23r**):*



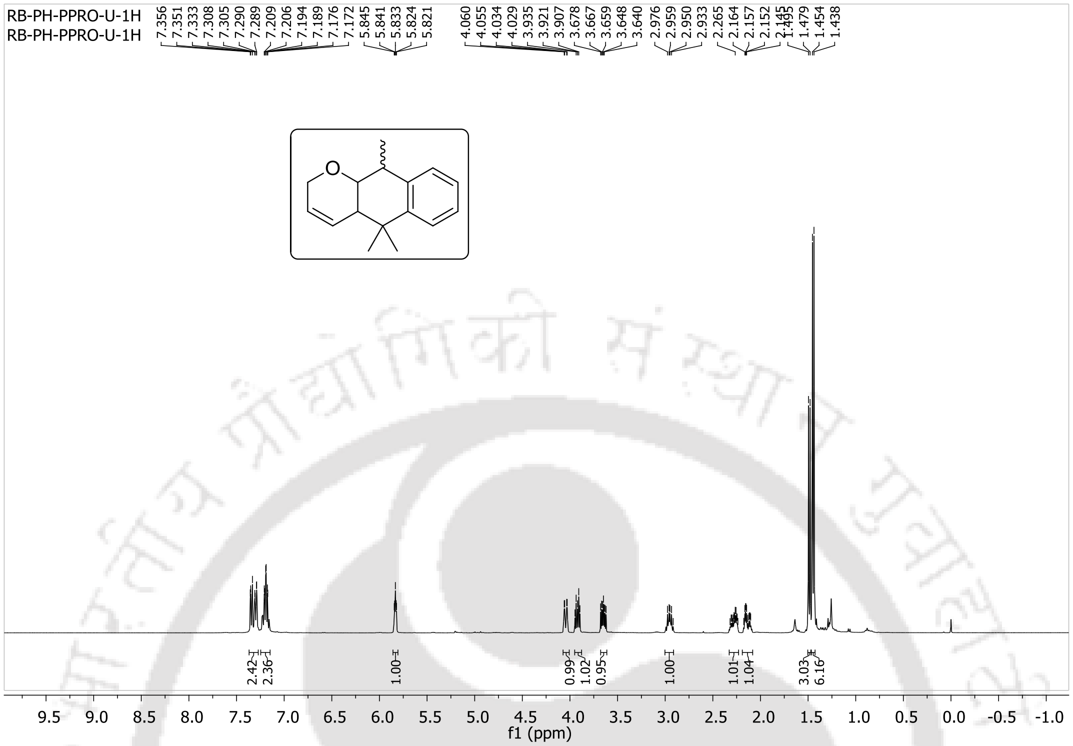
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.57; yield 68 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.29 (m, 1 H), 1.31-1.45 (m, 5 H), 1.50-1.56 (m, 2 H), 1.99-2.04 (m, 2 H), 2.18-2.24 (m, 1 H), 2.35-2.40 (m, 2 H), 2.43-2.50 (m, 1 H), 3.46-3.53 (m, 1 H), 3.60-3.66 (m, 1 H), 5.27 (t, *J* = 8.2 Hz, 1 H), 5.48 (s, 1 H), 6.20 (t, *J* = 4.1 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 25.8, 26.2, 27.1, 27.4, 29.2, 30.3, 59.4, 74.9, 111.7, 119.1, 122.5, 128.0, 130.1, 132.2, 136.3, 137.5, 146.5 ; IR (KBr, neat) 2922, 2228, 1447, 1253, 1090, 1051, 871, 825, 730 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO$ $(M + H)^+$ 294.1852, found 294.1871.

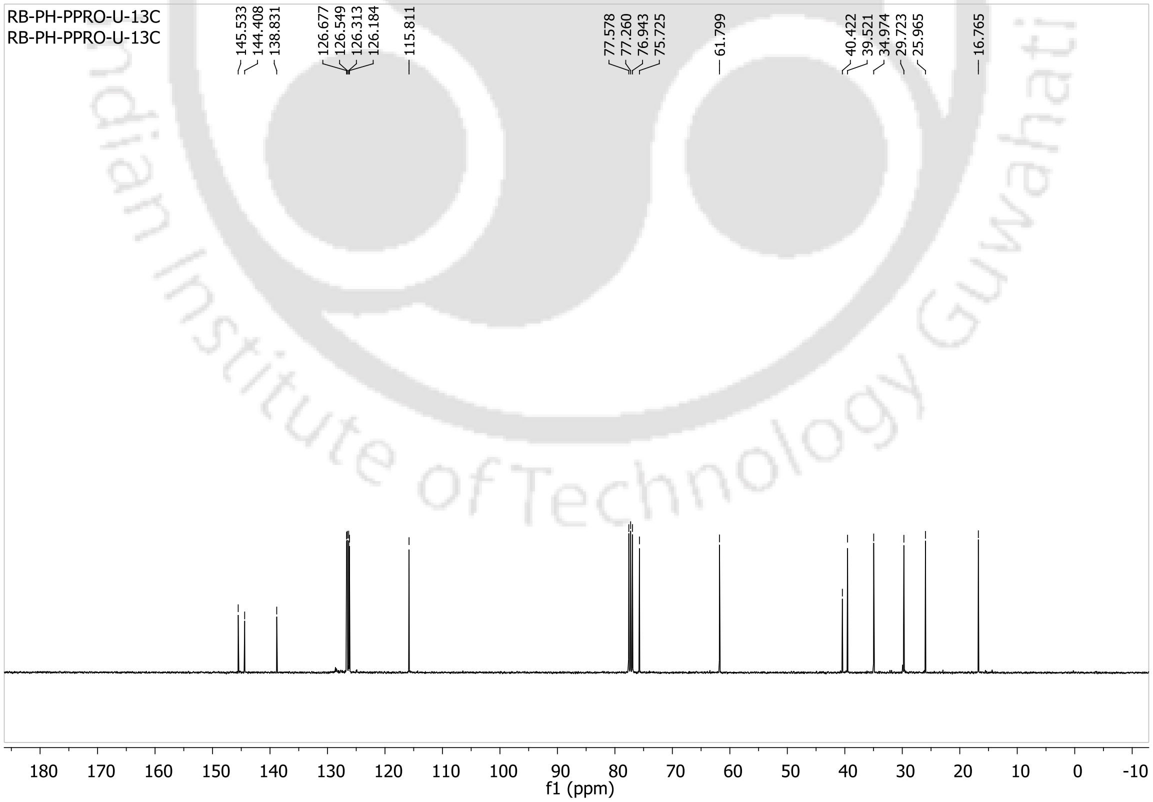
2A.8. Representative Spectra:

^{1}H and ^{13}C spectra of 6-phenyl-5-(prop-1-en-2-yl)-3,6-dihydro-2*H*-pyran 23a:

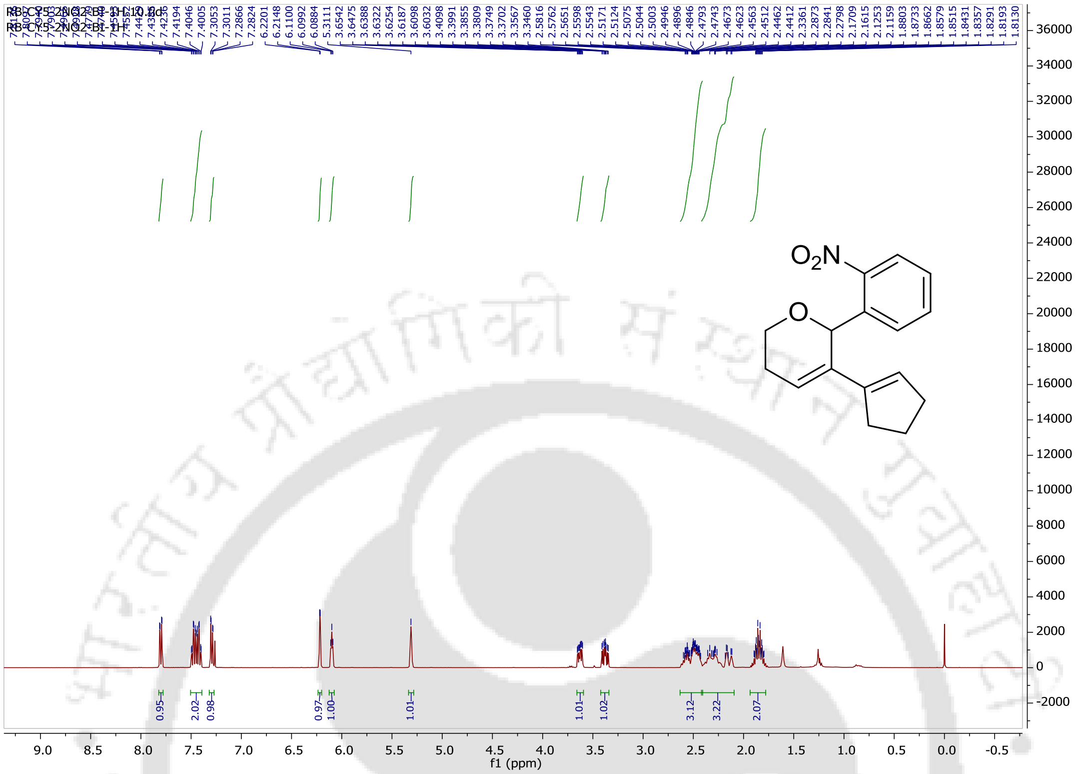


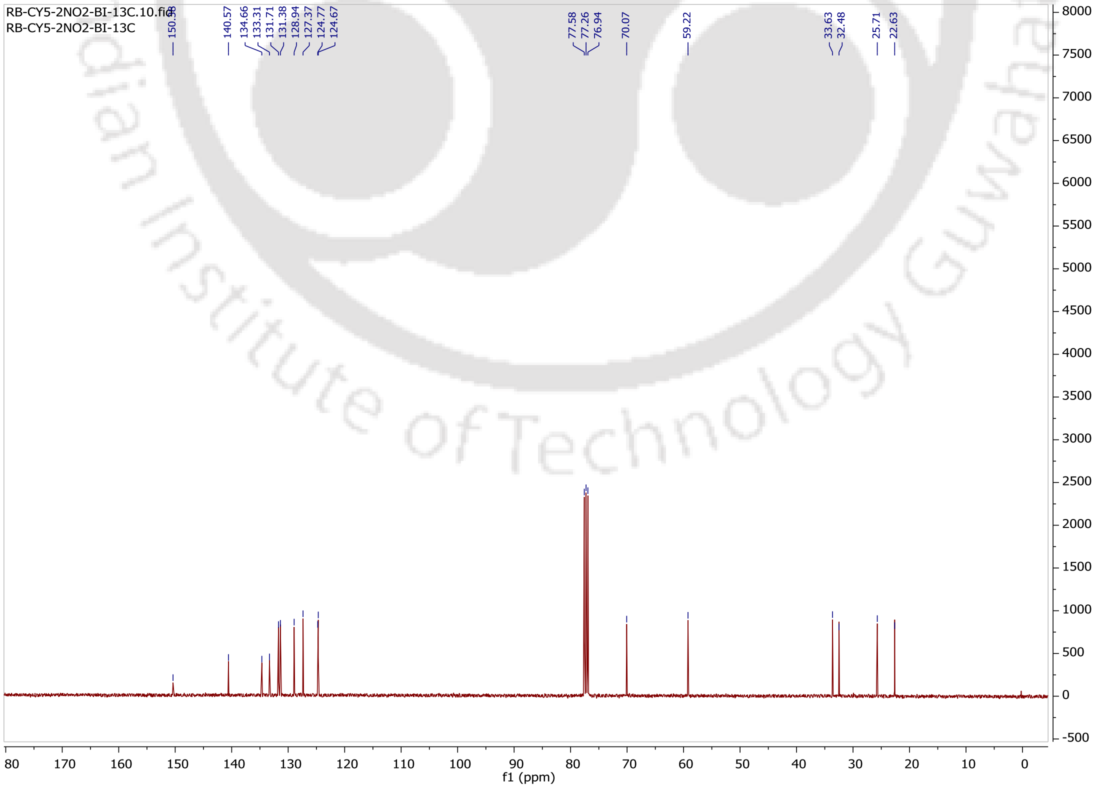
^{1}H and ^{13}C spectra of 5,5,10-trimethyl-4a,5,10,10a-tetrahydro-2*H*-benzo[*g*]chromene 23h:



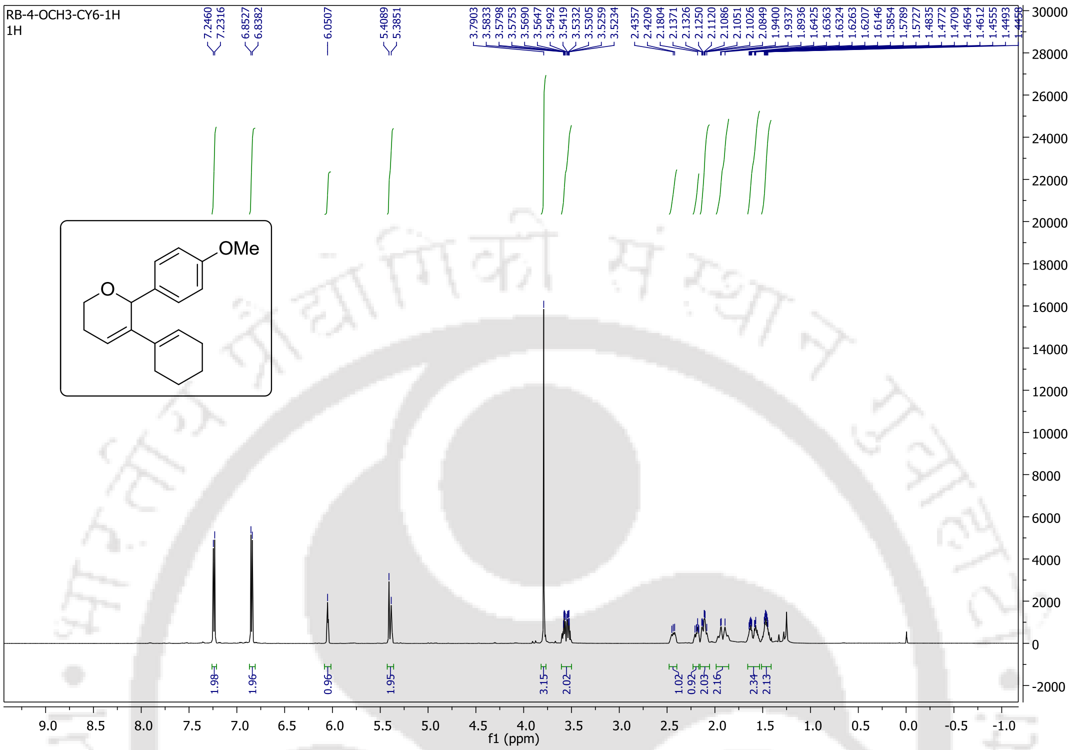


^{1}H and ^{13}C spectra of 5-(Cyclopent-1-en-1-yl)-6-(2-nitrophenyl)-3,6-dihydro-2*H*-pyran 23k:

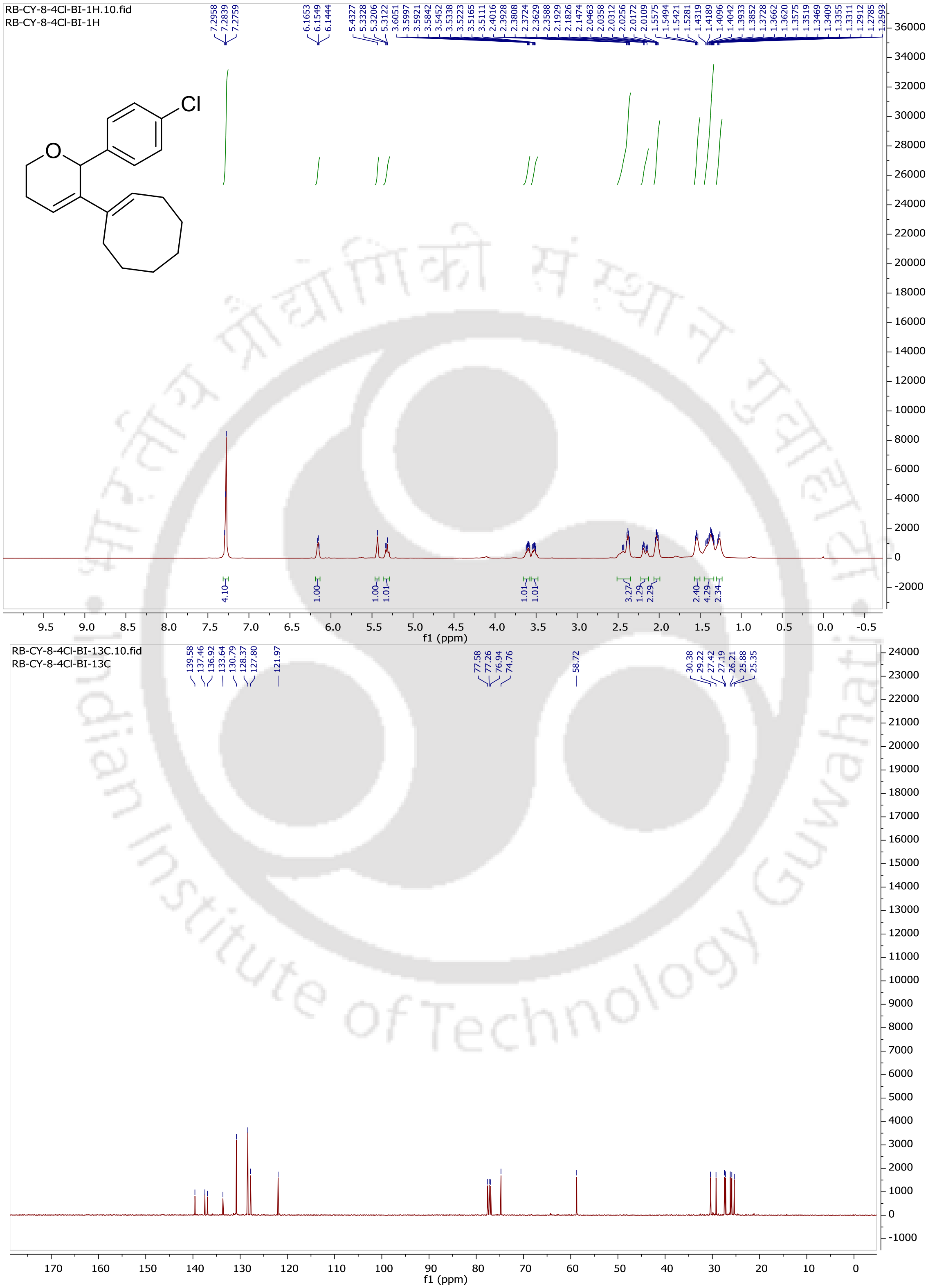




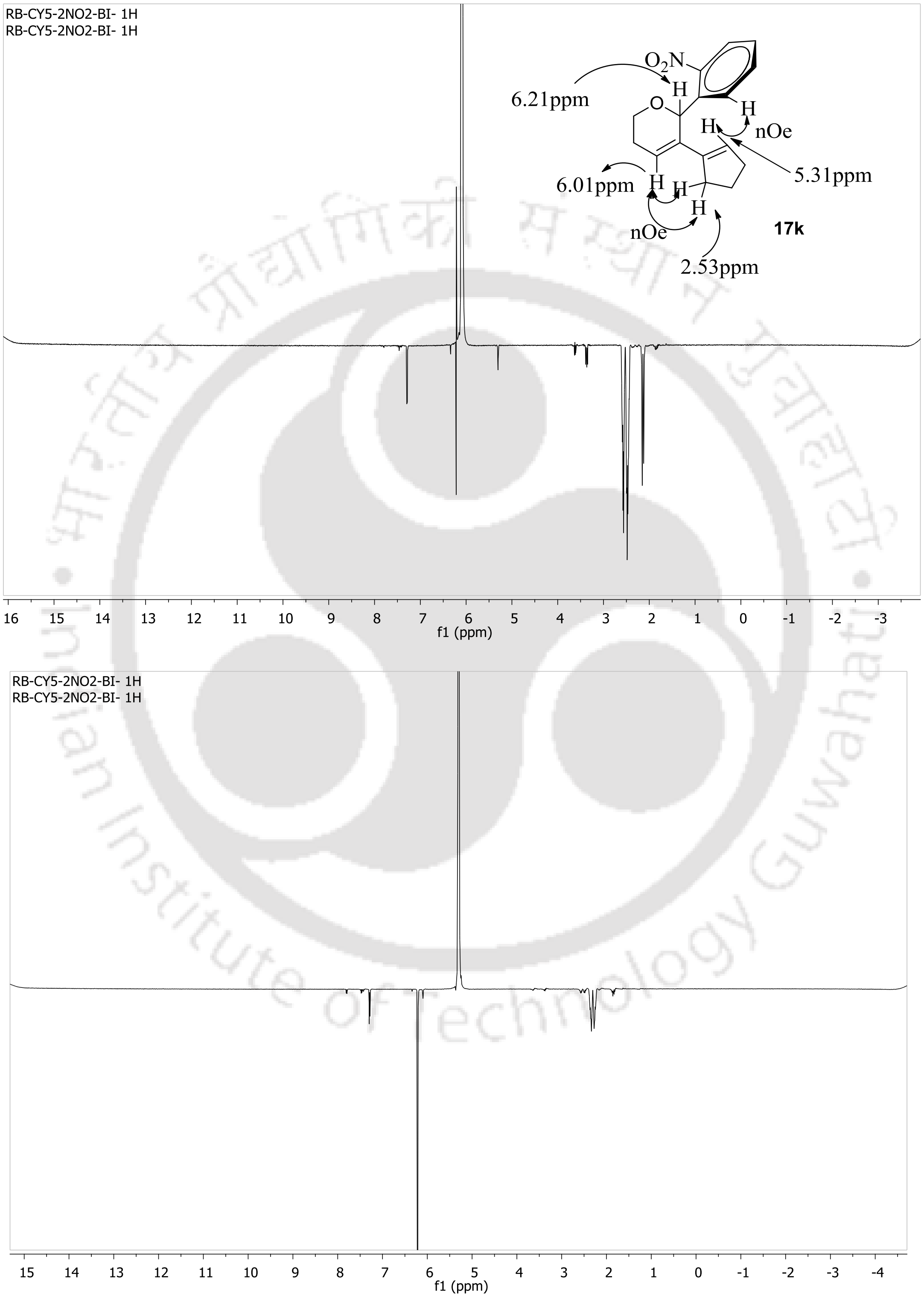
^{1}H and ^{13}C spectra of 5-(cyclohex-1-en-1-yl)-6-(4-methoxyphenyl)-3,6-dihydro-2*H*-pyran 23l:



^{1}H and ^{13}C spectra of 6-(4-Chlorophenyl)-5-(cyclooct-1-en-1-yl)-3,6-dihydro-2*H*-pyran 23q:



NOE spectra of compound 5-(cyclopent-1-en-1-yl)-6-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran 23k:



The crystal parameters of compound 5-(cyclopent-1-en-1-yl)-6-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran 23k:

	CCDC 1488115
Formula	$C_{16} H_{17} N O_3$
Formula weight	271.31
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	7.3532(13)
b/Å	12.219(2)
c/Å	15.266(3)
α/º	97.160(12)
β/º	90.233(11)
γ/º	90.152(12)
V/Å^3	1360.9(4)
Z	4
Abs. Coeff./mm^{-1}	0.092
Abs. Correction	None
GOF on F^2	0.954
Final R indices [I> 2σ(I)]	$R1$ = 0.0520
	$wR2$ = 0.1419
R indices [all data]	$R1$ = 0.0919
	$wR2$ = 0.1732

2A.9. References:

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4. (a) Yet, L. *Chem. Rev.*, **2000**, *100*, 2963. (b) Boivin, T. L. B. *Tetrahedron.* **1987**, *43*, 3309. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem*. **1988**, *53*, 911. (d) Li, C.-J.; Zhang, W.-C. *Tetrahedron.* **2000**, *56*, 2403. (e) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421. (f) Pham, M.; Allatabakhsh, A.; Minehan, T. G. *J. Org. Chem. 2008*, *73*, 741.
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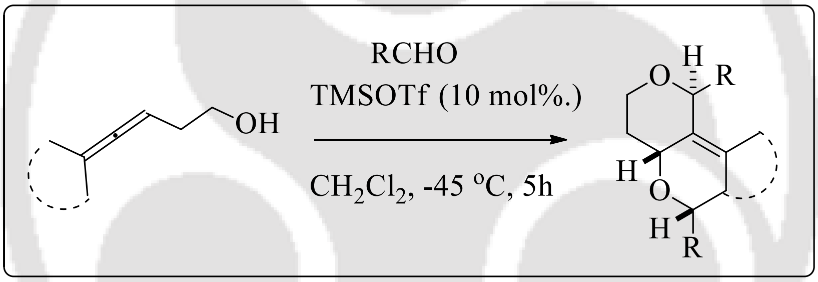
Chapter 2

Section B

TMSOTf catalyzed diastereoselective synthesis of pyranopyrans using β-allenols and aldehydes

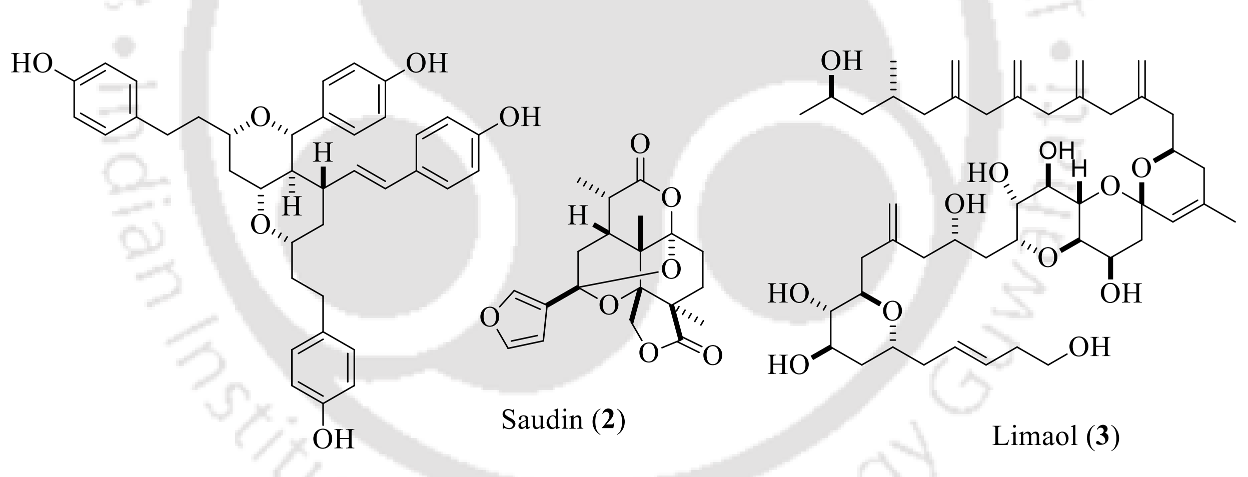


***J. Org. Chem.* 2018, 83, 14987-14998**

TMSOTf catalyzed diastereoselective synthesis of pyranopyrans using *β*-allenols and aldehydes

2B.1. Introduction and applications:

Pyranopyran skeletons are found in many biologically active natural products[1] (*Figure 2B.1.1*) and they are also used as synthetic intermediates for the synthesis of polycyclic ethers such as marine toxins.[2] Blepharocalyxin D (**1**) is a member of diarylheptanoid alkaloids and is isolated from the seeds of *Alpinia blepharocalyx*. It is an antiproliferative agent against murine colon 26-L5 carcinoma cells.[3] Similarly, caged diterpenoid saudin (**2**) was isolated in 1985 by Mossa and Cassady from the leaves of the *Clutia richardiana (L.)* of family *Euphorbiaceae*, found in the mountains of Saudi Arabia. This natural product was found to induce hypoglycemia in mice and therefore, could be an appealing lead for the treatment of diabetes.[4] Limaol (**3**), a polyhydroxy macromolecule, was isolated from marine dinoflagellate *Prorocentrum lima*. It shows cytotoxicity against certain cancer cell lines.[5]



Blepharocalyxin D (**1**)

Saudin (**2**)

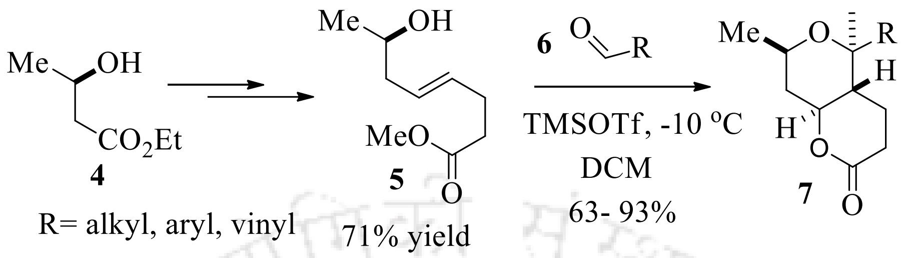
Limaol (**3**)

Figure 2B.1.1 Biologically active compounds containing pyranopyran rings.

2B.2. An Overview of Relevant Synthetic Methods:

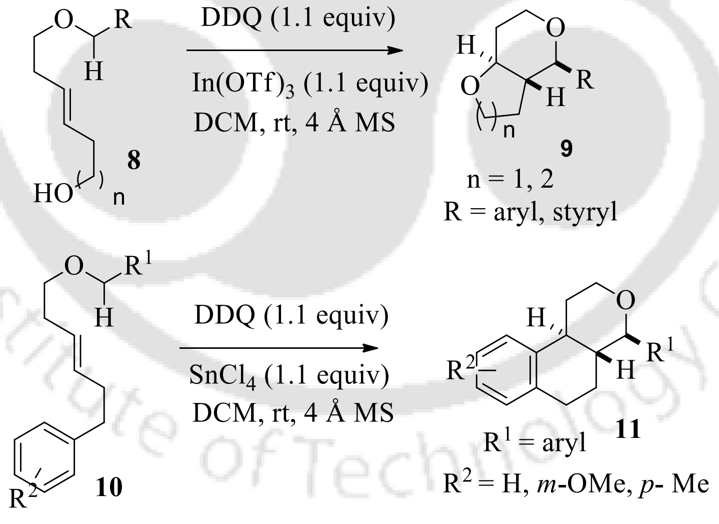
Review of literature reveals that pyran rings are generally prepared by hetero Diels-Alder reactions, olefin metathesis, Prins cyclization or Lewis acid catalyzed cyclizaion reaction of unsaturated alcohols. Some of the methods are discussed below.

In 2008, Willies and co-workers synthesized a trans fused pyranopyranones **7** from methyl (4*E*,7*R*)-7-hydroxyoctanoate (**5**) *via* intramolecular Prins cyclization with different aldehydes **6**. The reaction was catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at - 10 °C (*Scheme 2B.2.1*).[6]



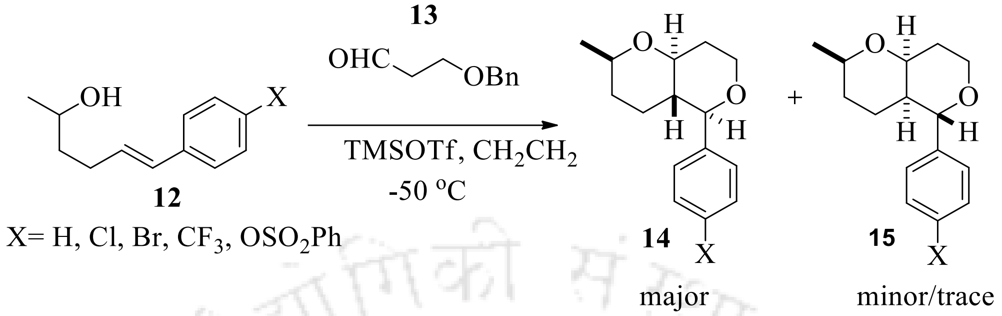
Scheme 2B.2.1

Subba Reddy and co-workers described a method of oxidative Prins cyclization reaction for the synthesis of *trans-* and *cis*-fused hexahydro-2*H*-furo[3,2-*c*]pyrans and octahydropyrano[4,3-*b*]pyrans **9** respectively in good yields with an excellent stereoselectivity mediated by DDQ and In(OTf)$_3$ (*Scheme 2B.2.2*). Homoallyl benzyl ethers **10** can also undergo a tandem Prins/Friedel-Crafts cyclization in the presence of stoichiometric amounts of DDQ and SnCl$_4$ *via* benzylic C–H bond activation to furnish the corresponding *trans-* and *cis*-fused hexahydro-1*H*-benzo[*f*]isochromenes **11** in good yields with complete stereoselectivity.[7]



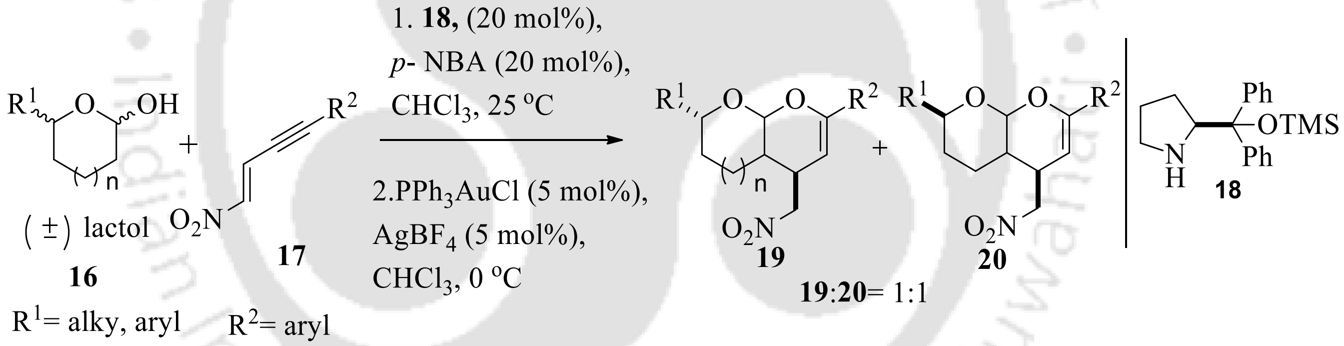
Scheme 2B.2.2

In 2012, Willies and co-workers reportedly synthesized bicyclic oxygen heterocycles (**14** and **15**) from *γ*, *δ*- unsaturated alcohols **12** and 3-(benzyloxy) propanal (**13**) (*Scheme 2B.2.3*). These pyranopyrans are the core units of diarylheptanoid blepharocalyxin D (**1**) (*Figure 2B.1.1*). The reaction was catalyzed by TMSOTf and the minor *cis*-fused isomer can be easily separated by column chromatography.[8]



Scheme 2B.2.3

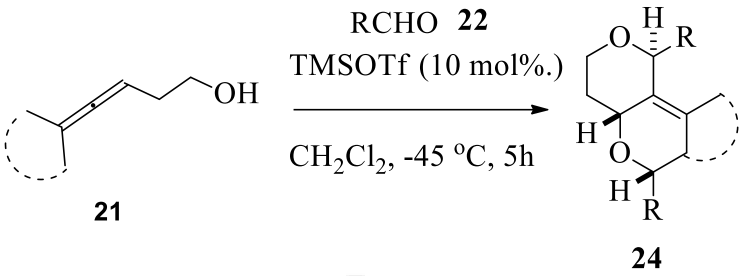
Liu and co-workers described an asymmetric synthesis of bicyclic O, O- acetals (**19** and **20**) from racemic lactols **16** and nitroenyne **17** *via* asymmetric organocatalysis and gold catalysis in a sequential process as shown in *Scheme 2B.2.4*.[9]



Scheme 2B.2.4

2B.3. Present Objective and Strategy:

In spite of several novel strategies available in the literature for the synthesis of pyranopyrans, most of them suffered from major drawbacks such as multistep synthesis of starting material, lack of selectivity etc. As such there is still much interest in the development of new methodologies for the synthesis of pyranopyrans because of their biological importance. Our interest in exploiting *β*-allenols for various synthetic procedures led us towards the development of newer methods for the synthesis of substituted pyranopyrans. In this chapter, we are going to present an efficient methodology for the synthesis of bicyclic compound hexahydropyrano[4,3-*b*]pyran skeleton *via* oxonium-ene reaction of *β*-allenols **21** and aldehydes **22** followed by [4+2] cycloaddition reaction catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) in moderate yields (*Scheme 2B.3.1*).



Scheme 2B.3.1

2B.4. Results and Discussions:

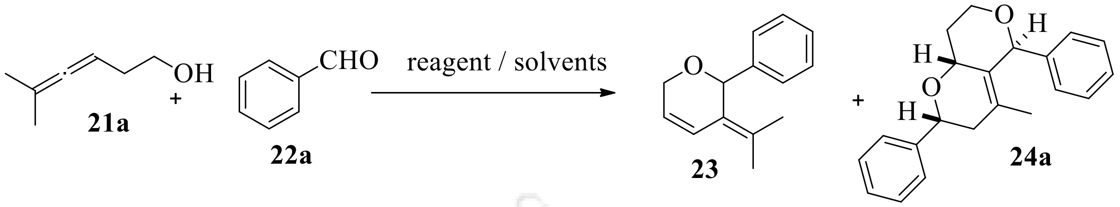
2B.4.1. Preparation of *β*-allenols:

The starting materials *β*-allenols **21a-d** were prepared as described in *Scheme 2A.4.1*.

2B.4.2. Optimization studies:

We started with *β*-allenols **21a** and benzaldehyde (**22a**) as model substrates, which were treated with TfOH (10 mol%) at 0 ^{o}C-room temperature in dichloromethane but the reaction did not give any product. However, decreasing the temperature to -45 ^{o}C provided two inseparable products 2-phenyl-3-(propan-2-ylidene)-3,6-dihydro-2*H*-pyran (**23**) and 4-methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-*b*]pyran (**24a**) in 57% overall yield with ratio (**23**: **24a**:: 5:2). The reaction was also performed in different conditions, and the results are shown in *Table 2B.4.2.1*. Further screening the reaction with other reagents such as TMSOTf (10 mol%) in dichloromethane at room temperature gave **23** with 48% yield. However, the reaction with TMSOTf (10 mol%) at -45 ^{o}C afforded the product 4-methyl-2,5-diphenyl-2,3,5,7,8,8*a*-hexahydropyrano[4,3-*b*]pyran (**24a**) with 40% yield. In an attempt to increase the yield of **24a,** the reaction was carried out at -78 ^{o}C with TMSOTf (10 mol%), but the reaction was not found to be fruitful. There was no reaction when the solvent is changed from dichloromethane to 1,2-dichloroethane. Increasing the loading of TMSOTf to 20 mol% and 3,4-dien-1-ol **21a** from 1.0 equiv. to 1.5 equiv. in dichloromethane at -45 ^{o}C also unable to produce higher yield of **24a**. On the other hand, increasing the amount of benzaldehyde (**22a)** from 1.0 equiv. to 2.0 equiv. at -45 ^{o}C in dichloromethane also did not increase the yield. So, assuming **21a** (1.5 equiv.), **22a** (1 equiv.) and TMSOTf (10 mol%) in dichloromethane at -45 ^{o}C for 5h is the most suitable reaction condition, for the synthesis of hexahydropyrano[4,3-*b*]pyran, we explored the variability of substrate scope in the following section.

Table 2B.4.2.1. Optimization conditions[a]



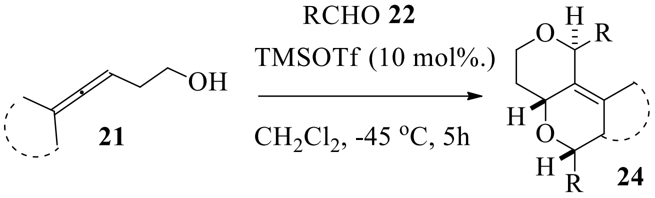
Entry.	Reagent (equiv)	Solvent	Temp./ °C	Time/h	Product(%) yield[b]
1	TfOH (0.1)	DCM	0 °C -rt	12	c (80)
2	TfOH (0.1)	DCM	-45 °C	5	**23**+**24a** (57)
3	TMSOTf (0.1)	DCM	rt	12	**23** (48)
4	**TMSOTf (0.1)**	**DCM**	**-45 °C**	**5**	**24a (40)[d]**
5	TMSOTf (0.1)	DCM	-78 °C	5	**24a** (32)[d]
6	TMSOTf (0.1)	DCE	-45 °C	5	c (75)[,d]
7	TMSOTf (0.2)	DCM	-45 °C	5	**24a** (38)[d]
8	TMSOTf (0.2)	DCM	-45 °C	5	**24a** (38)[e]

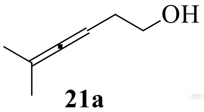
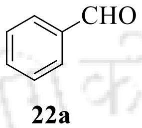
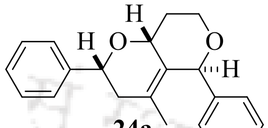
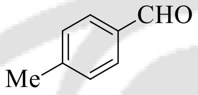
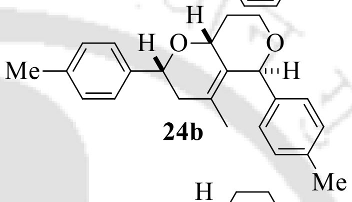
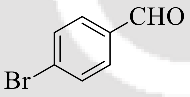
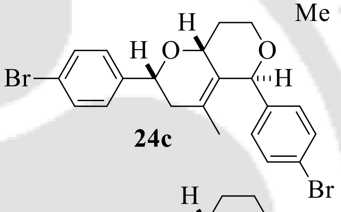
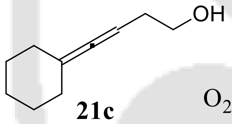
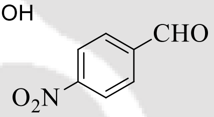
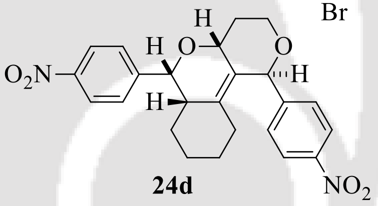
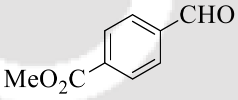
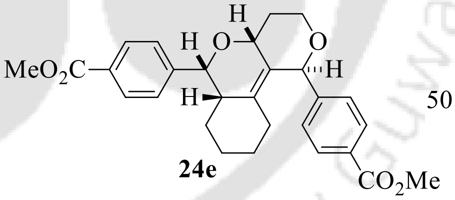
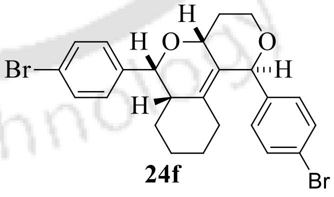
[a]reaction conditions **21** (1.5 equiv.), **22a** (1.0 equiv.) and solvent 4 mL. [b]Yields are isolated yield. [c]starting material recovered. [d]1.5equivalents of alcohol. [e]2.0 equivalents of benzaldehyde.

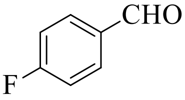
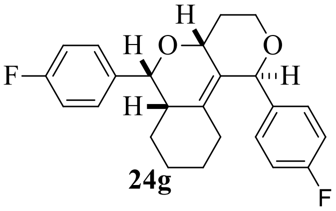
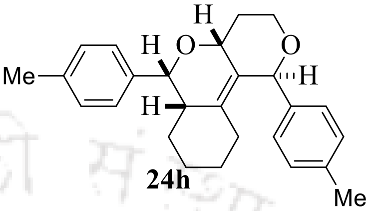
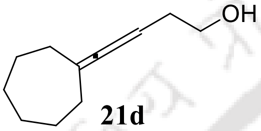
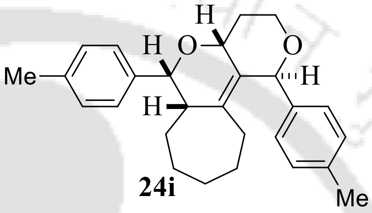
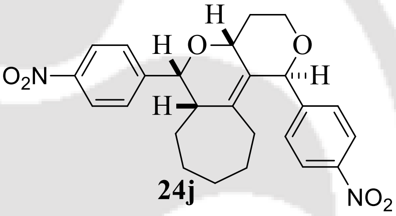
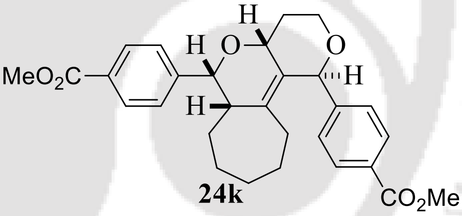
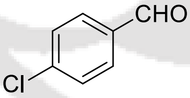
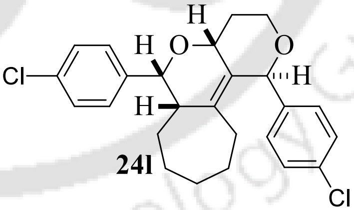
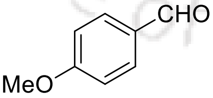
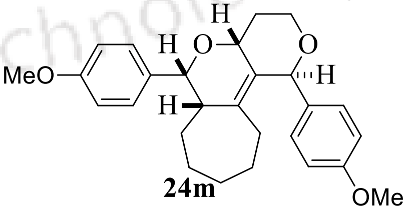
2B.4.3. Substrate scope of the reaction:

With the optimized condition in hand, the scope of the reaction was investigated by using different types of aldehydes and *β*-allenols as summarized in *Table 2B.4.3.1*. Treatment of alcohol **21a** with simple phenyl, electron donating methyl substituted and moderately electron withdrawing bromo-substituted aldehydes **22a-c** could afford the corresponding pyranopyran products **24a-c,** respectively with 40-58% yields. Reaction of 4-cyclohexylidenebut-3-en-1-ol (**21c**) with aldehydes having electron withdrawing groups and electron donating group on the aromatic ring afforded the corresponding pyranopyrans with moderate yields. It was observed that substrates having highly electron withdrawing groups on the aromatic ring of the aldehydes gave better yields than moderately electron withdrawing and electron donating groups on the aldehyde ring. Further reaction of alcohol **21d** with both electron donating and withdrawing groups on aldehyde ring also gave the desired products correspondingly. Aliphatic aldehydes failed to give the desired pyranopyran product. However, the reaction of 4-nitrobenzaldehyde

Table 2B.4.3.1. Synthesis of pyranopyrans[a]

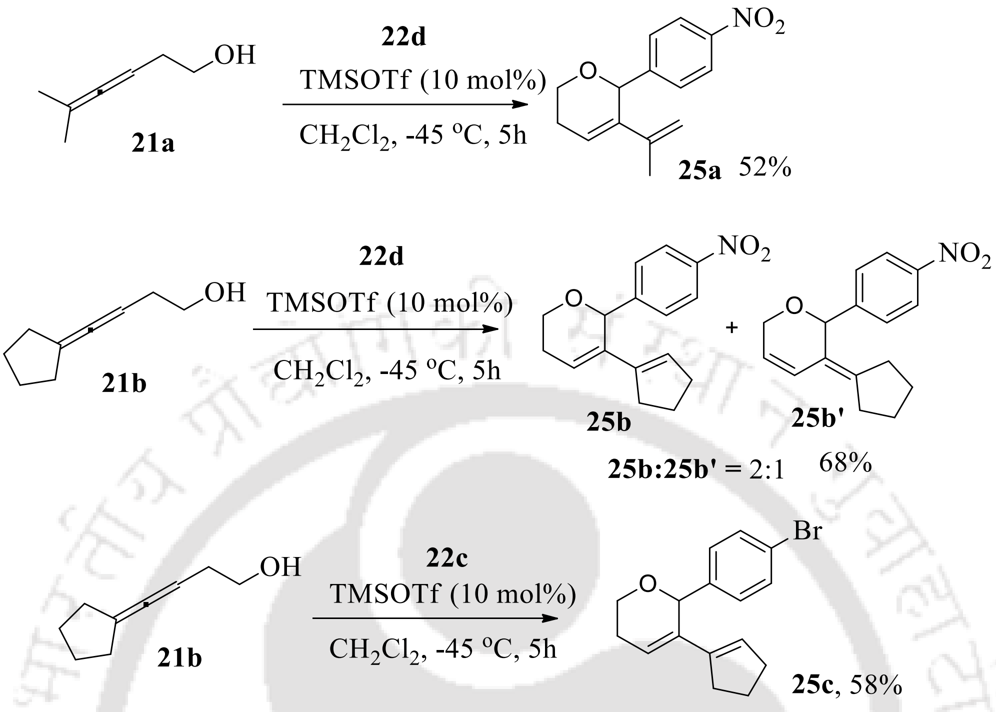


entry	alcohol	aldehyde	product	(%) yield[b]
1	 **21a**	 **22a**	 **24a**	40
2	**21a**	 **22b**	 **24b**	46
3	**21a**	 **22c**	 **24c**	58
4	 **21c**	 **22d**	 **24d**	55
5	**21c**	 **22e**	 **24e**	50
6	**21c**	**22c**	 **24f**	41

entry	alcohol	aldehyde	product	(%) yield^b
7	**21c**	 **22f**	 **24g**	40
8	**21c**	**22b**	 **24h**	42
9	 **21d**	**22b**	 **24i**	46
10	**21d**	**22d**	 **24j**	52
11	**21d**	**22e**	 **24k**	47
12	**21d**	 **22g**	 **24l**	48
13	**21d**	 **22h**	 **24m**	47

^{a}Reaction conditions: **21** (1.5 equiv), **22** (1.0 equiv), CH_2Cl_2 (2 mL), -45 °C. ^{b}Isolated yield. Compounds are characterized by ^1H, ^{13}C and mass spectrometric analysis

22d with acyclic β-allenol (**21a**) could not produce desired pyranopyran instead dihydropyran **25a** was obtained in 52% yield. This might be due to the electronic effect of the strongly electron-withdrawing nitro group present in the aldehyde molecule. Similarly, five membered cyclic *β*-allenol (**22b**) was also found to be not a good substrate for the formation of

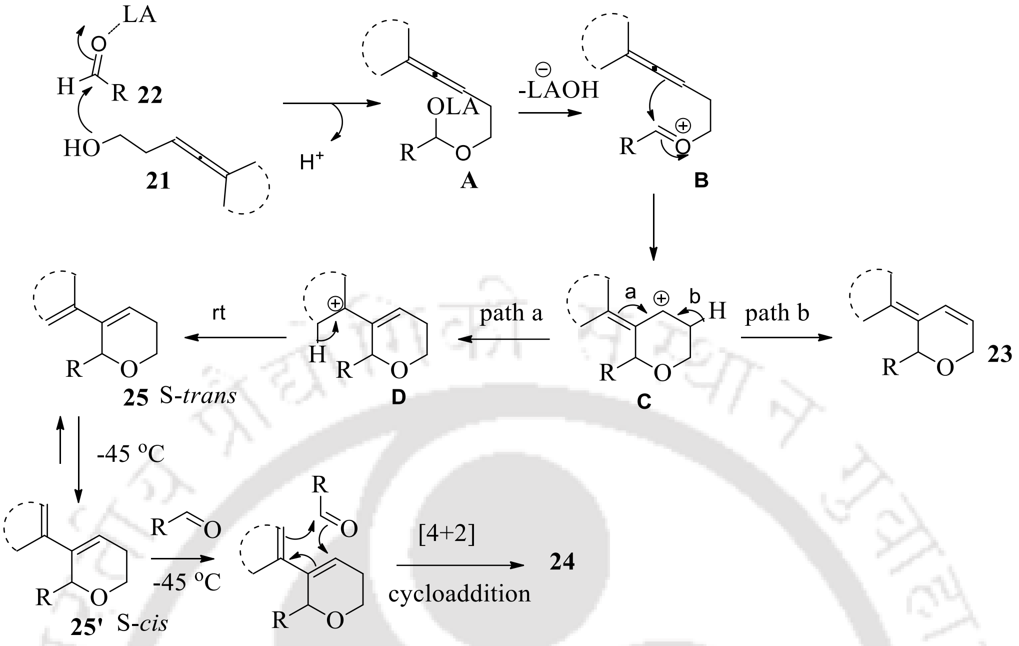


Scheme 2B.4.3.1

pyranopyrans unlike six and seven membered cyclic *β*-allenols. The reaction of *β*-allenol **22b** with aldehyde **22d** gave an isomeric mixture of **25b** and **25b′** with a corresponding ratio of 2:1 with 68% overall yield. The substrate **22b** is found to be not a good substrate for the synthesis of tricyclic compound as evident from the reaction of **22b** with **22c** which produces **25c** with 58% yield (*Scheme 2B.4.3.1*). This unusual behavior of **22b** might be due to the presence five membered ring in the tricyclic ring which destabilizes the overall configuration of the molecule.

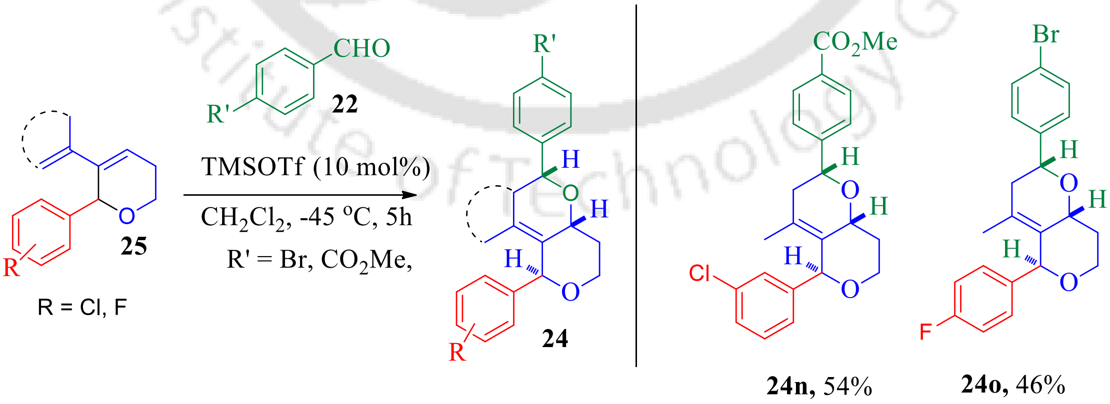
2B.5. Mechanism of the reaction:

A plausible mechanism that accounts for the regioselective synthesis of **23-25** is depicted in *Scheme 2B.5.1*. The Lewis acid activates the carbonyl group of aldehyde **22** for the nucleophilic attack by alcohol **21** to generate acetal **A**. The acetal after cleavage forms oxocarbenium ion **B**, which after undergoing cyclization generates intermediate carbocation **C**. The intermediate **C** after rearrangement produces carbocation **D** *via* path a, which after elimination of a proton gives final S-*trans* product **25** at room temperature. On the other hand, carbocation **C** after elimination of a proton *via* pathway b gives compound **23**. At lower temperature (-45 °C) compound **25** is in equilibrium with its S-*cis* product **25′**, which after reaction with an aldehyde in a hetero Diels-Alder fashion gives pyranopyran **24**.



Scheme 2B.5.1

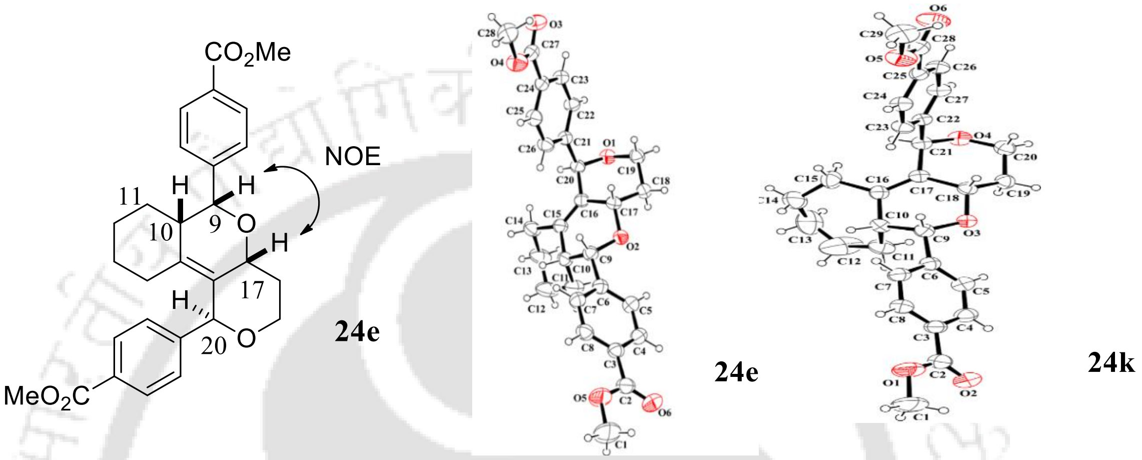
In order to prove the formation of compound **24** from compound **25** *via* intermediate **25′**, compound **25** (preparation and analysis see previous section **A**) was reacted with a different aldehyde under similar conditions and it was observed that pyranopyrans **24** was obtained in moderate yields (*Scheme 2B.5.2*). Accordingly, compounds **24n-o** were obtained in 54 and 46% yields, respectively.



Scheme 2B.5.2

2B.6. Structure and stereochemistry of the pyranopyrans:

The structure and stereochemistry of compound **24e** was confirmed by ^{1}H, ^{13}C, COSY and NOESY experiments. A strong NOE correlation between the H9 hydrogen at C-9 of the pyranopyran ring and the H17 hydrogen at C-17 of the ring junction of compound **24e** indicates the *cis* relationship between these two hydrogens. Similarly, there was no observation of NOE correlation between H17 and H20 of the pyranopyran ring.



24e

24e

24k

Figure 2B.6.1.X-ray crystallography structure of compound **24e** and **24k** with 35% ellipsoidal probability.

This clearly supports the *trans* relationship between the two aryl rings at C-9 and C-20. Finally, the stereochemistry of the pyranopyrans was further supported by X-ray crystallographic analysis compounds **24e** and **24k**.

2B.6.1. Explaination for regioselectivity and diastereoselectivity of the reaction:

The hetero Diels-Alder reaction is highly regio- and diastereo-selective. In our aspect, the regioselectivity can be explained by the fact that the frontier orbitals of dienes are polarized due to the presence electron donating CH_3 (in case of products **24a-f**) or $(-CH_2-)_4$ group (in

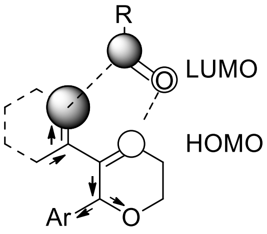
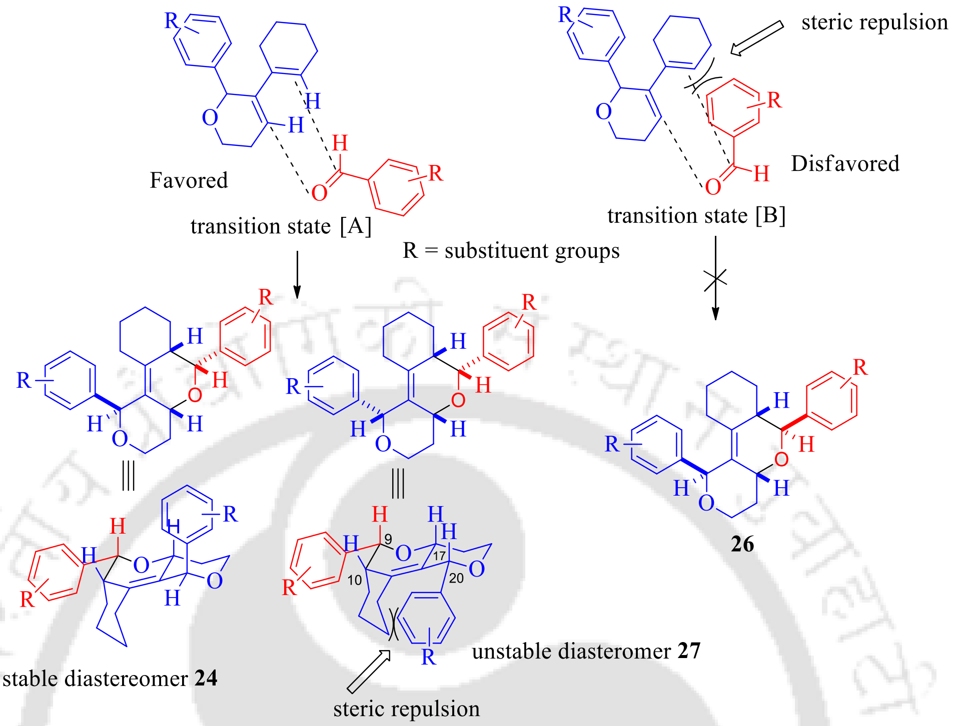


Figure 2B.6.1.1. HOMO and LUMO interaction and regioselectivity in hetero Diels Alder reaction case of products **24g-m**) as shown in *Figure 2B.6.1.1*. Therefore, the HOMO of the diene interacts with the LUMO of the dienophile to give the desired regioisomers.[10]



Scheme 2B.6.1.1

The observed diastereoselectivity of the reaction is due to the formation of more stable transition state **A** where there is less steric repulsion between the cyclohexenyl group of the dihydropyran and the hydrogen of the aldehyde group compared to transition state **B**, which experiences a strong steric repulsion between the cyclohexenyl ring of the dihydropyran and the aryl group of the aldehyde (*Scheme 2B.6.1.1*). Therefore, the desired products under these circumstances might be **24** or **27** with protons at C-9H, C-10H and C-17H are in all *cis* configuration. The diastereomer **27** is not stable due to the presence of steric repulsion between cyclohexyl ring and aryl group at C-20 position. Therefore, the desired product is **24** with two phenyl groups in *trans* configuration.

2B.7. Conclusion:

In conclusion we have developed a versatile approach for the synthesis of pyranopyrans from *β*-allenols and aldehydes catalyzed by TMSOTf in dichloromethane at -45 ^{o}C. Reaction is highly diastereoselective and produces only single isomers in moderate yields. And it is compatible to a wide range of functional groups.

2B.8. Experimental section:

2B.8.1. Instrumentation and characterization:

All reagents were purchased from commercial vendors as reagent grade and used without further purification. Column chromatography and TLC were performed using Silica gel (60-120 mesh size) and silica gel GF$_{254}$ (0.25 mm), respectively. Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded on a Fourier transform-infra red (FT-IR) machine either as neat liquid or KBr pellets. NMR spectra were recorded at 400 MHz (^{1}H, 400 MHz and ^{13}C, 100 MHz) and 600 MHz (^{1}H, 600 MHz and ^{13}C, 150 MHz) machines in $CDCl_3$ using tetramethylsilane as internal standard. Chemical shifts (δ) were reported in parts per million (ppm) and spin-spin coupling constants (*J*) are given in Hz. High resolution mass (HRMS) were measured using Q-TOF mass analyzer.

2B.8.2. Typical procedure for the synthesis of 4-methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-*b*]pyran (24a):

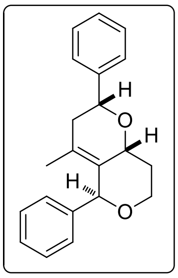
To a solution of benzaldehyde (**22a)** (1 mmol, 0.106 g) in dichloromethane (3 mL) at -45 °C, 5-methylhexa-3,4-dien-1-ol (**21a)** (1.5 mmol, 0.168 g) was added under N_2 atmosphere. After 5 minutes TMSOTf (0.1 mmol, 0.018 g) was added to the reaction mixture and it was kept for 5 h. It was brought to room temperature; dichloromethane was evaporated and the reaction mixture was quenched with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 x 10 mL) and the organic layer was washed with brine solution. The crude product was purified by column chromatography using ethyl acetate and hexane as eluents (Hexane:EtOAC::24:1) to give desired product **24a** as white oil.

2B.8.3. Representative procedure for the synthesis of pyrano-pyran derivatives (24n-o):

To a stirred solution of dihydro-2*H*-pyran **25** (0.4 mmol) under nitrogen atmosphere, 3 mL of dry DCM was added at -45 °C, followed by aldehyde **22** (0.4 mmol). After 5 minutes, TMSOTf (0.010 mL, 10 mol%) was added and the reaction mixture was kept for 4-5 h. The completion of the reaction was monitored by thin-layer chromatography. After bringing it to room temperature, it was evaporated and quenched with saturated $NaHCO_3$ solution. Finally, it was washed with saturated brine solution and extracted with EtOAc (2 x 10 mL). The crude product was purified by column chromatography (Hexane:EtOAc:: 24:1) to give the compound **24**.

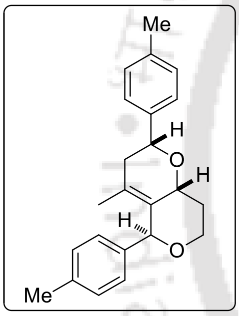
2B.9. Charaterization Data:

(2R,5S*,8aR*)-4-Methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran* (***24a***):



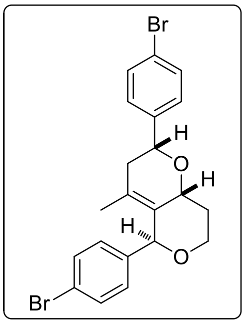
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 60 mg, 40%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 1.97-1.98 (m, 1 H), 2.00-2.10 (m, 1 H), 2.27-2.30 (m, 1 H), 2.51-2.56 (m, 1 H), 3.62-3.63 (m, 1 H), 3.81-3.83(m, 1 H), 4.34-4.35 (m, 1 H), 4.65-4.68 (m, 1 H), 5.9 (s, 1 H), 7.24-7.44 (m, 10 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.5, 34.7, 39.5, 60.4, 72.4, 74.2, 75.3, 126.2, 127.2,127.5, 127.9, 128.1, 128.7,128.9, 129.1, 139.2, 142.4; IR (KBr, neat) 2925, 1492, 1448, 1373, 1104, 1072, 970, 766, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}O_2$ $(M + H)^+$ 307.1693, found 307.1692.

(2R,5S*,8aR*)-4-Methyl-2,5-di-p-tolyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran* (***24b***)*:*



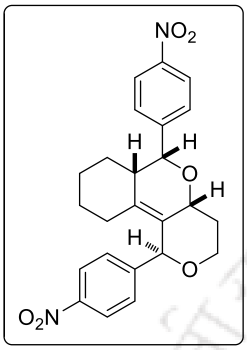
Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 79 mg, 46%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 1.86-1.93 (m, 1 H), 1.95-2.00 (m, 1 H), 2.25 (dt, J = 17.0 and 2.6 Hz, 1 H), 2.33 (s, 3 H), 2.37 (s, 3 H), 2.48-2.56 (m, 1 H), 3.61 (dt, J = 12.0 and 2.0 Hz, 1 H), 3.79 (dt, J = 10.4 and 3.0 Hz, 1 H), 4.30-4.34 (m, 1 H), 4.63 (dd, J = 10.4 and 3.0 Hz, 1 H), 5.86 (s, 1 H), 7.16-7.24 (m, 4 H), 7.29-7.33 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 21.3, 21.4, 34.7, 39.5, 60.4, 72.4, 74.2, 75.2, 126.2, 127.2, 127.9, 129.2, 129.3, 129.6, 136.2, 137.1, 137.4, 139.5; IR (KBr, neat) 2924, 1511, 1460, 1371, 1265, 1077, 968, 812, 738, cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{27}O_2$ $(M + H)^+$ 335.2006, found 335.2008.

(2R,5S*,8aR*)-2,5-bis(4-Bromophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran* (***24c***)*:*



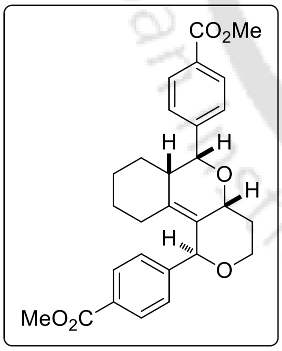
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.56; yield 125 mg, 54%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 1.86-1.93 (m, 1 H), 1.95-2.00 (m, 1 H), 2.25 (dt, J = 17.0 and 2.6 Hz, 1 H), 2.48-2.56 (m, 1 H), 3.61 (dt, J = 12.0 and 2.0 Hz, 1 H), 3.79 (dt, J = 10.4 and 3.0 Hz, 1 H), 4.30-4.34 (m, 1 H), 4.63 (dd, J = 10.4 and 3.0 Hz, 1 H), 5.86 (s, 1 H), 7.29 (d, J = 8Hz, 4H), 7.49 (d, J= 8 Hz, 2H), 7.51 (d, J= 8Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 34.5, 39.4, 60.6, 72.3, 73.8, 74.6, 121.6, 121.7, 127.9, 128.3, 128.8, 129.0, 131.8, 132.0, 138.3, 141.4; IR (KBr, neat) 2924, 1485, 1397, 1074, 1010, 865, 804, cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}Br_2O_2$ (M + H)$^+$ 462.9903, found 462.9906.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Nitrophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene* ***(24d)****:*



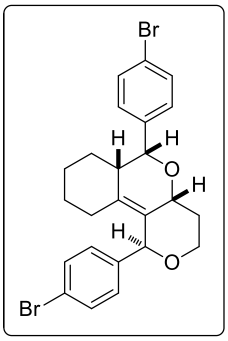
Pale yellow solid; R$_f$ (hexane/ EtOAc 24:1) 0.48 m. p. 165-169 °C. yield 127 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.16 (m, 1 H), 1.35-1.47 (m, 3 H), 1.80 -1.82 (m, 1 H), 1.90-1.92 (m, 2 H), 1.97-2.01 (m, 1 H), 2.08-2.11(m, 1 H), 2.36 (m, 1 H), 2.68 (d, *J*= 8.8, 1 H), 3.57 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.93 (dt, *J* = 12.2 and 2.7 Hz, 1 H), 4.23-4.25 (m, 1 H), 4.97 (d, *J* = 3.8 Hz, 1 H), 5.97 (s, 1 H), 7.54 (d, *J* = 8.6 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H), 8.24-8.27 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 29.0, 29.2, 31.2, 34.4, 44.4, 60.9, 72.2, 73.2, 76.7, 123.7, 124.1, 125.1, 126.7, 128.0, 138.4, 147.2, 147.5, 147.6, 148.0; IR (KBr, neat) 2931, 2856, 1603, 1519, 1346, 1191, 1080, 859, 726 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_6$ (M + H)$^+$ 437.1707, found 437.1718.

Dimethyl 4,4'-((1S,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene-1,6-diyl)dibenzoate* ***(24e)****:*



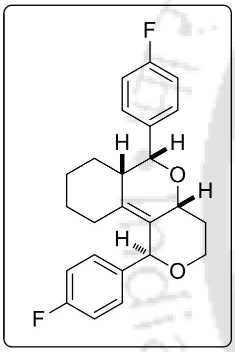
White solid ; R$_f$ (hexane/ EtOAc 24:1) 0.48. m. p. 110-113 °C yield. 127 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.45 (m, 4 H), 1.75-1.79 (m, 1 H), 1.81-1.89 (m, 2 H), 1.91-2.00 (m, 1 H), 2.03-2.08 (m, 1 H), 2.28-2.34 (m, 1 H), 2.62-2.68 (m, 1 H), 3.58 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.86 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 3.92 (s, 6 H), 4.22-4.26 (m, 1 H), 4.92 (d, *J* = 3.8 Hz, 1 H), 5.94 (s, 1 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 8.02-8.06 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 29.0, 29.2, 31.2, 34.6, 44.5, 52.3, 52.4, 60.8, 72.2, 73.4, 125.4, 125.9, 127.2, 128.9, 129.4, 129.7, 130.1, 138.0, 145.2, 145.9, 167.2, 167.3; IR (KBr, neat) 2928, 1722, 1611, 1436, 1280, 1109, 1018, 771, 735 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{31}O_6$ (M + H)$^+$ 463.2115, found 463.2120.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Bromophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene* ***(24f)****:*



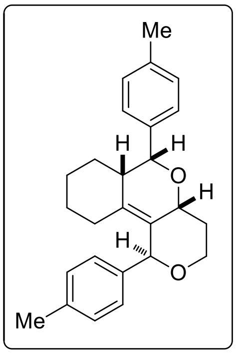
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.59; yield 103 mg, 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.43 (m, 4 H), 1.76-1.93 (m, 4 H), 2.00-2.05 (m, 1 H), 2.18-2.24 (m, 1 H), 2.59-2.64 (m, 1 H), 3.57 (dt, J = 12.2 and 1.8 Hz, 1 H), 3.82 (dt, J = 12.2 and 2.8 Hz, 1 H), 4.21-4.25 (m, 1 H), 4.79 (d, J = 3.6 Hz, 1 H), 5.85 (s, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.46-7.51 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 29.0, 29.2, 31.1, 34.6, 44.5, 60.5, 72.2, 73.1, 76.8, 120.8, 121.5, 125.3, 127.7, 129.1, 131.4, 131.9, 137.9, 138.9, 139.7; IR (KBr, neat) 2927, 1485, 1403, 1254, 1090, 1068, 1011, 865, 809 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{25}Br_2O_2$ $(M + H)^+$ 503.0216, found 503.0229.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Fluorophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene* ***(24g)****:*



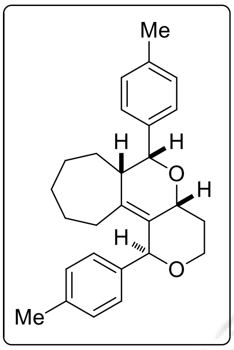
Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 76 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.40 (m, 4 H), 1.77-1.87 (m, 3 H), 1.89-1.97 (m, 1 H), 2.01-2.05 (m, 1 H), 2.18-2.23 (m, 1 H), 2.60-2.66 (m, 1 H), 3.58 (dt, J = 12.4 and 1.8 Hz, 1 H), 3.80 (dt, J = 12.4 and 1.8 Hz, 1 H), 4.25-4.29 (m, 1 H), 4.83 (d, J = 3.7 Hz, 1 H), 5.89 (s, 1 H), 7.02-7.08 (m, 4 H), 7.25-7.32 (m, 2 H), 7.38-7.42 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.8, 29.0, 29.2, 31.1, 34.7, 44.7, 60.3, 72.3, 73.1, 77.5, 115.1 (d, J = 21.1 Hz), 127.4, 127.5, 128.8, 128.9, 135.3 (d, J = 3.0 Hz), 136.3 (d, J = 3.0 Hz), 137.7, 161.9 (d, J = 243.0 Hz), 162.3 (d, J = 244.1 Hz); IR (KBr, neat) 2929, 1508, 1224, 1154, 1079, 834 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{25}F_2O_2$ $(M + H)^+$ 383.1817, found 383.1810.

(1S,4aR*,6R*,6aS*)-1,6-di-p-Tolyl-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-c]isochromene* ***(24h)****:*



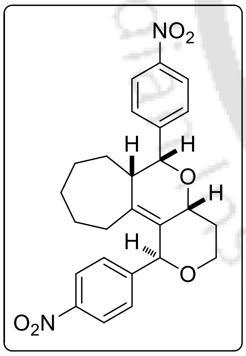
Colourless oil; R_f (hexane/ EtOAc 24:1) 0.55; yield 80 mg, 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.45 (m, 4 H), 1.75-1.84 (m, 3 H), 1.89-1.97 (m, 1 H), 2.00-2.05 (m, 1 H), 2.18-2.23 (m, 1 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 2.61-2.67 (m, 1 H), 3.62 (dt, J = 12.2 and 1.8 Hz, 1 H), 3.80 (dt, J = 12.2 and 2.8 Hz, 1 H), 4.27-4.32 (m, 1 H), 4.83 (d, J = 3.7 Hz, 1 H), 5.85 (s, 1 H), 7.14-7.25 (m, 6 H), 7.33 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.4, 27.0, 29.1, 29.3, 31.0, 34.8, 44.8, 60.4, 72.3, 73.5, 77.5, 125.6, 125.9, 127.3, 128.9, 129.5, 136.5, 136.8, 137.1, 137.5, 137.7; IR (KBr, neat) 2925, 1511, 1447, 1107, 1080, 962, 817, 740 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{31}O_2$ (M + H)$^+$ 375.2319, found 375.2300 .

(1S,4aR*,6R*,6aS*)-1,6-di-p-Tolyl-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran (**24i**):*



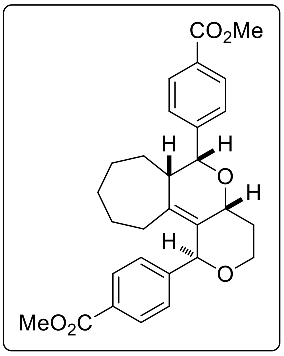
Colourless oil; R$_f$ (hexane/ EtOAc 24:1) 0.48; yield 90 mg, 46%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.28-1.34 (m, 3 H), 1.36-1.43 (m, 1 H), 1.59-1.69 (m, 4 H), 1.85-1.96 (m, 1 H), 2.01-2.04 (m, 2 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 2.39-2.44 (m, 1 H), 2.59-2.66 (m, 1 H), 3.63 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.80 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 4.28-4.32 (m, 1 H), 4.83 (s, 1 H), 5.81 (s, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7. 32 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.3, 21.4, 26.0, 27.2, 27.6, 29.4, 31.3, 35.4, 44.3, 60.6, 72.8, 74.3, 77.6, 125.7, 127.2, 128.9, 129.2, 129.6, 136.1, 136.3, 136.6, 137.1, 138.4 ; IR (KBr, neat) 2925, 1512, 1451, 1109, 1080, 818, 740 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{33}O_2$ (M + H)$^+$ 389.2475, found 389.2464.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Nitrophenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran (**24j**):*



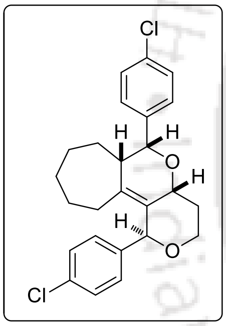
Pale yellow solid; R$_f$ (hexane/ EtOAc 24:1) 0.48. m. pt 189-193 °C. yield 117 mg, 52%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.27-1.37 (m, 6 H), 1.69-1.76 (m, 2 H), 1.98 (dq, *J*=12.2 and 2.7 Hz, 1 H), 2.08-2.16 (m, 2 H), 2.50-2.59 (m, 1 H), 2.68 (dt, *J* =12.2 and 1.8 Hz, 1 H), 3.60 (dt, *J*=12.2 and 2.7 Hz, 1 H), 3.92-3.97 (m, 1 H), 4.22-4.29 (m, 1 H), 4.94 (d, *J* =3.8 Hz, 1 H), 5.89 (s, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 8.25 (d, *J* = 8.0 Hz, 2 H), 8.27 (d, *J* = 8.0 Hz, 2 H) ^{13}C NMR (150 MHz, CDCl$_3$) δ 25.9, 26.9, 27.4, 29.3, 31.4, 35.1, 44.1, 61.2, 72.7, 73.9, 77.0, 123.7, 124.2, 126.7, 128.1, 128.5, 137.6, 146.8, 147.1, 147.6, 148.4; IR (KBr, neat) 2926, 1603, 1520, 1346, 109, 854, 738, 708, cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_6$ (M + H)$^+$ 451.1864, found 451.1881.

Dimethyl 4,4'-((1S,4aR*,6R*,6aS*)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran-1,6-diyl)dibenzoate (**24k**):*



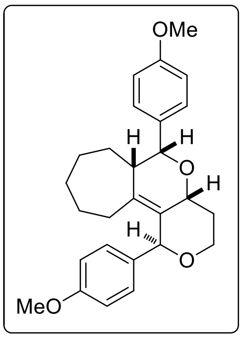
White solid; R_f (hexane/ EtOAc 24:1) 0.45. m. pt 162-165 °C. yield 113 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.32 (m, 4 H), 1.40-1.45 (m, 1 H), 1.60-1.72 (m, 3 H), 1.90-1.99 (m, 1 H), 2.01-2.10 (m, 2 H), 2.45-2.53 (m, 1 H), 2.61-2.68 (m, 1 H), 3.60 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.88 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.22-4.28 (m, 1 H), 4.90 (d, *J* = 2.0 Hz, 1 H), 5.85 (s, 1 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 8.02-8.07 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.0, 27.5, 29.4, 31.4, 35.2, 44.1, 52.3, 52.4, 61.0, 72.7, 74.2, 77.6, 125.8, 127.2, 128.8, 128.9, 129.5, 129.7, 130.2, 137.1, 144.5, 146.4, 167.1, 167.3; IR (KBr, neat) 2928, 1722, 1611, 1436, 1281, 1109, 1019, 772, 735, cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{33}O_6$ $(M + H)^+$ 477.2272, found 477.2275.

(1S,4aR*,6R*,6aS*)-1,6-bis(4-Chlorophenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran* ***(24l)****:*



Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 100 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.34 (m, 3 H), 1.38-1.43 (m, 1 H), 1.58-1.70 (m, 4 H), 1.85-1.95 (m, 1 H), 2.00-2.05 (m, 2 H), 2.38-2.43 (m, 1 H), 2.58-2.65 (m, 1 H), 3.58 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.82 (dt, *J* = 12.2 and 2.8 Hz, 1 H), 4.23-4.27 (m, 1 H), 4.80 (d, *J* = 2.5 Hz, 1 H), 5.78 (s, 1 H), 7.31-7.35 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.0, 27.5, 29.3, 31.3, 35.3, 44.1, 60.8, 72.7, 73.8, 77.6, 127.2, 128.4, 128.7, 128.8, 129.1, 132.6, 133.4, 137.0, 137.6, 139.7; IR (KBr, neat) 2927, 2855, 1488, 1263, 1088, 1014, 829, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{27}Cl_2O_2$ $(M + H)^+$ 429.1383, found 429.1382.

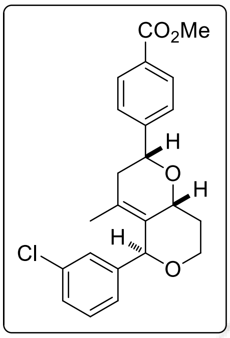
(1S,4aR*,6R*,6aS*)-1,6-bis(4-Methoxyphenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-b]pyran* ***(24m)****:*



Yellow oil; R_f (hexane/ EtOAc 24:1) 0.40; yield 98 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.34 (m, 3 H), 1.38-1.43 (m, 1 H), 1.62-1.69 (m, 4 H), 1.88-1.94 (m, 1 H), 2.00-2.05 (m, 2 H), 2.35-2.43 (m, 1 H), 2.59-2.66 (m, 1 H), 3.61 (dt, *J* = 12.2 and 1.8 Hz, 1 H), 3.78-3.82 (m, 7 H), 4.29-4.33 (m, 1 H), 4.81 (d, *J* = 2.3Hz, 1 H), 5.78 (s, 1 H), 6.88-6.93 (m, 4 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 7.34 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 27.2, 27.7, 29.4, 31.3, 35.4, 44.4, 55.4, 55.5, 60.5, 72.9, 74.1, 77.6, 113.7, 114.2, 126.9, 128.5, 129.2, 131.0, 133.6, 136.5, 158.5, 159.1; IR

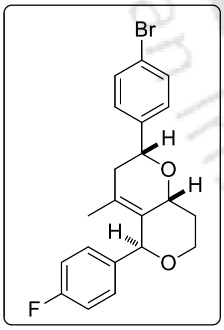
(KBr, neat) 2927, 1622, 1510, 1247, 1171, 1079, 832cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{33}O_4$ $(M + H)^+$ 421.2373, found 421.2386.

Methyl 4-((2R,5S*,8aR*)-5-(3-chlorophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran-2-yl)benzoate (**24n**):*



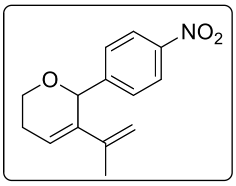
Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.60; yield 84 mg, 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 1.85-1.96 (m, 1 H), 1.99-2.04 (m, 1 H), 2.32 (dt, J = 17.0 and 2.8 Hz, 1 H), 2.43-2.51 (m, 1 H), 3.59 (dt, J = 12.2 and 2.0 Hz, 1 H), 3.84 (ddd, J = 12.0, 4.6 and 1.6 Hz, 1 H), 3.91 (s, 3 H), 4.29-4.32 (m, 1 H), 4.72 (dd, J = 10.8 and 3.4 Hz, 1 H), 5.84 (s, 1 H), 7.26-7.33 (m, 3 H), 7.41 (s, 1 H), 7.49 (d, J = 8.2 Hz, 2 H), 8.04 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 34.5, 39.3, 52.3, 60.7, 72.2, 73.8, 74.7, 125.3, 125.9, 127.3, 127.8, 128.4, 128.8, 129.5, 130.0, 135.1, 141.6, 147.5, 167.1; IR (KBr, neat) 2953, 2858, 1721, 1681, 1594, 1468, 1372, 1280, 1187, 1144, 1077, 1017, 970, 858, 792, 737, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}ClO_4$ $(M + H)^+$ 399.1358, found 399.1352.

(2R,5S*,8aR*)-2-(4-Bromophenyl)-5-(4-fluorophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-b]pyran (**24o**):*



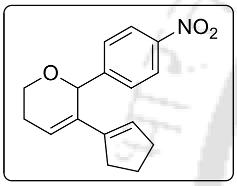
Brown gum; R_f (hexane/ EtOAc 24:1) 0.60; yield 72 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 3 H), 1.83-1.90 (m, 1 H), 1.91-2.00 (m, 1 H), 2.26 (dt, J = 17.0 and 2.8 Hz, 1 H), 2.42-2.50 (m, 1 H), 3.57 (dt, J = 12.2 and 1.6 Hz, 1 H), 3.81 (ddd, J = 12.2, 4.8 and 1.8 Hz, 1 H), 4.29-4.31 (m, 1 H), 4.62 (dd, J = 10.8 and 3.4 Hz, 1 H), 5.84 (s, 1 H), 7.05-7.09 (m, 2 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.36-7.40 (m, 2 H), 7.48 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 34.5, 60.4, 72.3, 73.8, 74.6, 115.7 (d, J = 84.6 Hz), 121.6, 127.8, 128.0, 128.9 (d, J = 8.0 Hz), 129.1, 131.8, 134.8 (d, J = 3.0 Hz), 141.5, 162.4 (d, J = 244.2 Hz); IR (KBr, neat) 2927, 2858, 1602, 1503, 1405, 1225, 1103, 1076, 1011, 823, 790, 742, 632 cm^{-1}; Anal. Calcd. For $C_{21}H_{20}BrFO_2$: C, 62.54; H, 5.00. Found C, 62.47; H, 5.02.

*6-(4-Nitrophenyl)-5-(prop-1-en-2-yl)-3,6-dihydro-2H-pyran (**25a**)*



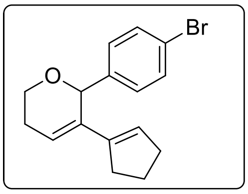
Brown gum; R_f (hexane/ EtOAc 24:1) 0.55; yield 96 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3 H), 2.22-2.28 (m, 1 H), 2.46-2.49 (m, 1 H), 3.50-3.54 (m, 1 H), 3.63-3.67 (m, 1 H), 4.49 (s, 1 H), 4.81 (s, 1 H), 5.54 (s, 1 H), 6.30 (t, *J* = 4.2 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 8.19 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 25.5, 59.0, 74.3, 113.0, 123.4, 125.1, 129.9, 136.5, 140.2, 147.5, 147.9; IR (KBr, neat) 2925, 2854, 1605, 1522, 1347, 1108, 1082, 1015, 854, 771 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1125, found 246.1118.

*5-(Cyclopent-1-en-1-yl)-6-(4-nitrophenyl)-3,6-dihydro-2H-pyran (**25b**) and 3-Cyclopentylidene-2-(4-nitrophenyl)-3,6-dihydro-2H-pyran (**25b'**)(**6s**:**6s'** = 2:1):*



Dark brown solid; R_f (hexane/ EtOAc 24:1) 0.57; mixed m. p. 110-113 °C; yield 73 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.84 (m, 3 H), 1.85-1.87 (m, 1 H), 2.20-2.29 (m, 2 H), 2.45-2.56 (m, 2 H), 3.50-3.68 (m, 2 H, major), 4.30-4.32 (m, 2 H, minor), 5.11 (s, 1 H, major), 5.48 (s, 1 H, major), 6.01-6.05 (m, 1 H, minor), 6.11 (t, *J* = 4.0 Hz, 1 H, major), 6.44 (s, 1 H, minor), 6.54-6.57 (m, 1 H, minor), 7.41 (d, *J* = 8.4 Hz, 2 H, minor), 7.50 (d, *J* = 8.6 Hz, 2 H, major), 8.17-8.20 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.6, 24.5, 31.3, 32.3, 34.9, 48.3, 60.4, 73.8, 83.9, 118.7, 121.1, 122.4, 122.42, 123.3, 126.0, 129.0, 129.1, 129.8, 132.3, 139.4, 140.2, 143.0, 145.3, 146.5, 147.2; IR (KBr, neat) 2962, 2853, 1638, 1520, 1408, 1345, 1260, 1090, 1060, 1018, 853, 752, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1281, found 272.1266.

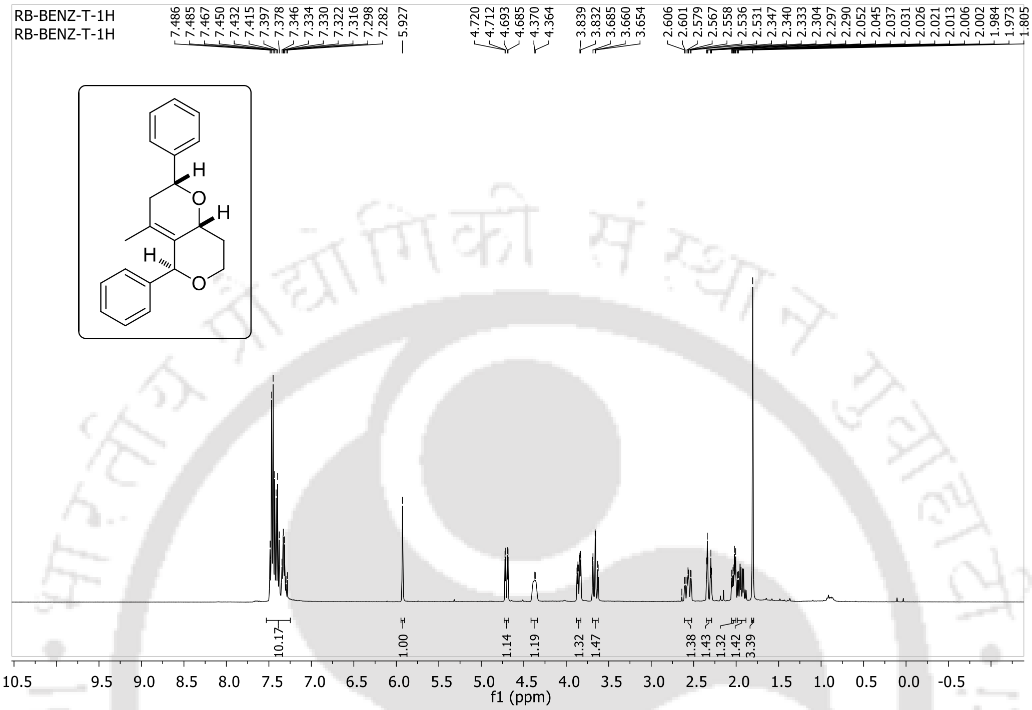
*2-(4-Bromophenyl)-3-cyclopentylidene-3,6-dihydro-2H-pyran (**25c**):*

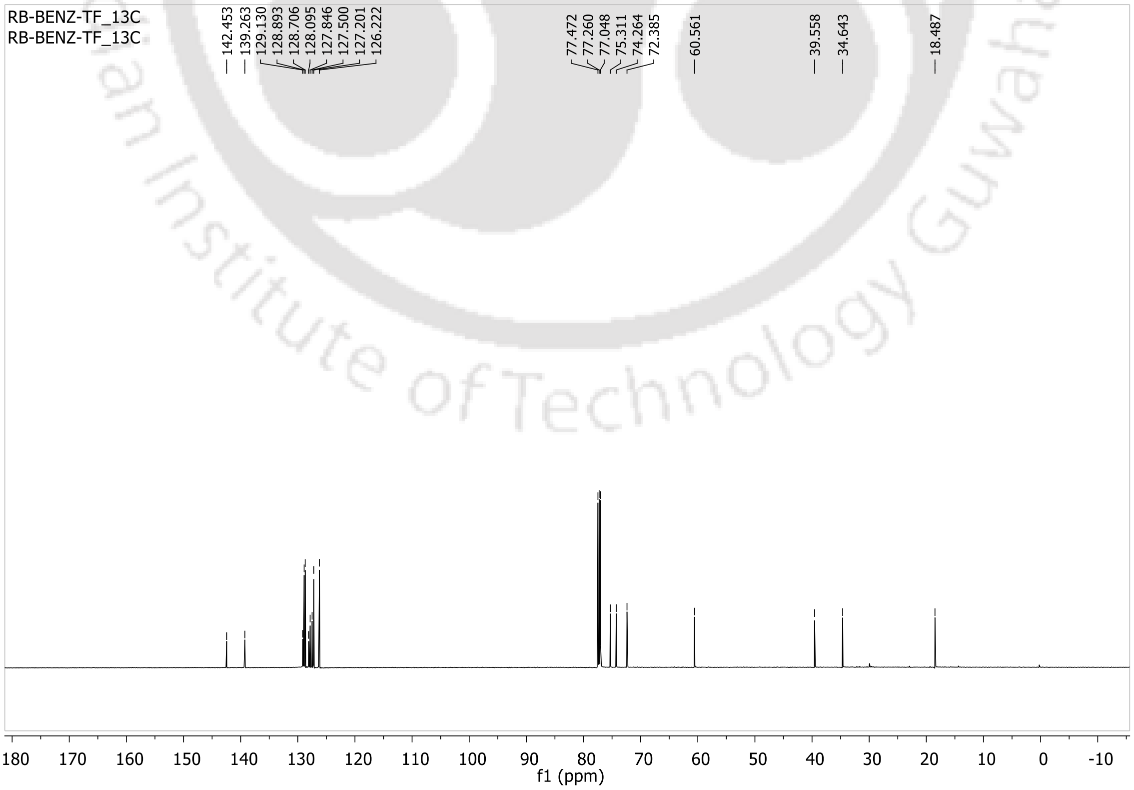


Dark brown gum; R_f (hexane/ EtOAc 24:1) 0.60; yield 72 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77-1.85 (m, 2 H), 2.15-2.30 (m, 3 H), 2.41-2.53 (m, 3 H), 3.52-3.64 (m, 2 H), 5.15 (s, 1 H), 5.38 (s, 1 H), 6.05 (t, *J* = 4.0 Hz, 1 H), 7.21 (dd, *J* = 6.8 and 1.6 Hz, 2 H), 7.45 (dd, *J* = 6.8 and 1.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 25.7, 32.4, 33.5, 58.8, 75.2, 122.0, 123.9, 127.0, 131.0, 131.4, 134.0, 140.1, 140.5; IR (KBr, neat) 2924, 2851, 1637, 1589, 1484, 1404, 1265, 1087, 962, 812, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}BrO$ $(M + H)^+$ 305.0536, found 305.0545.

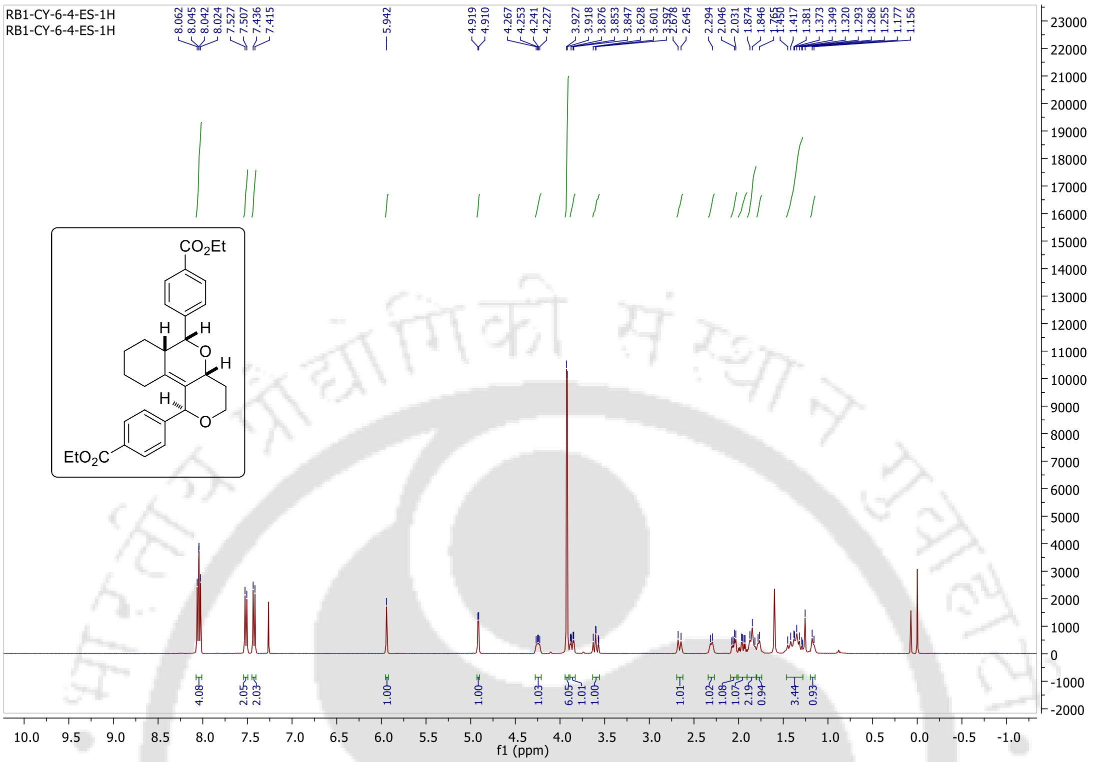
2B.10. Representative Spectra and crystal parameters:

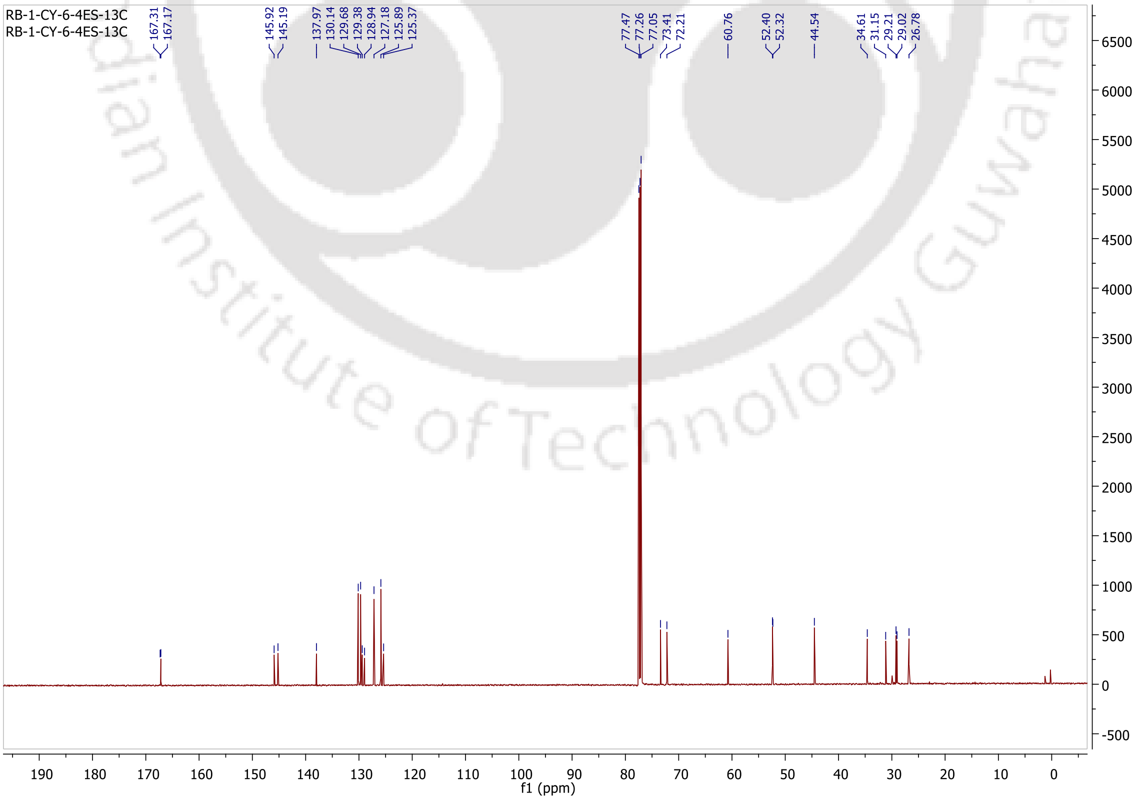
^{1}H and ^{13}C spectra of (2R,5S,8aR)-4-methyl-2,5-diphenyl-2,3,5,7,8,8a-hexahydropyrano[4,3-*b*]pyran 24a:



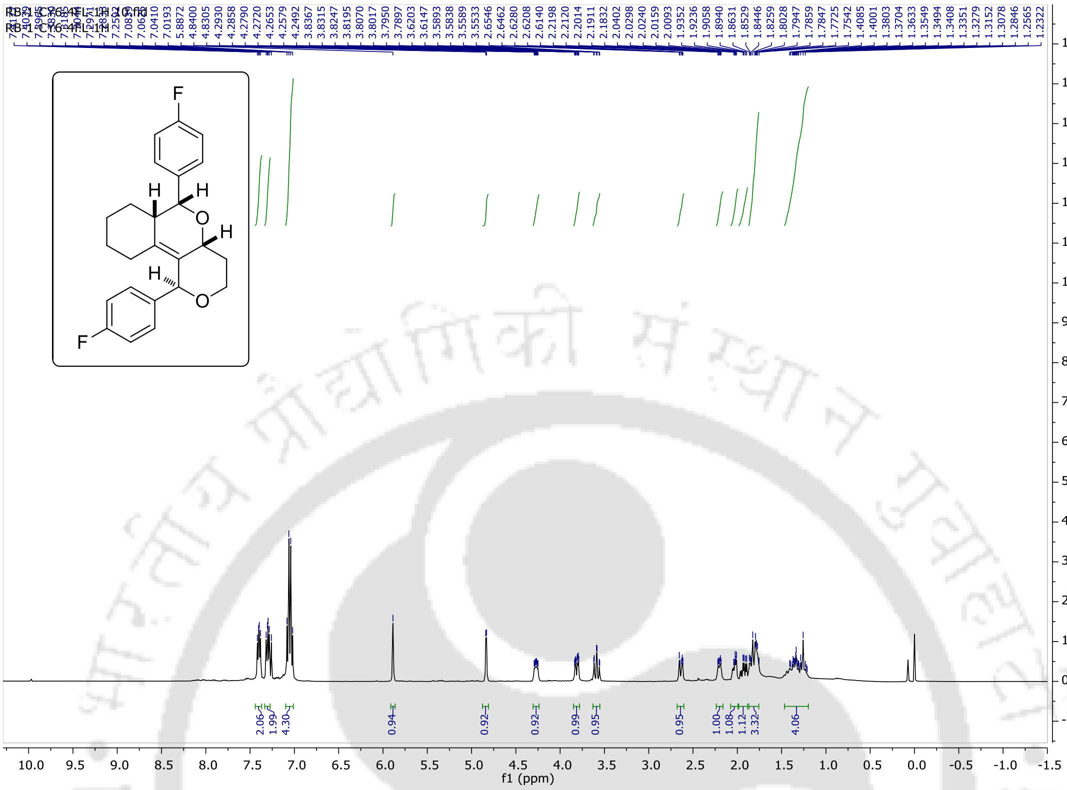


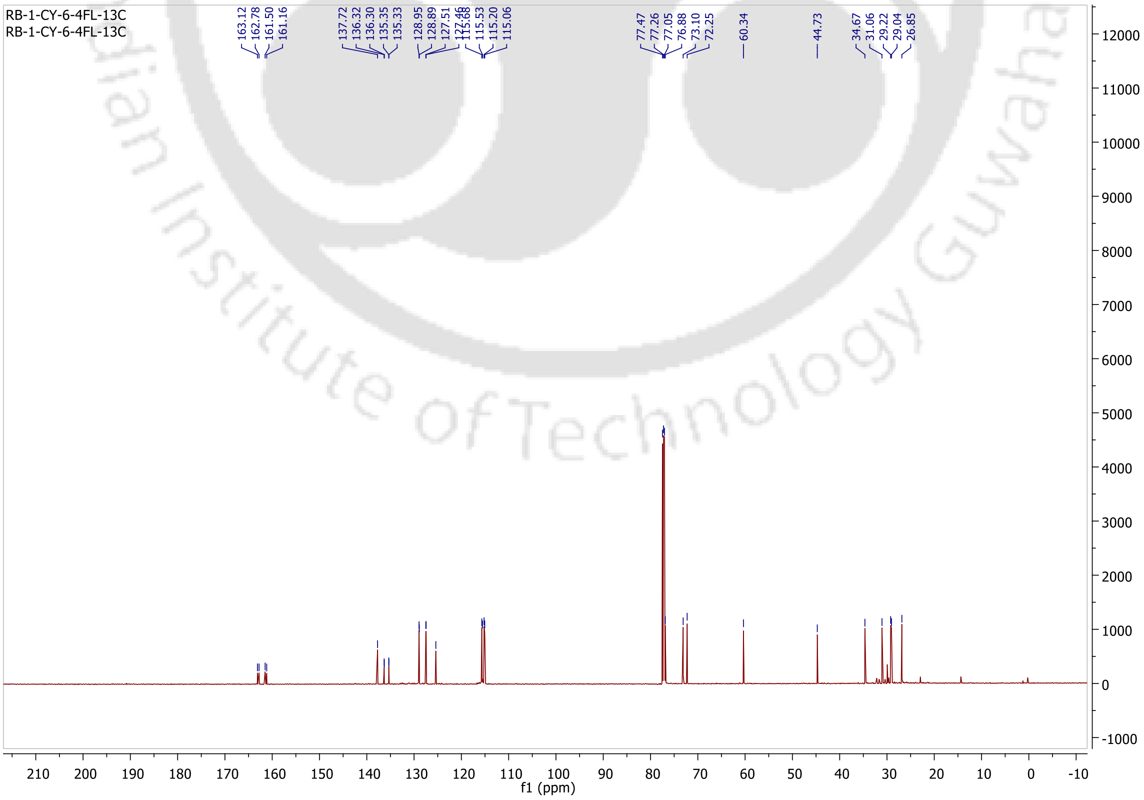
^{1}H and ^{13}C spectra of diethyl 4,4'-((1S*,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-*c*]isochromene-1,6-diyl)dibenzoate 24e:



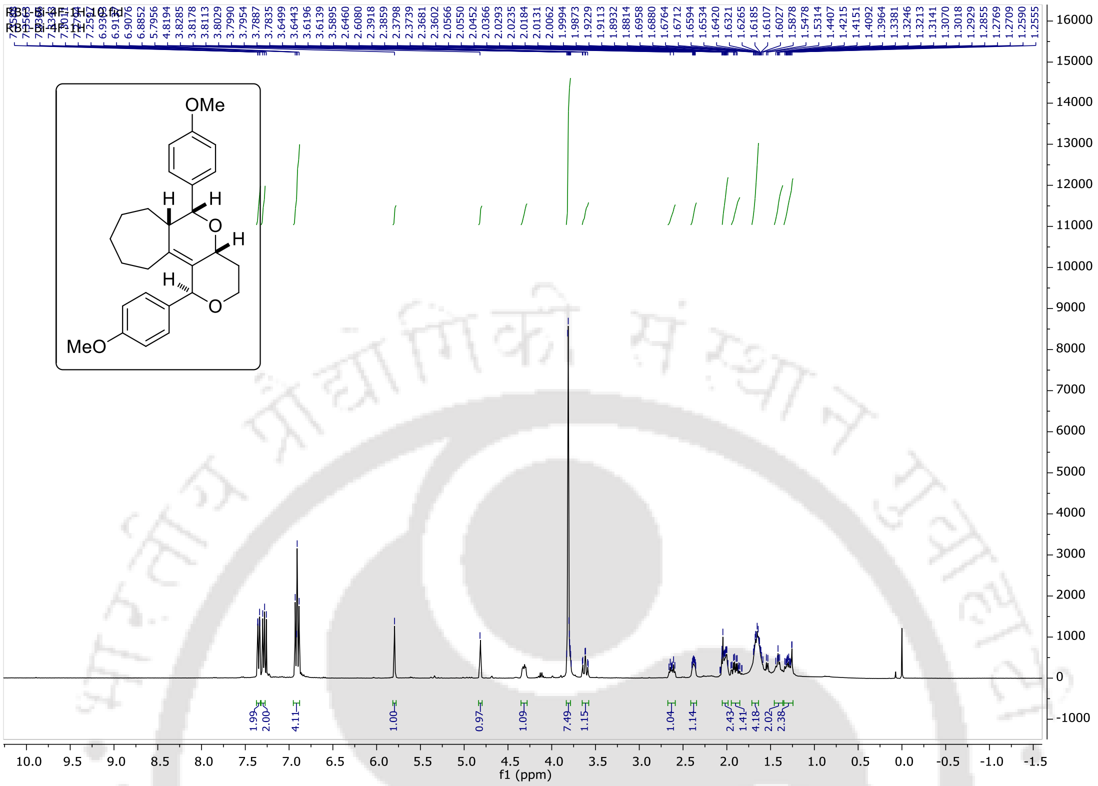


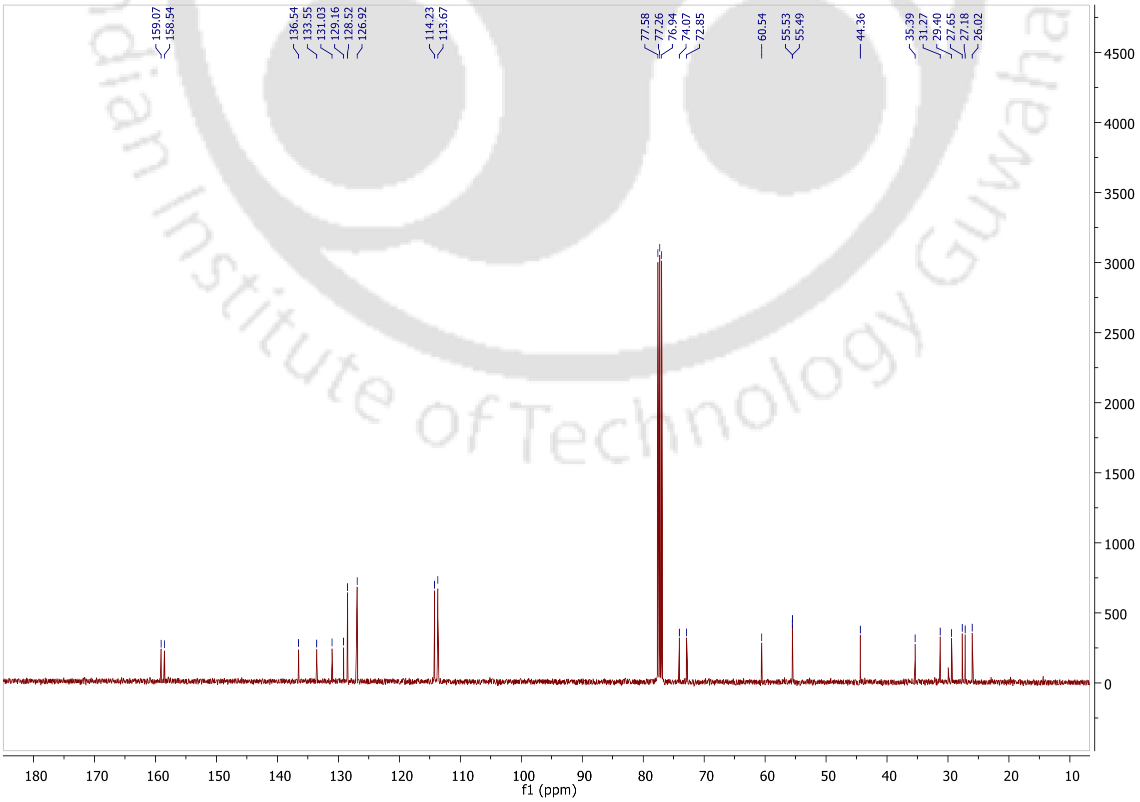
^{1}H and ^{13}C spectra of (1S*,4aR*,6R*,6aS*)-1,6-bis(4-Fluorophenyl)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-*c*]isochromene 24g:



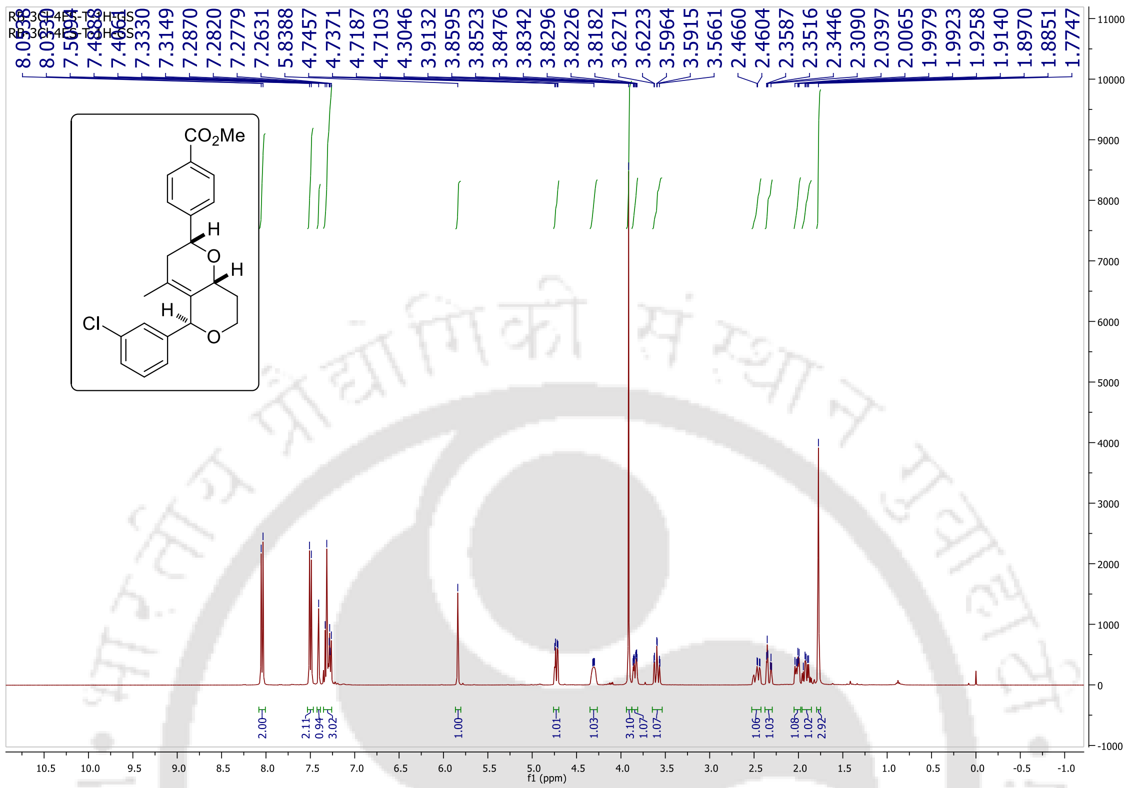


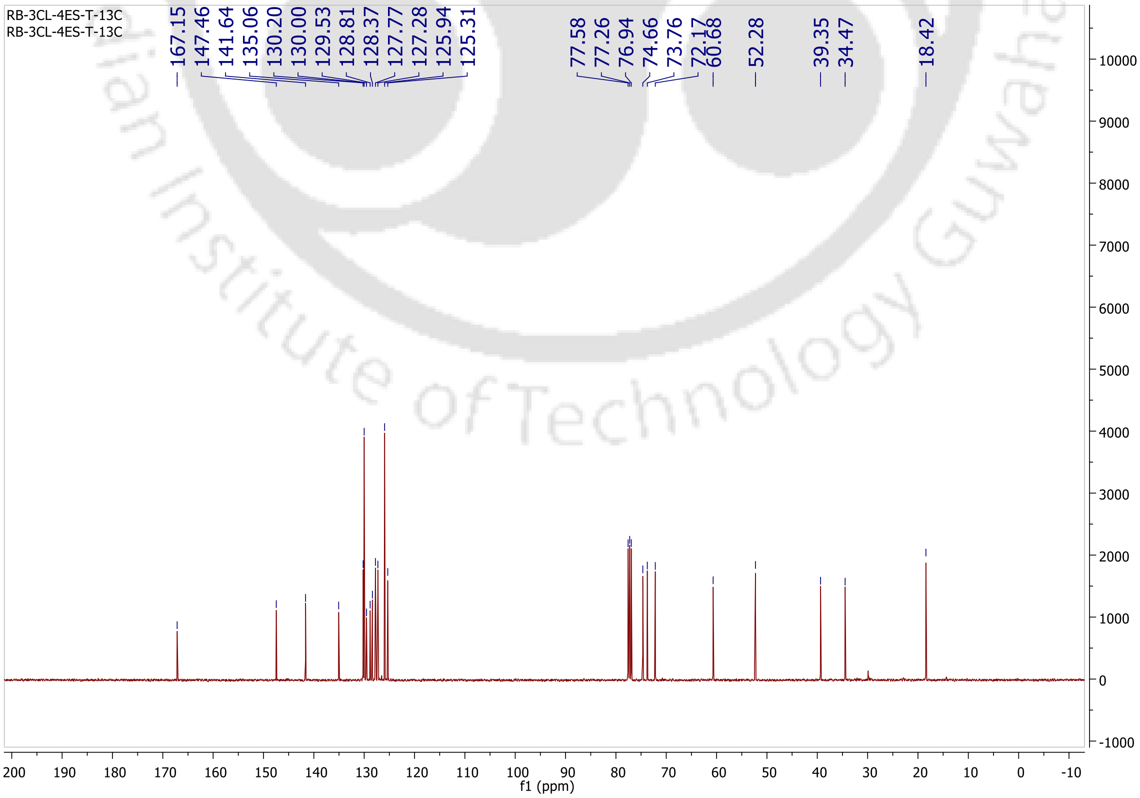
^{1}H and ^{13}C spectra of (1S*,4aR*,6R*,6aS*)-1,6-bis(4-Methoxyphenyl)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[*d*]pyrano[4,3-*b*]pyran 24m :



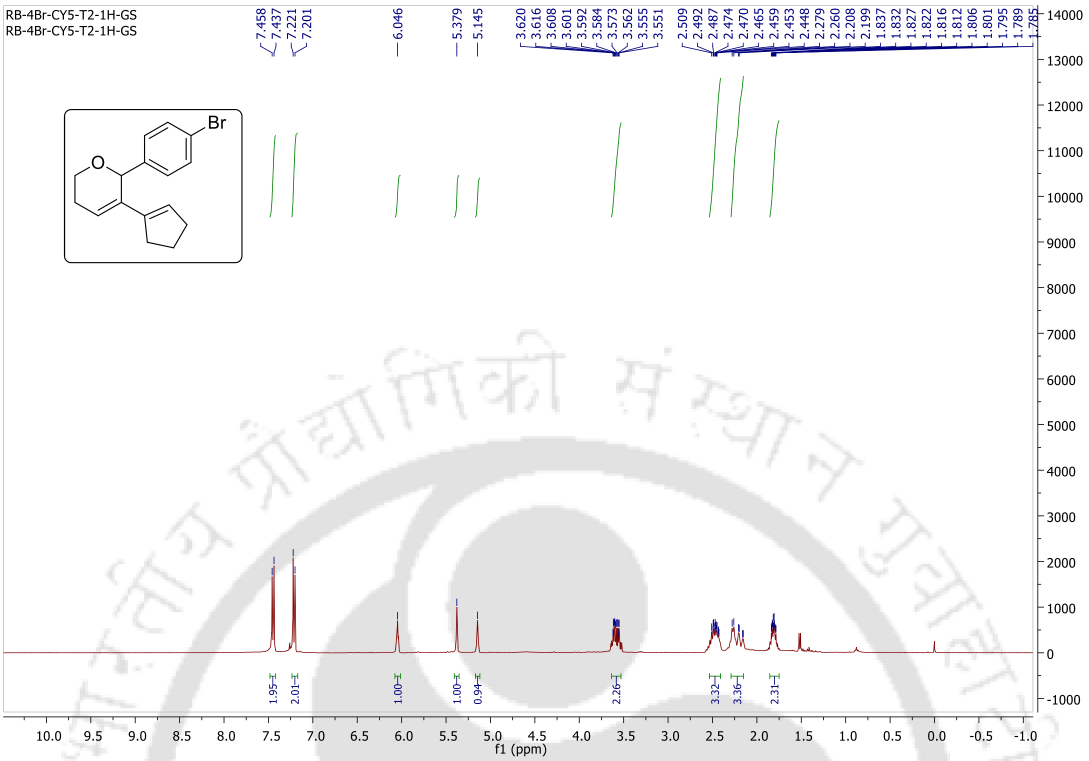


^{1}H and ^{13}C spectra of Methyl 4-((2R*,5S*,8aR*)-5-(3-chlorophenyl)-4-methyl-2,3,5,7,8,8a-hexahydropyrano[4,3-*b*]pyran-2-yl)benzoate 24n:

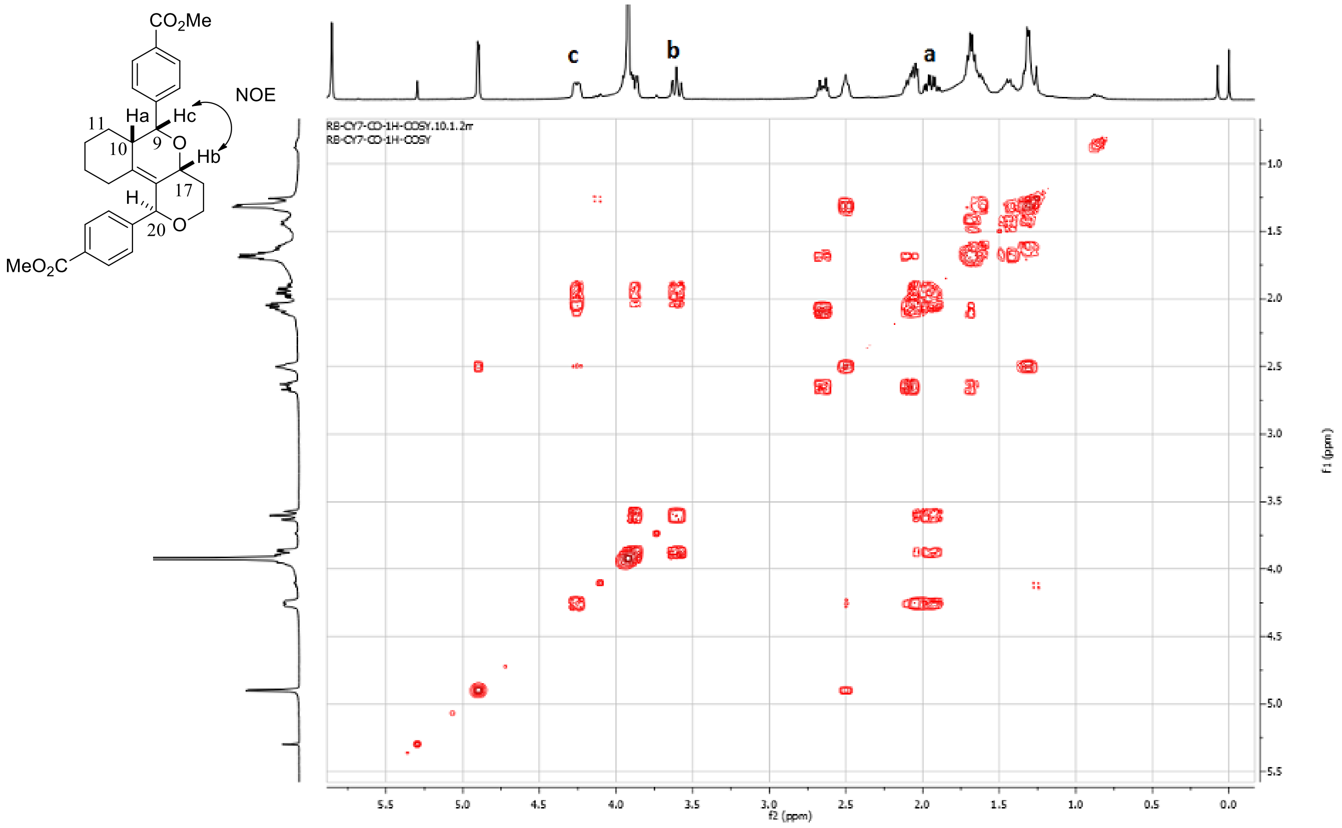


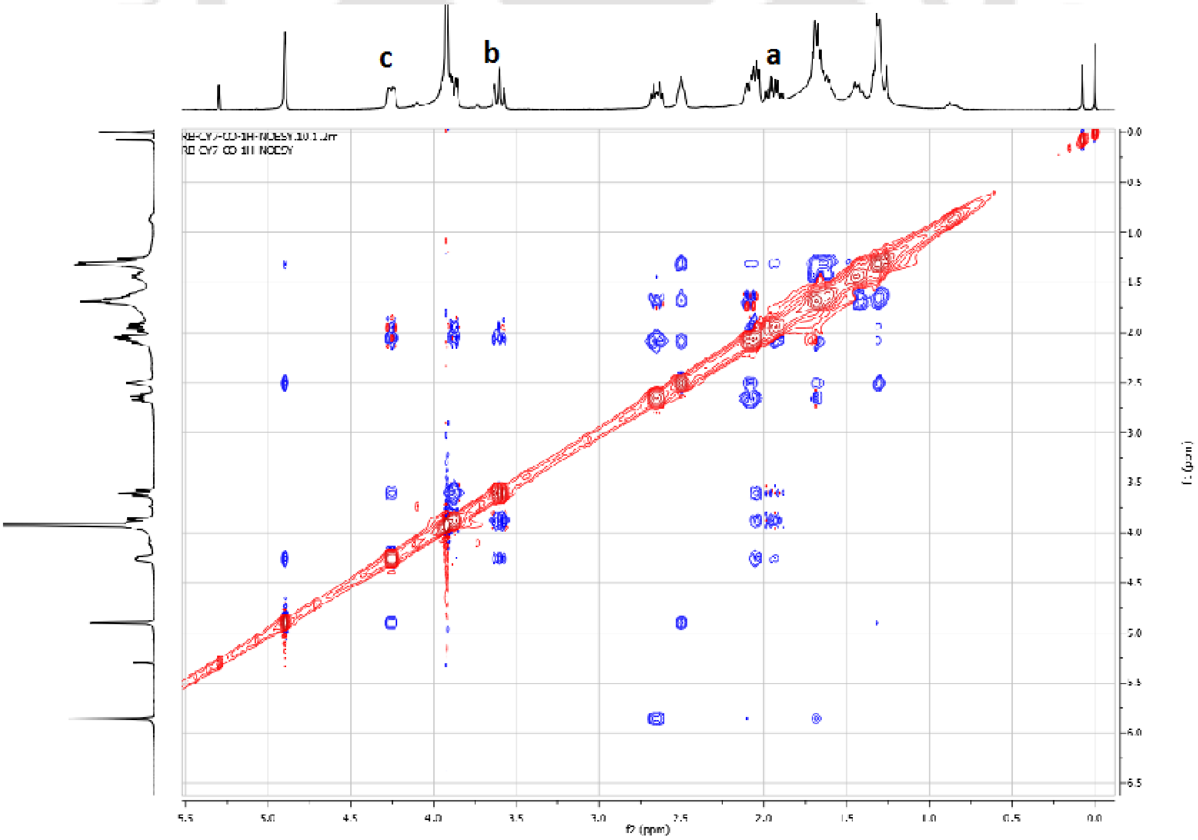


^{1}H and ^{13}C spectra of 2-(4-Bromophenyl)-3-cyclopentylidene-3,6-dihydro-2*H*-pyran 25c:



COSY and NOESY spectra of diethyl 4,4'-((1S*,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-*c*]isochromene-1,6-diyl)dibenzoate 24e:





The crystal parameters of compound Dimethyl 4,4'-((1S*,4aR*,6R*,6aS*)-1,3,4,4a,6,6a,7,8,9,10-decahydropyrano[4,3-*c*]isochromene-1,6-diyl)dibenzoate 24e:

	CCDC 1840405
Formula	$C_{28}H_{30}O_6$
Formula weight	462.52
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/c
a/Å	12.2759(7)
b/Å	11.3397(6)
c/Å	17.9816(10)
α/°	90.00
β/°	103.251(3)
γ/°	90.00
V/Å^3	2436.5(2)
Z	4
Abs. Coeff./mm^{-1}	0.088
Abs. Correction	None
GOF on F^2	1.084
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0521 *wR2* = 0.1435
R indices [all data]	*R1* = 0.0703 *wR2* = 0.1590

The crystal parameters of compound Dimethyl 4,4'-((1S*,4aR*,6R*,6aS*)-3,4,4a,6,6a,7,8,9,10,11-decahydro-1H-cyclohepta[d]pyrano[4,3-*b*]pyran-1,6-diyl)dibenzoate 24k:

	CCDC 1860367
Formula	C_{29} H_{32} O_6
Formula weight	476.55
T/K	293(2)
Crystal system	Orthorhombic
Space group	Pbca
a/Å	11.4720(5)
b/Å	17.9909(9)
c/Å	24.4226(12)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	5040.6(4)
Z	8
Abs. Coeff./mm^{-1}	0.087
Abs. Correction	None
GOF on F^2	0.966
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0637 $wR2$ = 0.1802
R indices [all data]	$R1$ = 0.1097 $wR2$ = 0.2284

2B.11. References:

1) (a) Aydogmus, Z.; Imre, S.; Ersoy, L.; Wray, V. *Nat. Prod. Res*. **2004**, *18*, 43. (b) Hall, J. G.; Reiss, J. A. *Aust. J. Chem*. **1986**, *39*, 1401. (c) Wright, A. D.; KHnig, G. M.; De Nys, R.; Sticher, O. *J. Nat. Prod*. **1993**, *56*, 394. (d) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc*. **2000**, *122*, 9099. (e) Norte, M.; Fernandez, J. J.; Souto, M. L.; Garcia-Gravalos, M. D. *Tetrahedron Lett*. **1996**, *37*, 2671. (f) Evidente, A. M. L.; Spanu, E.; Franceschini, A.; Lazzaroni, S.; Motta, A. *J. Nat. Prod*. **2003**, *66*, 313.
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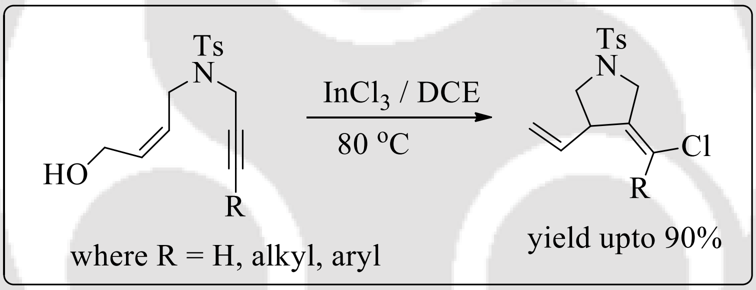
10) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Willey & Sons, New York, **1976**, pp 121-142.

Chapter 3

Stereo- and Regio-selective Synthesis of 4-Vinylpyrrolidine from N-Tethered Alkyne-Alkenol



ACS Omega 3, 576-584

Stereo- and Regio-selective Synthesis of 4-Vinylpyrrolidine from *N*-Tethered Alkyne-Alkenol

3.1. Importance and applications:

Pyrrolidines, a five membered saturated heterocycle, are a part of the vast *N*-containing heterocycles which exhibit many pharmaceutical[1] and biological activities[2] (*Figure 3.1.1*). Compound **1** is a direct renin inhibitors (DRIs), which can trigger blood pressure lowering effects.[3] Compound **2** which is a simple disubstituted pyrrolidine alkaloid, is a component of ant venom.[4] Anisomycin (**3**) is an antibiotic produced by *Streptomyces griseolus*. It inhibits eukaryotic protein synthesis as well as partial inhibition of DNA synthesis. Recently, it has been observed to be active against certain types of cancer.[5] On the other hand, Kainic acid (**4**) is a trisubstituted pyrrolidine moiety present in some seawoods. It is a potent neuroexcitatory amino acid agonist.[6] In addition to their importance in medicinal chemistry, enantiomerically pure pyrrolidines have been found to use as chiral auxiliaries for a number of different transformations.[7] Apart from these, pyrrolidine based organocatalysts and chiral ligands have been employed in a range of organic transformations.[8]

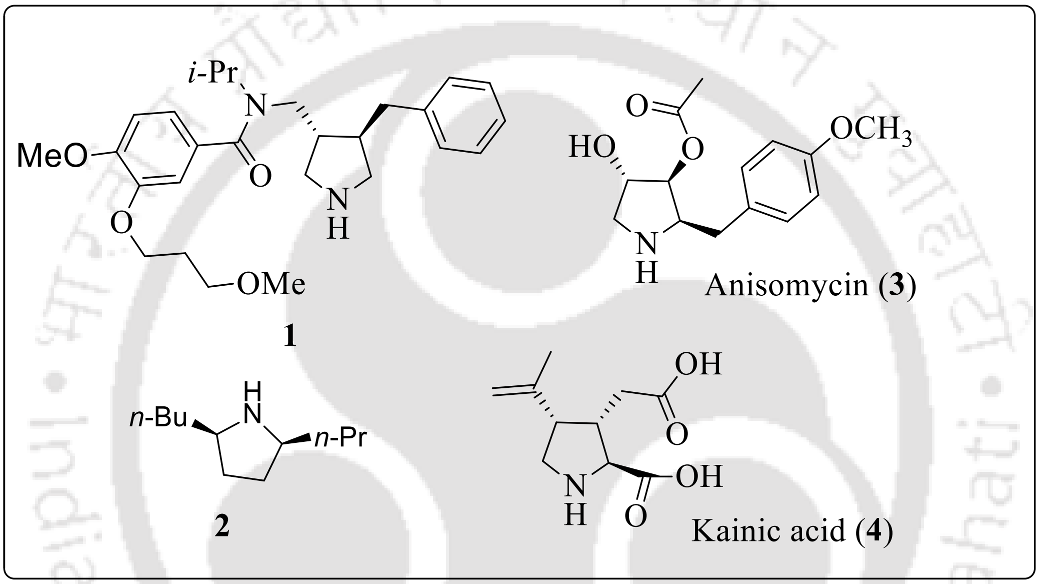
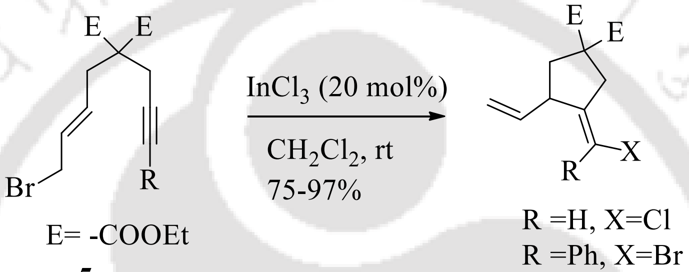


Figure 3.1.1: *Biologically important compounds containing pyrrolidines.*

3.2. Literature Methods:

Lewis acids such as $FeCl_3$[9] and $InCl_3$[10] are used for the cyclization of *N*-tethered alkyne-alkenol and *C*-tethered alkyne-allyl bromide, respectively. *N*-Tethered alkyne/alkenes are gaining importance in organic synthesis due to the formation of nitrogen heterocyclic compounds in a diastereoselective manner.[11]

In 2006, Cook and co-workers reported indium(III) chloride as an efficient catalyst for the cyclization of *C*-tethered allylic halides and alkynes in 1,6 positions **5**. Mechanistic evidence supports a cationic reaction pathway with Lewis acid activation of the allylic halogen and concomitant nucleophilic attack by the alkyne and trapping with halide led to atom transfer cyclization products **6** (*Scheme 3.2.1*).[10]

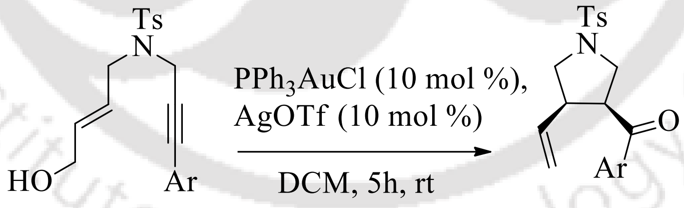


5

6

Scheme 3.2.1

Yeh and co-workers reported a gold(I)-catalyzed cycloisomerization reaction of *N*-tethered alkyne alkenol **7,** to give alkenylpyrrolidines **8** in good yields as shown in *Scheme 3.2.2*.[12]

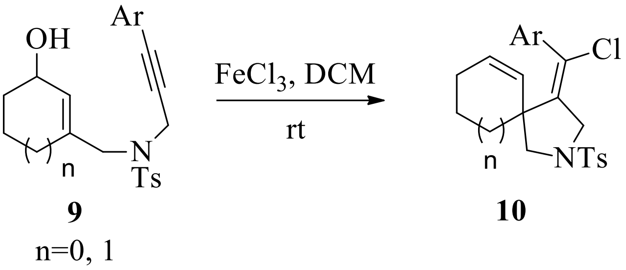


7

8

Scheme 3.2.2

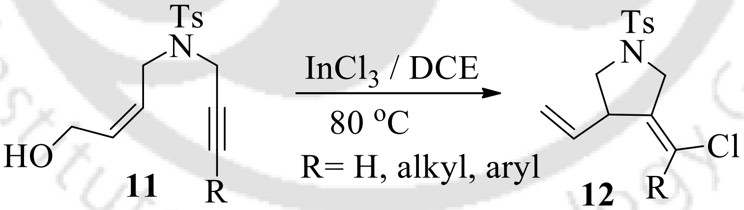
In 2012, Yeh and co-workers also described a mild and efficient $FeCl_3$-mediated synthesis of azaspiro[4.5] bicycles **10** from cyclic *N*-tethered enynols **9** (Scheme.*3.2.3*). In this reaction, $FeCl_3$ acts as both the Lewis acid and the chloride nucleophile for cyclization/chlorination reaction. The method is highly diastereoselective and gives only (*Z*)-4-(arylchloromethylene)-substituted azaspirocycles in good to excellent yields.[9]



Scheme 3.2.3

3.3. Present strategy and objective:

Indium(III) chloride can be used as Lewis acid catalyst[13] as well as stoichiometric reagent[14] in various organic transformations to construct heterocycles which involves both C-C and C-X (heteroatom) bond formations. The utility of indium(III) chloride as Lewis acids are encouraged by their unique *π*-acidity, alkynophilicity, relatively low toxicity, air, moisture compatibility and recyclability. Recently, we have developed methodologies for the synthesis of oxygen and nitrogen heterocyclic compounds *via* intramolecular C−C and C-O bond formation from *N*-tethered alkyne-epoxides[11c] and *N*-tethered alkyne consisting of alkanol and alkenol.[11d,e] Taking clue from the literature and our own works, a methodology for the synthesis of pyrrolidine using intramolecular C−C bond formation from *N*-tethered alkyne alkenol mediated by $InCl_3$ in moderate to good yields with good stereo- and regio-selectivity has been disclosed in this chapter.

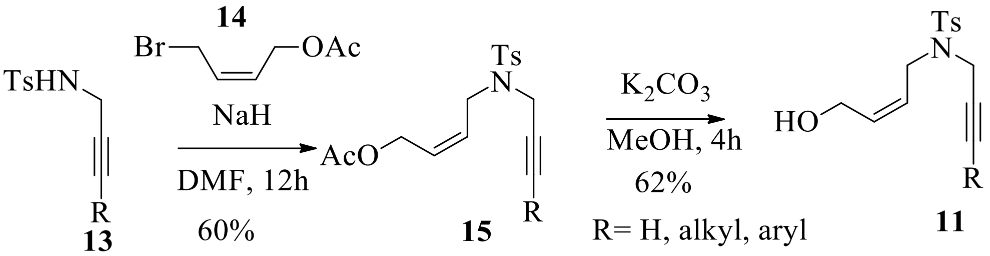


Scheme 3.3.1

3.4. Results and discussions:

3.4.1. Preparation of *N*-tethered alkyne alkenol:

The enyne alcohols **11** were prepared from the reaction of *N*-aryl-4-methylbenzenesulfonamide **13** and (*Z*)-4-bromobut-2-en-1-yl acetate **14** in the presence of NaH in DMF at 0 °C to room temperature to give alkyne-acetate **15**. The acetate group in compound **15** was then deprotected to give alkyne-alkenol **11** by using K_2CO_3 in methanol.[10,11e] (*Scheme 3.4.1.1*)

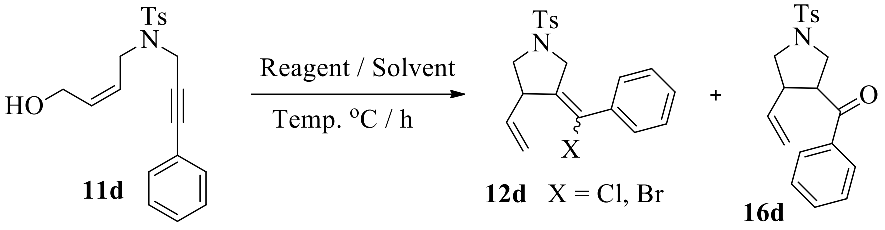


Scheme 3.4.1.1

3.4.2. Optimization studies:

To determine the optimum reaction condition, initially (*Z*)-*N*-(4-hydroxybut-2-en-1-yl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl) benzenesulfonamide **11d** was treated with one equivalent of $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature for 12 h, the reaction ended with no result, but starting material was recovered in 96% yield. So, the substrate **11d** was treated with various reagents and solvents under different reaction conditions. The results are summarized in *Table 3.4.2.1*. It was observed that treatment with 0.2 equivalent of $InCl_3$ in dichloromethane at room temperature yielded compound **12d** as *E*/*Z* mixture with a ratio of 18:82 in 10% overall yield. The structure of the compound **12d** was determined by ^1H and ^{13}C NMR spectroscopy and comparison with the known compunds.[11a,12] Increasing the amount of $InCl_3$ to 1.1 equivalents resulted only 18% yield with *E*/*Z* ratio of 18:82. The same reaction at 40 °C resulted in 25% yield with *E*/*Z* ratio of 20:80. The reaction with 0.2 equivalent of $InCl_3$ in 1,2-dichloroethane (DCE) at 80 °C for 12 h gave **12d** with a *E*/*Z* ratio of 15:85 in 18% overall yield. Changing solvent from DCE to CH_3CN, $CHCl_3$ and CCl_4 did not provide any good results. Addition of external chloride source, TMSCl did not affect the yield but reduce the *Z*-selectivity of the reaction. On the other hand, treatment with 1.1 equivalents of $InCl_3$ at 80 °C in DCE for 12 h gave 75% of the desired product with *E*/*Z* ratio 16:84. $InBr_3$ is less effective under these reaction conditions as it produces chlorinated as well as brominated products **12d-Cl** and **12d-Br** with a ratio of 28:72. The *E*/*Z* selectivity is found to be 42:58 in both the cases. This proves that solvent DCE also participate in the reaction. The ratio of *E*- and *Z*-configurations was determined from the crude ^1H NMR. Other Lewis acids such as $In(OTf)_3$, $CeCl_3$ were found to be inactive under the similar reaction conditions. However, $FeCl_3$ gave equal amount of chlorinated **12d** and carbonyl product **16d** with 30-40% yields

Table 3.4.2.1. Optimization of the reaction



Entry	Reagent (equiv)	Solvent	Temp./ °C	Time/h	%yield[a] 12d	16d	**12d**(*E*/*Z*)
1	$BF_3.OEt_2$ (1.0)	DCM	rt	12	0	0	---
2	$InCl_3$ (0.2)	DCM	rt	12	10	0	18:82
3	$InCl_3$ (1.1)	DCM	rt	12	18	0	18:82
4	$InCl_3$ (1.1)	DCM	40	12	25	0	20:80
5	$InCl_3$ (0.2)	DCE	80	12	18	0	15:85
6	$InCl_3$ (0.2)	CH_3CN	85	24	trace	0	---
7	$InCl_3$ (1.1)	CH_3CN	85	24	trace	0	---
8	$InCl_3$ (1.0)	$CHCl_3$	65	24	0^b	0^b	---
9	$InCl_3$ (1.0)	CCl_4	80	12	20	0	14:86
10	$InCl_3$ (0.2)/ TMSCl (1.0)	DCE	50	18	22	0	20:80
11	$InCl_3$ (1.1)	DCE	80	12	75	0	16:84
12	$InBr_3$(1.1)	DCE	80	12	$12^{c,d}$	0	$42:58^e$
13	$In(OTf)_3$ (0.2)	DCE	80	5	0^b	0^b	---
14	$In(OTf)_3$ (1.1)	DCE	80	5	0^b	0^b	---
15	$FeCl_3$ (1.2)	DCE	rt	12	30	30	30:70
16	$FeCl_3$ (1.2)	DCE	60	4	40	40	18:82
17	$CeCl_3.H_2O$ (1.1)	CH_3CN	80	24	0^b	0^b	---
18	TfOH (0.2)	DCE	rt	12	0^d	0^d	---
19	*p*-TsOH (0.2)	DCE	80	24	0^d	0^d	---

[a]Yields are isolated yield. [b]Starting material recovered. [c]**12d-Cl**, **12d-Br**; ratio of **12d-Cl/12d-Br** = 28:72. [d]Decomposed products.[e]The *E*/*Z* ratio is 42:58 for both chloro and bromo products.

under different reaction conditions. Brønsted acids such as *p*-TSA and triflic acid are ineffective as well. The low yield at lower temperature in CH_2Cl_2 and DCE might be due to the poor leaving property of hydroxyl group and hence requires higher temperature. It may be noted that extremely dry condition is essential for the formation of single chloroproduct without formation of carbonyl side product **16d**. Therefore, 1.1 equivalents of $InCl_3$ in DCE at 80 °C stand out to be optimum condition for the reaction.

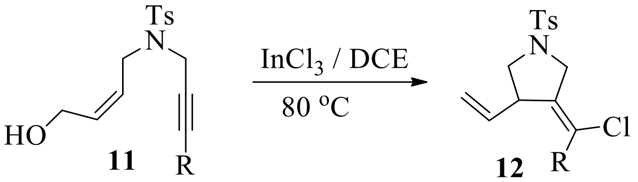
3.4.3. Substrate scope of the reaction:

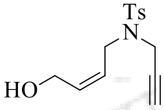
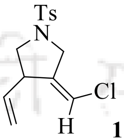
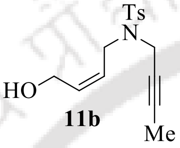
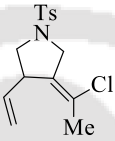
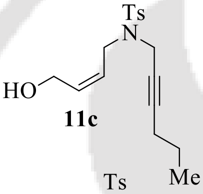
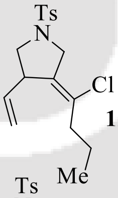
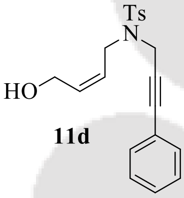
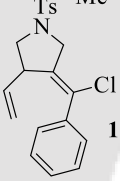
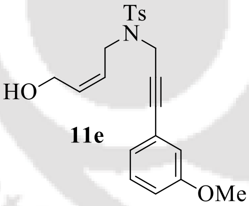
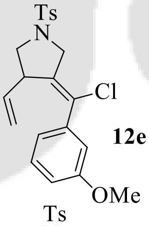
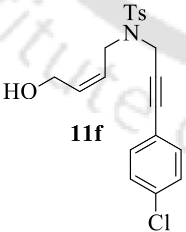
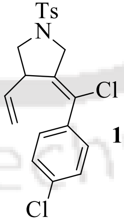
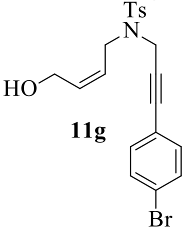
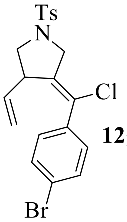
With these optimized conditions in hand, we further explored the scope of the reaction and limitations with a variety of substrates (*Table 3.4.3.1*). The reaction works well both for alkyl and aryl groups on the alkyne side chain delivering cyclized products in good yields. Substrates having electron donating and moderately electron-withdrawing groups on the aromatic ring of the alkyne side chain gave desired products in good yields. Steric effects play a considerable role in the yield of the reaction as reflected in substrates **11i** and **11j** which produced low yields compared to other substrates. On the other hand, unsubstituted alkyne (*Table 2, entry 1*) gave lower yield among the alkyl substituted alkynes. This might be due to the less stability of the intermediate carbocation **D** (where R = H, *Scheme 3.4.5.1*) formed during the reaction. The reaction produced exclusively pyrrolidine ring with exocyclic vinyl chloride at 3-position as well as vinylic group at 4-position. It is observed that the substrates having substituted aromatic moiety attached to alkyne side chain provides better *Z*-selectivity than alkyl groups in the alkyne side chain. This might be due to the steric hindrance of the bulky aromatic groups. There is an exception in the case of substrate **11j**. As the reaction becomes sluggish due to the presence of bulky 3,5-dimethyl phenyl group there is a chance of chloride transfer from the solvent DCE, which resulted in lower *Z*-selectivity.

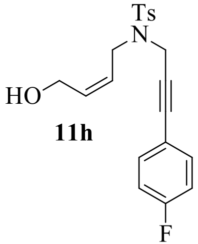
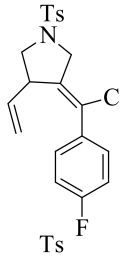
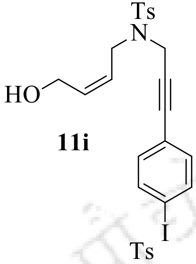
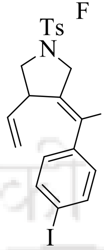
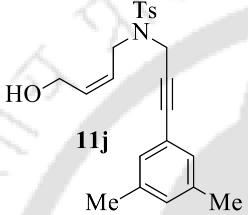
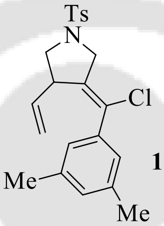
3.4.4. Stereochemistry of the *N*-vinyl pyrrolidines:

The structure and *E*-and *Z*-configuration of vinyl pyrrolidines were determined from ^{1}H NMR and NOE experiments of compounds *E*/*Z*-**12b** (*Figure 3.4.4.1*) and also by comparison of the *E*-configured **12b** with literature.[15] In the NOE spectrum of *E*-**12b**, we observed a strong correlation of methyl hydrogens (1.99 ppm) attached to C3 and C2-H as well as C2-H and *ortho*-hydrogen attached to toluenesulfonamide group, confirming the *E*-stereochemistry of the compound **12b**. In case of *Z*-**12b**, there is a strong correlation of methyl hydrogens (1.99 ppm) attached to C3 and axial hydrogen at C4 along with hydrogens attached to exocyclic olefin. This confirmed the *Z*-stereochemistry of the compound **12b**.

Table 3.4.3.1. Synthesis of 4-vinylpyrrolidine



Entry	Substrate**11**	Product **12**	Yield (%)^{a}	*E*/*Z*ratio^{b}
1	 **11a**	 **12a**	47	13:87
2	 **11b**	 **12b**	70	30:70
3	 **11c**	 **12c**	77	40:60
4	 **11d**	 **12d**	75	16:84
5	 **11e**	 **12e**	65	6:94
6	 **11f**	 **12f**	67	14:86
7	 **11g**	 **12g**	77	15:85

Entry	Substrate **11**	Product **12**	Yield (%)[a]	*E*/*Z* ratio[b]
8	 **11h**	 **12h**	90	14:86
9	 **11i**	 **12i**	45	14:86
10	 **11j**	 **12j**	25	40:60

[a]Yield refers to isolated yields. All the products were characterized by ^{1}H, ^{13}C and mass spectrometry. [b]The ratio of *E*/*Z* isomers is determined by ^{1}H NMR.

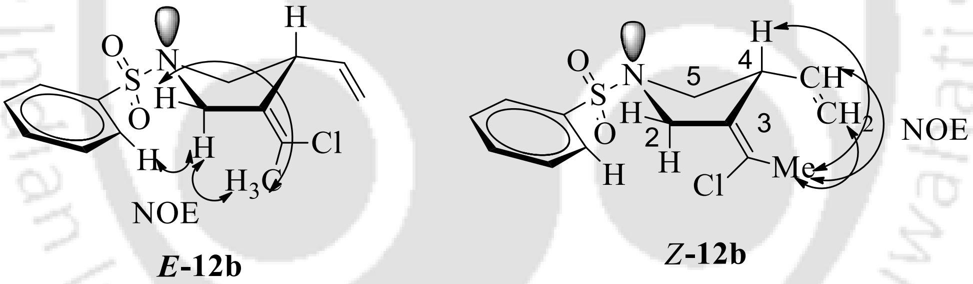
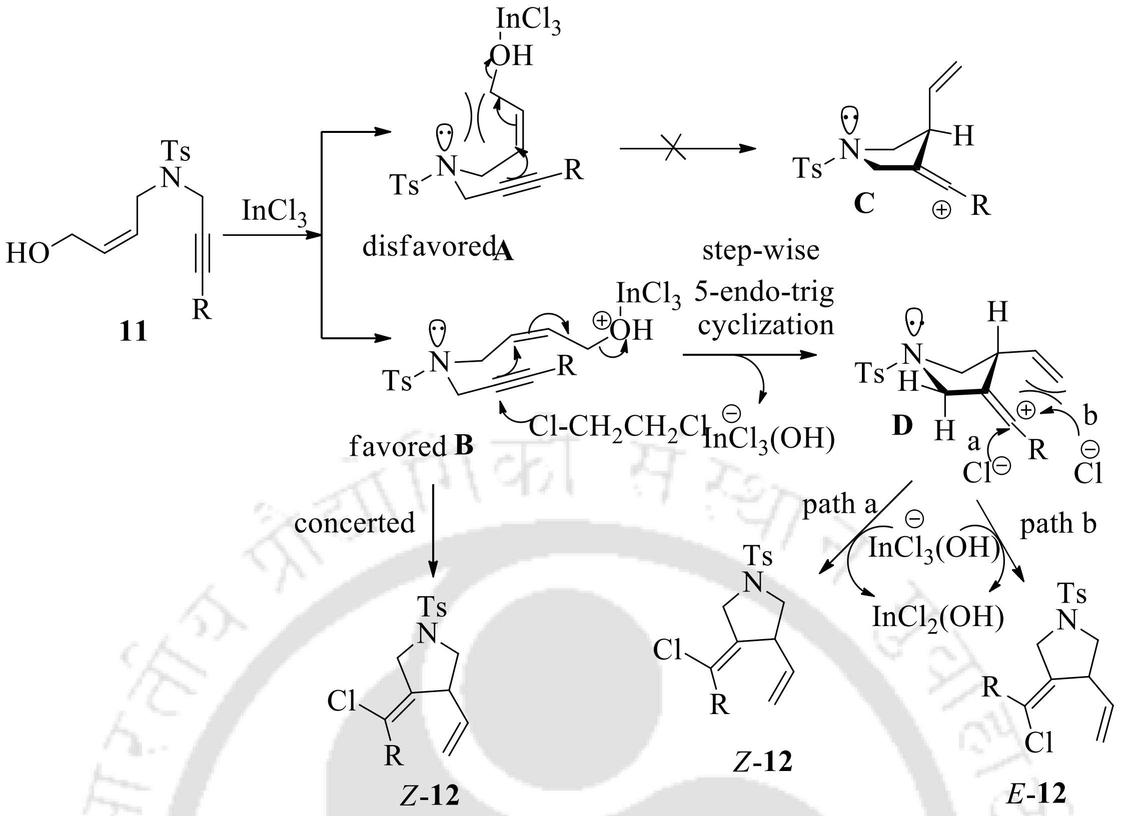


Figure 3.4.4.1. *NOE of compound E-**12b** and Z-**12b**.*

3.4.5. Plausible mechanism of the reaction:

On the basis of observations two mechanisms could be predicted for the reaction (*Scheme 3.4.5.1*). Stepwise carbocation formation and concerted reaction as proposed by Cook.[10] The Lewis acid activates the hydroxyl group of allylic alcohol to facilitate the nucleophilic attack by alkyne group to generate chair like transition states **A** and **B** of which **A** is disfavored due to the 1,3-diaxial interaction between the double bond and the lone pair over nitrogen of tosyl amine group.[11e] The more stable intermediate **B** after 5-endo-trig cyclization forms Carbocation **D**.



Scheme 3.4.5.1

There are two possible ways of attacking carbocation **D** by chloride ion. The pathway "b" is less likely due to the steric hindrance experienced by the incoming chloride ion with vinyl group and gives minor *E*-configured product *E*-**12**. On the other hand, attacking carbocation **D** *via* path "a" is more likely as incoming chloride ion experiences less such steric hindrance with axial hydrogen. Therefore, reaction *via* pathway "a" gives major *Z*-configured product *Z*-**12** (*Scheme 3.4.5.1*). The possibility of concerted mechanism as proposed by Cook whereby there is a simultaneous attacked by the solvent along with the formation of an indium-ate complex cannot be ruled out as reaction with $InBr_3$ in $ClCH_2CH_2Cl$ produced both chlorinated and brominated products **12d-Cl** and **12d-Br** with a ratio of 28:72 (*Table 3.4.2.1*, entry *12*). The *E*/*Z* ratio of both products is found to be 48:52. As the chlorinated product formed *via* concerted pathway is less compared to brominated product, the rate of reaction *via* step-wise reaction is faster than the concerted one and this also explains greater *Z* selectivity over *E* isomer. Further, the requirement of stoichiometric amount of $InCl_3$ in the present procedure also synchronize with this explanation. This is in contrast to Cook's procedure where 20 mol% of $InCl_3$ was used in CH_2Cl_2 to synthesize chlorinated cabocycles from allylic bromide in very good yields at room temperature. This indicates that allylic hydroxyl group is poor leaving group and hence requires higher temperature compared to allylic bromide. Thus, halogen transfer could come from solvent or an indium-ate complex and *E*/*Z* selectivity would vary depending on the concerted or stepwise pathways.

3.5. Conclusion:

In conclusion we have developed a methodology for the synthesis of vinyl substituted pyrrolidine with stereo- and regio-selectively in moderate to good yields. We have also demonstrated that $InCl_3$ can be used as a Lewis acid as well as chlorinating agent for the synthesis of chlorinated pyrrolidines. The major advantage of the method is that it generates pyrrolidine moiety having two functional groups i.e. exocyclic vinyl chloride at 3-position as well as vinylic group at 4-position of the pyrrolidine ring. The drawbacks of the procedure are the requirement of high temperature and stoichiometric amount of $InCl_3$.

3.6. Experimental Section:

3.6.1. General Information:

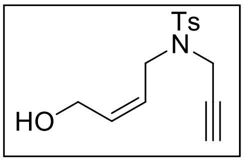
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (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 ^1H (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.

3.6.2. Representative procedure for the synthesis of vinyl pyrrolidines (12a-j):

*Synthesis of (Z)-3-(Chloromethylene)-1-tosyl-4-vinylpyrrolidine (**12a**):* To a stirred solution of *N*-tethered alkyne-alkenol **11a** (100 mg, 0.28 mmol) in dry 1,2-dichloroethane (4 ml) was added indium trichloride (68 mg, 0.308 mmol) at 80 °C under N_2 atmosphere. The reaction mixture was refluxed for 12h. After the completion of the reaction, dichloroethane was evaporated, washed with brine solution, organic layer was extracted with ethyl acetate (2x 15 mL) 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 (EtOAc: Hexane, 2:8) as eluents.

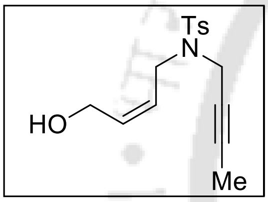
3.7. Characterization Data:

(Z)-N-(4-Hydroxybut-2-en-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**11a**)*:*



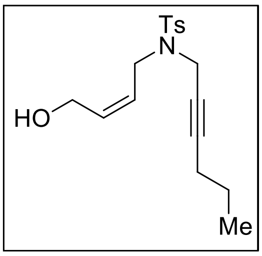
Yellow oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 300 mg, 62%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.00 (t, *J* = 2.4 Hz, 1 H), 2.34 (s, 3 H), 2.56 (brs, 1 H), 3.80 (d, *J* = 7.8 Hz, 2 H), 4.02 (s, 2 H), 4.14 (d, *J* = 6.6 Hz, 2 H), 5.35-5.39 (m, 1 H), 5.74-5.79 (m, 1 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 36.0, 43.1, 57.9, 74.1, 76.6, 125.1, 127.7, 129.6, 134.6, 135.5, 143.9; IR (KBr, neat) 3551, 2922, 2864, 2252, 2119, 1597, 1494, 1330, 1162, 1007, 766 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{18}NO_3S$ $(M + H)^+$ 280.1002, found 280.1009.

(Z)-N-(But-2-yn-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**11b**)*:*



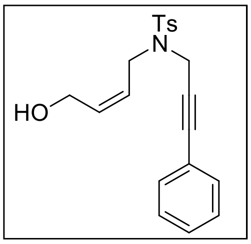
Colorless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 314 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.55 (t, *J* = 2.2 Hz, 3 H), 1.84 (brs, 1 H), 2.43 (s, 3 H), 3.86 (d, *J* = 7.2 Hz, 2 H), 4.01 (d, *J* = 2.4 Hz 2 H), 4.20 (d, *J* = 6.8 Hz, 2 H), 5.48-5.52 (m, 1 H), 5.84-5.88 (m, 1 H), 7.31 (d, *J* = 7.2 Hz, 2 H), 7.73 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.3, 21.6, 36.7, 43.0, 58.0, 71.8, 82.1, 125.8, 128.0, 129.5, 134.2, 135.8, 143.6; IR (KBr, neat) 3537, 2922, 2855, 2223, 1598, 1446, 1342, 1162, 1092, 898, 766 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{20}NO_3S$ $(M + H)^+$ 294.1158, found 294.1158.

(Z)-N-(Hex-2-yn-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**11c**)*:*



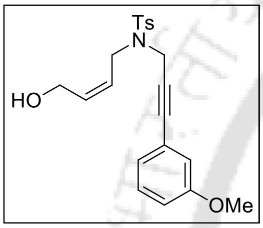
Yellow oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 265 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3 H), 1.23-1.29 (m, 2 H), 1.85-1.89 (m, 2 H), 2.41 (s, 3 H), 2.65 (brs, 1 H), 3.86 (d, *J* = 7.2 Hz, 2 H), 4.05 (d, *J* = 1.6 Hz, 2 H), 4.19 (d, *J* = 6.4 Hz, 2 H), 5.43-5.50 (m, 1 H), 5.81-5.87 (m, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.4, 20.3, 21.4, 21.7, 36.5, 42.9, 57.8, 72.4, 86.3, 125.4, 127.7, 129.4, 134.3, 135.7, 143.5; IR (KBr, neat) 3533, 2930, 2872, 2225, 1598, 1456, 1344, 1161, 1020, 900, 768 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{24}NO_3S$ $(M + H)^+$ 322.1471, found 322.1471.

(Z)-N-(4-Hydroxybut-2-en-1-yl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**11d**)*:*



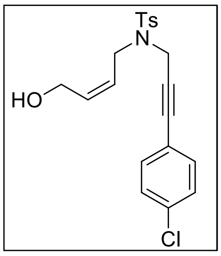
White solid; mp 47-49 °C; R_f (hexane/ EtOAc 3:2) 0.50; yield 134 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 2.40 (brs, 1 H), 3.95 (d, *J* = 7.2 Hz, 2 H), 4.21 (d, *J* = 6.8 Hz, 2 H), 4.28 (s, 2 H), 5.51-5.54(m, 1 H), 5.86-5.87 (m, 1 H), 7.07 (dd, *J* = 8.4 and 1.2 Hz, 2 H), 7.22-7.25 (m, 5 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 37.0, 43.3, 58.1, 81.6, 85.9, 122.0, 125.5, 127.9, 128.3, 128.7, 129.7, 131.6, 134.6, 135.6, 143.8; IR (KBr, neat) 3526, 2922, 2870, 1143, 1599, 1491, 1345, 1161, 1022, 896, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{22}NO_3S$ $(M + H)^+$ 356.1315, found 356.1320.

*(Z)-N-(4-Hydroxybut-2-en-1-yl)-N-(3-(3-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (**11e**):*



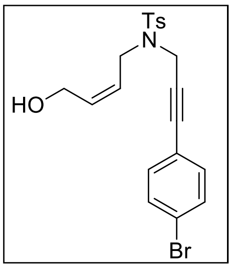
Yellow gum; R_f (hexane/ EtOAc 3:2) 0.50; yield 135 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 2.75 (s, 3 H), 3.93 (d, *J* = 6.8 Hz, 2 H), 4.21 (dd, *J* = 5.2 and 2.5 Hz, 2 H), 4.27 (s, 2 H), 5.49-5.54 (m, 1 H), 5.85-5.89 (m, 1 H), 6.60 (s, 1 H), 6.65 (d, *J* = 7.6 Hz, 1 H), 6.81-6.84 (m, 1 H), 7.12-7.16 (m, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.75 (dd, *J* = 8.4 and 2.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 36.9, 43.3, 55.3, 58.1, 81.5, 85.8, 114.6, 117.1, 123.0, 124.0, 125.4, 127.9, 129.4, 129.7, 134.6, 135.6, 143.9, 159.2; IR (KBr, neat) 3530, 2922, 2873, 2229, 1578, 1486, 1345, 1160, 1044, 949, 780 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{24}NO_4S$ $(M + H)^+$ 386.1421, found 386.1419.

*(Z)-N-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**11f**):*



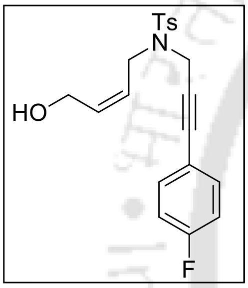
White solid; mp 80-82 °C; R_f (hexane/ EtOAc 3:2) 0.50; yield 270 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.96 (d, *J* = 7.2 Hz, 2 H), 4.23 (d, *J* = 6.8 Hz, 2 H), 4.30 (s, 2 H), 5.55-5.59 (m, 1 H), 5.89-5.93 (m, 1 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 37.0, 43.4, 58.3, 82.9, 84.9, 120.5, 125.9, 128.0, 128.8, 129.8, 132.9, 134.5, 134.9, 135.8, 143.9; IR (KBr, neat) 3528, 2927, 2870, 2249, 1596, 1491, 1341, 1163, 1059, 900, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}ClNO_3S$ $(M + H)^+$ 390.0925, found 390.0925.

*(Z)-N-(3-(4-Bromophenyl)prop-2-yn-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methyl benzenesulfonamide (**11g**):*



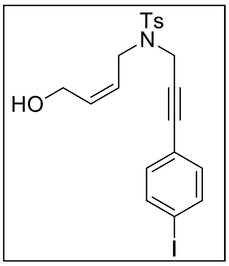
White solid; mp 98-100 °C; R_f (hexane/ EtOAc 3:2) 0.50; yield 136 mg, 50%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.95 (d, *J* = 7.2 Hz, 2 H), 4.23 (d, *J* = 6.6 Hz, 2 H), 4.29 (s, 2 H), 5.54-5.59 (m, 1 H), 5.88-5.92 (m, 1 H), 6.93 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 37.0, 43.4, 58.2, 83.1, 84.9, 121.0, 123.0, 125.7, 128.0, 129.8, 131.6, 133.1, 134.6, 135.7, 143.9; IR (KBr, neat) 3514, 2924, 2856, 2248, 1595, 1486, 1345, 1160, 1012, 897, 767 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}BrNO_3S$ $(M + H)^+$ 436.0420 (Br^{81}), found 436.0416.

*(Z)-N-(3-(4-Fluorophenyl)prop-2-yn-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**11h**):*



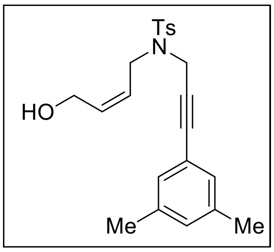
White solid; mp 45-47 °C; R_f (hexane/ EtOAc 3:2) 0.50; yield 186 mg, 50%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.96 (d, *J* = 7.2 Hz, 2 H), 4.23 (dd, *J* = 6.6 and 1.2 Hz, 2 H), 4.29 (s, 2 H), 5.55-5.59 (m, 1 H), 5.89-5.93 (m, 1 H), 6.94 (t, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 37.1, 43.4, 58.3, 81.6, 85.0, 115.7 (d, *J* = 22.0 Hz), 125.9, 128.0, 128.1, 129.8, 133.7 (d, *J* = 8.6 Hz), 134.5, 135.9, 143.9, 162.8 (d, *J* = 248.9 Hz); IR (KBr, neat) 3534, 2925, 2861, 2250, 1599, 1448, 1345, 1223, 1161, 1093, 895, 733 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}FNO_3S$ $(M + H)^+$ 374.1221, found 374.1221.

*(Z)-N-(4-Hydroxybut-2-en-1-yl)-N-(3-(4-iodophenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (**11i**):*



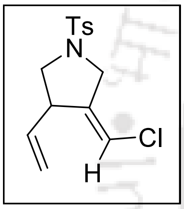
White solid; mp 103-105 °C; R_f (hexane/ EtOAc 3:2) 0.50; yield 275 mg, 50%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 3.94 (d, *J* = 7.2 Hz, 2 H), 4.22 (d, *J* = 6.6 Hz, 2 H), 4.28 (s, 2 H), 5.53-5.59 (m, 1 H), 5.87-5.94 (m, 1 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 37.1, 43.4, 58.3, 83.4, 85.1, 94.8, 121.6, 125.8, 128.1, 129.8, 133.2, 134.6, 135.8, 137.6, 143.9; IR (KBr, neat) 3509, 2922, 2854, 2220, 1597, 1482, 1345, 1160, 1057, 996, 765, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}INO_3S$ $(M + H)^+$ 482.0281, found 482.0289.

*(Z)-N-(3-(3,5-Dimethylphenyl)prop-2-yn-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene sulfonamide (**11j**):*



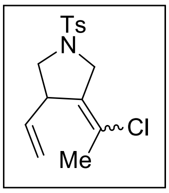
White oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 121 mg, 45%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.25 (s, 6 H), 2.37 (s, 3 H), 3.94 (d, *J* = 7.2 Hz, 2 H), 4.23 (brs, 2 H), 4.30 (s, 2 H), 5.55-5.59 (m, 1 H), 5.88-5.92 (m, 1 H), 6.68 (s, 2 H), 6.92 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.7, 37.1, 43.3, 58.3, 81.0, 86.4, 121.7, 125.9, 128.1, 129.4, 129.8, 130.7, 134.5, 135.9, 138.0, 143.8; IR (KBr, neat) 3442, 2922, 2854, 2220, 1598, 1456, 1346, 1161, 1020, 900, 766 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{26}NO_3S$ $(M + H)^+$ 384.1628, found 384.1635.

*(Z)-3-(Chloromethylene)-1-tosyl-4-vinylpyrrolidine (**12a**, E/Z mixture, E:Z::13:87, only Z-isomer is considered):*



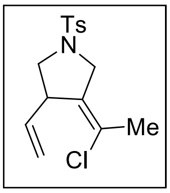
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 50 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 2.79 (dd, *J* = 12.0 and 7.2 Hz, 1 H), 3.08-3.10 (m, 1 H), 3.41 (dd, *J* = 12.0 and 5.2 Hz, 1 H), 3.56 (d, *J* = 15.6 Hz, 1 H), 3.77 (d, *J* = 16.0 Hz, 1 H), 5.12 (s, 1 H), 5.15 (d, *J* = 4.0 Hz, 1 H), 5.65-5.71 (m, 1 H), 5.78-5.79 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 40.7, 47.2, 49.2, 117.5, 125.8, 127.3, 127.8, 130.1, 133.4, 136.4, 144.2; IR (KBr, neat) 2923, 2853, 2226, 1597, 1457, 1347, 1166, 1056, 815, 752, 570 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{17}ClNO_2S$ $(M + H)^+$ 298.0663, found 298.0664.

*3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine (**12b,** E/Z mixture, E:Z::30:70):*



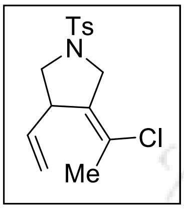
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 74 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.90 (s, 3 H), 2.36 (s, 3 H), 3.07 (dd, *J* = 9.4 and 6.0 Hz, 1 H, minor), 3.17 (dd, *J* = 9.0 and 6.6 Hz, 1 H, major), 3.22-3.28 (m, 2 H, major), 3.32-3.41 (m, 2 H, minor), 3.56 (d, *J* = 14.0 Hz, 1 H, minor), 3.65 (d, *J* = 15.6 Hz, 1 H, major), 3.88-3.91 (m, 1 H), 4.96-5.03 (m, 2 H), 5.57-5.63 (m, 1 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.63 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 22.5, 23.4, 45.8, 46.4, 50.4, 52.1, 53.3, 54.7, 116.0, 116.3, 125.1, 127.2, 128.0, 128.1, 129.9, 133.3, 135.3, 136.2, 144.0, IR (KBr, neat) 2923, 2854, 1598, 1450, 1348, 1164, 1093, 815, 754, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{19}ClNO_2S$ $(M + H)^+$ 312.0820, found 312.0821.

*(E)-3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine (E-**12b**):*



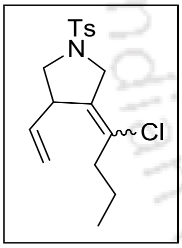
Yellow oil; R_f (hexane/ EtOAc 95:5, TLC was run two times) 0.55; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99 (d, *J* = 1.2 Hz, 3 H), 2.45 (s, 3 H), 3.16 (dd, *J* = 9.5 and 6.7 Hz, 1 H), 3.40 (dd, *J* = 9.5 and 1.9 Hz, 1 H), 3.48 (t, *J* = 6.9 Hz, 1 H), 3.65 (d, *J* = 14.0 Hz, 1 H), 3.96 (dt, *J* = 14.0 and 1.4 Hz, 1 H), 5.05-5.11 (m, 2 H), 5.66-5.72 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 23.5, 46.5, 50.4, 53.4, 116.2, 124.5, 128.1, 130.0, 132.5, 133.1, 135.3, 144.2.

*(Z)-3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine (Z-**12b**):*



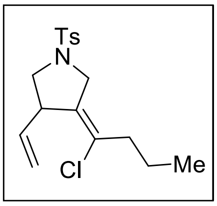
Yellow oil; R_f (hexane/ EtOAc 95:5, TLC was run two times) 0.50; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.98 (d, *J* = 0.5 Hz, 3 H), 2.44 (s, 3 H), 3.25 (dd, *J* = 9.0 and 6.5 Hz, 1 H), 3.31-3.35 (m, 2 H), 3.73 (dd, *J* = 15.0 and 2.0 Hz, 1 H), 3.98 (dt, *J* = 15.0 and 1.8 Hz, 1 H), 5.03-5.07 (m, 2 H), 5.66-5.72 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 22.6, 46.0, 52.2, 54.7, 116.4, 125.2, 128.2, 130.0, 132.3, 133.3, 136.2, 144.1.

*3-(1-Chlorobutylidene)-1-tosyl-4-vinylpyrrolidine (**12c**, E/Z mixture, E:Z:: 40**:**60):*



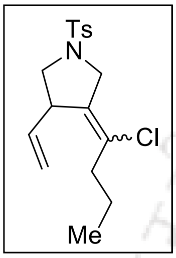
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 81 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3 H, major), 0.85 (t, *J* = 7.2 Hz, 3 H, minor), 1.46-1.57 (m, 2 H), 2.15-2.22 (m, 2 H), 2.44 (s, 3 H), 3.14 (dd, *J* = 9.6 and 6.4 Hz, 1 H, minor), 3.24 (dd, *J* = 9.6 and 7.2 Hz, 1 H, major), 3.30-3.33 (m, 1 H), 3.39 (dd, *J* = 9.6 and 2.0 Hz, 1 H, major), 3.49 (t, *J* = 6.8 Hz, 1 H, minor), 3.65 (d, *J* = 13.6 Hz, 1 H, minor), 3.74 (d, *J* = 14.8 Hz, 1 H, major), 3.94-3.96 (m, 1 H, major), 3.98-4.00 (m, 1 H, minor), 5.04-5.12 (m, 2 H), 5.64-5.75 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H, major), 7.70 (d, *J* = 8.0 Hz, 2 H, minor). ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.3, 13.5, 20.5, 20.7, 21.8, 37.2, 38.5, 45.8, 46.4, 50.2, 52.2, 53.2, 54.7, 116.0, 116.3, 128.1, 128.2, 129.5, 129.9, 130.4, 132.4, 132.5, 133.4, 135.4, 136.9, 144.0, 144.1; IR (KBr, neat) 2962, 2871, 1637, 1457, 1349, 1164, 1093, 815, 708, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{23}ClNO_2S$ $(M + H)^+$ 340.1133, found 340.1136.

*(E)-3-(1-Chlorobutylidene)-1-tosyl-4-vinylpyrrolidine (E-**12c**):*



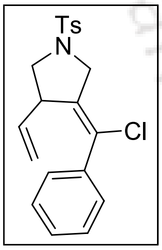
Yellow oil; R$_f$ (hexane/ EtOAc 95:5, TLC was run two times) 0.55; ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.54 (dd, *J* = 14.6 and 7.2 Hz, 2 H), 2.17 (t, *J* = 7.2 Hz, 2 H), 2.44 (s, 3 H), 3.15 (dd, *J* = 9.4 and 6.7 Hz, 1 H), 3.40 (dd, *J* = 9.4 and 1.6 Hz, 1 H), 3.49 (t, *J* = 6.7 Hz, 1 H), 3.67 (d, *J* = 13.7 Hz, 1 H), 3.98 (d, *J* = 13.7 Hz, 1 H), 5.04-5.11 (m, 2 H), 5.66-5.72 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 13.3, 20.5, 21.8, 38.6, 46.5, 50.3, 53.3, 116.1, 128.1, 129.5, 130.0, 132.5, 133.2, 135.4, 144.2.

*(Z)-3-(1-Chlorobutylidene)-1-tosyl-4-vinylpyrrolidine (Z-**12c**):*



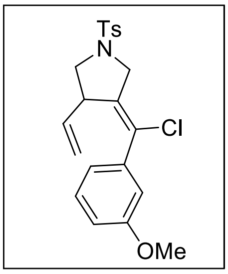
Yellow oil; R$_f$ (hexane/ EtOAc 95:5, TLC was run two times) 0.50; ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.84 (t, *J* = 7.4 Hz, 3 H), 1.46-1.53 (m, 2 H), 2.22 (dd, *J* = 13.7 and 7.0 Hz, 2, H), 2.44 (s, 3 H), 3.27 (dd, *J* = 9.6 and 6.4 Hz, 1 H), 3.31-3.35 (m, 2 H), 3.76 (d, *J* = 15.0 Hz, 1 H), 3.98 (dd, *J* = 15.0 and 1.3 Hz, 1 H), 5.05-5.08 (m, 2 H), 5.67-5.73 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 13.5, 20.7, 21.8, 37.2, 45.9, 52.2, 54.8, 116.3, 128.2, 130.0, 130.4, 132.4, 133.4, 137.0, 144.1.

*(Z)-3-(Chloro(phenyl)methylene)-1-tosyl-4-vinylpyrrolidine (**12d**, E/Z mixture, E:Z::16:84, only Z-isomer is considered):*



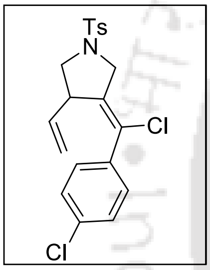
Brown oil; R$_f$ (hexane/ EtOAc 9:1) 0.50; yield 78 mg, 75%; ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.46 (s, 3 H), 3.28 (dd, *J* = 9.6 and 6.6 Hz, 1 H), 3.32 (dd, *J* = 9.6 and 3.0 Hz, 1 H), 3.36-3.40 (m, 1 H), 4.02 (d, *J* = 15.6 Hz, 1 H), 4.13 (d, *J* = 7.2 Hz, 1 H), 4.78 (d, *J* = 17.4 Hz, 1 H), 4.89 (d, *J* = 10.2 Hz, 1 H), 5.52-5.61 (m, 1 H), 7.27-7.30 (m, 5 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 21.8, 46.3, 52.8, 54.8, 116.8, 127.0, 128.2, 128.4, 128.5, 128.7, 129.0, 130.0, 132.8, 136.2, 136.3, 137.2, 144.1; IR (KBr, neat) 2978, 2849, 1634, 1483, 1347, 1161, 1064, 898, 748, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}ClNO_2S$ (M + H)$^+$ 374.0976, found 374.0984.

*(Z)-3-(Chloro(3-methoxyphenyl)methylene)-1-tosyl-4-vinylpyrrolidine (**12e**, E/Z mixture, E:Z::6:94, only Z-isomer is considered):*



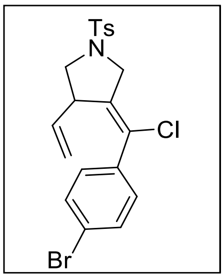
Colorless oil; R_f (hexane/ EtOAc 9:1) 0.50; yield 68 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.26 (dd, 9.2 and 6.4 Hz, 1 H), 3.34 (dd, 11.6 and 2.4 Hz,1 H), 3.36-3.43 (m, 1 H), 3.77 (s, 3 H), 4.00 (d, J = 15.6 Hz, 1 H), 4.12 (d, J = 15.6 Hz, 1 H), 4.83 (d, J = 17.2 Hz, 1 H), 4.93 (d, J = 9.6 Hz, 1 H), 5.55-5.64 (m, 1 H), 6.83 (d, J = 8.0 Hz, 2 H), 6.89 (d, J = 8.0 Hz, 1 H), 7.21 (t, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 46.3, 52.7, 54.8, 55.5, 114.1, 114.7, 116.9, 120.9, 126.8, 128.2, 129.4, 130.0, 132.8, 136.2, 136.4, 138.4, 144.1, 159.4; IR (KBr, neat) 2956, 2852, 1638, 1451, 1348, 1162, 1046, 815, 754, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}ClNO_3S$ $(M + H)^+$ 404.1082, found 404.1082.

(Z)-3-(Chloro(4-chlorophenyl)methylene)-1-tosyl-4-vinylpyrrolidine ***(12f,*** *E/Z mixture, E:Z::14:86, only Z-isomer is considered):*



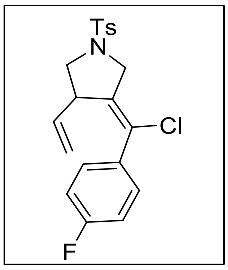
Yellow gum; R_f (hexane/ EtOAc 9:1) 0.50; yield 70 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 3.28-3.31 (m, 2 H), 3.34-3.38 (m, 1 H), 4.00 (d, J = 15.6 Hz, 1 H), 4.10 (d, J = 15.6 Hz, 1 H), 4.80 (dt, J = 17.2 and 1.2 Hz, 1 H), 4.92 (dd, J = 10.8 and 1.2 Hz, 1 H), 5.51-5.60 (m, 1 H), 7.23-7.27 (m, 4 H), 7.37 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 46.4, 52.8, 54.8, 117.1, 125.8, 128.2, 128.6, 129.0, 129.98, 130.0, 135.0, 135.6, 136.2, 137.0, 144.2; IR (KBr, neat) 2926, 2853, 1640, 1595, 1490, 1350, 1162, 1092, 830, 776, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{20}Cl_2NO_2S$ $(M + H)^+$ 408.0586, found 408.0585.

(Z)-3-((4-Bromophenyl)chloromethylene)-1-tosyl-4-vinylpyrrolidine ***(12g,*** *E/Z mixture, E:Z::15:85, only Z-isomer is considered):*



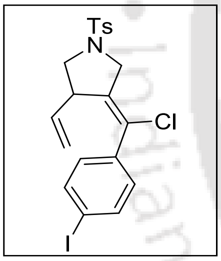
Brown gum; R_f (hexane/ EtOAc 9:1) 0.50; yield 80 mg, 77%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 3.19-3.23 (m, 2 H), 3.25-3.30 (m, 1 H), 3.92 (d, J = 15.6 Hz, 1 H), 4.03 (d, J = 15.6 Hz, 1 H), 4.73 (d, J = 17.4 Hz, 1 H), 4.85 (d, J = 10.2 Hz, 1 H), 5.45-5.51 (m, 1 H), 7.11 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 46.4, 52.9, 54.8, 117.2, 123.2, 128.2, 130.0, 130.2, 131.6, 131.9, 132.6, 136.0, 136.1, 137.0, 144.2; IR (KBr, neat) 2924, 2852, 1639, 1486, 1349, 1162, 1094, 816, 732, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{20}BrClNO_2S$ $(M + H)^+$ 454.0061(Br^{81}), found 454.0044.

(Z)-3-(Chloro(4-fluorophenyl)methylene)-1-tosyl-4-vinylpyrrolidine (**12h**, *E/Z mixture, E:Z::14:86, only Z-isomer is considered):*



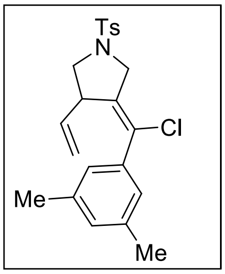
Brown oil; R$_f$ (hexane/ EtOAc 9:1) 0.50; yield 94 mg, 90%; ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.46 (s, 3 H), 3.95 (d, *J* = 4.8 Hz, 2 H), 3.36 (d, *J* = 6.6 Hz, 1 H), 4.00 (d, *J* = 15.6 Hz, 1 H), 4.10 (dd, *J* = 15.6 and 1.8 Hz, 1 H), 4.78 (d, *J* = 16.8 Hz, 1 H), 4.90 (d, *J* = 10.2 Hz, 1 H), 5.51-5.57 (m, 1 H), 6.98 (t, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 21.8, 46.4, 52.8, 54.8, 115.4 (d, *J* = 21.6 Hz), 117.0, 126.0, 128.0, 128.2, 129.9, 130.5 (d, *J* = 8.4 Hz), 132.6, 136.2, 136.6, 144.2, 162.8 (d, *J* = 247.8 Hz); IR (KBr, neat) 2926, 2854, 1599, 1507, 1353, 1161, 1095, 839, 777, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{20}ClFNO_2S$ $(M + H)^+$ 392.0882, found 392.0882.

(Z)-3-(Chloro(4-iodophenyl)methylene)-1-tosyl-4-vinylpyrrolidine (**12i**, *E/Z mixture, E:Z::14:96, only Z-isomer is considered):*



Deep brown gum; R$_f$ (hexane/ EtOAc 9:1) 0.50; yield 46 mg, 45%; ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.46 (s, 3 H), 3.26-3.32 (m, 2 H), 3.33-3.36 (m, 1 H), 3.98 (d, *J* = 15.6 Hz, 1 H), 4.09 (d, *J* = 15.6 Hz, 1 H), 4.82 (d, *J* = 17.4 Hz, 1 H), 4.93 (d, *J* = 10.2 Hz, 1 H), 5.53-5.59 (m, 1 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 7.8 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 7.7 Hz, 2 H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 21.8, 46.4, 52.9, 54.8, 95.0, 117.2, 125.9, 128.2, 129.8, 130.0, 130.1, 130.3, 132.6, 136.2, 136.6, 137.0, 137.6, 137.9, 144.2; IR (KBr, neat) 2923, 2853, 1597, 1480, 1348, 1161, 1093, 897, 816, 665 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{20}ClINO_2S$ $(M + H)^+$ 499.9942, found 499.9942.

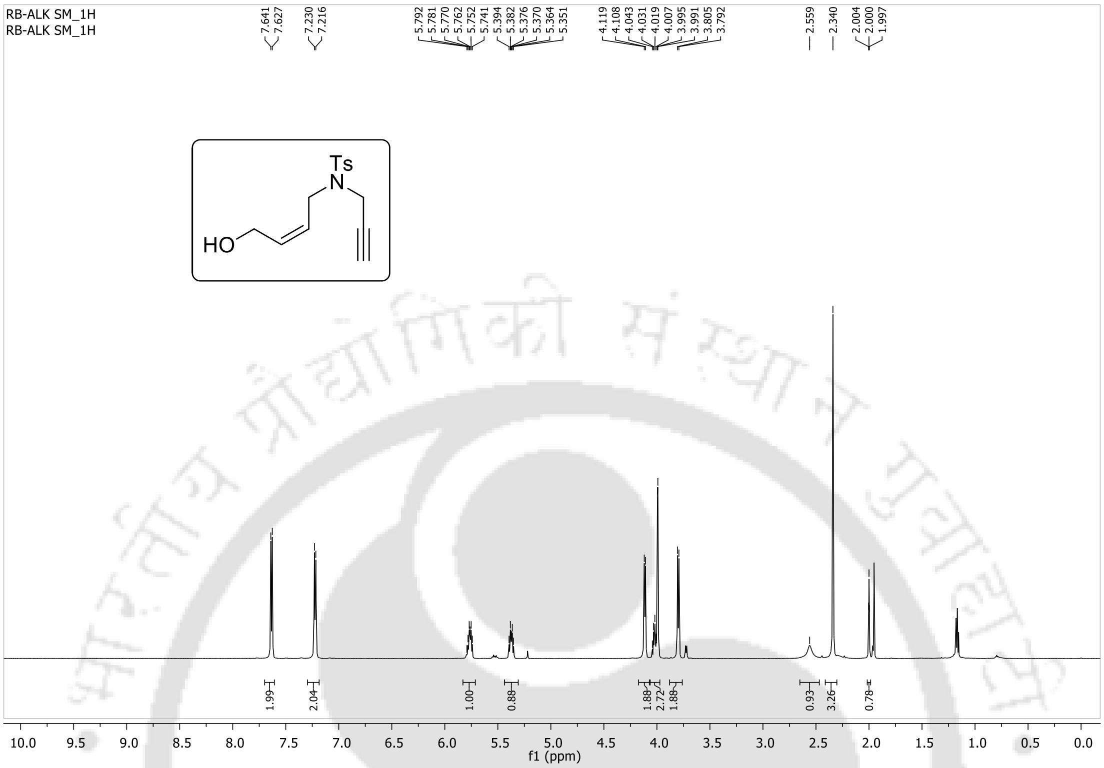
(Z)-3-(Chloro(3,5-dimethylphenyl)methylene)-1-tosyl-4-vinylpyrrolidine (**12j**, *E/Z mixture, E:Z::40:60):*

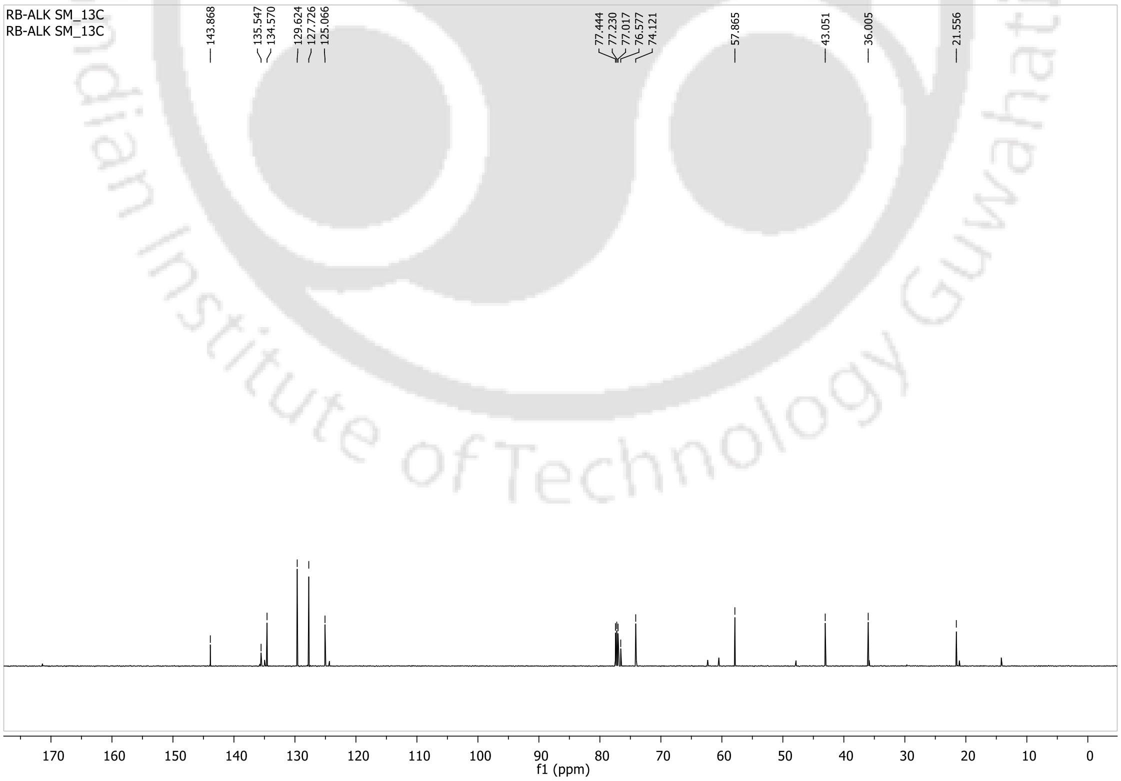


Yellow oil; R$_f$ (hexane/ EtOAc 9:1) 0.50; yield 26 mg, 25%; ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.26 (s, 6 H, major), 2.32 (s, 6 H, minor), 2.44 (s, 3 H, minor), 2.46 (s, 3 H, major), 3.22-3.28 (m, 3 H, minor), 3.32-3.39 (m, 3 H, major), 3.63-3.65 (m, 1 H, minor), 3.70 (d, *J* = 14.4 Hz, 1 H, major), 4.00 (d, *J* = 15.6 Hz, 1 H, major), 4.03 (dd, *J* = 14.4 and 2.4 Hz, 1 H, minor), 4.10 (dd, *J* = 15.6 and 1.8 Hz, 1 H), 4.81 (d, *J* = 16.8 Hz, 1 H, major), 4.92 (d, *J* = 10.2 Hz, 1 H, major), 5.11 (d, *J* = 10.2 Hz, 1 H, minor), 5.18 (d, *J* = 16.8 Hz, 1 H, minor), 5.56-5.60 (m, 1 H, major), 5.71-5.77 (m, 1 H, minor), 6.87 (s, 1 H), 6.91 (s, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H, minor), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H, minor), 7.77 (d, *J* = 8.4 Hz, 2 H, major). ^{13}C NMR (150 MHz, CDCl$_3$) δ 21.4, 21.5, 21.8, 46.4, 47.2, 51.2, 52.7, 52.9, 54.8, 116.6, 116.7, 125.9, 126.3, 128.0, 128.2, 129.9, 130.0, 130.7, 135.1, 136.7, 137.9, 138.4, 144.0, 144.1; IR (KBr, neat) 2921, 2852, 1636, 1445, 1348, 1162, 1092, 814, 702, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{25}ClNO_2S$ $(M + H)^+$ 402.1289, found 402.1294.

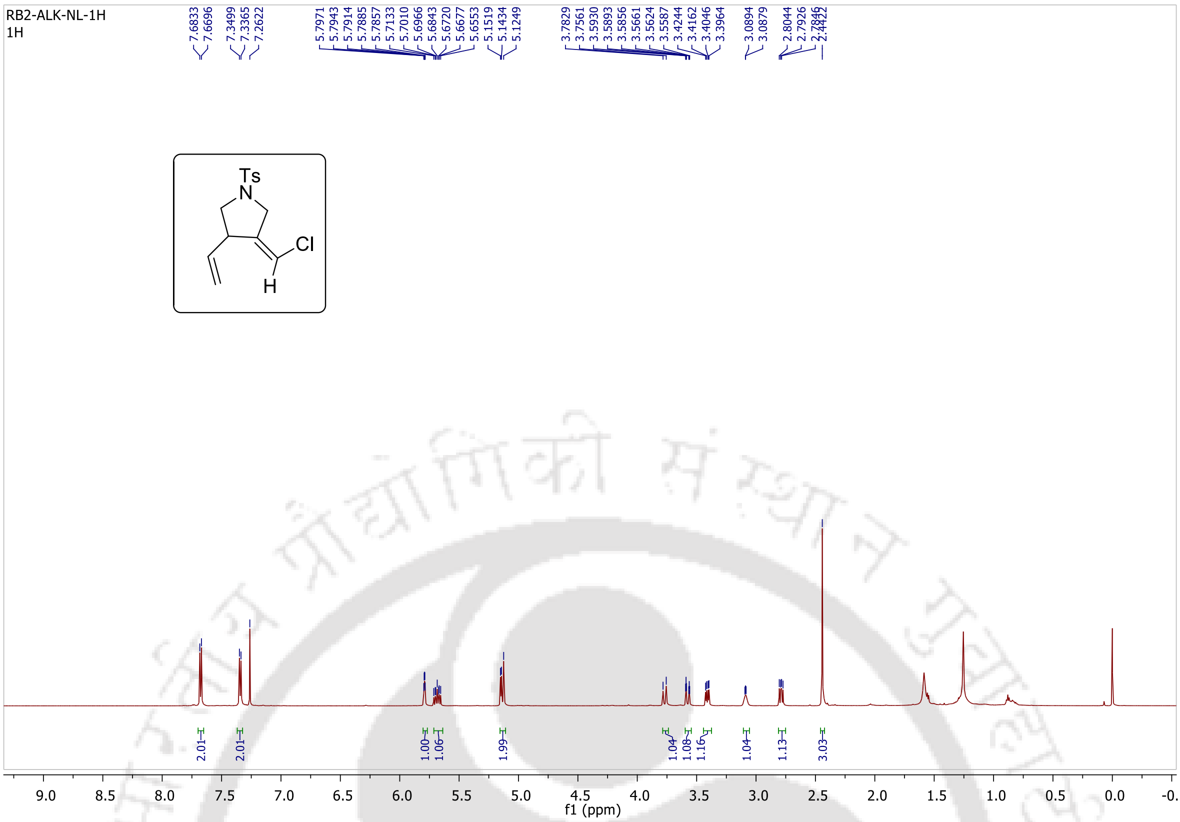
3.8. Representative Spectra:

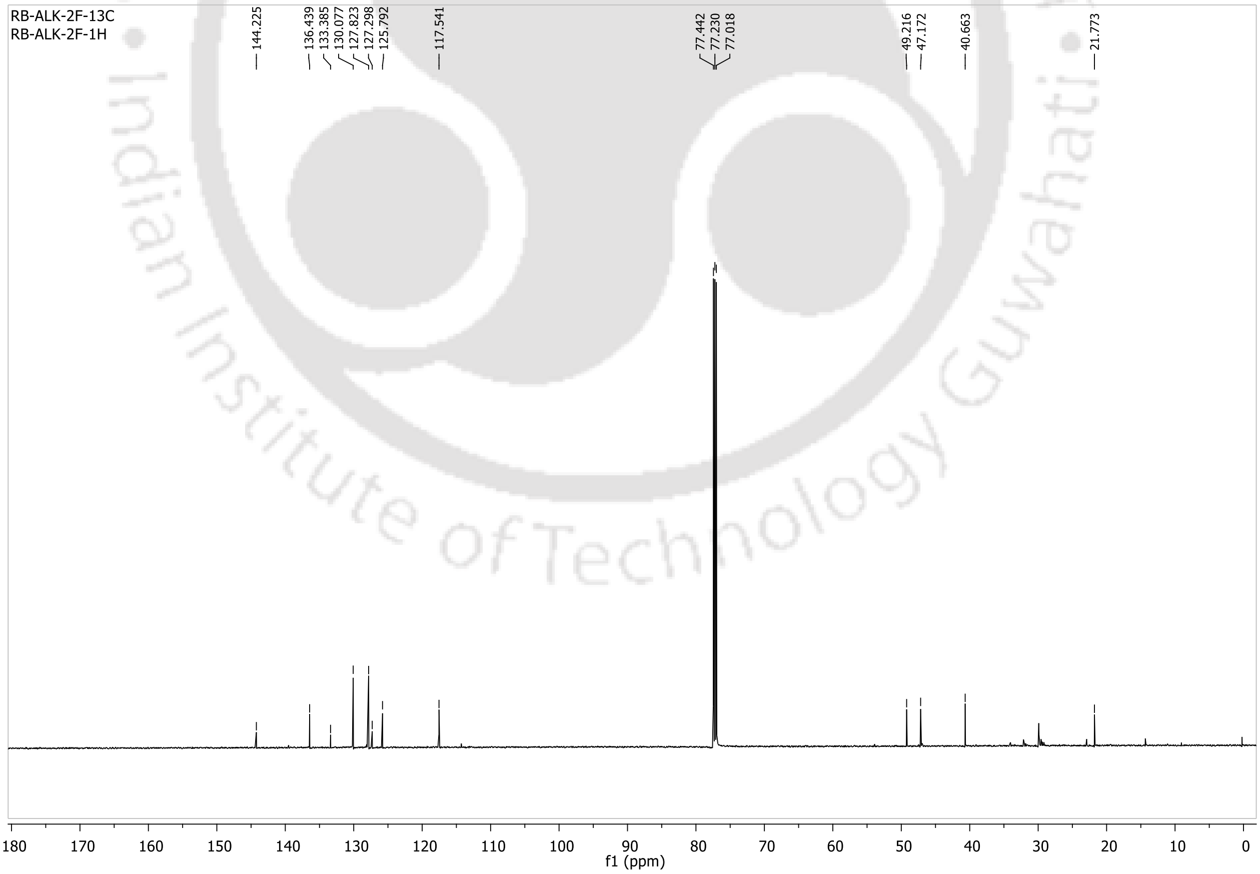
^{1}H and ^{13}C spectra of (*Z*)-*N*-(4-hydroxybut-2-en-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 11a:



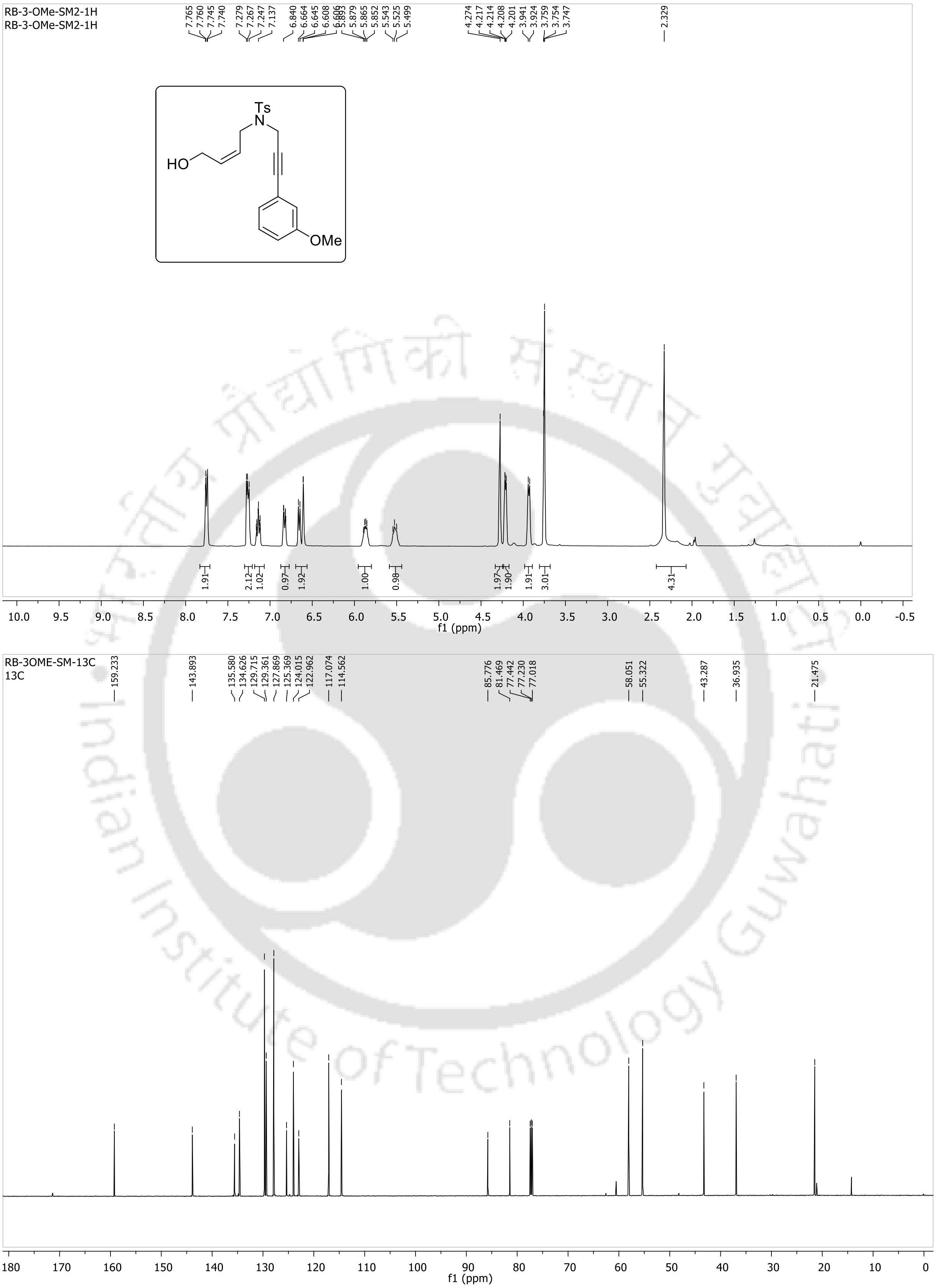


^{1}H and ^{13}C spectra of (*Z*)-3-(chloromethylene)-1-tosyl-4-vinylpyrrolidine 12a:

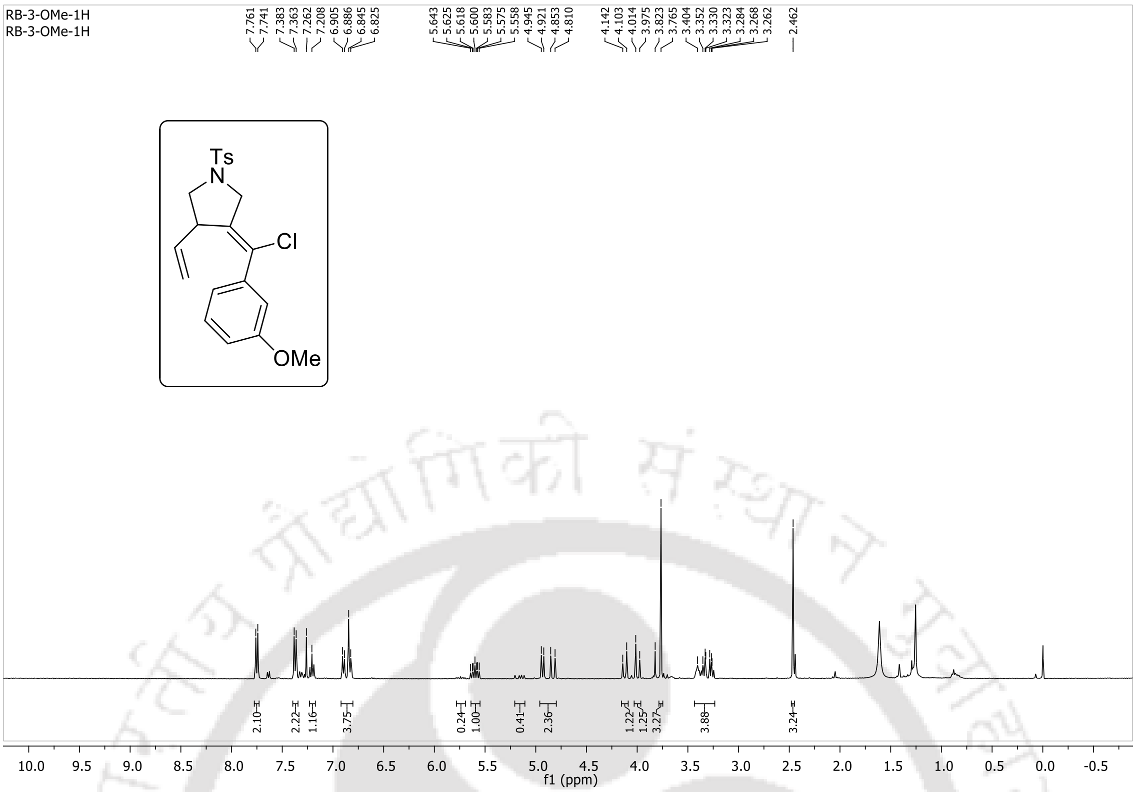


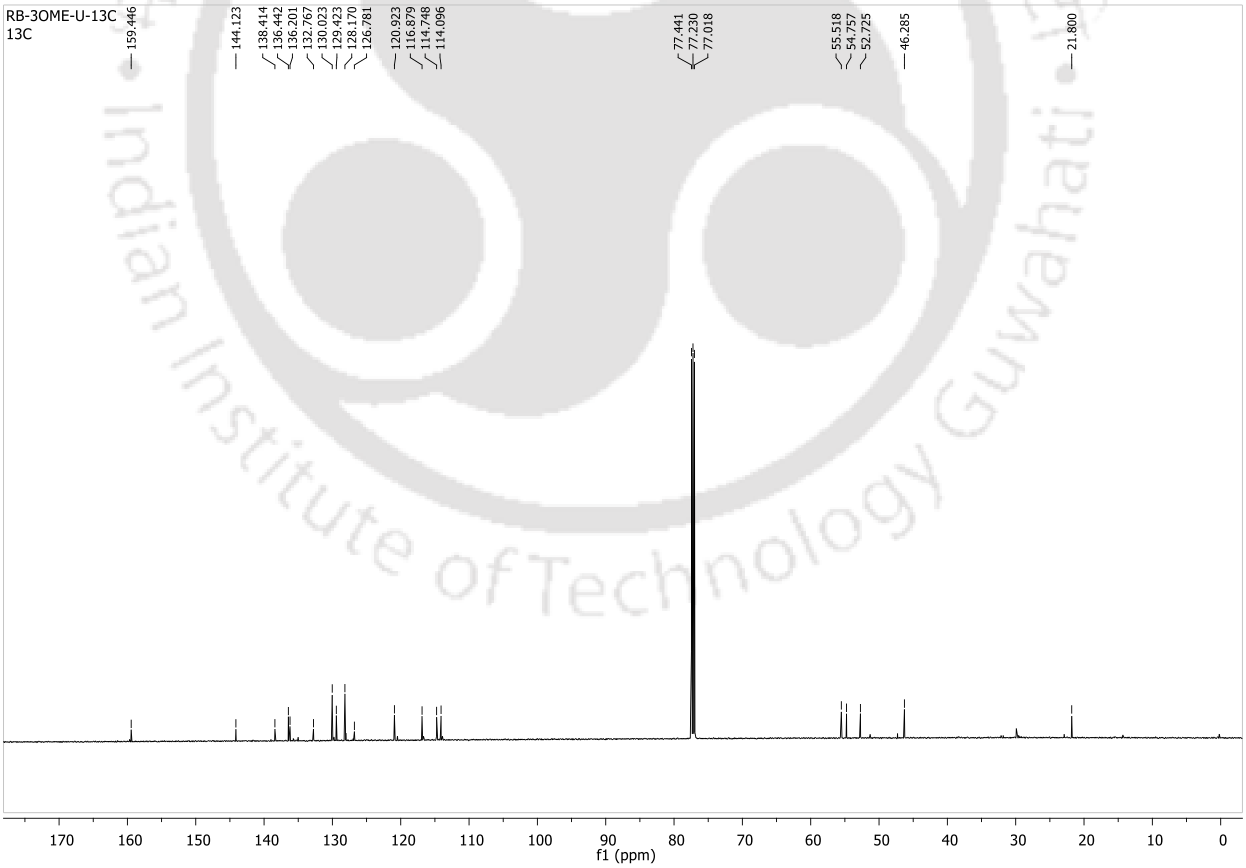


^{1}H and ^{13}C spectra of (*Z*)-*N*-(4-hydroxybut-2-en-1-yl)-*N*-(3-(3-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide 11e:

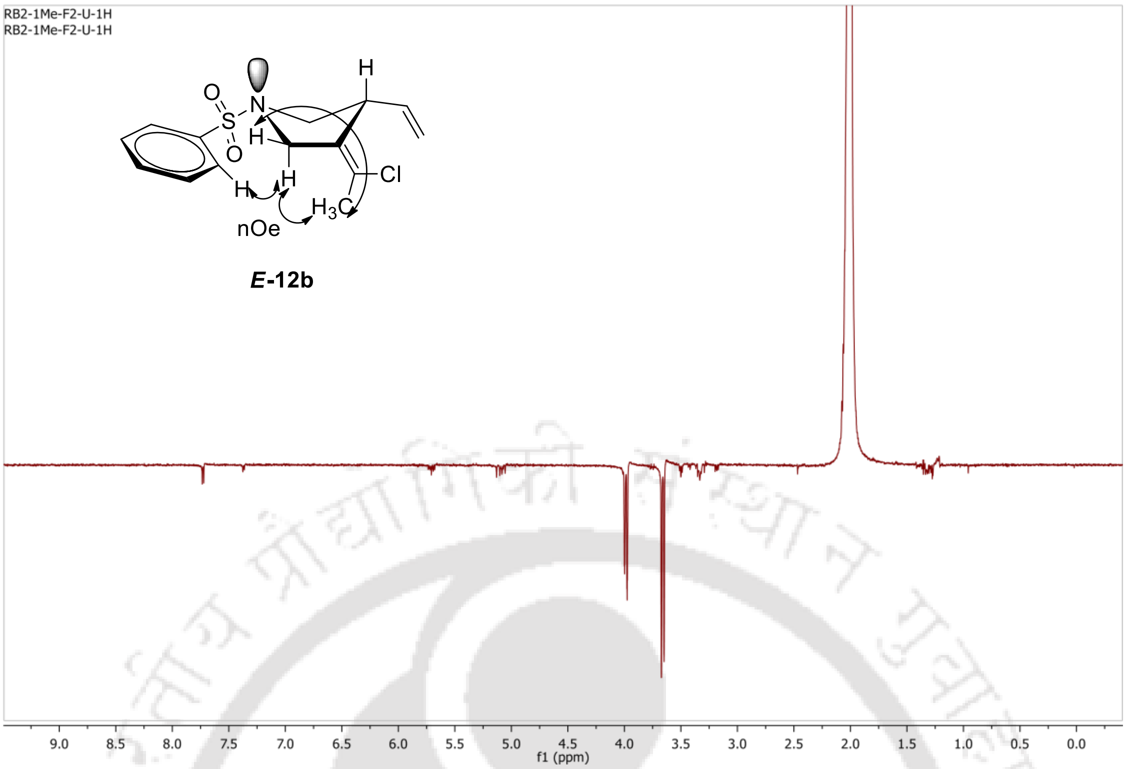


^{1}H and ^{13}C spectra of (*Z*)-3-(chloro(3-methoxyphenyl)methylene)-1-tosyl-4-vinylpyrrolidine 12e:

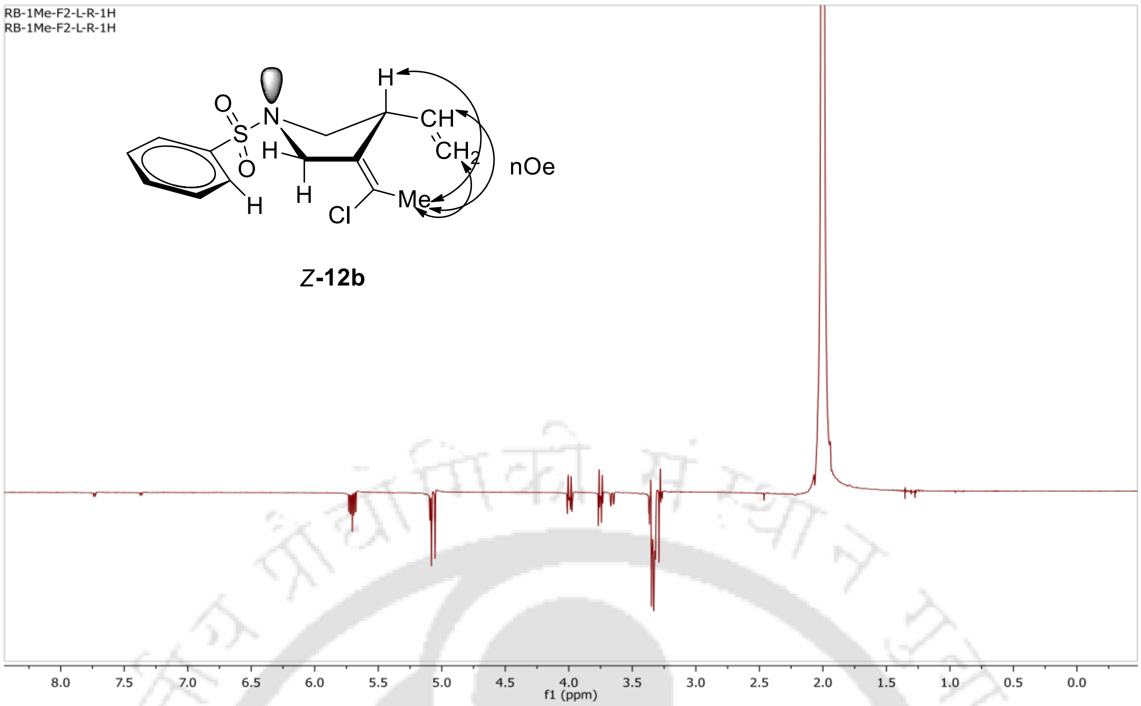




NOE spectra of compound (*E*)-3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine *E*-12b

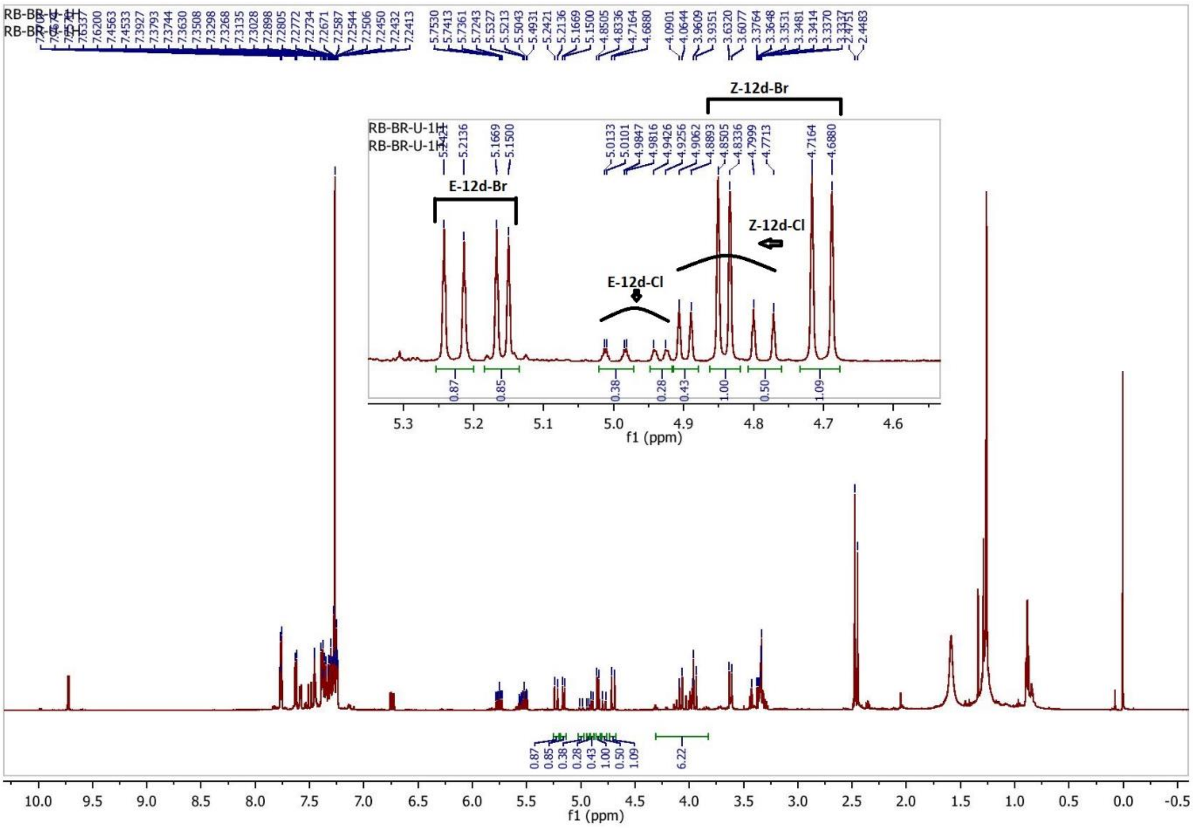


NOE spectra of compound (*Z*)-3-(1-Chloroethylidene)-1-tosyl-4-vinylpyrrolidine *Z*-12b:



^{1}H NMR and HRMS spectra of compounds 12d-Cl and 12d-Br

(Reaction performed with $InBr_3$ in $ClCH_2CH_2Cl$)



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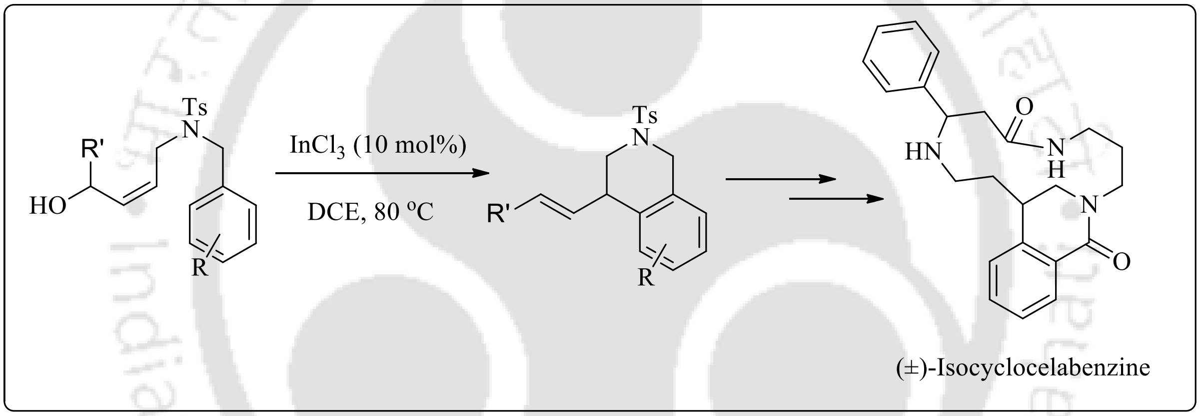
CHAPTER 4

Synthesis of 4-Vinyl-1,2,3,4-tetrahydroisoquinoline from N-Tethered Benzyl-Alkenol Catalyzed by Indium(III) Chloride: Formal Synthesis of (±)-Isocyclocelabenzine

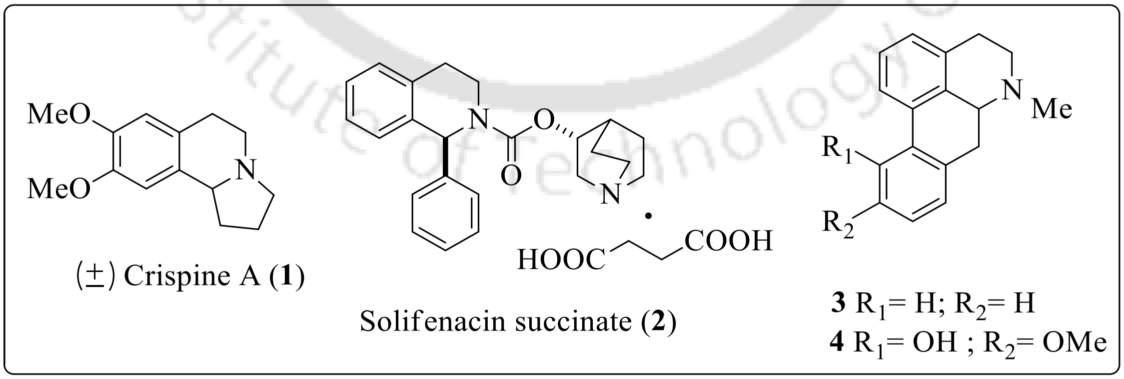


Synthesis, *DOI: 10.1055/s-0037-1610750*

Synthesis of 4-Vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-Tethered Benzyl-Alkenol Catalyzed by Indium(III) Chloride: Formal Synthesis of (±)-Isocyclocelabenzine

4.1. Importance and Applications:

Many *N*-containing heterocycles are known in nature, especially isoquinolines are found to be a major part in naturally occurring alkaloids (*Figure 4.1.1*). Tetrahydroisoquinoline (THIQ) is a substructure found in a number of plant alkaloids as well as in various synthetic organic compounds. They show an array of medicinal and pharmacological properties such as antihyperglycemic property[1], analgesic effects, effective against heart diseases and liver damages[2], anticonvulsant effects[3], as a calcium channel blocker[4], treatment for Parkinson's disease[5] etc. These biological properties are attributed to the substitution pattern on the isoquinoline scaffold. For example, (±) Crispine A (**1**), a natural isoquinoline alkaloid, was isolated from *Carduus crispus* and has been used for the treatment of cold, stomachache, rheumatism as well as showed inhibitory effects on the growth of some human cancer lines.[6] Another THIQ salt solifenacin succinate (**2**) has recently been approved for the treatment of overactive bladder with symptoms of urgency, frequency, and urge incontinence.[7] Alkaloids (±)-aporphine (**3**) and (±)-apocodeine (**4**) also have THIQ as their core structural unit (*Figure 4.1.1*).[8] In addition to their biological properties, THIQs also act as key intermediates in many reactions for the synthesis of several of substances.[9]



(±) Crispine A (**1**)

Solifenacin succinate (**2**)

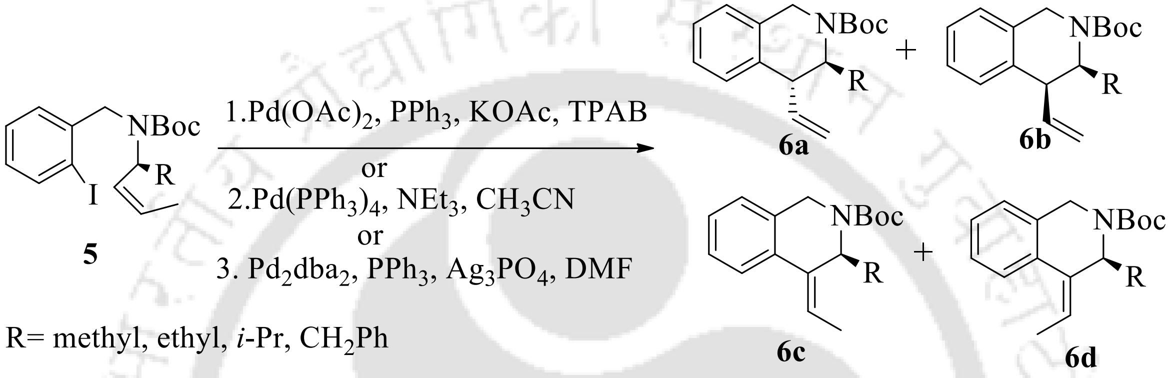
3 R_1= H; R_2= H
4 R_1= OH ; R_2= OMe

Figure 4.1.1. Bioactive molecules containing tetrahydroisoquinoline derivatives.

4.2. An overview of literature methods:

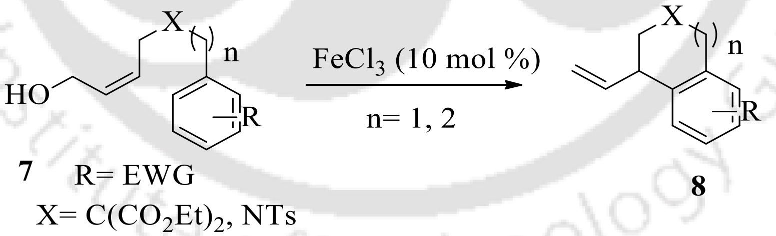
The most common approaches for synthesizing THIQ derivatives are Pictet-Spengler condensation reaction, Freidel Crafts reaction, Heck reaction etc. Over the year various synthetic strategies have been developed for the synthesis of tetrahydroisoquinoline derivatives. Some of the methods are discuss below.

Tietze and co-workers synthesized enantiopure 3,4-disubstituted tetrahydroisoquinolines from commercially available α-amino acid derivatives. The reaction followed an easy five step sequence and afterwards, an intramolecular Heck cyclization reaction occurred.[10] (*Scheme 4.2.1*)



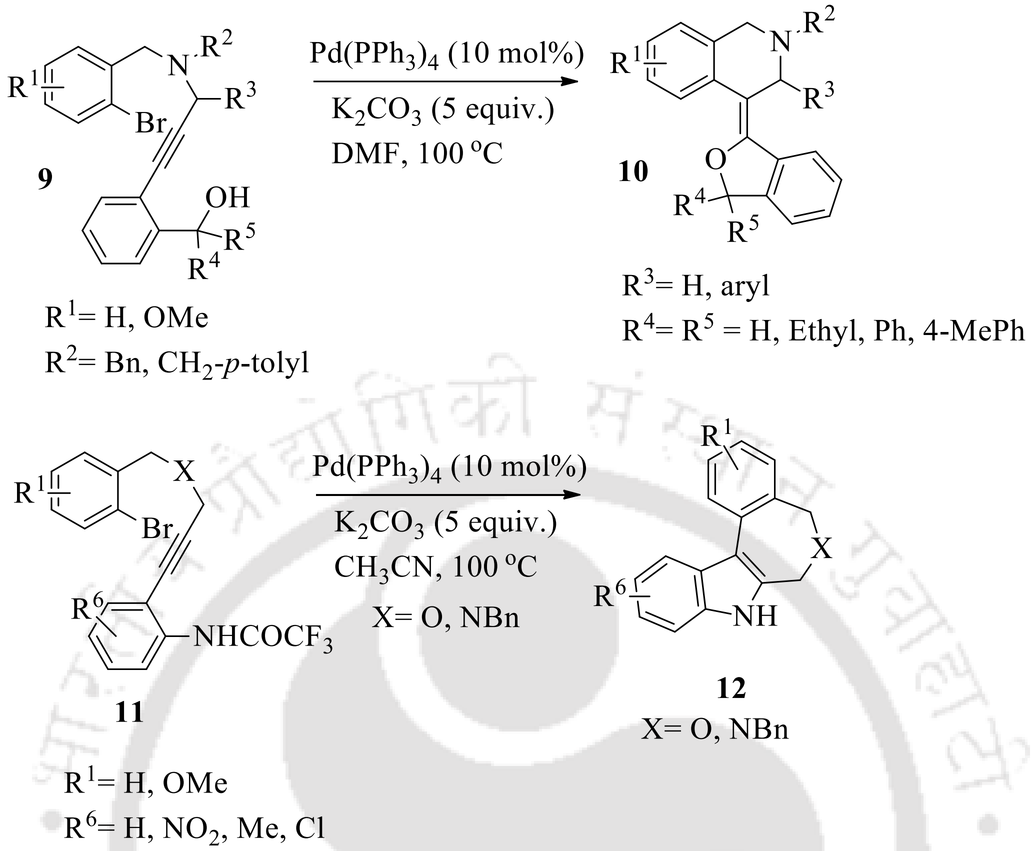
Scheme 4.2.1

In 2009, Bandini and co-workers reported a $FeCl_3$ catalyzed cyclization reaction of electron deficient arenes with π-activated alcohols **7** and it gave an access for the synthesis of a range of tetrahydronaphthalenes, tetrahydroisoquinolines and tetrahydrobenzo[*d*]azepines featuring tertiary benzylic stereocenters in excellent yields (up to 92%).[11](*Scheme 4.2.2*)



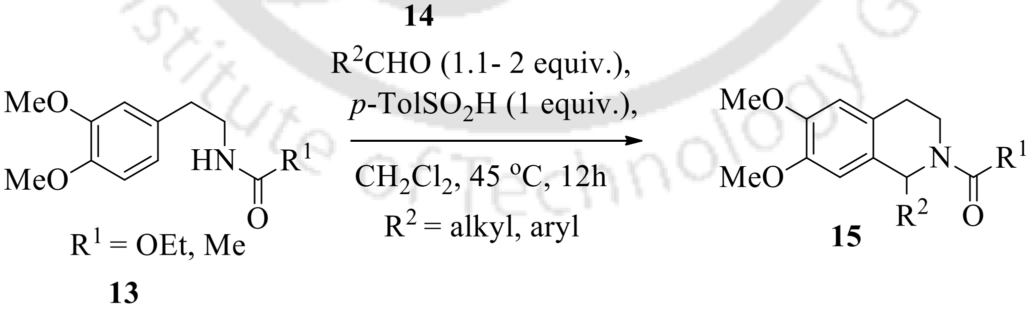
Scheme 4.2.2

In 2014, Perumal and co-workers reported a palladium-catalyzed highly regio- and stereoselective 6-*exo-dig* and 7-*endo-dig* cyclization of functionalized alkynes (**9** and **11**) to give (*E*)-4-(isobenzofuran-1(3*H*)-ylidene)-1,2,3,4-tetrahydroisoquinolines **10** and aze/oxepinoindoles respectively **12** (*Scheme 4.2.3*).[12]



Scheme 4.2.3

An efficient method for the synthesis of tetrahydroisoquinoline derivatives **15** were reported by Menéndez and co-workers *via* one pot reaction of amide-type compounds **13** (including carbamates, amides, ureas and diketopiperazines), aldehydes **14** and *p*-toluenesulfonic acid.[13] (*Scheme 4.2.4*)

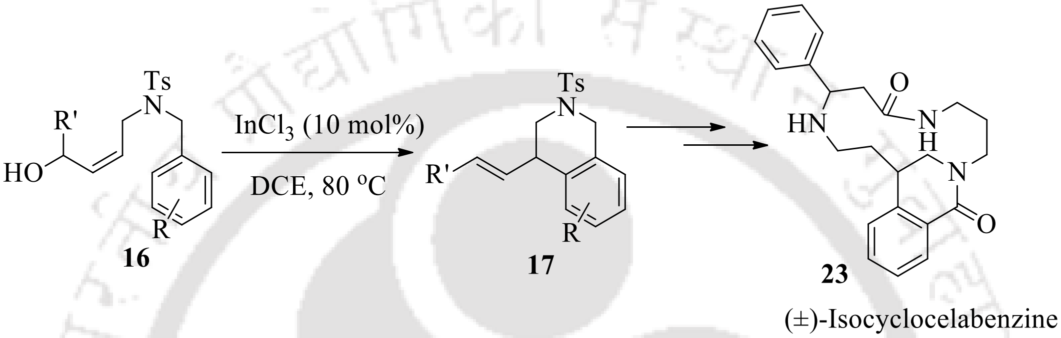


Scheme 4.2.4

4.3. Present strategy and objective:

In our previous chapter, we have described the synthesis of 4-vinylpyrrolidines mediated by indium(III) chloride ($InCl_3$) in which $InCl_3$ is used as both nucleophile as well as Lewis acid.

Based on these literature methods and previous reports from our group, we envisioned that, cyclization reaction of *N*-tethered benzyl-alkenol can afford tetrahydroisoquinoline derivatives fuctionalized with exocyclic vinyl group in high regioselectivity. So, in this chapter, synthesis of vinyl substituted tetrahydroisoquinoline derivatives *via* $InCl_3$ mediated Friedel-Crafts reactions using *N*-tethered benzyl-alkenol is described. The vinyl functionality is further utilized for the synthesis of 2-(1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol, a precursor for the synthesis of an alkaloid, (±)-Isocyclocelabenzine.(*Scheme 4.3.1*)

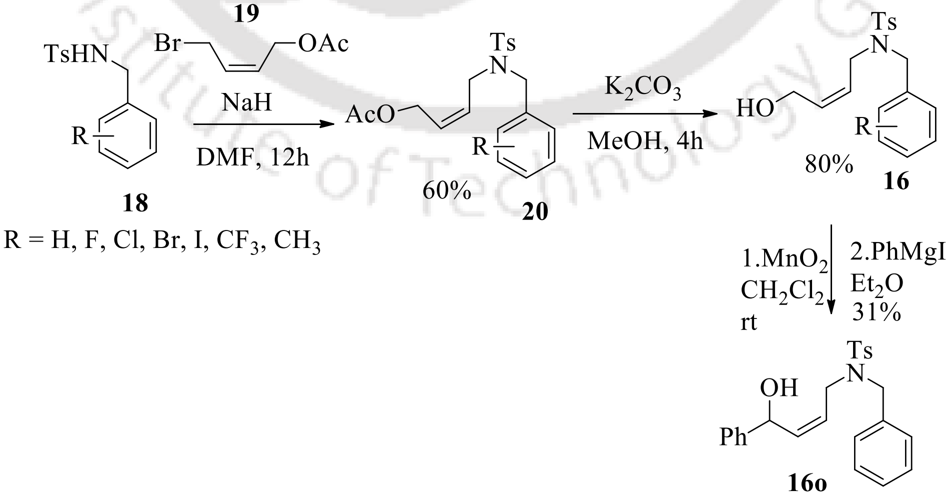


Scheme 4.3.1

4.4. Results and Discussions:

4.4.1. Preparation of benzyl alkenols:

The starting material **16** was synthesized from benzylsulfonamide **18** and bromo acetate **19** in the presence of sodium hydride. The obtained product **20** was then deprotected to give the required compound benzyl-alkenols.[14] The substrate **16o** was prepared by the oxidation of **16** to give an

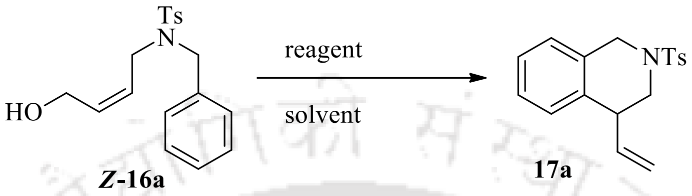


Scheme 4.4.1.1

aldehyde intermediate, which was then reacted with PhMgI (prepared *in situ*) to generate the secondary alcohol **16o**.

4.4.2. Optimization studies:

Table 4.4.2.1. Optimization conditions[a]



Entry	Reagent(equiv)	Solvent	Temp.0 ^{o}C	Time/h	SM(***E*-16a**)[b]	%Yield(**17a**)[c]
1.	InCl$_3$ (0.1)	DCM	0 to rt	12	86	0
2.	InCl$_3$ (0.1)	DCM	40	12	78	10
3.	InCl$_3$ (0.1)	DCE	40	12	75	8
4.	InCl$_3$ (0.1)	DCE	60	12	57	15
5.	InCl$_3$ (0.1)	DCE	80	12	0	97
6.	InCl$_3$ (0.1)	DCE	80	4	0	97
7.	In(OTf)$_3$ (0.1)	DCE	0 to rt	12	82	0
8.	In(OTf)$_3$ (0.1)	DCE	80	12	0	60
9.	Bi(OTf)$_3$ (0.1)	DCM	0 to rt	12	80	0
10.	Bi(OTf)$_3$ (0.1)	DCE	80	12	83	0
11.	BF$_3$•OEt$_2$ (1.2)	DCM	0 to rt	12	85	0
12.	TfOH (1.2)	DCM	0 to rt	12	0	30[d]
13.	*p*-TSA (1.2)	DCM	0 to rt	12	80	0
14.	*p*-TSA (1.2)	DCM	40	12	78	15
15.	*p*-TSA (1.2)	DCE	80	12	0	66

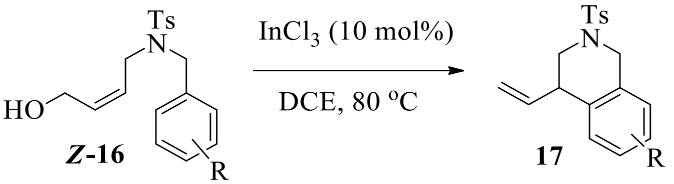
[a] Reaction condition: 3 (1.0 equiv), solvent (4 mL), [b] Starting material recovered (SM) upto 86%, [c] Yield refers to isolated yield, [d] Along with decomposed product.

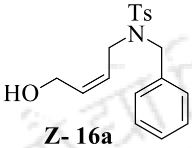
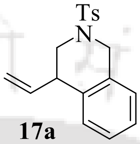
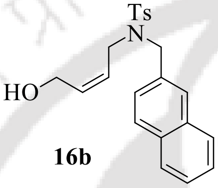
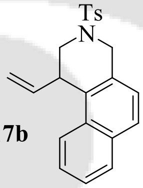
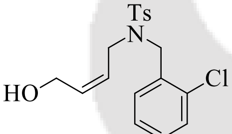
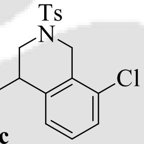
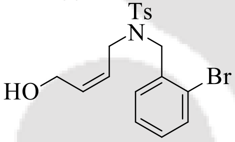
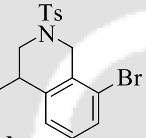
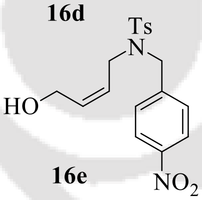
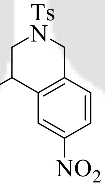
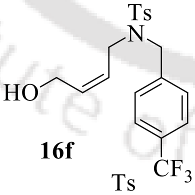
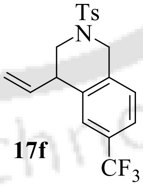
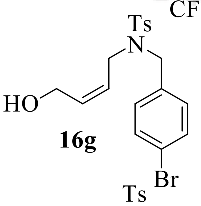
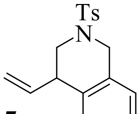
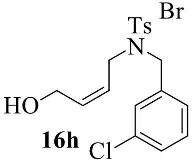
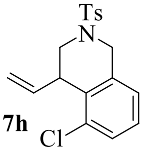
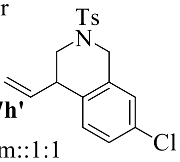
To start with *N*-tethered benzyl-alkenol ***Z*-16a** was treated with 0.1 equivalent of indium(III) chloride (InCl$_3$) at 0 ^{o}C to room temperature in dichloromethane (DCM) for 12 h, but starting material was recovered in 86% yield (*Table 4.4.2.1*, entry 1). When the reaction was performed at 40 °C, in both DCM and dichloroethane (DCE), tetrahydroisoquinoline **17a** was recovered in 10% and 8% yields, respectively (*Table 4.4.2.1*, entry 2-3). Having obtained the desired product, the reaction was then performed in DCE at 80 °C for 12h and to our delight THIQ **17a** was obtained in 97% yield (*Table 4.4.2.1*, entry 5). On careful observation, the same reaction was found to be completed in 4 h with 97% yield (*Table 4.4.2.1*, entry 6). On the other hand, indium(III) triflate ($In(OTf)_3$) in dichloromethane at 0 °C to room temperature failed to give product but starting material was recovered in 82% yield (*Table 4.4.2.1*, entry7), whereas in DCE at 80 °C gave only 60% yield (*Table 4.4.2.1*, entry 8). Other Lewis and Brønsted acids such as bismuth(III) triflate ($Bi(OTf)_3$), *p*-tolune sulphonic acid (*p*-TSA) and triflic acid (TfOH) (*Table 4.4.2.1*, entries 9-15) were found to be inappropriate reagents for this reaction.

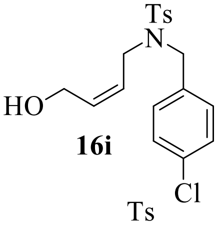
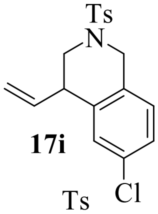
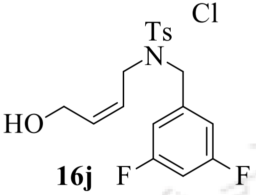
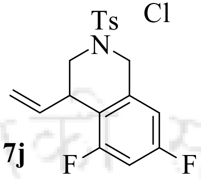
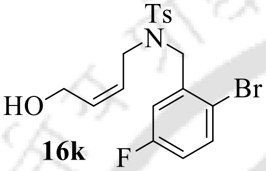
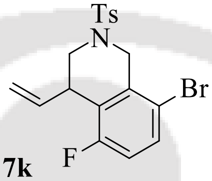
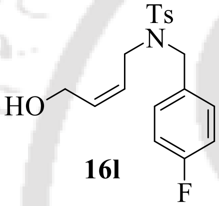
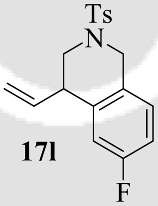
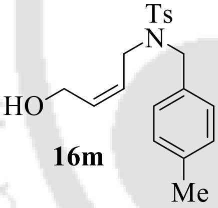
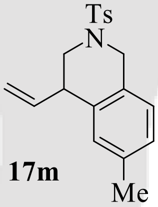
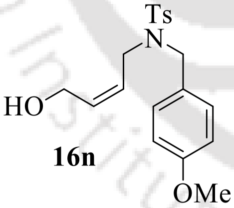
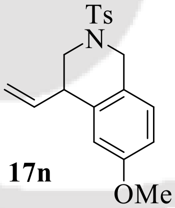
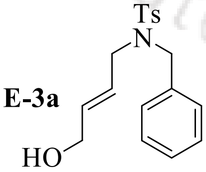
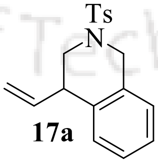
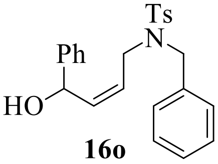
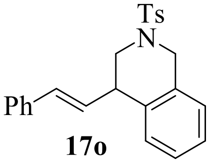
4.4.3. Substrate scope of the reaction:

We examined the substrate scope and the limitations of the reaction (*Table 4.4.2.1*) with the above reaction condition (*Scheme 4.3.1*). Aromatic rings having both electron donating and electron withdrawing groups gave the desired tetrahydroisoquinoline products in very high yield. However, with the variation of electronic effect in the aromatic ring, the yields of the reaction also varied. Electron donating –Me group in the aromatic ring of *N*-tethered aryl-alkenol gave 62% yield. Whereas highly electron withdrawing group ($-NO_2$) and donating group (-OMe) in the aromatic ring did not give the desired product. This may be due to the interaction of the Lewis acid with the oxygen of the $-NO_2$ and -OMe respectively.[15] On the other hand, substrate having highly electron withdrawing $-CF_3$ group in the benzene ring gave 80% yield. Variation in the *ortho*- and *para*- positions in the aromatic ring systems also gave the tetrahydroisoquinoline products in desirable yields. But we did get two isomeric products in the case of *meta*-substituted benzene ring, because of the availability of two sites for C- alkylation. Disubstituted benzene rings on *N*-tethered benzyl-alkenol also gave the desired product (entries 10-11, *Table 4.4.3.1*). The reaction with trans-allylic alcohol ***E*-16a** also works well and gave the desired product with 55% yield (*Table 4.4.3.1*, entry 15). After considering *cis* and *trans*-primary allylic alcohols, the reaction is shifted to secondary allylic alcohol **16o** and gave **17o** in 78% yield (*Table 4.4.3.1*, entry 16).

Table 4.4.3.1: Synthesis of Tetrahydroisoquinolines



Entry	Substrate **16**	Product **17**	% Yield[a]
1.	 **Z- 16a**	 **17a**	97
2.	 **16b**	 **17b**	70
3.	 **16c**	 **17c**	87
4.	 **16d**	 **17d**	76
5.	 **16e**	 **17e**	0
6.	 **16f**	 **17f**	80
7.	 **16g**	 **17g**	87
8.	 **16h**	 **17h**  **17h'** o:m::1:1	77

Entry	Substrate **16**	Product **17**	%Yield^a
9.	 **16i**	 **17i**	92
10.	 **16j**	 **17j**	73
11.	 **16k**	 **17k**	77
12	 **16l**	 **17l**	81
13.	 **16m**	 **17m**	62
14.	 **16n**	 **17n**	0
15.	**E-3a** 	 **17a**	55
16.	 **16o**	 **17o**	78

^{a}Yields refer to isolated yield. ^{b}Ratio is determined by ^{1}H NMR analysis.

4.4.4. Stereochemistry of the vinyl tetrahydroisoquinoline:

The structures of tetrahydroisoquinoline derivatives were determined from the ^{1}H and ^{13}C NMR analysis. In the NMR spectroscopy of compound **17a**, there is a peculiar peak of the exocyclic vinylic protons (5.11-5.16 ppm (m, 2 H), 5.70-5.77 ppm (m, 1 H)), which determined that the obtained compound is different from the starting material **16a** and formation of the vinyl isoquinolines. And also there is disappearance of the broad singlet belonging to hydroxyl proton. The X-ray crystallography of compound **17h** further supported the structures of the compounds. The crude NMR of compound **17c** also shows the reaction is highly regioselective.

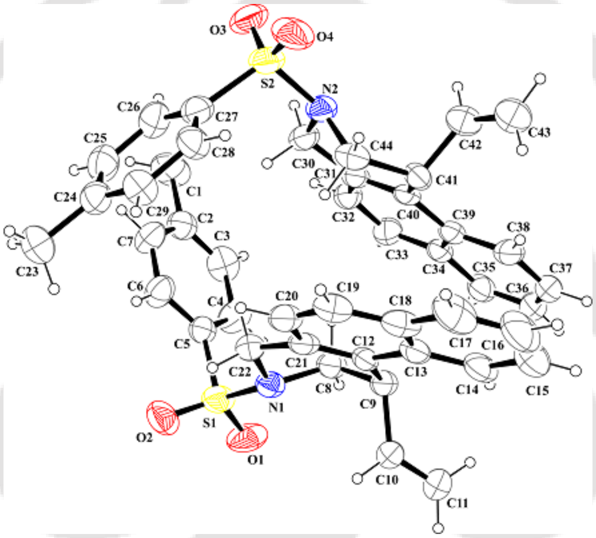
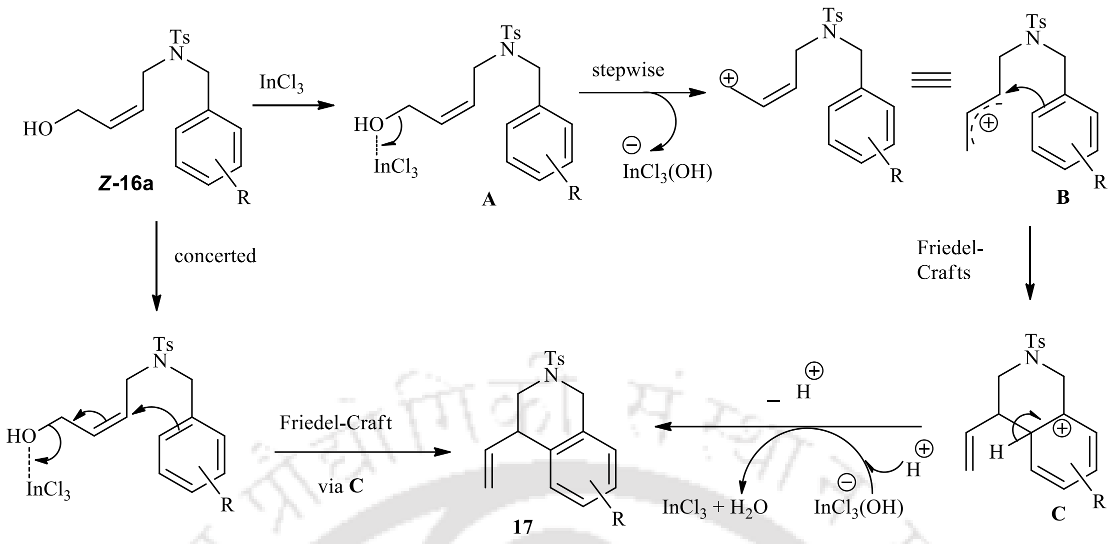


Figure 4.4.4.1. X- ray crystallography of compound **17h** with ellipsoidal probability 30%

4.4.5. Mechanism of the reaction:

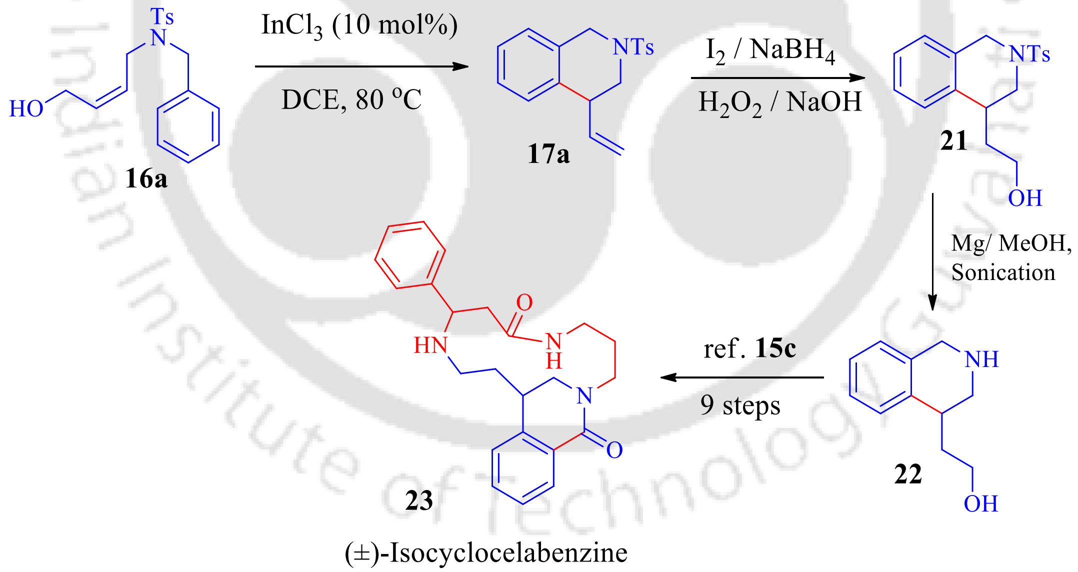
There may be two possible mechanisms for the formation of products, concerted as well as stepwise as shown in *Scheme 4.4.5.1.* Stepwise pathway involved the generation of stable allylic carbocation **B** by the reaction of $InCl_3$ with allylic alcohol, which after nucleophilic attack by aryl group gives carbocation **C**. The carbocation **C** after releasing one proton generated compounds **17**. On the other hand, concerted pathway involved the activation of allylic alcohol for the nucleophilic attack by aryl group simultaneously to generate a carbocation similar to **C** and finally elimination of a proton to produce final product **17**.



Scheme 4.4.5.1

4.4.6. Formal Synthesis of (±)-Isocyclocelabenzine:

To check the further applicability of the methodology, a formal synthesis of (±)-isocyclocelabenzine was undertaken (*Scheme 4.4.6.1*). (±)-Isocyclocelabenzine is a type of spermidine alkaloids, first isolated from *Maytenus mossmbicensis* by Wagner and co-workers.[16] The alkaloid has a 13-membered lactam ring linked to the benzoyl residue of spermidine unit.



Scheme 4.4.6.1

We started with the compound **16a**, whereby its vinylic functionality was oxidized by using hydroboration and oxidation technique to give the primary alcohol **21** with 80%.[17] The proton NMR spectrum of the compound **21** shows the disappearance of three vinylic protons at 5.0-6.0 ppm and appearance of a broad singlet peak at 1.34 ppm confirms the hydroxyl group. The tosyl group of amine was detosylated using Mg/CH_3OH to give the precursor **22** which can be further use for the synthesis of (±)-isocyclocelabenzine **23**.[18] The formation of the precursor **22** can be explained from both proton and carbon NMR spectra. In the proton NMR spectrum the singlet peak at 3.11 ppm for the $–CH_3$ group of the toluene sulfonamide disappeared and a broad singlet of two protons at 3.91 ppm for both –OH and –NH groups appeared. In the ^{13}C spectroscopy, the disappearance of four peaks of toluene sulfonamide group from aromatic region also concluded the formation of detosylated product.

4.5. Conclusion:

In conclusion, we have developed a mild and efficient method for the synthesis of vinyl substituted tetrahydroisoquinoloine derivatives *via* intramolecular cyclization of *N*-tethered benzyl-alkenols in high yields. The methodology is compatible with a wide range of functional groups. The advantage of the reaction is the generation of vinyl functionality regioselectively at such a position which can be used for the formal synthesis of (±)-isocyclocelabenzine alkaloid.

4.6. Experimental Section:

4.6.1. Instrumentation and characterization:

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (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.

4.6.2. Procedure for the Synthesis of 2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (17a):

To a solution of **16a** alcohol (150 mg, 0.45 mmol) in dry 1,2-dichloroethane was added indium(III) chloride (10 mol%, 10 mg) at 80 ^{o}C. The reaction mixture was refluxed for 3 h. After the completion of the reaction, as determined by TLC, the reaction mixture was washed with saturated sodium bicarbonate and brine solutions, extracted with EtOAc (2 x 15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product of **17a**, which was purified by column chromatography using ethyl acetate and hexane as eluents (hexane: ethylacetate:: 9: 1).

4.6.3. Synthesis of 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol (21):

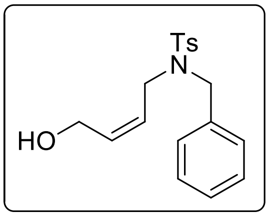
In a septum-capped round bottom flask, $NaBH_4$, (185 mg, 4.75 mmol) was added to dry THF (15 mL). Iodine (360 mg, 2.85 mmol) in dry THF (10 mL) was added to it under nitrogen atmosphere at 0 ^{o}C for 2 h. A THF solution of compound **17a** (600 mg, 1.9 mmol) was added and the reaction mixture was stirred for 12 h at 25 ^{o}C. It was quenched with water (2 mL) and THF (10 mL) and oxidized with H_2O_2 (30%, 10 mL)/NaOH (3N, 10 mL). The organic layer was extracted using diethylether (30 mL x 2) and the combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by column chromatography gave the desired compound **21** (80%) as a colourless gum. R_f= 0.55 (hexane:ethylacetate 3:2).

4.6.4. Synthesis of 2-(1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol (22) :

To a solution of 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol (**21**) (180 mg, 0.48 mmol,) in anhydrous methanol added Mg turnings (230 mg, 9.6 mmol,) and the reaction mixture was stirred under sonication for 5 h, at room temperature. After the completion of the reaction, the reaction mixture was quenched with brine, extracted with chloroform, dried over sodium sulfate and concentrated *in vacuo*. The compound was purified by colomn chromatography on silica gel (DCM: CH_3OH = 9: 1) to give the product **22** (60 mg, 70 % yield) as a colourless liquid.

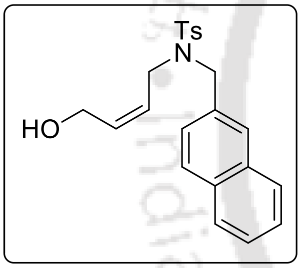
4.7. Charactererization Data:

(Z)-N-benzyl-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16a****:*



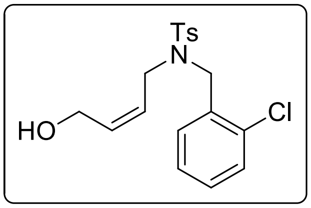
White solid; R_f (hexane/ EtOAc 3:2) 0.55; m. p. 65-68 ^{o}C, yield: 380 mg, 80%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.60 (brs, 1 H), 2.41 (s, 3 H), 3.78 (d, *J* = 7.2 Hz, 2 H), 3.88 (d, *J* = 6.8 Hz, 2 H), 4.32 (s, 2 H), 5.21-5.24 (m, 1 H), 5.56-5.61 (m, 1 H), 7.27-7.30 (m, 5 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 43.8, 51.4, 58.0, 126.4, 127.4, 128.2, 128.6, 128.8, 130.0, 132.5, 136.1, 137.2, 143.7; IR (KBr, neat) 3406, 2921, 2864, 1598, 1495, 1340, 1158, 1091, 1028, 932, 816, 766, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_3S$ (M + H)$^+$ 332.1320, found 332.1307.

(Z)-N-(4-hydroxybut-2-en-1-yl)-4-methyl-N-(naphthalen-2-ylmethyl)benzenesulfonamide ***16b****:*



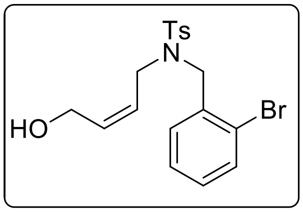
White solid; R_f (hexane/ EtOAc 3:2) 0.50; m. p. 70-73 ^{o}C, yield 300 mg, 78%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.85 (brs, 1 H), 2.43 (s, 3 H), 3.80 (d, *J* = 7.2 Hz, 2 H), 3.83 (d, *J* = 4.8 Hz, 2 H), 4.46 (s, 2 H), 5.19-5.22 (m, 1 H), 5.53-5.60 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.41 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.45 (dd, *J* = 7.2, 3.2 Hz, 2 H), 7.62 (s, 1 H), 7.72-7.81 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.8, 51.5, 57.9, 126.2, 126.3, 126.4, 126.5, 127.4, 127.5, 127.8, 127.9, 128.7, 130.0, 132.6, 133.1, 133.3, 133.5, 137.2, 143.7; IR (KBr, neat) 3420, 2922, 2865, 1598, 1439, 1339, 1158, 1090, 1017, 917, 816, 750, 660, 572 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}NO_3S$ (M + H)$^+$ 382.1477, found 382.1471.

(E)-N-(2-chlorobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16c****:*



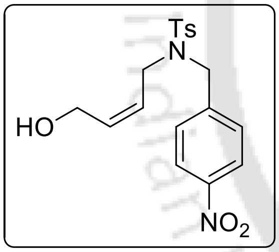
Yellow gum; R_f (hexane/ EtOAc 3:2) 0.50; yield 400 mg, 89%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.87 (brs, 1 H), 2.44 (s, 3 H), 3.85 (d, *J* = 7.2 Hz, 2 H), 3.95 (d, *J* = 6.4 Hz, 2 H), 4.45 (s, 2 H), 5.23-5.28 (m, 1 H), 5.58-5.64 (m, 1 H), 7.27 (m, 5 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 44.8, 48.5, 58.0, 126.0, 127.3, 127.4, 129.1, 129.6, 130.0, 130.2, 132.9, 133.3, 133.9, 136.8, 143.8; IR (KBr, neat) 3441, 2923, 2867, 1638, 1444, 1340, 1158, 1091, 1036, 911, 755, 657, 550 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}ClNO_3S$ $(M + H)^+$ 366.0931, found 366.0937.

(Z)-N-(2-bromobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16d:***



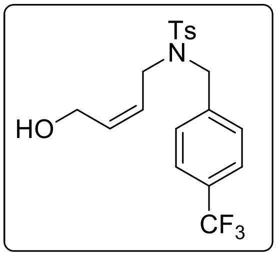
White gum; R$_f$ (hexane/ EtOAc 3:2) 0.50; yield 366 mg, 81%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.85 (brs, 1 H), 2.44 (s, 3 H), 3.85 (d, *J* = 7.2 Hz, 2 H), 3.94 (d, *J* = 6.4 Hz, 2 H), 4.43 (s, 2 H), 5.21-5.28 (m, 1 H), 5.59-5.62 (m, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.26-7.34 (m, 3 H), 7.50-7.54 (m, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 44.9, 51.2, 58.1, 123.3, 125.9, 127.4, 127.9, 129.4, 130.1, 130.2, 132.9, 133.0, 135.5, 136.9, 143.9; IR (KBr, neat) 3409, 2923, 2859,1596, 1441, 1340, 1158, 1092, 1024, 911, 813, 754, 659, 551 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}BrNO_3S$ $(M + H)^+$ 410.0426, found 410.0438.

(E)-N-(4-hydroxybut-2-en-1-yl)-4-methyl-N-(4-nitrobenzyl)benzenesulfonamide ***16e:***



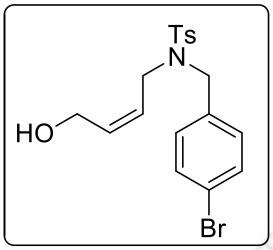
Yellow gum; R$_f$ (hexane/ EtOAc 3:2) 0.40; yield 320 mg, 75%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.78 (brs, 1 H), 2.46 (s, 3 H), 3.85 (d, *J*= 7.2, 2 H), 3.97 (d, *J* = 6.4 , 2 H), 4.40 (s, 2 H), 5.19-5.24 (m, 1 H), 5.62-5.68 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 8.17 (d, *J*= 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 44.8, 50.7, 58.0, 124.0, 125.8, 127.4, 129.1, 130.2, 133.3, 136.7, 144.2, 144.3, 147.8; IR (KBr, neat) 3405, 2925, 2862, 1654, 1522, 1346, 1158, 1091, 1017, 914, 771, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}N_2O_5S$ $(M + H)^+$ 377.1171 found 377.1216.

(E)-N-(4-hydroxybut-2-en-1-yl)-4-methyl-N-(4-(trifluoromethyl)benzyl)benzenesulfonamide ***16f:***



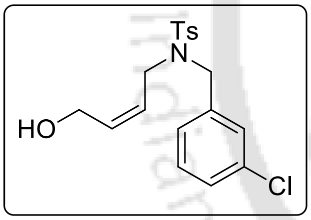
White solid; R$_f$ (hexane/ EtOAc 3:2) 0.48; m. p. 85-87 °C, yield 350 mg, 77%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.71 (brs, 1 H), 2.45 (s, 3 H), 3.82 (d, *J* = 7.2 Hz, 2 H), 3.96 (d, *J* = 4.4 Hz, 2 H), 4.37 (s, 2 H), 5.21-5.24 (m, 1 H), 5.61-5.68 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J*= 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 44.4, 50.9, 58.0, 122.9, 125.7, 125.76, 125.8, 125.84, 126.1, 127.4, 128.7, 130.1, 133.0, 137.0, 140.6, 144.0; IR (KBr, neat) 3422, 2925, 2865, 1619, 1420, 1326, 1159, 1122, 1066, 1018, 914, 816, 659, 548 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}F_3NO_3S$ (M + H)$^+$ 400.1194, found 400.1213.

(Z)-N-(4-bromobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16g****:*



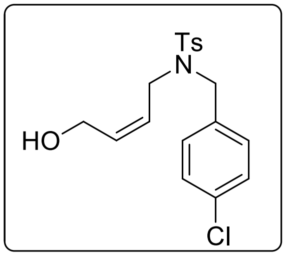
White solid; R$_f$ (hexane/ EtOAc 3:2) 0.55; m. p. 80-83 ^{o}C, yield 350 mg, 78%; ^{1}H NMR (400MHz, CDCl$_3$) δ 1.74 (brs, 1 H)2.45 (s, 3 H), 3.79 (d, *J* = 6.2, 2H), 3.95 (d, *J* = 6.0 Hz, 2 H), 4.26 (s, 2 H), 5.18-5.23 (m, 1 H), 5.60-5.66 (m, 1 H), 7.16 (d *J* = 6.0 Hz, 2 H), 7.33 (d, *J* = 6.0 Hz, 2 H), 7.44 (d, *J* = 6.0 Hz, 2 H), 7.73, d, *J* = 6.0 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 44.1, 50.7, 58.0, 122.1, 126.2, 127.4, 130.1, 130.2, 131.9, 132.8, 135.4, 137.1, 143.9; IR (KBr, neat) 3397, 2922, 2868, 1596, 1488, 1407, 1339, 1158, 1091, 1012, 910, 814, 767, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}BrNO_3S$ (M + H)$^+$ 410.0426, found 410.0433.

(E)-N-(3-chlorobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16h****:*



Yellow oil; R$_f$ (hexane/ EtOAc 3:2) 0.50; yield 370 mg, 80%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.10 (brs, 1 H), 2.44 (s, 3 H), 3.80 (d, *J*= 7.2, 2 H), 3.93 (d, *J* = 6.4, 2 H), 4.27 (s, 2 H), 5.16-5.22 (m, 1 H), 5.59-5.65 (m, 1 H), 7.15-7.17 (m, 1 H), 7.22 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.7, 44.1, 51.0, 57.9, 125.8, 126.6, 127.3, 128.2, 128.4, 130.0, 133.0, 134.6, 136.9, 138.3, 143.9; IR (KBr, neat) 3450, 2924, 2825, 1597, 1577, 1437, 1340, 1204, 1157, 1017, 921, 860, 814, 681, 657, 550 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}ClNO_3S$ (M + H)$^+$ 366.0931, found 366.0916.

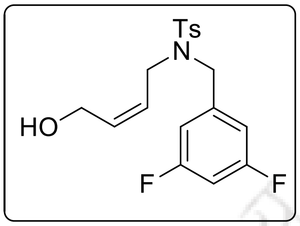
(Z)-N-(4-chlorobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16i****:*



Colourless oil; R$_f$ (hexane/ EtOAc 3:2) 0.50; m. p. 80-82 ^{o}C, yield 320 mg, 85%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.15 (brs, 1 H), 2.44 (s, 3 H), 3.78 (d, *J* = 7.0 Hz, 2 H), 3.93(d, *J* = 6.8 Hz, 2 H), 4.27(s, 2 H), 5.11-5.18 (m, 1 H), 5.70-5.88 (m, 1 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C

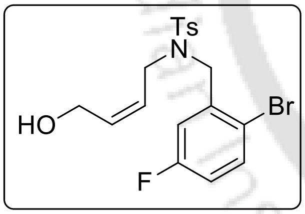
NMR (100 MHz, $CDCl_3$) δ 21.7, 44.0, 50.5, 57.9, 126.0, 127.3, 128.9, 129.8, 130.0, 132.9, 133.8, 134.8, 137.0, 143.8; IR (KBr, neat) 3417, 2923, 2867, 1597, 1492, 1445, 1336, 1158, 1090, 1015, 911, 814, 657, 566 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}ClNO_2S$ $(M + H)^+$ 366.0926, found 366.0928.

(Z)-N-(3,5-difluorobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16j:***



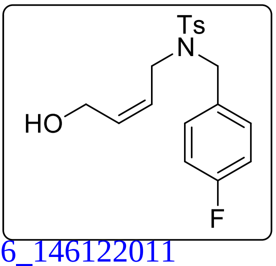
Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 350 mg, 77%; ^1H NMR (400MHz, $CDCl_3$) δ 2.06 (brs, 1 H), 2.36 (s, 3 H), 3.75 (d, *J* = 7.2 Hz, 2 H), 3.89 (d, *J* = 6.4 Hz, 2 H), 4.19 (s, 2 H), 5.11-5.14 (m, 1 H), 5.53-5.58 (m, 1 H), 6.59-6.64 (m, 1 H), 6.74 (d, *J* = 6.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 44.5, 50.5, 57.9, 103.4 (t, *J* = 25.0 Hz), 110.1 (d, *J* = 26 Hz) , 125.7, 127.3, 130.1, 133.2, 136.8, 140.8, 144.1, 163.2 (d, *J* = 248 Hz), 163.3 (d, *J* = 247 Hz) ; IR (KBr, neat) 3426, 2924, 2853, 1625, 1597, 1460, 1341, 1159, 1118, 992, 813, 660 HRMS (ESI) calcd. for $C_{18}H_{20}F_2NO_3S$ $(M + H)^+$ 368.1132, found 368.1134.

(Z)-N-(2-bromo-5-fluorobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16k****:*



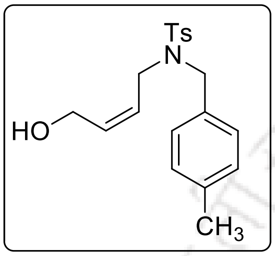
Colourless gum; R_f (hexane/ EtOAc 3:2) 0.50; yield 300 mg, 66%; ^1H NMR (400MHz, $CDCl_3$) δ 2.02 (brs, 1 H), 2.45 (s, 3 H), 3.89 (d, *J* = 7.2 Hz, 2 H), 4.00 (d, *J* = 6.6 Hz, 2 H), 4.38 (s, 2 H), 5.25-5.30 (m, 1 H), 5.62-5.67 (m, 1 H), 6.88 (dt, , *J* = 5.24 and 3.04 Hz, 1 H), 7.25-7.29 (m, 1 H), 7.35 (d, , *J* = 8.0 Hz, 2 H), 7.43-7.47 (m, 1 H), 7.75 (d, , *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 45.3, 51.1, 58.1, 116.6 (d, *J* = 22 Hz), 116.9, 117.1, 125.8, 127.4, 130.2, 133.4, 134.1, 134.2, 136.7, 138.2, 138.3, 144.1, 161.5 (d, *J* = 246.0 Hz); IR (KBr, neat) 3357, 2923, 2849, 1598, 1578, 1466, 1341, 1158, 1090, 1028, 813, 658, 556 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}BrFNO_3S$ $(M + H)^+$ 428.0331, found 428.0339.

(Z)-N-(4-fluorobenzyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide ***16l****:*



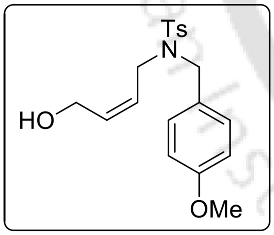
Colourless oil; R_f (hexane/ EtOAc 3:2) 0.50; yield 345 mg, 75%; ^1H NMR (400MHz, $CDCl_3$) δ 2.10 (brs, 1 H), 2.44 (s, 3 H), 3.78 (d, *J*= 6.8 Hz, 2 H), 3.93 (d, *J*= 6.8 Hz, 2 H), 4.27 (s, 2 H), 5.16-5.22 (m, 1 H), 5.58-5.63 (m, 1 H), 6.96-7.01 (m, 2 H), 7.23-7.26 (m, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.9, 50.6, 57.9, 115.6 (d, *J*= 21.0 Hz) 126.0, 127.3, 130.0, 130.1, 130.2, 131.8, 131.9, 132.7, 137.0, 143.8, 162.5 (d, *J*= 244.9 Hz); IR (KBr, neat) 3423,2924, 2855, 1603, 1509, 1339, 1226, 1158, 1091, 909, 816, 658, 548 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}FNO_3S$ $(M + H)^+$ 350.1226, found 350.1215.

(E)-N-(4-hydroxybut-2-en-1-yl)-4-methyl-N-(4-methylbenzyl)benzenesulfonamide ***16m****:*



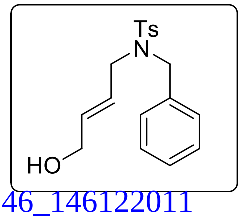
Colourless oil; R$_f$ (hexane/ EtOAc 3:2) 0.45; yield 390 mg, 85%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.09 (brs, 1 H), 2.31 (s, 3 H), 2.42 (s, 3 H), 3.76 (d, *J* = 7.2 Hz, 2 H), 3.89 (d, *J* = 6.8 Hz, 2 H), 4.26 (s, 2 H), 5.16-5.23 (m, 1 H), 5.22-5.61 (m, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.13(d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.6, 43.6, 50.9, 57.9, 126.2, 127.3, 128.5, 129.4, 129.9, 132.5, 132.9, 137.2, 137.8, 143.6; IR (KBr, neat) 3444, 2923, 2864, 1597, 1513, 1438, 1340, 1157, 1090, 1019, 909, 814, 657, 577 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_3S$ $(M + H)^+$ 346.1477, found 346.1470.

(Z)-N-(4-hydroxybut-2-en-1-yl)-N-(4-methoxybenzyl)-4-methylbenzenesulfonamide ***16n :***



Colourless oil; R$_f$ (hexane/ EtOAc 3:2) 0.40; yield 320 mg, 71%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.74 (brs, 1 H), 2.45 (s, 3 H), 3.77 (d, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.93 (d, *J* = 6.4 Hz, 2 H), 4.26 (s, 2 H), 5.17-5.24 (m, 1 H), 5.58-5.64 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.6, 50.8, 55.5, 58.0, 114.2, 126.6, 127.4, 127.9, 129.9, 130.0, 132.4, 137.3, 143.7, 159.6; IR (KBr, neat) 3451, 2924, 2855, 1612, 1511, 1458, 1336, 1249, 1156, 1093, 1031, 906, 814, 658, 548 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1427.

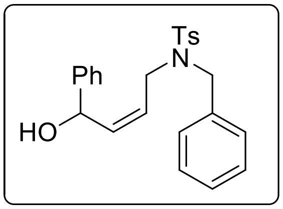
*(E)-N-(4-hydroxybut-2-en-1-yl)-N-(4-methoxybenzyl)-4-methyl-benzenesulfonamide (****E-16a****):*



Colourless oil; Rf (hexane/ EtOAc 3:2) 0.40; yield 332 mg, 70%; ^{1}H NMR (600MHz, $CDCl_3$) δ 2.44 (s, 3 H), 3.73 (d, *J* = 6.5 Hz, 2 H), 3.93 (d, *J* =

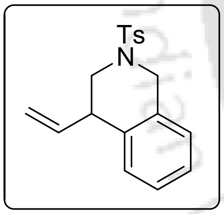
5.2Hz, 2 H), 3.93 (d, *J* = 6.4 Hz, 2 H), 4.26 (s, 2 H), 5.17-5.24 (m, 1 H), 5.58-5.64 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H); IR (KBr, neat) 3131, 3013, 2859, 1598, 1401, 1339, 1157, 1092, 1013, 896, 730, 550 cm^{-1}.

*(Z)-N-benzyl-N-(4-hydroxy-4-phenylbut-2-en-1-yl)-4-methylbenzenesulfonamide (**16o**):*



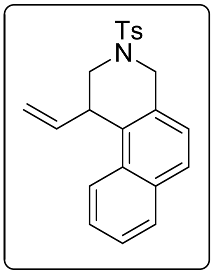
Colourless oil; Rf (hexane/ EtOAc 4:1) 0.60; yield 46 mg, 31%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.44 (s, 3 H), 3.77 (dd, *J* = 6.8, 7.0 Hz, 2 H), 4.23 (d, *J* = 14.8 Hz, 1 H), 4.33 (d, *J* = 14.8 Hz, 1 H), 5.00 (d, *J* = 5.4 Hz, 1 H), 5.39-5.46 (m, 1 H), 5.55 (dd, , *J* = 15.4, 6.2 Hz, 1 H), 7.19 (d, *J* = 7.2 Hz, 4 H), 7.25-7.34 (m, 8 H), 7.71 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 49.0, 51.2, 74.4, 125.6, 126.3, 127.5, 128.0, 128.1, 127.6, 128.7, 128.8, 130.0, 136.4, 137.1, 137.4, 142.4, 143.6; IR (KBr, neat) 3426, 2843, 1610, 1448, 1323, 1253, 1150, 1045, 1012, 810, 650 cm-1; Anal. calcd for $C_{24}H_{23}NO_2S$: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.84; H, 6.25; N, 3.48.

*2-Tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline **17a**:*



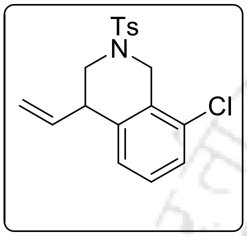
Yellow solid; R$_f$ (hexane/ EtOAc 9:1) 0.60; m. p. 80-82 ^{o}C, yield 137 mg, 97%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.35 (s, 3 H), 3.07 (dd, *J* = 4.8, 6.8 Hz, 1 H), 3.36 (dd, *J* = 4.8 and 6.8 Hz, 1 H), 3.56 (dt, *J* = 5.6 and 7.2 Hz, 1 H), 4.16 (q, *J* = 13.2, 14.8 Hz, 2 H), 5.11-5.16 (m, 2 H), 5.70-5.77 (m, 1 H), 6.95-6.97 (m, 1 H), 7.08-7.09 (m, 3 H), 7.26(d, *J* = 8.4 Hz, 2 H), 7.65(d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.7, 43.6, 47.9, 48.7, 117.8, 126.5, 127.0, 127.1, 128.0, 129.1, 129.9, 131.5, 133.3, 135.3, 138.7, 144.0; IR (KBr, neat) 2964, 2922, 2849, 1598, 1493, 1353, 1165, 1091, 956, 813, 743 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}NO_2S$ (M + H)$^+$ 314.1215, found 314.1229.

*3-Tosyl-1-vinyl-1,2,3,4-tetrahydrobenzo[f]isoquinoline **17b** :*



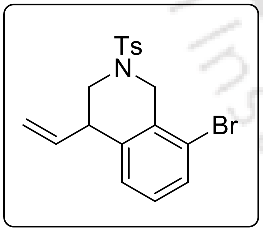
Brown solid; R$_f$ (hexane/ EtOAc 9:1) 0.50; m. p. 160-162 ^{o}C, yield 100 mg, 70%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.42 (s, 3 H), 2.90 (dd, *J* = 3.5 and 7.8 Hz, 1 H), 3.97 (d, *J* = 15.4 Hz, 1 H), 4.06-4.15 (m, 2 H), 4.77 (d, *J* = 15.2 Hz, 1 H), 4.99 (dt, *J* = 1.3 and 17.2 Hz, 1 H), 5.19 (dt, *J* = 1.2 and10.2 Hz, 1 H), 6.10-6.17 (m, 1 H), 7.13 (d, *J* = 8.5 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.42-7.52 (m, 2 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.76-7.80 (m, 3 H), 7.93 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.8, 51.5, 57.9, 126.3, 126.4, 126.5, 127.3, 127.5, 127.8, 127.9, 128.7, 130.0, 132.6, 133.1, 133.2, 133.5, 137.2, 143.7; IR (KBr, neat) 2921, 2851, 1597, 1458, 1341, 1307, 1163, 1090, 810, 746, 661 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}NO_2S$ $(M + H)^+$ 364.1366, found 364.1362.

8-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17c****:*



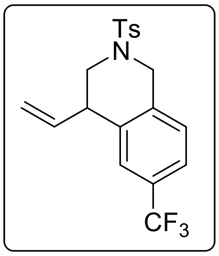
Brown solid; R_f (hexane/ EtOAc 9:1) 0.45; m. p. 100-102 °C, yield 125 mg, 87%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.17 (dd, *J* = 5.2 and 6.4 Hz, 1 H), 3.38 (dd, *J* = 4.4 and 7.2 Hz, 1 H), 3.61-3.64 (m, 1 H), 4.18 (d, *J* = 16.0 Hz, 1 H), 4.24, (d, *J* = 16.0 Hz , 1 H), 5.20 (s, 1 H), 5.19-5.24 (m, 2 H), 7.08 (m, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.19-7.22 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.7, 46.4, 48.1, 118.2, 127.6, 127.8, 127.9, 129.7, 130.0, 132.2, 133.1, 137.8, 138.2, 144.1; IR (KBr, neat) 3070, 2976, 2921, 2849, 1597, 1443, 1352, 1164, 1093, 1058, 950, 814, 779, 662, 549 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$ 348.0820, found 348.0827.

8-Bromo-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17d*** *:*



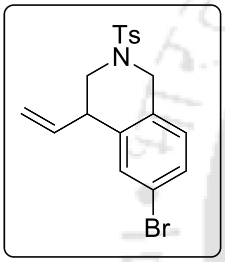
Brown solid; R_f (hexane/ EtOAc 9:1) 0.45; m. p. 104-106 °C, yield 115mg, 80%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.17 (dd, *J* = 4.8 and 6.8 Hz, 1 H), 3.37 (dd, *J* = 4.4 and 7.2 Hz, 1 H), 3.61-3.64 (m, 1 H), 4.12-4.17 (m, 2 H), 5.22 (d, *J* = 14.0 Hz, 2 H), 5.75-5.83 (m, 1 H), 7.5 (t, *J* = 7.0 Hz, 1 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 43.9, 48.2, 49.0, 118.2, 122.6, 127.9, 128.3, 128.4, 130.1, 131.0, 131.1, 131.2, 133.1, 138.1, 138.3, 144.2; IR (KBr, neat) 3068, 2921, 2853, 1597, 1563, 1438, 1350, 1163, 1091, 958, 813, 661, 550 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}BrNO_2S$ $(M + H)^+$ 392.0320, found 392.0307.

2-Tosyl-6-(trifluoromethyl)-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17f****:*



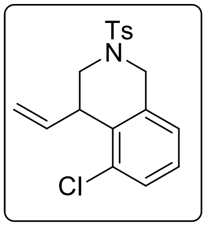
Brown solid; R_f (hexane/ EtOAc 9:1) 0.45; m. p. 90- 92 °C, yield 117 mg, 82%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.12 (dd, J = 4.8 and 7.0 Hz, 1 H), 3.49 (dd, J = 4.6 and 7.2 Hz, 1 H), 3.68 (dd, J = 6.6 and 7.0 Hz, 1 H), 4.22 (d, J = 15.6 Hz, 1 H), 4.33 (d, J = 15.6 Hz, 1 H), 5.24-5.29 (m, 2 H), 5.74-5.84 (m, 1 H), 7.17 (d, J = 8.3 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.41-7.43 (m, 2 H), 7.73 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 44.4, 50.9, 58.0, 125.8 (q, J = 15.0 Hz), 126.1, 127.4, 128.7, 130.1, 132.9, 137.0, 140.6, 144.0 ; IR (KBr, neat) 2927, 2849, 1598, 1458, 1423, 1336, 1166, 1123, 817, 661, 568 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{19}F_3NO_2S$ $(M + H)^+$ 382.1084, found 382.1106.

6-Bromo-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17g****:*



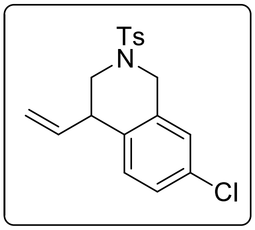
White solid; R_f (hexane/ EtOAc 9:1) 0.66; m. p. 128-130 °C, yield 135 mg, 87%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.06 (dd, J = 4.8 and 6.8 Hz, 1 H), 3.44 (dd, J = 5.2 and 6.8 Hz, 1 H), 3.58-3.62 (m, 1 H), 4.09 (d, J = 15.2 Hz, 1 H), 4.22 (d, J = 15.2 Hz, 1H), 5.22-5.26 (m, 2 H), 5.71-5.80 (m, 1 H), 6.91 (d, J = 8.8 Hz, 1 H), 7.26-7.29 (m, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.5, 47.6, 48.4, 77.6, 118.7, 120.8, 127.9, 128.2, 130.0, 130.1, 130.6, 132.0, 133.1, 137.6, 137.8, 144.1; IR (KBr, neat) 2972, 2923, 2847, 1479, 1456, 1343, 1162, 1089, 806, 709, 652 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}BrNO_2S$ $(M + H)^+$ 392.0320, found 392.0311.

7-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17h:***



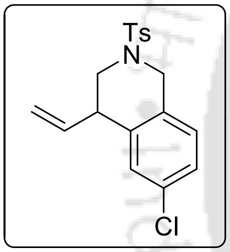
Brown solid; R_f (hexane/ EtOAc 9:1) 0.55; m. p. 80- 81 °C, yield 50 mg, 34%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.11 (dd, J = 7.2, 4.8 Hz, 1 H), 3.43 (dd, J = 4.8 and 7.2 Hz, 1 H), 3.59 (dd, J= 6.0 and 6.8 Hz, 1 H), 4.13 (d, J =15.2 Hz, 1 H), 4.23 (d, J = 15.2 Hz, 1 H) 5.21-5.23 (m, 2 H), 5.72-5.81 (m, 1 H), 7.03 (s, 1 H), 7.06-7.14 (m, 2 H), 7.34 (d, , J = 8.0 Hz, 2 H), 7.72 (d, , J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.2, 47.7, 48.2, 118.3, 126.4, 127.4, 128.0, 130.0, 130.6, 132.7, 133.3, 133.8, 138.2, 144.2; IR (KBr, neat) 2976, 2922, 2856, 1597, 1458, 1352, 1164, 1091, 964, 814, 753, 670, 586 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$ 348.0820, found 348.0819.

5-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17h'*****:**



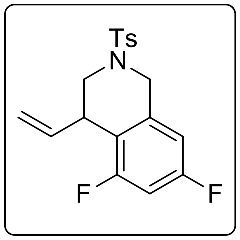
Brown solid; R_f (hexane/ EtOAc 9:1) 0.50; m. p. 108-110 ^{o}C, yield 48 mg, 33%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.42 (s, 3 H), 2.74 (dd, *J* = 3.4 and 8.2, 1 H), 3.76-3.84 (m, 2 H), 3.99 (d, *J* = 11.6 Hz, 1 H), 4.66 (d, *J* = 15.2 Hz, 1 H), 4.99 (d, *J* = 17.2 Hz, 1 H), 5.17 (d, *J* = 10.28 Hz, 1 H), 5.92-6.00 (m, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H) 7.34 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.7, 40.4, 47.4, 48.4, 117.4, 125.3, 127.9, 128.0, 128.1, 128.3, 130.0, 133.2, 133.0, 133.9, 134.9, 137.1, 144.1 ; IR (KBr, neat) 2921, 2850, 1596, 1458, 1444, 1351, 1165, 1091, 956, 816, 777, 657, 549 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_2S$ (M + H)$^+$ 348.0820, found 348.0829.

6-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17i****:*



White solid; R_f (hexane/ EtOAc 9:1) 0.66; m. p. 133-135 ^{o}C, yield 125 mg, 92%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.36 (s, 3 H), 2.99 (dd, *J* = 4.4 and 7.2 Hz 1 H), 3.38 (dd, *J* = 4.8 and 6.8 Hz 1 H), 3.53 (dt, *J* = 6.0 and 7.2 Hz, 1 H), 4.05 (d, *J* = 14.8 Hz, 1 H), 4.17 (d, *J*= 14.8 Hz, 1 H), 5.15-5.19 (m, 2 H), 5.65-5.72 (m, 1 H), 6.9 (d, *J* = 8.8, 1 H), 7.06-7.08 (m, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H),7.67 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.8, 43.6, 47.6, 48.5, 118.7, 127.3, 127.9, 128.0, 129.0, 130.0, 130.1, 133.0, 137.2, 137.8, 144.2; IR (KBr, neat) 2925, 1843, 1639, 1597, 1486, 1457, 1345, 1162, 1093, 1050, 811, 772, 684, 658, 575 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_2S$ (M + H)$^+$ 348.0825, found 348.0834.

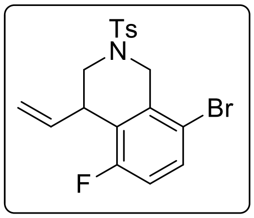
5,7-Difluoro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17j*** *:*



Brown solid; R_f (hexane/ EtOAc 9:1) 0.45; m. p. 128-130 ^{o}C, yield 105 mg, 73%; ^{1}H NMR (400MHz, CDCl$_3$) δ 2.43 (s, 3 H), 2.80 (dd, *J* = 4.0 and 8.0 Hz, 1 H), 3.68-3.71 (m, 1 H), 3.78 (d, *J* = 15.6, 1 H), 3.85 (d, *J* = 12.0 Hz, 1 H), 4.59 (d, *J* = 15.6 Hz, 1 H), 5.07 (dd, *J* = 1.0 and 16.4 Hz, 1 H), 5.14 (d, *J* = 10.4 Hz, 1 H), 5.93-5.98 (m, 1 H), 6.60-6.68 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.7, 36.7, 47.4, 48.1, 102.6 (t, *J*= 25.0 Hz) , 108.8 (q, *J* = 18.2 Hz), 116.7, 119.2, 119.3, 127.9, 130.0, 133.0, 135.0, 135.1, 137.5, 144.2, 161.2 (dd, *J* = 12.2 and 248.5 Hz), 161.7 (dd, *J* = 12,8 and 246.2 Hz); IR

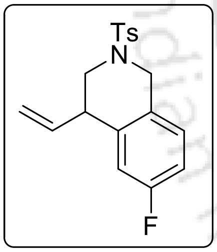
(KBr, neat) 3084, 2923, 2853, 1627, 1598, 1489, 1441, 1344, 1161, 1118, 994, 949, 850, 815, 765, 664, 554 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}F_2NO_2S$ $(M + H)^+$ 350.1026, found 350.1037.

8-Bromo-5-fluoro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17k****:*



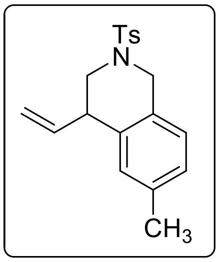
Yellow solid; R$_f$ (hexane/ EtOAc 9:1) 0.50; m. p. 120-123 °C, yield 115 mg, 80%; ^{1}H NMR (600MHz, $CDCl_3$) δ 2.45 (s, 3 H), 2.75 (d, *J* = 6.8 Hz, 1 H), 3.63 (d, *J* =10.4 Hz, 1 H), 3.75-3.78 (s, 1 H), 3.92 (d, *J* =7.6 Hz, 1 H), 4.66 (d, *J* =10.8 Hz, 1 H), 5.11 (d, *J* = 11.2 Hz, 1 H), 5.19 (d, *J* = 6.8 Hz, 1 H), 5.99-6.03 (m, 1 H), 6.86 (t, *J* = 6.0 Hz, 1 H), 7.37-7.42 (m, 3 H), 7.75-7.78 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 37.3, 47.5, 48.7, 115.4 (d, *J* = 22.5 Hz), 116.5, 116.6, 117.2, 125.9, 126.0, 127.9, 130.1, 131.9, 132.0, 133.0, 133.1, 133.2, 137.1, 144.2, 160.1 (d, *J* = 247.5 Hz); IR (KBr, neat) 2923, 2853, 1597, 1456, 1354, 1339, 1254, 1165, 1091, 1028, 955, 814, 773, 658, 549 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}BrFNO_2S$ $(M + H)^+$ 410.0221, found 410.0241.

6-Fluoro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17l:***



Yellow solid; R$_f$ (hexane/ EtOAc 9:1) 0.6; m. p. 92-94 °C, yield 125 mg, 81%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.05 (dd, *J* = 4.4 and 7.2 Hz, 1 H), 3.59-3.61 (m, 1 H), 3.61 (dd, *J* = 5.6 and 7.2 Hz, 1 H), 4.11 (d, *J* = 14.8 Hz, 1 H), 4.26 (d, *J* = 14.8 Hz, 1 H), 5.22-5.26 (m, 2 H), 5.74-5.79 (m, 1 H), 6.84-6.89 (m, 2 H), 6.99-7.02 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.7, 47.6, 48.4, 114.3 (d, *J*= 21.7 Hz), 115.5 (d, *J*= 21.6 Hz), 118.6, 127.1, 127.2, 127.9, 128.0, 128.1, 129.9, 133.2, 137.5, 137.9, 144.1, 161.7 (d, *J*= 243.9 Hz); IR (KBr, neat) 2972, 2923, 2847, 1479, 1456, 1343, 1162, 1089, 806, 709, 652 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}FNO_2S$ $(M + H)^+$ 332.1121, found 332.1115.

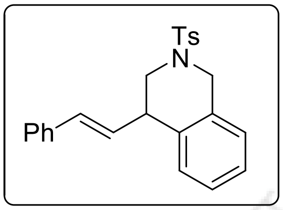
6-Methyl-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline ***17m****:*



White gum; R$_f$ (hexane/ EtOAc 9:1) 0.50; yield 105 mg, 66%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.27 (s,3 H), 2.41 (s, 3 H), 3.12 (dd, *J* = 4.4 and 7.2 Hz, 1 H), 3.41 (dd, *J* = 4.8 and 6.8 Hz, 1 H), 3.58 (dd, *J* = 5.6 and 7.2 Hz, 1 H), 4.10-4.24 (m, 2 H), 5.17-5.23 (m, 2 H), 5.76-5.86 (m, 1 H), 6.91-6.96 (m, 3

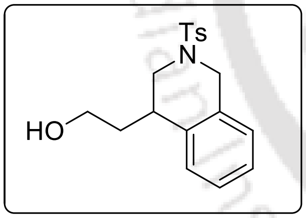
H), 7.32 (d, J = 8.0 Hz, 2 H), 7.72 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.7, 43.6, 47.8, 48.8, 117.6, 126.4, 127.8, 127.9, 128.5, 129.5, 129.9, 133.3, 135.1, 136.7, 138.8, 143.9; IR (KBr, neat) 2976, 2922, 2856, 1597, 1458, 1352, 1164, 1091, 964, 814, 753, 670, 586 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_2S$ (M + H)$^+$ 328.1371, found 328.1381.

*(E)-4-Styryl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**17o**)*:



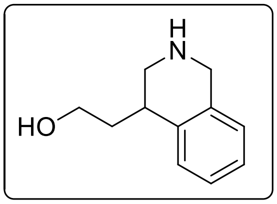
White gum; Rf (hexane/ EtOAc 4:1) 0.55; yield 35 mg, 78%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.14 (dd, J = 11.8, 7.2 Hz, 1 H), 3.57 (dd, J = 11.8, 6.0 Hz, 1 H), 3.82 (dd, J = 12.8, 7.2 Hz, 1 H), 4.20 (d, J = 15.0 Hz, 1 H), 4.36 (d, J = 15.0 Hz, 1 H), 6.15 (dd, J = 15.8, 8.7 Hz, 1 H), 6.57 (d, J = 15.8 Hz, 1 H), 7.06-7.08 (m, 1 H), 7.16-7.26 (m, 4 H), 7.28-7.36 (m, 6 H), 7.73 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 43.0, 48.0, 49.0, 126.6 (2C), 127.1, 127.2, 127.8, 128.0, 128.8, 129.3, 130.0, 130.1, 131.6, 132.9, 133.3, 135.6, 137.0, 143.9; IR (KBr, neat) 2925, 2916, 2867, 1357, 1124, 1056, 912, 845, 746, 660 cm^{-1}; Anal. calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60. Found: C, 74.09; H, 5.98; N, 3.53.

*2-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol **22**:*



White solid; R$_f$ (hexane/ EtOAc 1:1) 0.50; m. p. 117-119 °C yield 500 mg, 80%; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.81 (s, 1 H), 1.91 (m, 1H), 2.06 (m, 1 H), 2.42 (s, 3 H), 2.78 (dd, J = 3.6 and 8.4 Hz, 1 H), 3.09 (m, 1 H), 3.84 (m, 4 H), 4.61 (d, J = 14.8 Hz, 1 H), 7.02 (m, 1 H), 7.15 (m, 3 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 35.5, 38.1, 47.1, 47.8, 60.6, 126.6, 126.7, 127.0, 127.9, 129.1, 130.0, 131.4, 133.2, 137.7, 144.0; IR (KBr, neat) 3425, 2926, 2857, 1644, 1598, 1455, 1337, 1163, 1090, 1034, 949, 812, 669, 553 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_3S$ (M + H)$^+$ 332.1320, found 332.1330.

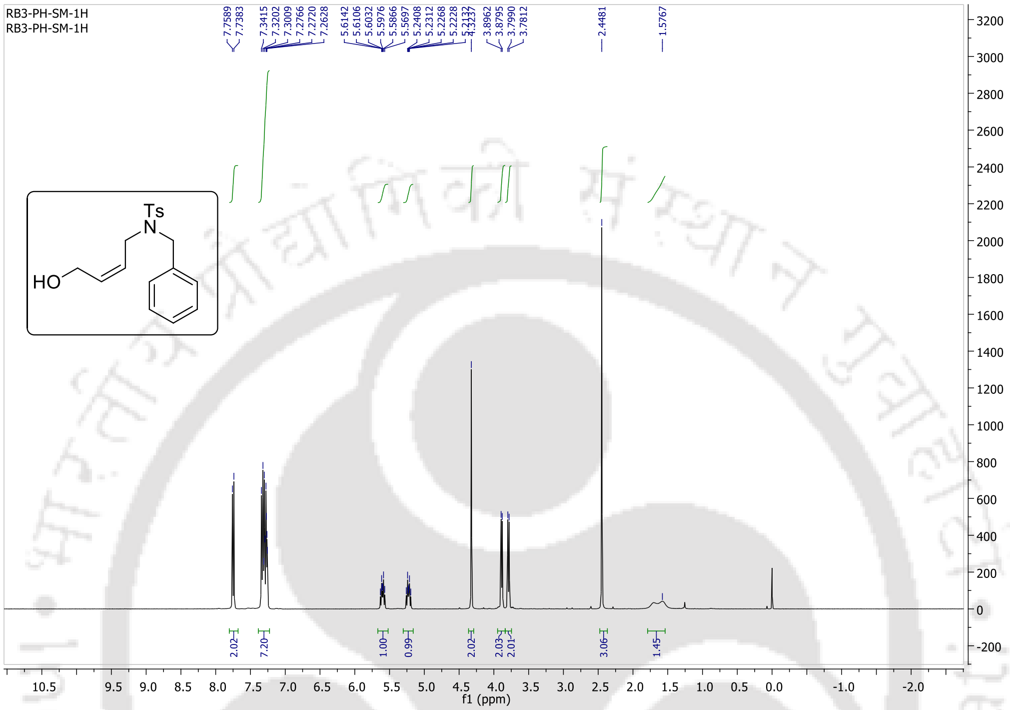
*2-(1,2,3,4-Tetrahydroisoquinolin-4-yl)ethanol **23**:*

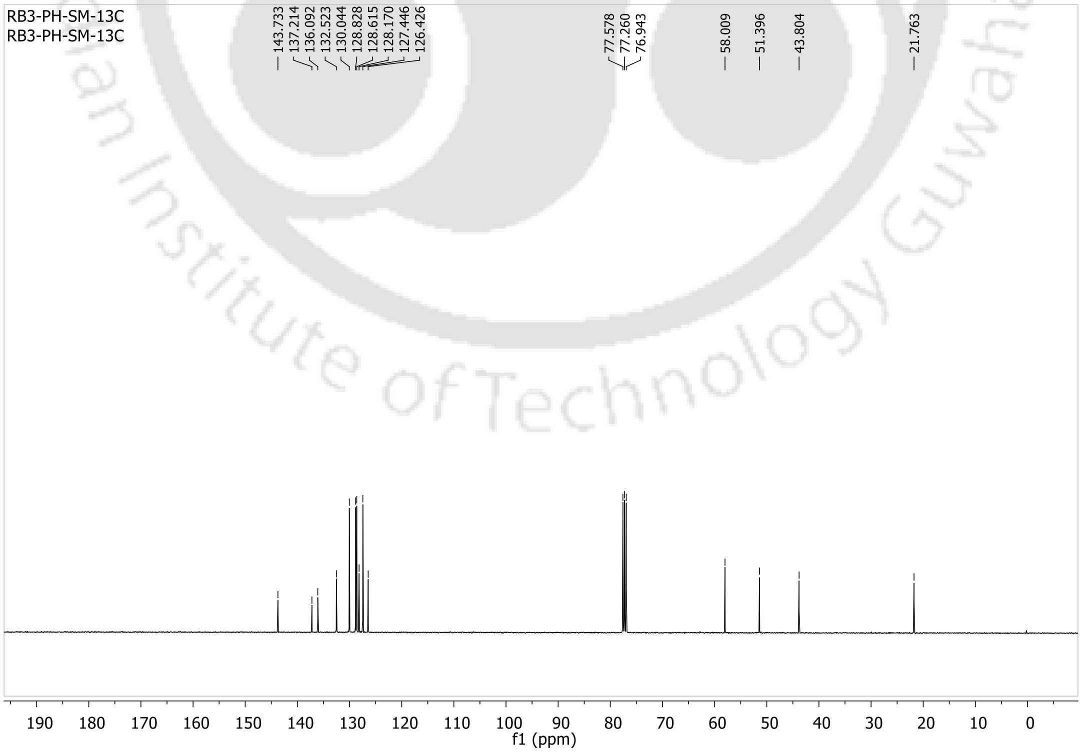


Colourless gum; R$_f$ (DCM/ CH_3OH 9:1) 0.55; yield 60 mg, 70%; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.03-2.06 (m, 2 H), 3.10-3.19 (m, 2 H), 3.22 (s, 1 H), 3.29 (d, J = 11.8 Hz, 1 H), 3.46-3.51 (m, 1 H), 3.83 (brs, 2 H), 4.12 (q, *J* = 6.0 and 15.4 Hz, 2 H), 7.05 (d, *J* = 6.6 Hz, 1 H), 7.11-7.13 (m, 1 H), 7.15-7.23 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 35.6, 39.5, 46.8, 47.9, 57.7, 126.7, 126.8, 127.3, 129.1, 133.2, 135.5; IR (KBr, neat) 3383, 2924, 2854, 1730, 1641, 1462, 1376, 1283, 909, 761, 722 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{16}NO$ $(M + H)^+$ 178.1227, found 178.1238.

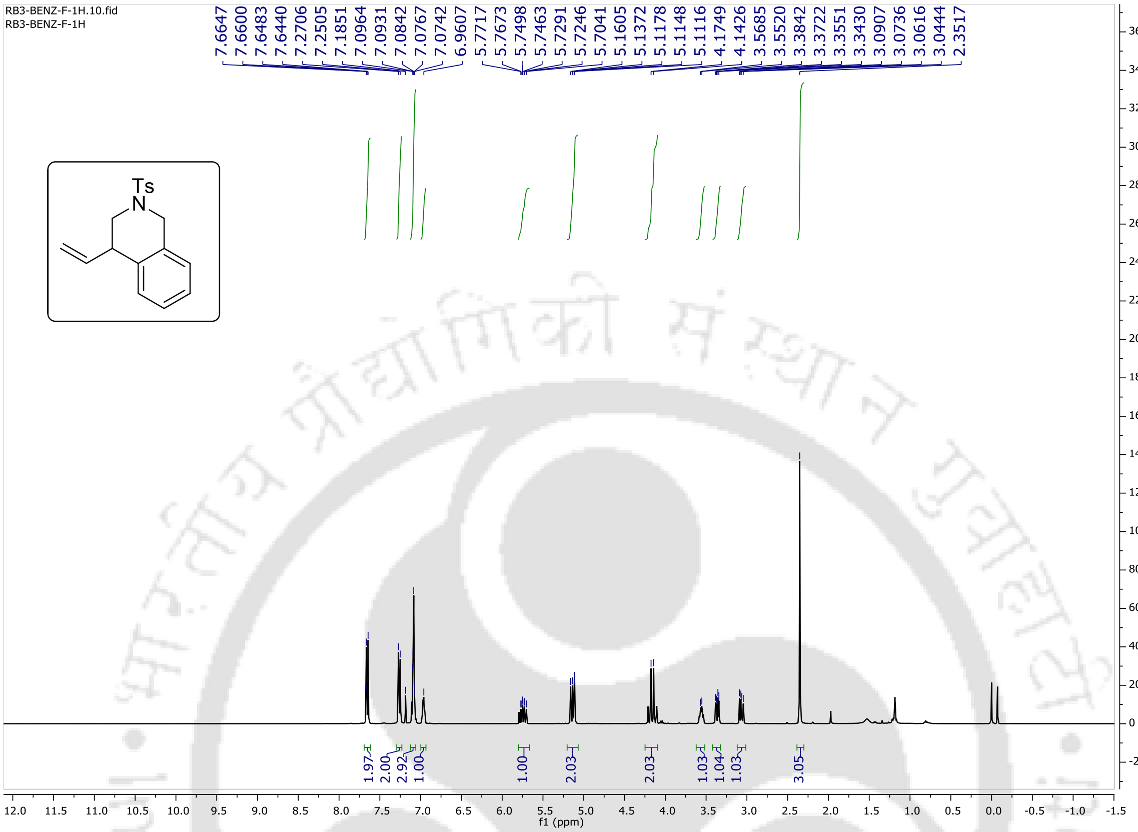
4.8. Representative Spectra and Crystal Parameters:

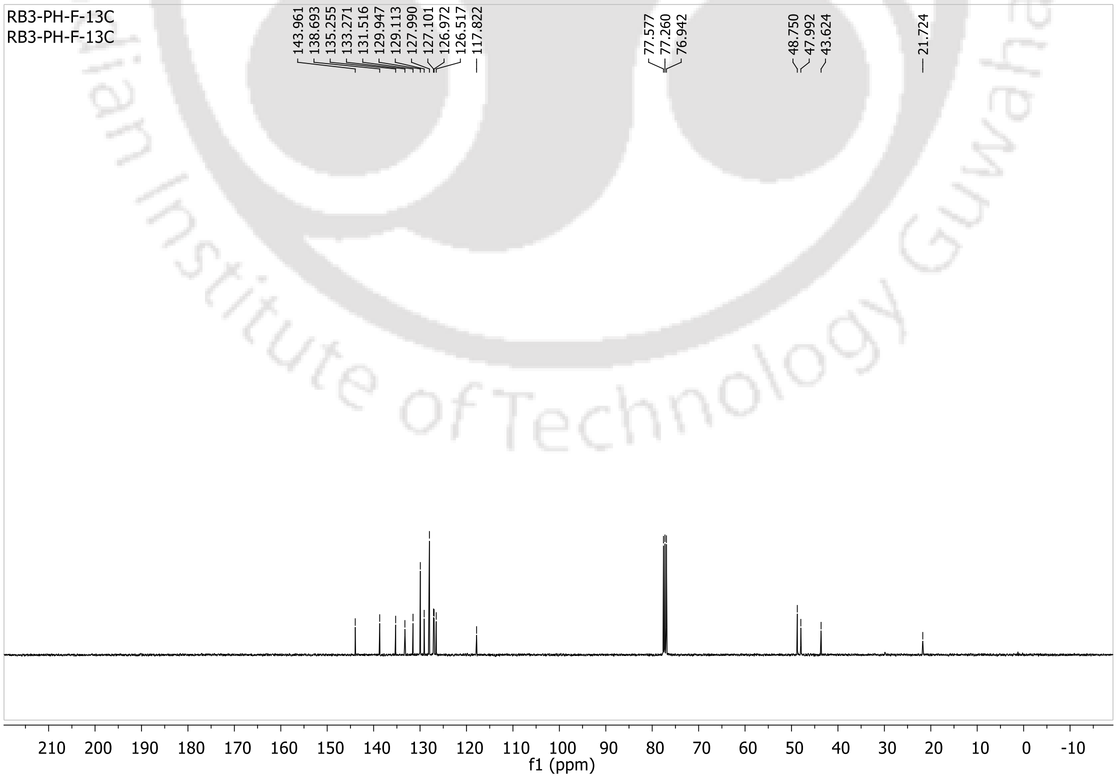
^{1}H and ^{13}C spectra of compound (*Z*)-*N*-benzyl-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide 16a:



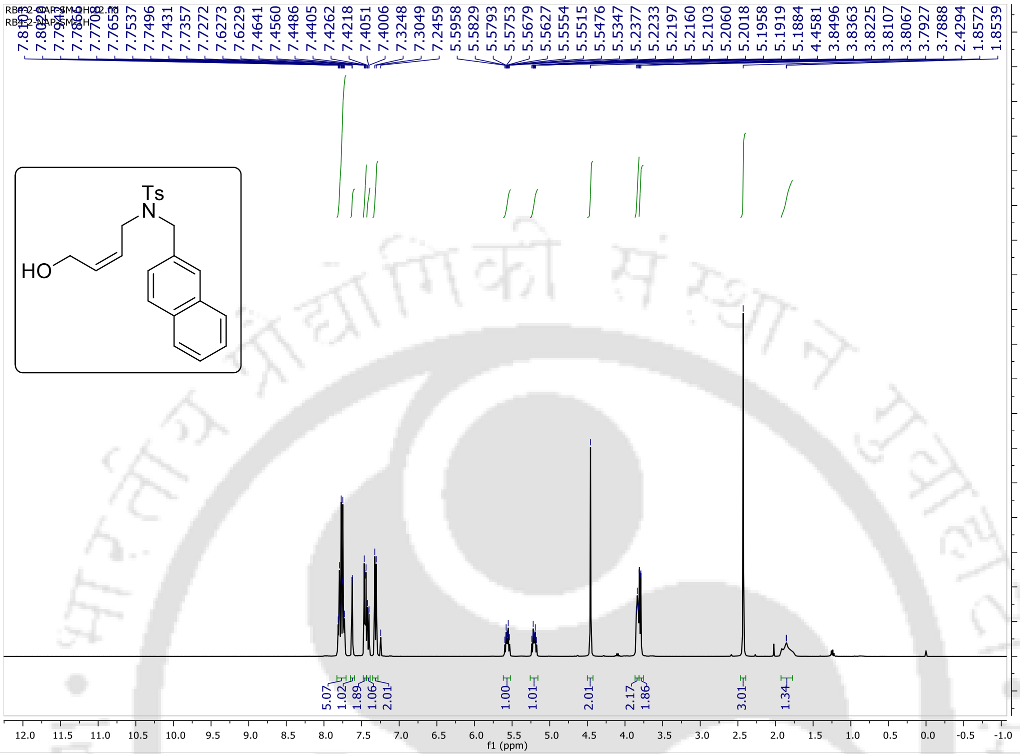


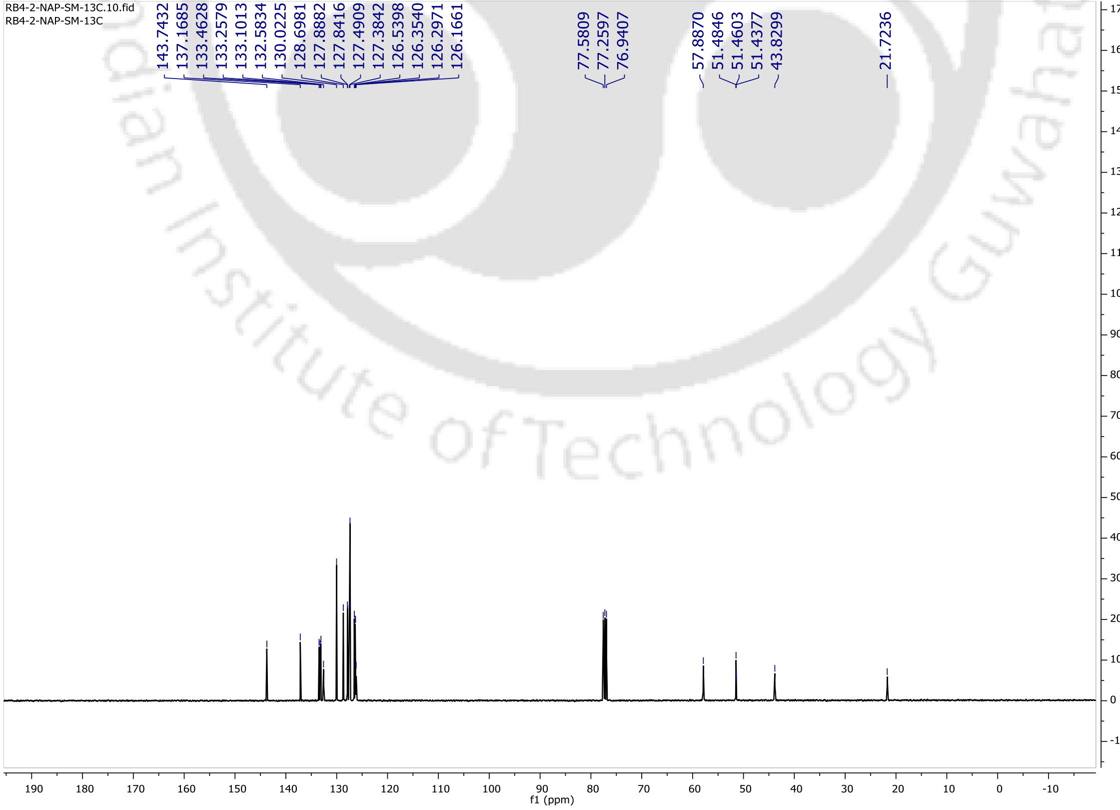
^{1}H and ^{13}C spectra of compound 2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline 17a:



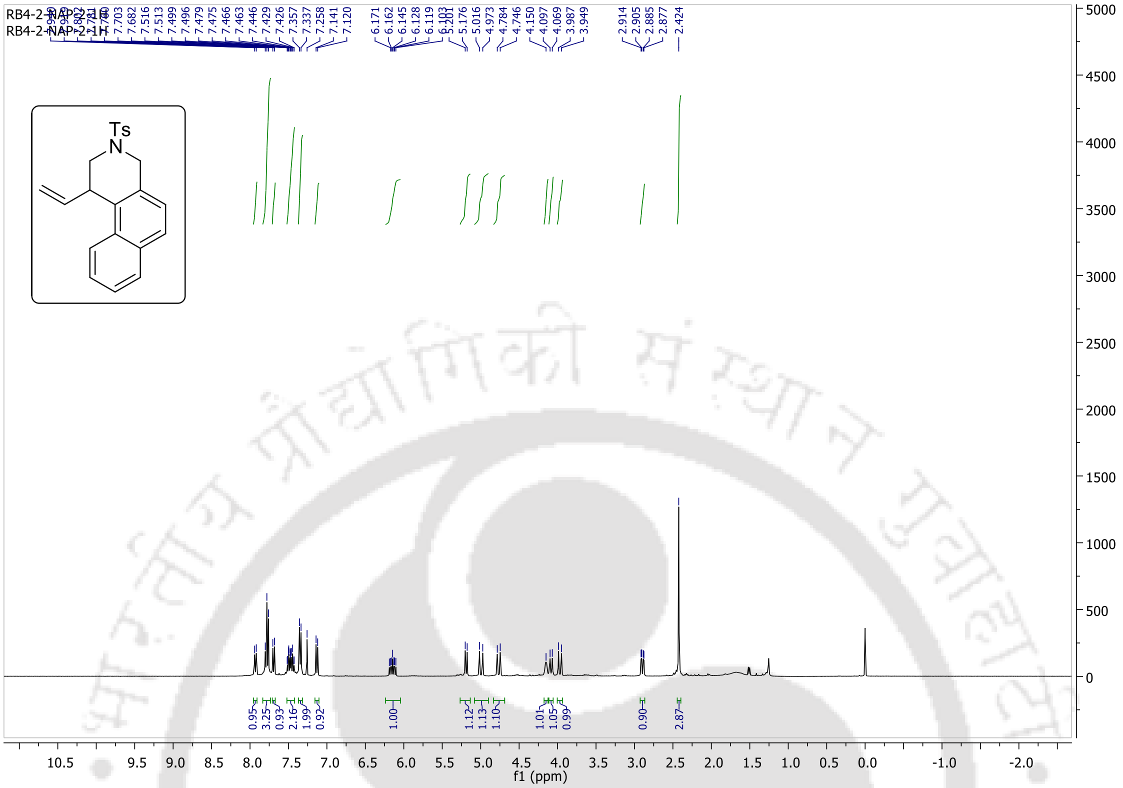


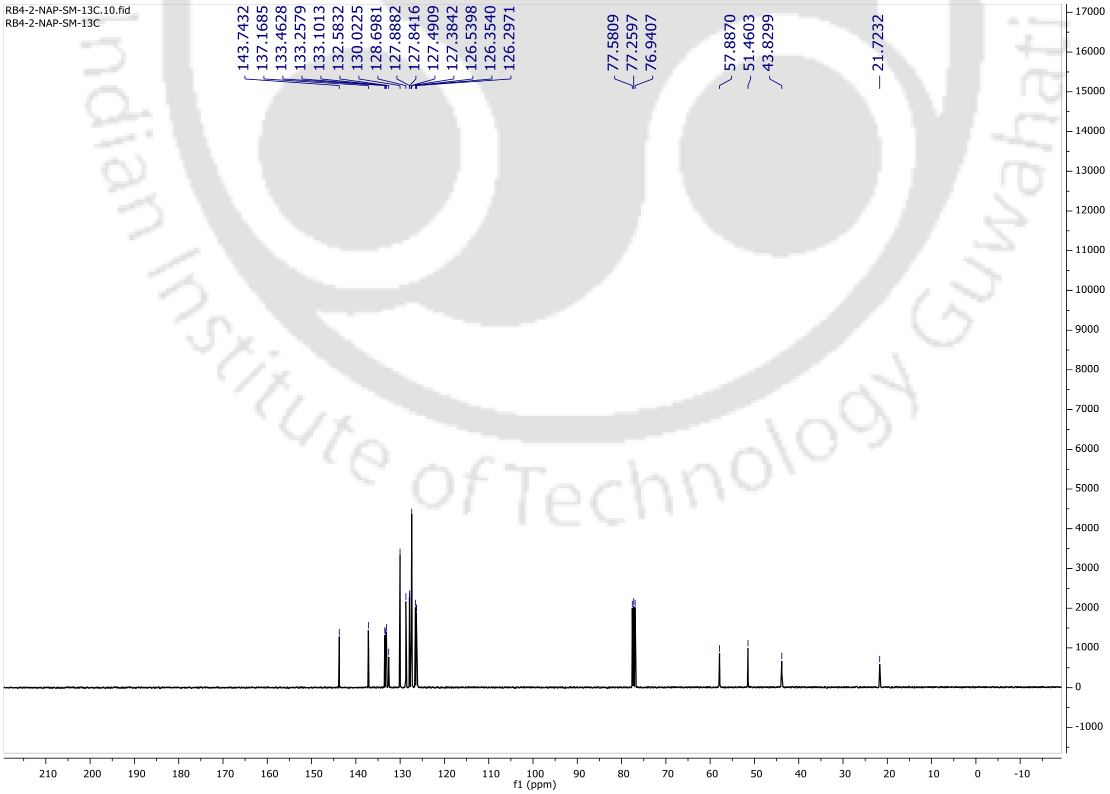
^{1}H and ^{13}C spectra of compound (*Z*)-*N*-(4-hydroxybut-2-en-1-yl)-4-methyl-*N*-(naphthalen-2-ylmethyl)benzenesulfonamide 16h:



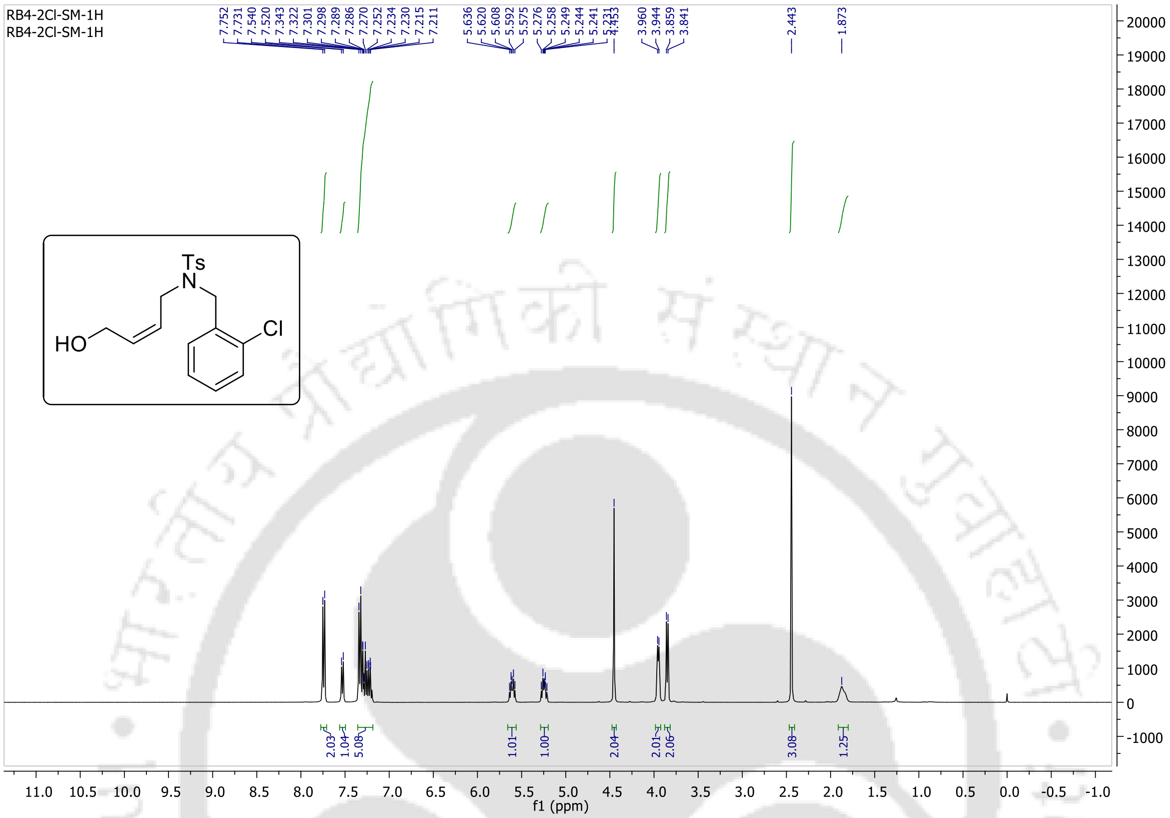


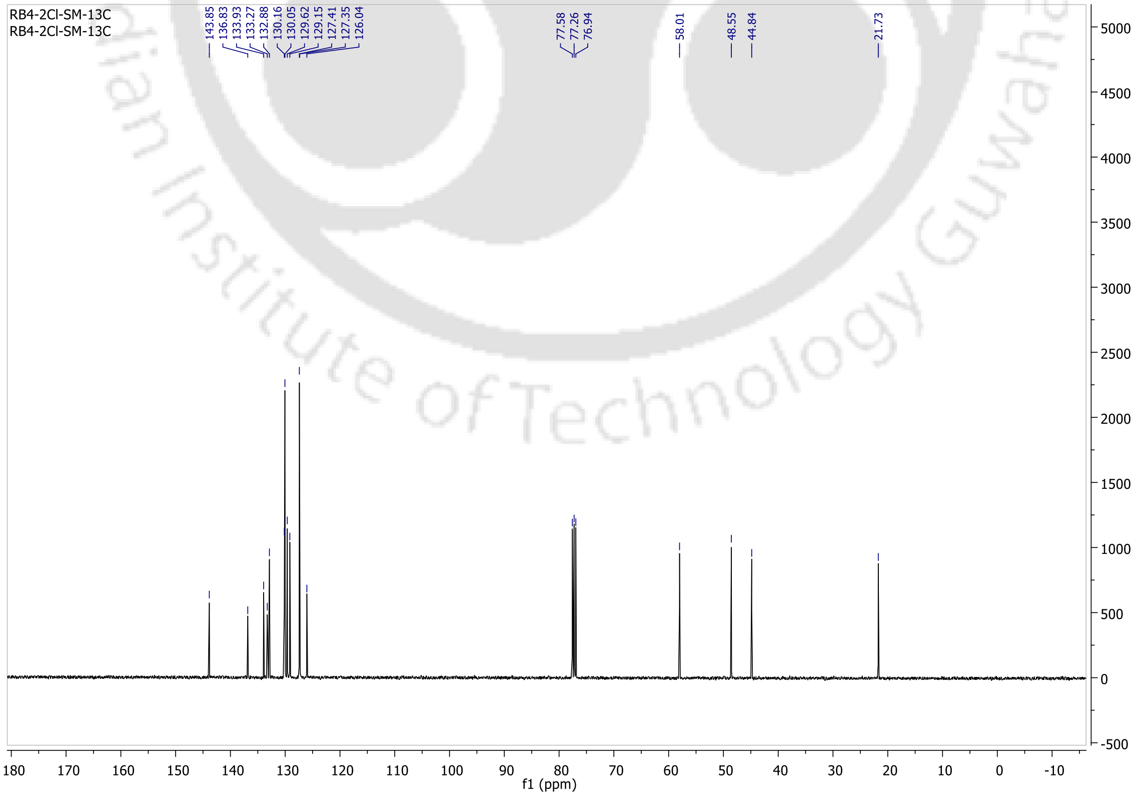
^{1}H and ^{13}C spectra of compound 3-tosyl-1-vinyl-1,2,3,4-tetrahydrobenzo[f]isoquinoline 17h:



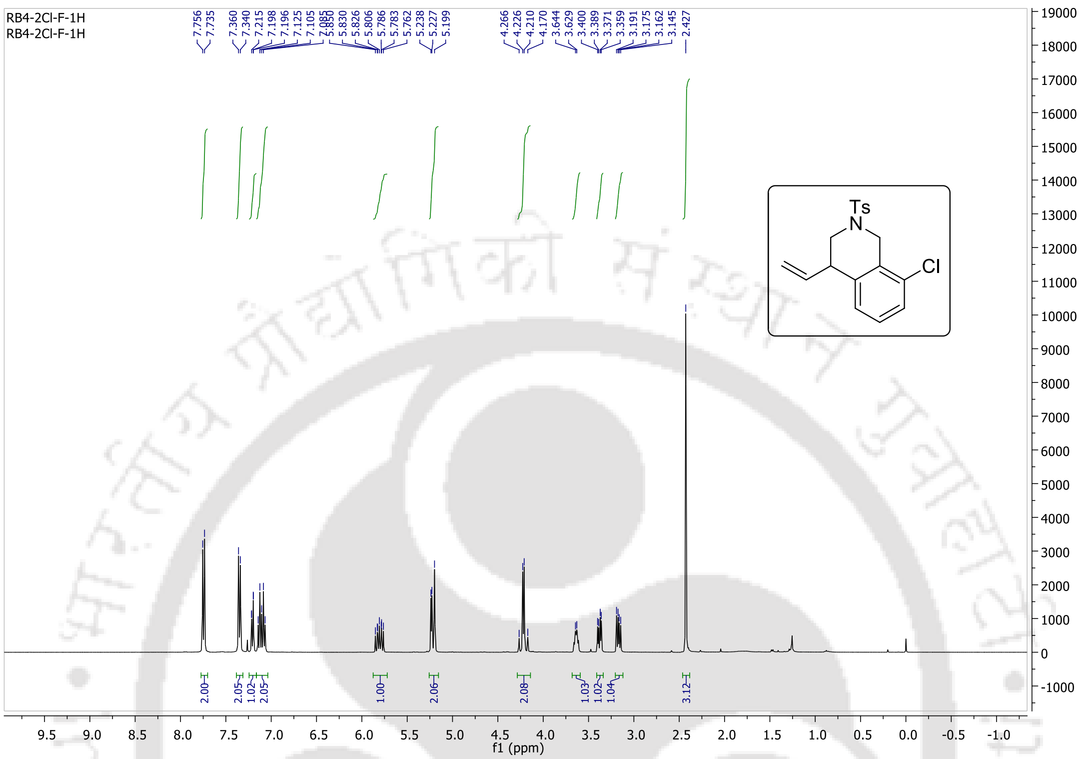


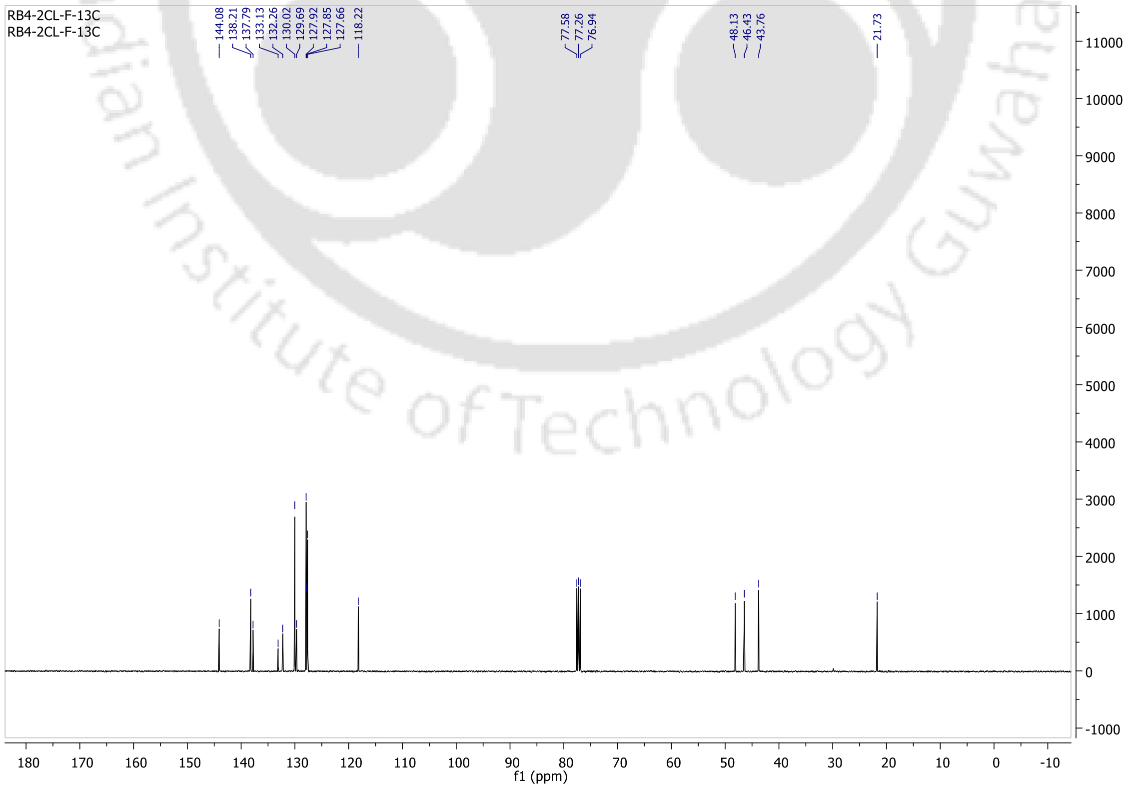
^{1}H and ^{13}C spectra of compound (*Z*)-*N*-(2-chlorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide 16j:



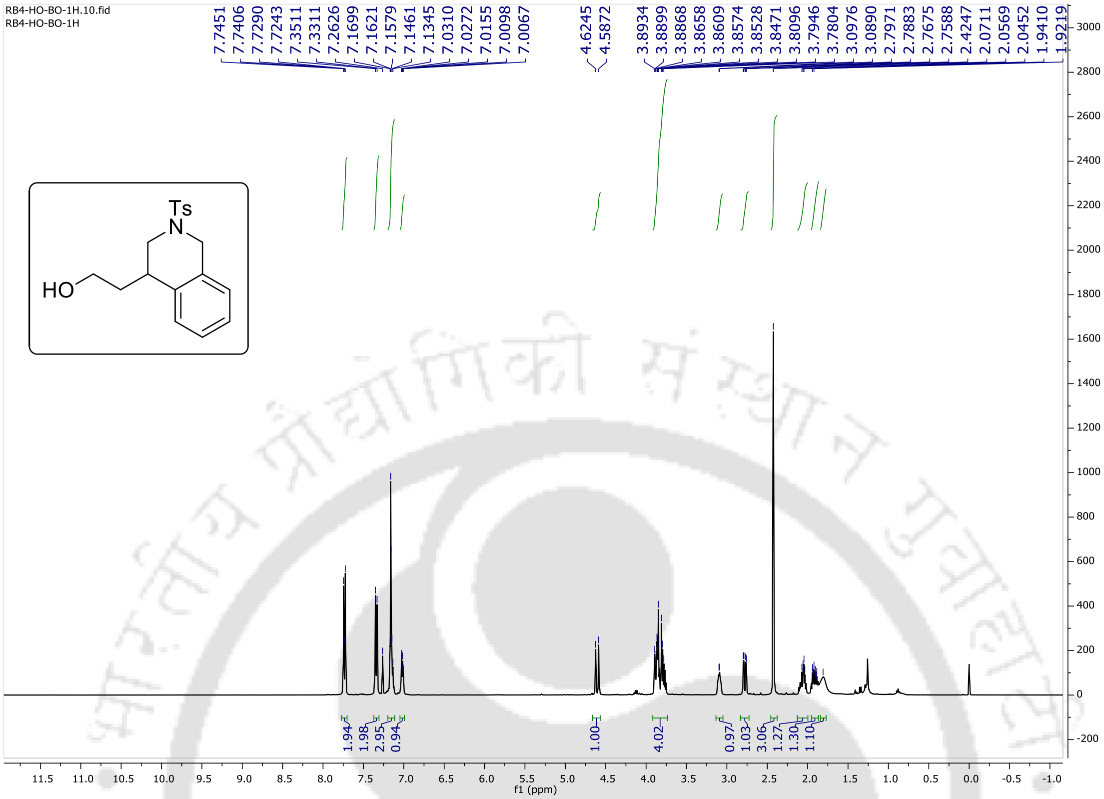


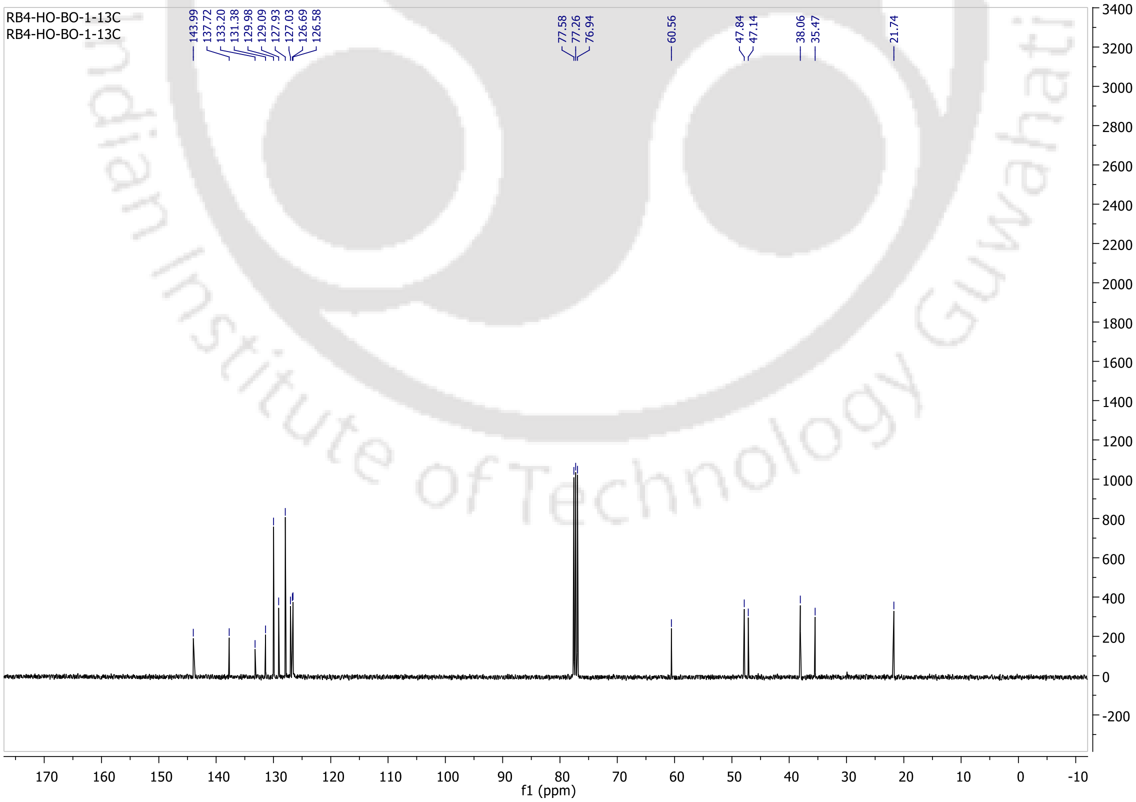
^{1}H and ^{13}C spectra of compound 8-chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline 17j:



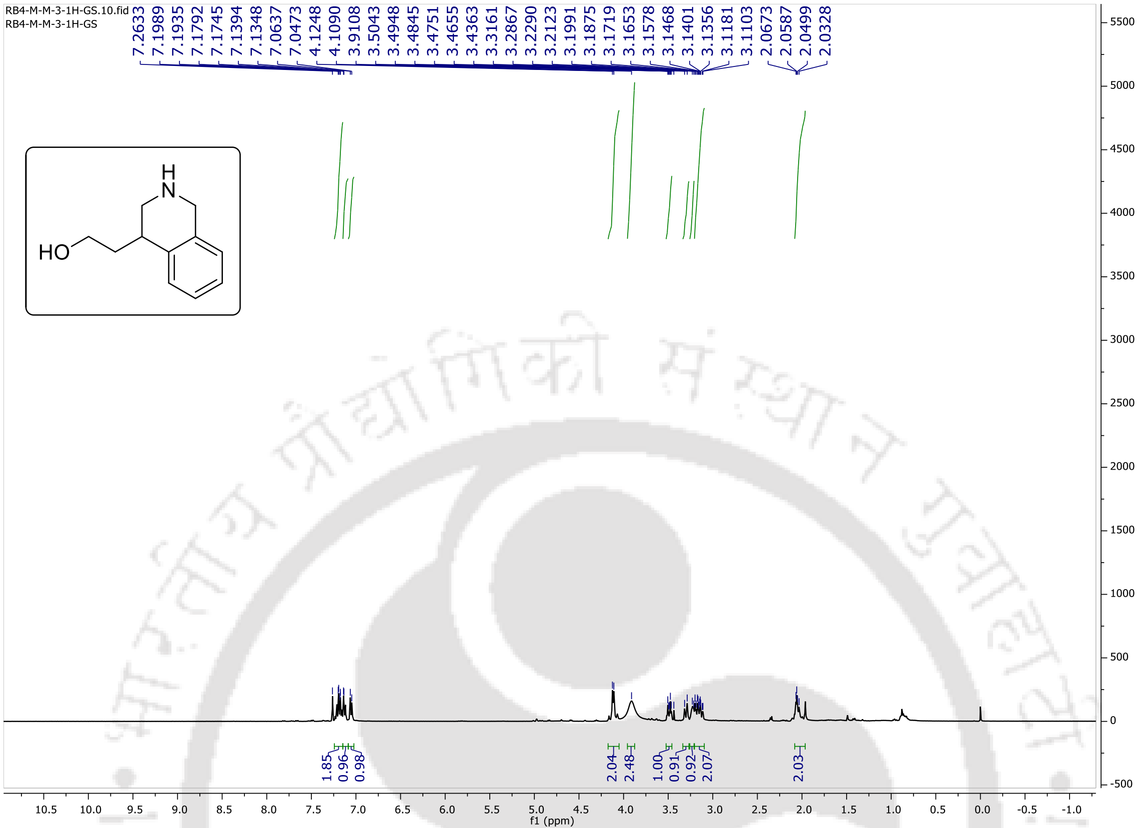


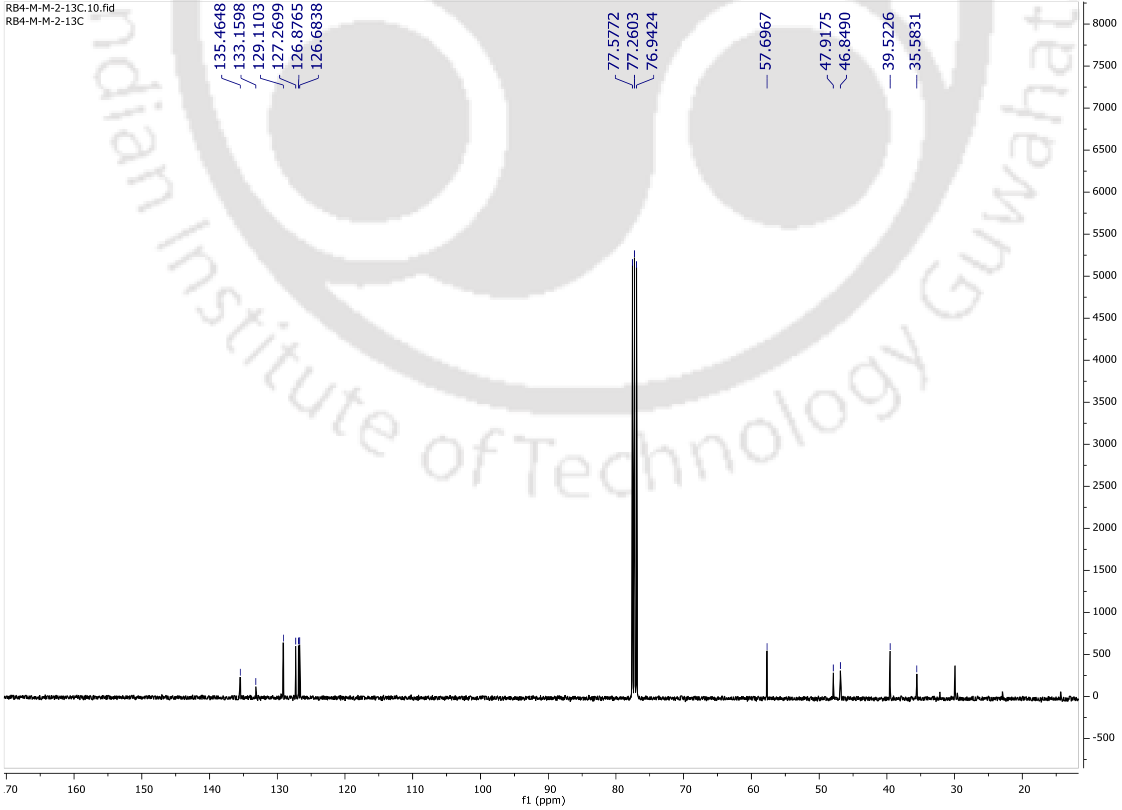
^{1}H and ^{13}C spectra of compound 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol 21:





^{1}H and ^{13}C spectra of compound 2-(1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol 22:





The crystal parameters of compound3-tosyl-1-vinyl-1,2,3,4-tetrahydrobenzo[f]isoquinoline 17h:

	CCDC 1922264
Formula	$C_{22}\,H_{20}\,N\,O_2S$
Formula weight	362.45
T/K	293(2)
Crystal system	Triclinic
Space group	P-1
a/Å	8.7100(6)
b/Å	11.9681(9)
c/Å	19.6311(16)
α/°	104.157(7)
β/°	97.020(6)
γ/°	100.773(6)
V/Å^3	1918.7(3)
Z	4
Abs. Coeff./mm^{-1}	None
Abs. Correction	0.954
GOF on F^2	*R1* = 0.0754
Final *R* indices [*I*> 2σ(I)]	*wR2* = 0.2365
	R1 = 0.1463
R indices [all data]	*wR2* = 0.2467

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List of Publications

1. “Stereo- and Regio-selective Synthesis of 4-Vinylpyrrolidine from *N*-Tethered Alkyne-Alkenol” **Devi, N. R.**; Behera, B. K.; Saikia, A. K. *ACS Omega*, **2018**, 3, 1, 576.
2. “Regio- and Diastereo-selective Synthesis of Dihydropyrans and Pyrano-Pyrans via Oxonium-ene Reaction of *β*-allenols and Aldehydes” **Devi, N. R.**; Sultana, S.; Borah, M.; Saikia, A. K. *J. Org. Chem*., **2018**, 83, 24, 14987.
3. “Synthesis of 4-Vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-Tethered Benzyl-Alkenol Catalyzed by Indium (III) Chloride: Formal Synthesis of (±)-Isocyclocelabenzine” **Devi, N. R.**; Shit, S.; Behera, B. K.; Saikia, A. K. *Synthesis*, DOI: 10.1055/s-0037-1610750.
4. “Synthesis of Substituted Tetrahydropyrans and Tetrahydrofurans via Intramolecular Hydroalkoxylation of Alkenols” Sultana, S.; **Devi, N. R.**; Saikia, A. K. *Asian J. Org. Chem*., **2015**, *4*, 1281.
5. “Diastereoselective synthesis of substituted hexahydrobenzo[de]isochromanes and evaluation of their antileishmanial activity” Saikia, A. K.; Sultana, S.; **Devi, N. R.**; Deka, M. J.; Tiwari, K.; Dubey, V. K. *Org. Biomol. Chem*., **2016**, *14*, 970.
6. “Stereoselective Synthesis of Hexahydrofuro[3,4-*b*]furan-4-ol and Its Dimer via Tandem Prins and Pinacol Rearrangement” Shit, S.; Devi, N.; **Devi, N. R.**; Saikia, A. K. *Org. Biomol. Chem*. **2019**, *17*, 7398.