New approaches towards the synthesis of oxygen heterocyclic compounds

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of

Doctor of Philosophy in Chemistry

Submitted by

Sujit Sarkar

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India
August 2018

Dedicated
To
My Parents and Grandmother

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**New approaches towards the synthesis of 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 acknowledgements have been made wherever the work described is based on the findings of other investigators.

8th August, 2018
IIT Guwahati

Sujit Sarkar

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

Professor Anil K. Saikia

CERTIFICATE

This is to certify that Mr. **Sujit Sarkar** has been working under my supervision since July 2013 as a regular registered Ph.D. student. I am forwarding his thesis entitled "**New approaches towards the synthesis of oxygen heterocyclic compounds**" being submitted for the Ph. D (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

8th August, 2018
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

ACKNOWLEDGEMENTS

The road to obtaining a Ph.D. degree is not always a smooth one. However, along the way I have encountered many remarkable people who help to make this journey a pleasurable. I would like to express sincere gratitude to everyone who directly or indirectly helped me transcend these significant milestones and motivated me on the path to success.

First and foremost, I would like to give my wholehearted appreciation to my thesis advisor Prof. Anil K. Saikia for accepting me into his group and his invaluable guidance, encouragement, inspiration and scientific advices throughout my Ph.D. which helped me to enhance my knowledge and inspired me to take right decisions at crucial moments. I am also thankful to him for giving me the freedom to explore organic chemistry and nurturing my love for the subject.

I would like to acknowledge my sincere gratitude to all my doctoral committee members, Prof. V. Manivannan, Dr. Dipankar Srimani, Dr. A.S. Achal kumar and Prof. Vikas Kumar Dubey for their insightful advices and valuable suggestions during my doctoral studies. My honest regards to all the faculty of the Department of Chemistry for their motivation and encouragement.

I am very greatful to the Ministry of Human Resource and Development (MHRD), India for financial support and IIT Guwahati for all the facilities that were made available to me. I also thankful to Central Instrument Facility (CIF), IIT Guwahati for providing the instrument facility and DST for providing the X-ray facility.

I am also indebted to all the members of the IITG staff for the valuable services they provided. In particular, I would like to thank Mr. Chandan Borgohain and Mr. Kesho Singh for giving advices whenever I needed help in NMR, Mr. Aniruddha Gogoi for measuring the mass spectra and Dr. Babulal Das for collecting the X-ray crystal data. I thank Prof. A. T. Khan (my M.Sc. supervisor) for his inspiration and encouragement to pursue my doctoral studies. I would like to thank my department colleagues.

Further, I would like to thank all my past and present group members for their friendship and assistance. I especially want to thank Dr. Madhurjya Borah for his assistance in familiarizing me with the Prins cyclization chemistry and always being willing to discuss problems and ideas with me. I am greatful to other members, Dr. Kiran Indukuri, Dr. Paramartha Gogoi, Dr. Sabera sultana Dr. Priya Gosh, Dr. Ramanjaneyulu Unnava, Dr. Manash Deka, Renubala, Upasana, Malay, Archana, Bipin, Subham, and Sudip for their help.

I extend my sincere thanks to other friends in IITG, especially Dr. Deb kumar das, Dr. Prasanta roy bagdi, Dr. Radhakrishna Gattu. Dr. Tamal Pramanic, Dr. Arun kumar, Dr. Kishant kumar with whom I enjoyed weekend cricket matches parties as well as the road-trips.

I also take this opportunity to thank all of my Ph.D. batchmates (July, 13), the other research scholars in the chemistry department and all my IITG friends, who have shared their thoughts and views with me.

My heartful thanks also go to my dearest friends from outside IITG, Malay, Manoj, Amit, Prasanta, Abhishek, Sourav, Nagasuresh, Souvik, Milon, Aritra and Ashutosh, Gopal da, Mrinal da for their constant support and encouragement.

I must thank my college (B.Sc) teacher, Shyam da, Sushanta da and Naba da for all their help during my studies.

Finally, I want to thank all of my family members. Without their love and support throughout the past 27 years, none of this would have been possible. They have been nothing short of incredible. I wish to express my sincere gratitude to my parents (Father, Late Gobinda Sarkar & Mother, Arati Sarkar), brother (Abhijit Sarkar) and Grandmother (Radharani) and I dedicate this work to them.

8th August, 2018
IIT Guwahati

Sujit Sarkar

LIST OF ABBREVIATIONS

Ac	acetyl	*m*-CPBA	meta-chloroperbenzoic acid
Bn	benzyl	mp	melting point
Bu	butyl	MS	molecular sieves
CCDC	cambridge crystallographic data centre	m/z	mass to charge ratio
CSA	camphorsulfonic acid	NMO	*N*-methylmorpholine *N*-oxide
Cy	cyclohexyl	NMR	nuclear magnetic resonance
DBMP	2,6-di-tert-butyl-4-methylpyridine	NOESY	nuclear overhauser enhancement spectroscopy
DCE	1,2-dichloroethane		
DCM	dichloromethane	ORTEP	oak ridge thermal ellipsoid plot
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	Ph	phenyl
DIAD	diisopropylazodicarboxylate	ppm	parts per million
DFT	Density Function Theory	Pr	propyl
DMF	*N*, *N*-dimethylformamide	*p*-TSA	*p*-toluenesulfonic acid
DMSO	dimethylsulfoxide	rt	room temperature
de	diastereomeric excess	TFA	trifluoroacetic acid
dr	diastereomeric ratio	TfOH	trflic acid
ee	enantiomeric excess	THF	tetrahydrofuran
HRMS	high resolution mass spectrometry	THP	tetrahydropyran
IR	infrared	TLC	thin layer chromatography
LA	Lewis acid	TMS	trimethylsilyl
LAH	lithiumaluminium hydride	TMSOTf	trimethylsilyl trifluoromethane sulfonate
LDA	lithiumdiisopropyl amine	Ts	*p*-toluenesulfonyl

m-CPBA meta-chloroperbenzoic acid

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/td	doublet of triplet/triplet of doublet	MHz	Mega-Hertz

Abstract

The research work presented in this thesis has been divided into four chapters based on the results and experimental findings during the complete course of the research period. The chapter **1** of the thesis describes introduction preferably to six membered oxygen heterocyclic compounds and their biological significance as well as literature methods for their synthesis. Chapter **2** describes synthesis of isochroman derivatives *via* oxa-Pictet-Spengler reaction of acrylyl enol ethers: formal synthesis of (±)–sonepiprazole (U-101387) and (±)-U-54537. Chapter **3** illustrates stereoselective synthesis of 4-*O*-tosyltetrahydropyrans *via* Prins cyclization reaction. In chapter **4,** regioselective synthesis of substituted 3,6-dihydropyran is elaborated from 3-butene-1-ol and aldehydes *via* Prins cyclization reaction using TfOH (Triflic Acid).

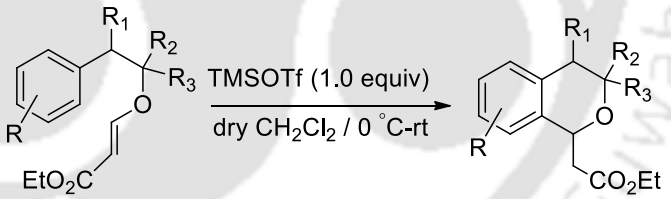
Chapter 1: Introduction to oxygen containing heterocyclic compounds

Saturated six membered oxygen heterocyclic compounds play a vital role and they are commonly occurring substructures found in Nature in various forms. In addition, they are the integral part of numerous natural products from antibiotics to vitamins and liposaccharides.

To build this class of heterocycles, many strategies have been developed over the years. The most widely used methods are the Prins cyclization, Hetero-Diels–Alder cyclization, intramolecular oxonium-ene cyclization, the intramolecular Michael additions and ring-closing metathesis. Other strategies include electrophile induced cyclizations of non-activated alkenes and Lewis acid promoted cyclizations of epoxy alcohols/ amines. These methods have their own advantages and disadvantages. Therefore, development of new and efficient methods is imperative specially to address the issue of diastereoselectivity. Among these methods Prins and Diels-Alder, cyclizations have attracted much attention due to the formation of exclusive single isomers, generation of multi-stereo centers and application in natural product synthesis.

Chapter 2: Synthesis of Isochroman Derivatives *via* Oxa-Pictet-Spengler Reaction of Acrylyl Enol Ethers: Formal Synthesis of (±) –Sonepiprazole (U-101387) and (±)-U-54537

Oxygen heterocycles fused with aromatic rings such as benzopyrans and isochromans are found as important structural motifs in a wide range of naturally occurring and biologically active molecules and pharmaceuticals. For example, sonepiprazole (U-101387) and U-54537 are used as D_4 antagonist, (PNU-109291) as 5-HT_{1D} agonist, and some compounds are used as Ca-receptor antagonist. Owing to their wide range of biological activities, synthesis of substituted isochromans has attracted the attention of the synthetic community and various methods have been developed. Isochromans are also synthesized using oxa-Pictet-Spengler reaction from 2-phenylethanol and an aldehyde or ketone with a fatty acid as catalyst. Recently, functionalization of isochroman core, including C-H activation, is considered as one of the alternative methods for the synthesis of substituted isochromans. Although it has advantage of synthesizing desired substituted isochromans, it suffers from increase in number of steps. Therefore, development of suitable methodology for the synthesis of substituted isochromans, in a single step, is highly desirable. Herein, we wish to describe a methodology for the synthesis of isochroman from aryl substituted acrylyl enol ethers *via* oxa-Pictet-Spengler reaction catalyzed by trimethylsilyl trifluoromethanesulfonate *(Scheme 1)*.



Scheme 1: *Synthesis of isochroman and the scope of the reaction*

It was observed from the *Scheme 1* that substrates, having simple aromatic ring and aromatic ring with electron donating substituents on the ring gave the desired isochromans in good yields. Substrate having bromo substituted aromatic ring decomposed under these reaction conditions. On the other hand, aromatic ring having electron withdrawing group could not produce the desired product but starting material was recovered in 95% yield. The reaction is highly diastereoselective and gave only single diastereomers with a *cis* relationship. The stereochemistry of the disubstituted products was determined by NOE experiments of compound **32d**. There is a strong NOE between protons at C-1 and C-3 of compound, which confirms that they are *cis* to each other (*Figure 1*).

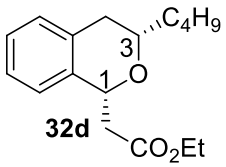
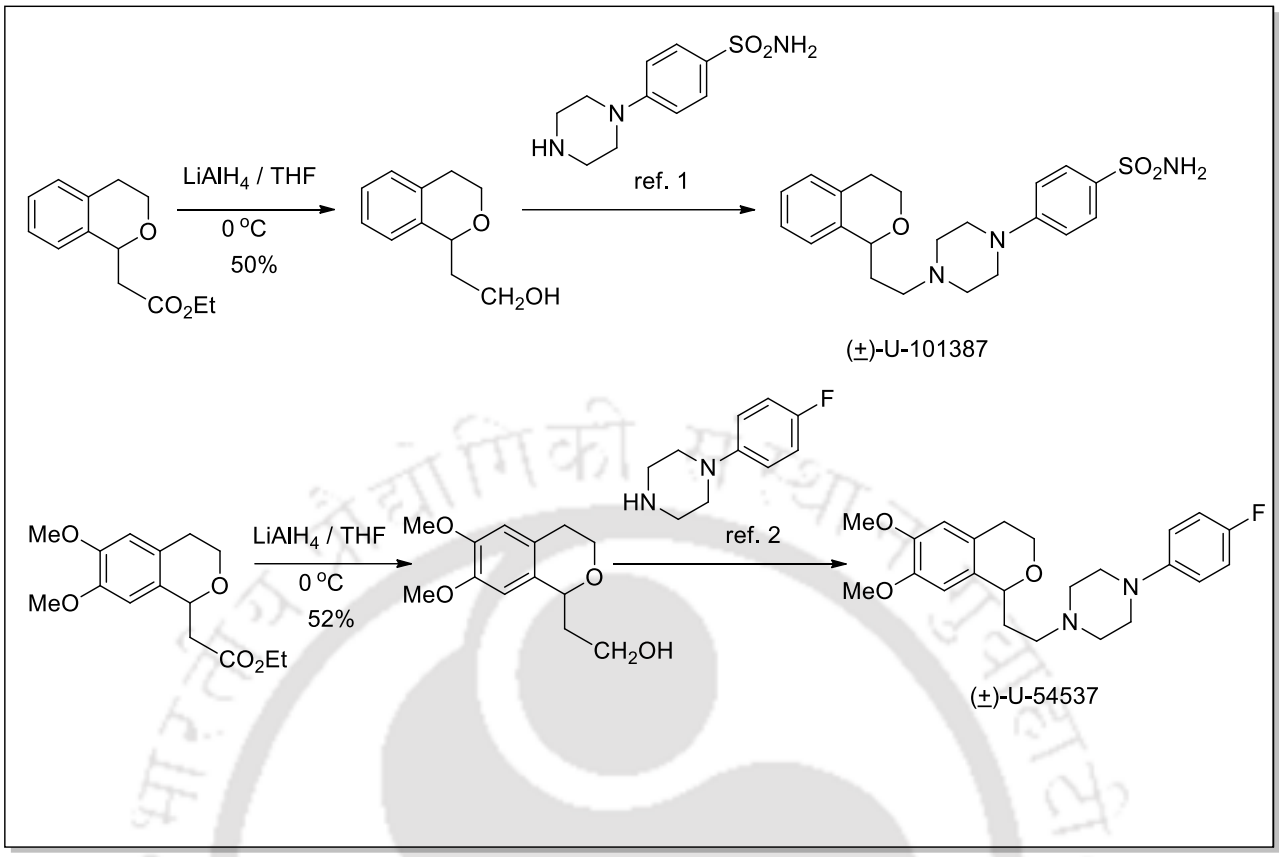


Figure 1: *NOE of compound 32d*

The strategy is applied for the synthesis of biologically active compound (±) sonepiprazole (U-101387) and (±)-U-54537, which are considered as D_4 antagonist *(Scheme 2).*

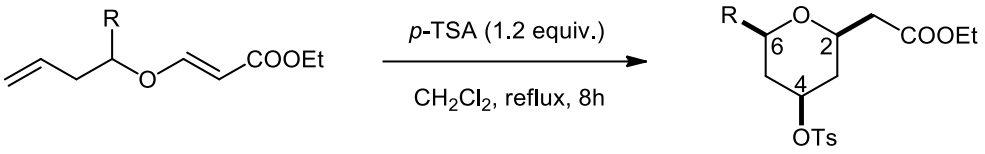


Scheme 2. *Synthesis of (±) sonepiprazole (U-101387) and (±)-U-54537*

In summary, we have developed a mild and efficient method for the synthesis of substituted isochromans *via* oxa-Pictet-Spengler reaction of acrylyl enol ether in good yields. The methodology is successfully applied for the synthesis of biologically active molecule (±)-sonepiprazole (U-101387) and *(±)*-U-54537.

Chapter 3: Stereoselective Synthesis of 4-*O*-Tosyltetrahydropyrans *via* Prins Cyclization

Saturated six membered cyclic ethers better known as tetrahydropyrans (THPs) are ubiquitious in nature and represent useful precursors for the synthesis of many biologically active molecules. We have reported stereoselective synthesis of dihydropyrans, terahydrofurans and tetrahydrothiophenes *via* Prins cyclization of homoallyl, homopropargyl alcohols and thiols. We also studied the dual role of *p*-TSA as Brønsted acid and nucleophile in aza-Prins cyclization reaction. Based on our experience in Prins cyclization reaction, we envisioned that *p*-TSA could act as a nucleophile and Brønsted acid in Prins cyclization reaction of acryloyl ethers. Herein, we wish to report a mild and efficient protocol for the synthesis of 4-*O*-tosyl tetrahydropyrans *via* Prins cyclization followed by attacking of tosylate group at 4th position of THP ring using *p*-TSA for the synthesis of tosylated tetrahydropyran compounds *via* Prins cyclization in which *p*-TSA acts as Brønsted acid as well as a nucleophile *(Scheme 3).*



Scheme 3. *Synthesis of 4-O-Tosyltetrahydropyrans via Prins cyclization reaction.*

These acryloyl enol ethers were subjected to the *p*-TSA mediated Prins cyclization reaction. All the substrates worked well and produced moderate to high yields with high diastereoselectivity. In case of simple phenyl substituted enol ether gave the corresponding product in 74% yield with a dr of 90:10. The substrates having electron withdrawing aromatic substituents gave higher yields due to stabilization of oxo-carbenium ion intermediate by electron withdrawing substituents. Whereas, electron donating aromatic substituent containing substrates gives less yield. The reaction is highly diastereoselective with *cis* relationship among the substituents on tetrahydropyran ring. The diastereoselectivity was confirmed by crude ^{1}H NMR. The *cis* stereochemistry was determined with the help of NOE experiment of compound. A strong NOE between hydrogen at C-2 and C-4 as well as interaction between C-2 and C-6 clearly suggests all substituents are in *cis* relationship (*Figure 2*).

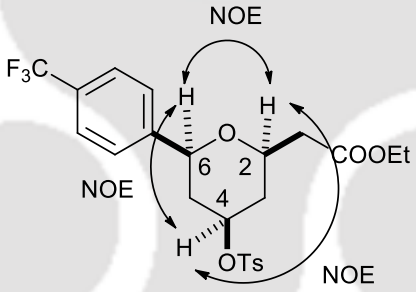
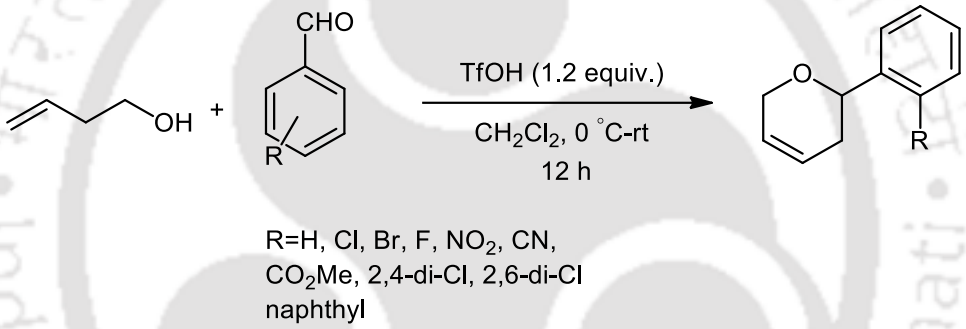


Figure 2. NOE *of (2R*,4S*,6S*)-Ethyl-4-(tosyloxy)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-carboxylate (**34f**)*

In conclusion, we have developed a methodology for stereoselective synthesis of tosyl substituted tetrahydropyrans through Prins cyclization reaction of homoallyl acryloyl enol ethers. The reaction is atom economic and good yields are achieved with high diastereoselectivity**.**

Chapter 4: Regioselective synthesis of substituted 3,6-dihydropyran from 3-butene-1-ol and aldehydes *via* Prins cyclization reaction mediated by TfOH (Triflic acid)

This chapter describes about Prins cyclization which is considered to be the most convenient tool for the synthesis of dihydropyran compound. As it provides the desired product in a single step with high regio-selectivity. On the other hand, one pot, multi component and selective reactions are considered as green synthetic routes. Considering these and in continuation of our research work, herein, we have developed one pot, three components, and mild and efficient method for the synthesis of 3,6-dihydropyran *via* Prins cyclization cyclization reaction mediated by TfOH (triflic acid) in good yields. The reaction is compatible with a wide range of functional groups such as ester, nitro, and halo. The aspect of this reaction is that it introduces the double bond at 4-position of the dihydropyrans *(Scheme 4)*.



Scheme 4. *Synthesis of 3,6-dihydropyran via Prins cyclization reaction mediated by TfOH.*

Index

CHAPTER 1

Introduction to Oxygen Heterocyclic Compounds

1.1. Background

The chemistry of heterocyclic compounds is the largest branch in the organic chemistry with more than half of the existed compounds coming under this category. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. If atleast one atom other than carbon forms a part of the ring system, then it is designated as a heterocyclic compound. Nitrogen, oxygen and sulfur are the most common hetero atoms but heterocyclic rings containing other hetero atoms (B, P, Si, Se etc.) are also well known. These compounds generally consist of small (3- and 4- membered) and common (5 to 7 membered) ring systems. In aliphatic heterocycles, six membered rings play a vital role as commonly occurring substructures found throughout the nature in various forms. These are the building blocks of numerous natural compounds from antibiotics to vitamins and liposaccharides due to their less ring strain and more abundance.[1]

This introductory chapter is intended to provide an insight into the evolution of some six membered oxygen containing biologically active compounds and their biological significance. This chapter also focuses on important synthetic routes for the synthesis of six membered cyclic ethers and their analogues *viz*., isochroman, dihydropyran, tetrahydropyran and dihydro-γ-pyrone derivatives and their application in natural product synthesis.

1.2. Importance of oxygen containing Heterocyclic Compounds

Five and six membered oxygen containing heterocycles possess significant biological properties among them dihydropyrans, tetrahydropyrans, tetrahydrofurans and isochromans are widely spread in natural products and in biologically active molecules. As for example martiriol **1**, a dihydropyran unit containing biological active molecule, isolated from the red algae of the genus *Laurencia*, shows potent activity against various tumour cell lines.[2] Salinomycin **2** a dihydropyran containing polyether isolated from a culture broth of *Streptomyces albus* which has been shown to possess interesting antibacterial and anticoccidial properties.[3] Laulimalide **3** is a structurally novel cancer therapeutic lead, recently isolated in trace quantities from pacific marine sponges.[4] Aspergillide C **4** constitute a novel class of dihydropyran containing 14-membered macrolides, isolated along with its structurally related aspergillides A an B by Kusumi *et al*. from the marine-derived fungus *Aspergillus ostianus* strain 01F313, cultured in a medium composed of bromine modified artificial sea water *(Figure 1.2.1).*[5]

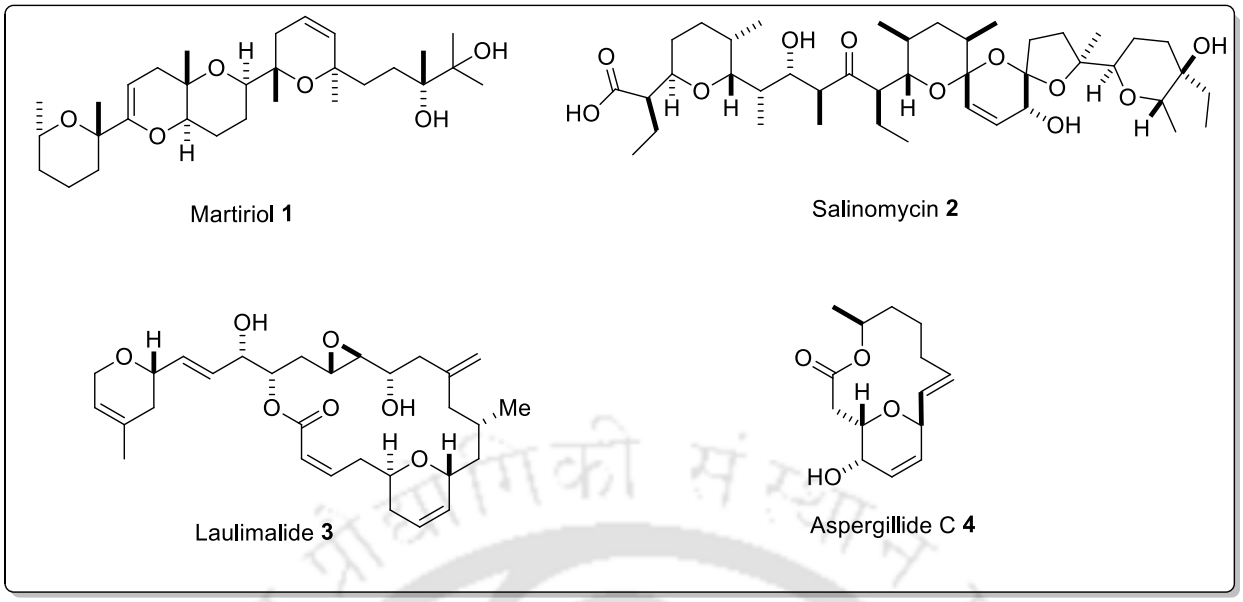


Figure 1.2.1. *Bioactive molecules containing dihydropyran ring*

Tetrahydropyran units are also widely spread among biologically active natural products such as polyether antibiotics, marine toxins and pheromones.[6] For example (-)-centrolobine **5** was isolated from the heart-wood of the tree *Centrolobiumtomentosum*, whereas its enantiomer (+)-centrolobine occurs in the closely related species *Centrolobiumrobustum*. Both enantiomers have antibiotic and anti-fungal activities.[7]

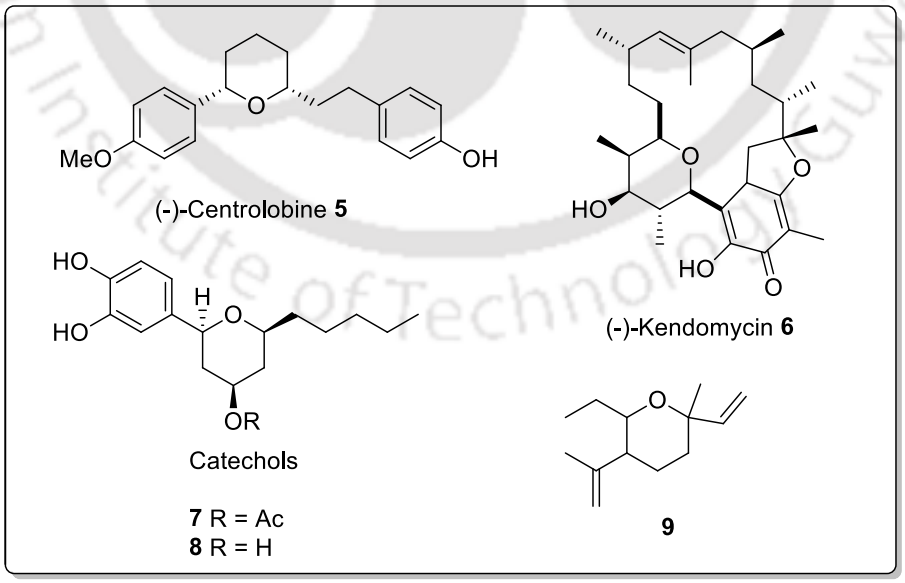


Figure 1.2.2. *Bioactive molecules containing tetrahydropyran ring*

Tetrahydropyran containing macrocycle, (–)-kendomycin **6** has a diverse and fascinating pharmacological profile. It was isolated in 1996 from *Streptomyces* bacteria and exhibits potent antagonism of the endothelin receptor agonism.[8] Catechols **7** and **8** isolated from the extracts of *Plectranthus sylvestris* (labiatae), a plant found in the woody hills in East Africa are potent antioxidants and possesses anti-inflammatory properties.[9] An Alkyl substituted tetrahydropyrans **9** are also used as aroma and flavouring substances for pharmaceuticals, cosmetics and food stuffs (*Figure 1.2.2*).[10]

Furan nucleus is also found in a large number of biologically active compounds. For example, sixteen membered macrodiolide pamamycin-607 **10** isolated from *Streptomyces alboniger* and *S. Aurantiacus* shows potent activity against gram-positive bacteria as well as against phytopathogenic fungi.[11] The mycotoxin (-)-citreoviridin **11**, isolated from *Penicillum citreoviride* is a potent inhibitor of the soluble mitochondrial ATPase.[12] Muscarine **12**, a furan containing biologically active alkaloid is the major toxic principle found in the well-known mushroom *Amanita muscaria* (Fly agaric).[13]

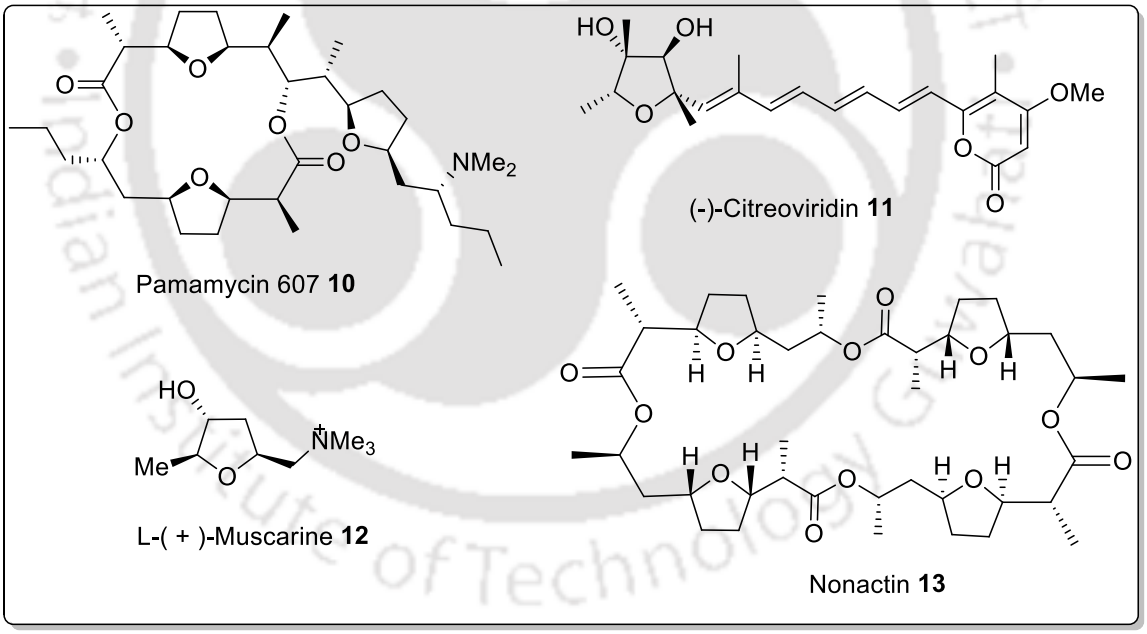


Figure 1.2.3. *Bioactive molecules containing tetrahydrofuran ring*

Muscarine acts as a selective agonist of the neurotransmitter acetylcholine on smooth muscles of the gastrointestinal tract, eye exocrine glands and heart.[14] Nonactin (**13**), an ionophoric macrolide antibiotic isolated from a variety of *Streptomyces* cultures has been shown to possess antitumor activity both against mammalian cell lines in *vitro* and against crocker sarcoma 180 in studies with mice (*Figure 1.2.3*).[15]

Another important class of cyclic ethers is isochromans in which a pyran ring fused with a benzene ring is present. Isochroman fragment is the core of various natural compounds, which exhibit a wide variety of pharmacological activities which are promising for the treatment of migraines, Parkinson's disease and Schizophrenia respectively.[16] Penidicitrininm B **14** isolated from *Penicillium citrinum strains*, and containing C-1 phenyl substituted isochroman ring possesses antioxidant properties.[17]

Similarly, a wide spread 1-Aryl-6,7-dimethoxyisochromans shows a wide range of biological activities such as analgesic, muscle relaxant, anti-depressant, anti-inflammatory, anti-histaminic, anti-coagulant, hypotensive with peripheral and central activities, and are adrenergic antagonists.[18] Biologically active compound **15** containing a isochroman ring shows affinity towards Ca-receptors.[19] Sonepiprazole U-101387 (**16**) which exhibits high affinity for the D_4 receptor is potentially useful for treatment of Schizophrenia. A series of dimethoxyisochromans *e.g.* U-54537 **17** have activity to decrease the blood pressure presumably by both peripheral and central α-adrenoreceptor blockade.[20] PNU-109291 (**18**) containing isochroman ring is selective 5-HT_{1D} receptor agonist with anti-migraine potential, like Sumatriptan *(Figure 1.2.4).*[19]

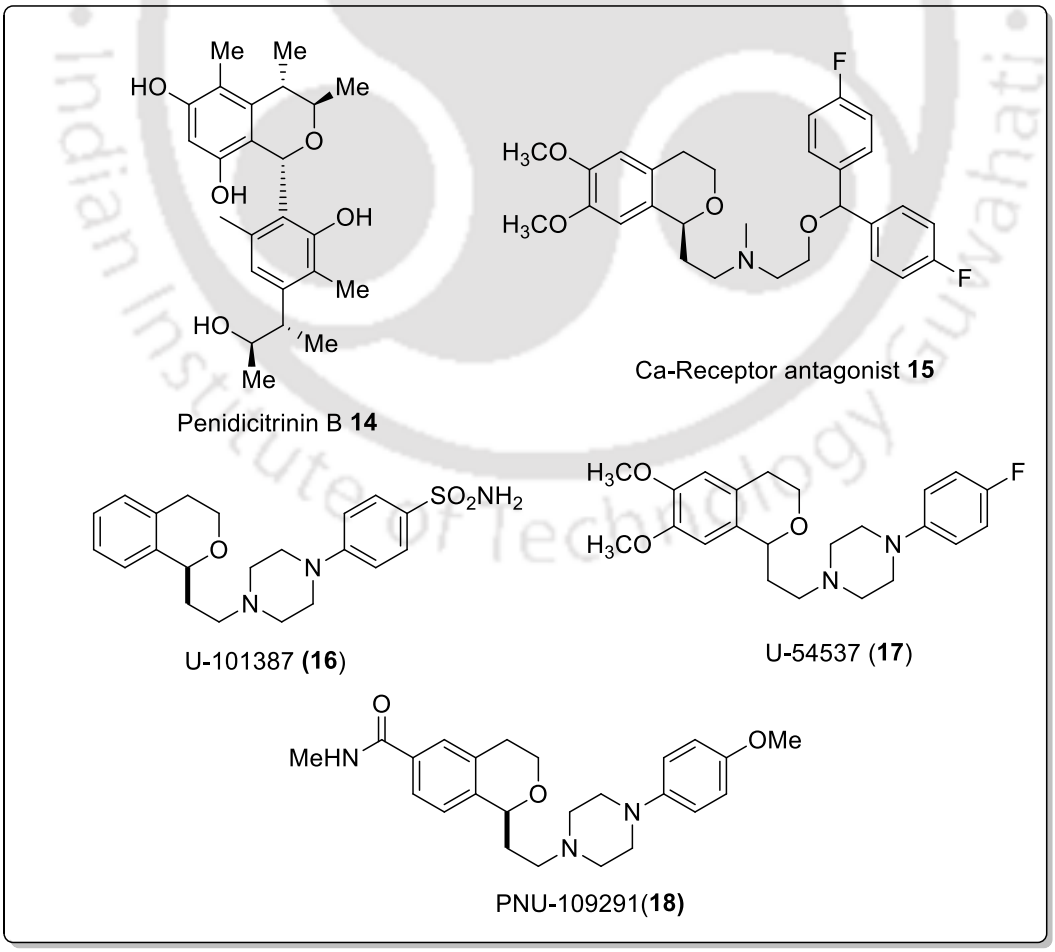


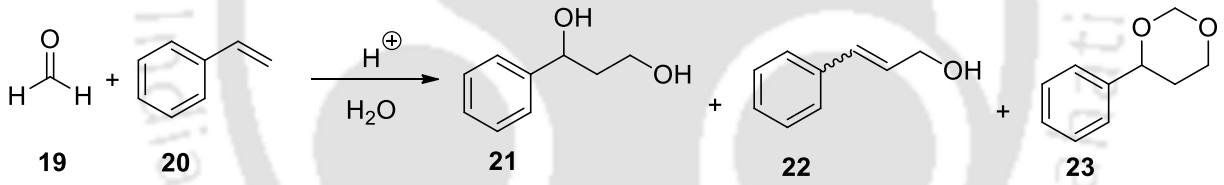
Figure 1.2.4. *Bioactive molecules containing isochroman ring*

1.3 An Overview for the Synthesis of Dihydropyrans, Tetrahydropyrans, Tetrahydrofurans and Isochromans

To build this class of heterocycles, many strategies have been developed over the years. The most widely used methods are the Prins cyclization reaction, Hetero-Diels–Alder (HDA) reaction, oxonium-ene cyclization, intramolecular Michael additions, ring-closing metathesis, hydroalkoxylation of alkenols, oxa-Pictet-Spengler reaction and Friedel−Crafts type intramolecular reaction and Baylis-Hillman reaction. Reported methods used for this oxygen containing heterocycles have their own advantages and disadvantages. Therefore, development of new and efficient methods is imperative specially to address the issue of diastereoselectivity.

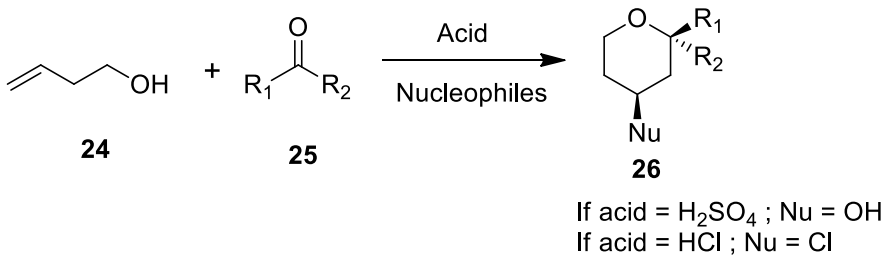
1.3.1. Prins cyclization reaction

The Prins reaction is one of the fundamental methods for C-C bond formation, first reported by H. J. Prins in the year 1919. In his initial studies, H. J. Prins performed the reaction of formaldehyde **19** and styrene **20** in aqueous acidic medium, resulting in a mixture of products such as diol **21**, unsaturated alcohol **22** and 1,3-dioxane **23** *(Scheme 1.3.1.1)*.[21]



Scheme 1.3.1.1

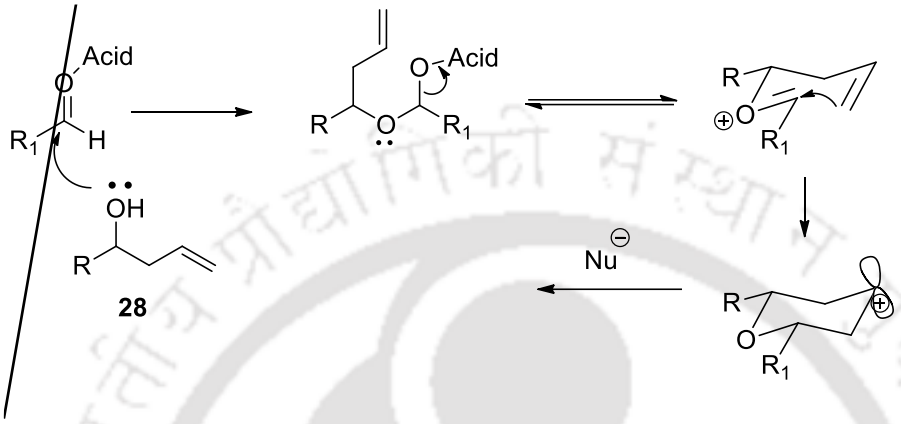
In 1955, Hanschke has further developed Prins reaction for the selective synthesis of THP rings **26** by combining 3-buten-1-ol **24** with a variety of aldehydes or ketones **25** in the presence of acid, called Prins cyclization reaction *(Scheme 1.3.1.2)*.[22]



Scheme 1.3.1.2

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 of the reaction was explained as follows.[23]

Homoallylic alcohol **28** reacts with 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**.



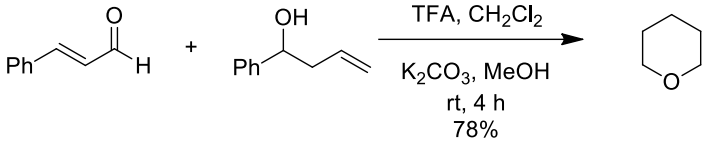
Scheme 1.3.1.3. *Mechanism of the Prins cyclization reaction*

According to Alder's DFT calculations, carbocation **31** 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 1.3.1.3).*

Chan and co-workers have reported the synthesis of symmetrical *cis* 4-fluorotetrahydropyrans **35** from the reaction of two equivalents of aldehyde **33** and alkoxyallylsilane **34** catalyzed by boron trifluoride etherate at -78 ^{o}C *(Scheme 1.3.1.4).*[24]

Scheme 1.3.1.4

Yadav *et al*. developed a concise and efficient total synthesis of diospongin A **55** which is active against osteoporosis, using Prins cyclization reaction and enzymatic kinetic resolution as key steps. 2,4,6-*cis*-trisubstituted tetrahydropyran ring **54** was achieved *via* Prins cyclization reaction of cinnamaldehyde **52** and homoallylic alcohol **53** catalyzed by trifluoroacetic acid *(Scheme 1.3.1.10).*[30]

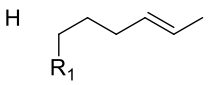


Scheme 1.3.1.10

Willis and co-workers have reported a Prins type cyclization of homoallylic acetals **56** for the synthesis of 2,4,5-trisubstituted tetrahydropyrans **57** and **58**. The reaction is versatile and by varying the acid ($TiCl_4$ or TFA) different C-4 substituted tetrahydropyrans were obtained *(Scheme 1.3.1.11).*[31]

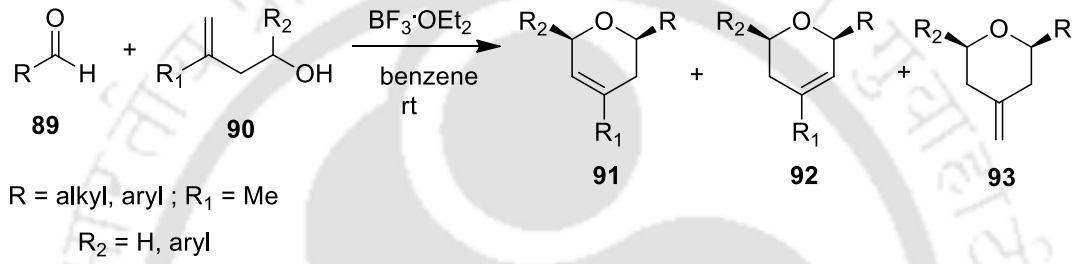
Scheme 1.3.1.11

Szabó and co-workers have reported a methodology for the synthesis of 2,3,5,6-substituted tetrahydropyrans **62** from the reaction of functionalized allylsilanes **59** and aldehydes **60** mediated by TMSOTf in dichloromethane at -78 °C with excellent stereoselectivity *(Scheme 1.3.1.12).* According to DFT calculations, the high stereoselectivity arises from electronically induced steric effects occurring in the key-intermediate of the cyclization.[32]



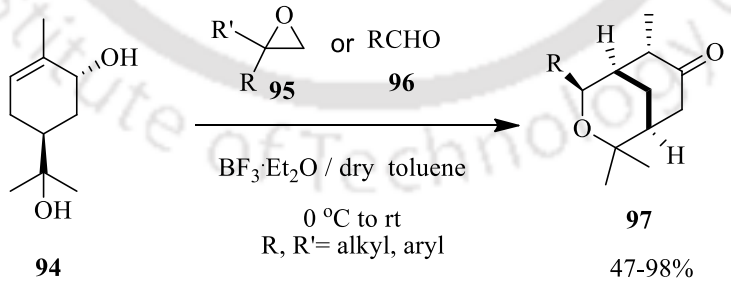
Scheme 1.3.1.12

Our group has also reported a diastereoselective methodology for the synthesis of dihydropyrans from 1, 1-disubstituted homolallylic alcohols **90** and aldehydes **89** *via* oxonium–ene cyclization reaction mediated by boron trifluoride etherate. The reaction of aromatic aldehydes with methyl substituted alcohols (R_1= Me and R_2 = H) gave endo cyclic compound **91** as the major product with a minor exocyclic product **93** whereas the aliphatic aldehydes with methyl substituted alcohols (R_1 = Me and R_2 = H) gave two isomeric endocyclic **91**/**92** with a ratio 3:1. Reaction of phenyl substituted alcohols (R_1= Ph and R_2 = H) with aromatic aldehydes gave single endocyclic isomer **91** but with aliphatic aldehydes it gave two isomeric endocyclic **91**/**92** with a ratio 3:1. The reaction of alcohols with substitution at C-1 position and aromatic aldehydes gave only exocyclic *cis*-product **93** in good yields but with aliphatic aldehydes it gave **91**/**92** with 3.5:6.5 *(Scheme 1.3.3.3).*[39]



Scheme 1.3.3.3

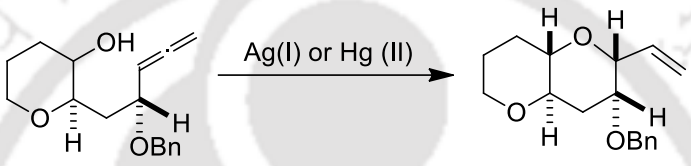
The same group also reported the synthesis of oxabicyclo[3.3.1]nonanone **97** *via* [3,5]-oxonium-ene reaction from the reaction of epoxides **95** or aldehydes **96** with commercially available *trans*-*p*-menth-6-ene-2,8-diol **94** mediated by boron trifluoride etherate in good yields 50-98%, *(Scheme 1.3.3.4).*[40]



Scheme 1.3.3.4

1.3.4. Hydroalkoxylation of alkenols

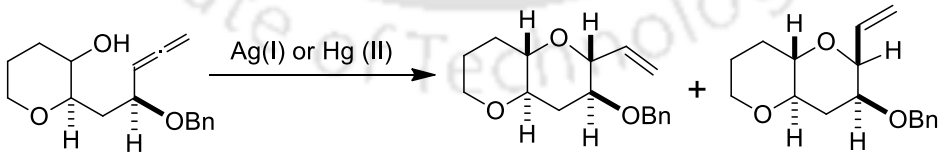
Intramolecular hydroalkoxylation of alkenols are also found importance in the synthesis of various five and six membered oxygen heterocyclic compounds. Mori and co-workers have reported the synthesis of fused tetrahydropyrans *via* intramolecular hydroalkoxylation of *δ*-hydroxy allenes installed on a tetrahydropyran template **98** catalyzed by silver(I)- and mercury(II) *(Scheme 1.3.4.1).* Cyclization of simple allenes with $AgClO_4$ (1.2 equivalents) in dichloroethane at 50 ^oC for 20h afforded bis-tetrahydropyran **99** in 88% yield where as with $AgNO_3$ (4.0 equivalents) in dioxane/ H_2O at 80 $^\circ C$ observed yield was 40%. The reactions with $AgBF_4$ and AgOTf were also effective in affording the product in moderate yields and the reaction with $Hg(OTf)_2$ caused significant decomposition of the reaction mixture even with a catalytic amount at a lower temperature (0 $^\circ C$).[41]



98 **99**

Scheme 1.3.4.1

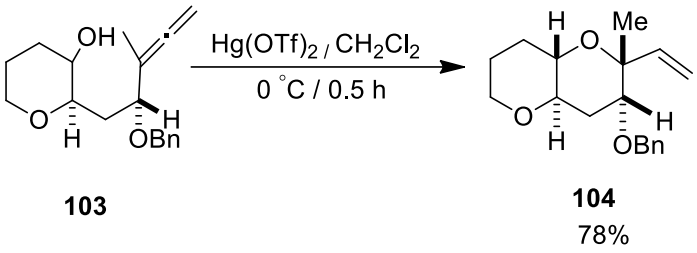
The hydroalkoxylation of the diastereomeric *δ*-hydroxy allene **100** was also examined and found that cyclization was also promoted by silver salts, but the yields were generally low and a mixture of diastereoisomers were formed. Treatment of **100** with $AgClO_4$ or $AgBF_4$ led to inseparable 8:1 mixtures of isomers **101** and **102** in 42% or 32% combined yields, respectively. Diastereomeric ratio increased to 49:1 when AgOTf was employed. In contrast to the silver(I)-mediated reactions, the mercury(II)-catalyzed hydroalkoxylation showed the opposite diastereoselectivity to afford a 1:2 mixture of products in 59% yield *(Scheme 1.3.4.2).*[41]



100 **101** **102**

Scheme 1.3.4.2

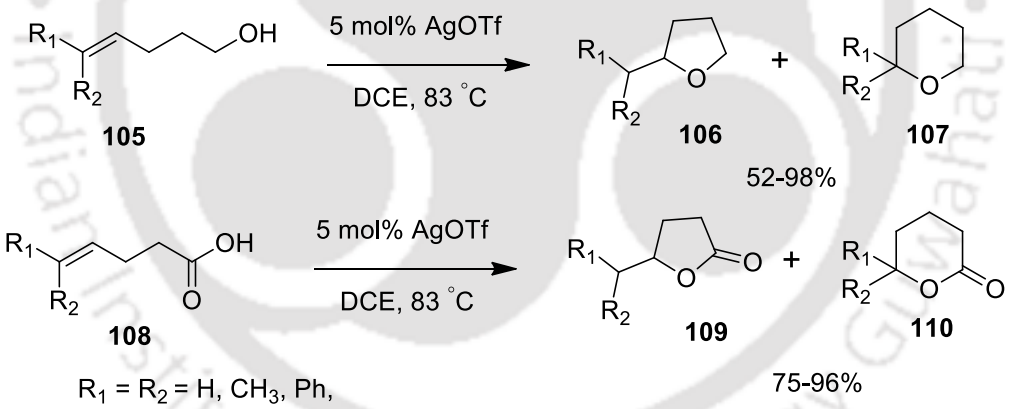
The cyclization of methyl-substituted allenes **103** at the internal allenic carbon atom was achieved more effectively with a catalytic amount of mercuric triflate rather than with silver salts *(Scheme 1.3.4.3).*[41]



103 **104** 78%

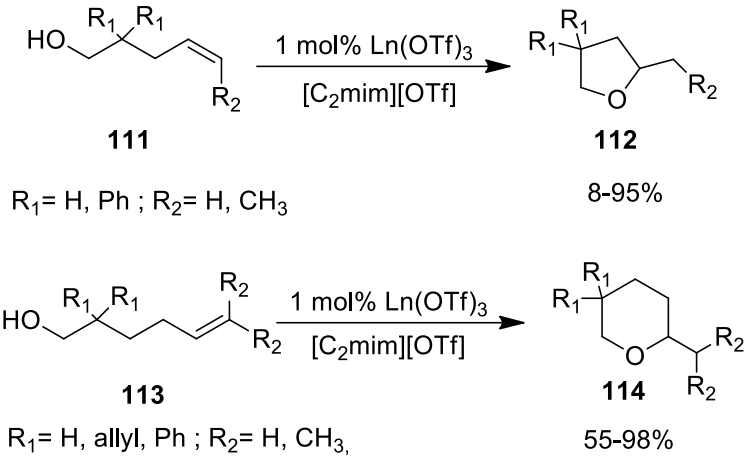
Scheme 1.3.4.3

Chaun and co-workers have reported a methodology for the synthesis of cyclic ethers **106**/**107** or lactones **109**/**110** *via* intramolecular hydroalkoxylation and hydroacyloxylation of inert olefins **105** or **108** catalyzed by 5 mol % silver(I) triflate giving good to excellent yields *(Scheme 1.3.4.4).* The use of a terminally monosubstituted olefin gave a mixture of the 5-exo and 6-endo cyclic products with the 5-exo product significantly favored. However, the 6-endo cyclic ethers were found to be the sole products for terminal di-substituted alkenes and a *γ*-hydroxyl alkene with a phenyl substitution at the terminus.[42]



Scheme 1.3.4.4

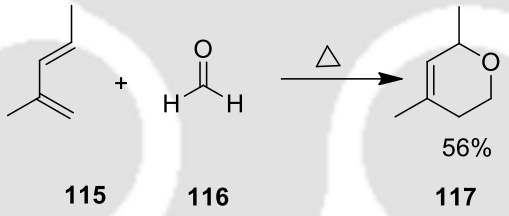
Marks and co-workers have reported the synthesis of substituted tetrahydrofurans **112** and pyrans **114** *via* intramolecular hydroalkoxylation of alkenols **111** and **113** respectively catalyzed by $Ln(OTf)_3$ in imidazolium-based ionic liquids *(Scheme 1.3.4.5).* The relative ordering of catalytic activity was found in the order $Yb^{3+} > Sm^{3+} > La^{3+}$. They have also done the kinetic study of the reaction and found the reaction as first-order dependence on $[Ln^{3+}]$ and [substrate].[43]



Scheme 1.3.4.5

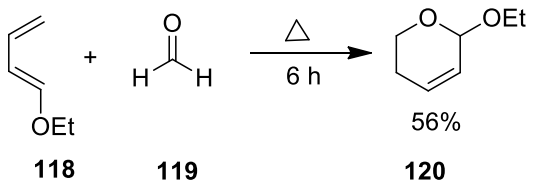
1.3.5. Hetero-Diels-Alder (HDA) reaction

Hetero Diels-Alder (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 **117** by reacting methylpentadiene **115** with formaldehyde **116** *(Scheme 1.3.5.1)*.[44] This was an unusal reaction as in this case formaldehyde was acting as a dienophile.



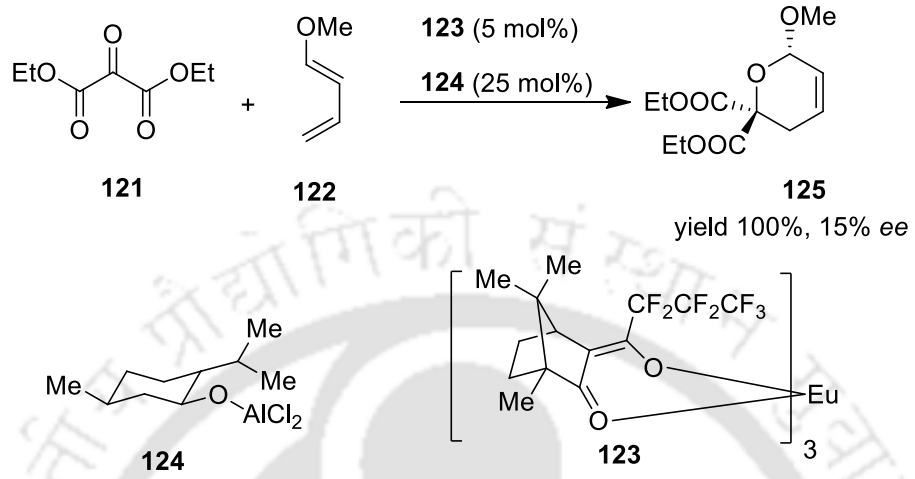
Scheme 1.3.5.1

In 1962 Kubler found that an electron donating group, usually alkoxy group on the 1-position of a diene **118** provides sufficient activation to permit the Diels-Alder reaction with formaldehyde **119**, to give 2-alkoxy-5,6-dihydro-2*H*-pyrans **120** *(Scheme 1.3.5.2)*.[45]



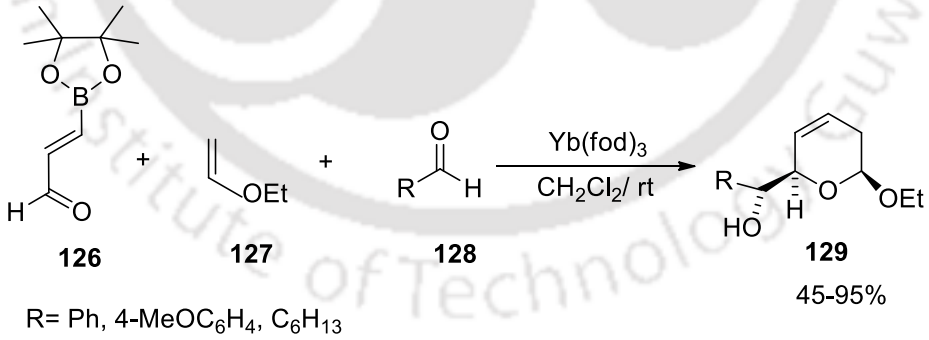
Scheme 1.3.5.2

Jankowski *et al*. have reported the enantioselective HDA reaction using combination of 5 mole % of chiral lanthanide catalysts tris[3-(heptafluoropropylhydroxymethy1ene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$], i.e., Koga catalyst **123** and 25 mol % of terpenyloxyaluminium dichlorides catalyst **124** for the reaction of ketomalonate **121** and 1-methoxy-1,3-butadiene **122**, which gave the reaction gave 100 % yield of **125** with 15% ee *(Scheme 1.3.5.3).*[46]



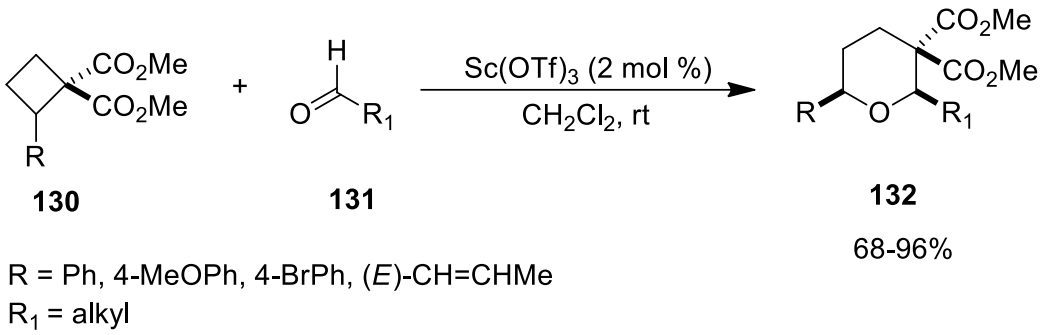
Scheme 1.3.5.3

Carreaux *et al*. have developed a strategy for the preparation of *α*-hydroxyalkyl dihydropyrans **129** using an approach based on a tandem hetero [4+2] allylboration reaction. The reaction begins with the [4+2] cycloaddition of (2*E*)-3-boryacrolein **126** with ethyl vinyl ether **127** followed by the addition of aldehyde **128** catalyzed by Yb(fod)$_3$ *(Scheme 1.3.5.4).*[47]



Scheme 1.3.5.4

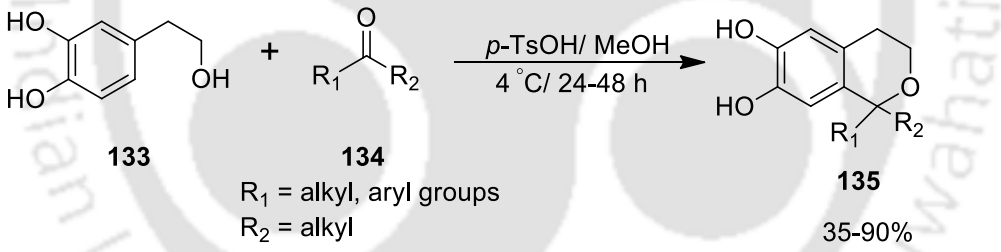
Johnson *et al*. have reported the synthesis of *cis*-2,6-disubstituted tetrahydropyrans **132** *via* HDA reaction between malonate derived cyclobutanes **130** and aldehydes **131** catalyzed by Sc(OTf)$_3$ with 2 mol % in dichloromethane at room temperature *(Scheme 1.3.5.5).*[48] The resulting THP products are of interest because of their prevalence in biologically relevant and structurally interesting molecules



Scheme 1.3.5.5

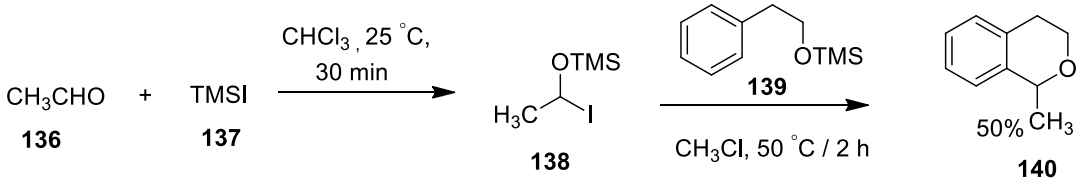
1.3.6. Oxa-Pictet-Spengler reaction

In 1922 first time Wünsch and Zott 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 his co-workers have developed a method for the synthesis of substituted isochromans **135** *via* oxa-Pictet-Spengler reaction between 2-(3,4-dihydroxy)phenylethanol **133** and carbonylic compounds **134** using *p*-toluenesulfonic acid as a catalyst in methanol at 4 °C *(Scheme 1.3.6.1)*. In these reaction conditions it was found that aldehydes react faster than ketones and those aromatic aldehydes gave higher yields than their aliphatic counterparts. No side product was observed in this reaction conditions.[49]



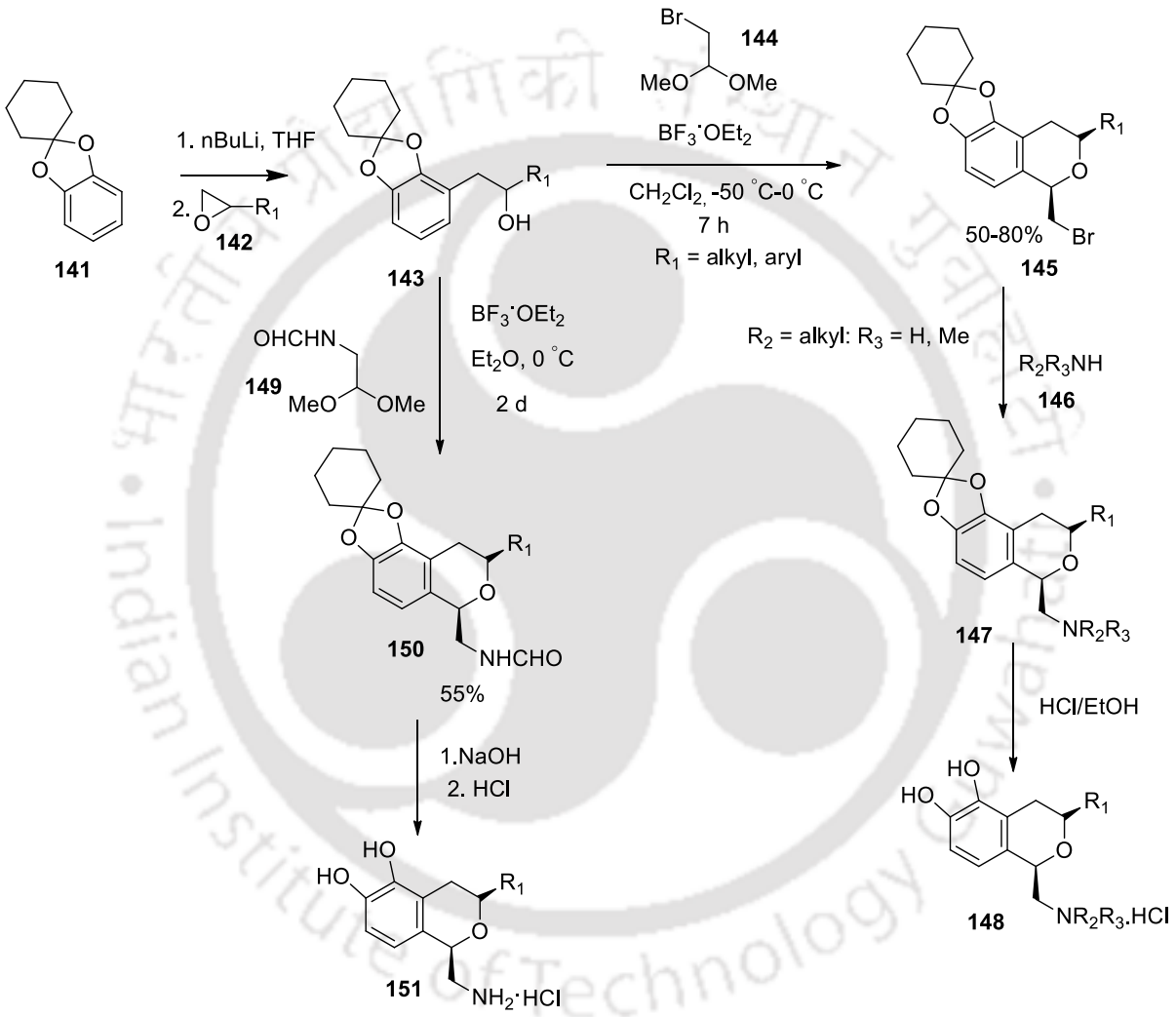
Scheme 1.3.6.1

Jung *et al*. have reported the synthesis of isochroman **140** by using protected *β*-phenethyl alcohol **139** and TMSI adduct of acetaldehyde **138** in chloroform at 50 °C *via* oxa-Pictet- Spengler and Friedel–Crafts reaction *(Scheme 1.3.6.2)*.[50]



Scheme 1.3.6.2

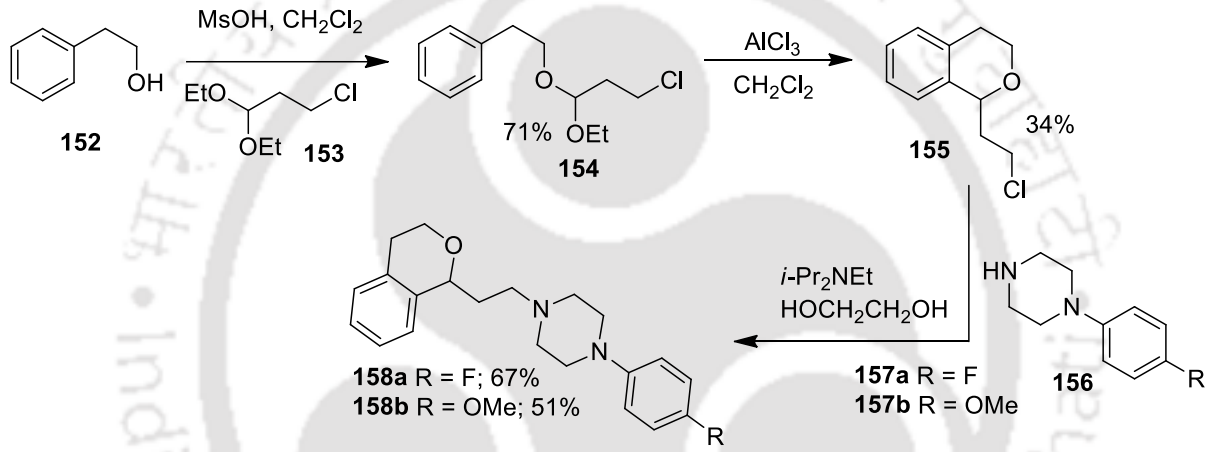
Michael and co-workers have reported the synthesis of 1,3-*cis* substituted isochromans *via* oxa-Pictet–Spengler reaction. They treated protected phenylethyl alcohol **143**, which was prepared *via* ring opening of epoxide **142** by the compound **141,** with bromoacetaldehyde dimethyl acetal **144** and with *N*-formyl aminoacetal **149** under boron trifluoride etherate to furnish **145** and **150** respectively. Treatment of **145** with substituted amine **146** followed by hydrolysis (HCl/ethanol) gave catecholamine hydrochloride salt **148**. Similarly, hydrolysis of **150** with sodium hydroxide followed by HCl/ethanol hydrolysis gave catecholamine hydrochloride salt **151** in good yields *(Scheme 1.3.6.3).*[51]



Scheme 1.3.6.3

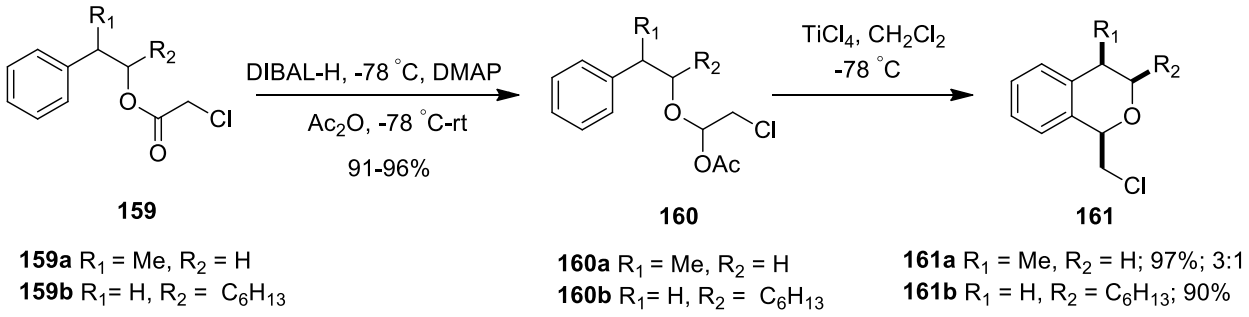
1.3.7. Intramolecular oxa-Pictet–Spengler cyclization

The intramolecular versions of the oxa-Pictet–Spengler cyclization comparise reactions in which the carbonyl component is attached to the *β*-aryl-ethanol in the form of a mixed acetal, a vinyl ether, an *α*-acetoxy ether or a halomethyl ether. Through this intramolecular oxa-Pictet–Spengler cyclization some natural compounds were synthesized such as **158a** and **158b** which exhibit an increased preference for the D_4 over the D_2 receptor, while retaining significant binding to other CNS receptors. The synthesis of these compounds were started with *β*-phenethyl alcohol **152** which was reacted with chloroacetal **153** to give mixed acetal **154**, this was isolated and subjected to an oxa-Pictet–Spengler cyclization to isochroman **155** with aluminum chloride as the Lewis acid promoter. Displacement of the halogen with different aryl piperazines (**157a** and **158b**) gave final products **158** in fair yields *(Scheme 1.3.7.1).*[52]



Scheme 1.3.7.1

Rychnovsky *et al*. have reported the synthesis of 1,3-*cis*-isochromans from chloroacetate **159b**, derived from a *β*-substituted *β*-phenylethyl alcohol, furnished exclusively 1,3-*cis*-isochromans **161b** in 90% yield through the intermediacy of **160b**. However, in the example involving the *α*-substituted congener **159a**, the same transformation from mixed acetal **160a** furnished 97% of **161a** as a 3:1 diastereomeric mixture *(Scheme1.3.7.2).*[53]



Scheme 1.3.7.2

From literature, it is worth mentioning that isochroman; tetrahydropyran compounds have impending application in various pharmacological activities and possess enormous potential for the synthesis of numerous natural products as well. As a consequence, chemists are always on a quest to the develop plethora of new and efficient catalytic route towards the synthesis of novel isochroman, tetrahydropyran molecules in eco-friendly manner with good yields. Thus, the thesis work is designed to employ for the synthesis of known and unknown isochroman, tetrahydropyran molecules *via* fine tuning of the reaction conditions which will be discussed in the successive chapters of this thesis.

1.4. References

1) Eicher, T.; Hauptmann, S. In *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed; 2003; Wiley-VCH Verlag GmbH, Weinheim.
2) (a) Souto, M. L.; Gavin, J. A.; Manriquez, C. P.; Norte, M.; Fernandez, J. J. *Tetrahedron* **2001**, *57*, 3117. (b) Soriente, A.; De Rosa, M. M.; Scettri, A.; Sodano, G.; Terencio, M. C.; Paya, M.; Alcarez, M. *Curro Med. Chem.* **1999**, *6*, 415.
3) (a) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, *49*, 4955. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.
4) Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc*. **2002**, *124*, 4956.
5) Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761.
6) (a) Polyether Antibiotics; Westly, J. W., Ed.; Dekker: New York, **1983**; Vols. I and II. (b) Faulkner, D. *J. Nat. Prod*. **2002**, *19*, 1. (c) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc*. **1999**, *121*, 10211. (d) Huang, H.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 9836. (e) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem*. **2004**, *69*, 1993. (f) Class, Y. J.; Deshong, P. *Chem. Rev*. **1995**, *95*, 1843. (g) Norcross, R. D.; Paterson, I. *Chem. Rev*. **1995**, *95*, 2041. (h) Evans, D. A.; Ratz, A, M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448. (i) Kang, S. H.; Lee, S. B.; *Tetrahedron Lett.* **1995**, *36*, 4089. (j) Lord, M. D.; Negri, J. T.; Paquette, L. A. *J. Org. Chem*. **1995**, *60*, 191.
7) (a) Colobert, F.; Mazery, R. D.; Solladié, G.; Carreňo, M. C. *Org. Lett*. **2002**, *4*, 3407. (b) Böhrsch, V.; Blechert, S. *Chem. Commun*. **2006**, 1968.
8) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231551 [A2960910], 1996. (b) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2008**, *130*, 13177.
9) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, L. C. *Org. Lett*. **2002**, *4*, 3407.
10) Oertling, H.; Brocke, C.; Loges, H.; Machinek, A. Eur. Pat. Appl. EP 2168957 A2, 2010, 30 pp.

11) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, H. K. *J. Am. Chem. Soc*. **2001**, *123*, 10131.

12) Whang, K.; Venkataramam, H.; Kim, Y. G.; Cha, J. K. *J. Org. Chem*. **1991**, *56*, 7174.

13) Taylor, E. C.; Jagdmann, Jr. G. E. *J. Org. Chem.* **1980**, *45*, 3375.

14) Chan, T. H.; Li, C. J. *Can. J. Chem*. **1992**, *70*, 2726.

15) Lee, J. Y.; Kim, B. H. *Tetrahedron* **1996**, *52*, 571.

16) (a) Lu, Z.; Lin, Z.; Wang, W.; Du, L.; Zhu, T.; Fang, Y.; Gu, Q.; Zhu, W. *J. Nat. Prod*. **2008**, *71*, 543. (b) Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H.; Edrada, R.; Muller, W. E. G.; Bayer, M.; Lin, W.; Wu, J.; Proksch, P. *Bioorg. Med. Chem*. **2009**, *17*, 7362. (c) Liu, H. –C.; Du, L.; Zhu, T.-J.; Li, D. –H.; Geng, M. Y.; Gu, Q. Q. *Helv. Chim. Acta* **2010**, *93*, 2224. (d) Bogdanov, M. G.; Todorov, I. S.; Manolova, P. G.; Cheshmedzhieva, D. V.; Palamareva, M. D. *Tetrahedron Lett*. **2004**, *45*, 8383.

17) (a) Muramatsu, W.; Nakano, K. *Org. Lett*. **2015**, *17*, 1549. (b) Parhi, B.; Gurjar, J.; Pramanik, S.; Midya, A.; Ghorai, P. *J. Org. Chem*. **2016**, *81*, 4654. (c) Peng, Z.; Wang, Y.; Zhi, Y. Zhao, D; Song, L.; C. Jiang, C. *J. Org. Chem.* **2018**, *83*, 7900.

18) (a) Dobson, T. A.; Humber, L. G. *J. Heterocyclic Chem*. **1975**, *12*, 591. (b) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Kokubu, N.; Inoue, Y.; Tsuruo, T.; Tashiro, T. *J. Med. Chem*. **1985**, *28*, 1026. (c) McCall, J. M.; McCall, R. B.; TenBrink, R. E.; Kamdar, B. V.; Humphrey, S. J.; Sethy, V. H.; Harris, D. W.; Daenzer, C. *J. Med. Chem*. **1982**, *25*, 75.

19) Richter, H.; Rohlmann. R.; Mancheño, O, G. *Chem. Eur. J*. **2011**, *17*, 11622.

20) Tenbrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435.

21) (a) Prins, H. J. *Proc. Acad. Sci. Amsterdam* **1919**, *22*, 51. (b) Prins, H. J. *Chem. Weekbl*. **1919**, *16*, 1510.

22) Hanschke, E. *Chem. Ber*. **1955**, *88*, 1053.

23) (a) Arundale, E.; Mikesa, L. A. *Chem. Rev*. **1952**, *51*, 505. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (c) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc*. **2002**, *124*, 4960.

24) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768.

25) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem*. **2001**, *66*, 4679.

26) Reddy, U. C.; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem*. **2008**, *73*, 1628.

27) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem*. **2009**, *74*, 2605.

28) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett*. **2002**, *4*, 3919.

29) Miranda, L. S. M.; Meireles, B. A.; Costa, J. S.; Pereira, V. L. P.; Vasconcellos, M. L. A. A. *Synlett* **2005**, 869.

30) Yadav, J. S.; Padmavani, B.; Reddy, B. V. S.; Venugopal, C.; Rao, A. B. *Synlett* **2007**, 2045.

31) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun*. **2001**, 835.
32) Kjellgren, J.; Szabó, K. J. *Tetrahedron Lett*. **2002**, *43*, 1123.
33) Castaldi, M. P.; Troast, D. M.; Porco, Jr. J. A. *Org. Lett*. **2009**, *11*, 3362.
34) Hu, X.-H.; Liu, F.; Loh, T.-P. *Org. Lett*. **2009**, *11*, 1741.
35) Reddy, U. C.; Saikia, A. K. *Synlett* **2010**, 1027.
36) Huang, H.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 9836.
37) (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305. (c) Berrisford, D. J.; Bolm, C. *Angew. Chem. Int. Ed.* **1995**, *34*, 1717.
38) Saha, P.; Ghosh, P.; Sultana, S.; Saikia, A. K. *Org. Biomol. Chem*. **2012**, *10*, 8730.
39) Bonbdalapati, S.; Reddy, U. C.; Saha, P.; Saikia, A. K. *Org. Biomol. Chem*. **2011**, *9*, 3428.
40) Saha, P.; Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Org. Lett*. **2010**, *12*, 1824.
41) Suzuki, Y.; Kuwabara, A.; Koizumi, Y.; Mori, Y. *Tetrahedron* **2013**, *69*, 9086.
42) Yang, C. G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett*. **2005**, *7*, 4553.
43) Dzudza, A.; J. Marks, T. *J. Org. Lett*. **2009**, *11*, 1523.
44) Gresham, T. L.; Steadman, T. R. *J. Am. Chem. Soc*. **1949**, *71*, 737.
45) Kubler, D. G. *J. Org. Chem*. **1962**, *27*, 1435.
46) Quimpère, M.; Jankowski, K. *J. Chem. Soc. Chem. Commun*. **1987**, 676.
47) Carreaux, F., Deligny, M., Carboni, B., Toupet, L., Dujardin, G. *Chem. Commun.* **2003**, 276.
48) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 14202.
49) Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531.
50) Jung, E. M.; Mossman, B. A.; Lyster, A. *J. Org. Chem*. **1978**, *43*, 3698.
51) Michaelides, M. R.; Schoenleber, R.; Thomas, S.; Yamamoto, D. M.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem*. **1991**, *34*, 2946.
52) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, *2*, 0187.
53) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett*. **1998**, *39*, 7271.

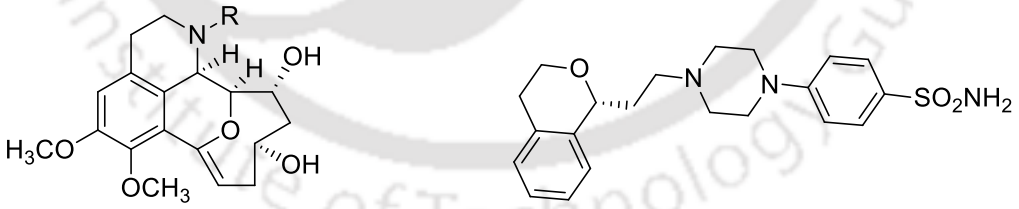
CHAPTER 2

Synthesis of Isochroman Derivatives *via* Oxa-Pictet-Spengler Reaction of Acrylyl Enol Ethers: Formal Synthesis of (±) – Sonepiprazole (U-101387) and (±)-U-54537

2.1. Biological Importance of Isochromans

Cyclic ethers are one of the most common structural motifs spread across biologically active natural products and synthetic pharmaceuticals, and significant efforts have been devoted to their synthesis. For example, isochroman motif constitutes the framework of many natural products, also present in many structures of drugs as well as that of synthetic and semisynthetic compounds of interest. Molecules belonging to this small family have been synthetically studied since 1912, when Schmidlin and Garcia-Banùs, first reported the unexpected formation of 1,3-diphenylisochroman from the reaction of benzaldehyde with benzylmagnesium chloride.[1] Isochromans are also useful intermediates for the synthesis of isocoumarins, benzophenones, benzodiazepine-4-ones and other compounds.[2]

Excentricine (**1a**) and *N*-methylxcentricine (**1b**), alkaloids were isolated from the roots of *Stephania excentrica* carrying the isochroman moiety.[3] Compound U-101387 (**2**) a dopamine D4 antagonist potentially useful for treatment of Schizophrenia (Figure 2.1.1)[2].



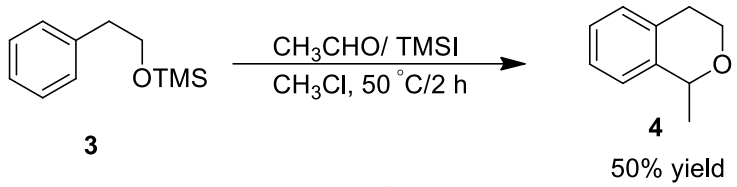
1(**a**) R= H, Excentricine
1(**b**) R= Me, *N*- Methylxcentricine

2 U-101387

Figure 2.1.1. *Biologically active natural products containing isochroman moiety*

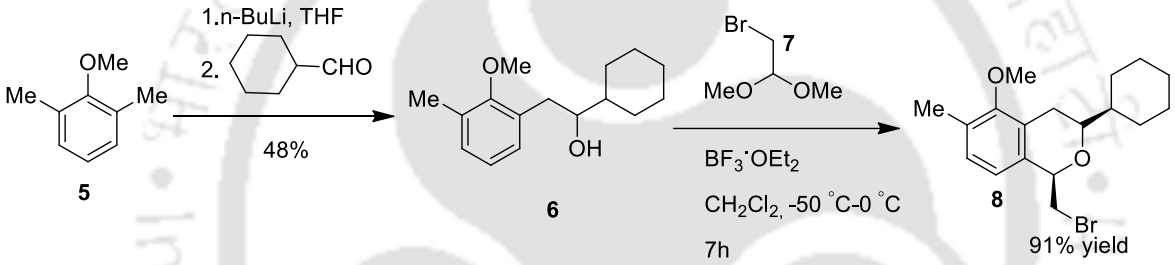
2.2. Literature Methods

Jung et al. have reported the synthesis of Isochroman by using protected *β*-phenethyl alcohol, and TMSI adduct of acetaldehyde *(Scheme 2.2.1).*[4]



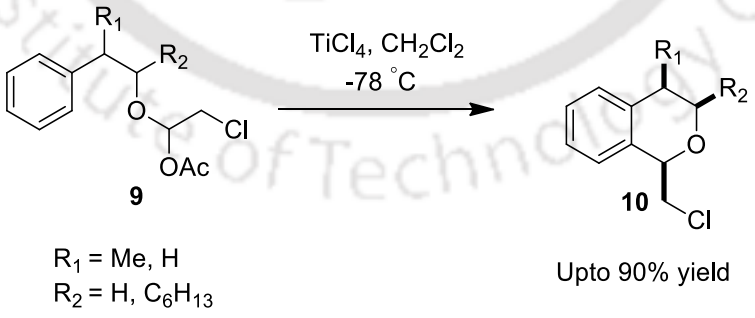
Scheme 2.2.1

Michaelidis and co-workers reported the synthesis of 3-cyclohexylisochroman **8** derivatives from phenolic ether **5,** followed by reaction with cyclohexane carboxaldehyde gave the required substituted phenylethyl alcohol **6**. Which upon cyclocondensed in an oxa-Pictet–Spengler reaction with or with out bromoacetal **7** to give desired substituted isochroman **8** *(Scheme 2.2.2).*[5]



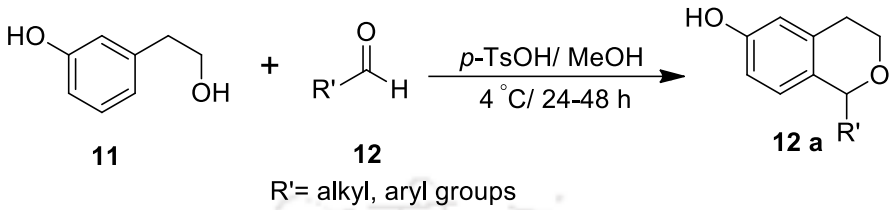
Scheme 2.2.2

Rychnovsky's *et al* has reported the synthesis of trisubstituted isochroman **10** by using acetal **9** with $TiCl_4$ *(Scheme 2.2.3).*[6]



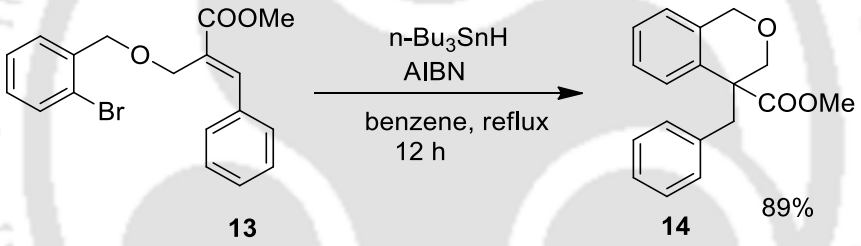
Scheme 2.2.3

Guiso and his co-workers developed the synthesis of substituted isochroman **12a** *via* oxa-Pictet Spengler reaction between substituted phenyl ethyl alcohol **11** and aldehydes **12** as shown below *(Scheme 2.2.4).*[7]



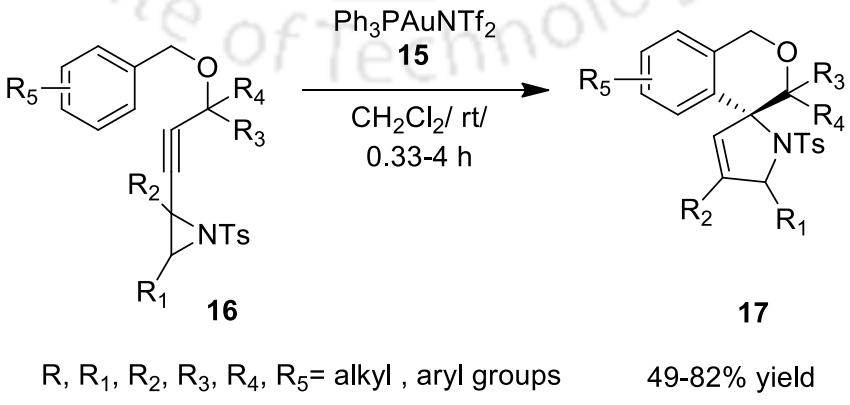
Scheme 2.2.4

Kim and his co-workers developed a radical cyclization synthesis of isochroman **14** *via* Baylis-Hillman reaction as shown below *(Scheme 2.2.5).*[8]



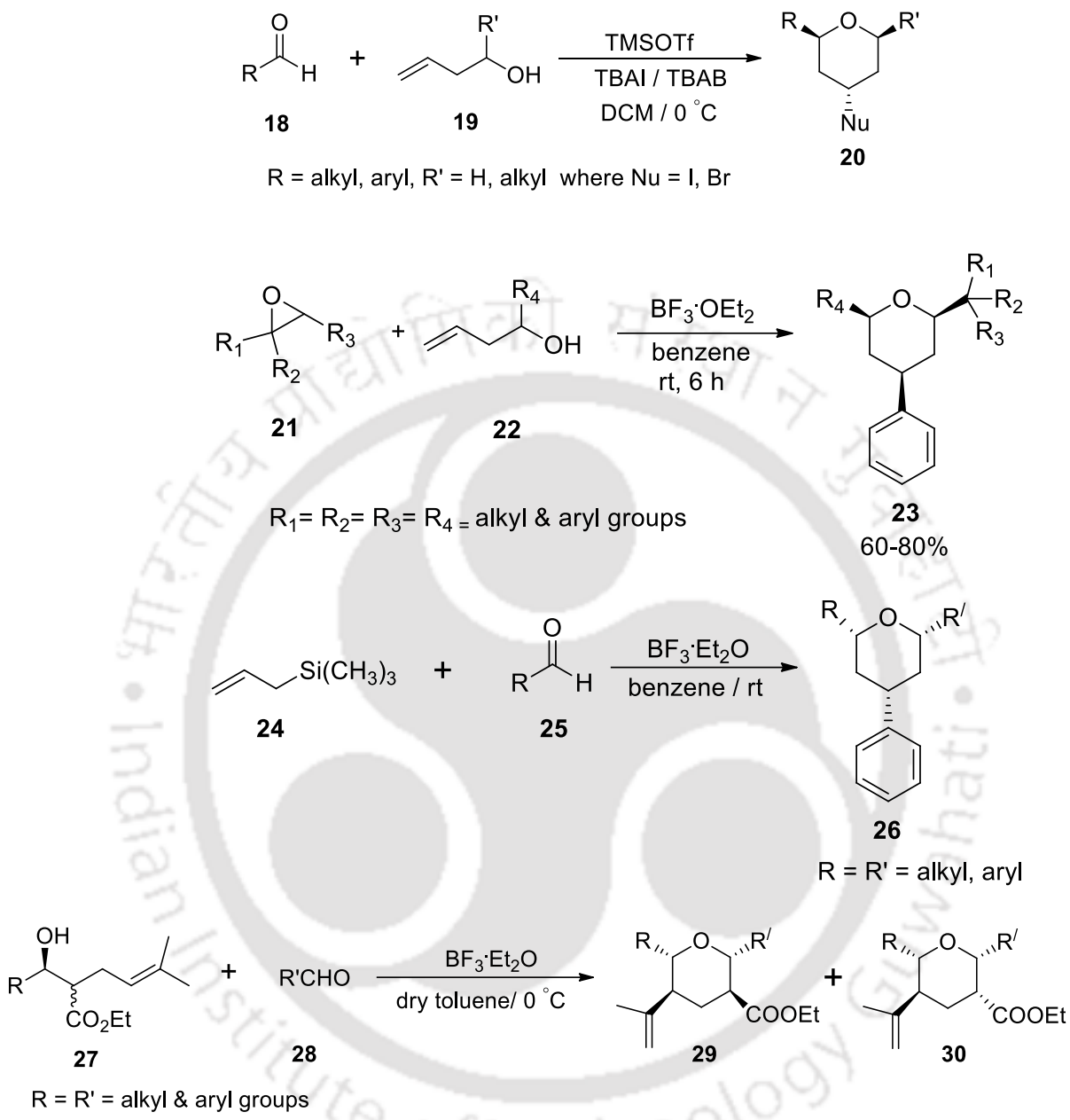
Scheme 2.2.5

Patrick Pale *et al.* have developed a method for the synthesis of substituted isochroman **17** by using the gold (I) complex with the starting material **16** *(Scheme 2.2.6).*[9]



Scheme 2.2.6

Saikia *et al.* have developed following Lewis acids mediated procedures for the synthesis of tetrahydropyrans *(Scheme 2.2.7).*[10]



Scheme 2.2.7

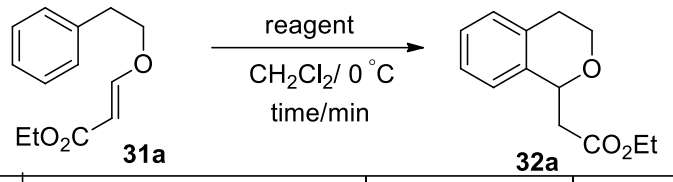
A literature survey of the existing methodologies to access isochromans and tetrahydropyrans reveals a range of efficient and selective pathways. While various routes possess their individual assets, a number of limiting issues recur throughout the literature. Many methods require the lengthy synthesis of a reaction precursor and require rigorous or difficult to achieve reaction conditions or employ undesirable reagents such as those with toxicity issues and lack of steric and region selectivity. As such there is still much interest in the development of new methodologies to address the aforementioned issues for novel routes to isochromans.

2.3. Results and Discussions

Heterocyclic structures are considered as prominent features in synthetic chemistry because of their existence in many natural products and biologically active molecules. Particularly, oxygen heterocyclic compounds fused with aromatic ring systems such as chroman and isochroman derivatives are reported to be biologically active. Owing to their wide range of biological activities, synthesis of substituted isochromans has attracted the attention of the synthetic community and various methods have been developed for the functionalization of isochroman core in recent years. Therefore, development of suitable methodology for the synthesis of substituted isochromans, in a single step, is most desirable. Friedel-Crafts and Pictet-Spengler reactions are two important C-C bond forming reactions and are demonstrated in the synthesis of structurally diverse molecules. Herein, we wish to disclose a methodology for the formal synthesis of (±) –sonepiprazole (U-101387) and (±)-U-54537.

To start with, a suspension of vinylogous ester (1.0 equivalent) in dry dichloromethane (4 mL) at 0 °C was added TMSOTf (1.0 equivalent) drop wise under a nitrogen atmosphere. The reaction mixture was brought to room temperature, and stirred for 12 h. After completion of the reaction, the reaction mixture was washed with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the title compounds **32.**

Table 2.3.1. Optimization of the reaction



31a **32a**

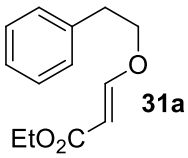
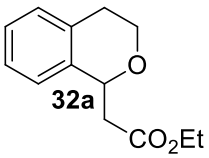
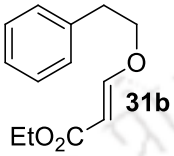
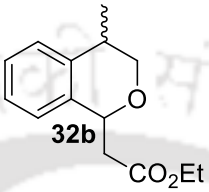
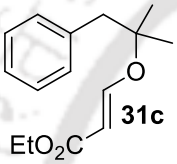
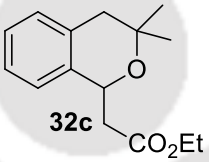
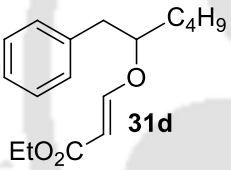
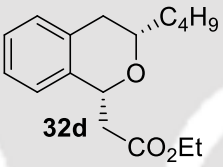
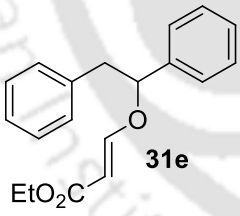
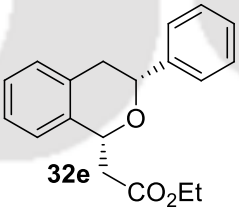
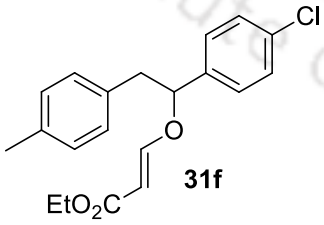
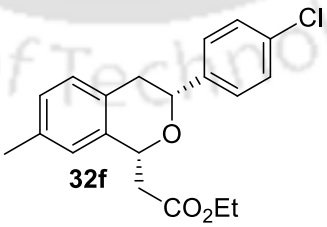
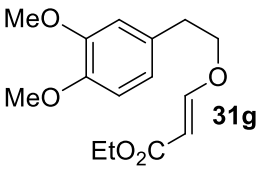
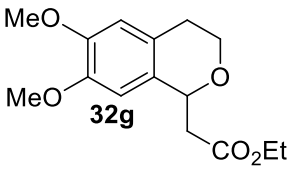
Entry	Reagent (equiv.)	Time/h	Yield(%)[a]
1	$In(OTf)_3$ (1.0)	12	--[b]
2	$Sc(OTf)_2$ 1.0)	12	--[b]
3	$Bi(OTf)_3$ (1.0)	12	--[b]
4	$Cu(OTf)_2$ (1.0)	12	--[b]
5	Ag(OTf) (1.0)	12	--[b]
6	$Zn(OTf)_2$ (1.0)	12	--[b]
7	$BF_3{\cdot}OEt_2$ (1.0)	12	--[b]
8	TfOH (1.0)	1	--[c]
9	TFA (1.0)	4	--[c]
10	HCl (0.1)	4	--[c]
11	TMSOTf (1.0)	12	71
12	TMSOTf (0.5)	24	40

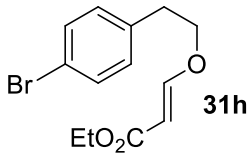
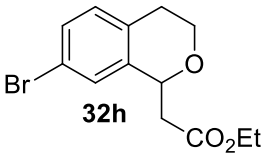
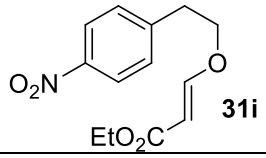
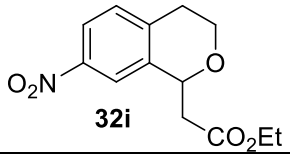
[a]Yield refers to isolated yield. [b]No reaction, starting material was recovered. [c]complex mixture.

When substrate **31a** treated with TMSOTf (1.0 equivalent) in dichloromethane (4 mL) at 0 °C to room temperature for 12h gave ethyl 2-(isochroman-1-yl) acetate **32a** in 71% yield. The reaction is also performed with (0.5 equivalent) of TMSOTf but gave only 40% yield (entry 12, *Table 2.3.1*). Other triflates such as $In(OTf)_3$, $Bi(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, Ag(OTf) and $Sc(OTf)_3$ failed to give desired product, but starting material was recovered in 95% yield. Similarly, boron trifluoride etherate is also found to be inefficient for the reaction. On the other hand, Brønsted acids HCl and trifluoroacetic acid (TFA) gave mixture of products *(Table 2.3.1).*

To examine the scope of the reaction varieties of substrates were considered and the results are summarized in *Table 2.3.2.* It was observed from the *Table 2.3.2,* that substrates having simple aromatic ring and aromatic ring with electron donating substituents on the ring **31a-31e, 31f-g** (entries a-e, f-g) gave the desired isochromans in good yields. Substrate having bromo substituted aromatic ring **31h** (entry h) decomposed under these reaction conditions. On the other hand, aromatic ring having nitro electron withdrawing group **31i** (entry i) could not produce the desired product but starting material was recovered in 95% yield.

Table 2.3.2. Synthesis of isochromans

Entry	Substrate **31**	Product **32**	dr[a]	Yield (%)[b]
a			100:0	71
b			50:50	73[b]
c			100:0	69
d			100:0	71
e			100:0	72
f			100:0	52
g			100:0	70

h	 **31h**	 **32h**	-	d
i	 **31i**	 **32i**	-	0

[a]Yield refers to isolated yield. All the compounds are characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. [b]Diastereomeric mixture with a ratio of 1:1, and the ratio was determined by ^{1}H NMR spectroscopy.

The reaction is highly diastereoselective and gave only single diastereomers with a *cis* relationship (entries d-f). The stereochemistry of the disubstituted products was determined by NOE experiments of compound **32d** *(Figure 2.2.1).* There is a strong NOE between protons at C-1 and C-3 of compound **32d**, which confirms that they are *cis* to each other.

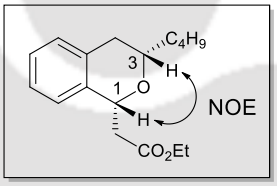
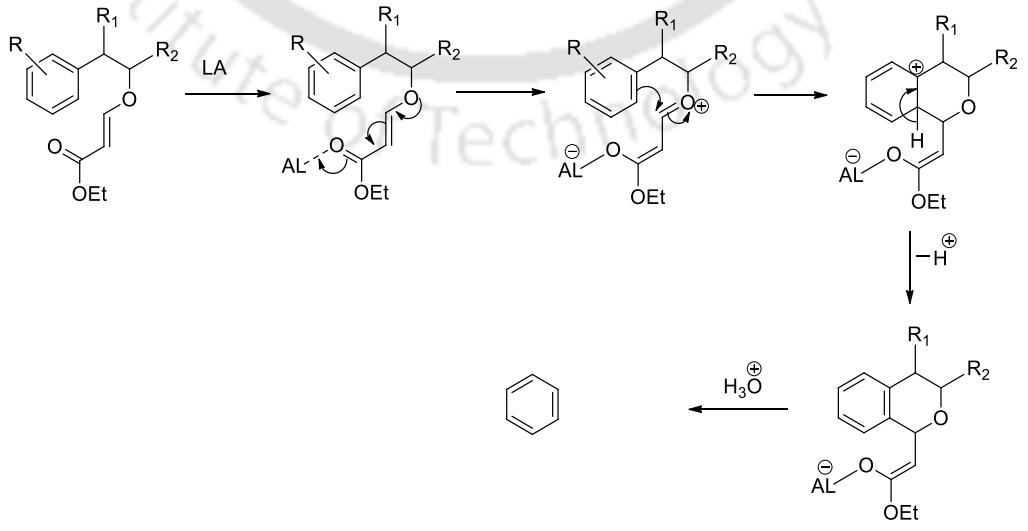


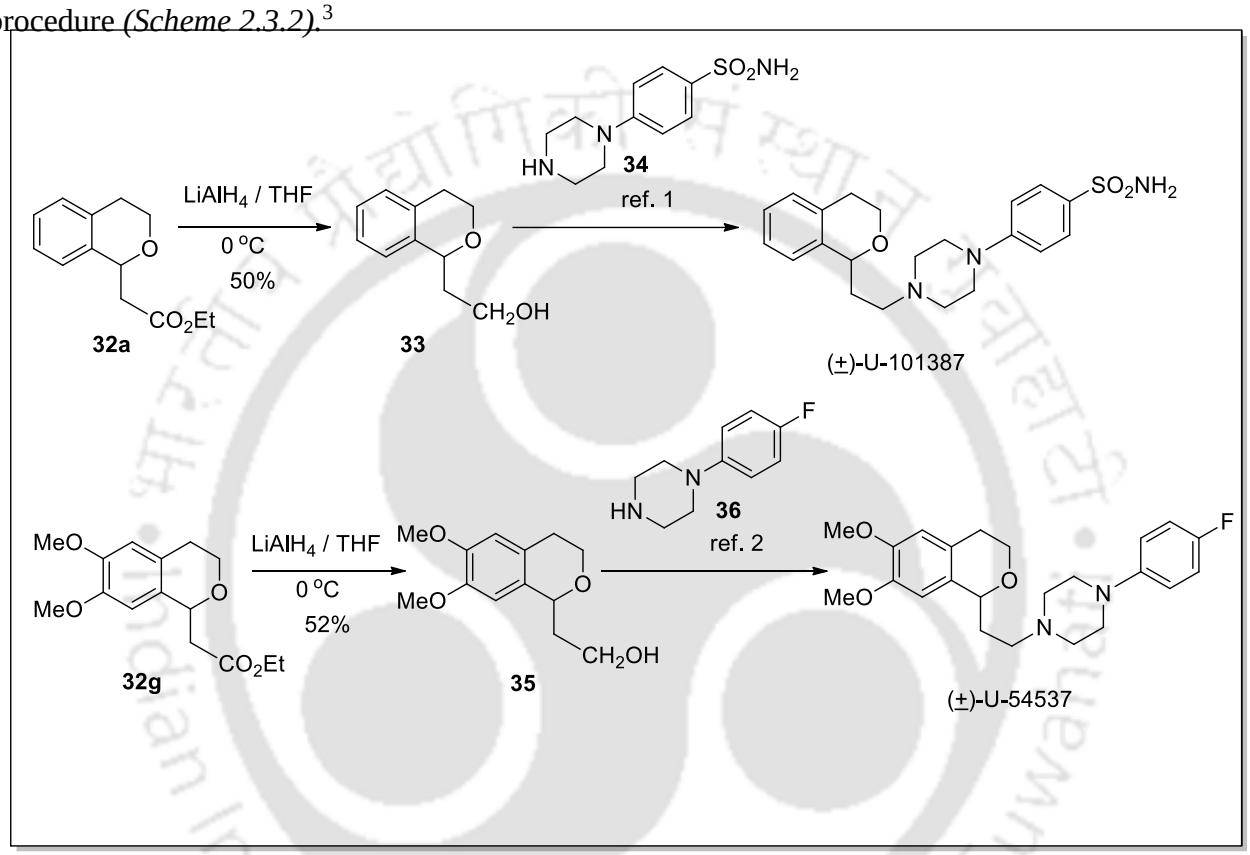
Figure 2.3.1. NOE of compound 32d

The mechanism of the reaction can be explained as follows. The Lewis acid activates ester group of **31** to generate oxocarbenium ion **A**, which after intramolecular nucleophilic attack by aromatic ring gives carbocation **B**. The carbocation **B** then releases a proton to produce enolate **C**, which upon protonation of the enolate gives desired isochroman **32** *(Scheme 2.3.1).*



Scheme 2.3.1. Plausible mechanism of the reaction

The strategy is applied for the synthesis of biologically active compound (±) Sonepiprazole (U-101387) and (±)-U-54537, which are considered as D_4 antagonist. There are few methods for the synthesis of sonepiprazole,[2,10] and U-54537.[3] The synthesis of (±)-sonepiprazole is started with isochroman **32a**, which upon reduction with $LiAlH_4$ in tetrahydrofuran (THF) at 0 °C gave its alcohol derivative **33** in 50% yield. The alcohol **33** can be coupled with 4-(piperazin-1-yl)benzenesulfonamide **34** using literature method.[10] Similarly, the precursor alcohol **35** for the synthesis of (±)-U-54537 is prepared by reduction of ester **32g**, with $LiAlH_4$ in THF at 0 °C in 52% yield. The alcohol **35** can be converted to final product (±)-U-54537 using literature procedure *(Scheme 2.3.2)*.[3]



Scheme 2.3.2. Synthesis of Sonepiprazole (±)-(U-101387) and (±)-U-54537

Conclusions

We have developed a mild and efficient method for the synthesis of substituted isochromans *via* oxa-Pictet-Spengler reaction of acrylyl enol ether in good yields. The methodology is successfully applied for the synthesis of biologically active molecule (±)-sonepiprazole (U-101387) and (±)-U-54537.

2.4. Experimental Section

2.4.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. 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 open capillary tubes using a Büchi B-540 melting point apparatus and are uncorrected. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Fourier transform-infra red (**FT-IR**) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. **NMR** spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (400, 600 MHz) or ^{13}C (100, 150 MHz). **HRMS** spectra were recorded in ESI mode using Agilent Q-TOF mass spectrometer. Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic Mock λ radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in different Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

2.4.2. General procedure for the preparation of Enol ether (31a-g):

To a solution of alcohol (1.0 equivalent) in dichloromethane (3 mL), *N*-methylmorpholine (1.0 equivalent) and ethyl propiolate (1.1 equivalents) were added. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed on a rotary evaporator and extracted with ethyl acetate (3×10 mL), washed with brine (30 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under rotary evaporator, and the crude product was purified on silica gel column chromatography using ethyl acetate and hexane (5:95) as eluents.

2.4.3. General Procedure for the preparation of Isochroman (32a-g):

To a suspension of enol ether (1.0 equivalent) in dry dichloromethane (4.0 mL) at 0 $^{\circ}$C was added TMSOTf (1.0 equivalent) dropwise under a nitrogen atmosphere. The reaction mixture was brought to room temperature, and stirred for 12 h. After completion of the reaction, the reaction mixture was washed with saturated sodium bicarbonate solution (5.0 mL). The product was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (5:95) as eluents to afford the title compounds **32**.

2.4.4. General Procedure for the reduction of Ester 32a:

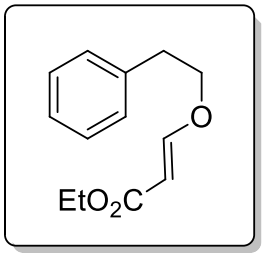
To an oven dried 100 mL two necked round bottom flask, $LiAlH_4$ (Lithium aluminium hydride) was taken 0.1448 g (3.82 mmol) under N_2 atmosphere and suspended to it in 50 mL dry ether and kept it in an ice bath. After that a solution of 0.70 g (3.1802 mmol) of ethyl 2-isochroman-1-yl **32a** was dissolved in a small quantity of dry ether and purged it into the round bottom flask drop wise. After completion of (by checking TLC) the reaction the mixture was quenched with 1(N) HCl and subsequently worked up with EtOAc. The organic phase was dried over sodium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel **(**20% EtOAc in hexane), to afford the title compounds **33** (0.352 g, 50% yield) of product.

2.5. References

1) Mohacsi, E.; Schmidlin, J.; Ber. A. G. *Dtsch. Chem. Ges*. **1912**, *207*, 3193.
2) Larghi, L. E.; Kaufman, S.T. *Synthesis*, **2006,** *2*, 0187.
3) Deng, J. Z.; Zhao, S. X. *J. Nat. Prod.* **1997**, *60*, 294.
4) Jung, E. M.; Mossman, B. A.; Lyster, A. *J. Org. Chem.* **1978**, *43*, 3698.
5) Michaelides, M. R.; Schoenleber, R.; Thomas, S.; Yamamoto, D. M.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2946.
6) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.
7) Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531.
8) Gowrisankar, S.; Lee, S.; H.; Kim, N. J. *Bull. Korean Chem. Soc*. **2007**, *28*, 2501.
9) Blanc, A. K. N.; Miaskiewicz, S.; Robinette, M.; Weibel, M. J. *J. Org. Chem*. **2012**, *77*, 4323.
10) (a) Saikia, A. K.; Bondalapati, S.; Indukuri, K.; Gogoi, P. *Chem. Lett*. **2011**, *40*, 1176. (b) Reddy, C. U.; Bondalapati, S.; Saikia, A. K. Eur. *J. Org. Chem*. **2009**, *10*, 1625. (c) Indukuri, K.; Bondalapati, S.; Kotipalli, T.; Gogoi, P.; Saikia, A. K. *Synlett*, **2012**, *23*, 2335. (d) Saha, P.; Bhunia, A.; Saikia, A. K. *Org. Biomol. Chem*., **2012**, *10*, 2470.

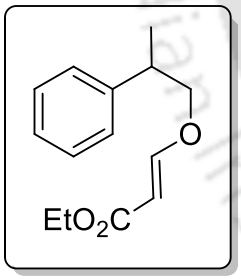
2.6. Characterization Data

(E)-Ethyl 3-phenethoxyacrylate (31a):



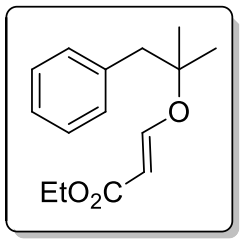
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.62; (yield 178 mg, 81%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3 H), 3.01 (t, *J* = 7.2 Hz, 2 H), 4.05 (t, *J* = 7.2 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.20 (d, *J* = 12.6 Hz, 1 H), 7.22 (d, *J* = 7.2 Hz, 2 H), 7.25 (t, *J* = 8.4 Hz, 1 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.57 (d, *J* = 12.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 35.5, 60.0, 71.6, 96.9, 127.0, 128.8, 129.1, 137.5, 162.4, 168.0; **IR** (KBr, Neat): 772, 1045, 1134, 1326, 1625, 1709, 2928 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{17}O_3$ $(M + H)^+$ 221.1172, found 221.1171.

(2R*, 4S*)-2-Isopropyl-4-phenyltetrahydro-2*H*-pyran (31b):



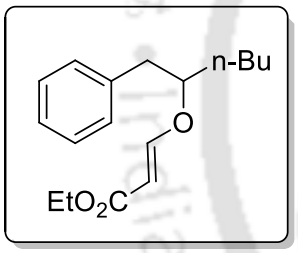
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.65; (yield 194 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.33 (d, *J* = 7.2 Hz, 3 H), 3.11-3.18 (m, 1 H), 3.85 (dd, *J* = 10.0 and 7.6 Hz, 1 H), 3.94 (dd, *J* = 10.0 and 6.8 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.19 (d, *J* = 12.4 Hz, 1 H), 7.20-7.26 (m, 3 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.57 (d, *J* = 12.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 18.1, 39.4, 59.9, 76.2, 96.7, 127.1, 127.4, 128.8, 142.8, 162.5, 168.0; **IR** (KBr, Neat): 700, 762, 1048, 1124, 1372, 1495, 1625, 1716, 2928 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{19}O_3$ $(M + H)^+$ 235.1329, found 235.1321.

(E)-Ethyl 3-((2-methyl-1-phenylpropan-2-yl)oxy)acrylate (31c):



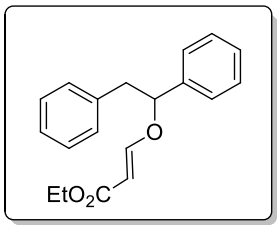
Pale yellow oil; R_f (hexane/ EtOAc 7:3) 0.67; (yield 210 mg, 72%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (s, 6 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 2.77 (s, 3 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.66 (d, *J* = 12.0Hz, 1 H), 7.20-7.27 (m, 2 H) 7.31 (t, *J* = 6.8 Hz, 2 H), 7.57 (d, *J* = 12.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.6, 30.4, 40.5, 42.4, 60.6, 69.1, 71.4, 124.0, 126.3, 126.9, 129.4, 133.9, 136.5, 171.7; **IR** (KBr, Neat): 758, 1043, 1083, 1176, 1367, 1454, 1624, 1713, 2926, 2957 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{21}O_3$ $(M + H)^+$ 249.1480, found 249.1478.

(E)-Ethyl 3-((1-phenylhexan-2-yl)oxy)acrylate (31d):



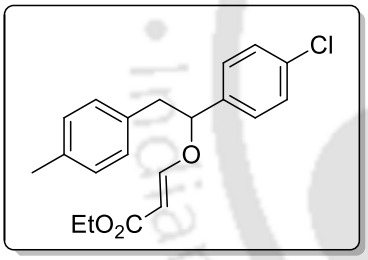
Pale yellow oil; R_f (hexane/ EtOAc 9:1) 0.60; (yield 210 mg, 76%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.23-1.43 (m, 7 H), 1.54-1.60 (m, 2 H), 2.84 (dd, *J* = 14.4 and 5.6 Hz, 1 H), 2.89 (dd, *J* = 14.4 and 6.8 Hz, 1 H), 4.07 (dd, *J* = 12.4 and 4.4 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 5.24 (d, *J* = 12.0 Hz, 1 H), 7.16 (d, *J* = 6.8 Hz, 2 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.26-7.31 (m, 2 H), 7.42 (d, *J* = 12.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9, 14.3, 22.5, 27.3, 33.6, 40.7, 59.6, 84.9, 97.1, 126.6, 128.5, 129.5, 137.1, 162.4, 168.2; **IR** (KBr, neat): 700, 830, 1048, 1133, 1243, 1369, 1620, 1709, 2873, 2959 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{25}O_3$ $(M + H)^+$ 277.1798, found 277.1786.

(E)-Ethyl 3-(1,2-diphenylethoxy)acrylate (31e):



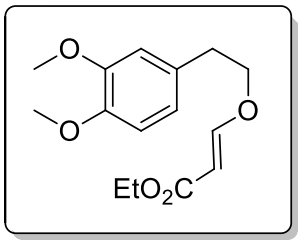
Pale yellow oil; R_f (hexane/ EtOAc 9:1) 0.62; (yield 222 mg, 75%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.2 Hz, 3 H), 3.03 (dd, *J* = 14.0 and 5.6 Hz, 1 H), 3.22 (dd, *J* = 14.0 and 8.0 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.03 (dd, *J* = 7.6 and 5.6 Hz, 1 H), 5.19 (d, *J* = 12.4 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.19-7.26 (m, 4 H), 7.28-7.34 (m, 4 H), 7.43 (d, *J* = 12.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.5, 44.3, 59.8, 85.3, 98.7, 126.4, 126.9, 128.4, 128.5, 128.8, 129.7, 136.9, 139.7, 161.5, 167.8; **IR** (KBr, Neat): 771, 1040, 1095, 1163, 1369, 1736, 2860, 2931 cm^{-1}; **HRMS** (ESI) calcd. For $C_{19}H_{21}O_3$ $(M + H)^+$ 297.1485, found 297.1493.

(E)-Ethyl 3-(1-(4-chlorophenyl)-2-(p-tolyl)ethoxy)acrylate (31f):



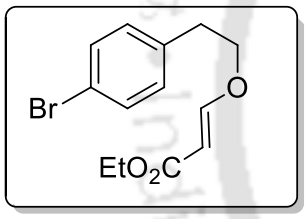
Dark brown oil; R_f (hexane/ EtOAc 9:1) 0.53; (yield 208 mg, 63%); **^{1}H NMR** (400 MHz, $CDCl_3$): 1.19 (t, *J* = 7.2 Hz, 3 H), 2.34 (s, 3 H), 3.03 (dd, *J* = 14.0 and 5.2 Hz, 1 H), 3.22 (dd, *J* = 14.0 and 7.6 Hz, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 4.99 (dd, *J* = 8.0 and 5.2 Hz, 1 H), 5.17 (d, *J* = 12.4 Hz, 1 H), 7.09-7.15 (m, 4 H), 7.20-7.28 (m, 4 H), 7.42 (d, J = 12.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 21.3, 44.2, 59.8, 85.2, 98.5, 126.3, 126.8, 128.4, 129.5, 129.6, 136.7, 137.0, 138.2, 161.5, 167.9; **IR** (KBr, Neat): 699, 816, 1047, 1132, 1323, 1514, 1642, 1709, 2925, 2981 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{22}ClO_3$ $(M + H)^+$ 345.1252, found 345.1252.

(2E)-Ethyl 3-(3,4-dimethoxyphenethoxy)acrylate (31g):



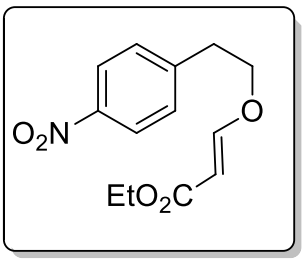
Pale yellow oil; R_f (hexane/ EtOAc 4:1) 0.51; (yield 229 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.88 (t, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.97 (d, *J* = 6.6 Hz, 2 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 5.14 (d, *J* = 12.6 Hz, 1 H), 6.68 (s, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 12.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 35.0, 55.9, 59.8, 60.5, 71.8, 96.8, 111.5, 112.3, 121.0, 130.0, 148.0, 149.1, 167.8, 171.2; **IR** (KBr, Neat): 766, 813, 1030, 1136, 1264, 1465, 1625, 1709, 2933 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{21}O_5$ $(M + H)^+$ 281.1384, found 281.1381.

(E)-Ethyl 3-(4-bromophenethoxy)acrylate (31h):



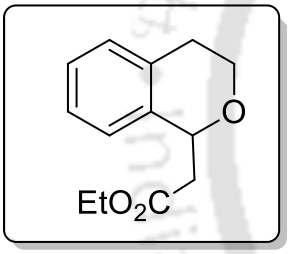
Yellow oil; R_f (hexane/ EtOAc 20:1) 0.70; (yield 221 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 4.02 (t, *J* = 6.4 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.19 (d, *J* = 12.4 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 12.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.6, 34.9, 60.0, 71.1, 97.1, 120.9, 130.8, 131.9, 136.6, 162.1, 166.2; **IR** (KBr, Neat): 772, 808, 1011, 1180, 1240, 1488, 1724, 2873, 2930 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{16}BrO_3$ $(M + H)^+$ 299.0277, found 299.0277.

(E)-Ethyl 3-(4-nitrophenethoxy)acrylate (31i):



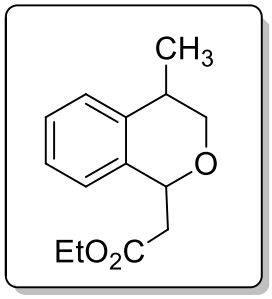
Brown solid, mp 102-104 ^{o}C; R_f (hexane/ EtOAc 3:1) 0.35; (yield 190 mg, 72%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 3.10 (t, *J* = 6.4 Hz, 2 H), 4.07 (t, *J* = 6.4 Hz, 2 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.18 (d, *J* = 12.4 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 12.8 Hz, 1 H), 8.15 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 35.3, 60.1, 70.4, 97.4, 124.0, 130.0, 145.4, 161.8, 167.7 **IR** (KBr, Neat): 772, 856, 1047, 1137, 1346, 1520, 1626, 2856, 2981 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{16}NO_5$ $(M + H)^+$ 266.1023, found 266.1036.

Ethyl 2-(isochroman-1-yl)acetate (32a):



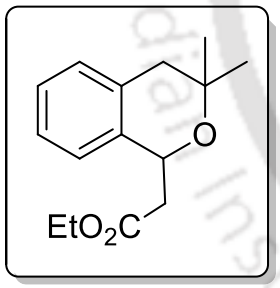
Colourless oil; R_f (hexane/ EtOAc 9:1) 0.52; (yield 154 mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3 H), 2.27 (dt, *J* = 12.6 and 3.6 Hz, 1 H), 2.39 (dd, *J* = 15.0 and 6.0 Hz, 1 H), 2.88 (dd, *J* = 15.0 and 3.6 Hz, 1 H), 3.74 (ddd, *J* = 15.0, 8.4 and 4.8 Hz, 1 H), 3.81 (ddd, *J* = 11.4, 9.0 and 3.6 Hz, 1 H), 4.13 (ddd, *J* = 11.4, 9.0 and 4.8 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 5.25 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 7.00-7.06 (m, 1 H), 7.11-7.13 (m, 1 H), 7.16-7.19 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.4, 29.0, 42.0, 60.9, 63.3, 73.1, 124.7, 126.4, 126.9, 129.3, 134.1, 137.0, 171.5; **IR** (KBr, Neat): 749, 1013, 1108, 1160, 1282, 1494, 1622, 1737, 2856, 2980 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{17}O_3$ $(M + H)^+$ 221.1172 found 221.1173.

Ethyl 2-(4-methylisochroman-1-yl)acetate (diastereomeric mixture, 1:1, 32b):



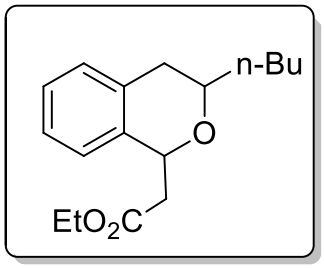
Pale yellow oil; R_f (hexane/ EtOAc 9:1) 0.59; (yield 171 mg, 73%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24-1.30 (m, 6 H), 1.35 (d, *J* = 7.2 Hz, 3 H), 2.74-2.84 (m, 2 H), 2.85-3.10 (m, 1 H), 3.51 (dd, *J* = 16.8 and 10.8 Hz, 1 H, isomer 1), 3.80-3.90 (m, 1 H), 4.06 (dd, *J* = 16.8 and 7.2 Hz, 1 H, isomer 2), 4.22 (q, *J* = 7.2 Hz, 2 H), 5.22 (dd, *J* = 14.4 and 4.8 Hz, 1 H, isomer 1), 5.30 (dd, *J* = 14.4 and 4.0 Hz, 1 H, isomer 2), 7.03 (d, *J* = 6.4 Hz, 1 H), 7.16-7.32 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.4, 18.1, 20.8, 32.1, 32.8, 41.8, 41.9, 60.8, 68.7, 69.2, 73.3, 73.4, 124.5, 124.6, 126.3, 126.4, 127.0, 127.1, 127.5, 127.6, 128.5, 128.6, 136.3, 136.3, 139.4, 139.6, 171.4; **IR** (KBr, neat): 749, 885, 1082, 1161, 1284, 1370, 1454, 1620, 1738, 2870, 2975 cm^{-1}; **HRMS** (ESI) calcd. for $C_{14}H_{19}O_3$ $(M + H)^+$ 235.1329 found 235.1325.

Ethyl 2-(3,3-dimethylisochroman-1-yl)acetate (32c):



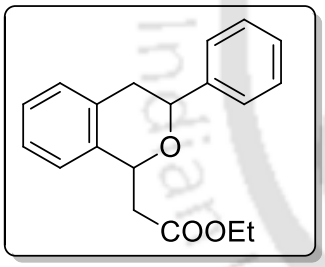
Brown oil; R_f (hexane/ EtOAc 9:1) 0.62; (yield 171 mg, 69%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.32 (s, 3 H), 2.54 (d, *J* = 15.6 Hz, 1 H), 2.68 (dd, *J* = 15.2 and 8.4 Hz, 1 H), 2.88 (d, *J* = 12.4 Hz, 1 H), 3.92 (dd, *J* = 14.8 and 4.0 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 5.20 (dd, *J* = 8.4 and 3.6 Hz, 1 H), 7.05-7.08 (m, 2 H), 7.15-7.19 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.6, 30.4, 40.5, 42.4, 60.6, 69.1, 71.4, 124.0, 126.3, 126.9, 129.4, 133.9, 136.5, 171.7; **IR** (KBr, Neat): 758, 1021, 1167, 1373, 1605, 1738, 2871, 2965, 3028 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{21}O_3$ $(M + H)^+$ 249.1485 found 249.1478.

Ethyl 2-(3-butylisochroman-1-yl)acetate (32d):



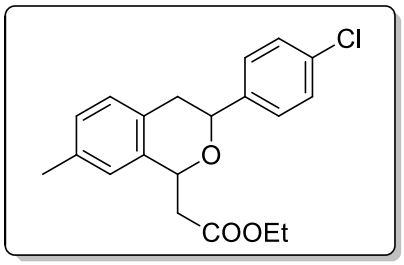
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.54; (yield 196 mg, 71%); **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.30-1.38 (m, 2 H), 1.50-1.68 (m, 4 H), 2.65 (dd, *J* = 14.8 and 5.2 Hz, 1 H), 2.67-2.78 (m, 2 H), 2.96 (dd, *J* = 14.8 and 4.0 Hz, 1 H), 3.61-3.68 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 5.19 (dd, *J* = 8.8 and 3.2 Hz, 1 H), 7.03-7.06 (m, 1 H), 7.07-7.11 (m, 1 H), 7.14-7.19 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.3, 14.5, 22.9, 27.9, 35.1, 35.8, 42.0, 60.8, 74.3, 74.9, 124.0, 126.4, 126.9, 129.2, 134.8, 137.3, 171.8; **IR** (KBr, Neat): 747, 1095, 1162, 1369, 1455, 1740, 2855, 2926 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{25}O_3$ $(M + H)^+$ 277.1798 found 277.1786.

Ethyl 2-(3-phenylisochroman-1-yl)acetate (32e):



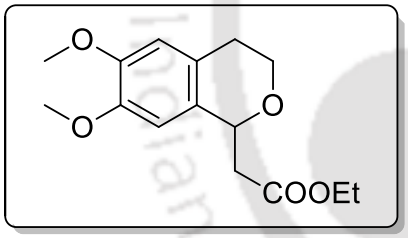
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.56; (yield 213 mg, 72%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3 H), 2.82 (dd, *J* = 15.2 and 8.4 Hz, 2 H), 2.94-3.05 (m, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.77 (dd, *J* = 10.8 and 3.6 Hz, 1 H), 5.44 (dd, *J* = 8.0 and 2.8 Hz, 1 H), 7.14 (t, *J* = 7.2 Hz, 2 H), 7.21-7.30 (m, 3 H), 7.35 (t, *J* = 7.2 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.4, 37.0, 42.3, 60.8, 74.6, 75.9, 124.3, 125.8, 126.7, 127.0, 127.6, 128.5, 129.1, 134.4, 136.8, 142.3, 171.5; **IR** (KBr, neat): 753, 1029, 1184, 1242, 1369, 1495, 1716, 2856, 2981 cm^{-1}; **HRMS** (ESI) calcd. for $C_{19}H_{21}O_3$ $(M + H)^+$ 297.1485 found 297.1493.

Ethyl 2-(3-(4-chlorophenyl)-7-methylisochroman-1-yl)acetate (32f):



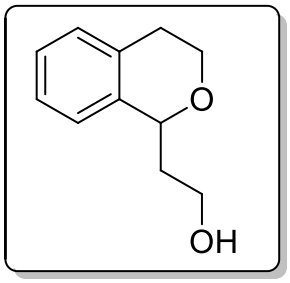
Yellow oil; R_f (hexane/ EtOAc 9:1) 0.40; (yield 172 mg, 52%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 2.20 (dd, *J* = 15.6 and 12.0 Hz, 1 H), 2.52 (s, 3 H), 2.77 (dd, *J* = 14.4 and 8.4 Hz, 1 H), 3.02 (dd, *J* = 14.8 and 3.2 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.62 (d, *J* = 10.4 Hz, 1 H), 5.40 (d, *J* = 7.6 Hz, 1 H), 6.90-7.00 (m, 2 H), 7.11-7.15 (m, 2 H), 7.23-7.30 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 37.0, 42.3, 60.8, 74.6, 75.9, 124.3, 125.8, 126.7, 127.0, 127.6, 128.5, 129.1, 134.4, 136.8, 142.3, 171.5; **IR** (KBr, Neat): 769, 1024, 1080, 1328, 1475, 1594, 1705, 2855, 2928 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{22}ClO_3$ $(M + H)^+$ 345.1252 found 345.1242.

Ethyl 2-(6,7-dimethoxyisochroman-1-yl)acetate (32g):



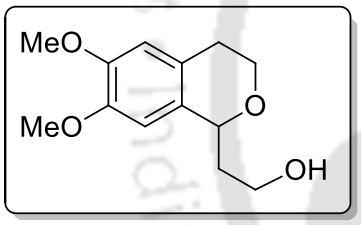
Brown solid, mp 110-112 ^oC; R_f (hexane/ EtOAc 4:1) 0.45; (yield 196 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3 H), 2.66 (dt, *J* = 16.0 and 4.4 Hz, 1 H), 2.74 (dd, *J* = 15.2 and 9.6 Hz, 1 H), 2.84 (dd, *J* = 15.2 and 4.0 Hz, 1 H), 2.85-2.92 (m, 1 H), 3.76-3.82 (m, 1 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.07-4.13 (m, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 5.19 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 6.54 (s, 1 H), 6.61 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 14.3, 28.4, 42.0, 55.9, 56.1, 60.7, 63.0, 72.7, 107.7, 111.7, 126.1, 128.6, 147.6, 148.0, 171.4; **IR** (KBr, Neat): 772, 1028, 1163, 1220, 1374, 1518, 1735, 2855, 2984 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{21}O_5$ $(M + H)^+$ 281.1384 found 281.1381.

2-(Isochroman-1-yl)ethanol (33):



Yellow oil; R_f (hexane/ EtOAc 5:1) 0.50; (yield 352 mg, 50%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.03-2.09 (m, 1 H), 2.21-2.26 (m, 1 H), 2.69 (dt, *J* = 15.6 and 3.6 Hz, 1 H), 2.73-2.82 (brs, 1 H), 3.01-3.07 (m, 1 H), 3.78 (ddd, *J* = 10.8, 6.6 and 3.6 Hz, 1 H), 3.82-3.88 (m, 2 H), 4.16-4.20 (m, 1 H), 4.99 (dd, *J* = 9.0 and 1.8 Hz, 1 H), 7.04-7.06 (m, 1 H), 7.11-7.13 (m, 1 H), 7.16-7.20 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 29.2, 37.8, 61.3, 63.9, 76.6, 124.7, 126.5, 126.7, 129.2, 133.9, 137.6; **IR** (KBr, Neat): 744, 1055, 1107, 1261, 1376, 1426, 1491, 2854, 2964, 3425 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{15}O_2$ $(M + H)^+$ 179.1067, found 179.1066.

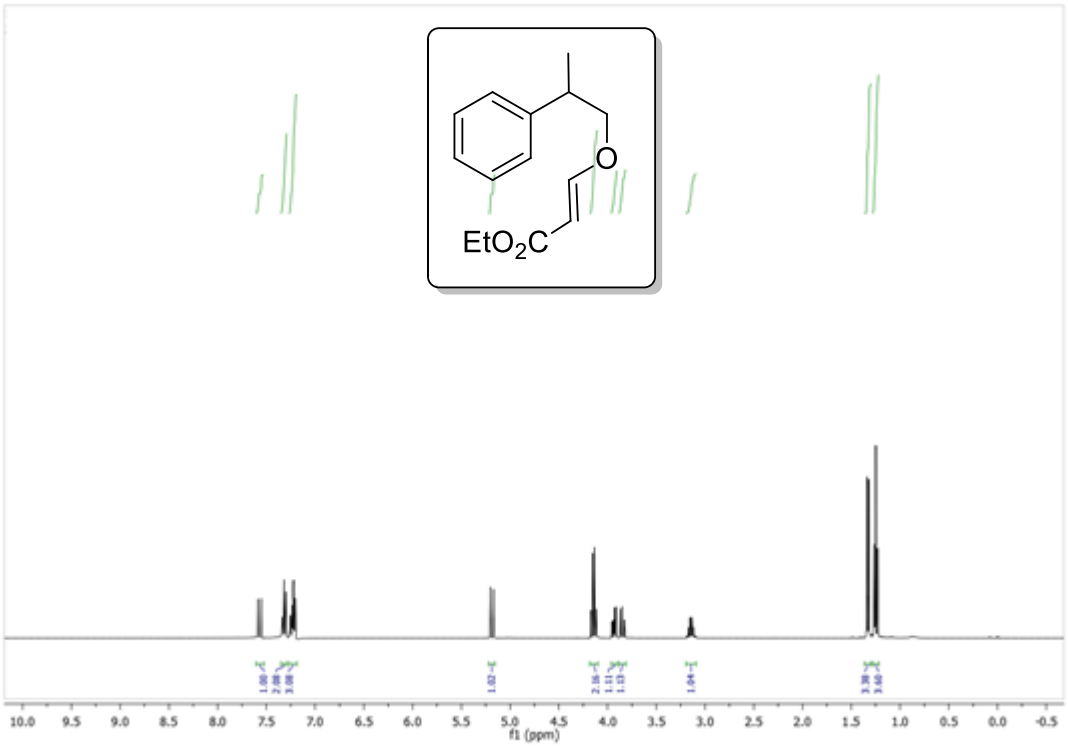
2-(6,7-Dimethoxyisochroman-1-yl)ethanol (35):

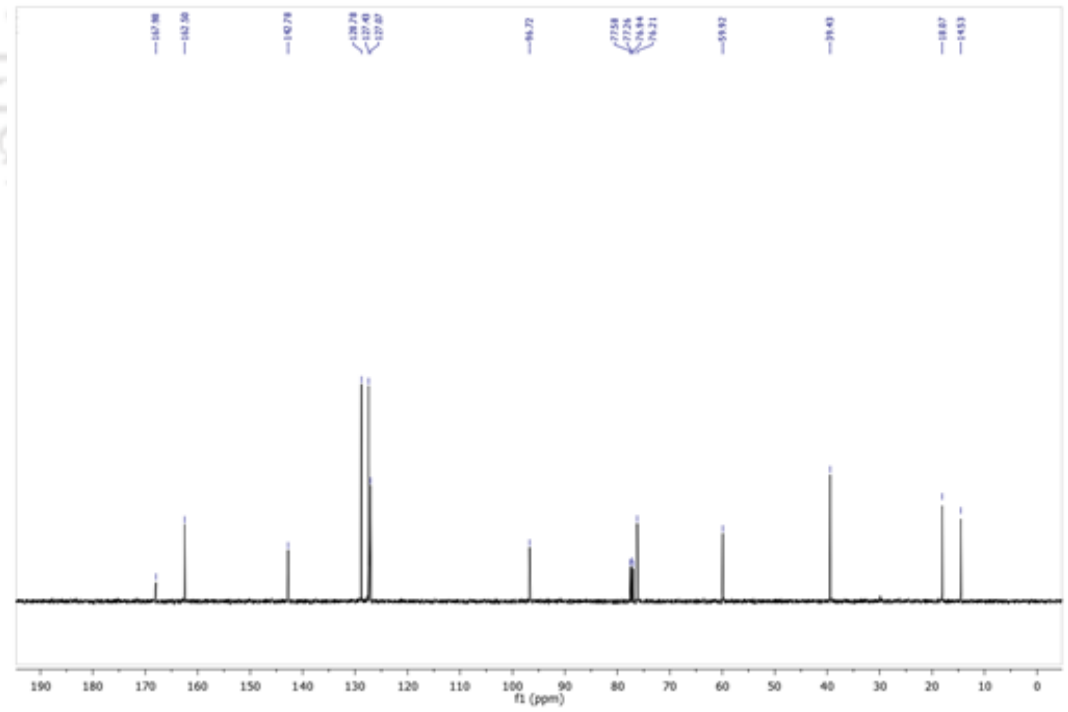


Colourless oil; R_f (hexane/ EtOAc 4:1) 0.50; (yield 123.0 mg, 52%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.01-2.07 (m, 1 H), 2.17-2.22 (m, 1 H), 2.59 (dt, *J* = 16.0 and 4.0 Hz, 1 H), 2.91-2.98 (m, 1 H), 3.74-3.76 (m, 1 H), 3.83-3.86 (m, 2x-CH_3, -CH_2-, 8 H), 4.10-4.20 (m, 2 H), 4.93 (d, *J* = 8.0 Hz, 1 H), 6.52 (s, 1 H), 6.60 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 28.6, 37.8, 55.9, 56.0, 60.6, 63.6, 75.5, 107.8, 111.7, 125.9, 129.4, 147.6, 147.8; **IR** (KBr, Neat): 771, 1047, 1137, 1217, 1346, 1625, 2934, 2981, 3496 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{19}O_4$ $(M + H)^+$ 239.1278, found 239.1278.

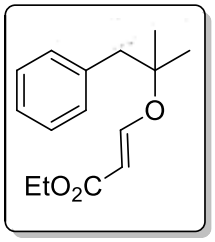
2.7. Selected Spectra

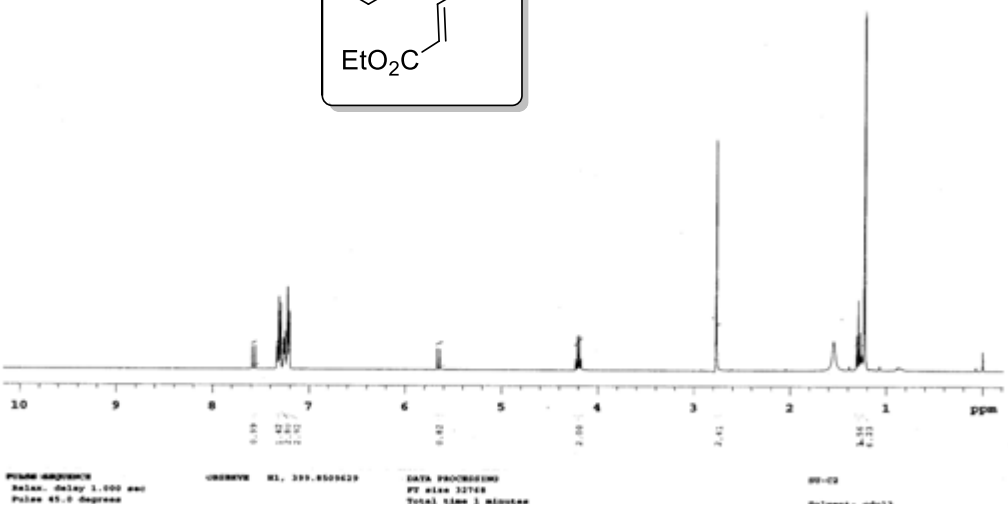
^{1}H and **^{13}C NMR** spectra of compound **31b**

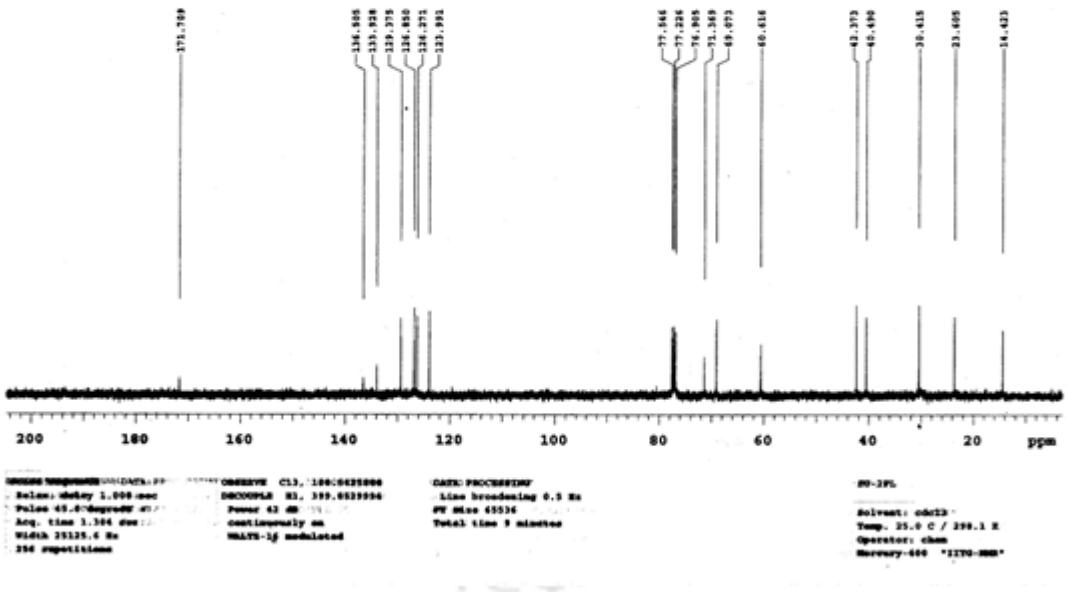




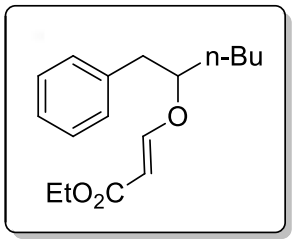
^{1}H and **^{13}C NMR** spectra of compound **31c**

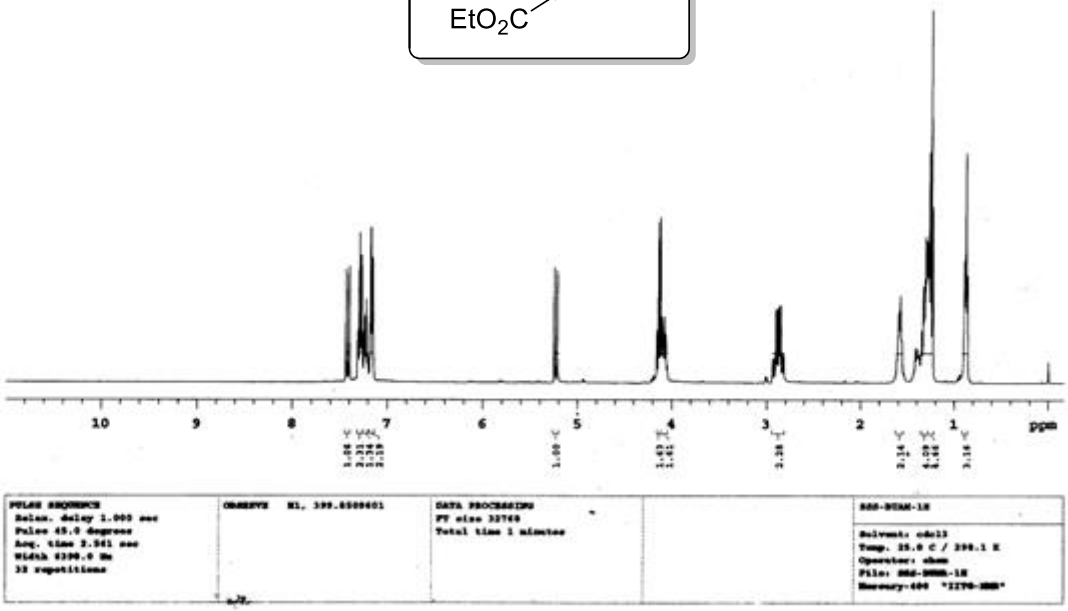


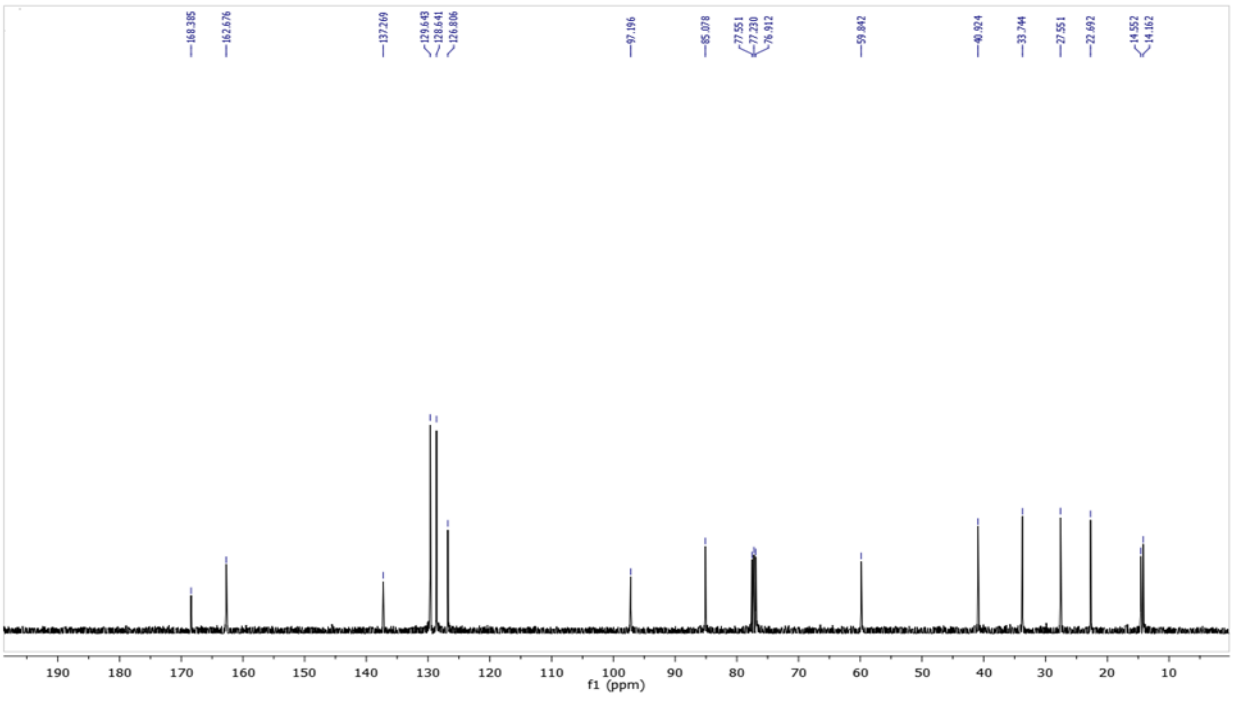




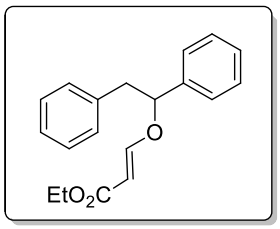
^{1}H and **^{13}C NMR** spectra of compound **31d**

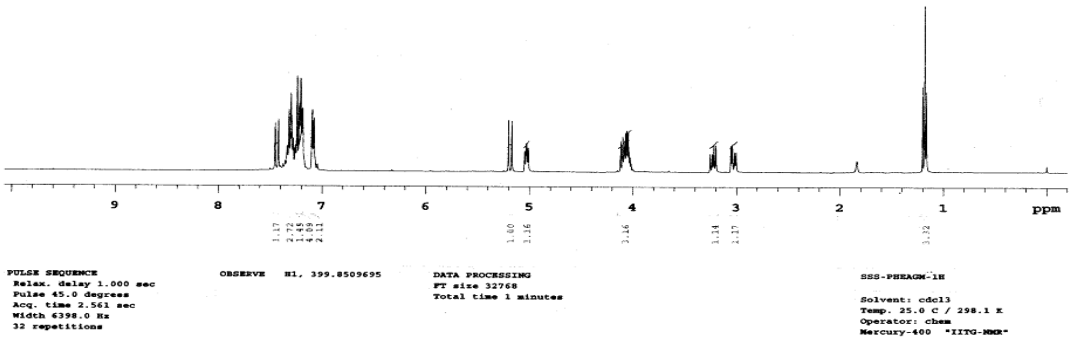


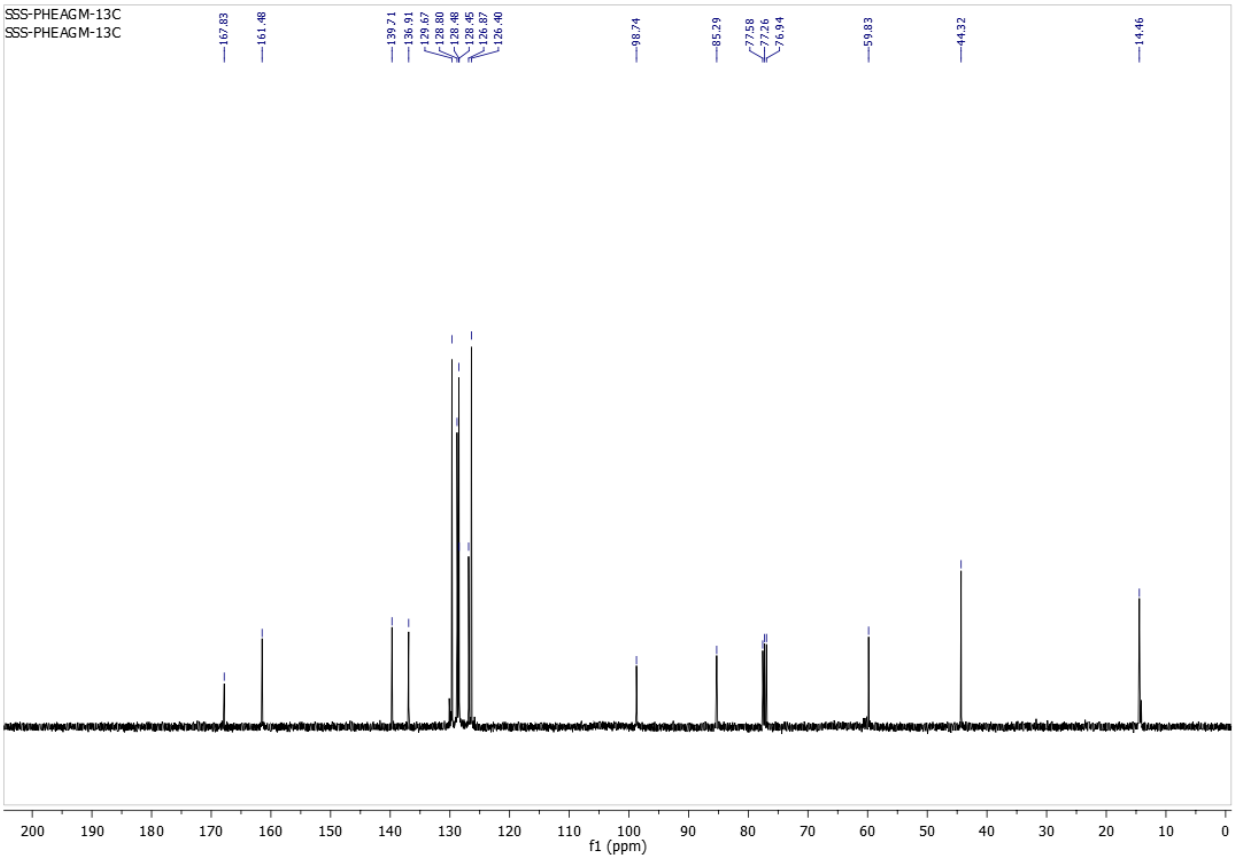




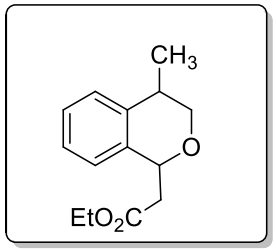
^{1}H and **^{13}C NMR** spectra of compound **31e**

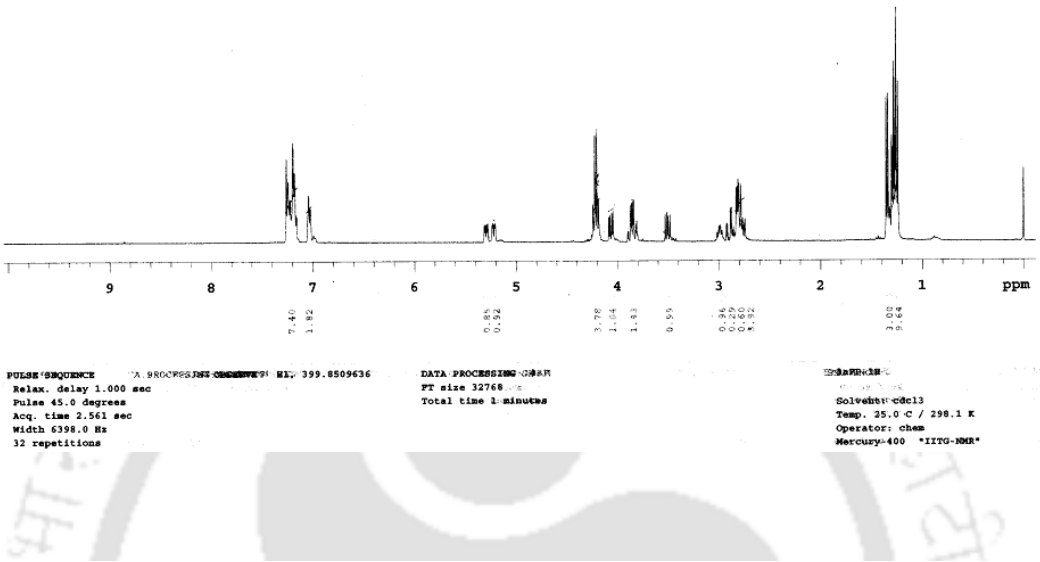


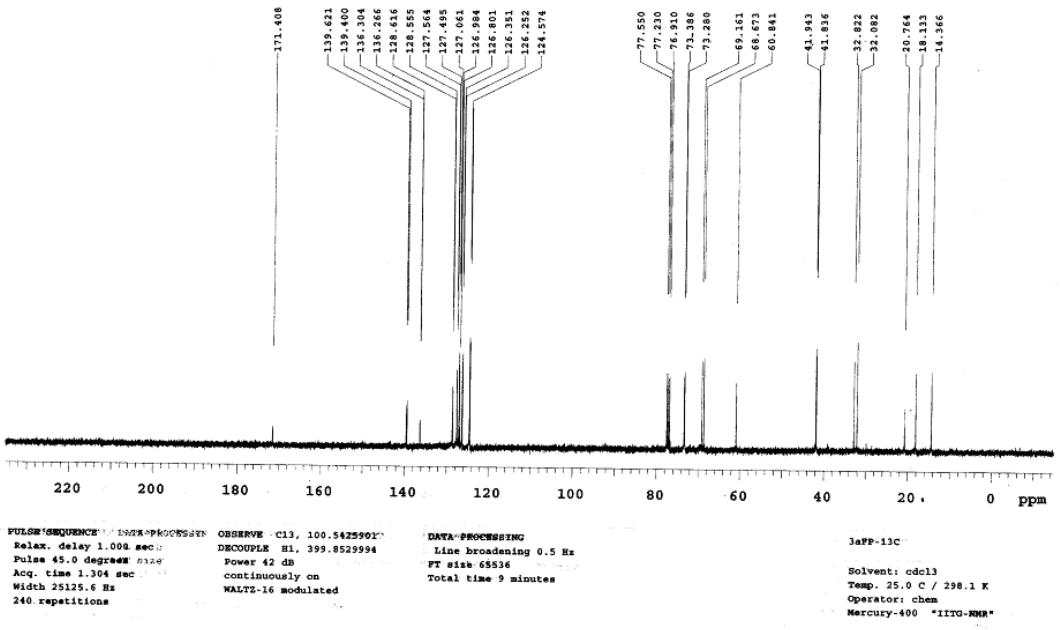




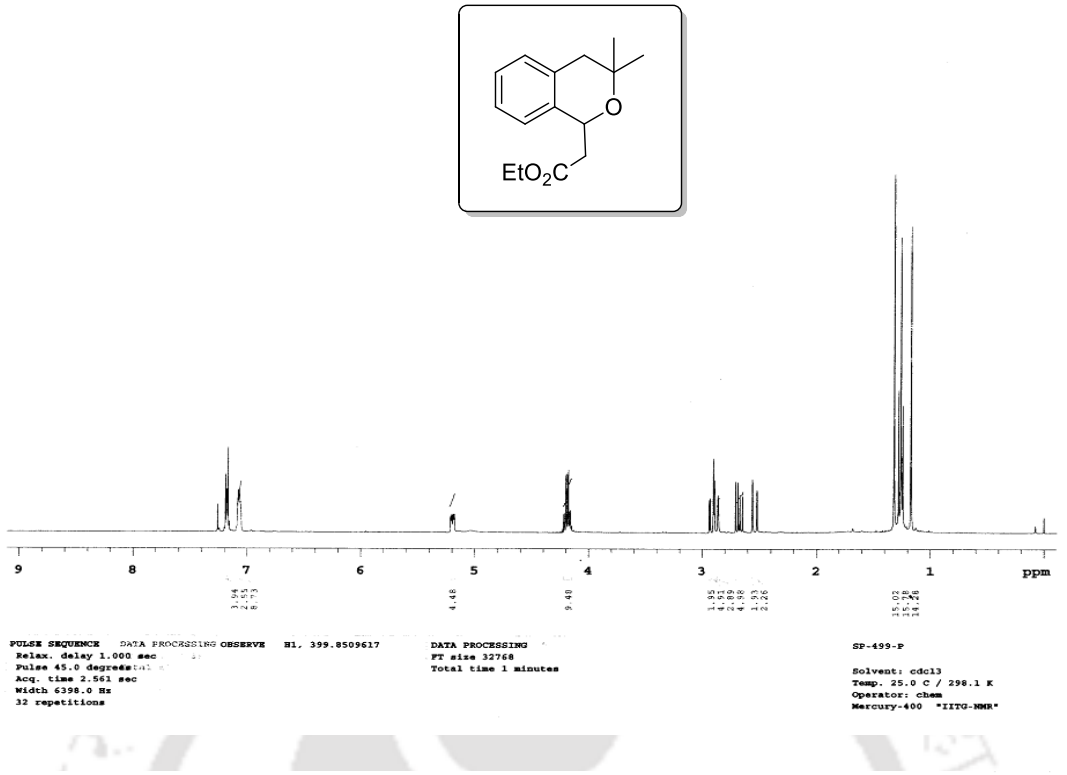
^{1}H and **^{13}C NMR** spectra of compound **32b**

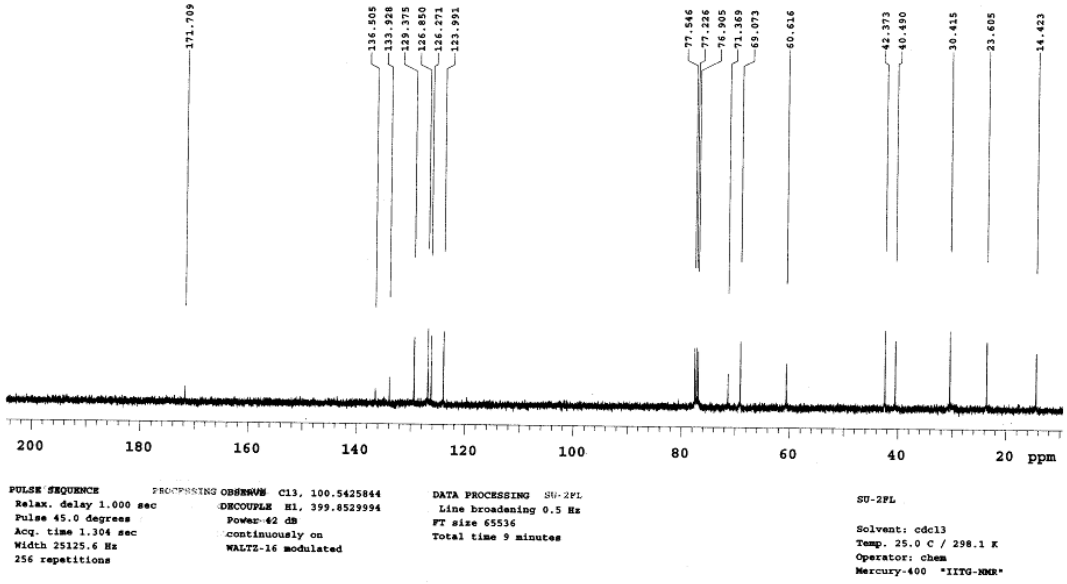




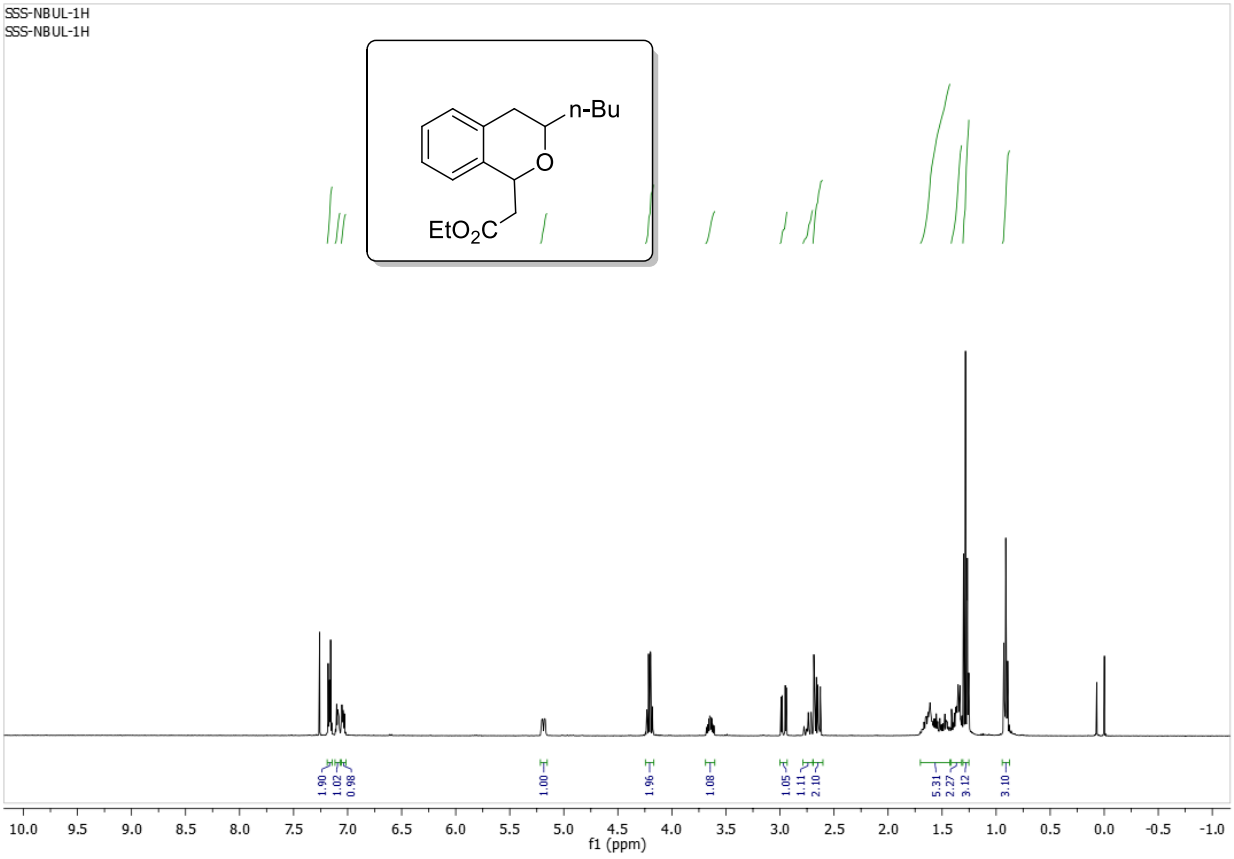


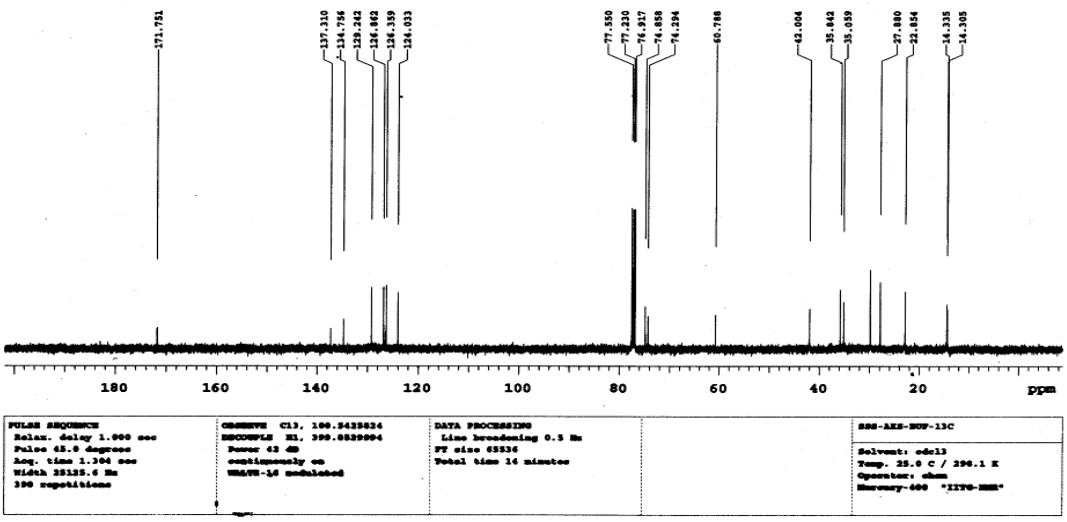
^{1}H and **^{13}C NMR** spectra of compound **32c**



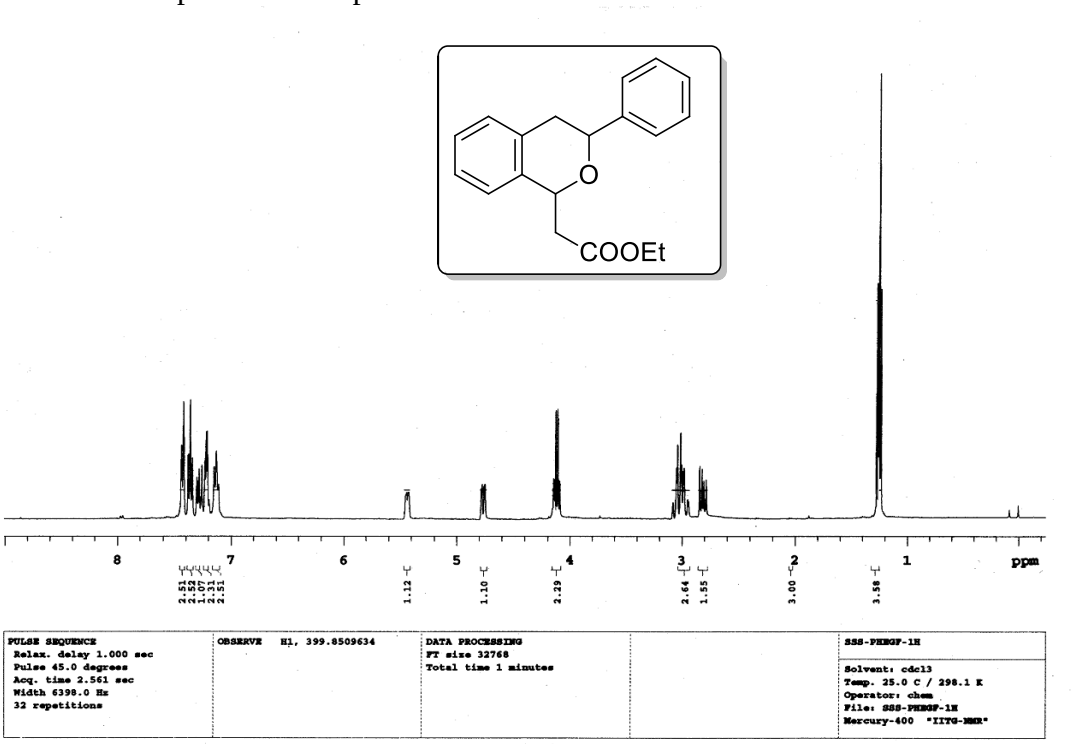


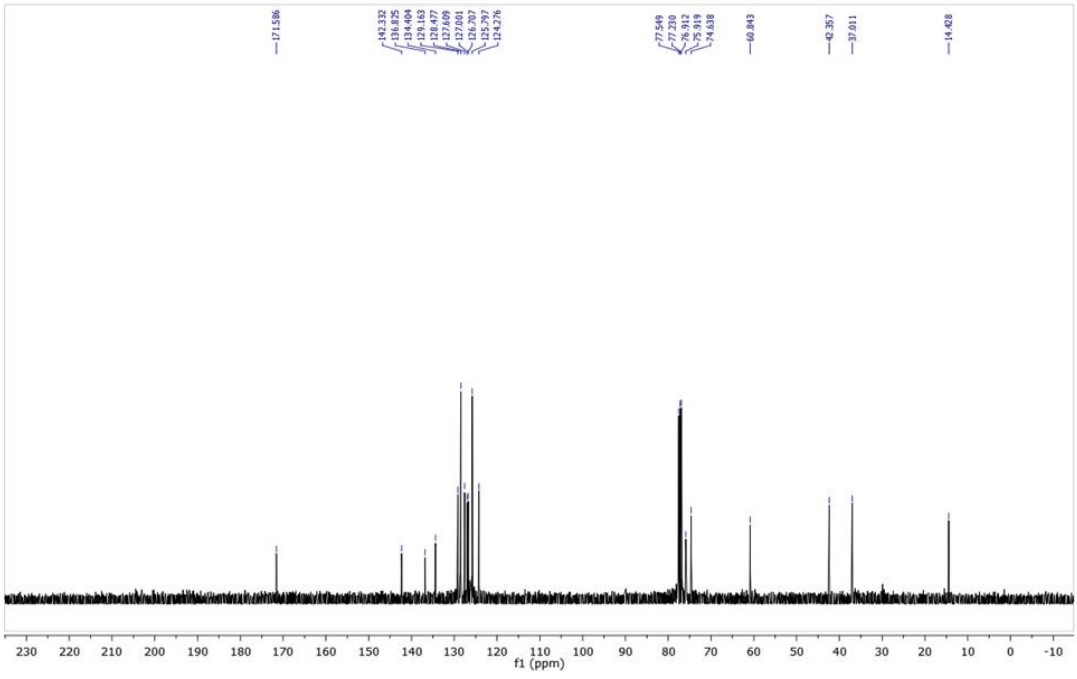
^{1}H and **^{13}C NMR** spectra of compound **32d**





^{1}H and **^{13}C NMR** spectra of compound **32e**





CHAPTER 3

Stereoselective Synthesis of 4-*O*-Tosyl tetrahydropyrans *via* Prins Cyclization Reaction of Enol ethers

3.1. Importance of Tetrahydorpyran Derivatives

Saturated six membered cyclic ethers better known as THPs are ubiquitious in nature and represent useful precursors for the synthesis of many biologically active molecules.[1] For example, neopeltolide **1** constitute a novel class of bioactive marine natural products, isolated from a deep-water Caribbean sponge of the family neopeltidae, collected from the north Jamaican coast. It exhibits significantly potent in *vitro* cytotoxicity towards several different cancer cell lines, including A-549 human lung adenocarcinoma, human ovarian sarcoma, and murine leukemia cell lines, with IC_{50} of 1.2, 5.1, and 0.56 nM, respectively, and also inhibited the growth of the fungal pathogen *Candida albicans* with a minimum inhibitory concentration of 0.62 μg/ mL.[2] 4-Hydroxytetrahydropyran containing natural products, catechols **2** and **3** isolated from extracts of *Plectranthus sylvestris* (labiatae), a plant found in the woody hills in East Africa are potent antioxidants and possess anti-inflamatory properties.[3] Similarly, apicularen A **4**, isolated from various strains of the myxobacterial genus *Chondromyces* and show antiproliferative properties against a variety of cancer cell lines such as ovarian, prostate, lung, kidney, cervix, leukemia, and histiocytic cells with IC_{50} values in the range of 0.23-6.79 nM. It has also proven to be a potential medicine for antiangiogenesis *(Figure 3.1.1).*[4]

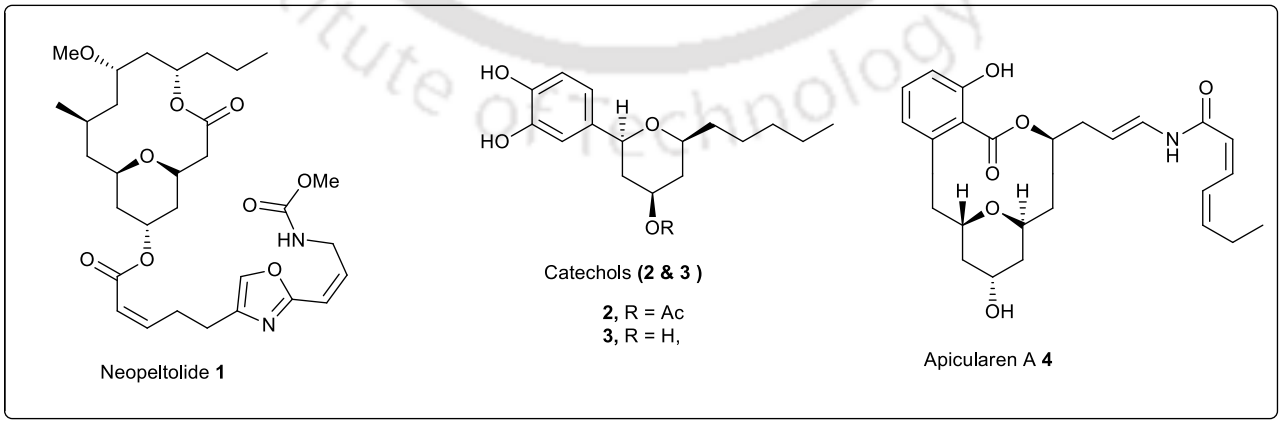


Figure 3.1.1. *Some biologically active tetrahydropyran derivatives*

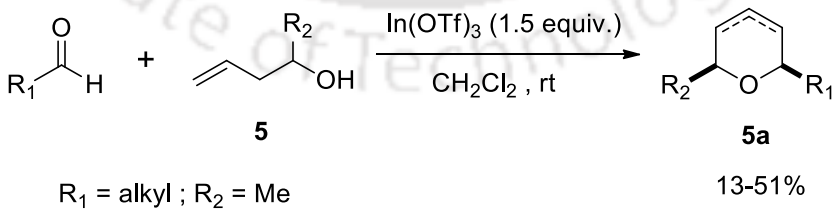
Over the years, the 4-substituted tetrahydropyrans rings have been synthesized using either Lewis or Brønsted acids *via* Prins cyclization reaction of homoallyl alcohols and aldehydes followed by trapping with various nucleophiles such as hydroxy,[5] halo,[6] aryls,[7] tosyl[8] and nitrile[9] groups. Recently another important approach for the synthesis of these compounds has been reported *via* hydroxyl-Prins cyclization of homoallyl acrylyl ethers mediated by TFA and K_2CO_3.[10]

Our group has reported stereoselective synthesis of dihydropyrans, terahydrofurans and tetrahydrothiophenes *via* Prins cyclization of homoallyl, homopropargyl alcohols and thiols. [11]

3.2. Literature Methods

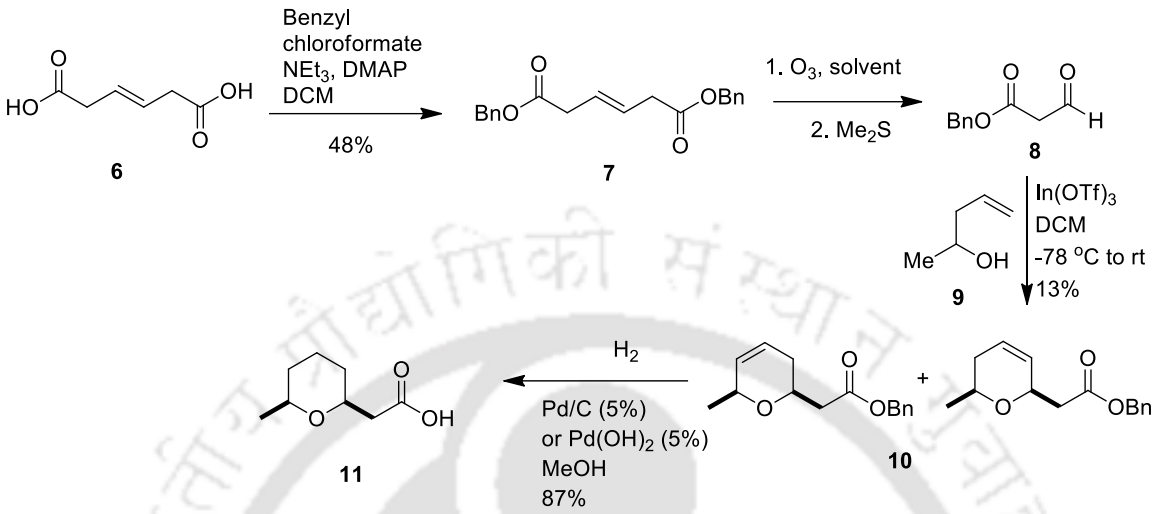
Review of literature reveals that dihydropyrans are generally prepared by hetero Diels-Alder reactions, olefin metathesis, Prins cyclization or base-promoted cyclizations of sulfinyl dienols. Among these, Prins cyclization is the most convenient because it provides the desired product in a single step and it is also useful in natural product synthesis. Usually, Lewis acid is used for this reaction and in most of the cases, the product is 4-hydroxy tetrahydropyrans.

Adrian P. Dobbs and his co-workers have reported the diastereoselective synthesis of *cis*-2,6-disubstitutd dihydropyrans **5a** *via* Prins cyclisation reaction. In this case they used aldehydes and homoallylic alcohols **5** catalyzed by indium (III) trifluoromethanesulfonate. But the yield is very less and also the reaction is not regioselective. It gives mixture of inseparable dihydropyrans **5** *(Scheme 3.2.1).*[12] The dihydropyrans are obtained in the racemic form.



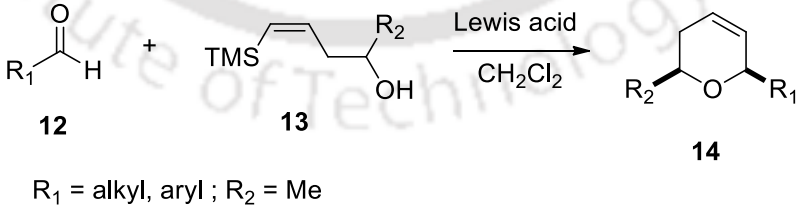
Scheme 3.2.1

They applied this methodology for the synthesis of natural product (±)-civet **11** as shown in *(Scheme 3.2.2).* Overall yield of the reaction is very less, only 2.2%. From this method, they obtained civet as an oil *(Scheme 3.2.2).*[12]

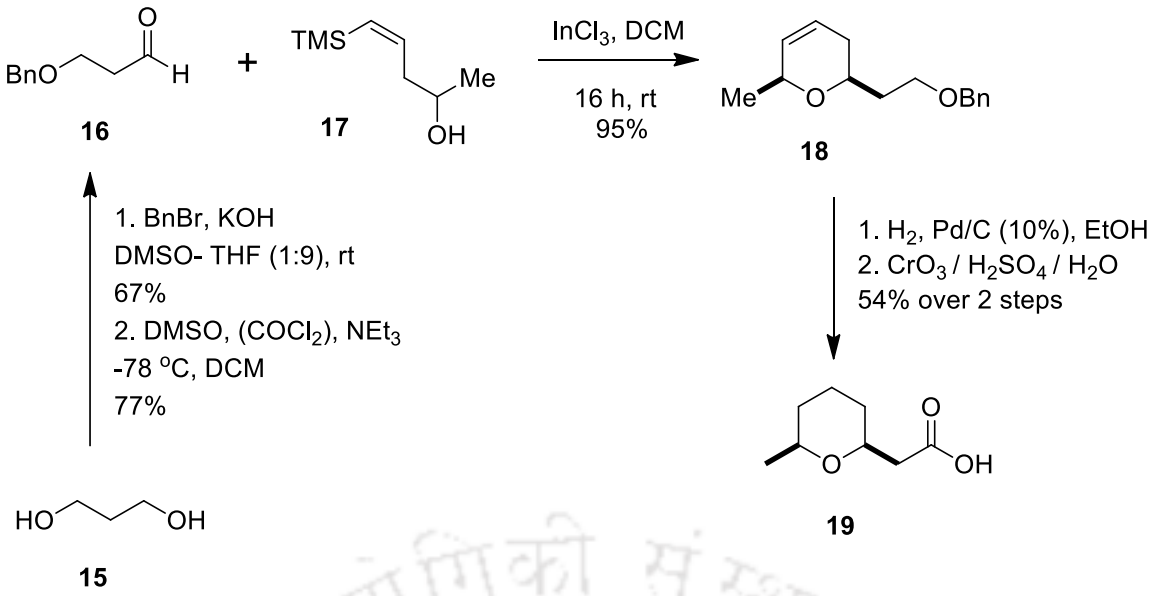


Scheme 3.2.2

To make the reaction regioselective, Dobbs and his coworkers extended their work *via* silyl-Prins reaction by introducing a silicon moiety to the olefin component **13** which *via β*-effect generated dihydropyran **14** with complete regioselectivity. A random screening revealed that many Lewis acids are capable of promoting the silyl-Prins reaction *e.g.* $BF_3{\cdot}OEt_2$ (-78 °C, yield 90%), TMSOTf (-78 °C, yield 86%) and $InCl_3$ (rt, yield 88%) are proving to be the most successful *(Scheme 3.2.3).* They repeated the synthesis of civet using this silyl Prins methodology as shown in *(Scheme 3.2.4).* Unlike civet obtained earlier as oil, here they obtained civet as crystal.[12]

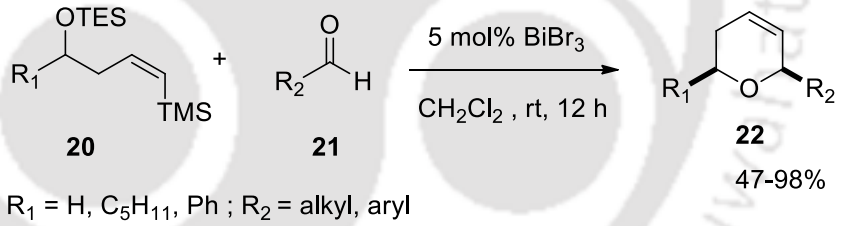


Scheme 3.2.3



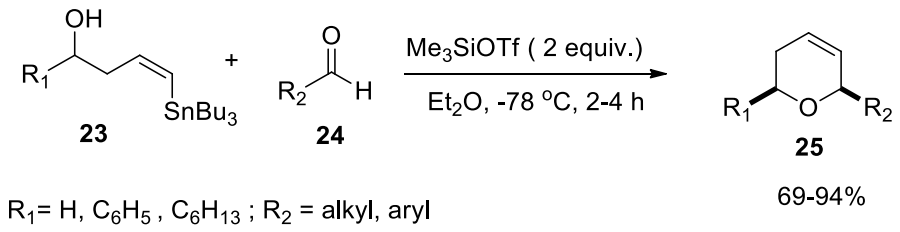
Scheme 3.2.4

Hinkle and co-workers have also reported a tandem silyl-Prins reaction between *δ*-triethyl-silyloxyvinyltrimethylsilanes **20** and a variety of aldehydes **21** to afford *cis*-2,6-disubstituted dihydropyrans **22** using 5 mol% of $BiBr_3$ in dichloromethane *(Scheme 3.2.5).* The diastereoselectivities in the crude products were significantly affected by aldehyde substitution, with electron-rich aldehydes providing 2-3:1 (*cis*: *trans*) and neutral (or electron poor) aldehydes affording *dr* ≥ 19:1(*cis*: *trans*).[13]



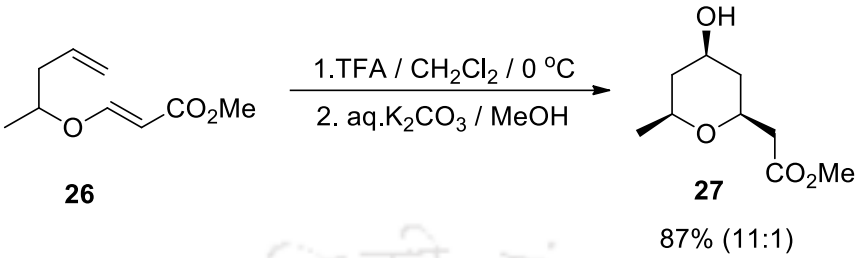
Scheme 3.2.5

A stannyl-Prins cyclization was reported by Furman and coworkers for stereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans **25**. The reaction of vinylstannanes **23** with aldehydes **24** in the presence of TMSOTf afforded *cis*-2,6-disubstituted dihydropyrans **25** in good yields with excellent stereoselectivity *(Scheme 3.2.6).* Although the dihydropyrans are obtained in the racemic form but the use of optically pure vinylstannane afforded optically pure 2,6-disubstituted dihydropyrans.[14]



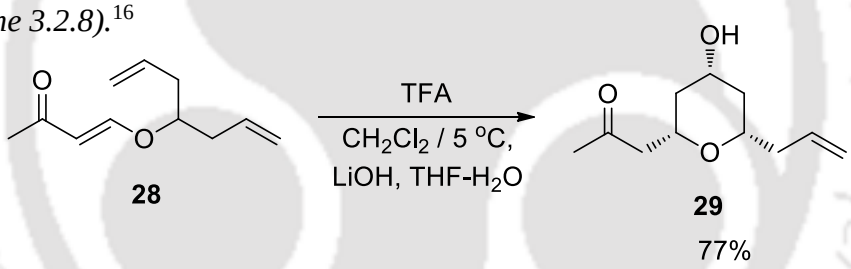
Scheme 3.2.6

In 1987, one variation has been reported in Prins cyclization by Fráter and Nussbaumer that is the use of enol ethers **26** as the source of the oxocarbenium ion. They catalyzed the reaction by using TFA and the reaction afforded C-4 hydroxy substituted tetrahydropyran ring **27** as a diastereomic mixture *(Scheme 3.2.7).*[15]



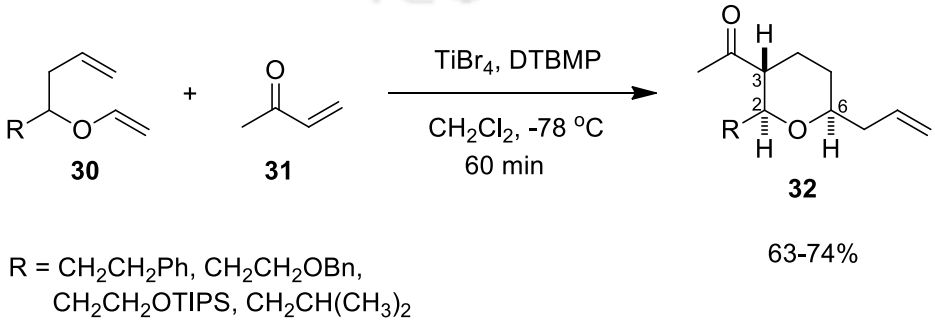
Scheme 3.2.7

Another example of using enol ether as the source of the oxocarbenium ion intermediate was reported by Kozmin for the synthesis of 4-hydroxy tetrahydrofuran **29**. The cyclization of enol-ether **28** was promoted by TFA (trifluoroacetic acid). The resulting trifluoroacetate was hydrolyzed using LiOH to afford the *cis*-tetrahydropyran **29** in good yield. The reaction proved to be efficient in the construction of the three stereogenic centers and only one isomer was observed *(Scheme 3.2.8).*[16]



Scheme 3.2.8

Rychnovsky and co-workers have reported the synthesis of 2,3,6-trisubstituted tetrahydropyrans **32** from a Mukaiyama-Michael cascade reaction of homoallylic enol ethers **30** and 3-butene-2-one **31** promoted by $TiBr_4$ and DTBMP i.e. 2,6-di-*tert*-butyl-4-methylpyridine *(Scheme 3.2.9).* The resulting tetrahydropyrans **32** are obtained in good yields with a single diastereomer.[17]

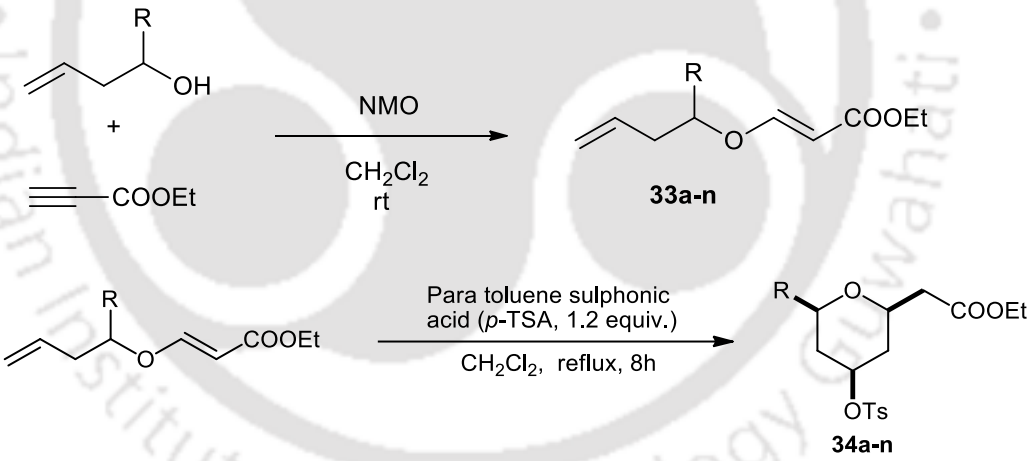


Scheme 3.2.9

3.3. Results and Discussions

To start with, we reacted (*E*)-ethyl 3-(but-3-en-1-yloxy)acrylate **33a** with 1.2 equivalents of *p*-TSA in dichloromethane (DCM) at reflux temperature and the reaction proceeded smoothly to afford ethyl 2-((2*R**,4*S**)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl) acetate in 68% yield as a mixture of isomer with a *cis* and *trans* ratio 93:7, having *cis* relationship among the substituents as a major compound. Catalytic amount of *p*-TSA was not giving good yield and excess of *p*-TSA (more than 1.2 equivalents) gave decomposed product. It has also been found that only dry DCM is the suitable solvent, other polar protic solvent like CH_3OH, EtOH, CH_3COOH and polar aprotic solvent like CH_3CN, THF, DMF, DMSO was not able to give the desired product.

To check substrate scope with established optimal reaction conditions, a variety of homoallyl acryloyl ethers, which were synthesized according to literature methods by Michael addition of homoallyl alcohols to ethyl propiolate using NMO as a base in DCM solvent at ambient temperature *(Scheme 3.3.1)*.[11a]



Scheme 3.3.1

These acryloyl enol ethers were subjected to the *p*-TSA mediated Prins cyclization reaction as shown in *Table 3.3.1*. All the substrates worked well and produced moderate to good yield with high diastereoselectivity. In case of simple phenyl substituted enol ether **33b** gave the corresponding product in 74% yield with a dr of 90:10. The substrates having moderate electron withdrawing aromatic substituents **33c, 33d, 33e, 33f, 33i, 33k** (entries c, d, e, f, i and k**)** is suitable for this reaction compare to electron donating substituents. Whereas, strong electron withdrawing substituent **33o** containing nitro group (entry o) and strong donating aromatic substituent **33g** containing methoxy group (entry g) did not gave the desired product. This is because of the fact that methoxy group interact with *p*-TSA and nitro group as an electron withdrawing group prevents the formation of stable oxocarbonium ion. The reaction is suitable for other substituent **33l** containing ester group (entry l) and substituent **33m and 33n** containing aliphatic group (entry m, n) are compatible for this reaction. The reaction is highly diastereoselective with *cis* relationship between the substituents on tetrahydropyran ring. The diastereoselectivity was confirmed by crude **^{1}H, ^{13}C NMR** and **NOE** experiments. A strong **NOE** between H at C-2 and H at C-4 as well as interaction between H at C-2 and H at C-6 clearly suggests all substituents are in *cis* relationship *(Figure 3.2.1).*

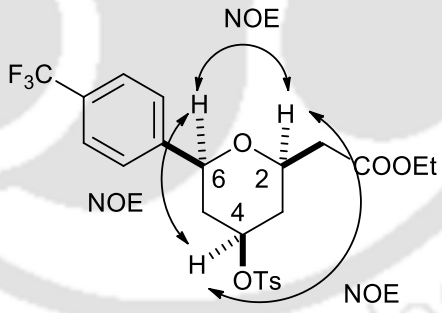
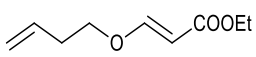
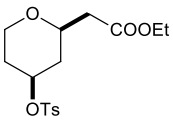
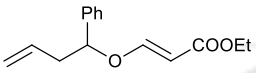
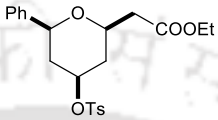
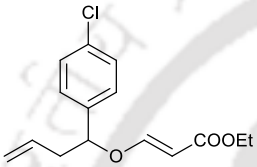
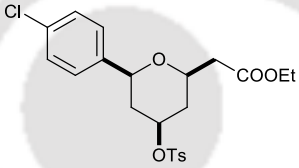
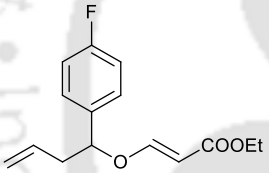
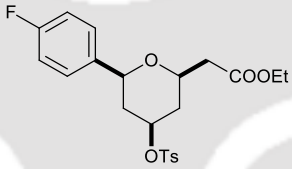
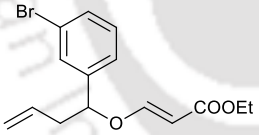
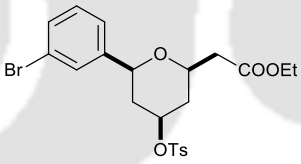
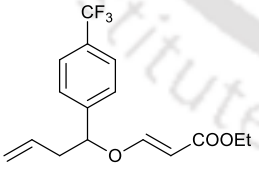
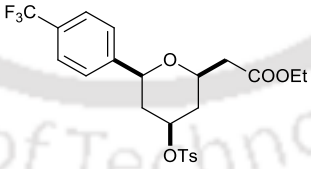
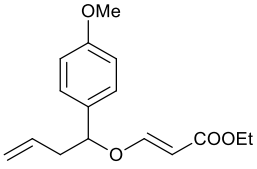
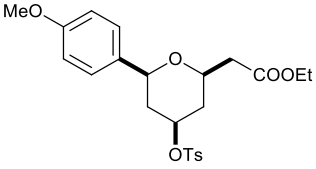
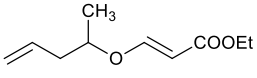
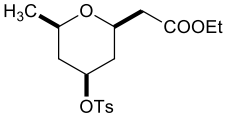
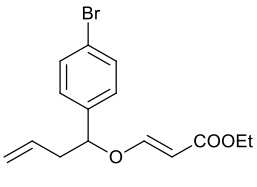
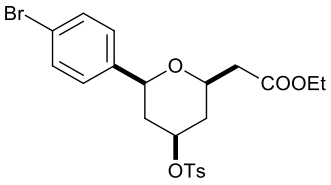
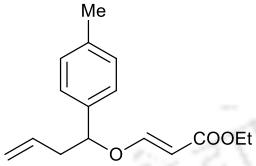
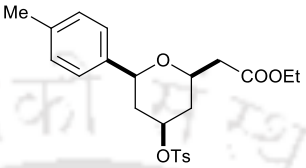
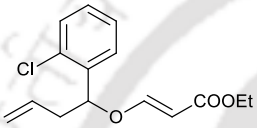
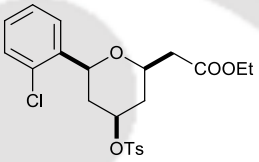
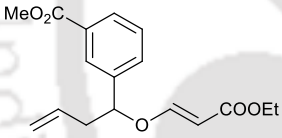
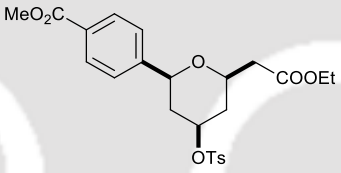
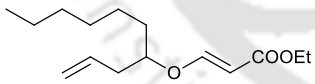
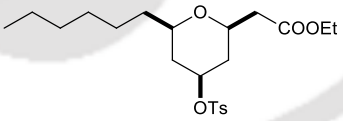
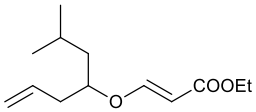
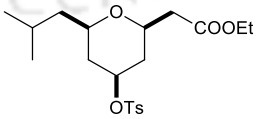
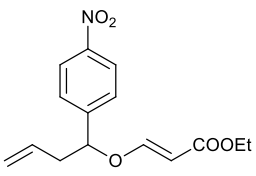
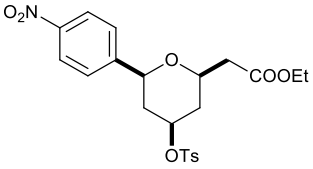


***Figure 3.3.1. NOE** of (2R*,4S*,6S*)-Ethyl-4-(tosyloxy)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-carboxylate (**34f**)*

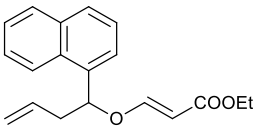
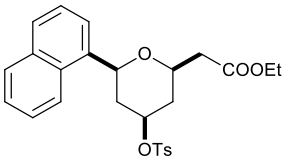
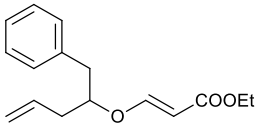
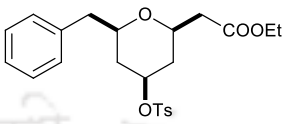
Table 3.3.1. Synthesis of *O*-Tosyltetrahydropyrans *via* Prins cyclization reaction

Entry	Substrate **33**	Product **34/35**	dr[a]	Yield (%)[b]
a			93:07	68
b			90:10	74
c			91:9	79
d			85:15	76
e			90:10	84
f			89:11	89
g			-	0
h			96:04	74

Continued…….

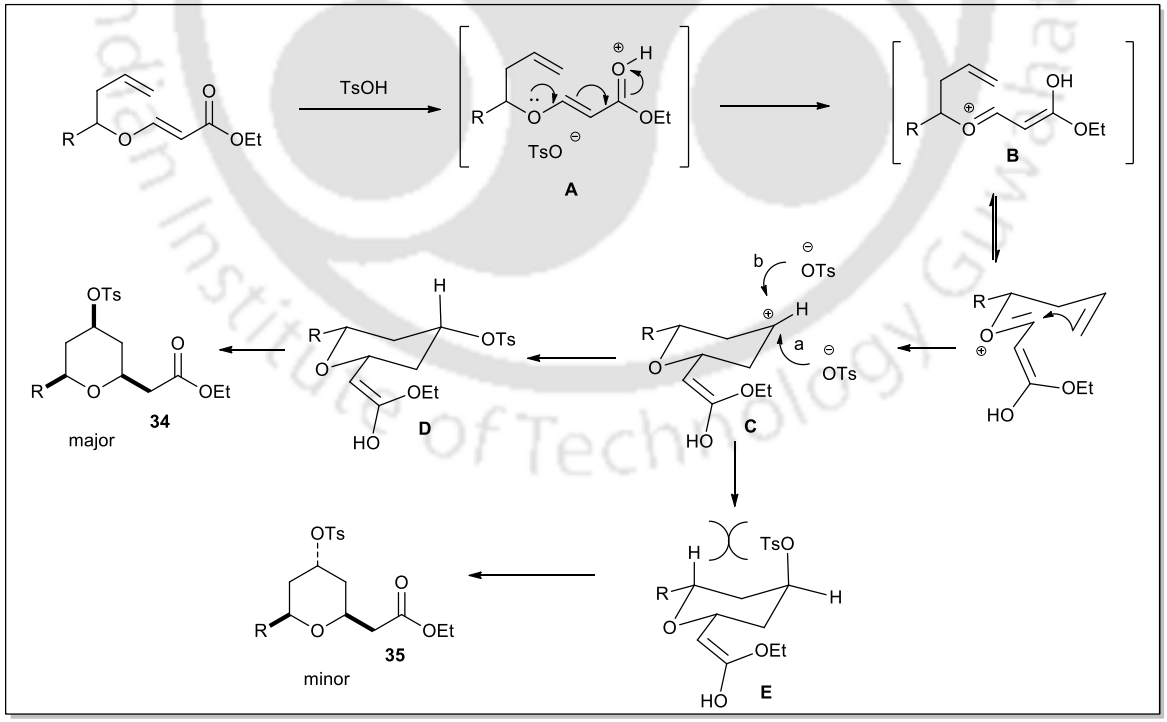
Entry	Substrate **33**	Product **34/35**	dr[a]	Yield (%)[b]
i			97:03	75
j			97:03	62
k			97:03	72
l			91:09	64
m			90:10	54
n			91:09	52
o			-	0

Continued……

p			94:06	64
q			95:05	54

[a]Ratio is determined by **^{1}H NMR** spectroscopy. [b]Yields refer to isolated yields

The mechanism of the reaction can be explained as follows *(Scheme 3.3.2)*. *p*-TSA activates carbonyl group of the ester functionality of enol ether by protonating the carbonyl group **A**, leading to the formation of oxocarbenium ion **B**, which after Prins cyclization forms tetrahydropyranyl cation **C**. The tosyl nucleophile attacks the carbocation **C** equatorially to give **34** as a major product and **35** as a minor product. This might be due to stability difference between intermediates **D** and **E**.



Scheme 3.3.2. Plausible mechanism of the reaction

Conclusions

We have developed a methodology for stereoselective synthesis of tosyl substituted tetrahydropyrans through Prins cyclization reaction of homoallyl acryloyl enol ethers. The reaction is atom economy and good yields are achieved with high diastereoselectivity. This methodology could be useful for the synthesis of other substituted pyran ring by manipulating tosyl functionality.

3.4. Experimental section

3.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1.

3.4.2. Synthesis of starting materials

The homoallyl acryloyl ethers were synthesized as per literature procedure and the structure and purity of known compounds **33a-n** were confirmed by comparison of their spectral data (**^{1}H NMR** and **^{13}C NMR**) with those reported known in literature.[11a]

3.4.3. General Procedure for the Synthesis of of 4-*O*-Tosyltetrahydropyrans Compounds (34a-n):

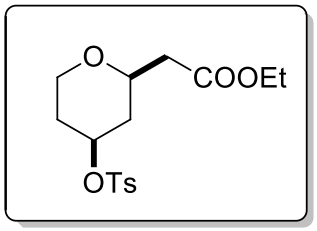
To (*E*)-ethyl 3-(but-3-en-1-yloxy) acrylate (340 mg, 0.5 mmol) in dichloromethane (3 mL) was added *p*-TSA (408 mg, 0.6mmol). The reaction mixture was stirred at reflux temperature for 8h. The progress of the reaction was monitored by TLC with 1:4 ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbon ate and the product was extracted with ethyl acetate and then the organic layer was washed with brine. The organic layer was dried over (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography using ethyl acetate and hexane as eluent over silica gel to give ethyl 2-((2*R**,4*S**)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (**34a)** in 68% yield.)

3.5. References

1) (a) *Polyether Antibiotics*; Westly, J. W., Ed.; Marcell Dekker,: New York, **1983;** Vols. I and II. b) Faulkner, D. J. *Nat. Prod. Rep.* **2002,** *19,* 1. c) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999,** *121,* 10211. (d) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000,** *122,* 9836. (e) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004,** *69,* 1993. (f) Class, Y. J.; Deshong, P. *Chem. Rev*. **1995,** *95,* 1843. (g) Norcross, R. D.; Paterson, I. *Chem. Rev*. **1995**, *95,* 2041.
2) Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; Mc Carthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007,** *70,* 412.
3) Juch, M.; Rüedi, P. *Helv. Chem. Acta* **1997,** *80,* 436.
4) (a) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998,** *51,* 1075. (b) Kwon, H. J.; Kim, D. H.; Shik, J. S.; Ahn, J. W. *J. Microbiol. Biotechnol.* **2002,** *12,* 702.
5) Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008,** *10,* 4839.
6) (a) Bondalapati, S.; Reddy, U. C.; Kundu, D. S.; Saikia, A. K. *J. Fluorine Chem.* **2010,** *113,* 320. (b) Yadav, J. S.; Reddy, B. V. S.; Anusha, B.; Reddy, U. V.S.; Reddy, V. V. B. *Tetrahedron Lett.* **2010,** *51,* 2872. (c) Launay, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010,** *6,* 41. (d) Yang, J.; Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **1999,** *40,* 1627. (e) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009,** *11,* 357.
7) (a) Yang, X. F.; Wang, M.; Zhang, Y.; Li, C. J. *Synlett* **2005,** *19,* 12. (b) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Eur. J. Org. Chem.* **2009,** *16,* 25. (c) Reddy, U. C.; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem.* **2008,** *73,* 1628. (d) Reddy, B. V. S.; Chaya, D. N.; Yadav, J. S.; Chatterjee, D.; Kunwar, A. C. *Tetrahedron Lett.* **2011,** *52,* 2961.
8) Ahmed, N.; Konduru, N. K. *Beilstein J. Org. Chem.* **2012,** *8,* 177.
9) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Reddy, G. M. *Tetrahedron Lett.* **2007,** *48,* 4903.
10) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003,** *5,* 1499.
11) (a) Sultana, S.; Indukuri, K.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013,** *78,* 12182. (b) Gogoi, P.; Das, V. K.; Saikia, A. K. *J. Org. Chem.* 2014, **79**, 8592.
12) Chio, F. K., Warne, J., Gough, D., Penny, M., Green, S., Coles, S. J., Hursthouse, P. J., Hassall, L., McGuire, T. M., Dobbs, A. P. *Tetrahedron* **2011**, *67*, 5107.
13) Lian, Y.; Hinkle, R. J. *J. Org. Chem*. **2006**, *71*, 7071.
14) Dziedzic, M.; Furman, B. *Tetrahedron Lett*. **2008**, *49*, 678.
15) Nussbaumer, C.; Fràter, G. *J. Org. Chem*. **1987**, *52*, 2096.
16) Nussbaumer, C.; Fràter, G. *Helv. Chem. Act*. **1987**, *70*, 396.
17) Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2005**, *127*, 16044.

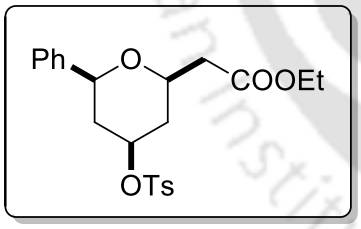
3.6. Characterization Data

Ethyl-2-((2R*,4S*)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34a, diasteriomeric mixture, 93:7):



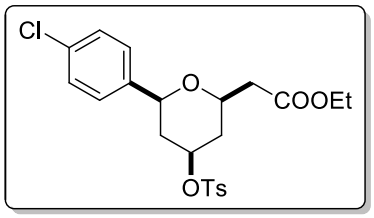
Pale yellow gum; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 112 mg, 68%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.46-1.52 (m, 1 H), 1.67−1.75 (m, 1 H), 1.84−1.88 (m, 1 H), 1.97−2.00 (m, 1 H), 2.36 (dd, *J* = 15.6 and 5.4 Hz, 1 H), 2.45 (s, 3 H), 2.52 (dd, *J* = 15.6 and 8.4 Hz, 1 H), 3.36 (dd, *J* = 12.0 and 1.2 Hz, 1 H), 3.69-3.75 (m, 1 H), 3.96 (dd, *J* = 12.0 and 4.2 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.56−4.62 (m, 1 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.79 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): 14.3, 21.8, 32.6, 38.1, 41.1, 60.9, 65.6, 72.6, 77.9, 127.8, 130.1, 134.5, 145.0, 170.7; **IR** (KBr, neat): 576, 670, 899, 1083, 1175, 1362, 1598, 1738, 2863, 2968 cm^{-1}. **HRMS** (ESI) calcd. for $C_{16}H_{23}O_6S$ $(M + H)^+$ 343.1210, found 343.1239.

Ethyl-2-((2R*,4R*,6S*)-6-phenyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34b, diasteriomeric mixture, 93:7):



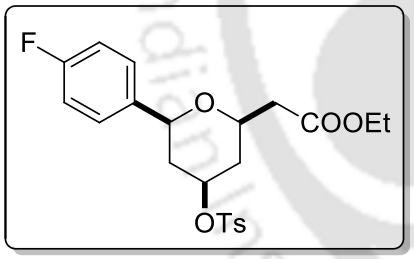
White solid, mp 87-89 ˚C; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 150 mg, 74%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.55-1.60 (m, 1 H), 1.68-1.74 (m, 1 H), 2.06−2.10 (m, 1 H), 2.21−2.24 (m, 1 H), 2.45 (s, 3 H), 2.46 (dd, *J* = 15.6 and 6.0 Hz, 1 H), 2.65 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 3.92−3.96 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.37 (d, *J* = 10.8 Hz, 1 H), 4.75-4.80 (m, 1 H), 7.26-7.36 (m, 7 H), 7.81 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.3, 21.8, 37.6, 39.6, 40.8, 41.0, 41.1, 60.8, 60.9, 72.3, 78.0, 126.0, 127.8, 127.9, 128.0, 128.5, 128.6, 130.1, 134.4, 140.8, 145.0, 170.7; **IR** (KBr, neat): 579, 669, 758, 956, 1097, 1176, 1366, 1413, 1598, 1735, 2873 cm^{-1}. **HRMS** (ESI) calcd. for $C_{22}H_{27}O_6S$ $(M + H)^+$ 419.1536, found 419.1536.

Ethyl-2-((2R*,4R*,6S*)-6-(4-chlorophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34c, diastereomeric mixture, 99:1):



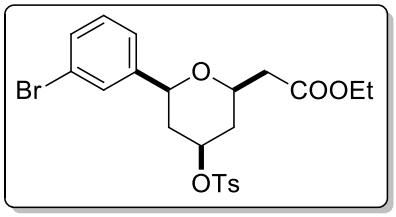
Pale yellow gum; R_f (hexane/ EtOAc 95:5) 0.50; (yield 173 mg, 79%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.52-1.59 (m, 1 H), 1.62-1.68 (m, 1 H), 2.06−2.09 (m, 1 H), 2.20−2.23 (m, 1 H), 2.45 (s, 3 H), 2.46 (dd, *J* = 15.6 and 5.4 Hz, 1 H), 2.63 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 3.92−3.94 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 3.35 (dd, *J* = 11.4 and 1.8 Hz, 1 H), 4.75-4.79 (m, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.3, 21.9, 37.5, 39.7, 41.0, 60.9, 72.4, 76.5, 77.6, 127.3, 127.8, 128.7, 130.1, 133.7, 134.3, 139.4, 145.1, 170.6; **IR** (KBr, neat): 555, 667, 757, 815, 956, 1090, 1189, 1494, 1599, 1738, 2854, 2927 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{26}ClO_6S$ $(M + H)^+$ 453.1133, found 453.1123.

Ethyl-2-((2R*,4R*,6S*)-6-(4-fluorophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34d, diastereomeric mixture, 95:5):



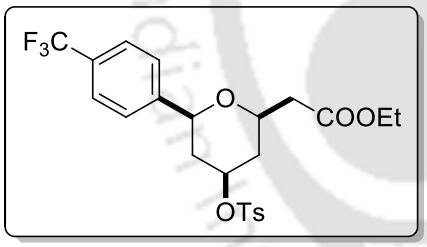
Pale yellow gum; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 160 mg, 76%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.53-1.56 (m, 1 H), 1.65-1.71 (m, 1 H), 2.05−2.09 (m, 1 H), 2.21−2.24 (m, 1 H), 2.45 (dd, *J* = 15.6 and 5.4 Hz, 1 H), 2.46 (s, 3 H), 2.64 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 3.91−3.95 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.35 (dd, *J* = 11.4 and 1.8 Hz, 1 H), 4.74-4.80 (m, 1 H), 7.00 (t, *J* = 8.4 Hz, 2 H), 7.22-7.25 (m, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.9, 37.6, 39.7, 41.0, 60.9, 72.4, 76.6, 77.8, 115.4 (d, *J* = 19.5 Hz), 127.6 (d, *J* = 7.5 Hz), 127.9, 130.1, 134.4, 136.7, 145.1, 162.5 (d, *J* = 246.0 Hz), 170.6; **IR** (KBr, neat): 551, 668, 768, 1085, 1176, 1367, 1599, 1733, 2928 cm^{-1}. **HRMS** (ESI) calcd. for $C_{22}H_{26}FO_6S$ $(M + H)^+$ 437.1429, found 437.1435.

Ethyl-2-((2R*,4R*,6S*)-6-(3-bromophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34e, diastereomeric mixture, 95:5):



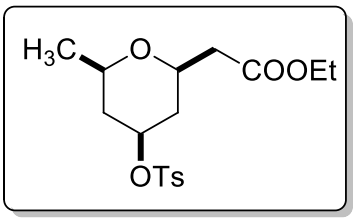
Pale yellow gum; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 202 mg, 84%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.41-1.47 (m, 1 H), 1.56-1.62 (m, 1 H), 2.12−2.16 (m, 1 H), 2.24−2.28 (m, 1 H), 2.45 (s, 3 H), 2.49 (dd, *J* = 15.6 and 5.4 Hz, 1 H), 2.65 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 3.96−4.00 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.60 (dd, *J* = 11.4 and 1.8 Hz, 1 H), 4.75-4.81 (m, 1 H), 7.09-7.13 (m, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.44-7.47 (m, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.9, 37.7, 38.2, 41.2, 60.9, 72.5, 76.4, 77.7, 121.6, 127.6, 127.9, 129.3, 130.2, 132.7, 134.4, 140.1, 145.1, 170.5; **IR** (KBr, neat): 556, 667, 770, 815, 957, 1078, 1177, 1366, 1495, 1598, 1735, 2929, 2980 cm^{-1}. **HRMS** (ESI) calcd. for $C_{22}H_{26}BrO_6S$ $(M + H)^+$ 499.0608, found 499.0628.

Ethyl-2-((2R*,4R*,6S*)-4-(tosyloxy)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-2-yl)acetate (34f, diastereomeric mixture, 98:2):



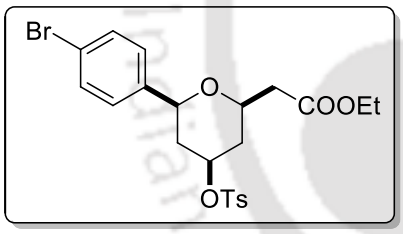
White solid, mp 120-122 ˚C; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 210 mg, 89%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 1.55-1.61 (m, 1 H), 1.62-1.69 (m, 1 H), 2.07−2.10 (m, 1 H), 2.25−2.29 (m, 1 H), 2.46 (s, 3 H), 2.47 (dd, *J* = 15.6 and 5.4 Hz, 1 H), 2.65 (dd, *J* = 15.6 and 7.8 Hz, 1 H), 3.94−3.68 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.44 (dd, *J* = 11.4 and 1.8 Hz, 1 H), 4.77-4.82 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.9, 37.5, 39.8, 41.0, 60.9, 72.5, 76.5, 77.5, 125.5, 126.2, 126.8 (q, *J* = 270.0 Hz), 127.9, 130.1, 130.2 (q, *J* = 36 Hz), 134.3, 144.8, 145.2, 170.6; **IR** (KBr, neat): 555, 671, 759, 841, 1018, 1163, 1370, 1599, 1622, 1735, 2860, 2930 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{26}F_3O_6S$ $(M + H)^+$ 487.1397, found 487.1388.

Ethyl 2-((2R*,4S*,6R*)-6-methyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34h, diastereomeric mixture; 86:16):



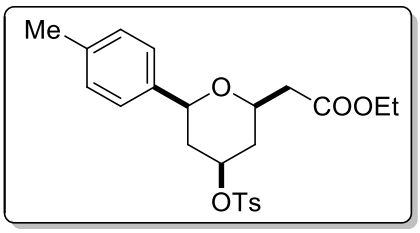
Yellow gum; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 263mg, 74%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.2 Hz, 3 H), 1.17 (t, *J* = 7.2, 3 H), 1.25−1.37 (m, 2 H), 1.84−1.90 (m, 2 H), 2.28 (dd, *J* = 15.4 and 5.4 Hz, 1 H), 2.36 (s, 3 H), 2.46 (dd, *J* = 15.4 and 7.6 Hz, 1 H), 3.34-3.36 (m, 1 H), 3.64-3.75 (m, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 4.48−4.55 (m, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.2, 21.4, 21.7, 37.3, 39.5, 40.9, 60.2, 71.5, 71.7, 77.9, 127.6, 129.9, 134.3, 144.8, 170.6; **IR** (KBr, neat): 572, 671, 894, 1081, 1174, 1360, 1594, 1730, 2862, 2961 cm^{-1}; **HRMS** (ESI) calcd. for $C_{17}H_{25}O_6S$ $(M + H)^+$ 357.1366, found 357.1364.

Ethyl-2-((2R*,4R*,6S*)-6-(4-bromophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34i, diastereomeric mixture; 92:8):



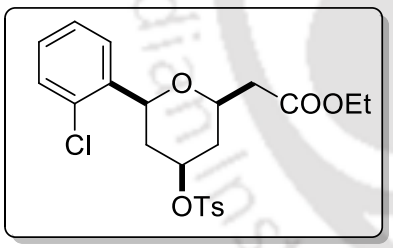
Reddish oil; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 372mg, 75%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.51−1.69 (m, 2 H), 2.04-2.09 (m, 1 H), 2.18-2.26 (m, 1 H), 2.46 (s, 3 H), 2.47 (dd, *J* = 15.0 and 7.2 Hz, 1 H), 2.65 (dd, *J* = 15.0 and 7.8 Hz, 1 H), 3.90-3.96 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.35 (d, *J* = 10.5 Hz, 1 H), 4.71-4.80 (m, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H); 7.35 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.9, 37.5, 39.7, 41.0, 60.9, 72.4, 76.4, 77.6, 122.7, 124.5, 127.9, 129.1, 130.2, 134.3, 143.0, 145.1, 176.8; **IR** (KBr, neat): 559, 679, 758, 842, 1012, 1169, 1374, 1600, 1628, 1739, 2862, 2932 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{26}BrO_6S$ $(M + H)^+$ 497.0628 (^{79}Br), found 497.0640.

Ethyl 2-((2R*,4R*,6S*)-6-(p-tolyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34j, diastereomeric mixture; 96:4):



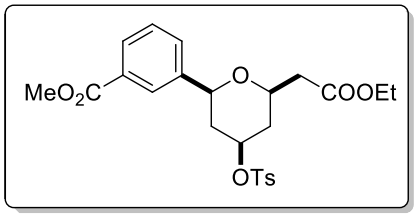
Yellow oil; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 267 mg, 64%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3 H), 1.51-1.60 (m, 1 H),), 1.64−1.75 (m, 2 H), 2.10 (d, *J* = 10.0 Hz, 1 H), 2.22 (d, *J* = 10.0 Hz, 1 H), 2.33 (s, 3 H), 2.47 (s, 3 H), 2.63-2.70 (m, 1 H), 3.91-3.95 (m, 1 H), 4.10-4.16 (m, 2 H), 4.32−4.38 (m, 1 H), 4.75-4.85 (m, 1 H), 7.13-7.18 (m, 4 H), 7.36 (d, *J* = 8.4 Hz, 2 H); 7.82 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.3, 21.9, 37.7, 39.6, 41.1, 60.8, 72.3, 77.0, 78.2, 126.0, 127.8, 129.3, 130.1, 134.4, 137.8, 137.9, 145.0, 170.7; **IR** (KBr, neat): 556, 672, 754, 842, 1012, 1162, 1371, 1594, 1621, 1734, 2865, 2932 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{29}O_6S$ $(M + H)^+$ 433.1679, found 433.1693.

Ethyl-2-((2R*,4R*,6S*)-6-(2-chlorophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34k, diastereomeric mixture; 92:8):



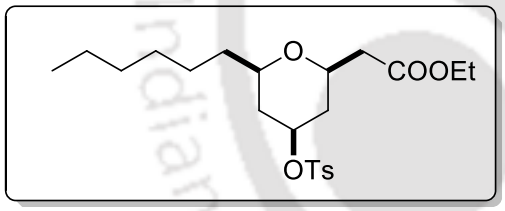
Yellow oil; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 326 mg, 72%); **^{1}H NMR** (600 MHz, $CDCl_3$): 1.21 (t, *J* = 7.2 Hz, 3 H), 1.43−1.50 (m, 1 H), 1.56−1.62 (m, 1 H), 2.11-2.14 (m, 1 H), 2.23-2.26 (m, 1 H), 2.43 (s, 3 H), 2.48 (dd, *J* = 15.6 and 5.4 Hz, 1 H), 2.65 (dd, *J* = 15.6 and 7.2 Hz, 1 H), 3.96-4.00 (m, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 4.67 (dd, *J* = 12.0 and 1.6 Hz, 1 H), 4.76-4.81 (m, 1 H), 7.16-7.18 (m, 1 H), 7.22-7.27 (m, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H); 7.46 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.7, 37.8, 38.2, 38.7, 41.2, 70.0, 72.6, 76.5, 121.5, 121.7, 127.7, 128.2, 129.4, 130.2, 132.9, 134.4, 140.4, 145.2, 170.9; **IR** (KBr, neat): 793, 814, 1097, 1362, 1474, 1598, 1738, 2853, 2926 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{26}ClO_6S$ $(M + H)^+$ 453.1133, found 453.1117.

Methyl-4-((2S*,4R*,6R*)-6-(2-ethoxy-2-oxoethyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)benzoate(34l, diastereomeric mixture; 96:4):



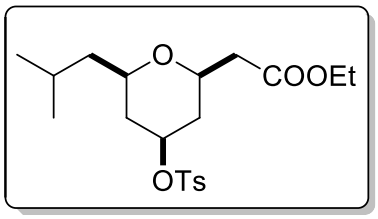
Colorless oil; R_f (hexane/ EtOAc 90:10), 0.50; (yield, 305mg, 64%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 1.50-1.70 (m, 1 H), 1.98-2.10 (m, 1 H), 2.24−2.27 (m, 1 H), 2.33−2.36 (m, 1 H), 2.46 (s, 3 H), 2.63-2.67 (m, 1 H), 3.90 (s, 3 H), 4.07−4.13 (m, 3 H), 4.41 (d, *J* = 10.8 Hz, 2 H), 4.70-4.80 (m, 1 H), 7.34 (t, *J* = 8.4 Hz, 4 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.3, 14.4, 21.9, 37.4, 39.7, 41.0, 61.0, 72.1, 76.7, 77.1, 125.6, 125.8, 127.8, 129.8, 130.1, 134.3, 145.1, 145.2, 167.0, 170.6 ; **IR** (KBr, neat): 559, 672, 756, 842, 1012, 1161, 1372, 1594, 1626, 1734, 2861, 2938 cm^{-1}; **HRMS** (ESI) calcd. for $C_{24}H_{29}O_8S$ $(M + H)^+$ 477.1578, found 477.1594.

Ethyl-2-((2R*,4S*,6R*)-6-hexyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34m, diastereomeric mixture; 82:18):



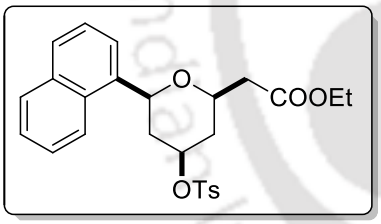
Yellow oil; R_f (hexane/ EtOAc 95:5), 0.50; (yield, 223mg, 54%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 6 H), 1.22-1.42 (m, 12 H), 1.91-1.96 (m, 2 H), 2.35 (dd, *J* = 15.0 and 4.8 Hz, 1 H), 2.45 (s, 3 H), 4.52 (dd, *J* = 15.0 and 8.4 Hz, 1 H), 3.22-3.27 (m, 2 H), 3.68-3.72 (m, 2 H), 4.13-4.17 (m, 2 H), 4.59-4.64 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.2, 14.3, 21.7, 22.6, 25.4, 29.8, 31.8, 35.7, 37.7, 38.0, 41.1, 60.8, 72.0, 75.6, 78.3, 127.8, 130.1, 134.4, 144.8, 170.9; **IR** (KBr, neat): 508, 668, 813, 952, 1033, 1177, 1379, 1443, 1640, 1735, 2925 cm^{-1}; **HRMS** (ESI) calcd. for $C_{22}H_{35}O_6S$ $(M + H)^+$ 427.2149, found 427.2140.

Ethyl-2-((2R*,4R*,6S*)-6-isopropyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34n, diastereomeric mixture; 93:7):



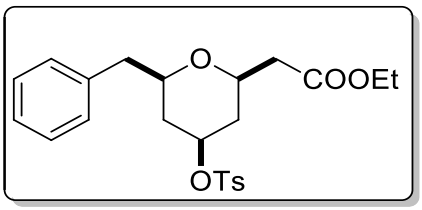
Orange gum; R_f (hexane/ EtOAc 90:10), 0.50; (yield, 207mg, 52%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 0.83 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 1.10-1.14 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.34-1.44 (m, 2 H), 1.45-1.48 (m, 1 H), 1.68-1.72 (m, 1 H), 1.88-1.96 (m, 2 H), 2.35 (dd, *J* = 15.0 and 4.8 Hz, 1 H), 2.46 (s, 3 H), 2.51 (dd, *J* = 15.0 and 8.4 Hz, 1 H), 3.31-3.35 (m, 1 H), 3.68-3.73 (m, 1 H), 4.08-4.16 (m, 2 H), 4.57-4.66 (m, 1 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.79 (d, *J* = 7.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.4, 21.9, 22.1, 23.3, 24.6, 37.8, 38.6, 41.3, 44.8, 60.8, 72.1, 73.8, 78.3, 127.8, 130.1, 134.5, 145.0, 170.9; **IR** (KBr, neat): 579, 669, 793, 844, 935, 1097, 1190, 1367, 1598, 1738, 2869, 2955 cm^{-1}; **HRMS** (ESI) calcd. for $C_{20}H_{31}O_6S$ $(M + H)^+$ 399.1836, found 399.1820.

Ethyl-2-((2R*,4R*,6S*)-6-(naphthalen-1-yl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34p, diastereomeric mixture; 95:5):



Light yellow oil; R_f (hexane/ EtOAc 90:10), 0.50; (yield, 330mg, 64%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 1.57-1.67 (m, 1 H), 1.75-1.85 (m, 1 H), 2.10−2.17 (m, 1 H), 2.29−2.35 (m, 1 H), 2.44 (s, 3 H), 2.49 (dd, *J* = 15.6 and 5.2 Hz, 1 H), 2.64-2.72 (m, 1 H), 3.98-4.03 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 4.80-4.86 (m, 1 H), 7.33-7.39 (m, 3 H), 7.44-7.47 (m, 2 H), 7.72 (s, 1 H), 7.78-7.83 (m, 5 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.5, 22.0, 37.8, 39.8, 41.2, 61.0, 72.6, 77.1, 78.1, 124.3, 124.8, 126.5, 127.9, 128.0, 128.3, 128.5, 130.2, 133.3, 133.4, 134.5, 138.3, 145.2, 170.8; **IR** (KBr, neat): 552, 660, 744, 816, 955, 1060, 1188, 1357, 1593, 1732, 2845, 2917 cm^{-1}; **HRMS** (ESI) calcd. for $C_{26}H_{29}O_6S$ $(M + H)^+$ 469.1679, found 469.1691.

Ethyl-2-((2R*,4S*,6R*)-6-benzyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (34q, diastereomeric mixture; 100:0):

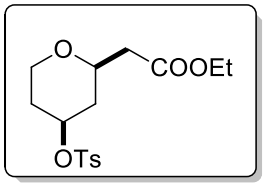


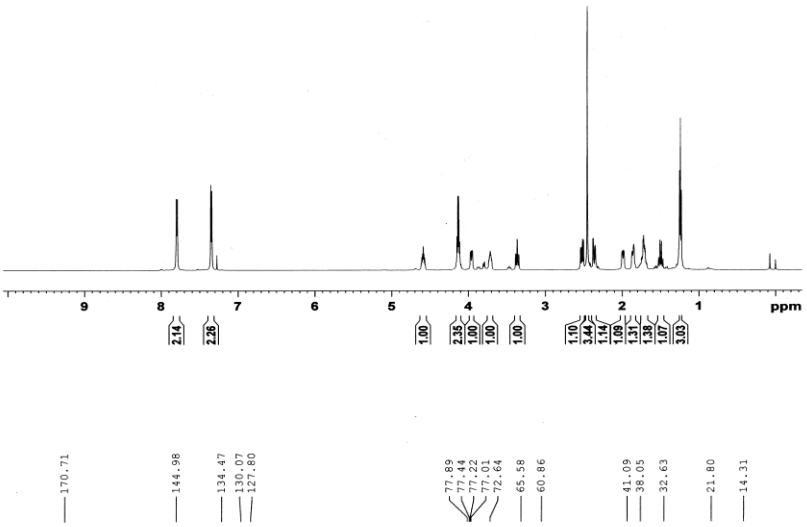
Light yellow oil; R_f (hexane/ EtOAc 90:10), 0.50; (yield, 233mg, 54%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.2 Hz, 3 H), 1.33-1.46 (m, 2 H), 1.88-1.97 (m, 2 H), 2.35 (dd, *J* = 15.2 and 5.0 Hz 1 H), 2.44 (s, 3 H), 2.51 (dd, *J* = 15.2 and 8.0 Hz, 1 H), 2.61 (dd, *J* = 13.9 and 5.6 Hz, 1 H), 2.85 (dd, *J* = 13.9 and 7.0 Hz, 1 H), 3.45−3.51 (m, 1 H), 3.67-3.73 (m, 1 H), 4.01-4.08 (m, 2 H), 4.53-4.62 (m, 1 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 7.16-7.26 (m, 3 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.3, 21.8, 37.5, 37.6, 41.2, 42.2, 60.8, 72.1, 76.3, 78.1, 126.5, 127.8, 128.4, 129.5, 129.6, 130.1, 134.5, 137.8, 145.0, 170.7; **IR** (KBr, neat): 555, 666, 749, 838, 932, 1082, 1188, 1363, 1590, 1732, 2853, 2928 cm^{-1}; **HRMS** (ESI) calcd. for $C_{23}H_{29}O_6S$ $(M + H)^+$ 433.1679, found 433.1693.

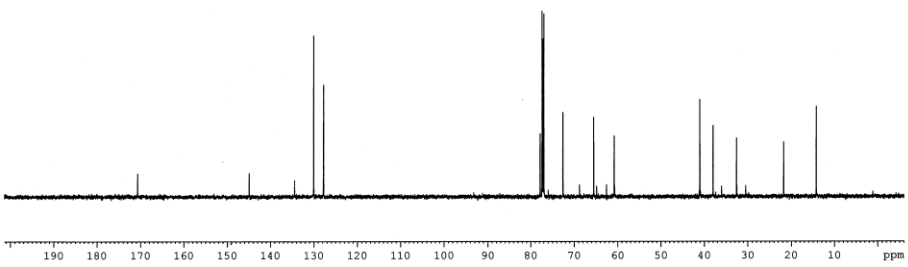
.

3.7. Selected Spectra

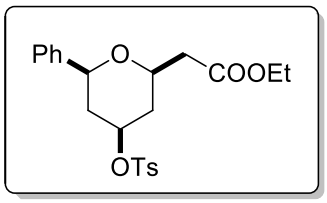
^{1}H and **^{13}C NMR** spectra of compound **34a:**

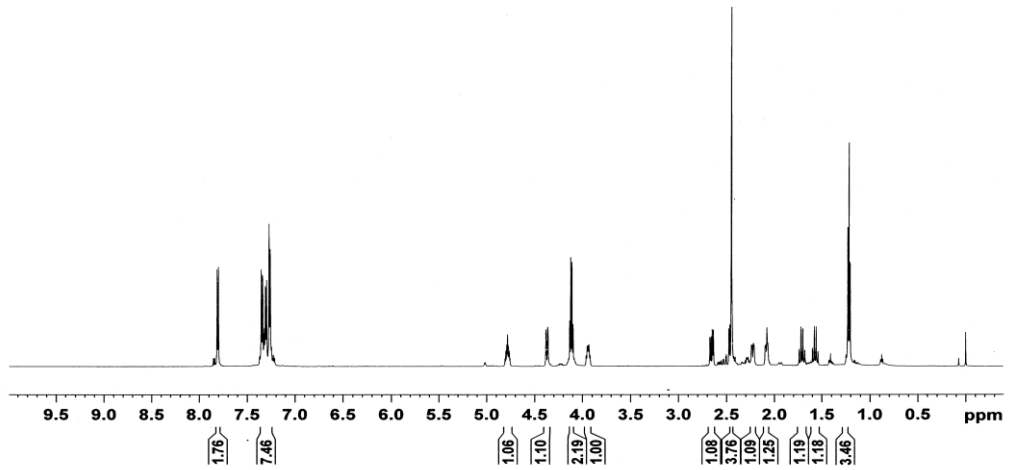


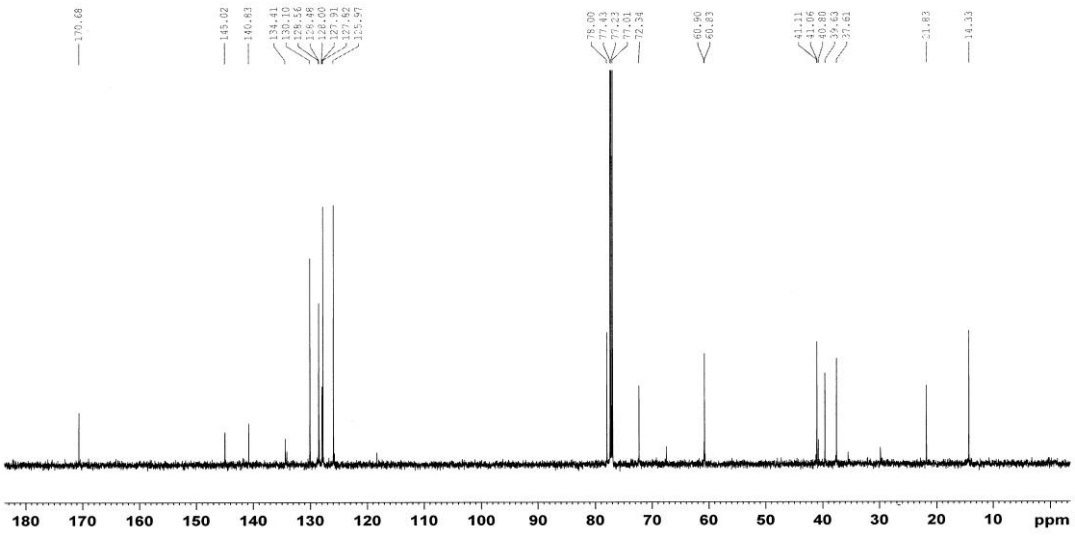




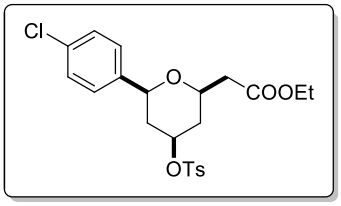
^{1}H and **^{13}C** NMR spectra of compound **34b:**

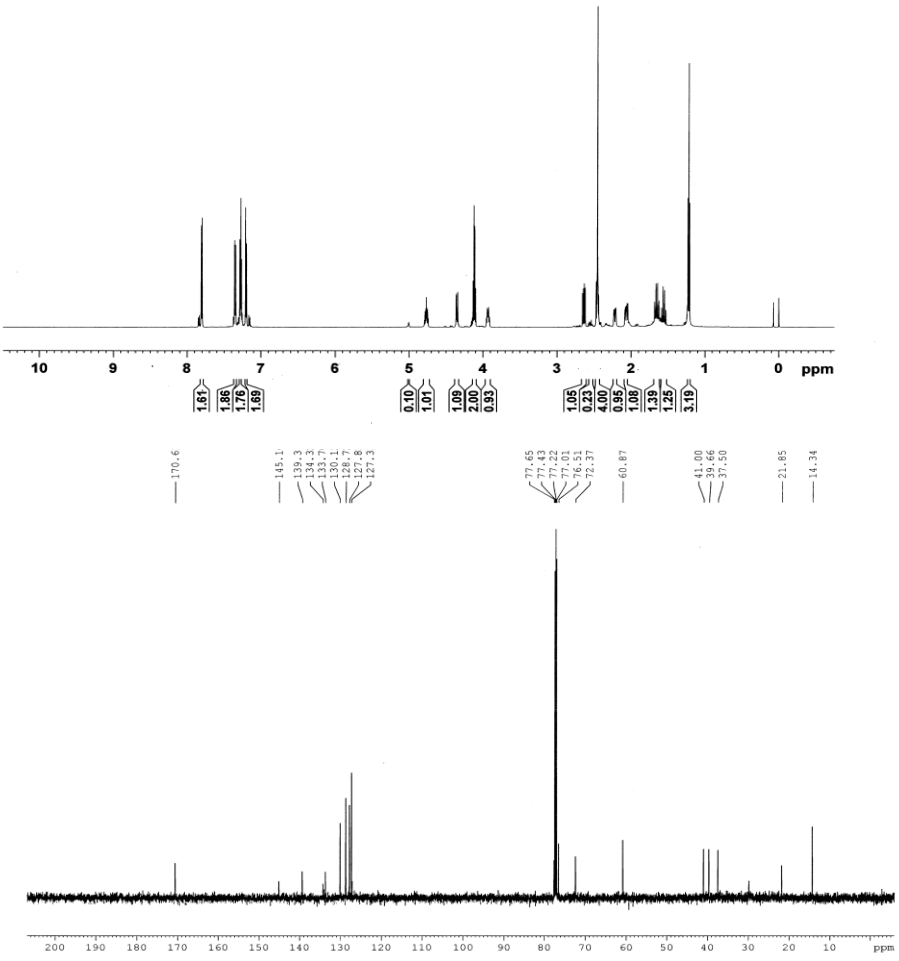




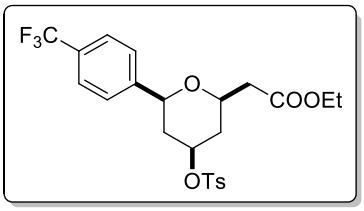


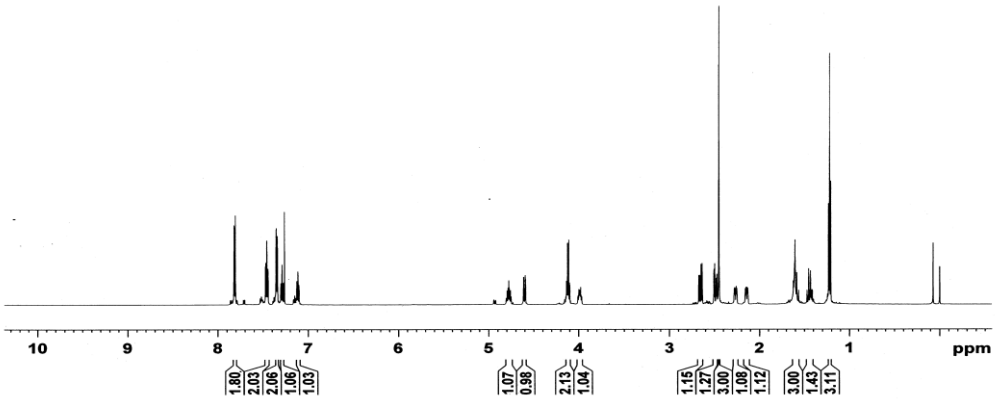
^{1}H and **^{13}C NMR** spectra of compound **34c:**

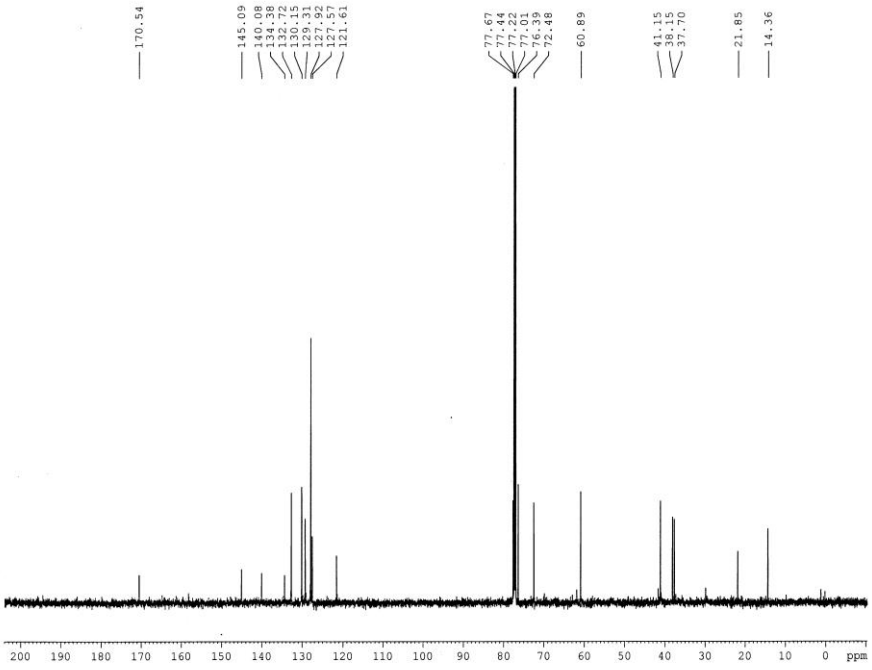




^{1}H and **^{13}C** Spectra of compound **34f**







CHAPTER 4

Regioselecective synthesis of substituted 3,6-dihydropyran from 3-butene-1-ol and aldehydes *via* Prins cyclization mediated by TfOH (Triflic acid)

4.1. Importance of Dihydropyrans

Multicomponent reactions have attracted a considerable attention in synthetic organic chemistry due to their ability to form a series of bonds in a single step.[1] In particular, multicomponent reactions can provide functionalized heterocyclic compounds with high stereoselectivity.[2] Dihydropyran units are valuable compounds of interest for the reason that these units constitute important structural unit in many natural products of biological importance. Compounds such as martiriol and salinomycin carry dihydropyran unit in which double bond in cyclic system is responsible for the biological activity. Martiriol **1**, for that matter, is a biologically active molecule, isolated from the red algae of the genus *Laurencia*, shows potent activity against various tumour cell lines.[3] Similarly, salinomycin **2**, isolated from a culture broth of *Streptomyces albus* is known to possess interesting antibacterial and anticoccidial properties.[4] The presence of double bond in cyclic system is not only responsible for their biological properties but also serve as a functional group for further manipulations in organic synthesis.[5] They can also be used as building blocks in organic synthesis *(Figure 4.1.1)*.[6]

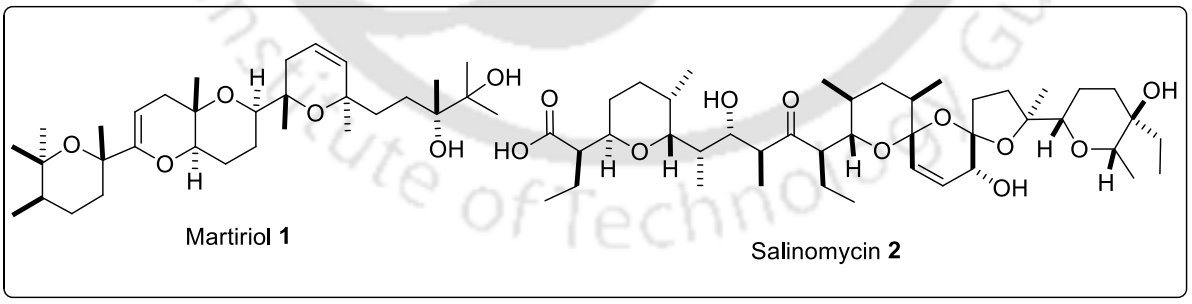
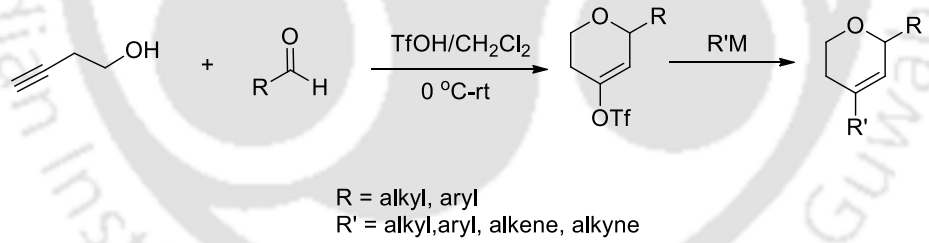


Figure 4.1.1. *Bioactive molecules containing dihydropyran ring*

4.2. Literature Methods

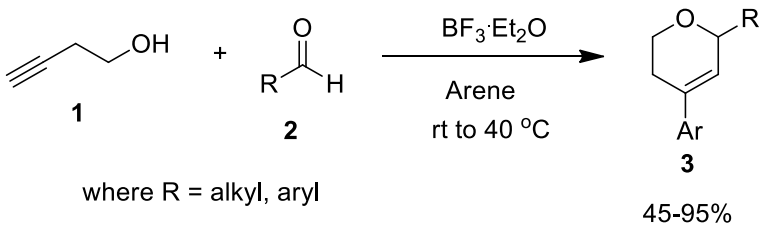
Over the years, many strategies have been developed for the synthesis of dihydropyrans, which include hetero-Diels-Alder reactions,[7] olefin metathesis,[8] base promoted cyclizations of sulfinyl dienols,[9] oxonium-ene reactions,[10] [4+2] annulations,[11] intramolecular C-C bond formation of alkyne-epoxide,[12] and Prins cyclization reactions.[13] Among existing methodologies, the Prins cyclization has emerged as a powerful tool as it provides the desired product in a single step with high diastereoselectivity.

Our group had reported a methodology for the synthesis of 4-trifluoromethanesulfonate substituted 3, 6-dihydropyrans and their Application in various C-C coupling reactions mediated by TfOH. Herein, we report a one-pot, three component and highly regioselective Prins cyclization reaction for efficient synthesis of 3,6-dihydro-2*H*-pyran-4-yl trifluoromethane-sulfonates from homopropargylic alcohols and aldehydes mediated by triflic acid in which triflic acid acts as Brønsted acid as well as a nucleophile. In this work, we have developed an unprecedented Prins cyclization for the synthesis of dihydropyran that contains triflate group at the vinylic position of the ring. The dihydropyran thus formed is transformed into different 4-alkyl and aryl substituted products using Suzuki, Heck, Stille and Sonogashira coupling reactions. The reaction can be generalized as shown in *(Scheme 4.2.1).*[14]



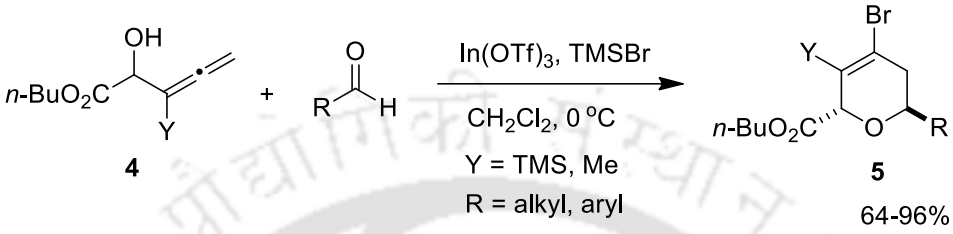
Scheme 4.2.1

Saikia and co-workers also have reported the synthesis of 4-aryl-5,6-dihydro-2*H*-pyrans **3** from the reaction of carbonyl compounds **2** with homopropargyl alcohol **1** in arenes mediated by boron trifluoride etherate by using alkyne-Prins-Friedel-Crafts reaction *(Scheme 4.2.2).*[15]



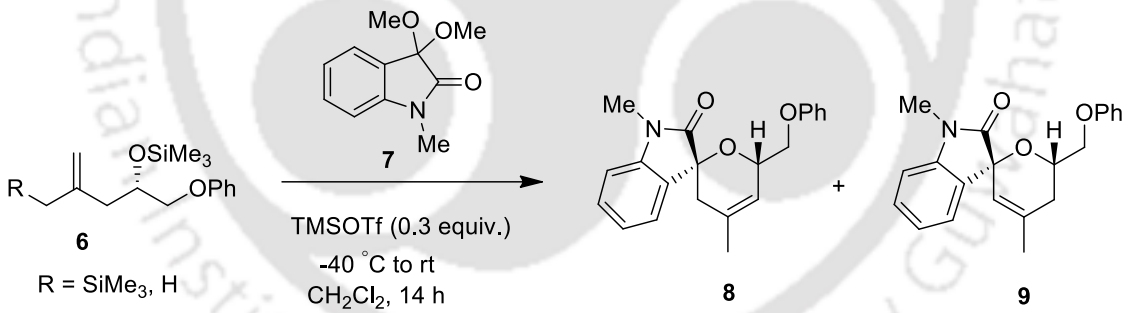
Scheme 4.2.2

Loh and co-workers have reported the synthesis of 2,6-*trans* dihydropyrans **5** from the reaction of allenic alcohols **4** and aldehydes in the presence of indium triflate in good yields *(Scheme 4.2.3).* However, a good diastereoselectivity was obtained by using bulky-silicon substituted allenic alcohols under the same condition. The reason of high *trans* diastereoselectivity is due to the anomeric effect as well as lone pair stabilization of the δ^+ of the oxo-carbenium intermediate by the ester group.[16]



Scheme 4.2.3

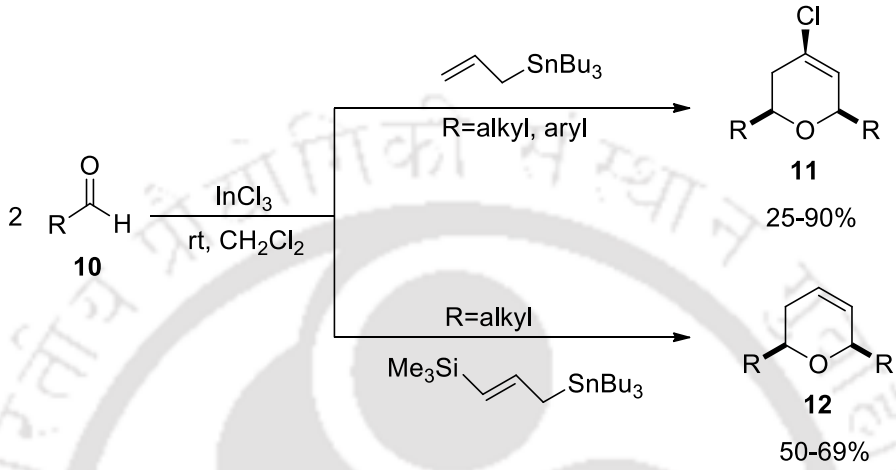
Porco, Jr. and co-workers have reported the synthesis of spirocyclic oxindole pyrans having 4-methyl substituted dihydropyran unit **8**/**9**. These spirocyclic compounds are prepared from the reaction of substituted homoallylic alcohols **6** with isatin ketals **7** in the presence of TMSOTf *(Scheme 4.2.4).*[17]



Entry	R	Additive	Yield
1	$SiMe_3$	DBMP (0.1 equiv.)	**8** = 38%, **9**= 19%
2	H	DBMP (0.1 equiv.)	**8** = 46%, **9** = 20%
3	H	None	**8** = 58%, **9**= 24%

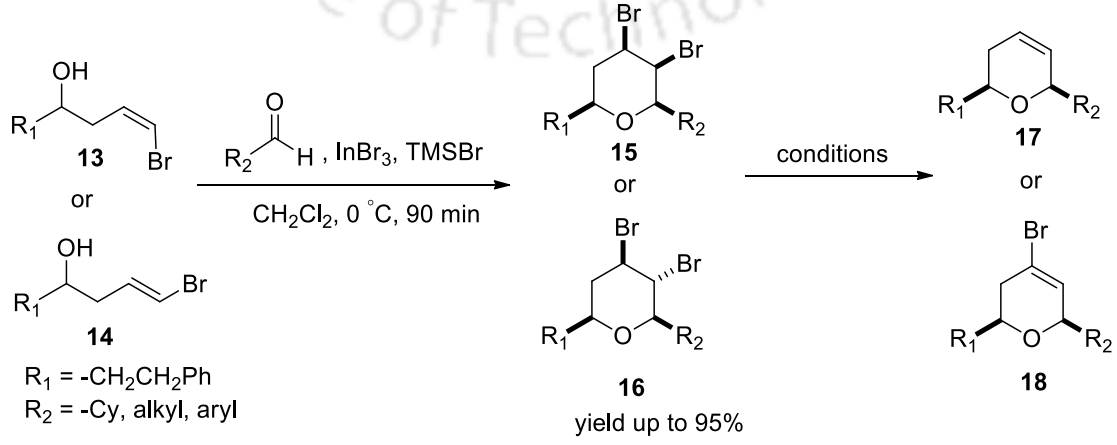
Scheme 4.2.4

Li *et al.* reported a novel route to access diastereoselective 4-halotetrahydropyrans in high yields *via* carbonyl allylation-Prins cyclization. The Prins cyclization reaction between two equivalents of aldehydes **10** with 1.0 equivalent of allyltributylstannane in presence of indium chloride and methylene chloride at room temperature produced 4-chlorotetrahydropyrans **11** with high diastereoselectivity. But, the reaction with 3-trimethylsilylallyltributylstannane under the same reaction conditions led to a diastereoselective formation of 3,4-dihydropyrans **12** *(Scheme 4.2.5).*[18]



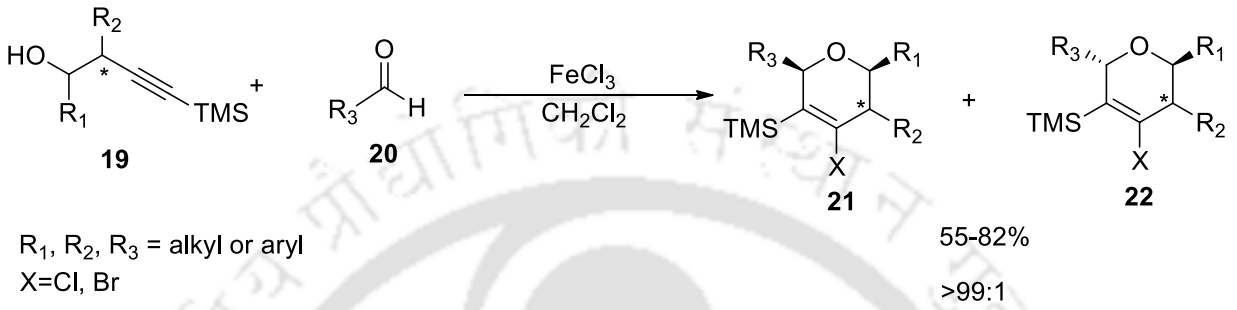
Scheme 4.2.5

Loh and his group developed an efficient Prins cyclization reaction to construct 2,6-*cis*-4,5-dibromo-tetrasubstituted THP rings with high stereoselectivity and in good yields. The reaction between *γ*-brominated homoallylic alcohol **13** or **14** and aldehydes promoted by 1.0 equivalent of $InBr_3$ with 1.2 equivalents of TMSBr in CH_2Cl_2 at 0 °C to afford 2,4,5,6-tetrasubstituted tetrahydropyrans **15** or **16** as a single isomer. The stereochemistry of the bromine substituent at the 5-position was controlled by the geometric configuration of the *γ*-brominated homoallylic alcohols. Dibromo-THP products were further functionalized to various substituted pyran-containing compounds *(Scheme 4.2.6.).*[19]



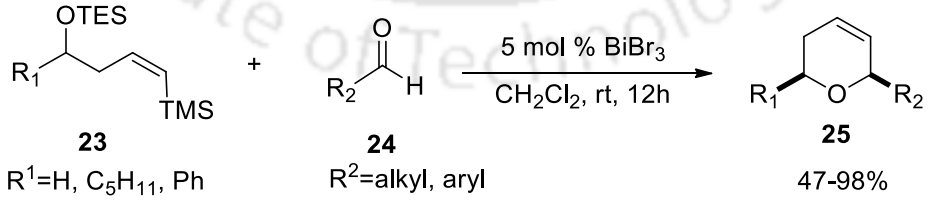
Scheme 4.2.6

Martín and his group showed a novel route for the synthesis of tetra- and penta-substituted dihydropyrans *via* silylalkyne-Prins cyclization. The coupling between chiral secondary homopropargylic alcohols **19** bearing a trimethylsilyl group at the triple bond and aldehydes **20** in the presence of iron(III) halides, provided (2,5,6-trialkyl-4-halo-5,6-dihydro-*2H*-pyran-3-yl)trimethylsilane **21** in good yields. The protocol is highly stereoselective, affording *cis*-dihydropyran as a major isomer *(Scheme 4.2.7.).*[20]



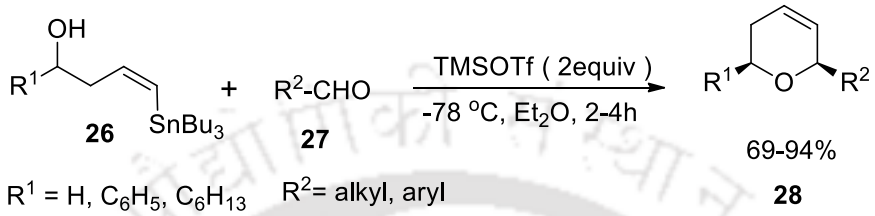
Scheme 4.2.7

Hinkle and co-workers reported a tandem silyl-Prins reaction between *δ*-triethyl-silyloxyvinyltrimethylsilanes **23** and a variety of aldehydes **24** to afford *cis*-2,6-disubstituted dihydropyrans (DHPs) **25** using 5 mol % of $BiBr_3$ in CH_2Cl_2 *(Scheme 4.2.8.).*[21] The diastereoselectivities in the crude products are significantly affected by aldehyde substitution, with electron-rich aldehydes, providing 2-3:1 (*cis:trans*) and neutral (or electron-poor) aldehydes affording dr ≥ 19:1 (*cis:trans*).

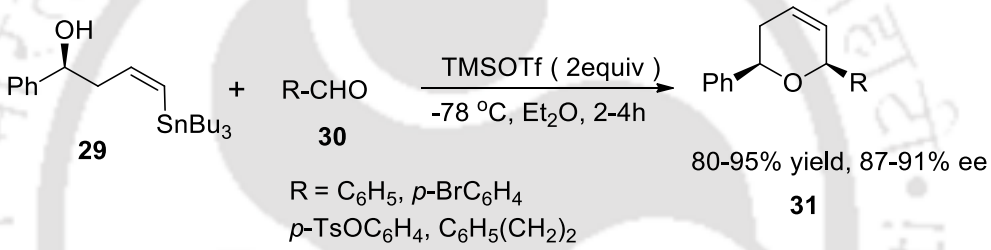


Scheme 4.2.8

Furman and co-workers reported a stereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans (DHPs) *via* stannyl-Prins cyclization. The reaction of vinylstannes **26** with aldehydes **27** in the presence of TMSOTf afforded *cis*-2,6-disubstituted dihydropyrans **28** in good yields with excellent stereoselectivity *(Scheme 4.2.9.).*[22] Although the dihydropyrans are obtained in the racemic form but the use of optically pure vinylstanne afforded optically pure 2,6-disubstituted dihydropyrans *(Scheme 4.2.10.).* Finally, they applied this methodology for the synthesis of natural product (-)-centrolobine. [22]



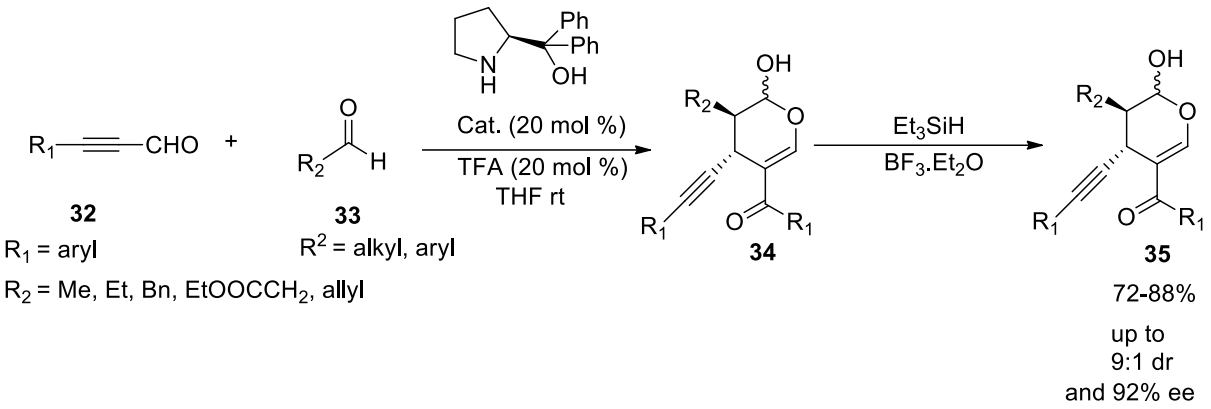
Scheme 4.2.9



Scheme 4.2.10

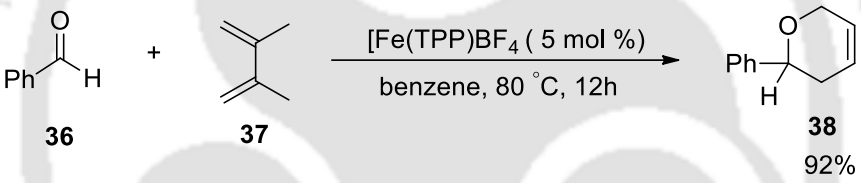
Apart from Prins cyclization, there are several other synthetic routes reported in the literature for the synthesis of dihydropyrans.

Sun and his group developed a novel strategy for one-pot formation of chiral polyfunctionalized 3,4-dihydropyrans through organocatalytic hydration/aldol/oxa-Diels Alder domino reaction method. Alkynl aldehyde **32** was reacted with aldehyde **33** in the presence of (*S*)-diphenylprolinol catalyst using TFA as an additive in THF at room temperature to furnish the 3,4-dihydropyran hemiacetal **34** and its diastereomer *syn*-**34**. The products **34** and *syn*-**34** were then reduced with $Et_3SiH/BF_3{\cdot}Et_2O$ to furnish chiral 3, 4-dihydropyrans products **35** and *syn*-**35** with good to high yields, moderate to good diastereoselectivities, and high enantioselectivities. In this protocol, the self-condensation of alkynals was first time implemented under organocatalytic conditions *(Scheme 4.2.11).*[23]



Scheme 4.2.11

Kurahashi and co-workers reported an unprecedented hetero-Diels−Alder-type [4+2] cycloaddition for the synthesis of dihydropyrans from unactivated aldehydes and simple dienes. The reaction of aldehyde **36** with diene **37** in the presence of the cationic iron(III) porphyrin catalyst (5 mol %) in benzene at 80 °C for 12 h afforded the pyran motif **38** in excellent yield. In this protocol, the high functional group tolerance and robustness of the catalyst were shown. Further, the reaction was performed in water using unactivated ketone such as cyclohexanone with a diene to show the potential applicability of the catalyst *(Scheme 4.2.12).*[24]

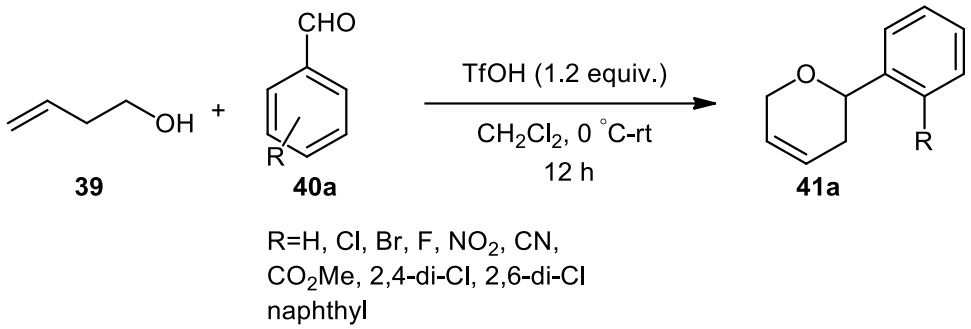


Scheme 4.2.12

4.3. Results and Discussions

One-pot, multi component and selective reactions are considered as green synthetic routes.[24] Again, Prins cyclization[25] reactions are known for C-C and C-O bond forming reaction in a single step. Considering the importance of these reactions, herein, we report a one-pot, three components and highly selective Prins cyclization reaction for efficient synthesis of 3,6-dihydro-2*H*-pyran from 3-butene-1-ol, alcohols and aldehydes mediated by triflic acid. In this work, we have developed an unprecedented Prins cyclization for the synthesis of dihydropyran that contains double bond at the fourth position of the ring.

For this investigation, 3-butene-1-ol i.e. **39** (1.5 equivalents) and benzaldehyde **40a** (1.0 equivalent) were treated with 1.2 equivalents of triflic acid (TfOH) in dry dichloromethane at room temperature for 12h, 2-phenyl-3,6-dihydro-2*H*-pyran **41a** was obtained in 72% yield. The reaction is regioselective and only 3,6-dihydropyran was formed in the reaction *(Scheme 4.3.1).*



Scheme 4.3.1

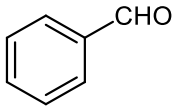
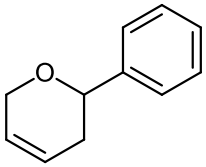
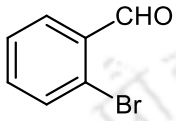
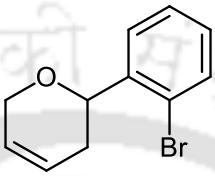
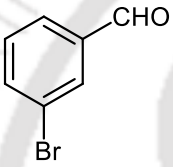
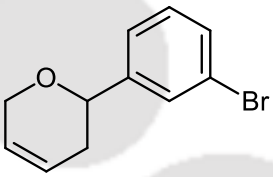
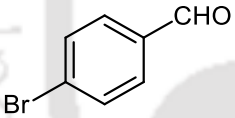
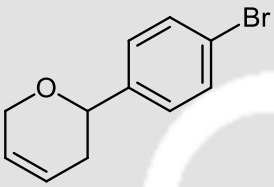
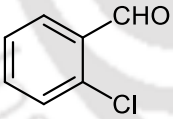
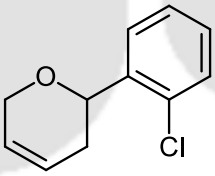
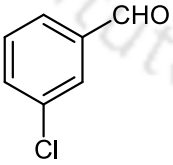
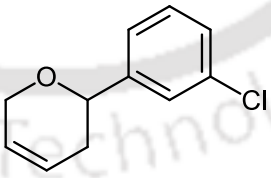
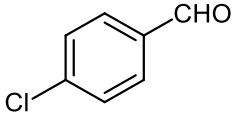
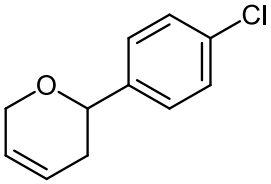
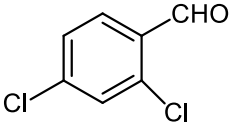
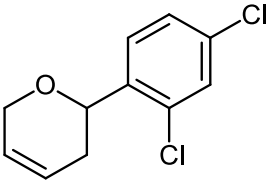
Initially, aldehyde **40a** (1.0 equivalent) was reacted with but-3-en-1-ol **39** (1.5 equivalents) in dry DCM (3.0 mL), using TfOH (0.1 equivalent) as Lewis acid. The product 3,6-dihydro-2*H*-pyran **41a** was obtained in 30% yield. The reaction was optimized with other Lewis acids such as $In(OTf)_3$, $Sc(OTf)_3$, $InCl_3$ and $ZrCl_4$ and Brønsted acid TsOH *(Table 4.3.1).* Brønsted acid (TsOH) gave desired product in 28% and 31% yields at catalytic and stoichiometric loadings, respectively. In a similar manner, Lewis acids $In(OTf)_3$ and $Sc(OTf)_3$ gave desired product with low yields. The chlorinated Lewis acid, $InCl_3$ and $FeCl_3$ did not produce any product even after prolonging the reaction for 24h. But, $ZrCl_4$ produced the desired product in very low yield 15%. It was observed that TfOH was the most efficient reagent in terms of yields (72%), shown in *Table 4.3.1* (entry 3).

Table 4.3.1. Optimization of the reaction

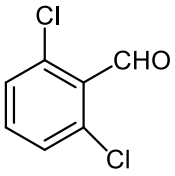
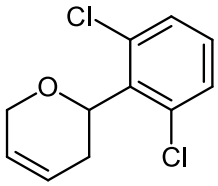
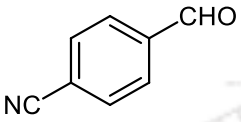
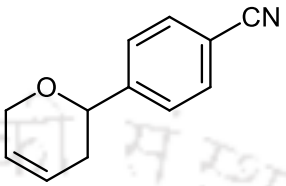
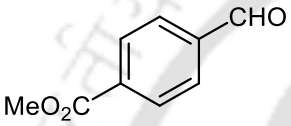
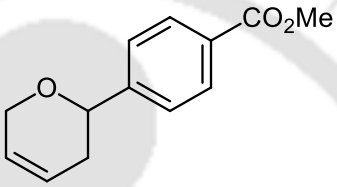
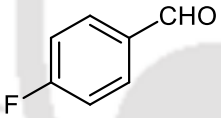
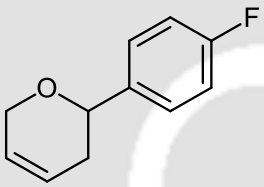
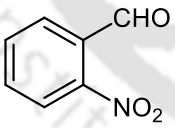
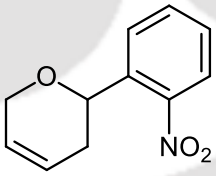
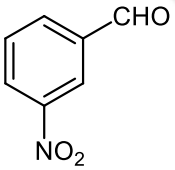
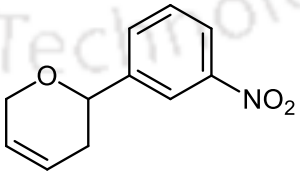
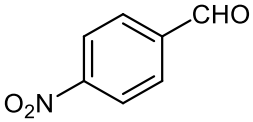
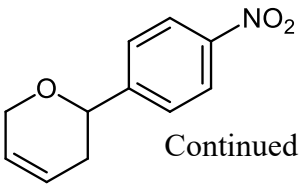
Entry	Equivalents/mol%	Time (h)	Condition	Yield (%)[a]
1	TfOH (0.1 equiv.)	12	0 °C to rt	30
2	TfOH (1.0 equiv.)	12	0 °C to rt	50
3.	**TfOH (1.2 equiv.)**	**12**	**0 °C to rt**	**72**
4	$In(OTf)_3$ (10)	24	0 °C to rt	17
5	$Sc(OTf)_3$ (10)	24	0 °C to rt	24
6	$InCl_3$ (100)	24	0 °C to rt	-
7	$ZrCl_4$ (100)	12	0 °C to rt	15
8	*p*-TsOH (10)	12	0 °C to rt	28
9	*p*-TsOH (100)	12	0 °C to rt	31
10	$FeCl_3$ (100)	24	0 °C to rt	-

After optimization of the reaction condition, the scope of the reaction was investigated with various aromatic aldehydes having substituents on the aromatic ring and the results are summarised in *Table 4.3.1.*

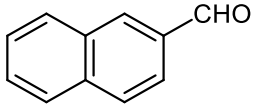
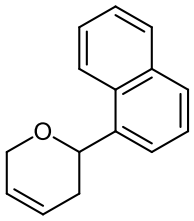
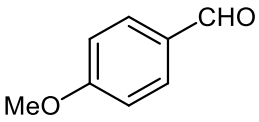
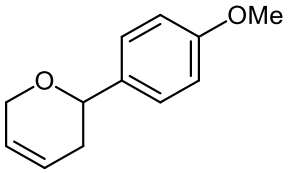
Table 4.3.1 Synthesis of dihydropyrans *via* Prins cyclization reaction.

Entry	Aldehyde **40**	Product **41**	Yield (%)[a]
a			72
b			72
c			78
d			70
e			62
f			65
g			- 60
h			54

Continued……

Entry	Aldehyde **40**	Product **41**	Yield (%)[a]
i			52
j			71
k			70
l			74
m			78
n			82
o			76

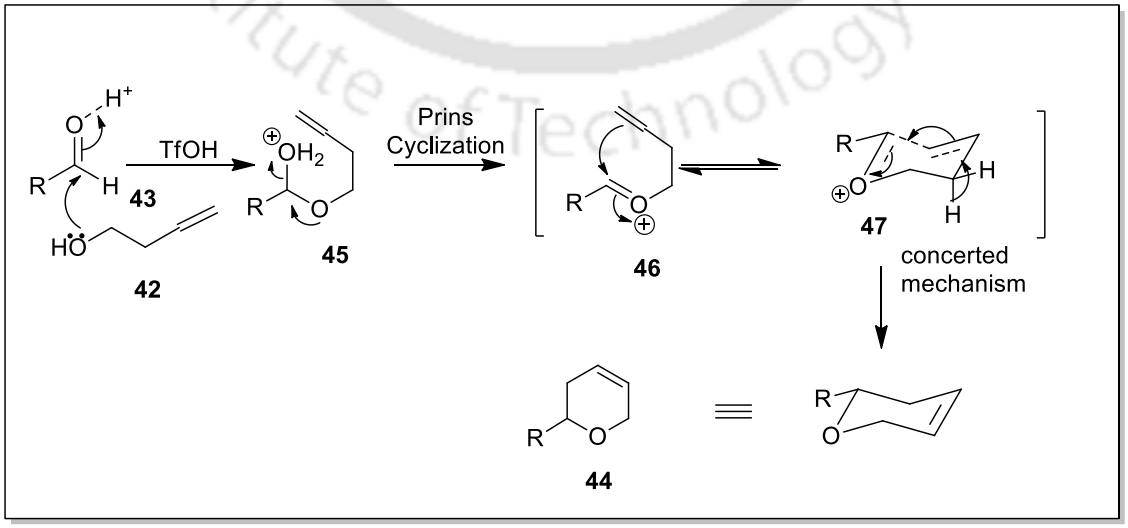
Continued…….

p			73
q			decomposed

[a]Refers to isolated yield.

It was observed from the *Table 4.3.1* that both strong aromatic electron withdrawing as well as moderate electron withdrawing aldehydes gave good yields. To study the steric effect, *ortho*-, *meta*- and *para*-chlorobenazaldehydes (entries e-g) were reacted with alcohol **39**, but the effect is not noticeable. On the other hand, highly sterically hindered 2,4-dichlorobenzaldehyde (entry h) and 2,6-dichlorobenzaldehyde (entry i) gave low yields. 4-Methoxybenzaldehyde (entry q) was found to be decomposed under these reaction conditions. It has been also found that aliphatic and secondary alcohols are not suitable for this reaction. This is because of less reactivity of aliphatic aldehydes than aromatic aldehydes.

The possible mechanism of the reaction can be explained as follows. The carbonyl group of the aldehyde molecule at first activated by the acidic proton of the triflic acid. This activation facilitates for nucleophilic attack by 3-butene-1-ol (alcohols **42**) to form oxocarbenium ion **46**, which after oxonium-ene cyclization *via* a concerted mechanism to forms dihydropyran **44**. *(Scheme 4.3.2).*



Scheme 4.3.2 Plausible mechanism of the reaction

Moreover, the structure of the product was also confirmed from single XRD-data and the ORTEP is shown *Figure 4.3.1*.

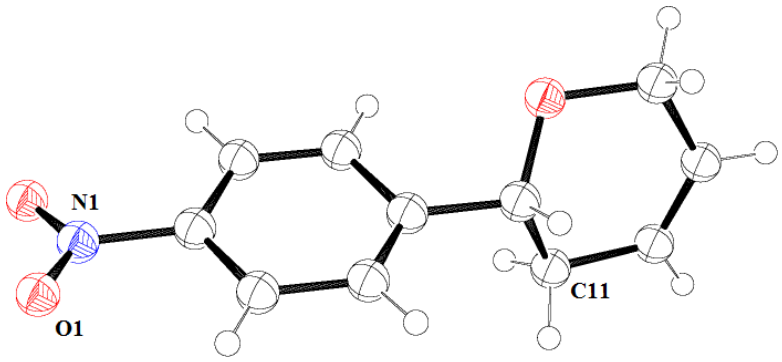


Figure 4.3.1 ORTEP diagram of 41o (CCDC number 1851004)

Conclusions

We have developed one-pot, three components, mild and efficient method for the synthesis of 3,6-substituted dihydropyrans *via* Prins cyclization reaction in good yields. The reaction is compatible with a wide range of functional groups such as ester, cyanide, nitro, and halo. The important aspect of this reaction is that it introduces a double bond at 4-position of the dihydropyrans.

4.4. Experimental section

4.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.4.1.

4.4.2. General Procedure for the Synthesis of 3, 6-dihydro-2H-pyran Compounds 41a-p:

To a stirring solution of aldehyde (1.0 equivalent) and 3-butene-1-ol (1.5 equivalents) in dry dichloromethane (5 mL/ equivalent) was added triflic acid (1.2 equivalents) dropwise at 0 °C. The reaction mixture was brought to room temperature and stirred for a specific time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with saturated sodium bicarbonate solution (5.0 mL). The product was extracted with CH_2Cl_2 (2×10 mL) and washed with brine. Organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds. The crystallization of compound **41o** is done by dissolving in minimum amount of methanol and keeping the solution for a weak at room temperature. The crystals are washed with cold methanol for several times to get the clean crystal.

4.4.3. General Procedure for the Synthesis of 2-phenyl-3,6-dihydro-2H-pyran Compounds 41a-p:

To a stirring solution of benzaldehyde **40a** (1 equivalent) and 3-butene-1-ol **39** (1.5 equivalents) in CH_2Cl_2 (5 mL/ equivalent) was added triflic acid (1.2 equivalents) dropwise at 0 °C. The reaction mixture was brought to room temperature and stirred for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, CH_2Cl_2 (10 mL) was added and the reaction mixture was washed with saturated sodium bicarbonate solution and brine solution. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using rotary evaporator to leave the crude product which was purified by column chromatography over silica gel using ethyl acetate and hexane as eluents to give 2-phenyl-3,6-dihydro-2H-pyran **41a** as a colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; yield 105 mg, 72%.

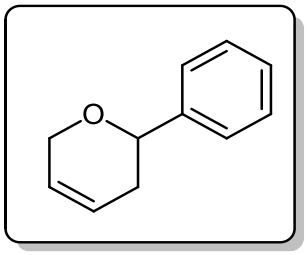
4.5. References

1. (a) Tieze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Yus, D. J.; Ramon, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (c) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (d) *Multicomponent Reaction*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. (a) Strubing, D.; Neumann, H.; Hubner, S.; Klaus, S.; Beller, M. *Tetrahedron* **2005**, *61*, 11345. (b) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297.
3. (a) Souto, M. L.; Gavin, J. A.; Manriquez, C. P.; Norte, M.; Fernandez, J. J. *Tetrahedron* **2001**, *57*, 3117. (b) Soriente, A.; De Rosa, M. M.; Scettri, A.; Sodano, G.; Terencio, M. C.; Paya, M.; Alcarez, M. *Curro Med. Chem.* **1999**, *6*, 415.
4. (a) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, *49*, 4955. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.
5. (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. (g) Miranda, P. O.; Diaz, D. V.; Padrón, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979.
6. (a) Donslund, B. S.; Monleón, A.; Ibsen, L. Jørgensen, K. A. *Chem. Commun.* **2015**, *51*, 13666. (b) Mack, D. J.; Guo, B.; Njardarson, J. T. *Chem. Commun.* **2012**, *48*, 7844. (c) Chouthaiwale, P. V.; Tanaka, F. *Chem. Commun.* **2014**, *50*, 14881. (d) Mori-Quiroz, L. M.; Maleczka, R. E. Jr. *J. Org. Chem.* **2015**, *80*, 1163. (e) Sun, S.; Cheng, C.; Yang, J.; Tahery, A.; Jiang, D.; Zhang B.; Gu, Y. *Org. Lett.* **2014**, *16*, 4520. (f) Peh, G. R.; Floreancig, P. E. *Org. Lett.* **2015**, *17*, 3750. (g) Isobe, M.; Chang, W. C.; Tsou, P. K.; Ploysuk, C.; Yu, C. H. J. *Org. Lett.* **2015**, *80*, 6222. (h) Weise, C. F.; Lauridsen, V. H.; Rambo, R. S.; Iversen, E. H.; Olsen, M. L.; Jørgensen, K. A. *J. Org. Chem.* **2014**, *79*, 3537.
7. (a) Sako, S.; Kurahashi, T.; Matsubara, S. *Chem. Commun*. **2011**, *47*, 6150. (b) Li, Z.; Jung, H.; Park, M.; Lah, M. S.; Koo, S. *Adv. Synth. Catal*. **2011**, *353*, 1913. (c) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc*. **2012**, *134*, 5512. (d) Chaladaj, W.; Kowalczyk, R.; Jurczak, J. *J. Org. Chem*. **2010**, *75*, 1740. (e) Mal, K.; Das, S.; Maiti, N. C.; Natarajan, R.; Das, I. *J. Org. Chem*. **2015**, *80*, 2972.
8. (a) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817. (b) Wildemann, H.; Dünkelmann, P.; Müller, M.; Schmidt, B. *J. Org. Chem.* **2003**, *68*, 799. (c) Donnard, M.; Tschamber, T.; Nouën, D. L.; Desrat, S.; Hinsinger, K.; Eustache, J. *Tetrahedron* **2011**, *67*, 339.

9. (a) De La Pradilla, R. F.; Tortosa, M. *Org. Lett*. **2004**, *6*, 2157. (b) De La Pradilla, R. F.; Tortosa, M.; Lwoff, N.; del Águila, M. A.; Viso, A. *J. Org. Chem*. **2008**, *73*, 6716.
10. (a) Bonbdalapati, S.; Reddy, U. C.; Saha, P.; Saikia, A. K. *Org. Biomol. Chem*. **2011**, *9*, 3428. (b) Saha, P.; Ghosh, P.; Sultana, S.; Saikia, A. K. *Org. Biomol. Chem*. **2012**, *10*, 8730.
11. (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 9836. (b) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc*. **2015**, *137*, 54.
12. Ghosh, P.; Saha, P.; Bondalapati, S.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2014**, *79*, 4119.
13. (a) Arundale, E.; Mikeska, L. A. *Chem. Rev*. **1952**, *52*, 505. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, *64*, 661. (c) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M.; Fleming, I.; Heathcock, C. H.; Eds.; Pergamon Press: New York, 1991; Vol. 2, pp. 527. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem*. **2003,** *68*, 7143. (e) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc*. **2004**, *126*, 8652. (f) Yadav, J. S.; Thrimurtulu, N.; Lakshmi, K. A.; Prasad, A. R.; Reddy, B. V. S. *Tetrahedron Lett.* **2010**, *51*, 661. (g) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2002**, *4*, 577.
14. Ghosh, P.; Kautarya, A.; Saikia, A. K. *RSC Adv.* **2016**, *6*, 44774.
15. Reddy, U. C.; Saikia, A. K. *Synlett* **2010**, *6*, 1027.
16. Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett*. **2009**, *11*, 1741.
17. Castaldi, M. P.; Troast, D. M.; Porco, Jr. J. A. *Org. Lett*. **2009**, *11*, 3362.
18. Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993.
19. Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063.
20. Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 1633.
21. Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071.
22. Dziedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678.
23. Dong, L. J.; Fan, T. T.; Wang, C.; Sun, J. *Org. Lett.* **2013**, *15*, 204.
24. Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2012**, *134*, 5512.

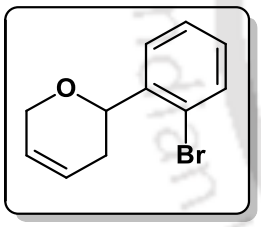
4.6. Characterization Data

2-Phenyl-3,6-dihydro-2*H*-pyran (41a):



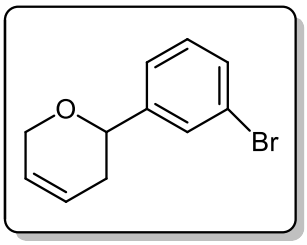
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; (yield, 115 mg, 72%); **^{1}H NMR** (600 MHz, $CDCl_3$): 2.27−2.37 (m, 2 H), 4.36−4.38 (m, 2 H), 4.60 (dd, *J* = 10.2 and 3.4 Hz, 1 H), 5.82−5.83 (m, 1 H), 5.91−5.93 (m, 1 H), 7.26-7.37 (m, 5 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.6, 67.3, 76.3, 125.2, 126.6, 127.1, 128.2, 129.1, 143.2; **IR** (KBr, neat): 762, 894, 1029, 1141, 1246, 1351, 1422, 1455, 1690, 2869, 2929 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{13}O$ $(M + H)^+$ 161.0961, found 161.0962.

2-(2-Bromophenyl)-3,6-dihydro-2*H*-pyran (41b):



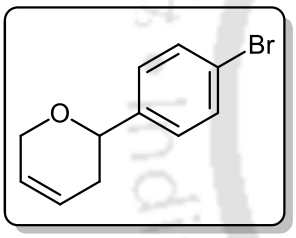
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.18; (yield, 171 mg, 72%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.13-2.15 (m, 1 H), 2.43-2.46 (m, 1 H), 4.38-4.44 (m, 2 H), 4.88 (d, *J* = 10.4 Hz, 1 H), 5.80-5.82 (m, 1 H), 5.90-5.92 (m, 1 H), 7.11-7.14 (td, *J* = 17.0 and 4.6 Hz, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H), 7.50 (dd , *J* = 8.0 and 1.3 Hz, 1 H), 7.75 (dd , *J* = 7.8 and 1.8 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 32.2, 67.4, 75.4, 122.3, 125.1, 126.8, 128.0, 128.5, 129.4, 133.1, 142.6; **IR** (KBr, neat): 784, 1072, 1141, 1213, 1420, 1690, 2871 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}BrO$ $(M + H)^+$ 239.0066, found 239.0066.

2-(3-Bromophenyl)-3,6-dihydro-2*H*-pyran (41c):



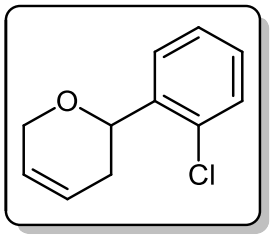
Yellow oil; R_f (hexane/ EtOAc 50:1) 0.18; (yield 185 mg, 78%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.26-2.29 (m, 2 H), 4.35-4.36 (m, 1 H), 4.51-4.53 (m, 2 H), 5.82-5.91(m, 2 H), 7.22 (t, *J* = 7.8 Hz, 1 H), 7.28-7.30 (m, 1 H), 7.31-7.41 (m, 1 H), 7.54-7.55 (m, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.5, 67.2, 75.5, 123.2, 124.7, 125.1, 127.1, 129.7, 130.7, 131.2, 145.6; **IR** (KBr, neat): 784, 1072, 1141, 1213, 1420, 1690, 2871 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}BrO$ $(M + H)^+$ 239.0066, found 239.0066.

2-(4-Bromophenyl)-3,6-dihydro-2*H*-pyran (41d):



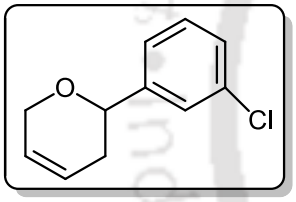
Yellow oil; R_f (hexane/ EtOAc 50:1) 0.18; (yield 166 mg, 70%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.25-2.27 (m, 2 H), 4.34-4.35 (m, 2 H), 4.53-4.88 (m, 1 H), 5.80-5.82 (m, 1 H), 5.90-5.91 (m, 1 H), 7.25-7.26 (m, 2 H), 7.48 (dd, *J* = 7.8 and 2.8 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.5, 67.2, 75.6, 121.9, 124.8, 127.1 128.2, 132.2, 142.3; **IR** (KBr, neat): 784, 1072, 1141, 1213, 1420, 1690, 2871 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}BrO$ $(M + H)^+$ 239.0066, found 239.0066.

2-(2-Chlorophenyl)-3,6-dihydro-2*H*-pyran (41e):



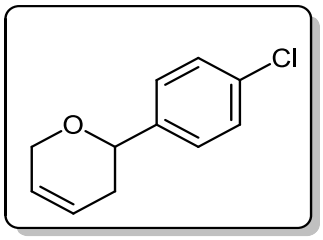
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; (yield, 120 mg, 62%), **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.16-2.19 (m, 1 H), 2.40-2.45 (m, 1 H), 4.39-4.41 (m, 2 H), 4.91-4.93 (m, 1 H), 5.81-5.83 (m, 1 H), 5.91-5.93 (m, 1 H), 7.20 (td, *J* = 7.6 and 1.7 Hz, 1 H), 7.30 (td, *J* = 7.3 and 1.3 Hz Hz, 1 H), 7.32 (td, *J* = 7.3 and 1.2 Hz, 1 H), 7.58 (dd, *J* = 7.8 and 1.7 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 32.2, 67.4, 73.1, 125.1, 126.8, 127.7, 127.9, 129.0, 129.8, 132.2, 141.0; **IR** (KBr, neat): 875, 1073, 1142, 1214, 1421, 1689, 2870, 2928 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}ClO$ $(M + H)^+$ 195.0571, found 195.0572.

2-(3-Chlorophenyl)-3,6-dihydro-2*H*-pyran (41f):



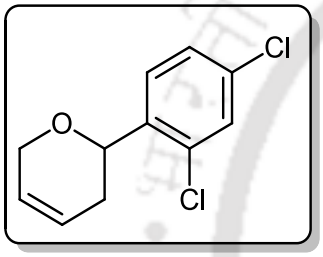
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; (yield, 126 mg, 65%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.26-2.31(m, 2 H), 4.35-4.37 (m, 2 H), 4.53 (dd, *J* = 9.6 and 10.2 Hz, 1 H) 5.82-4.83 (m, 1 H), 5.89-5.92 (m, 1 H), 7.25-7.26 (m, 3 H), 7.39 (s, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.4, 67.2, 75.5, 124.6, 124.8, 126.7, 127.0, 128.2, 130.3, 134.9, 145.3; **IR** (KBr, neat): 875, 1073, 1142, 1214, 1421, 1689, 2870, 2928 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}ClO$ $(M + H)^+$ 195.0571, found 195.0572.

2-(4-Chlorophenyl)-3,6-dihydro-2*H*-pyran (41g):



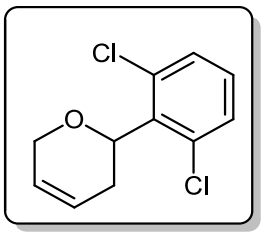
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.20; (yield, 116 mg, 60%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.22−2.25 (m, 2 H), 4.35 (s, 2 H), 4.52-4.54 (m, 1 H), 5.82-5.92 (m, 2 H), 7.31 (s, 4 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.3, 67.2, 75.5, 124.8, 127.0, 127.9, 129.1, 133.7, 141.7; **IR** (KBr, neat): 613, 765, 900, 1066, 1091, 1148, 1213, 1421, 1692, 2869, 2929 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}ClO$ $(M + H)^+$ 195.0571, found 195.0572.

2-(2,4-Dichlorophenyl)-3,6-dihydro-2*H*-pyran (41h):



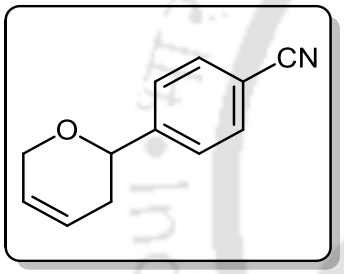
Colurless oil; R_f (hexane/ EtOAc 50:1) 0.19; (yield, 118 mg, 52%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.07-2.12 (m, 1 H), 2.38-2.43 (m, 1 H), 4.37-4.39 (m, 2 H), 4.87 (dd, *J* = 10.2 and 10.8 Hz, 1 H), 5.80-5.92 (m, 2 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.34 (d, *J* = 9.6 Hz, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 32.1, 67.3, 72.7, 124.9, 126.8, 128.2, 128.7, 129.5, 132.7, 134.0, 139.7; **IR** (KBr, neat): 775, 1052, 1119, 1219, 1437, 1659, 2857, 2923 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{11}Cl_2O$ $(M + H)^+$ 229.0181, found 229.0182.

***2-(2,6-Dichlorophenyl)-3,6-dihydro-2H-pyran* (41i):**



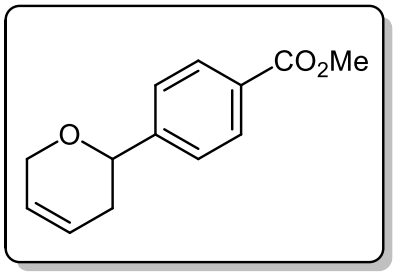
Coluress oil; R_f (hexane/ EtOAc 50:1) 0.19; (Yield, 118 mg, 52%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.04-2.07 (m, 1 H), 2.92-2.30 (m, 1 H), 4.35 (s, 2 H), 5.34 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 5.83-5.86 (m, 1 H), 5.92-5.95 (m, 1 H), 7.1 (t, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 1 H), 7.39 (s, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 28.4, 67.1, 73.9, 124.8, 127.0, 129.7, 130.0, 130.4, 134.2, 135.6, 136.5; **IR** (KBr, neat): 775, 1052, 1119, 1219, 1437, 1659, 2857, 2923 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{11}Cl_2O$ $(M + H)^+$ 229.0181, found 229.0182.

4-(3,6-Dihydro-2*H*-pyran-2-yl)benzonitrile (41j):



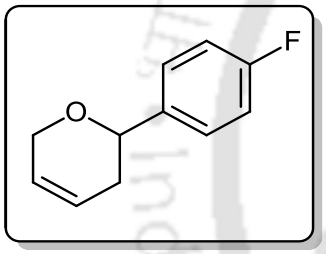
White gum; R_f (hexane/ EtOAc 95:5) 0.50; (yield, 131 mg, 71%); **^{1}H NMR** (600 MHz, $CDCl_3$): 2.28−2.29 (m, 2 H), 4.37−4.39 (m, 2 H), 4.62 (dd, *J* = 9.5 and 4.3 Hz, 1 H), 5.83−5.90 (m, 1 H), 5.91−5.94 (m, 1 H), 7.50 (d, *J* = 8.1 Hz, 2 H),7.65 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.5, 67.2, 75.4, 111.8, 119.6, 124.5, 127.0, 127.1, 132.9, 148.6; **IR** (KBr, neat): 762, 894, 1029, 1141, 1246, 1351, 1422, 1455, 1690, 2869 cm^{-1}; **HRMS** (ESI) calcd. for $C_{12}H_{12}NO$ $(M + H)^+$ 186.0913, found 186.0915.

Methyl 4-(3,6-dihydro-2*H*-pyran-2-yl)benzoate (41k):



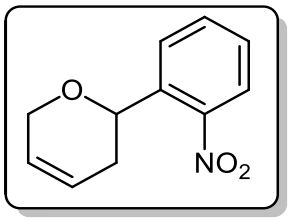
White gum; R_f (hexane/ EtOAc 90:10) 0.50; (yield, 153 mg, 70%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.3 (s, 2 H), δ 3.91 (s, 3 H), 4.37 (s, 2 H), 4.60-4.62 (m, 1 H), 5.81-5.84 (m, 1 H), 5.90-5.93 (m, 1 H), 7.44 (dd, *J* = 12.6 and 15.0 Hz, 2 H), 8.01-8.03 (m, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.5, 52.7, 67.1, 75.7, 124.7, 126.3, 127.0, 129.8, 130.3, 148.4, 167.6; **IR** (KBr, neat): 771, 860, 1072, 1113, 1142, 1213, 1282, 1418, 1690, 1725, 2850, 2925 cm^{-1}; **HRMS** (ESI) calcd. for $C_{13}H_{15}O_3$ $(M + H)^+$ 219.1016, found 219.1014.

2-(4-Fluorophenyl)-3,6-dihydro-2*H*-pyran (41l):



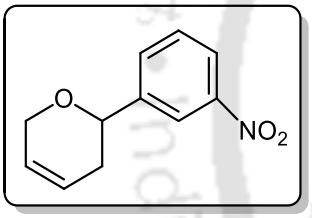
Colourless oil; R_f (hexane/ EtOAc 50:1) 0.19; (yield, 131 mg, 74%); **^{1}H NMR** (600 MHz, $CDCl_3$): 2.14-2.27 (m, 2H), 4.26-4.30 (m, 2 H), 4.42−4.50 (m, 1 H), 5.73−5.74 (m, 1 H), 5.82−5.84 (m, 1 H), 6.94 (t, *J* = 8.4 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.26 (t, *J* = 7.8 Hz, 1 H), 7.35-7.38 (m, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.2, 66.8, 75.8, 115.4 (d, *J* = 21.2 Hz), 124.7, 127.7 (d, *J* = 7.9 Hz), 129.3, 137.4, 139.5, 162.4 (d, *J* = 243.7 Hz); **IR** (H, neat): 775, 897, 1071, 1141, 1219, 1421, 1690, 2869, 2925 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}FO$ $(M + H)^+$ 179.0867, found 179.0869.

2-(2-Nitrophenyl)-3,6-dihydro-2*H*-pyran (41m):



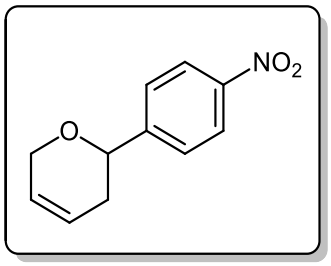
Light yellow oil; R_f (hexane/ EtOAc 50:1) 0.25; (yield, 159 mg, 78%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.26-2.30 (m, 1 H), 2.51-2.55 (m, 1 H), 4.35-4.40 (s, 2 H), 5.11 (dd, *J* = 10.3 Hz and 13.4 Hz, 1 H), 5.80-5.83 (m, 1 H), 5.91-5.93 (m, 1 H), 7.42-7.44 (m, 1 H), 7.63 (td, *J* = 7.8 and 1.32 Hz, 1 H), 7.81(dd, *J* = 7.8 and 1.38 Hz, 1 H), 7.91 (dd, *J* = 7.8 and 1.32 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.3, 67.4, 72.0, 124.7 124.9, 126.7, 128.7, 128.8, 134.1, 138.6, 148.5 ; **IR** (KBr, neat): 751, 789, 901, 1073, 1141, 1211, 1353, 1419, 1531, 1689, 2873, 2929 cm^{-1} ; **HRMS** (ESI) calcd. for $C_{11}H_{12}NO_3$ $(M + H)^+$ 206.0812, found 206.0812.

2-(3-Nitrophenyl)-3,6-dihydro-2*H*-pyran (41n):



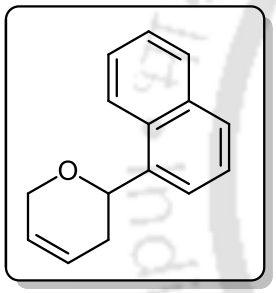
Ligh yellow oil; R_f (hexane/ EtOAc 50:1) 0.25; (yield, 168 mg, 82%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.33-2.35 (m, 2 H), 4.4 (s, 2 H), 4.66 (dd, *J* = 9.6 and 4.2 Hz, 1 H), 5.85-5.90 (m, 1 H), 5.92-5.93 (m, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.2 (d, *J* = 7.5 Hz, 1 H), 8.13 (dd, *J* = 7.8 and 1.38 Hz, 1 H), 8.3 (s, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.4, 67.1, 74.5, 121.5, 123.0, 124.4, 127.1, 130.0, 132.5, 145.4, 149.0; **IR** (KBr, neat): 751, 789, 901, 1073, 1141, 1211, 1353, 1419, 1531, 1689, 2873, 2929 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}NO_3$ $(M + H)^+$ 206.0812, found 206.0812.

2-(4-Nitrophenyl)-3,6-dihydro-2*H*-pyran (41o):



Ligh yellow oil; R_f (hexane/ EtOAc 50:1) 0.25; (yield, 155 mg, 76%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.30−2.31 (m, 2 H), 4.39-4.40 (s, 2 H), 4.66 (dd, *J* = 10.0 and 3.8 Hz, 1H), 5.84−5.90 (m, 1 H), 5.91−5.93 (m, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 8.22 (d, *J* = 8.76 Hz, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$): 33.5, 67.1, 75.1, 124.3, 124.4, 127.0, 127.1, 147.9, 150.7; **IR** (KBr, neat): 572, 671, 894, 1081, 1174, 1360, 1594, 1730, 2862, 2961 cm^{-1}; **HRMS** (ESI) calcd. for $C_{11}H_{12}NO_3$ $(M + H)^+$ 206.0812, found 206.0812.

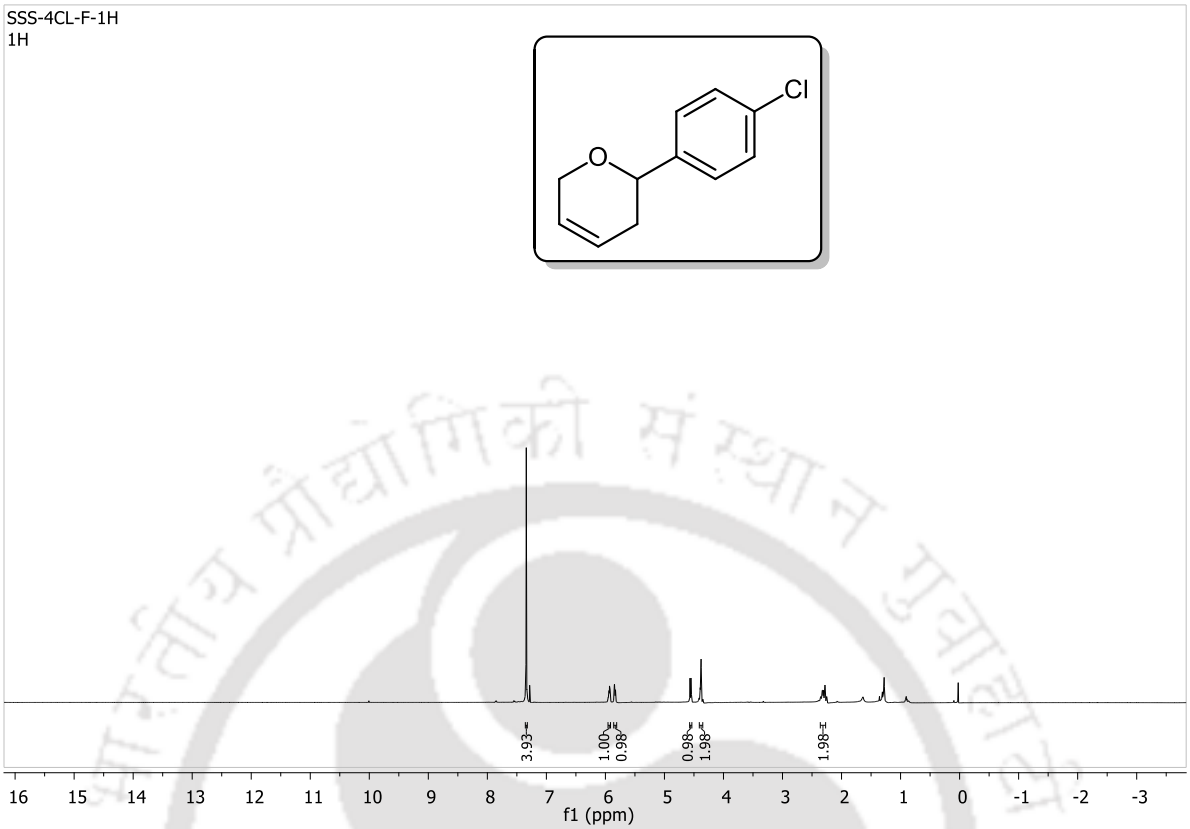
2-(Naphthalen-1-yl)-3,6-dihydro-2*H*-pyran (41p):

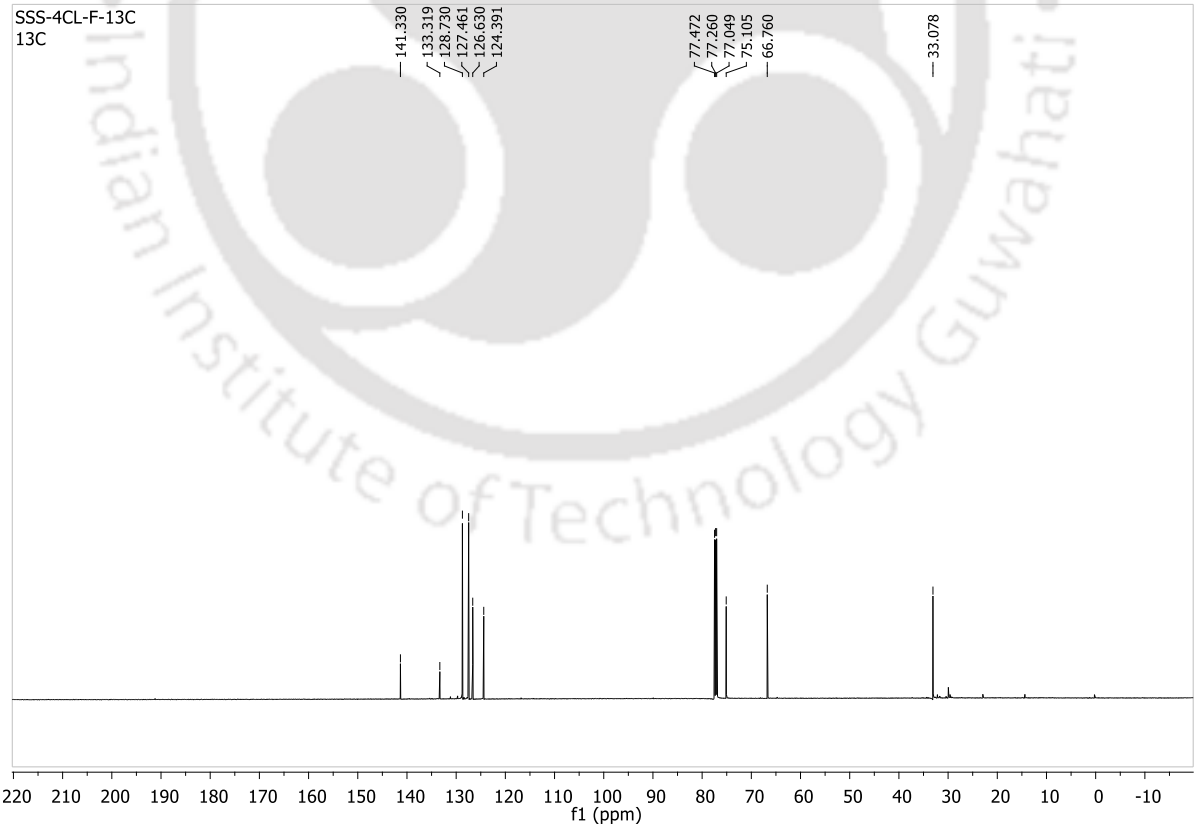


Colourless solid gum; R_f (hexane/ EtOAc 50:1) 0.20; (yield, 134 mg, 64%); **^{1}H NMR** (600 MHz, $CDCl_3$): 2.33−2.40 (m, 1 H), 2.42−2.50 (m, 1 H), 4.42−4.43 (m, 2 H), 4.72 (dd, *J* = 10.2 and Hz, 1 H), 5.84−5.90 (m, 1 H), 5.94−6.00 (m, 1 H), 7.45-7.51 (m, 3 H), 7.83-7.84 (m, 4 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 33.6, 67.3, 76.3, 124.8, 125.1, 125.2, 126.4, 126.7, 127.1, 128.3, 128.7, 128.8, 133.5, 133.9, 140.6; **IR** (KBr, neat): 771, 860, 1072, 1113, 1142, 1213, 1282, 1418, 1690, 1725, 2850, 2925 cm^{-1}; **HRMS** (ESI) calcd. for $C_{15}H_{15}O$ $(M + H)^+$ 211.1117, found 211.111.

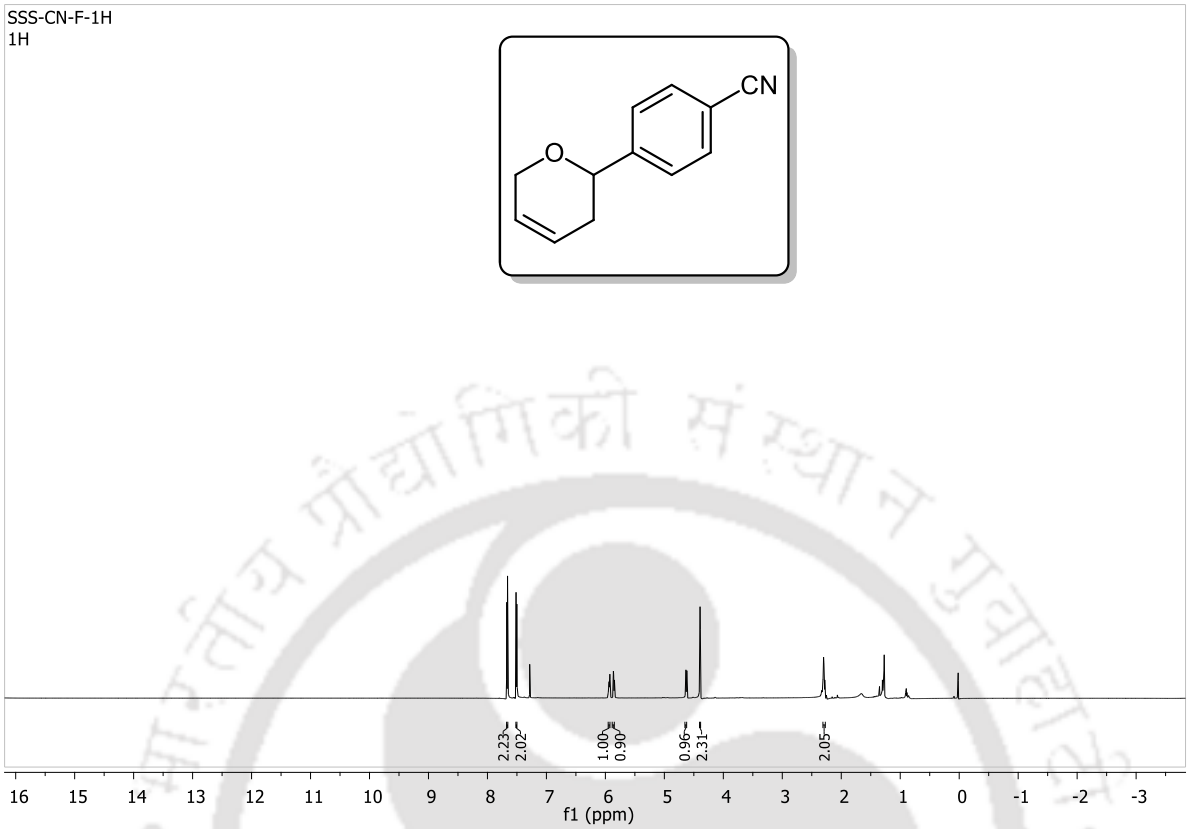
4.7. Selected Spectra

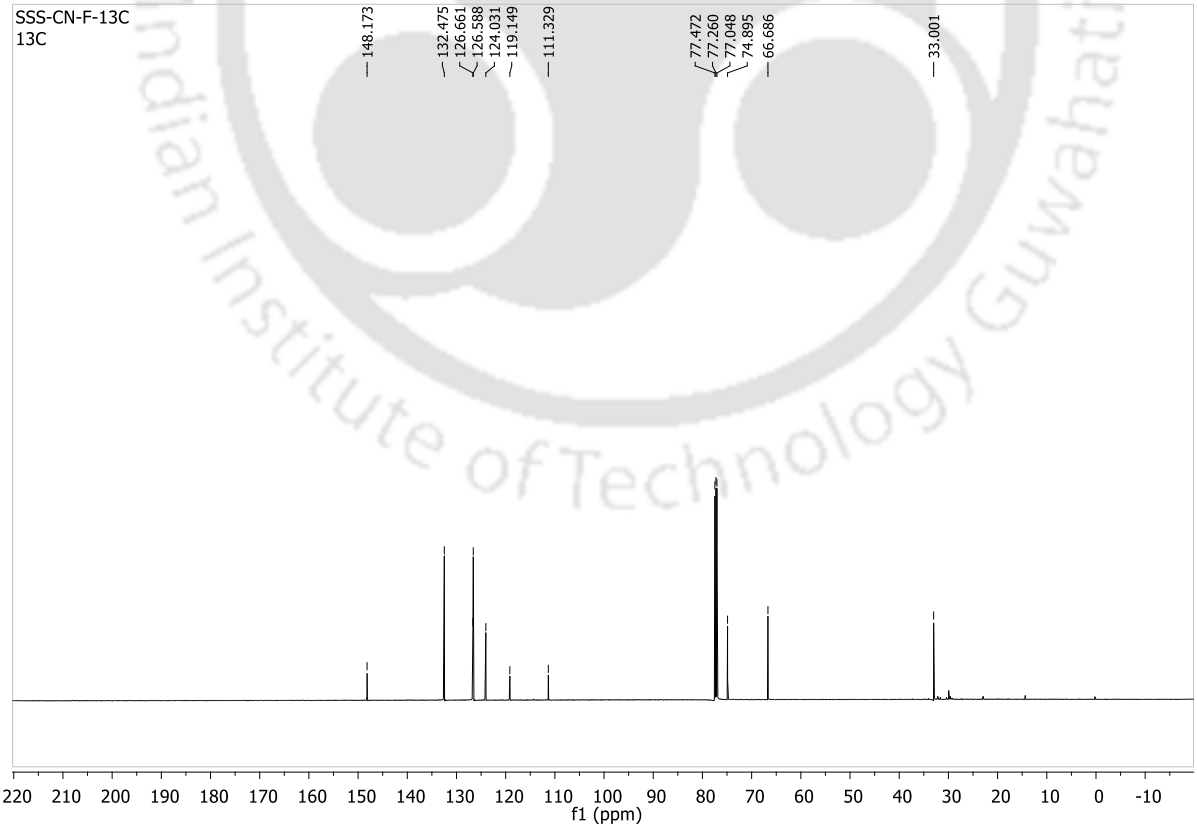
^{1}H and **^{13}C NMR** spectra of compound **41g**



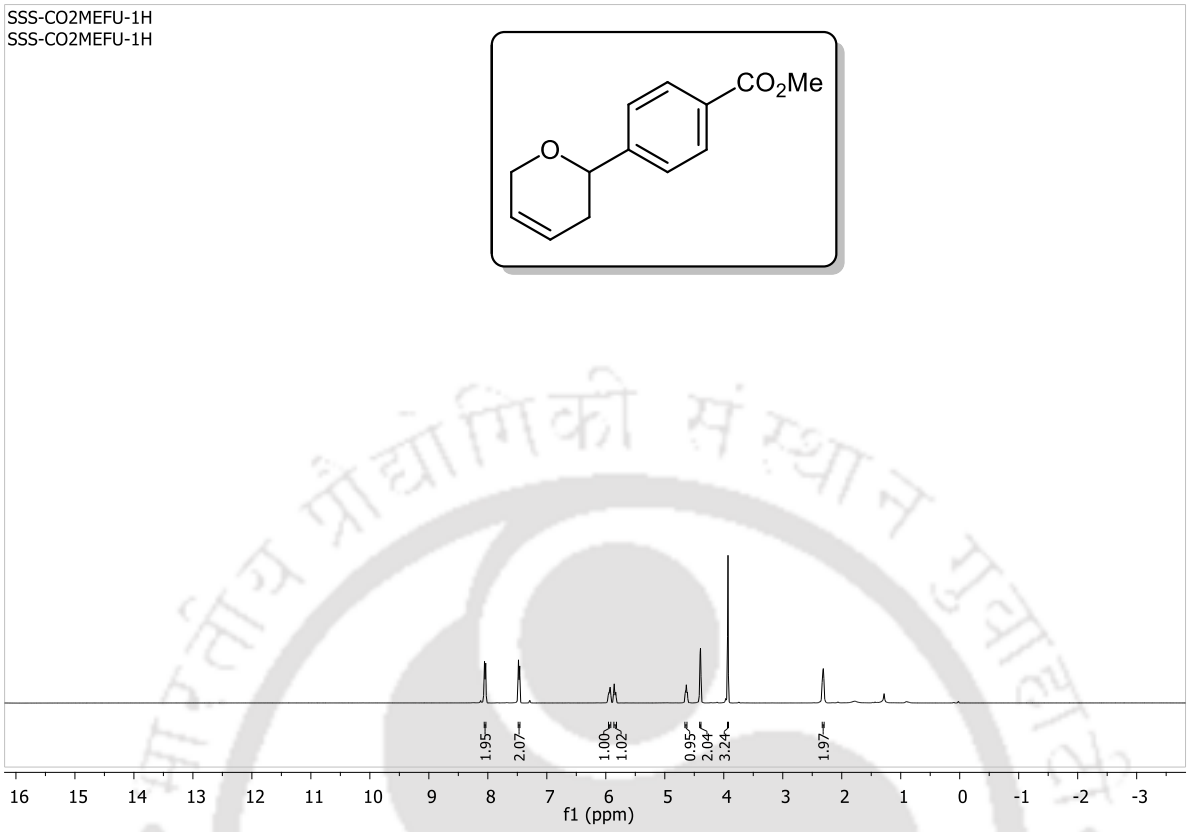


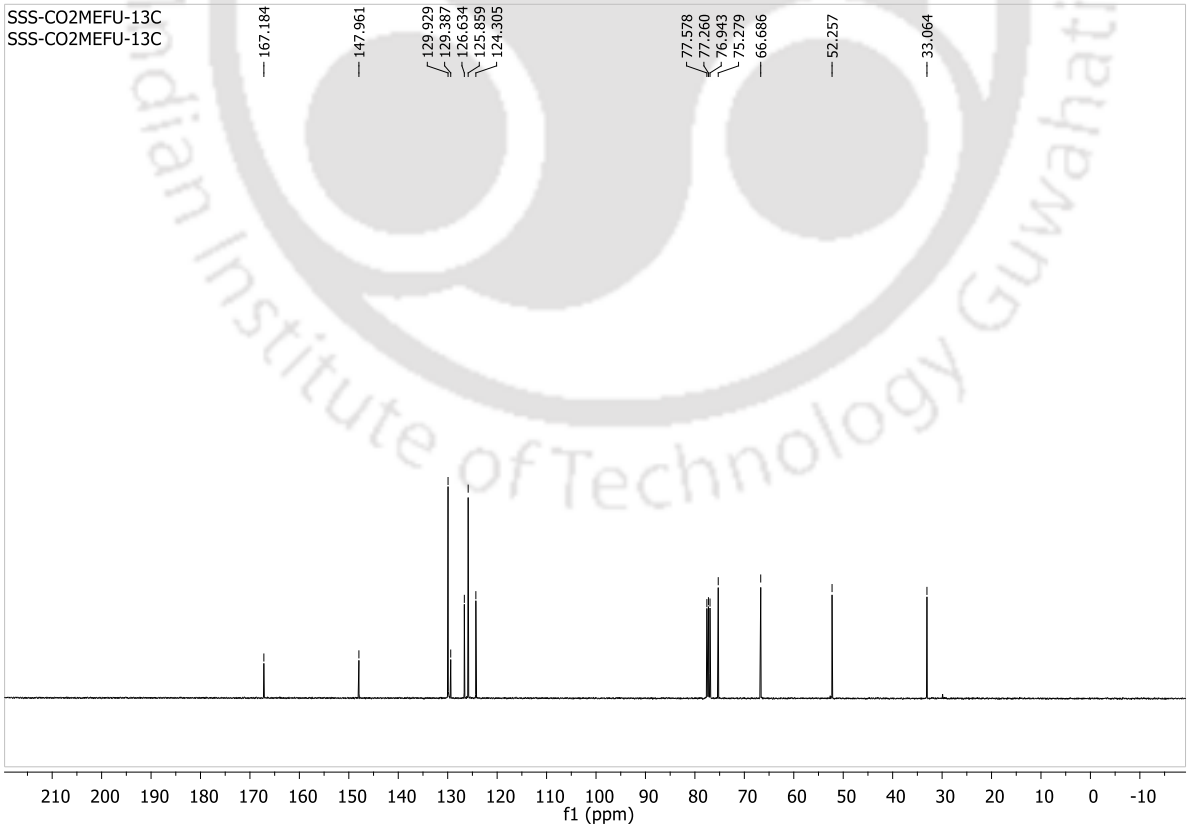
^{1}H and **^{13}C NMR** spectra of compound **41j**



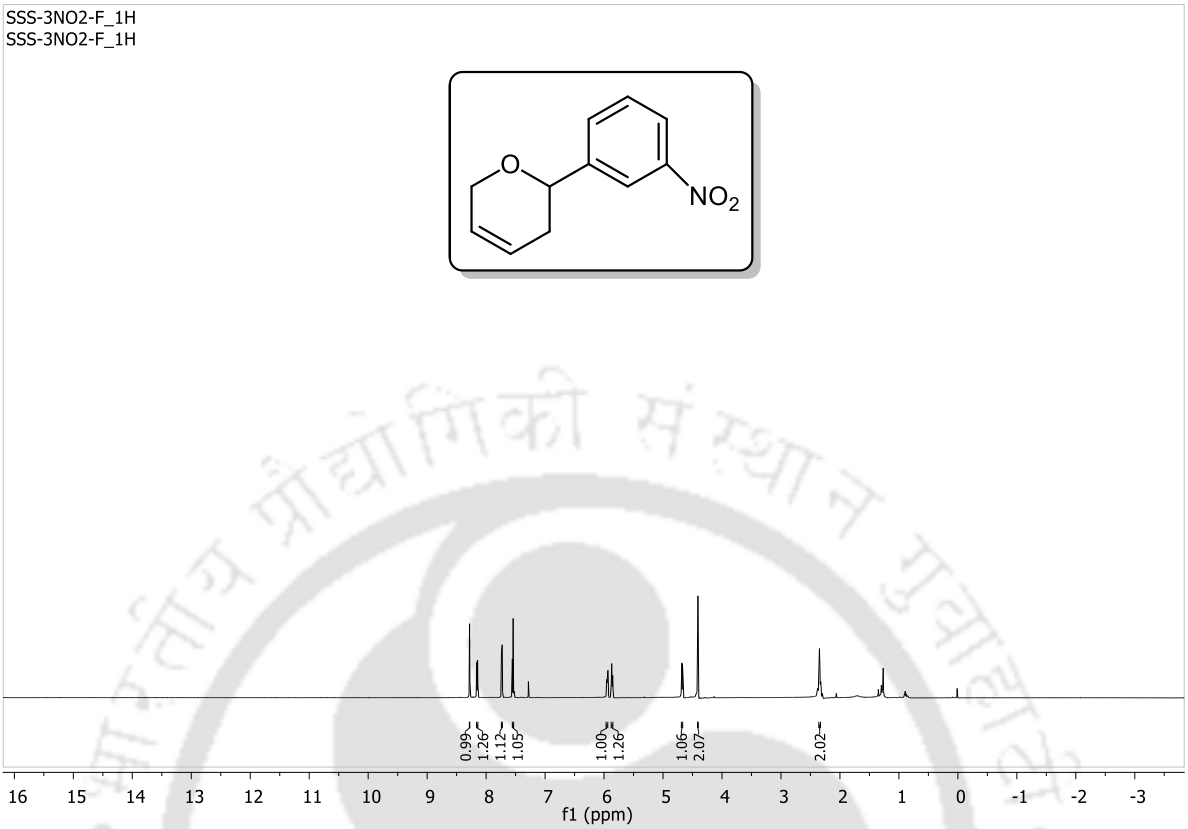


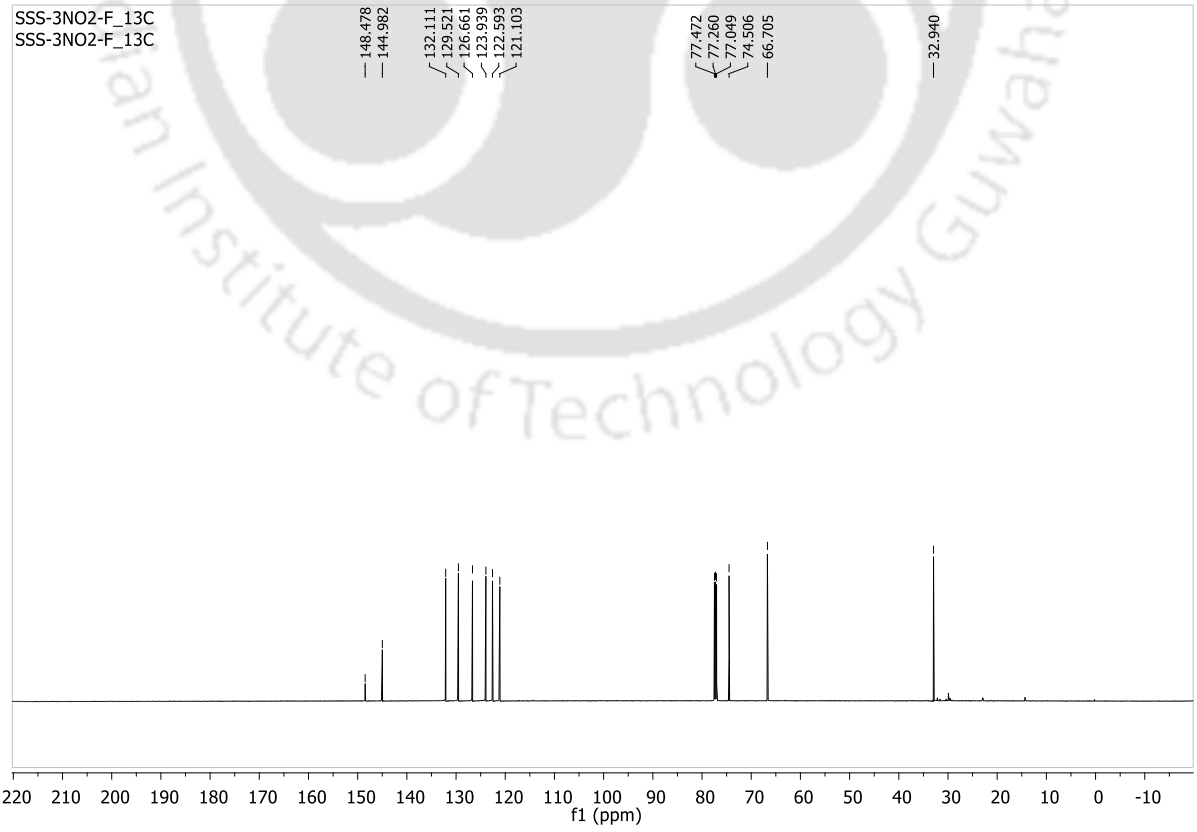
^{1}H and **^{13}C NMR** spectra of compound **41k**





^{1}H and **^{13}C NMR** spectra of compound **41n**





Crystal Parameters

The crystal parameters of compound **41o**

Parameters	CCDC 1851004
Formula	C_{11} H_{11} N_1 O_3
Formula weight	205.21
T/K	296(2)
Crystal system	orthorhombic
Space group	P n a 21
a/Å	6.8174(14)
b/Å	18.848(11)
c/Å	7.8481(12)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	1008.4(6)
Z	4
Abs. Coeff./mm^{-1}	0.099
Abs. Correction	Multi-Scan
GOF on F^2	1.001
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0828
	wR2 = 0.0992
R indices [all data]	*R1* = 0.2542
	wR2 = 0.1679

The crystallographic data for the compound **41o** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1851004.

.

List of Publications

1. "Synthesis of Substituted Isochromans *via* Oxa-Pictet-Spengler Reaction of Vinylogous Enol Esters" **Sarkar, S.**; Sultana, S.; Indukuri, K.; Unnavaa, R.; Saikia, A. K. *Synthesis*, **2016,** *48*, 1727.
2. "Regioselective One-Pot, Three-Component Synthesis of Substituted 2*H*-Indazoles from Nitroarylaldehyde, Alkyne and Amine Catalyzed by CuBr/$Zn(OTf)_2$ System" Unnava, R.; Indukuri, K.; **Sarkar, S**.; Saikia A. K. *RSC Adv*. **2014,** *4*, 55296.