Stereoselective Synthesis of Tetrahydro -pyrans, -thiopyrans and -quinolines

A Dissertation Submitted to the
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Submitted by

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Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis 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.

4th April, 2012 Somasekhar Bondalapati
IIT Guwahati

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CERTIFICATE

This is to certify that Somasekhar Bondalapati has been working under my supervision since July, 2007 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Stereoselective Synthesis of Tetrahydro -pyrans, -thiopyrans and –quinolines**" 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.

4th April, 2012
IIT Guwahati

Prof. Anil K. Saikia
Supervisor
Department of Chemistry
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I also take this opportunity to thank all of my Ph.D. batchmates (July, 07), the other research scholars in the chemistry department and all my IITG friends, who have shared their thoughts and views with me.

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Somasekhar Bondalapati

LIST OF ABBREVIATIONS

Ac	acetyl	ppm	parts per million
Bn	benzyl	Pr	propyl
Bu	butyl	*p*-TSA	*p*-toluenesulfonic acid
Bz	benzoyl	RCM	ring-closing metathesis
CAN	cerium(IV)ammonium nitrate	r.t.	room temperature
CCDC	cambridge crystallographic data centre	TBS	*t*-butyldimethylsilyl
COSY	correlation spectroscopy	Tf	trifluoromethanesulfonyl
DCE	1,1-dichloroethane	TFA	trifluoroacetic acid
DCM	dichloromethane	THF	tetrahydrofuran
DMF	*N*, *N*-dimethylformamide	TLC	thin layer chromatography
DMSO	dimethylsulfoxide	TMS	trimethylsilyl
dr	diastereomeric ratio	Ts	*p*-toluenesulfonyl
IR	infrared	*m*-CPBA	meta-chloroperbenzoic acid
mp	melting point	m/z	Mass to charge ratio
MS	molecular sieves	R_f	Retention factor
NMR	nuclear magnetic resonance	TMEDA	N,N,N',N'-tetramethylenediamine
NOESY	nuclear overhauser enhancement spectroscopy	MEM	methoxymethyl
ORTEP	oak ridge thermal ellipsoid plot	HRMS	High resolution mass spectrometry
PCC	pyridinium chlorochromate	Ph	phenyl

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

s	singlet	m	multiplet
d	doublet	brs	broad signal
dd	doublet of doublet	Hz	Hertz
t	triplet	MHz	Mega-Hertz
p	pentate		

Contents

CHAPTER 1

Introduction to Saturated Six-Membered Heterocycles

1.1. Classification and Nomenclature

Organic molecules can have mainly two kinds of structures e.g. acyclic and cyclic. The cyclic systems containing only carbon atoms are called carbocyclic (e.g. cyclohexane, benzene) and the cyclic systems containing carbons and at least one other element are called heterocyclic. Though a number of heteroatoms are known to be part of the heterocyclic rings, the most common heteroatoms are nitrogen, oxygen or sulphur. A heterocyclic ring may be saturated or unsaturated. Nearly half of the known organic compounds contain at least one heterocyclic ring. Many heterocyclic compounds occur naturally and are actively involved in biology e.g., nucleic acids (purine and pyrimidine bases), vitamins (Thiamine, Riboflavin), heme, chlorophyll and macrolides. The study of heterocyclic chemistry is a vast and expanding area of chemistry because of their applications in medicine, agriculture, photodiodes and other fields.

Heterocyclic compounds can be classified as aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic analogues of amines, ethers and thioethers and their properties are influenced by the ring strain. The three and four membered aliphatic heterocyclic rings are more strained and reactive compared to five and six membered analogues. The common aliphatic heterocyclic compounds are oxirane **1**, aziridine **2**, thiirane **3**, oxetane **4**, azetidine **5**, thietane **6**, tetrahydrofuran **7**, pyrrolidine **8**, tetrahydrothiophene **9**, tetrahydropyran **10**, piperidine **11** and tetraydothiopyran **12**.

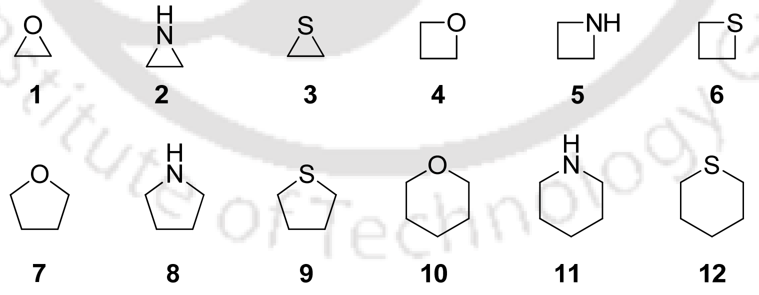
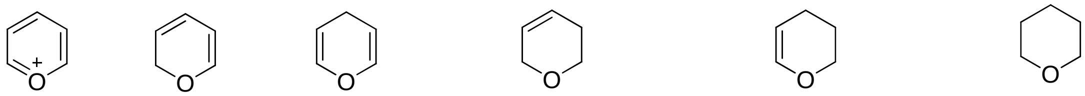


Figure 1.1. *Some common three to six membered saturated heterocycles*

The most widely used systematic method for naming three to ten membered monocyclic heterocycles of various degree of unsaturation containing one or more heteroatoms is Hantzsh-Widman system.[1] This nomenclature specifies the ring size, position of the heteroatom and the degree of unsaturation in the ring. In this method, the ring atoms are normally numbered such that the heteroatom carries the least number. Yet, difficulty arises with the names of unsaturated heterocycles containing a sp^3 hybridized atom in the ring for instance, pyran, a heterocycle formally the product of the addition of a single hydride ion to the pyrylium cation **13**. However, as this addition could occur either at C-2 or C-4, two isomers of pyran are possible, which are called as 2*H*-pyran **14** and 4*H*-pyran **15**, respectively (*Figure 1.2*).

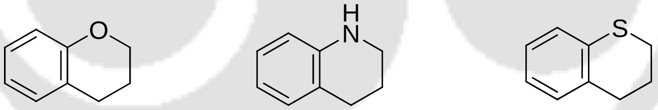


13 pyrylium **14** 2*H*-pyran **15** 4*H*-pyran **16** 3,6-dihydro-2*H*-pyran **17** 3,4-dihydro-2*H*-pyran **18** tetrahydro-2*H*-pyran

***Figure 1.2**: Systematic names of the heterocycles having sp^3 carbon in the ring*

It is also common to use the prefixes dihydro and tetrahydro while referring to compounds that are partly or fully reduced. For illustration 3,6-dihydro-2*H*-pyran **16** in which "dihydro" refers to the two added hydrogen atoms, which are required to reduce one double bond from the parent compound 2*H*-pyran. It is also important to note that the lowest possible number is always selected for the heteroatom. For example, the fully reduced pyrylium cation is referred to as 3,4,5,6-tetrahydro-2*H*-pyran **18** (*Figure 1.2*).

Heterocycles with fused six membered rings: six membered saturated heterocycles namely piperidine, tetrahydropyran, and tetrahydrothiopyran fused with benzene ring give rise to various possible structures such as chroman **19**, 1,2,3,4-tetrahydroquinoline **20** and thiochroman **21**.

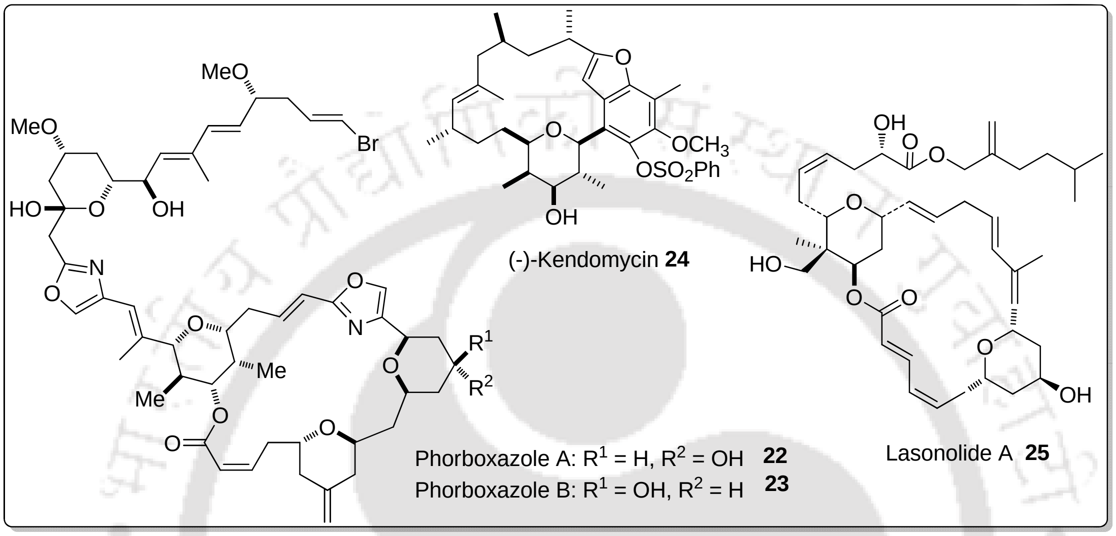


19 chroman **20** 1,2,3,4-tetrahydroquinoline **21** thiochroman

***Figure I.3.** Benzofused derivatives of six membered heterocycles*

1.2. Importance of Tetrahydro-pyrans, -thiopyrans and -quinolines

The six membered ring heterocycles of oxygen, nitrogen and sulfur are structural motifs of many bioactive molecules such as polyether antibiotics, marine toxins and pheromones.[2.] Tetrahydropyran is an important unit in pharmaceuticals. Consequently, a huge amount of effort has been devoted towards developing ever more efficient methods to synthesize them. For example, over the last ten years thousands of tetrahydropyran containing compounds have been entered into preclinical and clinical trials.[3] Phorboxazoles **22** and **23** (*Figure 1.2.1*) possess antifungal activity and are potent antineoplastic agents and also show high activity across the entire panel (mean GI_{50} 1.58 $\times 10^{-9}$M) with specific cell lines being inhibited at subnanomolar concentrations.[4] The macrocycle, (-)-kendomycin **24** has a diverse and fascinating pharmacological profile. It was isolated in 1996 from *Streptomyces* bacteria and exhibits potent antagonism of the endothelin receptor agonism.[5] Lasonolide A, **25** isolated from a shollow water Caribbean sponge, species *Forcepia* shows potent activity against A-549 human lung carcinoma.[6]

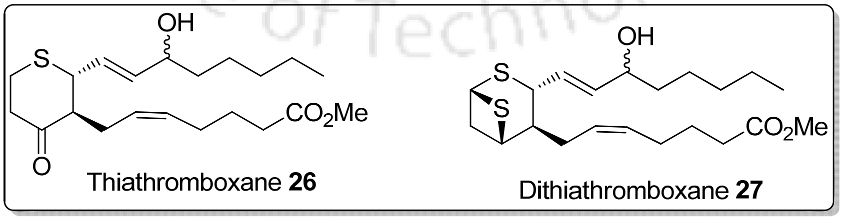

(-)-Kendomycin **24**

Phorboxazole A: R^1 = H, R^2 = OH **22**
Phorboxazole B: R^1 = OH, R^2 = H **23**

Lasonolide A **25**

Figure 1.2.1. *Important natural products containing tetrahydropyran as a core unit*

Compared to the tetrahydropyrans their sulfur analogues thiotetrahydropyrans are less frequently encountered in nature. A reasonable number of thiacyclohexane derivatives are found in petroleum oil.[7] The thiacyclohexane ring also plays a key role in the biological activities of a number of pharmaceutical agents such as cephalosporins,[8] thiathromboxane **26** and dithiathromboxane A_2 **27**.[9] Recently, there has been increased interest in developing new therapeutic agents based on thiacyclohexane structures.[10] In addition, thiacyclohexanes can be transformed to a variety of structures through simple reactions, such as hydrogenolysis, oxidation, and olefination.[11]


Thiathromboxane **26**

Dithiathromboxane **27**

Figure 1.2.2. *Thiotetrahydropyrans as pharmaceutical agents*

Tetrahydroquinolines are benzo fused derivatives of piperidines, present in numerous alkaloids and biologically active compounds.[12] In the past, an ethanolic extract of *Galipea officinalis* was used against fever and inflammation. This extract contained mainly three alkaloids **28**, **29** and **30** depicted in (*Figure1.2.3*) and they all show activity against *Mycobacterium tuberculosis.*[13] Many relatively simple synthetic 1,2,3,4-tetrahydroquinolines are already used or have been tested as potential drugs (*Figure1.2.3*). Among them, oxamniquine **31**, a schistosomicide (schistosomiasis is a parasitic disease),[14] nicainoprol **32**, an antiarrhytmic drug,[15] and virantmycin **33**, a novel antibiotic,[16] are the best known. Tetrahydroquinoline L-689,560 **34** is one of the most potent NMDAR (*N methyl d-aspartate receptor)* antagonists yet described.[17]

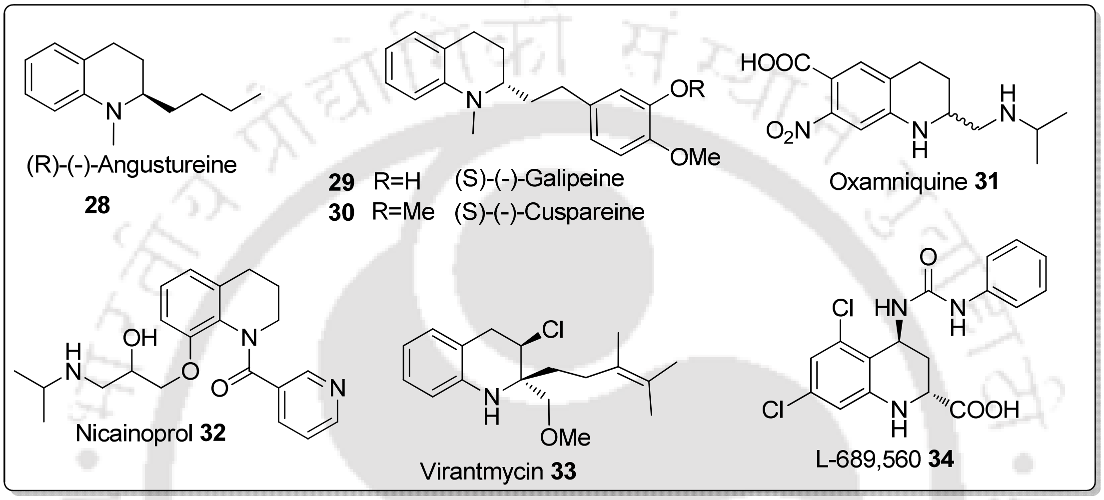


Figure 1.2.3. *1,2,3,4-tetrahydroquinolines as potential drugs*

1.3. General Approaches for the Synthesis of Tetrahydro-pyrans, -thiopyrans and -quinolines

The following four major strategies are applied for the construction of these heterocycles.

i) Prins cyclization reactions

ii) Intramolecular-ene cyclizations

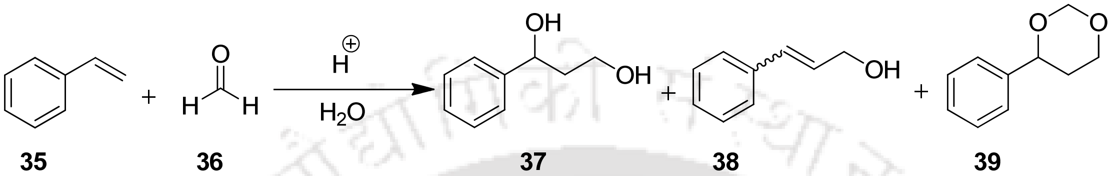
iii) Hetero-Diels-Alder cyclization

iv) Intramolecular Michael additions.

This thesis mainly deals with the construction of heterocycles involving Prins cyclizations and intramolecular-ene cyclizations. A brief summary of different applications involving these two types of reactions are discussed below.

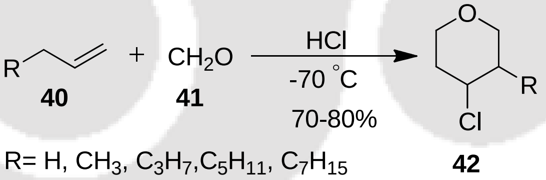
1.3.1. The Prins Cyclization

Prins reaction was first reported by H. J. Prins in the year 1919.[18] In his initial study using water as a solvent, he performed the reaction with styrene **35** and formaldehyde **36**. Mixture of 1,3-butanediol **37**, unsaturated alcohol **38** and 1,3-dioxanes **39** were obtained as products (*Scheme 1.3.1.1*).



Scheme 1.3.1.1.

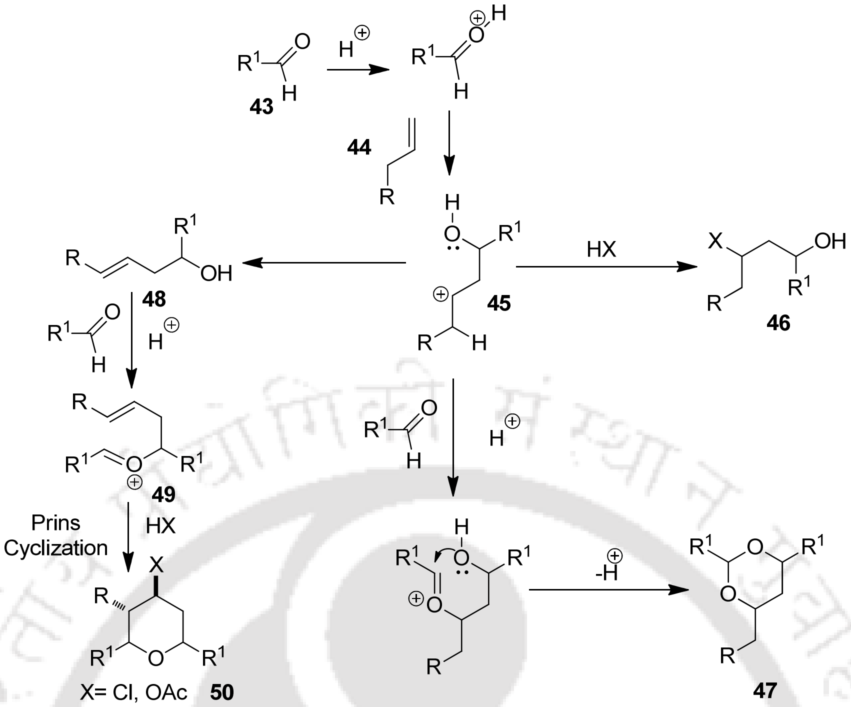
In the late 1960s the reaction was developed by Stapp to form tetrahydropyran derivatives.[19] This reaction proceeded in anhydrous media and involved the condensation of aliphatic terminal olefins **40** with paraformaldehyde **41** and hydrochloric acid to give 3-alkyl-4-chlorotetrahydropyrans **42** (*Scheme1.3.1.2*). Furthermore, he demonstrated that homoallyl alcohols are the intermediates of this reaction, which induced the development of Prins cyclization that provides a powerful access to tetrahydropyran derivatives.



Scheme 1.3.1.2.

1.3.2. Mechanism of the Prins Reaction

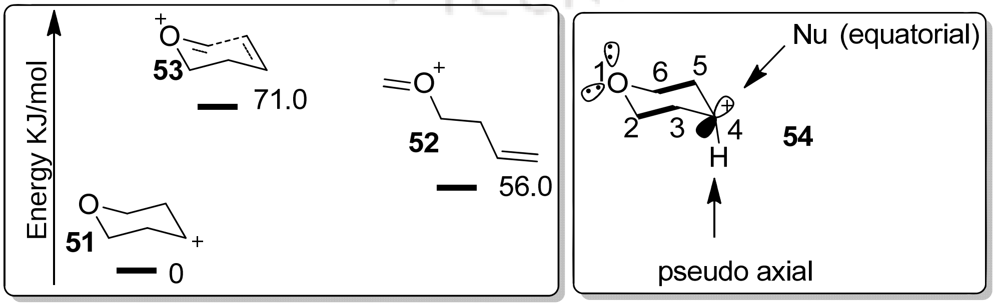
The general mechanism is shown in (*Scheme 1.3.2.1*). The alkene **44** reacts with carbonyl compounds **43** in the presence of Lewis (or) Bronsted acid and generates β-hydroxy carbocation as a key intermediate **45**, which either can react with a nucleophile such as chloride, water or acetate to give **46,** or adds to a second molecule of aldehyde to give **47** or loses a proton to give homoallylic alcohol **48**. Thus, the in situ generated homo allylalcohol **48** reacts with another molecule of aldehyde in the presence of acidic medium to afford oxocarbenium ion **49**, which after Prins cyclization and subsequent addition of neucleophile gives the 2,4,6-trisubstituted-tetrahydropyran **50**.[20]



Scheme1.3.2.1. *Mechanism of the Prins reaction*

1.3.3. Stereoselectivity in Prins Cyclization

There have been numerous reports in the literature on the Prins cyclization, which demonstrate excellent diastereoselectivity in favor of equatorial trapping of the cyclic carbocation by the nucleophiles. Alder has performed the DFT calculations on different possible reaction intermediates.[21] Carbocation **51** in its chair conformation is more stable by 56.0 kJ/mol than cation **52** in its most stable staggered conformation, which reveals that the reaction proceeds through a chair like transition state very close to **53** (*Scheme 1.3.3.1*). According to DFT calculations, carbocation in its chair conformation **54** 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

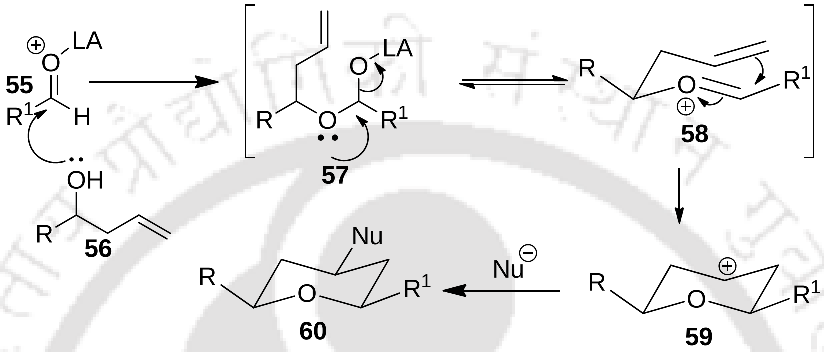


Scheme 1.3.3.1.

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.

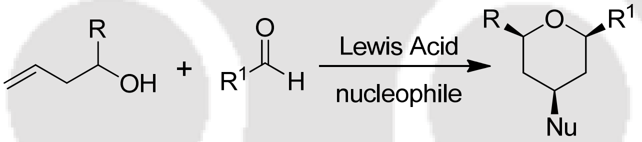
1.3.4. Scope of the Prins Reaction

In the simplest case, oxa-prins cyclization involves a homoallylic alcohol, an aldehyde and a Lewis acid. A general mechanism is shown in (*Scheme 1.3.4.1*). Aldehyde **55** reacts with



Scheme 1.3.4.1. *Mechanism of the Prins cyclization reaction*

Table 1.3.4.1. Scope of the prins cyclization with a large array of nucleophiles



1	Lewis acid (Nucleophile)[a] /Nucleophile[b]	Nu
2	TiF_4, $NEt_4.5HF$, $BF_3.OEt_2$	F
3	HCl, $TiCl_4$, $SnCl_4$, $AlCl_3$, $InCl_3$, $ZnCl_2$, $SbCl_5$, $ZrCl_4$,$NbCl_5$, $In(OTf)_3$/TMSCl	Cl
4	$SnBr_4$, $TiBr_4$, $InBr_3$, $FeBr_3$	Br
5	I_2, TMSCl/NaI, CeCl $_3.7H_2O$/LiI, TMSCl/NaI	I
6	CF_3COOH, Montmorillonite KSF, $O_3ReOSiPh_3$, $Sc(OTf)_3$, Amberlyst 15, Amberlite® IR-120, $Ce(OTf)_3.H_2O$/IL/Ph_2CO	OH
7	$BF_3.OEt_2$/AcOH, TsOH/AcOH, TESOTf/TMSOAc/AcOH	OAc
8	TFA/NaN_3	N_3
9	$In(OTf)_3$/NH_4SCN	SCN
10	$BF_3.OEt_2$/CH_3CN, PMA/CH_3CN, $CeCl_3.7H_2O$-AcCl/ CH_3CN	$NHCOCH_3$
11	$BF_3.OEt_2$/Arene	Ar
12	$BF_3.OEt_2$/CuI/ Ph—≡—H	$PhCOCH_2$

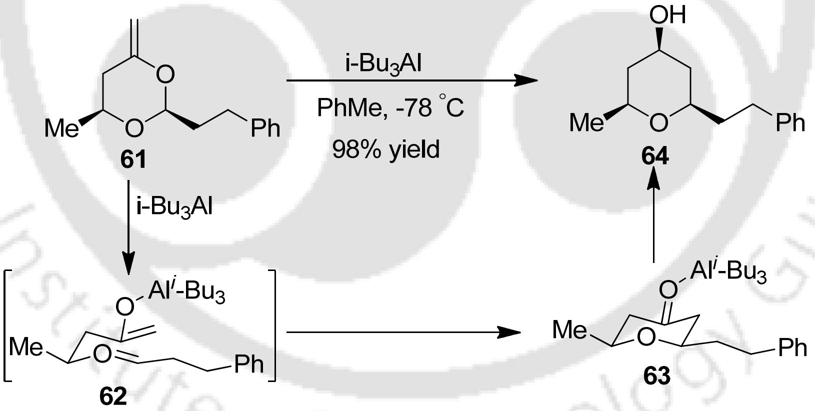
[a]Nucleophile comes from lewis acid, [b]separate nucleohile source has to be added

homoallylic alcohol **56** in the presence of lewis acid to generate an oxocarbenium ion **58** as a key intermediate, which undergoes 6-endo cyclization to give selectively a secondary tetrahydropyranyl cation **59**, which is trapped by the nucleophile to produce tetrahydropyran **60**. Thus, the carbocation that is generated at 4th position in Prins cyclization can be trapped with a wide range of nucleophiles (*Table1.3.4.1*). This tendency enables it to have many variations in the Prins cyclization.[22]

1.3.5. Cyclization Involving Electron-rich Double Bonds

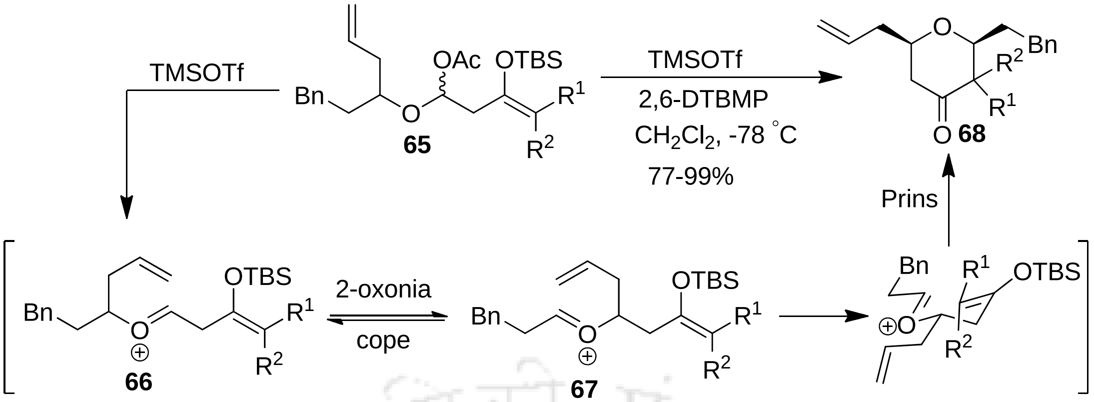
Apart from the simple alkenes, more nucleophillic alkenes such as enol ethers, ene-carbamates, allylsilanes and vinylsilanes have also been implemented in Prins cyclizations. In these reactions, the generated carbocation at the 4th position is quenched by the group present adjacent to it and the out come of the reaction depends on the functional group present on the double bond.

Petasis had shown the efficient synthesis of tetrahydropyranols. 1,3-Dioxan-4-ones **61** react with triisobutylaluminum to generate an oxocarbenium intermediate **62**, which undergoes cyclization with aluminum enolate to produce tetrahydropyranone **63**. This tetrahydropyranone **63** finally undergoes reduction to furnish tetrahydropyranols **64** in high yields. (*Scheme 1.3.5.1*).[23]



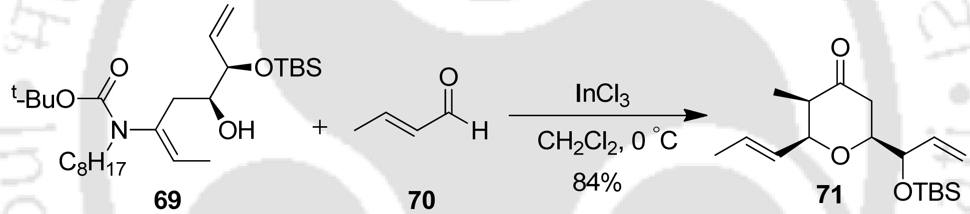
Scheme 1.3.5.1.

A facile route to tetrahydropyranones using acetoxyethers was devised by Rychnovsky based on the oxonium-cope rearrangement.[24] The treatment of acetoxyethers **65** with TMSOTf produces oxocarbenium ion **66**, which is in equilibrium with the oxocarbenium ion **67** via oxonia-Cope rearrangement (*Scheme 1.3.5.2*). Since the oxocarbenium ion bearing a highly nucleophillic enol ether, it undergoes Prins cyclization to deliver the tetrahydropyranone **68.**



Scheme 1.3.5.2.

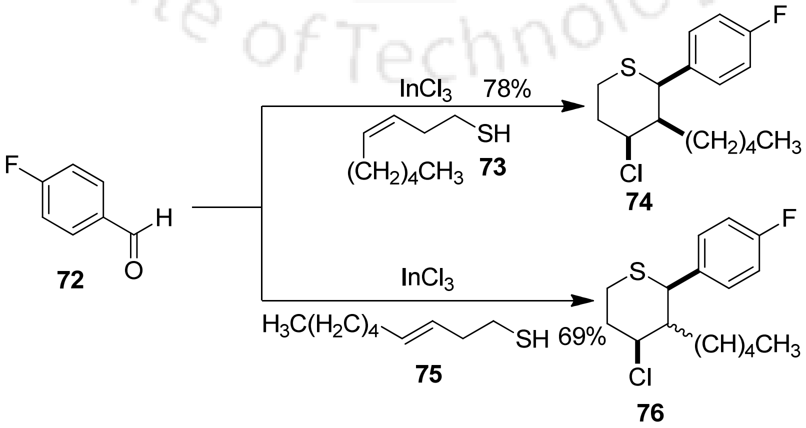
Funk and co-workers developed a diastereoselective synthesis of 2,3,6-trisubstituted tetrahydropyran-4-ones via Prins cyclizations of enecarbamates.[25] As exemplified in (*Scheme 1.3.5.3*), the reaction of **69** with unsaturated aldehyde **70** led to trisubstituted 2,3,6-*cis,cis*-tetrahydropyran-4-one **71**.



Scheme 1.3.5.3.

1.3.6. Thia-Prins Cyclizations

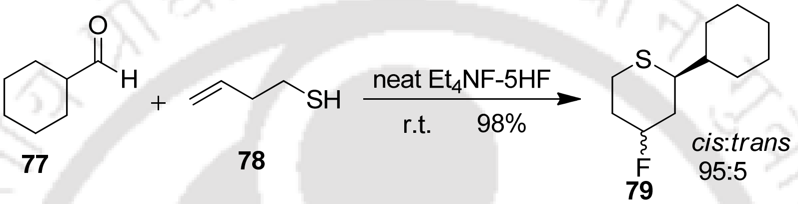
Recently, thia-Prins cyclization received considerable attention and showed significant progress in the synthesis of tetrahydrothiopyrans. The reaction of *cis*-aliphatic homoallyl mercaptan **73**



Scheme 1.3.6.1.

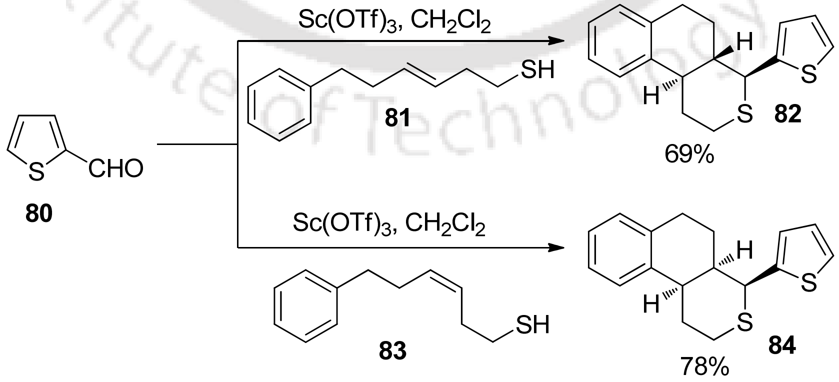
with 4-fluoro-benzaldehyde **72** generated unsymmetrical 2,3,4-trisubstituted tetrahydrothiopyrans **74** in 78% yield and with good diastereoselectivity. The diastereoselectivity remains nearly the same in all cases favoring the *cis-trans–cis*-isomers. Similarly *trans*-aliphatic homoallylic mercaptan **75** gave compound **76** in 69% yield (*Scheme 1.3.6.1*).[26]

Kishi *et al.* have investigated thia-Prins cyclization of various kinds of aldehydes **77** with homoallylic thiol **78** in ionic liquid HF salts to obtain 4-fluorothiacyclohexanes **79** in excellent yields. Although *cis* products were obtained selectively (higher than 92%), the formation of a small amount of *trans* products were also observed (*Scheme 1.3.6.2*).[27]



Scheme 1.3.6.2.

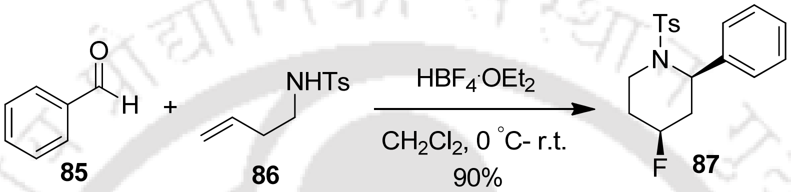
Homoallylic thiols such as (*E*)-6-arylhex-3-enyl thiol **81** undergo smooth cross coupling with aldehydes **80** in the presence of catalytic amount of Sc(OTf)$_3$ to afford the *trans*-fused hexahydro-1H-benzo[f]isothiochromenes **82** via thia-Prins/Friedel-Crafts cyclization. However, the cross-coupling of (*Z*)-olefins such as 6-arylhex-3-enyl thiols **83** with aldehydes affords the corresponding hexahydro-1H-benzo[f]isothiochromenes **84** with complete *cis* selectivity (*Scheme 1.3.6.3*).[28]



Scheme 1.3.6.3.

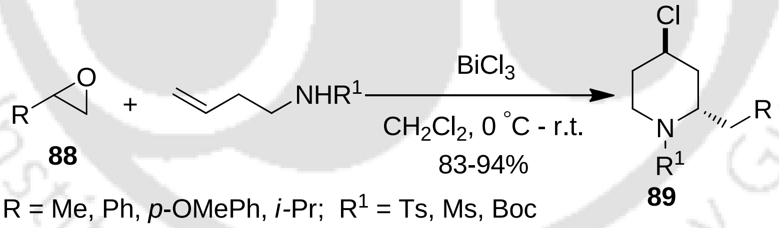
1.3.7. Aza-Prins Cyclizations

The reports on aza-prins cyclization, in which, homoallyl amine is used as counterpart of homoallyl alcohol in oxa-prins cyclization are limited. Like oxa-Prins reaction, which leads to the formation of tetrahydropyrans, the aza-Prins cyclization leads to piperidines. For example, the reaction of aldehydes **85** with N-tosyl homoallylamine **86** in the presence of a solution of tetrafluoroboric acid-diethyl ether complex in dichloromethane at ambient temperature gave the 4-fluoropiperidines **87** in good yields and with high *cis*-selectivity (*Scheme 1.3.7.1)*.[29]



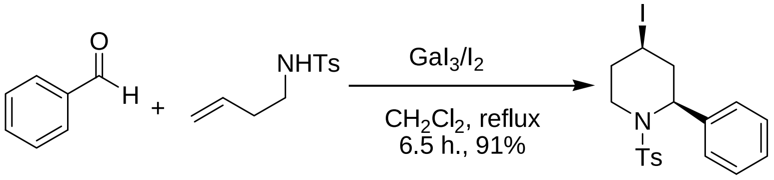
Scheme 1.3.7.1.

2-Alkyl substituted piperdines **89** were synthesized from the reaction of epoxides **88** with homoallylamines in the presence of $BiCl_3$. The reaction produces selectively *trans*-2,4-disubstituted piperidine derivatives in good yields. (*Scheme1.3.7.2*).[30]



Scheme 1.3.7.2.

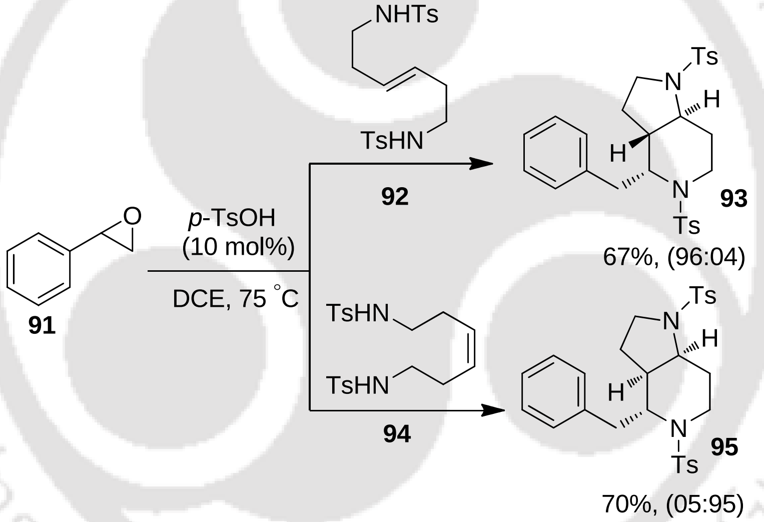
Yadav and co-workers have developed a method for the synthesis of 4-iodopiperidines by means of aza-Prins-cyclization using a catalytic amount of gallium (III) iodide and a stoichiometric amount of iodine. Thus, the reaction of benzaldehyde with N-tosylhomoallyl amine in the presence of 10 mol % of GaI_3 and a stoichiometric amount of molecular iodine at ambient temperature gave the corresponding 4-iodo-2-phenylpiperidine **90** in 91% yield with *cis*-selectivity (*Scheme1.3.7.3*).[31]



90

Scheme 1.3.7.3.

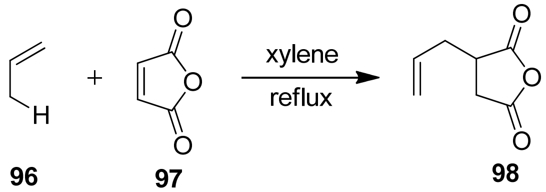
Aryl epoxides **91** undergo coupling smoothly with (*E*)-hex-3-ene-1,6-ditosylamide **92** in the presence of 10 mol% *p*-TsOH in 1,2-dichloroethane at 75 ˚C to produce the corresponding 1,5-ditosyl-octahydro-*1H*-pyrrolidino-[3,2-*c*]pyridines **93** in good yields with high *trans*-selectivity, whereas the coupling of (*Z*)-hex-3-ene-1,6-ditosylamide **94** gave *cis*-fused octahydro-1*H*-pyrrolidino[3,2-*c*] pyridines **95** predominantly (*Scheme1.3.7.4)*.[32]



Scheme 1.3.7.4.

1.4. Ene Reaction

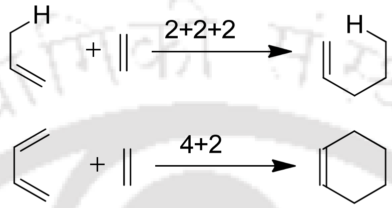
The “ene” reaction was first studied by Alder in 1943. He observed that propene **96** reacted with maleic anhydride **97** at elevated temperature to give allyl succinic anhydride **98** as shown in (*Scheme 1.4.1*). He described this process as an “indirect substitution-addition” of a compound



Scheme 1.4.1.

bearing a double bond (enophile) to an olefine possessing an allylic hydrogen atom (ene). Later this transformation became known as the “ene” reaction.[33]

Mechanisticllay the “ene” reaction has many similarities with the well-known Diels-Alder reaction. The latter, involves the cycloaddition of a diene and a dieneophile, while the former reaction results from interaction of a molecule containing at least one allylic hydrogen (the "ene" component) and an eneophile. These reactions are illustrated for their simplest compounds in (*Scheme 1.4.2*).



Scheme 1.4.2.

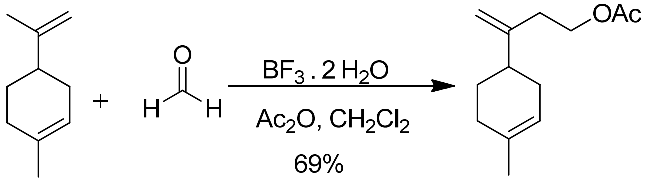
Diels-Alder reaction involves the 4π-electrons of the diene and 2π-electrons of the dienophile, while in the ene reaction (2π+2σ)-electrons of ene and 2π-electrons of the enophile are involved. Also, both reactions are thermally allowed, concerted, suprafacial transformations. In the suprafacial orbital interaction of the ene reaction, the two electrons of the allylic C–H σ-bond replace the two π–electrons of the diene in the Diels-Alder reaction. Thus, the activation energy of ene reaction is greater than that of the Diels-Alder reaction as a consequence, the ene reaction usually proceeds at elevated temperatures (or) requires highly activated substrates.

The ene (alkene) component of the ene reaction can react with a quite broad range of enophiles, which include alkenes, alkynes, allenes, carbonyls, imines and aza double bonds. The ene reaction is faster when the enophile contains one or more heteroatoms as in case of carbonyl or a nitroso group compared to simple alkene as enophile, in both of its intra- and inter-molecular versions.[34]

1.4.1. Intermolecular Carbonyl-ene Reaction

The intermolecular carbonyl-ene reaction is an useful and completely atom-efficient C-C bond forming reaction.[34] These reactions generally require highly reactive substrates, such as glyoxalate esters, chloral, formaldehyde, etc.[35] Frontier orbital considerations suggest that the major interaction between reacting components involves the LUMO of the carbonyl and the HOMO of the olefin. Therefore, carbonyl activation by complexation with Lewis acids facilitate the ene reaction, as a consequence of significant lowering of LUMO energy. For instance, the thermal reaction of (+)-limonene **99** with formaldehyde is not successful even at 180-200 ˚C.

However, the acetate **100** is formed in 69% yield with in one hour at room temperature if the reactions in the presence of BF_3 dihydrate (*Scheme 1.4.1.1*).[36]

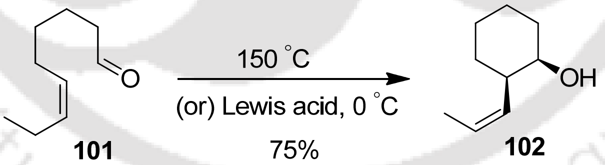


99 **100**

Scheme 1.4.1.1.

1.4.2. Intramolecular Carbonyl-ene Reaction

Intramolecular ene reactions (ene cyclizations) are much more facile than their intermolecular counterpart. Therefore, the carbonyl functionality does not need to be highly activated, and the reaction will proceed under milder conditions. The intramolecular ene reaction of unsaturated carbonyl compounds is an attractive approach to the synthesis of highly functionalized cyclic compounds. For example, the simple aliphatic unsaturated aldehyde **101** will react thermally at 150 ˚C or at 0 ˚C in the presence of a Lewis acid to give the *syn* isomer **102** in 75% yield. However, the corresponding intermolecular reaction between an alkyl aldehyde and an internal alkene does not proceed at all (*Scheme 1.4.2.1*).[37]

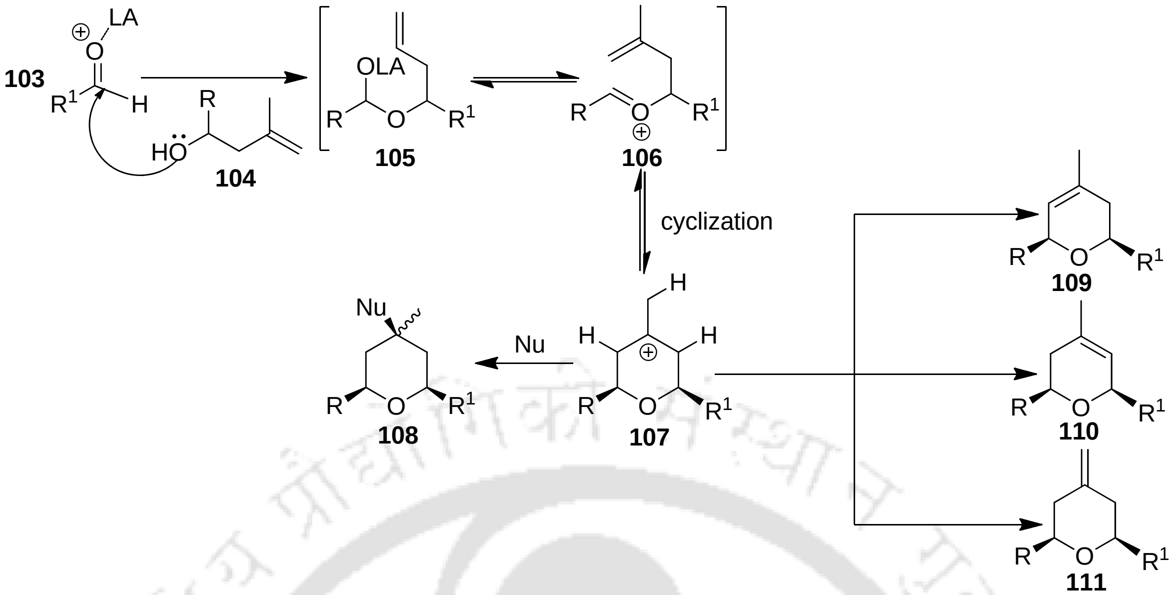


101 **102**

Scheme 1.4.2.1.

1.4.3. Intramolecular Oxonium-ene Reactions

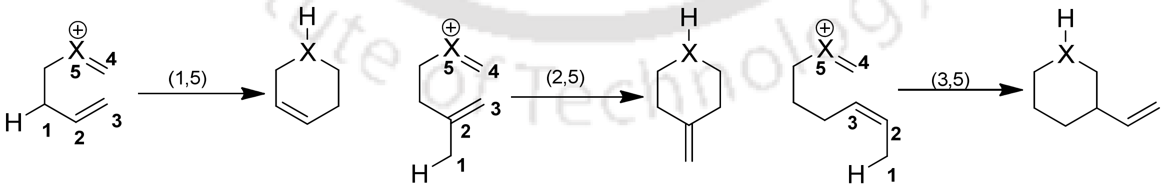
Oxonium ions are highly electrophillic and important reactive intermediates in synthetic organic chemistry. Numerous methods for highly diastereoselective additions of carbon or heteroatom nucleophiles onto oxonium ions have been identified, such as Prins cyclizations,[22] acid mediated additions to acetals,[38] allyl group transfers,[39] and additions of carbonyls to electrophiles.[40] In the year 1988, Overmann introduced oxonium ion mediated intramolecular ene reaction.[41]



Scheme 1.4.3.1.

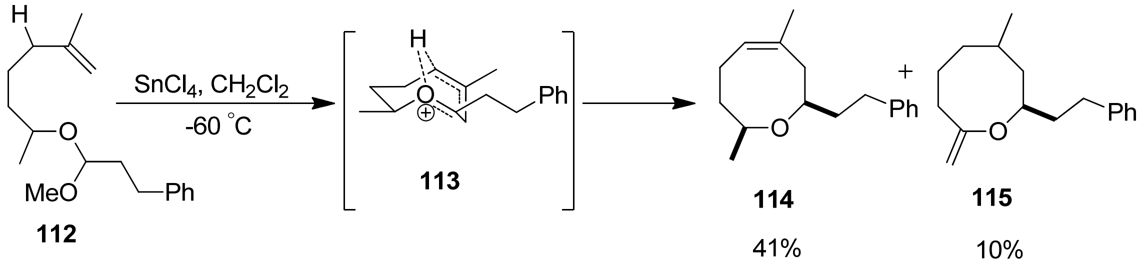
Mechanistically intramolecular oxonium-ene reaction and prins reaction are not much distinct from each other. In both the reactions oxo-carbenium ion **106** is the common intermediate, which undergoes cyclization with alkene nucleophile to form carbocation **107** as a key intermediate. This carbocation is trapped by nucleophile in the case of Prins reaction. Whereas in the case of oxonium-ene reaction the carbocation undergoes elimination process as shown in (*Scheme1.4.3.1*).

Since, the ene and enophile can be connected in many ways, the ambiguity is inevitable. To make it unambiguous, Mikami classified the intramolecular ene reaction into three main categories namely (1,5), (2,5) and (3,5) depending upon the connectivity between enophile to the ene (*Scheme 1.4.3.2*).[42]



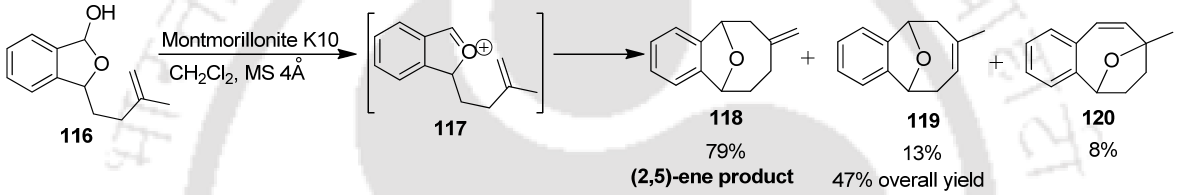
Scheme 1.4.3.2. Classification of the intramolecular ene cyclization

The past few years have witnessed the development of various cyclic ethers using oxonium-ene reaction as a powerful tool. Overman and coworkers have described the synthesis of tetrahydro-*2H*-oxocines. The treatment of unsaturated acetal **112** with $SnCl_4$ generates an oxonium ion **113**, which then undergoes cyclization via (1,5)-oxonium-ene reaction to afford mixture of 8-membered cyclic ethers **114** and **115** with excellent diastereoselectivity (*Scheme 1.4.3.3*).[43]



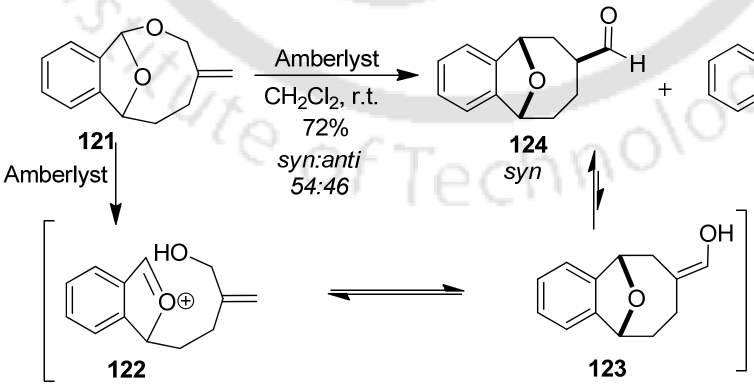
Scheme 1.4.3.3.

Mikami and co-workers have studied the (2,5)-oxonium-ene reaction. Lactol **116** on treatment with mesoporous solid acids such as montmorillonite K-10 produces tricyclic compound with exocyclic double bond **118** as a major product and its endo cyclic regioisomers **119** and **120** as minor products (*Scheme 1.4.3.4*).[42]



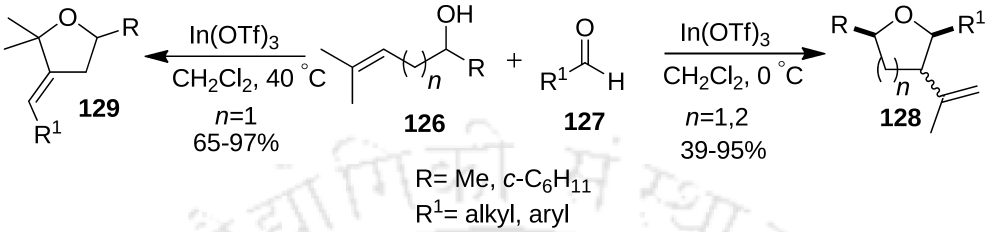
Scheme 1.4.3.4.

In addition to (2,5)-oxonium-ene reaction, Mikami investigated the mechanism of the reaction by trapping the (2,5) ene product in its enol form **123**, which immediately transformed to corresponding aldehydic forms **124** and **125** to restrict the regioisomerization to its endo cyclic isomers (*Scheme 1.4.3.5*).[44]



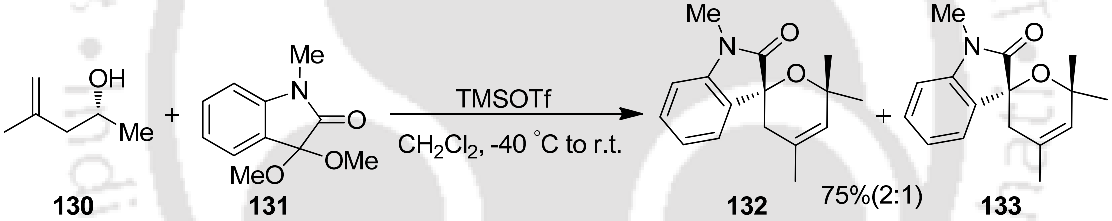
Scheme 1.4.3.5.

Loh and coworkers have developed a facile method for the synthesis of tetrahydrofurans and pyrans **128** from the reaction of aldehyde **127** and unsaturated alkenes having γ and δ hydroxyl groups **126** promoted by $In(OTf)_3$ via intramolecular (3,5)-oxonium-ene reaction at 0 °C (*Scheme 1.4.3.6*). By increasing the reaction temperature from 0 to 40 °C, they observed the formation of exocyclic isomer **129** as a major product. However, this rearrangement is limited to the tetrahydrofurans skeletons only, but not to the tetrahydropyran counterparts.[45]



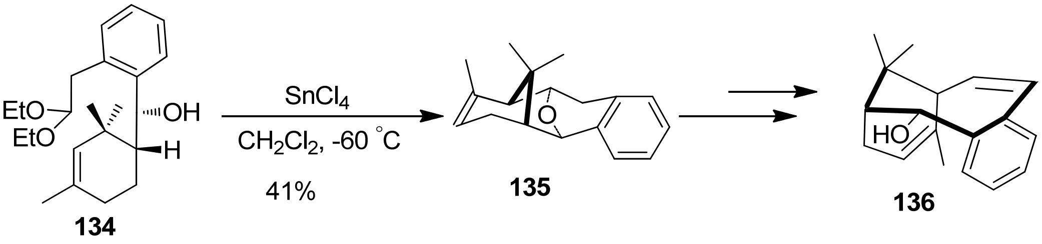
Scheme 1.4.3.6.

Porco described that enantiopure spirocyclic oxindole pyrans **132, 133** can be efficiently prepared by highly stereoselective oxonium-ene cyclization of homoallylic alcohols **130** and isatin ketals **131**. The transformation was proceeded through an *E*-1,1-disubstituted oxocarbenium ion, in which the larger aryl substituent of the oxindole moiety adopted a *pseudo*-equatorial orientation (*Scheme 1.4.3.7*).[46]



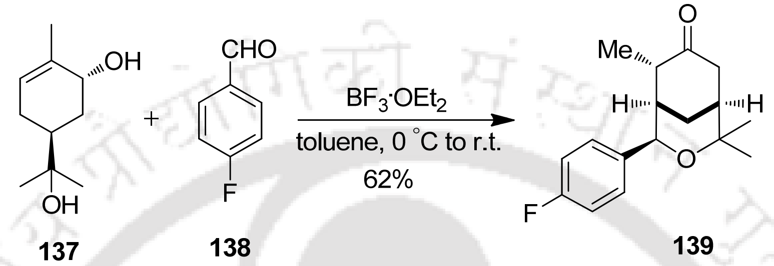
Scheme 1.4.3.7.

C-Aromatic taxane nucleus has been synthesized by employing an oxonium-ene cyclization reaction as the key step (*Scheme 1.4.3.8)*. Easily accessible unsaturated acetal **134** on treatment with $SnCl_4$ produces tetracyclic intermediate **135**, which further used to construct C-aromatic taxane nucleus **136**.[47]



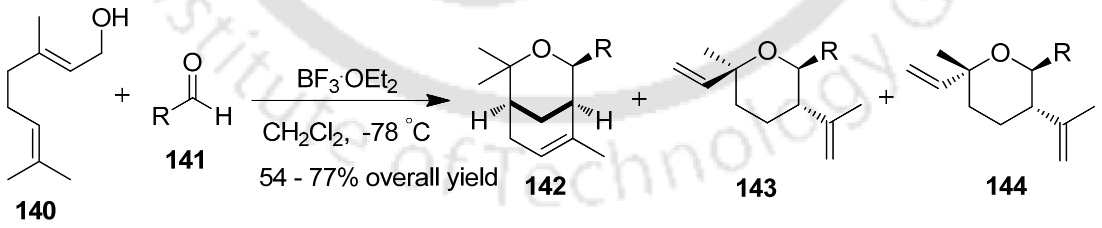
Scheme 1.4.3.8.

Saikia and coworkers have developed lewis acid mediated intramolecular (3,5)-oxonium-ene reaction to generate oxygenated bicyclic compounds with high diastereoselectivity (*Scheme 1.4.3.9*). The reaction of *trans*-*p*-menth-6-ene-2,8-diol **137** with 4-fluoro benzaldehyde **138** generated oxabicyclo[3.3.1]-nonanone **139** in 62% yield. The substrate scope of the reaction was further improved by replacing aldehydes with epoxides under identical reaction conditions to obtain the bicylic compounds in moderate yields.[48]



Scheme 1.4.3.9.

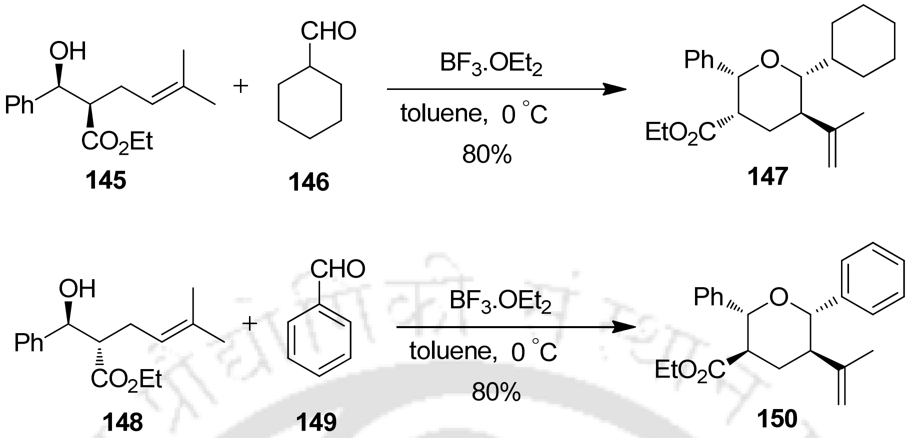
An efficient methodology for the synthesis of oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans has been developed from the reaction of readily available geraniol and aldehydes mediated by boron trifluoride etherate (*Scheme 1.4.3.10*). The reaction of geraniol **140** with sterically hindered aldehydes such as aromatic and cyclohexyl carboxaldehyde **141** in the presence of boron trifluoride etherate produces oxabicyclo[3.3.1]nonenes **142** as a major product. However, the reaction with simple aliphatic aldehydes and epoxides produces mixture of tetrahydropyrans **143** and **144** as the major products.[49]



R = Ph, 4-NO_2Ph, 2-NO_2Ph, 4-ClPh, 4-MeOPh, 4-CO_2MePh, 4-FPh, C_3H_7, PhCH_2CH_2, *c*-C_6H_{11}, C_3H_7

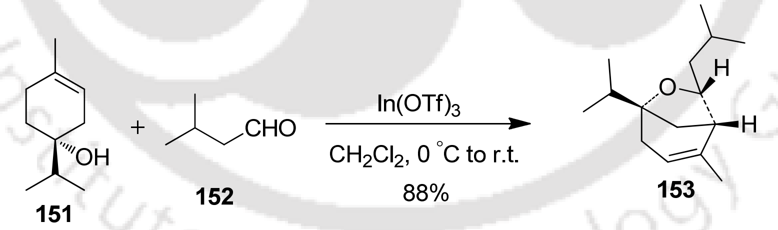
Scheme 1.4.3.10.

More recently, Saikia and coworkers investigated the effect of *syn* and *anti* configuration of unsaturated alcohols on the stereo chemistry of the products 2,3,5,6-tetrasubstituted tetrahydropyrans. The *syn* alcohol **145** reacted with aldehydes **146** in the presence of boron trifluoride etherate to furnish tetrahydropyrans **147** via (3,5)-oxonium-ene reaction. On the other hand, the reaction of *anti* alcohol **148** with aldehydes **149** gave tetrahydropyran **150** (*Scheme 1.4.3.11*).[50]



Scheme 1.4.3.11.

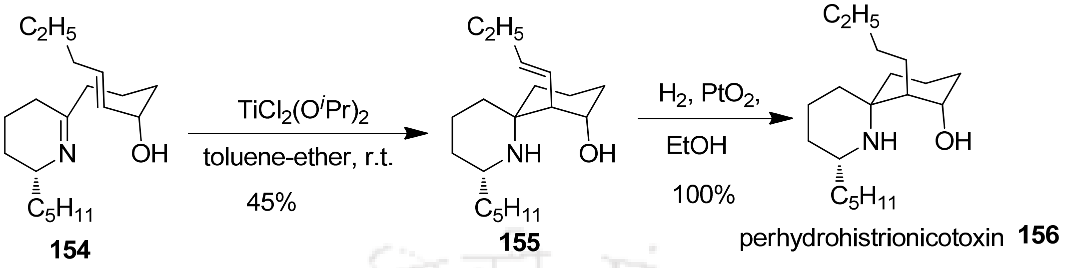
Further, the (3,5)-oxonium-ene raction has been applied succesfully in the elegant synthesis of 6-oxabicyclo[3.2.1]octene, which is the subunit of many natural products. The (-)-terpinen-4-ol **151** undergoes smooth coupling with aldehydes **152** in the presence of In(OTf)$_3$ to produce 6-oxabicyclo[3.2.1]octenes **153** in good yields and with excellent diasteroselectivity. The optimized condition of the reaction is presented in the (*Scheme 1.4.3.12)*. The advantage of the method is that epoxides can also undergo cyclization with (-)-terpinen-4-ol under same reaction conditions.[51]



Scheme 1.4.3.12.

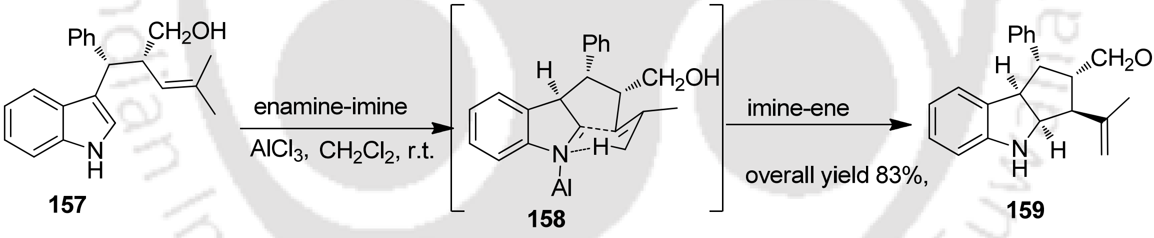
1.4.4. Intramolecular Imino-ene Reaction

The intermolecular imino-ene reaction provides direct access to the synthesis of homoallylic amines through the formation of a new carbon-carbon bond between an alkene (ene) and an imine (enophile). However, the intramolecualr imino-ene reaction mainly used to afford cyclic amines. Tanner described a convergent enantioselective total synthesis of the neurotoxic spirocyclic alkaloid (-)-perhydrohistrionicotoxin **156** (*Scheme 1.4.4.1*). In this process a Lewis acid-mediated intramolecular imine ene reaction was used as a key step for the spirocyclization of unsaturated imine **154**.[52]



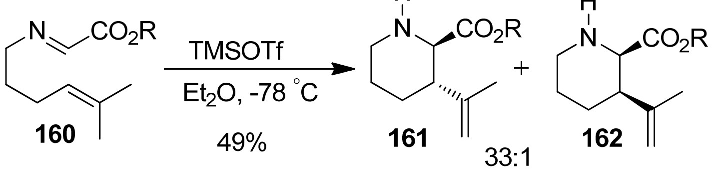
Scheme 1.4.4.1.

A versatile approach for the diastereoselective synthesis of cyclopentyl[b]indolines and cyclohexyl[b]indulines has been developed by Chen.[53] The reaction of indole bearing a tethered olefinic functionality **157** with $AlCl_3$ proceeds through enamine-imine isomerization, followed by intramolecular imino-ene reaction to produce cyclopentyl[b]indoline **159** in good yields with excellent diastereoselectivity (*Scheme 1.4.4.2*).



Scheme 1.4.4.2.

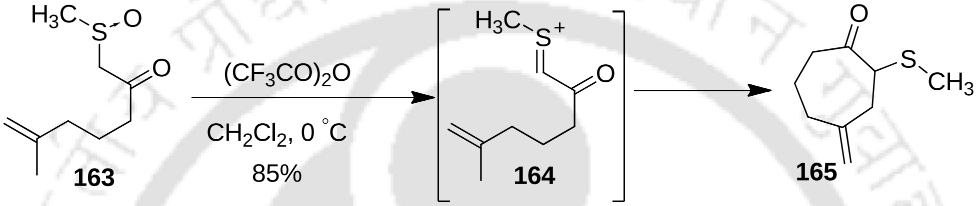
Tietze and coworkers have applied the intramolecular imino-ene reaction in the synthesis of unnatural non-proteinogenic α-amino acid derivatives. The (5-methyl-4-hexenylimino)acetate **160** undergoes cyclization in the presence of TMSOTf to afford the *cis*- and *trans*-3-isopropenyl-2-piperidine-carboxylates **161** and **162** in the ratio **33:1** (*Scheme 1.4.4.3*).[54]



Scheme 1.4.4.3.

1.4.5. Intramolecular Thionium-ene Reaction

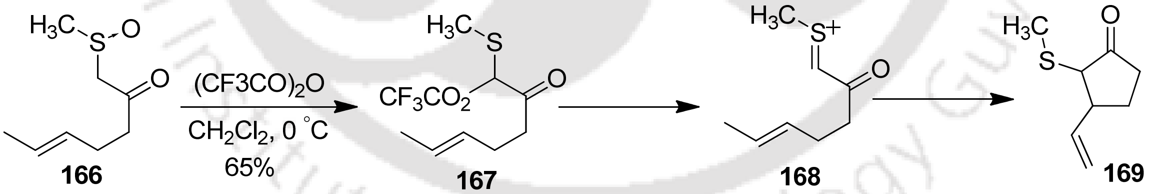
There are no reports in the literature for the synthesis of tetrahydrothiopyrans via thionium-ene reaction. However, the highly activated thionium ion is the most frequently encountered intermidiate in the well documented Pummerer rearrangement in the organic synthesis, which is used to undergo cationic cyclizations with various alkenes to furnish annulated products. For example, alkene tethered *β*-oxo sulfoxides **163** when treated with trifluoroacetic anhydride, generates thionium ion **164** via Pummerer rearrangement, which undergoes cyclization to give cycloalkanones **165** (*Scheme 1.4.5.1*).[55]



163 **164** **165**

Scheme 1.4.5.1.

Similarly, when *β*-oxo sulfoxide **166** was exposed to trifluoroacetic anhydride, initially the pummerer rearrangement product **167** was observed, which immediately converts into a highly reactive acyl-thonium ion **168**, followed by alkene cyclization onto the thionium-ion **168** to afford cyclic ketone **169** (*Scheme 1.4.5.2.*).[56]



166 **167** **168** **169**

Scheme 1.4.5.2.

Conclusion:

Both Prins cyclizations and intramolecular ene reactions are powerfull and versatile tools for the synthesis of various functionalized oxygen, nitrogen and sulfur containing heterocycles. Since these cyclizations occur under mild conditions and proceed through cyclic transition states, high degree of diasteroselectivity is observed in the outcomes of the reaction. Further more, the cationic intermediates that are formed during course of these cyclizations are trapped by various nucleophiles either by intramolecular fashion or by inter molecular fashion, which enable them to aceess highly functionalized complex skeletons. Moreover these are also involved in the fascinating and elegant syntheses of complex polycyclic skeletons of natural and unnatural biologically active molecules.

1.5. References

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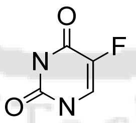
CHAPTER 2

Stereoselective Synthesis of 4-Fluorotetrahydropyran

2.1. Importance and Applications of Organofluorine Compounds

The element fluorine is prominent and its fluoride ion is abundant (0.065%) in the earth's crust. It is the most abundant of all the halogens. However, as an element, fluorine is extremely reactive and difficult to prepare. It was first isolated in 1886 by the French chemist Henry Moissan, for which he was awarded the Nobel Prize in 1906. Since then, fluorine has attracted the interest of the scientific community because of its unique properties (small size, strong electronegativity, low polarisability). The introduction of one (or more) fluorine atom(s) in an organic molecule, alters its physical, chemical properties and reactivity, which are significantly different from those of the non-fluorinated counterpart(s), without significant modification of steric factors.[1] To date molecules containing at least one fluorine atom are widespread. They are used in various fields, particularly in agrochemicals, electronics, and medicine. One example of a fluorinated compound that is used in everyday life is the polymer Teflon. In addition, the field that has greatly expanded the utility of fluorinated compounds is medicinal chemistry.[2]

Heidelberger[3] synthesized the first fluorinated drug 5-fluorouracil **1** (an anti-tumor drug). Although, 5-fluorouracil is similar in shape to that of uracil, it does not function similarly. This drug inhibits RNA replication of enzymes, thereby eliminating RNA synthesis and stopping the growth of cancerous cells. These vital properties of 5-fluorouracil have brought dramatical change in the field of medicinal chemistry to synthesize numerous fluorinated drug molecules.

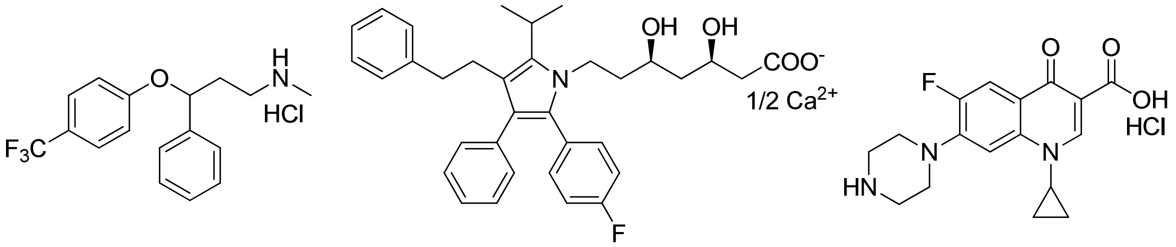


5-Fluorouracil (1)

Figure 2.1.1.

Nowadays, pharmaceutical research involving fluorinated molecules is conducted on a routine basis[4] and some fluorinated drugs are among the best sellers, such as the antidepressant fluoxetine **2**, the anticholesterol atorvastatin **3** and the antibacterial ciprofloxacin **4**.

The pharmacological superiority of fluorinated compounds over their non fluorinated analogues may be distinguished as follows. Covalently bound fluorine (C-F bond length 138 pm) has



Fluoxetine (2) **Atorvastatin (3)** **Ciprofloxacin (4)**

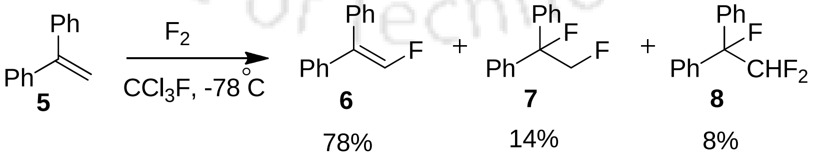
Figure 2.1.2. *Examples of some fluorinated aromatic and heterocyclic pharmaceuticals*

significant larger steric requirement than hydrogen (C-H bond length 109 pm). Fluorinated compounds usually have a sufficient similarity in size and shape to their non-fluorinated analogues to fit in a given enzyme receptor, so that they tend to have similar inherent biological activity. On the other hand, the carbon-fluorine bond is very strong (485 KJ mol^{-1}, compared to C-H, 416 KJ mol^{-1}), therefore, they tend to be more resistant to metabolic degradation. Selective fluorination emerges as a good method to tune the lipophilicity of a molecule, as the introduction of one or more fluorine atoms can increase the lipophilicity in an incremental manner.

There are two fundamental approaches to introduce a fluorine atom directly into an organic molecule by the formation of C-F bond. One is, by electrophilic fluorination by the reagents which are able to transfer F$^+$ ion to electron rich site. The second is, by nucleophilic fluorination, involving a negatively charged fluoride ion.

2.2. Electrophilic Fluorination

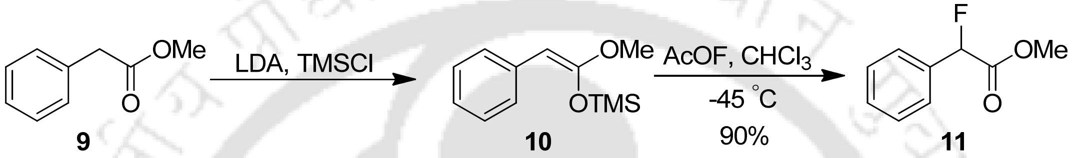
Elemental fluorine is essentially an electrophilic fluorinating reagent. However, there are many drawbacks associated with elemental fluorine mainly due to its high reactivity, lack of selectivity and high toxicity. One example is shown in the fluorination of 1,1-diphenylethene **5**, which gives a mixture of mono-, di- and poly-fluorinated products **6**, **7** and **8** (*Scheme 2.2.1)*.[5]



Scheme 2.2.1. *Fluorination of 1, 1-diphenylethylene with F_2.*

The difficulties associated (high reactivity and hazards) with direct fluorination have stimulated the development of alternate sources of positive fluorine. A large number of electrophilic fluorinating reagents have been developed over the years. One of the main classes of reagents is organofluoroxy, which consists of RO-F bond. An early example was the fluoroxytrifluoromethane, which has been extensively used for the fluorination of pharmaceutical products.[6] Another example of a popular organofluoroxy reagent is acetyl hypofluorite, which was shown to fluorinate aromatic rings.[7] Acetyl hypofluorite[8] has been intensively studied for addition to double bonds,[9] and fluorination of lithium enolates.[10]

The synthesis of α-fluorocarboxylic esters has also been achieved from their corresponding carboxylic esters using AcOF.[11] In this process the ester **9** is first converted into its trimethylsillyl ketene acetal **10**, which on reaction with AcOF produces its α-fluorocarboxylic ester **11** in good yield (*Scheme 2.2.2*).

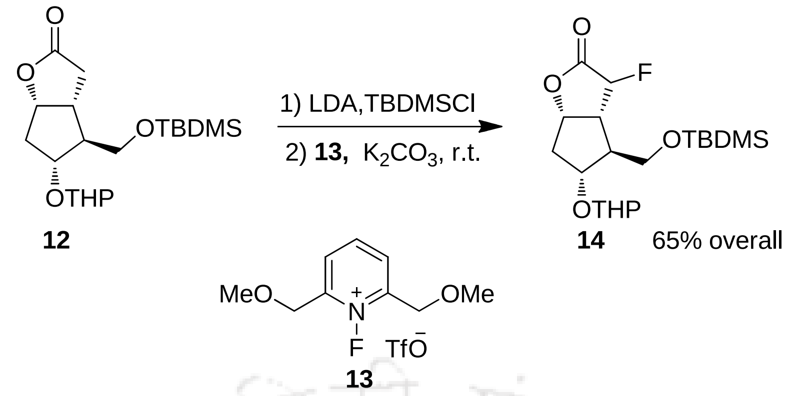


Scheme 2.2.2. *Fluorination of carboxylic ester*

Other XO-F electrophilic fluorinating agents have been developed such as perchloryl fluoride $FClO_3$, xenon difluoride XeF_2 or cesium fluoroxysulfate $CsSO_4F$. But many have shown strong oxidizing property or selectivity issues slowly reduced their utility.[12]

Major progress in the field of electrophilic fluorinating reagents, is achieved by the development of the *N*-F reagents. The main advantage of this class of reagents comes from the lower electronegativity of the nitrogen compared to oxygen, and the corresponding higher strength of the *N*-F bond compared to the O-F bond, giving them improved stability, thereby, making them easier to handle. We can distinguish three types of *N*-F electrophilic fluorinating agents: the *N*-fluoropyrimidium triflates and their derivatives, the sulfonyl derivatives $RSO_2N(F)R^1$ and selectfluor and its derivatives.

Umemoto and coworkers, have developed N-fluoropyrimidium triflate and its derivatives, which are widely used to fluorinate aromatic rings, carbanions, enol ethers and their derivatives. The choice of the counter ion is important and needs to be non-nucleophilic for their stability. Nevertheless, many counter ions have been explored (X^- = -OTf, $-BF_4$, $-ClO_4$ and $-SbF_6$), among all triflates are found to be very reactive.[13] A good example of the application of *N*-fluoropyrimidinium triflate is the preparation of the fluorinated Corey lactone **14** using 2,6-dimethoxymethyl-*N*-fluoropyrimidium triflate **13** (*Scheme 2.2.3*).[14]



Scheme 2.2.3. *Fluorination of corey's lactone*

Another efficient and air stable electrophiilc fluorinating agent, selectfluor **15**, is prepared and extensively studied by Banks and co-workers.[15] The best feature of this reagent is its reactivity, which can be tuned by modifying the substituent on the second nitrogen. In order to increase its reactivity, a stronger electron-withdrawing group is required and the reagents can be classified from the less reactive to strongly reactive: $C_8H_7 < CH_2Cl < CF_3CH_2$.[16]They have found a wide range of applications, including fluorination of aryl groups, nucleosides,[17] and steroids.[18]

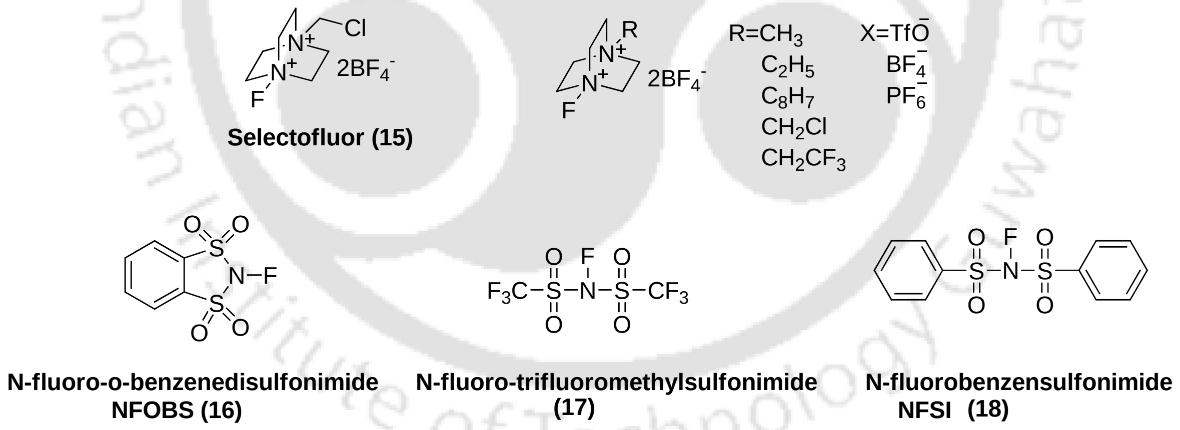


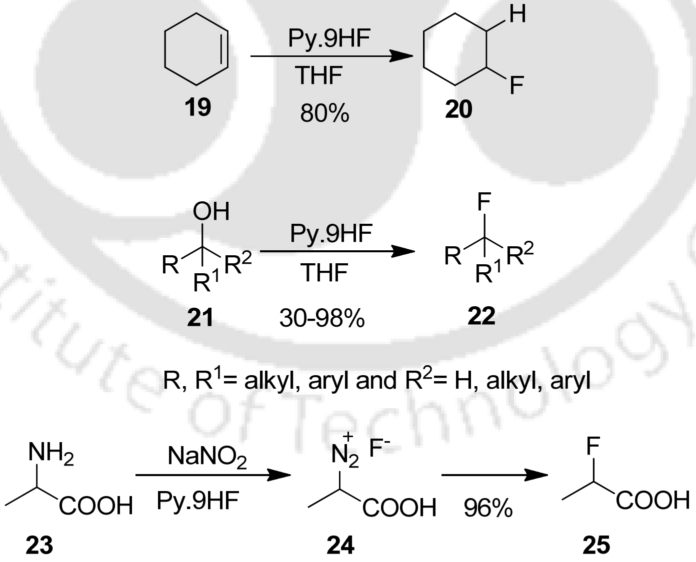
Figure 2.2.1. *Structural Examples of Electrophilic NF Reagents*

Barnette [19] described an interesting reactivity of *N*-alkyl/aryl-*N*-fluorosulfonamides **16-18** in the presence of a base with a broad variety of compounds including ketones, acids, malonates, organomagnesiums, and arenes, with fluorine transfer occurring in moderate to good yields. Unlike the pyridinium triflates and selectflluor, the fluorosulfonimides are neutral and are also easy to handle (*Figure 2.2.1*).

2.3. Nucleophilic Fluorination

The other general strategy used to fluorinate substrates, involves nucleophilic fluorination, using fluoride ion itself or reagents able to release fluoride ion. Although, a large variety of fluoride salts are commercially available, such as KF, the properties of fluoride in fluoride salts make it a hard auxiliary, since, it strongly gets solvated in the protic solvents. Also, it forms a tight ion pair in most of the aprotic solvents; therefore, the ion pairing must cope with to increase its nucleophilic properties. The availability of fluoride ion can be increased in aprotic solvents by using a bulky cation, which delocalises the positive charge and then reduces ion pairing. One good example of such a reagent is the popular tetrabutylammonium fluoride (TBAF).

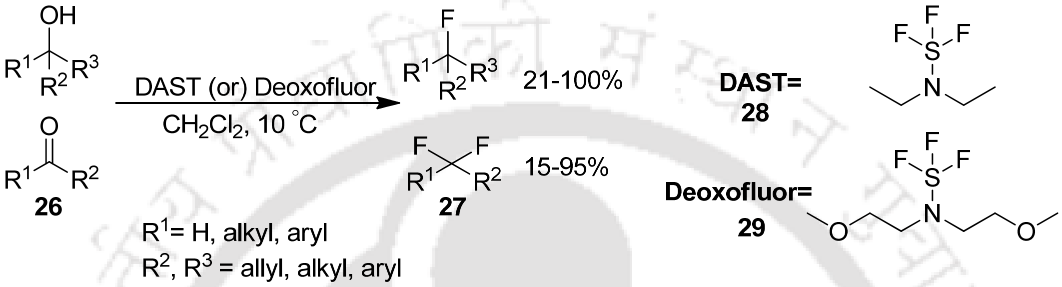
Anhydrous hydrogen fluoride (AHF) is one of the most widely used and inexpensive fluorinating agents. Hydrogen fluoride is a low boiling (19.5 °C) liquid and it is highly corrosive in nature. In order to make it easier to handle, it can be used in association with amines, such as triethylamine $Et_3N.3HF$ or pyridine (Olah's reagent; Pyridine.9HF).[20] The most frequently used among these reagents, is HF-pyridine (Olah's Reagent), applications of which (*Scheme 2.3.1*) include preparation of alkyl fluorides from alcohols or alkenes acyl fluorides from acyl chlorides and deaminative fluorination of amino acids and arylamines.



Scheme 2.3.1. *Applications of Olah's reagent*

In 1975, Middleton had reported the preparation of diethylaminosulfur trifluoride **28** popular as DAST, a powerful fluorinating reagent which could replace hydroxyl groups and carbonyl oxygens by fluorine, to generate mono and gem-difluorinated products respectively (*Scheme 2.3.2*). Lal and coworkers[22] reported in 1999, the preparation and the use of a bis(2-

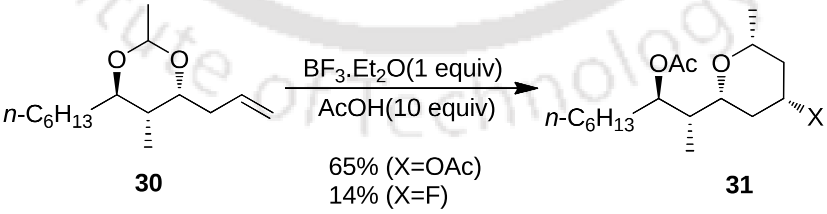
methoxyethyl)aminosulfur trifluoride **29**, known as deoxofluor, it is an improvement of the traditional deoxofluorinating agent DAST with better thermal stability (DAST is well known to undergo explosive degradation when used above 90 °C). Deoxofluor is a versatile nucleophilic fluorinating reagent with enhanced safety measures. It rapidly deoxofluorinates a wide variety of alcohols, aldehydes and ketones under milder conditions to yield the corresponding fluorinated compounds with efficiency and selectivity.



Scheme 2.3.2. *Deoxifluorination of alcohols and carbonylcompounds*

2.4. The Prins Cyclization Reaction in Fluorine Chemistry

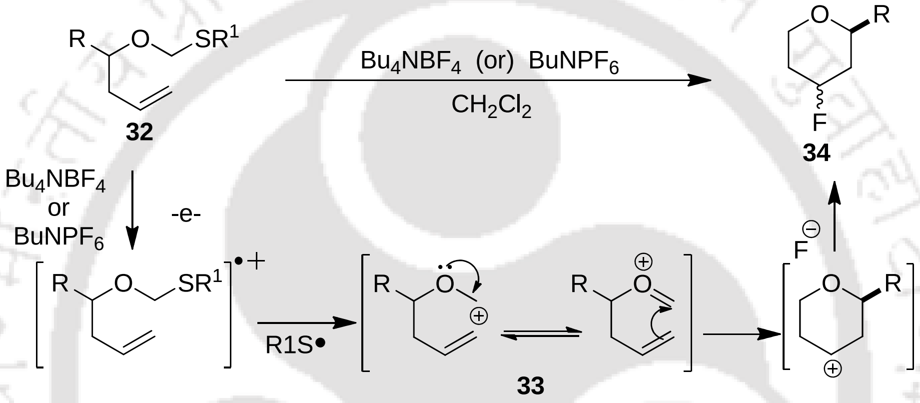
The introduction of fluorine into a tetrahydropyranyl moiety comes under the category of nucleophillic fluorination approach. Rychnovsky and coworkers first observed the formation of 4-fluorotetrahydropyran **31** as unexpected by-product of Prins cyclization reaction of acetal **30**, when $BF_3.OEt_2$ was used as a Lewis acid and especially when the nucleophile is acetic acid (*Scheme 2.4.1*). Here the fluorine atom gets incorporated due to fluoride ion quenching the carbocation intermediate.[23]



Scheme 2.4.1.

The Prins cyclization is a novel approach to C-F bond formation in organic chemistry with an advantage of not using any additional fluorinating agent. A few methods have been developed for the synthesis of fluorinated tetrahydropyrans. In most of the cases, Lewis acid which can act as a source of fluorine is opted as a choice of reagent.

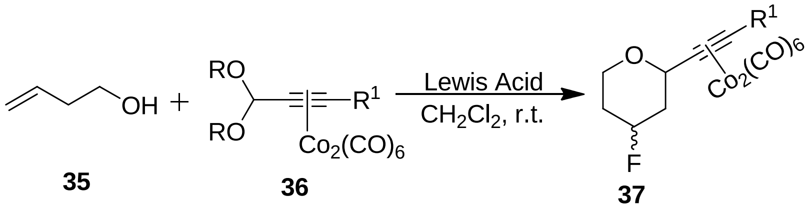
Anodic oxidation of α-organothio ethers results in the cleavage of the carbon-sulfur bond and the introduction of carbon nucleophiles onto the carbon, suggesting the effectiveness of organothio groups as electro auxiliaries (*Scheme 2.4.2*).[24a] This intramolecular cyclization was achieved by the anodic oxidation of α-phenylthio- or α-methylthioethers **32** having a carbon-carbon double bond at γ-position. The anodic oxidation in Bu_4NBF_4 or Bu_4NPF_6 in CH_2Cl_2 resulted the cleavage of the C-S bond and immediately converted to oxocarbenium ion **33**, followed by C-C bond formation with one of the olefinic carbon and the introduction of fluoride onto the other olefinic carbon to give 4-flurotetrahydropyran **34**. The similar transformation has been achieved by using triorganotin as an electroauxilary.[24b]



$R = C_7H_{15}$, $R^1 = Me$	Bu_4NBF_4	64% cis/trans = 3.3/1
$R = C_9H_{19}$, $R^1 = Ph$	Bu_4NBF_4	61% cis/trans = 4.8/1
	Bu_4NPF_6	87% cis/trans = 1.4/1

Scheme 2.4.2.

In Prins cyclization reaction, conjugated alkynyl aldehydes are inactive or give poor yields. Dicobalt hexacarbonyl complexes **36** derived from propargylic acetals undergo Lewis acid-mediated Nicholas–Prins cyclization in the presence of homoallylic alcohols. The complexation

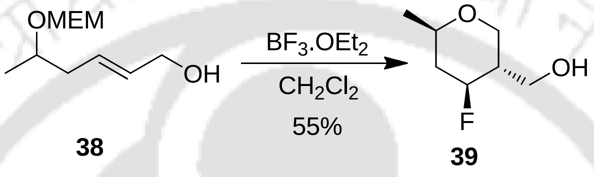


$R^1 = Ph$; R = Me	HBF_4	85%; *cis/trans* = 42/58
$R^1 = SiMe_3$; R = Et	HBF_4	80%; *cis/trans* = 41/59
$R^1 = Me$; R = Et	$BF_3.OEt_2$	52%; *cis/trans* = 83/17

Scheme 2.4.3.

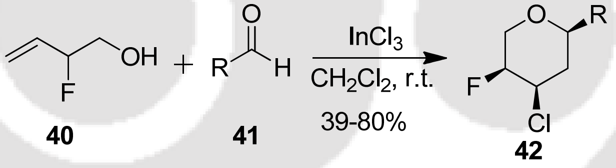
of the triple bond contributes to the suppression of the side reactions and very significantly increases both the yield and the diastereoselectivity of the reaction. The Nicholas–Prins enables the synthesis of 2-alkynyl-4-fluoro-tetrahydropyrans **37** from dicobalt hexacarbonyl complexes of propargylic acetals **36** and homoallylic alcohol **35**. Yields ranging from 52-85% were obtained using HBF_4 or $BF_3{\cdot}OEt_2$ as mediator (*Scheme 2.4.3*).[25]

Willis group reported $BF_3{\cdot}Et_2O$ mediated cyclization of (*E*)-unsaturated homoallylic MEM acetal **38** in CH_2Cl_2 for the formation of all equatorial 2,5-disubstituted 4-fluorotetrahydropyran **39** in 55% yield with good diastereoselectivity (*Scheme 2.4.4*).[26]



Scheme 2.4.4.

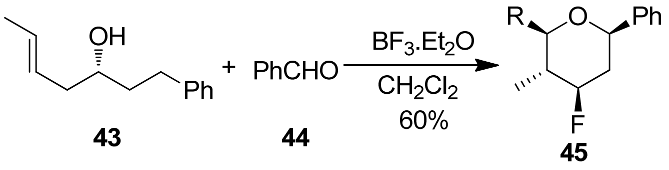
Dobbs and coworkers described Prins cyclization involving 2-fluorobut-3-en-1-ol **40** in the presence of $InCl_3$ with various aldehydes **41**. This produces 4-chloro-5-fluoropyrans **42** in high diastereoisomeric selectivity (*Scheme 2.4.5*), where chloride ion is the nucleophile. It is noteworthy that the resultant pyrans always have the fluorine in an axial position.[27]



R=CH_2Ph, nC_3H_7, C_6H_{11},Ph,$C_6H_4NO_2$

Scheme 2.4.5.

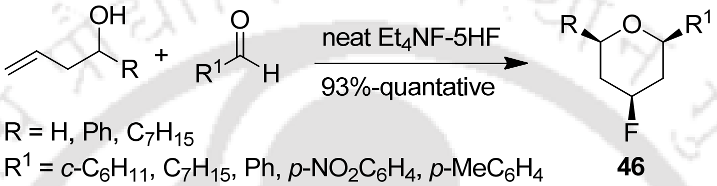
The formation of 4-fluorotetrahydropyrans **45** from homoallylalcohol **43** and aldehydes **49** mediated by $BF_3{\cdot}Et_2O$ was first investigated by Nokami[28a] and was subsequently explored to various homoallylalcohols and wide range of aldehydes to obtain series of distinct products by O'Hagan (*Scheme 2.4.6*).[28b] The reaction proceeds rapidly and produces mixture of



Scheme 2.4.6.

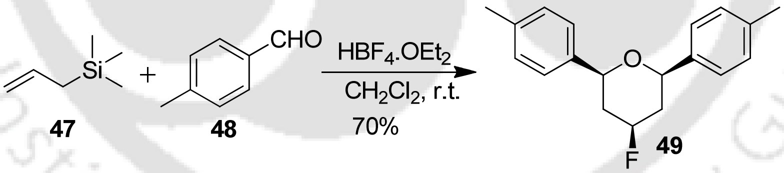
diastereomers with ratios ranging from 56:44 to 84:16 at ambient temperature, an improvement in the diastereoselectivity was achieved by performing the reaction at -20 ˚C.

Recently, Fuchigami and coworkers developed a methodology for the synthesis of 4-fluorotetrahydropyrans **46** using ionic liquid HF salts without use of any organic solvents. Quantitative yields were obtained using $Et_4NF.5HF$ (*Scheme 2.4.7*).[29] The method was extended to ketones, but it showed quite low or no reactivity. Similarly, aza-Prins cyclization proceeded smoothly to provide 4-fluoropiperidines and thia-Prins cyclization proceeded to provide 4-fluorotetrahydrothiopyrans.



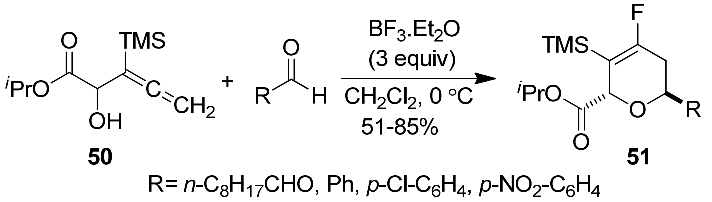
Scheme 2.4.7.

Yadav and coworkers[30] have developed a direct one-pot method for the synthesis of 4-fluorotetrahydropyrans **49** from aldehydes **48** and allyltrimethylsilane **47** by means of a tandem Hosomi-Sakurai allylation and Prins-cyclization using a ethereal solution of tetrafluoroboric acid, which provides an easy access to synthesize symmetrical 2,6-disubstituted 4-fluorotetrahydro-pyrans under milder conditions (*Scheme 2.4.8*).



Scheme 2.4.8.

Loh and coworkers[31] reported an efficient $BF_3.Et_2O$ promoted Prins cyclization for the synthesis of fluorinated 2,6-*trans* dihydropyrans **51** in moderate to good yields by using allenic alcohols **50**



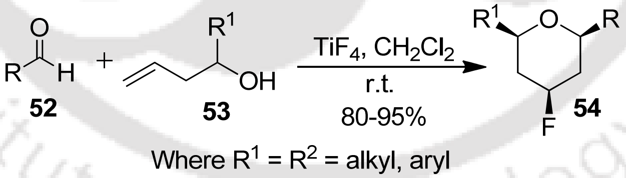
Scheme 2.4.9.

and various aldehydes as substrates, to accomplish this, the allenic alcohol bearing an ester group at α-position is necessary (*Scheme 2.4.9*).

2.5. Present Work

In spite of the several methods available in the literature for the synthesis of fluorinated tetrahydropyran via Prins cyclization, most of the procedures suffer from major drawbacks such as multistep synthesis,[27] low yield, nonselective and formation of hydroxylated by-products.[32] We are involved in the development of the new methods for the synthesis of 4-amido, 4-aryl -tetrahydropyrans using Prins cyclization via a common intermediate tetrahydropyranyl cation followed by trapping with an appropriate nucleophile.[33] Our interest in developing newer methods for the synthesis of highly substituted tetrahydropyrans by using Prins cyclization, led us to consider this approach in the development of an efficient method for the synthese of 4-fluorotetrahydropyrans. Herein we describe an efficient method for the synthesis of 4-fluorotetrahydropyrans from carbonyl compound and homoallylalcohol mediated by titanium tetrafluoride in good yields and excellent stereochemistry.

In an initial reaction, benzaldehyde (1.0 mmol) was treated with homoallylic alcohol (1.2 mmol) in presence of the titanium tetrafluoride (1.0 mmol) in CH_2Cl_2 at room temperature (*Scheme 2.5.1*). The product, 4-fluoro-2-phenyltetrahydropyran was obtained in 82% yield within 3 h. The reaction is stereoselective and all substituents are in equatorial position and are in *cis* relationship to each other.

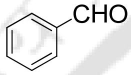
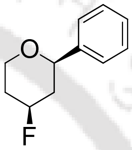
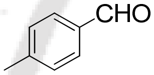
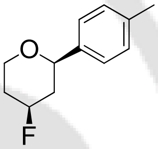
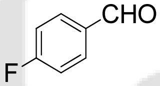
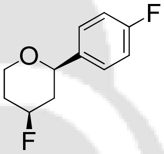
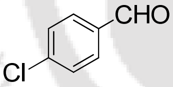
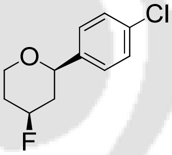
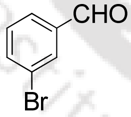
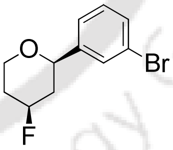
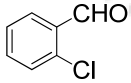
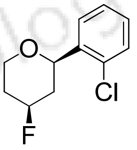
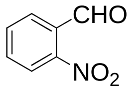
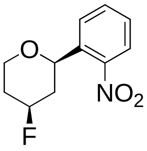
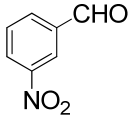
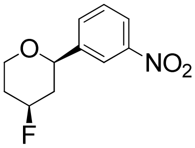


Scheme 2.5.1. *Synthesis of 2,6-disubstituted 4-fluoro tetrahydropyrans*

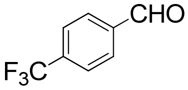
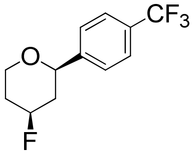
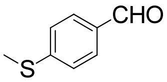
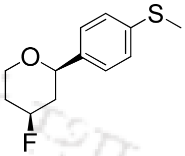
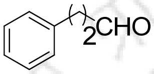
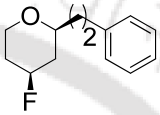
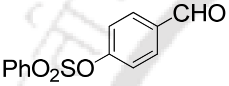
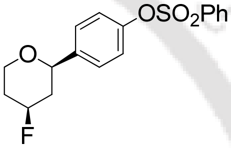
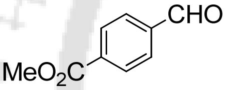
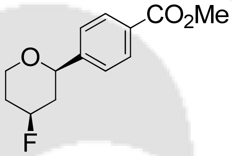
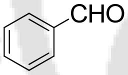
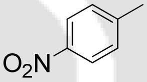
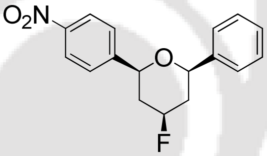
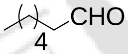
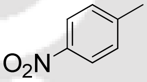
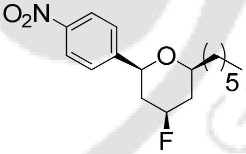
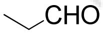
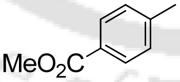
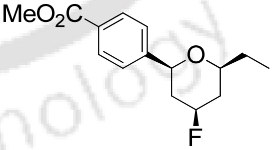
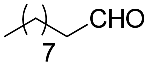
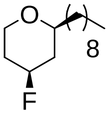
This result encouraged us to explore the scope of the reaction. First, a series of aromatic aldehydes were examined under the above reaction conditions. It was observed that, all types of aldehydes give good yields with high diastereoselectivity. The results are outlined in the (*Table 2.5.1*). The substituents on the aromatic ring have promising effect on the reactivity of the aldehydes. The aldehydes, bearing an electron-withdrawing group on aromatic ring, are comparatively more reactive and gave high yields than the aldehydes with an electron-donating group on aromatic ring. Next, we examined the reaction of homoallylalcohol with various aliphatic aldehydes under identical reaction conditions. Interestingly, they also gave good yields with all *cis*-diastereoselectivity.

In all the cases studied, the reactions proceeded rapidly at room temperature under mild conditions; 4-fluorotetrahydropyran **54a-54q** (*Table 2.5.1*) could be obtained in high purity without any side products. Both aliphatic and aromatic aldehydes give good yields with high degree of diastereoselectivity as determined from the ^{1}H and ^{13}C NMR spectrum of the crude

Table 2.5.1. synthesis of 4-fluoro tetrahydropyrans

Entry	Aldehyde **52**	Alcohol **53** R^1=	Time /h	Product **54**	Yield^a(%)
a		H	3		82
b		H	3		84
c		H	3		83
d		H	3		86
e		H	3		84
f		H	3		90
g		H	2.5		89
h		H	2.5		92

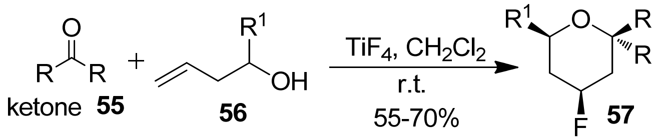
Continued……………

Entry	Aldehyde **52**	Alcohol **53** R^1=	Time /h	Product **54**	Yield[a](%)
i		H	3		90
j		H	4		85
k		H	3		90
l		H	4		80
m		H	3		90
n			2.5		92
o			3		80
p			3		80
q		H	3		85

[a]Yield refers to isolated yield. All compounds are characterised by ^{1}H, ^{13}C, ^{19}F NMR, IR spectroscopy.

product. Conformations of the di- and tri-substituted tetrahydropyrans thus obtained are of chair form and all the substituents are in equatorial position. This was confirmed by NOE experiment and finally by single crystal X-ray analysis (*Figure 2.5.1*).

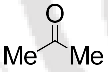
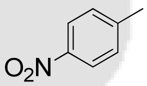
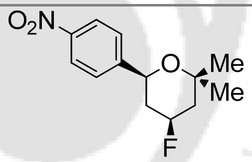
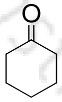
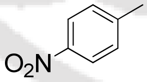
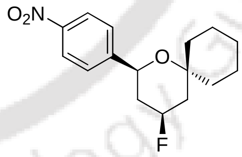
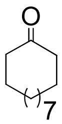
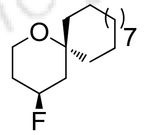
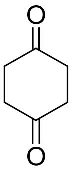
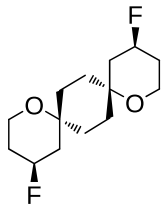
To extend the scope of the reaction, we performed the reaction with acyclic and cyclic ketones (*Scheme 2.5.2*). They were comparatively less reactive and gave moderate yields. Cyclic ketones cyclohexanone and cyclododecanone gave spirocyclic compounds **57b** and **57c** in 70% and 50% yields, respectively. Cyclic diketone such as cyclohexane- 1,4-dione gave spirocyclic compound **57d** in 55% yield.



Where R= alkyl, R^1= alkyl, aryl

Scheme 2.5.2. *Reaction of homoallylic alcohol with ketone*

Table 2.5.2. *synthesis of highly substituted 4-fluoro tetrahydropyrans*

Entry	Ketone **55**	Alcohol **56** R^1=	Time (h)	Product **57**	Yield[a] (%)
a			5		65
b			5		70
c		H	6		50
d		H	6		55

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[a]Yield refers to isolated yield. All compounds are characterised by ^{1}H, ^{13}C, ^{19}F NMR, IR spectroscopy.

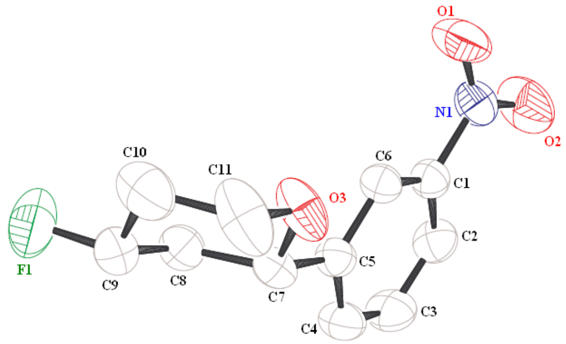
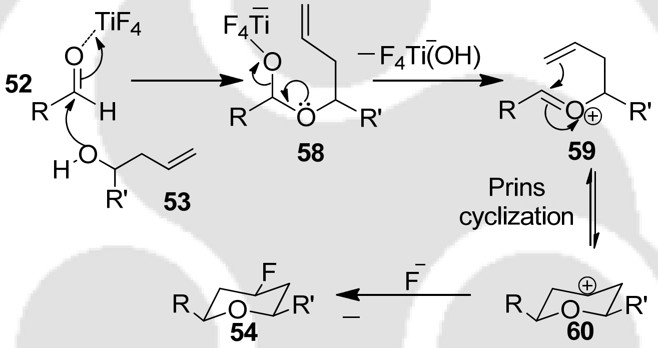


Figure 2.5.1. *ORTEP diagram of 4-Fluoro-2-(3-nitrophenyl)-tetrahydropyran*

The mechanism of the reaction can be explained as follows. Titanium tetrafluoride acts as a Lewis acid and activate the aldehydes for the nucleophilic attack by homoallylic alcohol **53** leading to the intermediate **58** and a fluoride ion (*Scheme 2.5.3*). The intermediate **58** forms oxocarbenium ion **59**, which after cyclization gives tetrahydropyranyl cation **60**. Cation **60** traps fluoride ion to give 4-fluorotetrahydropyran **54**.



Scheme 2.5.3. *Plausible mechanism of the reaction*

Conclusion:

In summary, we have demonstrated that titanium tetrafluoride can be used as a Lewis acid as well as fluorinating agent for the synthesis of fluorotetrahydropyran via Prins cyclization reaction in good to excellent yields. The advantages of this method are: the high yields in case of both aromatic and aliphatic aldehydes, high stereoselectivity, short reaction time, one-pot and non-formation of side products. The method can be extended to cyclic ketones for the synthesis of spirocyclic compounds in moderate yields.

2.6. Experimental Section

2.6.1. 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 with a Büchi B-540 melting point apparatus. 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 $CDCl_3$ or/with $[D_6]$ DMSO with tetramethylsilane as the internal standard for ^1H (400 MHz) or ^{13}C (100 MHz). HRMS spectra were recorded using WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic $Mock_{\alpha}$ 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 difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

2.6.2. Synthesis of substituted homoallyl alcohols 53n and 53p: The alcohols **53n** and **53p** were synthesized according to the literature procedures. Both the compounds are known and the analyses were consistent with the literature.[34]

2.6.3. General Procedure for the Synthesis of Compounds 54a-54q & 57a-57d:

To a mixture of aldehyde (or) ketone (1.0 eqiv) and TiF_4 (1.0 eqiv) in dry CH_2Cl_2 (2 mL) was added 3-buten-1-ol (1.2 eqiv) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 2.5 to 3h. After completion of the reaction the solvent was removed by rotary evaporator. The resultant residue was extracted with ethyl acetate (2x15 mL) and the combined organic layer was washed with brine and water, dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel) using ethyl acetate and hexane (EtOAc:hexane, 1:4) as eluent to give desired compound.

Synthesis of 4-Fluoro-2-phenyltetrahydropyran (54a, Table 2.5.1): To a mixture of benzaldehyde (200 mg, 1.88 mmol) and TiF_4 (234 mg, 1.88 mmol) in dry CH_2Cl_2 (2 mL) was added 3-buten-1-ol (163 mg, 2.26 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 2.5 h. After completion of the reaction the solvent was removed by rotary evaporator. The resultant residue was extracted with ethyl acetate (2x15 mL) and the combined organic layer was washed with brine and water, dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel) using ethyl acetate and hexane (EtOAc:hexane, 1:4) as eluent to give 278 mg (82%) of 1c as a colorless liquid.

2.7. References and Notes

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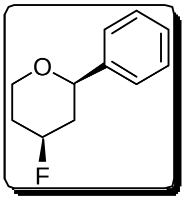
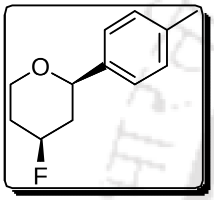
2.8. Spectral Data

(2*R,4*S**)-4-Fluoro-2-phenyltetrahydro-2*H*-pyran (54a):**



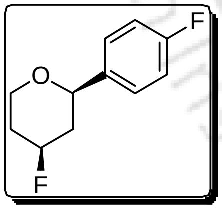
Colorless liquid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 1.70–1.90 (m, 2 H), 2.00–2.12 (1 H, m), 2.30–2.34 (1 H, m), 3.55 (1 H, dt, *J* = 12.4, 1.20 Hz), 4.17–4.22 (1 H, m), 4.30 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.68– 4.90 (1 H, m), 7.25–7.35 (5 H, m). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 33.2 (d, *J* = 17.5 Hz), 40.7 (d, *J* = 16.7 Hz), 65.7 (d, *J* = 12.2 Hz), 78.1 (d, *J* = 10.6 Hz), 89.6 (d, *J* = 176.2 Hz), 126.1, 128.1, 128.7, 141.5. **^{19}FNMR** (CDCl$_3$–C$_6$F$_6$, 376 MHz): δ -7.95 (m, –CF–). **IR**: 2959, 2854, 1375, 1160, 1081, 1040, 588, 981, 757, 588 cm^{-1}. **Anal. Calcd** for C$_{11}$H$_{13}$FO: C, 73.31; H, 7.27. Found: C, 73.38; H, 7.21

(2*R,4*S**)-4-Fluoro-2-(*p*-tolyl)tetrahydro-2*H*-pyran (54b):**



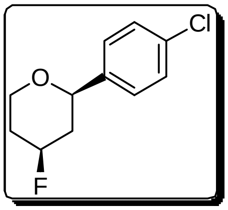
Colorless liqid; **^{1}H NMR** (CDCl$_3$, 400MHz): δ 1.71–1.90 (m, 2H), 2.07–2.13 (1 H, m,), 2.27–2.32 (1 H, m), 2.33 (3H, s), 3.55 (1 H, tt, *J* = 14.0, 2.0 Hz), 4.16–4.22 (1 H, m), 4.27 (1 H, dd, *J* = 11.6, 2.0 Hz), 4.69–4.89 (1 H, m), 7.15 (2 H, d, *J* = 8.0 Hz), 7.23 (2 H, d, *J* = 8.0 Hz). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 21.3, 33.1 (d, *J* = 17.5 Hz), 40.6 (d, *J* = 16.8 Hz), 65.6 (d, *J* = 11.4 Hz), 77.9 (d, *J* = 11.5 Hz), 89.6 (d, *J* = 175.4 Hz), 126.0, 129.3, 137.7, 138.5. **^{19}F NMR** (CDCl$_3$–C$_6$F$_6$, 376 MHz): δ -7.88 (m, –CF–). **IR**: 2959, 2855, 1372, 1160, 1082, 1040, 981, 814, 596 cm^{-1}. **Anal. Calcd** for C$_{12}$H$_{15}$FO: C, 74.20; H, 7.78. Found: C, 74.25; H, 7.81.

(2*R,4*S**)-4-Fluoro-2-(4-fluorophenyl)-tetrahydro-2*H*-pyran (54c):**



Semisloid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 1.64–1.90 (2 H, m), 2.10–2.15 (1 H, m), 2.27–2.35 (1 H, m), 3.56 (1 H, tt, *J* = 12.4,1.6 Hz), 4.17–4.24 (1 H, m), 4.30 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.71– 4.91 (1 H, m), 7.00–7.10 (2 H, m), 7.31–7.34 (2 H, m). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 33.1 (d, *J* = 17.5 Hz), 40.8 (d, *J* = 16.7 Hz), 65.6 (d, *J* = 12.2 Hz), 77.1 (d, *J* = 10.6 Hz), 89.6 (d, *J* = 175.4 Hz), 115.5 (d, *J* = 21.4 Hz), 127.8 (d, *J* = 7.6 Hz), 137.3, 162.5 (d, *J* = 244.8 Hz). **^{19}F NMR** (CDCl$_3$–C$_6$F$_6$, 376 MHz): δ -8.30 (m, –CF–), 47.14. **IR**: 2961, 2855, 1605, 1514, 1373, 1225, 1157, 1082, 1040, 982, 834, 595 cm^{-1}. **Anal. Calcd** for C$_{11}$H$_{12}$F$_2$O: C, 66.66; H, 6.10. Found: C, 66.71; H, 6.12.

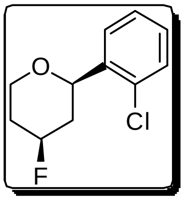
(2*R,4*S**)-4-Fluoro-2-(4-chlorophenyl)-tetrahydro-2*H*-pyran (54d):**



Semisolid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 1.71 (1 H, p, *J* = 10.0 Hz), 1.85 (1 H, dp, *J* = 11.2, 4.8 Hz), 2.10–2.17 (1 H, m), 2.28–2.37 (1 H, m), 3.56 (1 H, tt, *J* = 12.4, 1.6 Hz), 4.18–4.24 (1 H, m), 4.30 (1 H, dd, *J* = 11.6, 2.0 Hz), 4.72–4.92 (1 H, m), 7.27–7.35 (4 H, m). **^{13}C NMR** (CDCl3, 100 MHz): δ

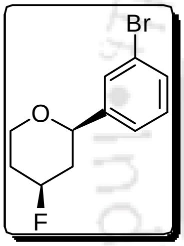
33.1 (d, *J* = 18.3 Hz), 40.6 (d, *J* = 17.6 Hz), 65.7 (d, *J* = 12.2 Hz), 77.0 (d, *J* = 10.6 Hz), 89.4 (d, *J* = 176.2 Hz), 127.4, 128.8, 133.7, 140.0. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.30 (m, –CF–). **IR**: 2961, 2855, 1494, 1371, 1160, 1084, 1041, 982, 825, 589 cm^{-1}. **Anal. Calcd** for $C_{11}H_{12}ClFO$: C, 61.55; H, 5.63. Found: C, 61.59; H, 5.65.

(2*R,4*S**)-4-Fluoro-2-(2-chlorophenyl)-tetrahydro-*2H*-pyran (54e):**



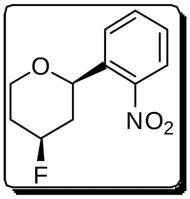
Semisolid; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.50–1.61 (1 H, m), 1.80–1.93 (1 H, m), 2.11–2.17 (1 H, m), 2.45–2.51 (1 H, m), 3.60 (1 H, tt, *J* = 14.0, 1.6 Hz), 4.20–4.26 (1 H, m), 4.70 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.75–4.95 (1 H, m), 7.20–7.26 (1 H, m), 7.28–7.35 (2 H, m), 7.55–7.57 (1 H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 33.1 (d, *J* = 18.3 Hz), 39.3 (d, *J* = 16.7 Hz), 65.6 (d, *J* = 11.4 Hz), 74.6 (d, *J* = 12.2 Hz), 89.2 (d, *J* = 176.2 Hz), 127.3, 127.4, 128.9, 129.5, 131.5, 139.2. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.20 (m, –CF–). **IR**: 2963, 2856, 1445, 1372, 1159, 1083, 982, 755, 593 cm^{-1}. **Anal. Calcd** for $C_{11}H_{12}ClFO$: C, 61.55; H, 5.63. Found: C, 61.57; H, 5.68.

(2*R,4*S**)-4-Fluoro-2-(3-bromophenyl)-tetrahydro-*2H*-pyran (54f):**



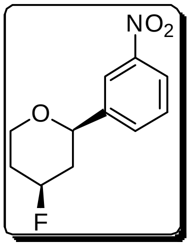
Semisolid; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.64–1.75 (1 H, m), 1.78–1.90 (1 H, m), 2.10–2.14 (1 H, m), 2.28–2.30 (1 H, m), 3.54 (1 H, tt, *J* = 12.4, 1.6 Hz), 4.17–4.23 (1 H, m), 4.28 (1 H, dd, *J* = 11.6, 2.0 Hz), 4.70–4.90 (1 H, m), 7.20–7.27 (2 H, m), 7.40–7.43 (2 H, m), 7.52 (1 H, s). **^{13}CNMR** ($CDCl_3$, 100 MHz): δ 33.0 (d, *J* = 17.6 Hz), 40.7 (d, *J* = 12.2 Hz), 65.6 (d, *J* = 12.2 Hz), 77.0 (d, *J* = 10.0 Hz), 89.2 (d, *J* = 176.2 Hz), 122.8, 124.6, 129.2, 130.2, 131.0, 143.7. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.30 (m, –CF–). **IR**: 2960, 2854, 1568, 1427, 1369, 1159, 1082, 1041, 983, 783, 695, 599 cm^{-1}. **Anal. Calcd** for $C_{11}H_{12}BrFO$: C, 50.99; H, 4.67. Found: C, 51.05; H, 4.70.

(2*R,4*S**)-4-Fluoro-2-(2-nitrophenyl)-tetrahydro-*2H*-pyran (54g):**



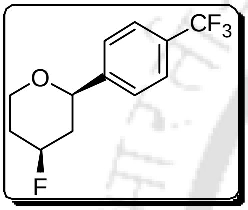
Solid, mp 86-88 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.57–1.67 (1 H, m), 1.81–1.93 (1 H, m), 2.12–2.18 (1H,m), 2.58–2.65 (1 H,m), 3.58 (1 H, tt, *J* = 12.4, 1.6 Hz), 4.17–4.24 (1 H, m), 4.70 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.78–4.98 (1 H, m), 4.90 (1 H, dd, J = 12.8, 1.6 Hz), 7.42–7.47 (1 H, m), 7.64–7.68 (1 H, m), 7.81 (1 H, d, J = 8.0 Hz), 7.94 (1 H, d, J = 8.0 Hz). **^{13}CNMR** ($CDCl_3$, 100MHz): δ 33.0 (d, J = 18.3 Hz), 39.3(d, J = 18.3 Hz), 65.7 (d, J = 12.2 Hz), 73.5 (d, J = 12.2 Hz), 88.9 (d, J = 176.1 Hz), 124.5, 128.2, 128.6, 133.9, 137.0, 147.4. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.37(m, –CF–). **IR**: 2936, 2858, 1527, 1348, 1158, 1080, 1038, 982, 746, 595 cm^{-1}. **Anal. Calcd** for $C_{11}H_{12}FNO_3$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.70; H, 5.35; N, 6.26.

(2*R,4*S**)-4-Fluoro-2-(3-nitrophenyl)-tetrahydro-*2H*-pyran (54h):**



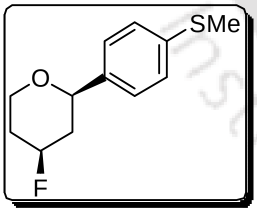
Solid, mp 94-96 °C; ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 1.65–1.76 (1 H, m), 1.80–1.94 (1 H, m), 2.12–2.19 (1 H, m), 2.37–2.43 (1 H, m), 3.59 (1 H, tt, *J* = 14.4, 2.0 Hz), 4.22–4.28 (1 H, m), 4.44 (1 H, dd, *J* = 11.6, 2.0 Hz), 4.75–4.95 (1 H, m), 7.53 (1 H, t, *J* = 8.0 Hz), 7.67 (1 H, d, *J* = 8.0 Hz), 8.15 (1 H, d, *J* = 8.0 Hz), 8.25 (1 H, s). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 32.9 (d, *J* = 18.3 Hz), 40.6 (d, *J* = 17.5 Hz), 65.6 (d, *J* = 12.2 Hz), 76.6 (d, *J* = 11.4 Hz), 89.0 (d, *J* = 176.9 Hz), 121.1, 122.9, 129.6, 131.9, 143.7, 148.5. ^{19}**F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.71 (d, *J* = 48.5 Hz, –CF–). **IR**: 2959, 2858, 1531, 1352, 1160, 1080, 1042, 985, 736, 595 cm^{-1}. **Anal. Calcd** for $C_{11}H_{12}FNO_3$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.62; H, 5.42; 6.25.

(2*R,4*S**)-4-Fluoro-2-(4-trifluoromethylphenyl)-tetrahydro-*2H*-pyran (54i):**



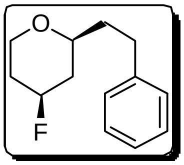
Semi solid; ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 1.63–1.75 (m, 1 H), 1.80–1.92 (1 H, m), 2.10–2.20 (1 H, m), 2.32–2.39 (1 H, m), 3.57 (1 H, tt, *J* = 14.0, 2.0 Hz), 4.20–4.26 (1 H, m), 4.37 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.73–4.93 (1 H, m), 7.46 (2 H, d, *J* = 8.0 Hz), 7.61 (2 H, d, *J* = 8.0 Hz). ^{13}**C NMR** (CDCl3, 100 MHz): δ 33.0 (d, *J* = 17.6 Hz), 39.3 (d, *J* = 17.5 Hz), 65.6 (d, *J* = 12.2 Hz), 77.0 (d, *J* = 11.5 Hz), 89.0 (d, *J* = 177.0 Hz), 124 (q, *J* = 271.8 Hz), 125.7, 126.2, 130.0 (q, *J* = 32.1 Hz), 145.5. ^{19}**F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.29 (m, – CF–), 99.30 (s, 3F). **IR**: 2963, 2857, 1622, 1326, 1162, 1126, 1099, 1068, 984, 834, 608 cm^{-1}. **Anal. Calcd** for $C_{12}H_{12}F_4O$: C, 58.07; H, 4.87. Found: C, 58.12; H, 4.90.

(2*R,4*S**)-4-Fluoro-2-(4-methylsulfanylphenyl)-tetrahydro-*2H*-pyran (54j):**



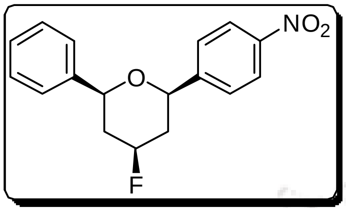
Semisolid; ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 1.68–1.77 (1 H, m), 1.80–1.90 (1 H, m), 2.00–2.15 (1 H, m), 2.28–2.34 (1 H, m), 2.45 (3 H, s), 3.57 (1 H, tt, *J* = 12.4, 2.0 Hz), 4.16–4.22 (1 H, m), 4.28 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.70–4.90 (1 H, m), 7.23–7.28 (4 H, m). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 16.1, 33.1 (d, *J* = 17.5 Hz), 40.6 (d, *J* = 16.8 Hz), 65.6 (d, *J* = 12.2 Hz), 77.0 (d, *J* = 12.0 Hz), 89.5 (d, *J* = 176.1 Hz), 126.6, 126.9, 138.2, 138.4. ^{19}**F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.00 (m, –CF–). **IR**: 2959, 2854, 1496, 1371, 1160, 1082, 1039, 981, 818, 590 cm^{-1}. **Anal. Calcd** for $C_{12}H_{15}FOS$: C, 63.69; H, 6.68. Found: C, 63.72; H, 6.66.

(2*S,4*S**)- 4-Fluoro-2-phenethyl-tetrahydro-*2H*-pyran (54k):**



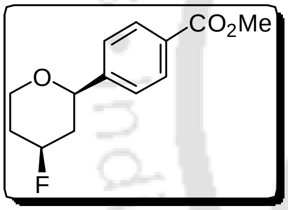
Semisolid; ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 1.45 (1 H, p, *J* = 11.2 Hz), 1.65–1.78 (2 H, m), 1.86–1.95 (1 H, m), 1.98–2.10 (2 H, m), 2.63–2.71 (1 H,m), 2.74–2.82 (1 H, m), 3.20–3.27 (1H, m), 3.35 (1 H, tt, *J* = 12.4, 1.6 Hz), 4.00–4.12 (1 H, m), 4.52–4.71 (1 H, m), 7.16– 7.20 (2 H, m), 7.26–7.30 (2 H, m). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 31.8, 33.3 (d, J = 17.5 Hz), 37.9, 38.9 (d, J = 16.8 Hz), 65.1 (d, J = 12.2 Hz), 74.8 (d, J = 10.7 Hz), 89.4 (d, J = 174.7 Hz), 126.1, 128.6, 128.7, 142.0. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -7.75 (m, –CF–). **IR**: 2955, 2853, 1454, 1365, 1164, 1084, 1047, 1009, 994, 700, 571 cm^{-1}. **Anal. Calcd** for $C_{13}H_{17}FO$: C, 74.97; H, 8.23. Found: C, 74.95; H, 8.27.

(2*R,4*S**,6S*)-4-Fluoro-2-(4-nitrophenyl)-6-phenyltetrahydro-*2H*-pyran (54l):**



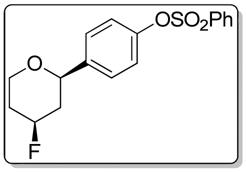
Semisolid; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.76 (1 H, p, J = 11.6Hz), 1.86 (1H, p, J = 11.6 Hz), 2.46–2.51 (2 H, m), 4.60 (1 H, dd, J = 11.6, 2.0 Hz), 4.70 (1H,dd, J = 12.0, 2.0 Hz),4.93–5.14 (1 H, m), 7.31–7.45 (5 H, m), 7.60 (2 H, d, J = 9.2 Hz), 8.23 (2 H, d, J = 9.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 40.2 (d, J = 12.9 Hz), 40.4 (d, J = 13.7 Hz), 76.4 (d, J = 12.2 Hz), 77.7 d, J = 17.6 Hz), 89.2 (d, J = 178.5 Hz), 123.9, 126.1, 126.8, 128.3, 128.8, 141.0, 147.7, 148.7. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -9.50 (d, J = 48.5 Hz, – CF–). **IR**: 2926, 2854, 1520, 1347, 1158, 1073, 1054, 852, 698, 586 cm^{-1}. **Anal. Calcd** for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.80; H, 5.38; N, 4.62.

Methyl 4-((2*R,4*S**)-4-fluorotetrahydro-*2H*-pyran-2-yl)benzoate (54m):**



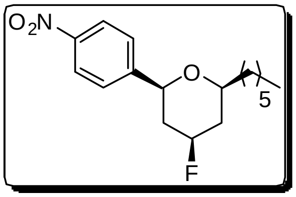
Solid, mp 80-82 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.76 (1 H, p, J = 11.2 Hz), 1.80–1.92 (1 H, m), 2.11–2.17 (1 H, m), 2.31–2.39 (1 H, m), 3.57 (1 H, dt, J = 12.8, 2.0 Hz), 3.91 (3 H, s), 4.20–4.26 (1 H, m), 4.39 (1 H, dd, J = 11.6, 1.6 Hz), 4.72–4.93 (1 H, m), 7.42 (2 H, d, J = 8.4 Hz), 8.00 (2 H, d, J = 8.4 Hz). **^{13}CNMR** ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 18.3 Hz), 40.7 (d, J = 17.5 Hz), 52.3, 65.6 (d, J = 11.4 Hz), 77.0 (d, J = 12.1 Hz), 89.3 (d, J = 176.1 Hz), 125.8, 129.7, 129.9, 146.5, 167.0. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.24 (m, –CF–). **IR**: 2961, 2858, 1714, 1358, 1279, 1159, 1081, 1033, 960, 772, 590 **cm_1**. **Anal. Calcd** for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.58; H, 6.28.

4-((2*R,4*S**)-4-Fluorotetrahydro-*2H*-pyran-2-yl)phenyl benzenesulfonate (54n):**



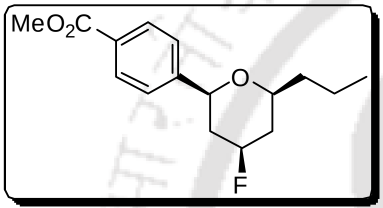
Semisolid; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.69 (1 H, p, J = 11.6 Hz), 1.75–1.89 (1 H, m), 2.10–2.14 (1 H, m), 2.27–2.35 (1 H, m), 3.54 (1 H, dt, J = 12.4, 1.6 Hz), 4.16–4.22 (1 H, m), 4.29 (1 H, dd, J = 11.2, 1.6 Hz), 4.69–4.89 (1 H, m), 6.96 (2 H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.50–7.54 (2 H, m), 7.64–7.68 (1 H, m), 7.82 (2 H, d, J = 8.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 33.0 (d, J = 16.8 Hz), 40.7 (d, J = 17.6 Hz), 65.6 (d, J = 12.2 Hz), 77.0 (d, J = 18.3 Hz), 89.3 (d, J = 175.4 Hz), 122.6, 127.3, 128.7, 129.4, 134.5, 135.6, 140.6, 149.2. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -8.36 (m, –CF–). **IR**: 3079, 2980, 2855, 1705, 1605, 1520, 1346, 1198, 1108, 1058, 854, 700, 529 cm^{-1}. **Anal. Calcd** for $C_{17}H_{17}FO_4S$: C, 60.70; H, 5.09. Found: C, 60.78; H, 5.12.

(2*S,4*R**,6*S**)-4-Fluoro-2-hexyl-6-(4-nitrophenyl)tetrahydro-*2H*-pyran (54o):**



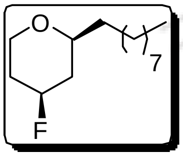
Semisolid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 0.86 (3 H, t, *J* = 7.2 Hz), 1.18–1.40 (10 H, m), 1.42–1.72 (2 H, m), 2.14–2.20 (1 H, m), 2.20–2.40 (1 H, m), 3.45–3.51 (1 H, m), 4.44(1 H, dd, *J* = 11.6, 1.6 Hz), 4.72–4.92 (1 H, m), 7.50 (2 H, d, *J* = 8.4 Hz), 8.17 (2 H, d, *J* = 8.4 Hz). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 14.2, 22.7, 25.5, 29.4, 31.9, 36.0, 38.2 (d, *J* = 16.8 Hz), 40.4 (d, *J* = 17.5 Hz), 75.6 (d, *J* = 12.6 Hz), 76.9 (d, *J* = 16.2 Hz), 89.3 (d, *J* = 176.2 Hz), 123.8, 126.6, 147.5, 149.2. **^{19}F NMR** (CDCl$_3$–C$_6$F$_6$, 376 MHz): δ -8.91 (m, –CF–). **IR**: 2930, 2857, 1605, 1521, 1348, 1162, 1079, 1014, 854, 750, 602 cm^{-1}. **Anal. Calcd** for C$_{17}$H$_{24}$FNO$_3$: C, 66.00; H, 7.82; N, 4.53. Found: C, 65.97; H, 7.86; N, 4.57.

Methyl 4-((2*S,4*R**,6*S**)-4-fluoro-6-propyltetrahydro-*2H*-pyran-2-yl)benzoate (54p):**



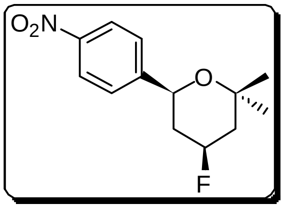
Semisolid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 0.94 (3 H, t, *J* = 6.8 Hz), 1.30–1.75 (6H, m), 2.10–2.20 (1H,m), 2.30–2.40 (1 H, m), 3.40–3.52 (1 H, m), 3.90 (3H, s), 4.40 (1 H, dd, *J* = 11.6, 1.6 Hz), 4.72– 4.93(1 H, m), 7.43(2 H, d, *J* = 8.4 Hz), 8.01 (2 H, d, *J* = 8.4 Hz). **^{13}CNMR** (CDCl$_3$, 100 MHz): δ 14.2, 18.8, 38.2, 38.3 (d, *J* = 22.1 Hz), 40.4 (d, *J* = 16.7 Hz), 52.3, 75.3 (d, *J* = 10.7 Hz), 76.3 (d, *J* = 11.5 Hz), 88.6 (d, *J* = 175.4 Hz),125.9, 129.5,129.9,147.0,167.1. **^{19}FNMR** (CDCl$_3$–C$_6$F$_6$, 376MHz): δ -8.68 (m, –CF–). **IR**: 2957, 2872, 1724, 1614, 1435, 1368, 1279, 1160, 1111, 1077, 1019, 856, 769, 705, 603 cm^{-1}. **Anal. Calcd** for C$_{16}$H$_{21}$FO$_3$: C, 68.55; H, 7.55. Found: C, 68.57; H, 7.52.

(2*S,4*S**)-4-Fluoro-2-nonyltetrahydro-*2H*-pyran (54q):**



Semisolid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 0.88 (3 H, t, *J* = 6.8 Hz), 1.10–1.80 (17 H, m), 1.99–2.11 (2 H, m), 2.17–2.41 (1 H, m), 3.20– 3.30 (1 H, m), 3.31–3.44 (1 H, m), 3.97–4.10 (1 H, m), 4.50–4.80 (1 H, m). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 14.3, 22.9, 25.6, 29.4, 29.5, 29.6, 29.8, 32.1, 33.3 (d, *J* = 17.5 Hz), 36.3, 39.0 (d, *J* = 16.8 Hz), 65.1 (d, *J* = 11.4 Hz), 76.0 (d, *J* = 10.7 Hz), 89.6 (d, *J* = 175.4 Hz). **^{19}F NMR** (CDCl$_3$–C$_6$F$_6$, 376 MHz): δ -7.54 (m, –CF–). **IR**: 2926, 2855, 1465, 1367, 1164, 1084, 1010, 869, 722, 609 cm^{-1}. **Anal. Calcd** for C$_{14}$H$_{27}$FO: C, 72.99; H, 11.81. Found: C, 72.97; H, 11.85.

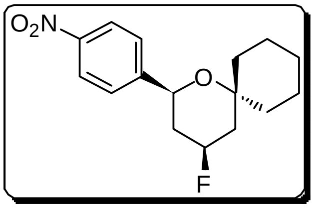
(4*S,6*S**)-4-Fluoro-2,2-dimethyl-6-(4-nitrophenyl)tetrahydro-*2H*-pyran (57a):**



Semisolid; **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 1.31 (3 H, s), 1.41 (3 H, s), 1.47–1.64 (2 H, m), 2.11–2.17 (1 H, m), 2.30-2.40 (1 H, m), 4.71 (1 H, dd, *J* = 11.6, 1.6 Hz), 4.90–5.11 (1 H, m), 7.55 (2 H, d, *J* = 8.8 Hz), 8.21 (2 H, d, *J* = 8.8 Hz). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 23.3, 31.9, 40.8 (d, *J* = 17.6 Hz), 42.7 (d, *J* = 16.0 Hz), 70.6 (d, *J* = 11.4 Hz), 74.3 (d, *J* = 11.4 Hz), 87.7 (d, *J* = 173.9 Hz), 123.9, 126.9, 147.5, 149.6. **^{19}F NMR** (CDCl$_3$–C$_6$F$_6$, 376 MHz): δ -13.10 (m, –

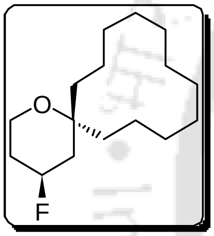
CF–). **IR**: 2977, 2857, 1602, 1520, 1349, 1191, 1076, 1015, 854, 698, 592 cm^{-1}. **Anal. Calcd** for $C_{13}H_{16}FNO_3$: C, 61.65; H, 6.37; N, 5.53. Found: C, 61.68; H, 6.41; N, 5.49.

(2*S,4*S**)-4-Fluoro-2-(4-nitrophenyl)-1-oxaspiro[5.5]undecane (57b):**



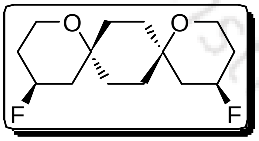
Semisolid; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.25–1.39 (2 H, m), 1.41–1.60 (7 H, m), 1.70–1.80 (2 H, m), 1.95–2.00 (1 H, m), 2.15–2.21 (1 H, m), 2.38–2.44 (1 H, m), 4.67 (1 H, dd, *J* = 12.0, 2.0 Hz), 4.92–5.12 (1 H, m), 7.57 (2 H, d, *J* = 8.4 Hz), 8.21 (2 H, d, *J* = 8.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 21.5, 21.9, 26.0, 31.3, 40.3, 40.6 (d, *J* = 17.6 Hz), 42.1 (d, *J* = 16.0 Hz), 69.0 (d, *J* = 11.5 Hz), 75.1 (d, *J* = 11.5 Hz), 87.4 (d, *J* = 173.1 Hz), 123.8, 126.7, 147.4, 149.9. **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -12.88 (m, –CF–). **IR**: 2933, 2858, 1601, 1520, 1348, 1174, 1075, 858, 697, 560 cm^{-1}. **Anal. Calcd** for $C_{16}H_{20}FNO_3$: C, 65.51; H, 6.87; N, 4.78. Found: C, 65.56; H, 6.91; N, 4.75.

4-Fluoro-1-oxaspiro[5.11]heptadecane (57c):



Semisolid; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.23–1.40 (18 H, m), 1.46–1.55 (2 H, m), 1.59–1.77 (2 H, m), 1.80–1.98 (2 H, m), 2.42– 2.45 (2H, m), 3.51–3.58 (1H, m), 3.78–3.90 (1H,m), 4.74–4.94 (1 H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 18.7, 19.2, 22.1, 22.6, 22.8, 24.5, 24.8, 26.3, 26.5, 30.1, 32.6 (d, *J* = 18.3 Hz), 40.4 (d, *J* = 16.0 Hz), 40.5 (d, *J* = 9.90 Hz), 58.3 (d, *J* = 11.0 Hz), 87.8 (d, *J* = 170.0 Hz). **^{19}F NMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -12.83 (m, –CF–). **IR**: 2930, 2863, 1470, 1362, 1205, 1130, 1074, 943 722, 571 cm^{-1}. **Anal. Calcd** for $C_{16}H_{29}FO$: C, 74.95; H, 11.40. Found: C, 74.92; H, 11.44.

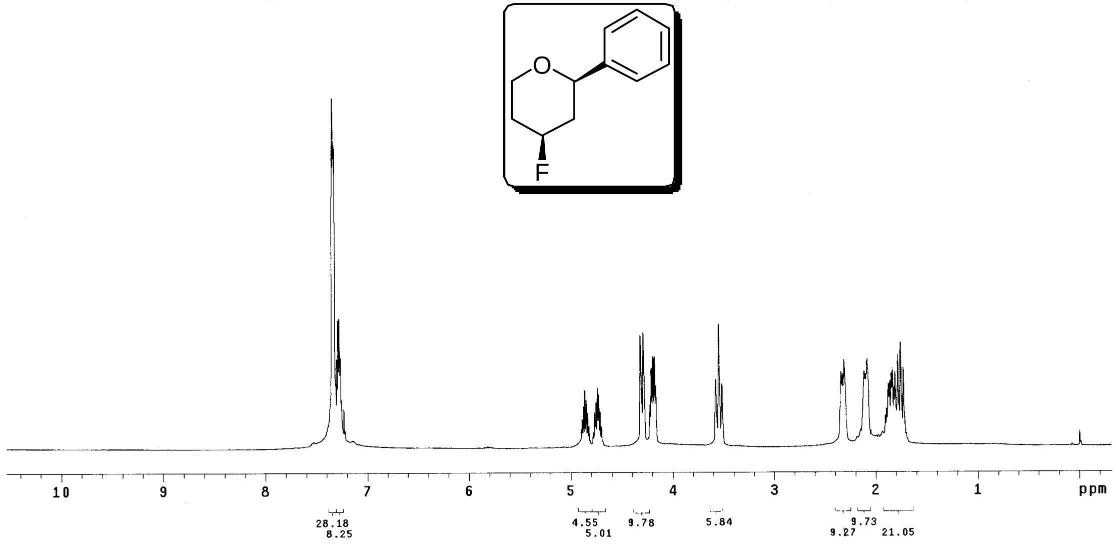
4,13-Difluoro-1,10-dioxa-dispiro[5.2.5.2]hexadecane (57d):

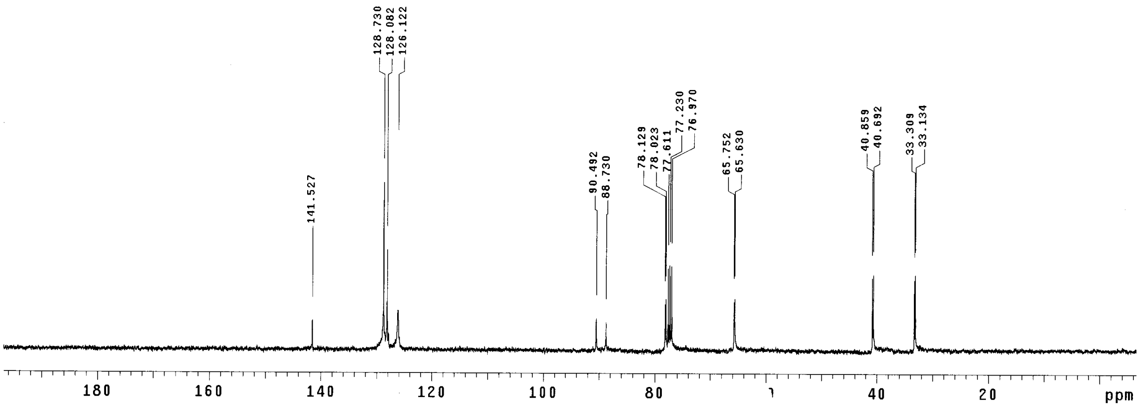


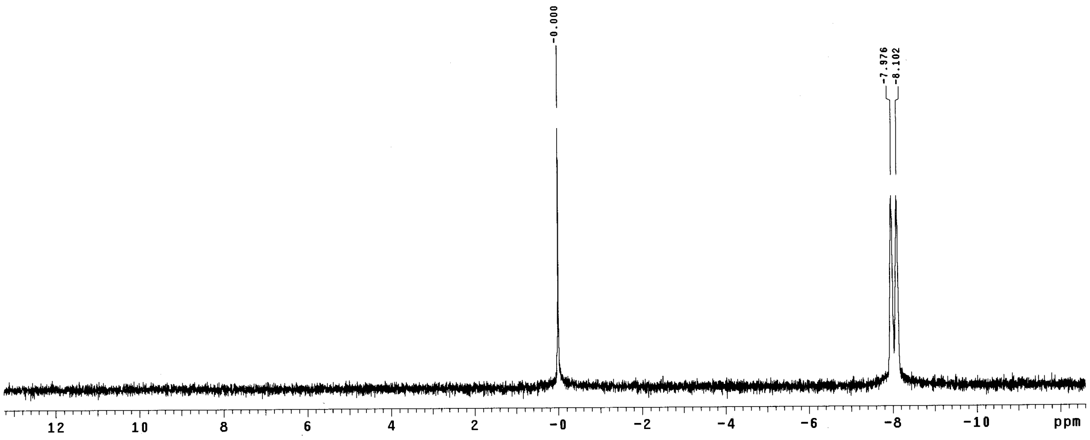
Solid, mp 113–114 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.39– 1.82 (8H,m), 1.84–2.00 (6 H, m), 1.95–2.00 (2 H, m), 3.44–3.60 (2 H, m), 3.75–3.86 (2 H, m), 4.75–4.94 (2 H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 28.4, 31.4, 32.4 (d, *J* = 18.3 Hz), 42.5 (d, *J* = 17.5 Hz), 57.7 (d, *J* = 6.9 Hz), 72.4 (d, *J* = 6.1 Hz), 87.5 (d, *J* = 11.5 Hz), 87.4 (d, *J* = 171.6 Hz). **^{19}FNMR** ($CDCl_3$–C_6F_6, 376 MHz): δ -13.17 (m,–CF–). **IR**: 2935, 2858, 1639, 1379, 1145, 1068, 1028, 825, 729, 537 cm^{-1}. **Anal. Calcd** for $C_{14}H_{22}F_2O_2$: C, 64.59; H, 8.52. Found: C, 64.62; H, 8.54.

2.9. Selected Spectra of 4-fluorotetrahydropyrans

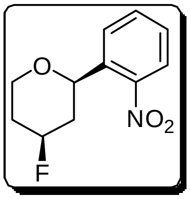
^{1}H, ^{13}C and ^{19}F NMR spectra of **(2*R***,**4*S***)-4-Fluoro-2-phenyltetrahydro-*2H*-pyran**

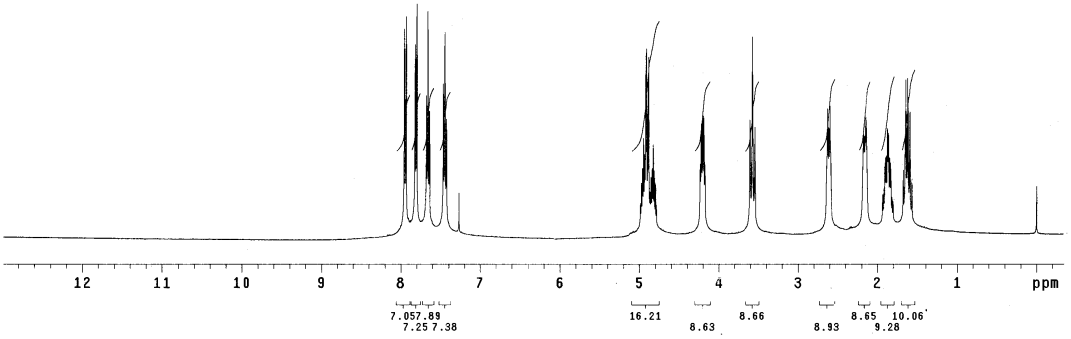


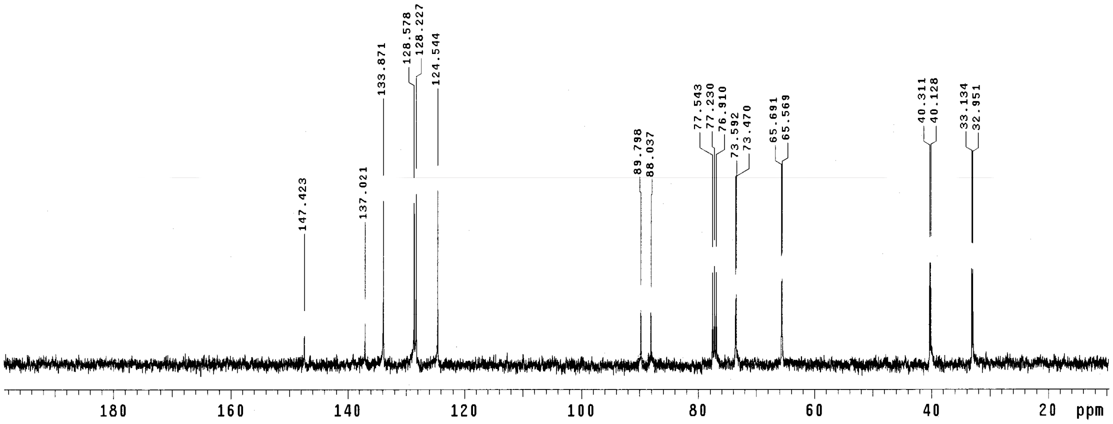


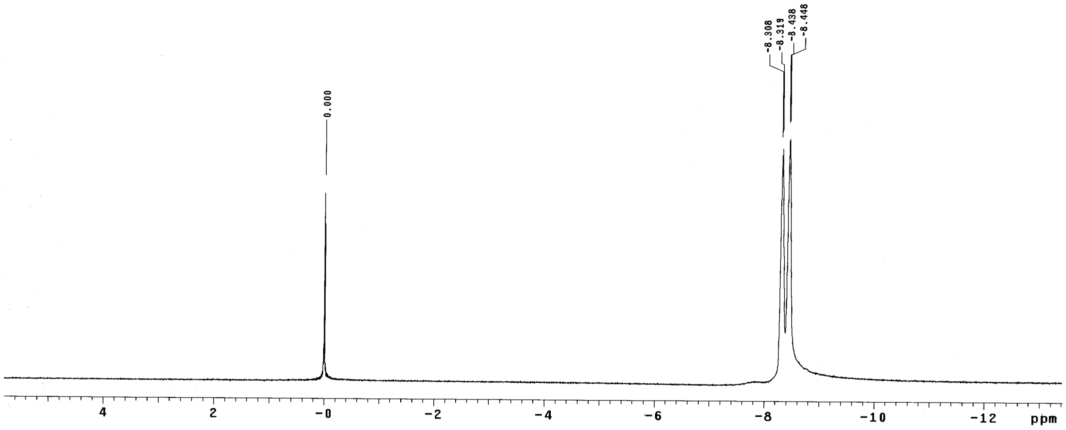


^{1}H, ^{13}C and ^{19}F NMR spectra of **(2*R**,4*S**)-4-Fluoro-2-(2-nitrophenyl)tetrahydro-*2H*-pyran**

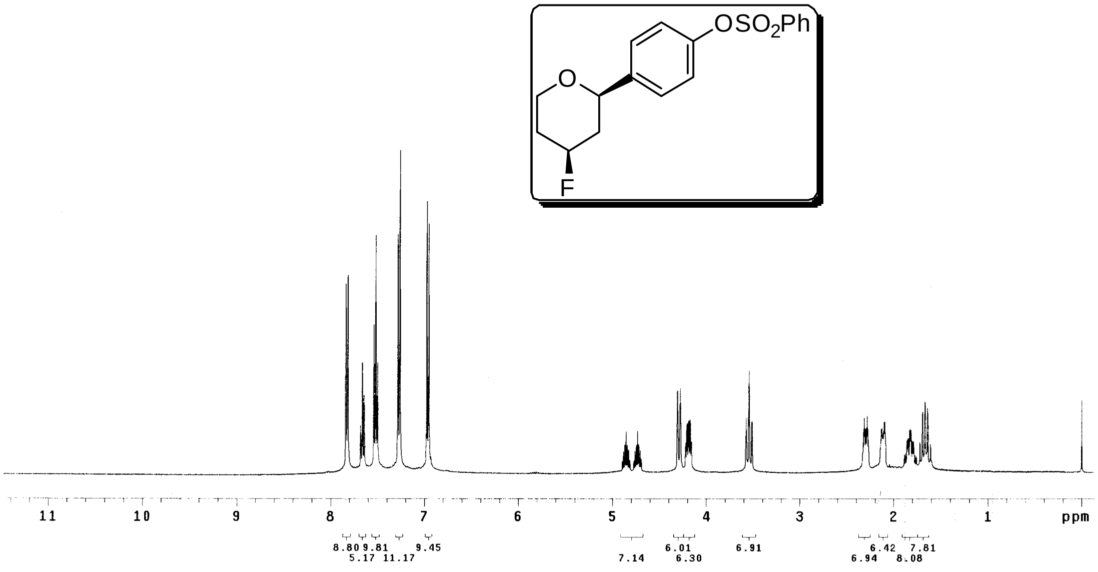


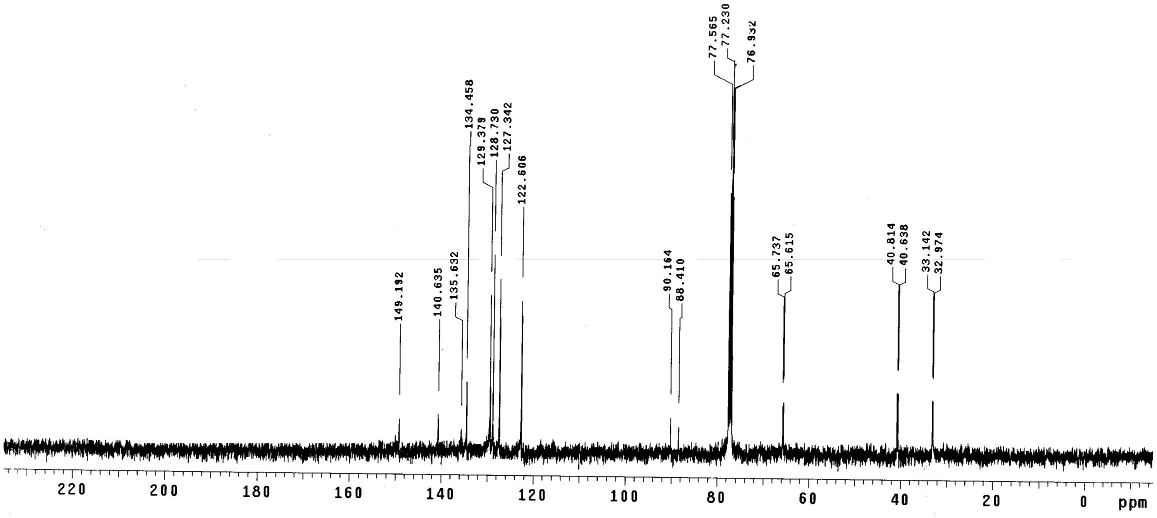


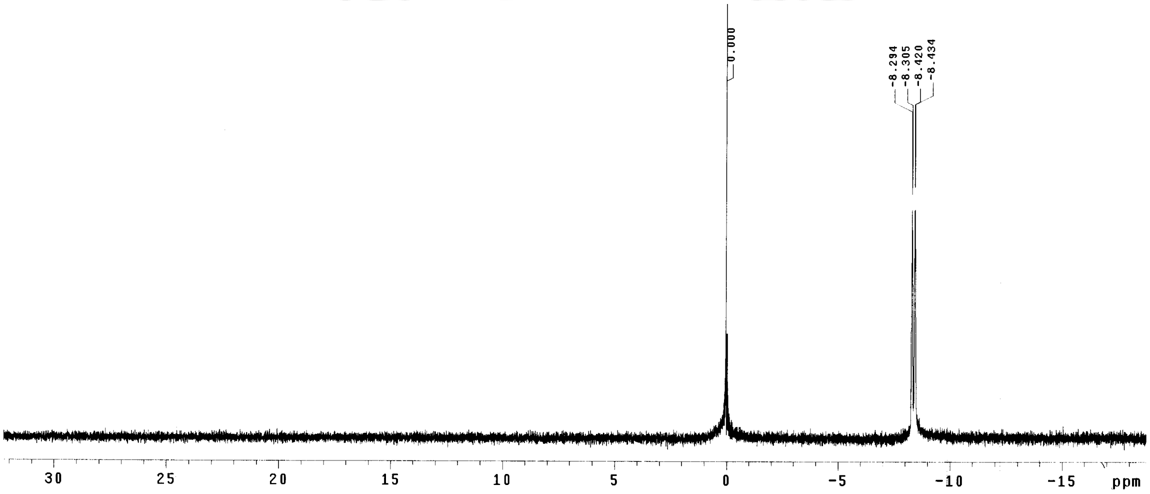




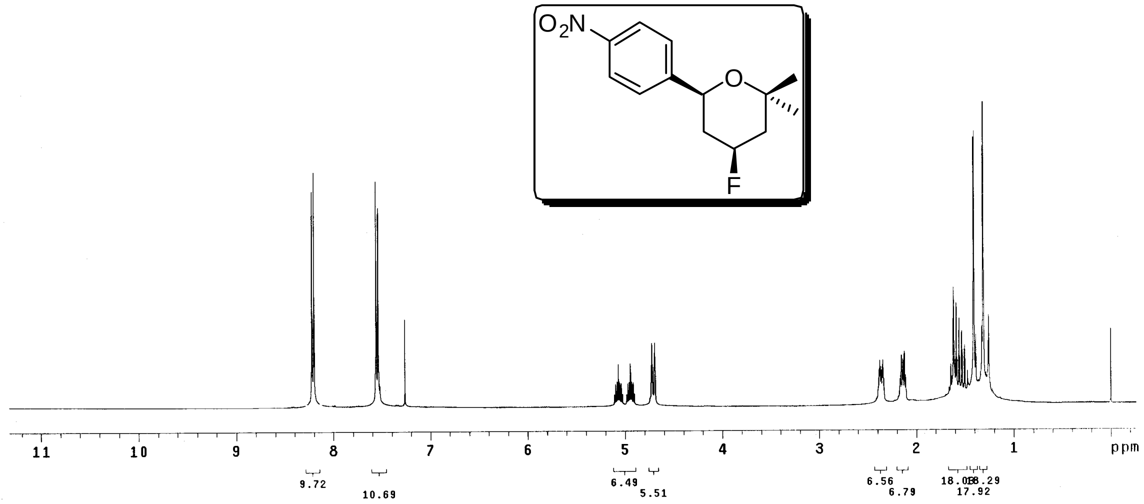
^{1}H, ^{13}C and ^{19}F NMR spectra of **4-((2*R**,4*S**)-4-Fluorotetrahydro-2*H*-pyran-2-yl)phenyl benzenesulfonate**

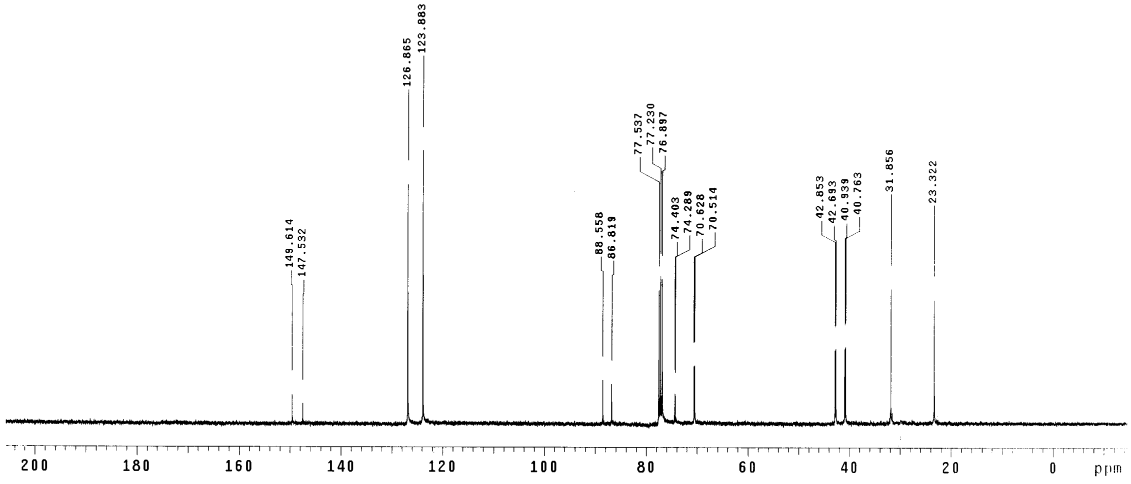


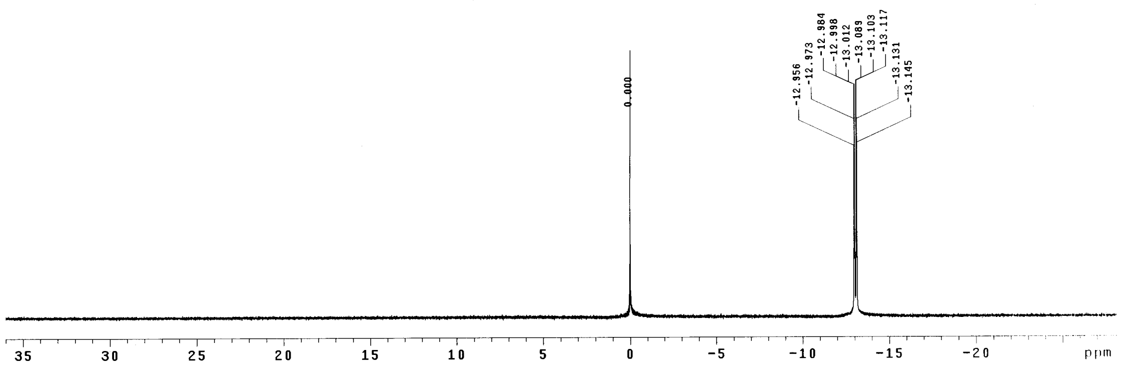




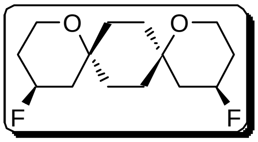
^{1}H, ^{13}C and ^{19}F NMR spectra of **(4*S**,6*S**)-4-Fluoro-2,2-dimethyl-6-(4-nitrophenyl)-tetrahydro-*2H*-pyran**

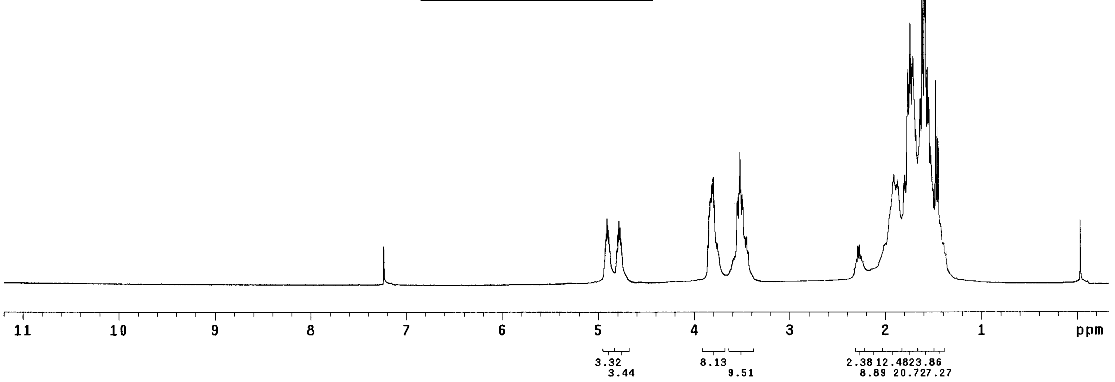


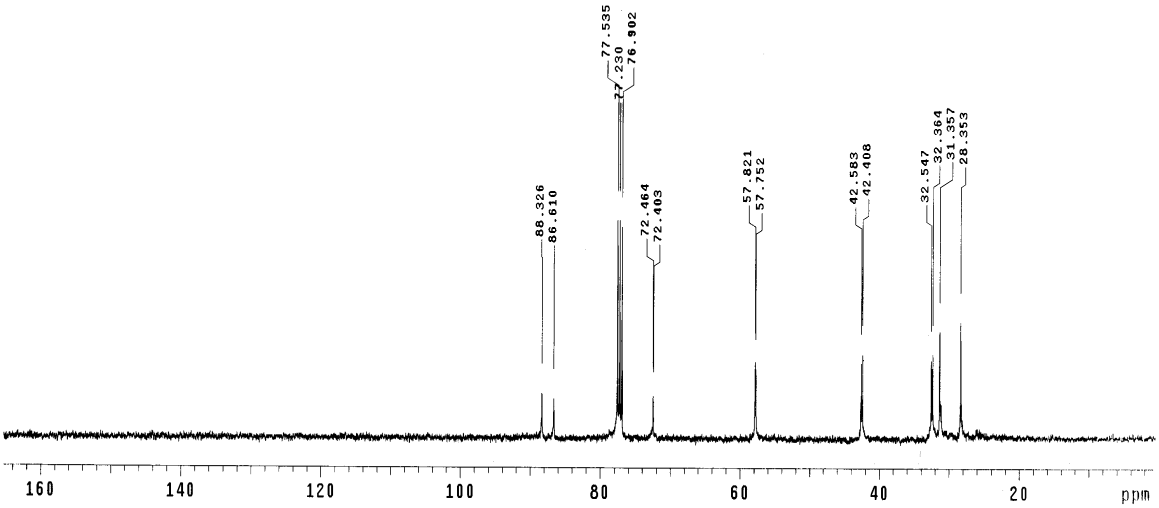


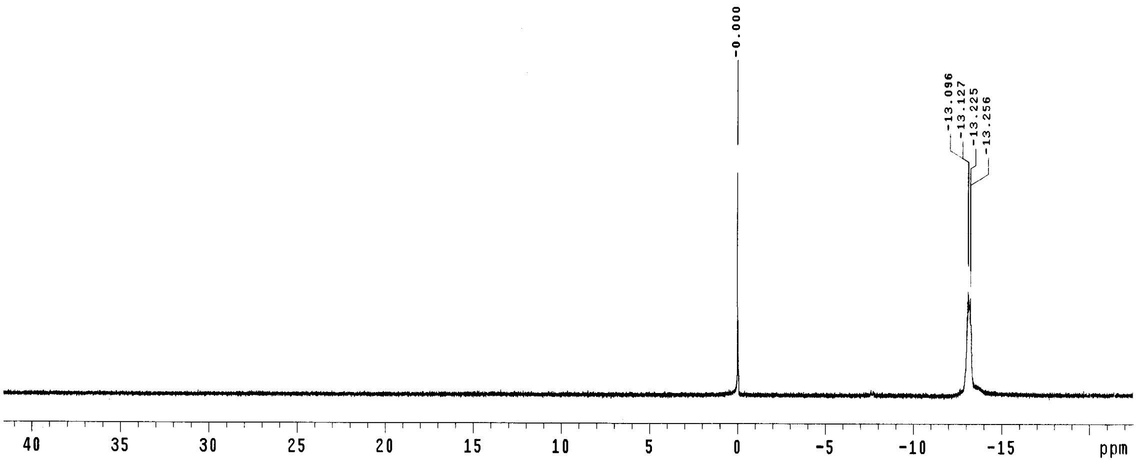


^{1}H, ^{13}C and ^{19}F NMR spectra of **4,13-Difluoro-1,10-dioxa-dispiro[5.2.5.2]hexadecane**









2.10. Crystal Parameters

The Crystal Parameters of Compound **54h**

Crystal Parameters	**54h-** CCDC 731432
Formula	C11 H12 F N O3
Formula weight	225.22
T/K	296(2)
Crystal system	Orthorhombic
Space group	Pbca
a/Å	14.2913(3)
b/Å	8.4013(2)
c/Å	17.6925(4)
α/º	90.00
β/º	90.00
γ/º	90.00
V/Å^3	2124.26(8)
Z	8
Abs. Coeff./mm^{-1}	0.114
Abs. Correction	None
GOF on F^2	1.058
Final *R* indices	*R1* = 0.0400
[$I > 2\sigma$(I)]	*wR2* = 0.1106
R indices [all data]	*R1* = 0.0471
	wR2 = 0.1188

CHAPTER 3

Synthesis of Dihydro- and Tetrahydropyrans *via* Oxonium-ene Cyclization Reaction

3.1. Importance and Applications

The dihydro- and tetrahydropyrans are core units of many biologically active complex natural products, such as (-)-dactylolide **1,** (-)-zampanolide **2,** bryostatin **3,** and laulimalide **4** (*Figure 3.1*).[1] (-)-Dactylolide **1**, a new cytotoxic metabolite, shows cytotoxic activity of (63% inhibition of L1210 and 40% inhibition of SK-OV-3 tumor cell lines at 3.2 μg/mL).[2a] Zampanolide **2**, a potent cytotoxic agent (IC50) 1-5 ng/mL against several cancer cell lines.[2b] Laulimalide **4** is a macrolide obtained from a marine sponge. It exibits potent cytotoxicity toward numerous cancer cell lines and microtubule stabilizing activity similar to that of paclitaxel and the epothilones.[3]

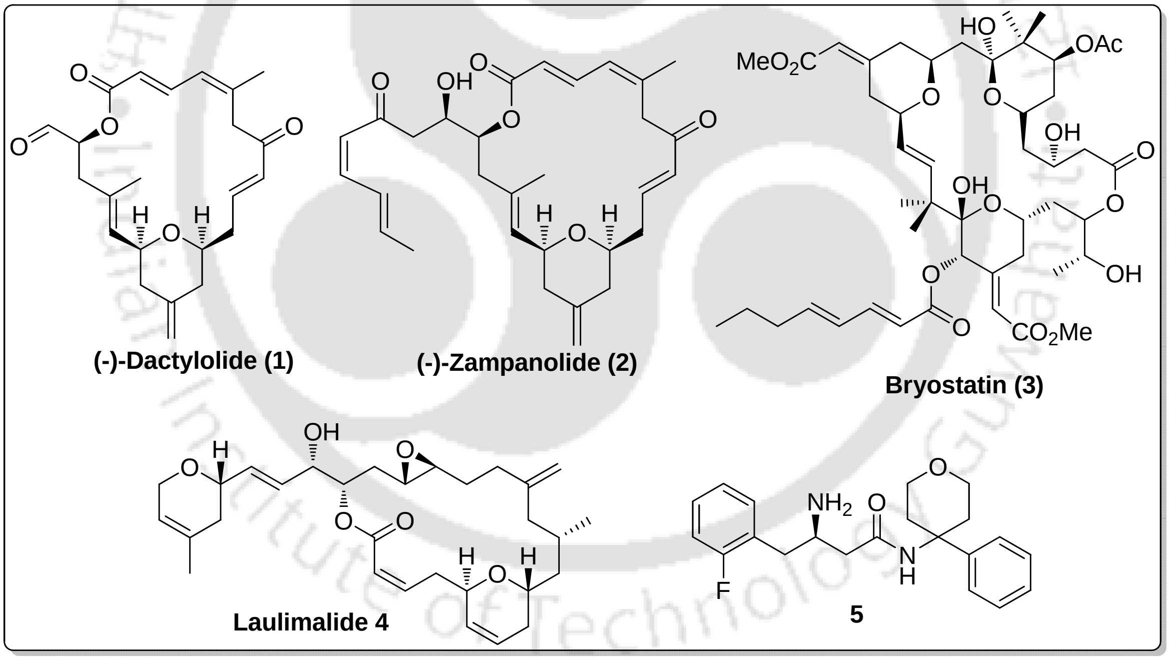


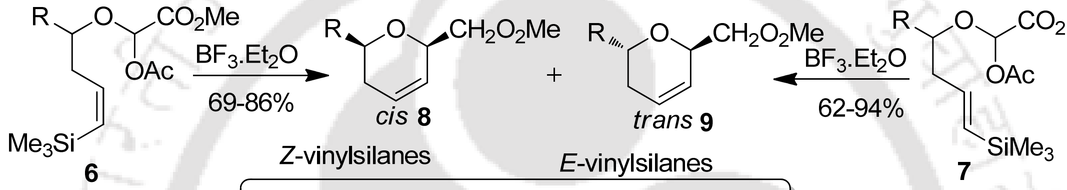
Figure 3.1. *Some biologically important molecules containing dihydro- and tetrahydropyrans as core units.*

On the other hand, the 4-amidotetrahydropyran unit is found in many biologically active molecules and natural products such as ambruticinsVS, glycamino acid, sialic acid, and others.[4] The 4-amidotetrahydropyran (**5**) exhibits anti diabetic properties.[5] 4-Aminotetrahydropyrans are also used as photosensitive materials in photographic films[6] and have been found to be melanocortin receptor agonists.[7]

3.2. Literature Methods for the Synthesis of Dihydro- and Tetrahydropyrans

Over the years many strategies have been developed for the synthesis of dihydro- and tetrahydropyrans, which include Prins cyclization, intramolecular silyl-modified Sakurai reaction (ISMS), oxonium-ene cyclization, ring closing metathesis and Wittig reaction.

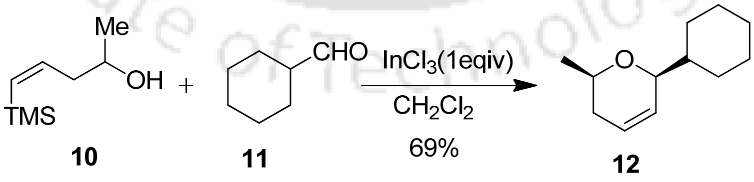
Semeyn *et al*. had investigated the effect of geometry of (*Z*)-vinylsilanes **6** and (*E*)- vinylsilanes **7** on the *cis*/*trans* diastereoselectivity of 2, 6-disubstituted-3, 4-dihydropyrans products (*Scheme 3.2.1*). The (*Z*)-vinylsilane on treatment with boron trifluoride etherate produces *cis* diastereomer **8** as a major isomer. Whereas, the (*E*)-vinyl silane on reaction with aldehyde gives *trans* diastereomer **9** as a major isomer.[8]



R=	*cis*:*trans*	R=	*cis*:*trans*
Et	93:7	Me	30:70
C-C_6H_{11}	92:8	*C*-C_6H_{11}	11:89
Bn	95:5	t-*Bu*	17:83
CH_2OBn	98:2	Bn	72:28

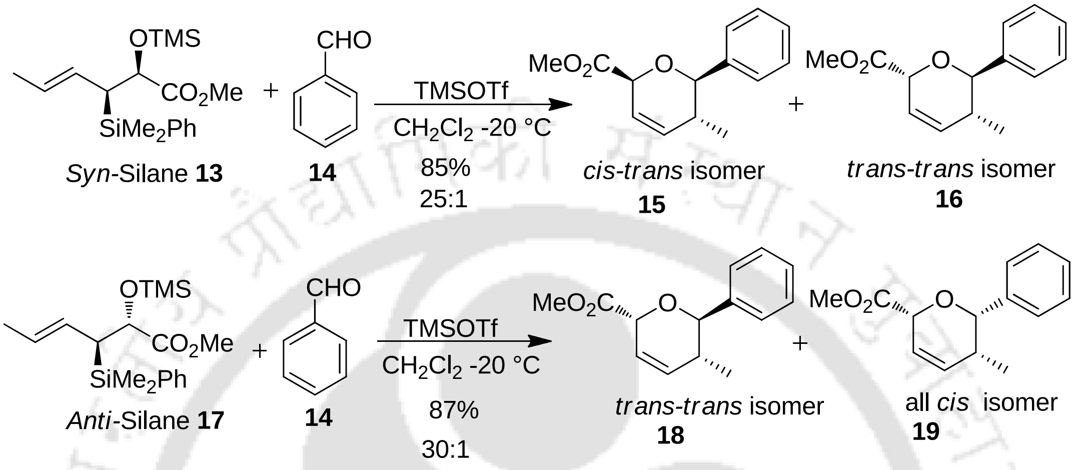
Scheme 3.2.1.

In a similar approach Dobbs and coworkers showed the effective use of stoichiometric amount of $InCl_3$ as a Lewis acid catalyst to promote the cyclization of aldehydes **11** with (*Z*)-vinylsilanes **10** to 3,4-dihydropyrans **12** in good yields with excellent diastereoselectivity (*Scheme 3.2.2*).[9]



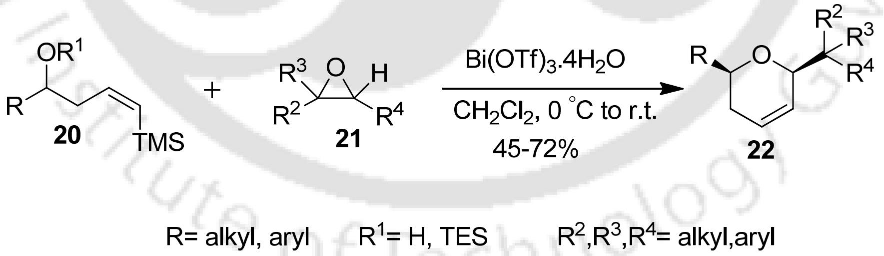
Scheme 3.2.2.

Panek and coworkers demonstrated a method for the synthesis *cis*-2,6- and *trans*-2,6-dihydropyrans by the reaction of β-hydroxyallylsilanes with aldehydes in the presence of TMSOTf (*Scheme 3.2.3*). This raction first generates an oxocarbenium ion intermediate, followed by intramolecular sillyl Prins cyclization reaction. The cyclization of *syn*-silane **13** with aldehyde **14** gave the *cis*-2,6-*trans*-5,6-trisubstituted dihydropyran **15** as the major product and *trans*-2,6-*trans*-5,6-trisubstituted dihydropyran **16** as minor product. Whereas, the cyclization of *anti*-silane **17** with aldehyde **14** provided *trans*-2,6-*trans*-5,6-trisubstituted dihydropyran **18** as the major isomer with all *cis* dihydropyran **19** as minor isomer.[10]



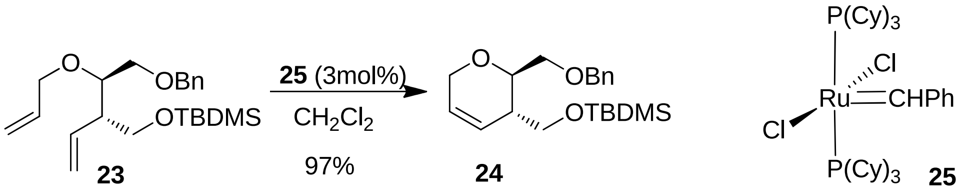
Scheme 3.2.3.

Hinkle has reported a Bi(OTf)$_3$ catalyzed cascade reaction, involving rearrangement of epoxides **21** to aldehyde electrophiles, which subsequently undergo cyclization with (*Z*)-δ-hydroxyalkenylsilane **20** via intramolecular silyl-modified Sakurai reaction (ISMS) to afford 2,6-disubstituted 3,6-dihydro-*2H*-pyrans **22** in moderate yields (*Scheme 3.2.4*).[11]



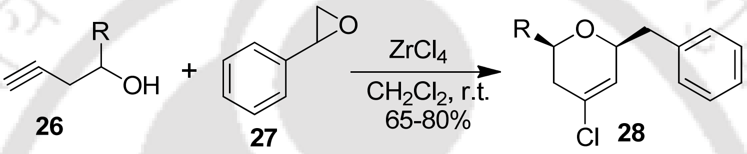
Scheme 3.2.4.

Schmidt *et al.* have implemented ring-closing metathesis for the synthesis of dihydropyrans. The ring-closing metathesis of allyl homoallyl ether **23** having two adjacent protected hydroxymethyl side chains catalysed by Grubbs 1st generation catalyst **25**, afforded the dihydropyran **24** in excellent yield (*Scheme 3.2.5*).[12]



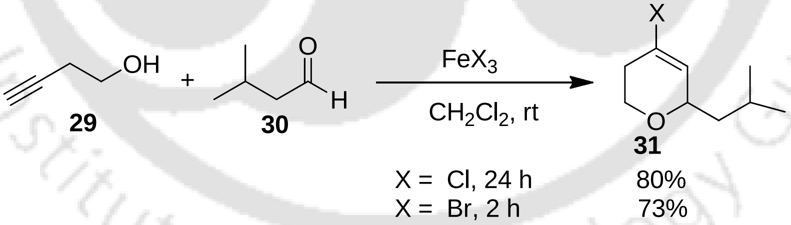
Scheme 3.2.5.

Epoxides **27** which function as an aldehyde equivalent, undergo cyclization with homopropargylic alcohols **26** in the presence of zirconium tetrachloride under mild conditions to afford the corresponding dihydropyran derivatives **28** in excellent yields under mild conditions (*Scheme 3.2.6*).[13]



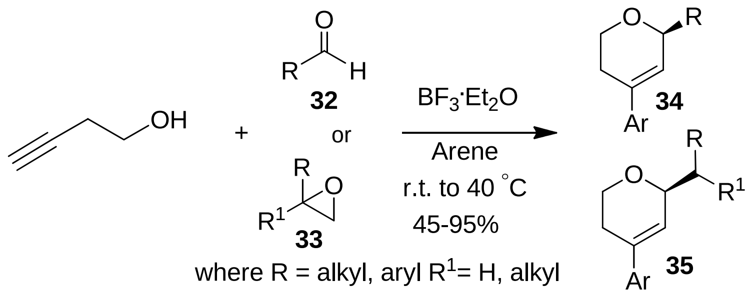
Scheme 3.2.6.

Recently, Martin has also explored the synthetic potential of cyclizations involving homopropargylic alcohol.[14] Reactions of homopropagylic alcohols **29** and aldehydes **30** mediated by anhydrous $FeCl_3$ or $FeBr_3$ gave 4-halo-2-alkyl-5,6-dihydro-*2H*- pyrans **31** in yields ranging from 30 to 98% (*Scheme 3.2.7*).



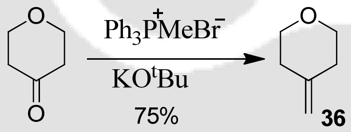
Scheme 3.2.7.

More recently, Saikia and coworkers have developed an efficient method for the synthesis of 4-aryldihydropyrans **34** from carbonyl compounds **32**, homopropargylic alcohols, and arenes mediated by boron trifluoride etherate via Prins-Friedal-Crafts reaction (*Scheme3.2.8*). Furthermore, the method has also been extended to terminal epoxides **33**, which gives dihydropyrans **35**.[15]



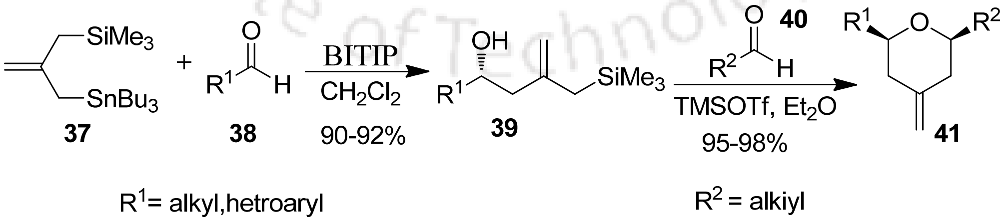
Scheme 3.2.8.

A number of procedures in the literature for the preparation of tetrahydropyrans with an exomethylene double bond. Some of these introduce the exomethylene moiety on to a preformed tetrahydropyran ring. For example, Kabata *et al.* in their preparation of a precursor of α-2,5-dihydroxy-vitamin D_3 used Wittig methodology to produce the exomethylene tetrahydropyrans **36** (*Scheme 3.2.9*).[16]



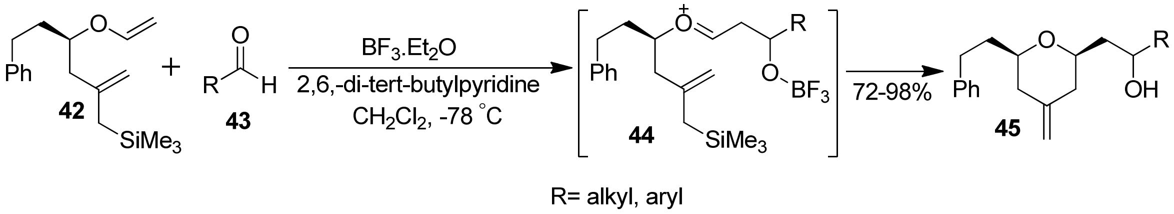
Scheme 3.2.9

Schiff *et al.* have reported a facile enantioselective synthesis of *cis*-2,6-disubstituted 4-methylene tetrahydropyran derivatives through a two-step process (*Scheme 3.2.10).*[17] The first step is asymmetric allylation of an aldehyde **38** with allyl stannane **37** in the presence of a BINOL titanium isopropoxide catalyst to generate the enantiopure hydroxyl allylsilane **39**. The second step, trimethylsillyltriflate promoted annulation of the allyl silane with a second aldehyde **40**, to afford the *cis*-2,6-tetrahydropyran **41** containing an exo-methylene in the 4th position.



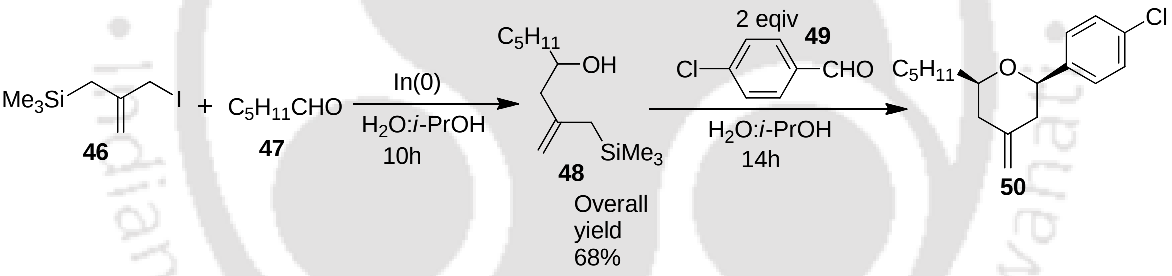
Scheme 3.2.10.

Rychnovsky has developed tandem Mukaiyama aldol-Prins (MAP) cyclization reaction using allylsilane derivatives and aldehydes for the synthesis of 4-methylene tetrahydropyrans (*Scheme 3.2.11*).[18] The cascade reaction involves the Mukaiyama aldol condensation of an aldehyde **43** and an alkyl enol ether **42** to generate an intermediate oxocarbenium ion **44**. This oxocarbenium ion is then trapped with an allylsilane to produce tetrahydropyran **45**.



Scheme 3.2.11.

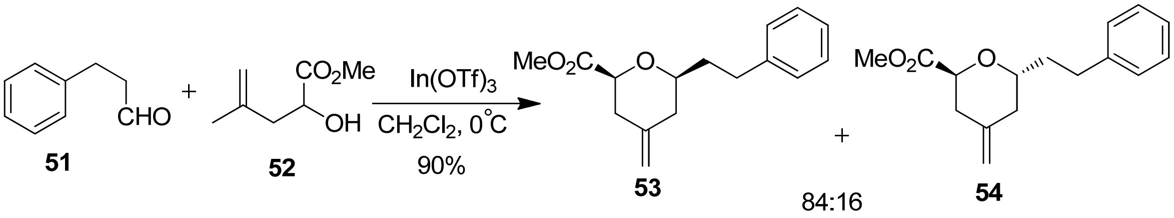
Minehan and coworkers developed an environmentally benign method for the synthesis of *cis*-2,6-disubstituted-4-methylene tetrahydropyran systems through an one-pot, two-step process (*Scheme 3.2.12*),[19] in which allylation of aldehyde **47** occurs with sillyl substituted allyl iodide **46** in the presence of indium metal to generate substituted homoallylalcohol **48**, followed by annulation of homoallylalcohol with a second aldehyde **49** to give *cis*-2,6-disubstituted-4-methylenetetrahydropyran **50**.



Scheme 3.2.12.

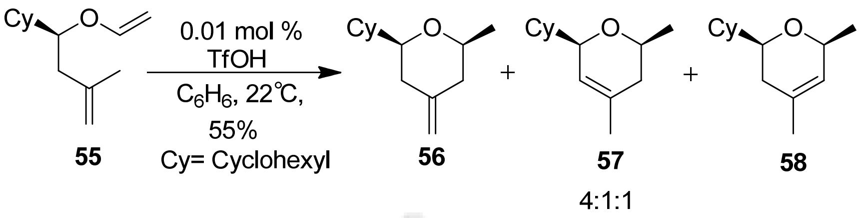
Loh and coworkers[20] described a two component reaction between homoallylalcohol **52** and aldehyde **51** catalyzed by In(OTf)₃ for the synthesis of 4-methylene tetrahydropyrans, which proceeds through intramolecular (2,5)-oxonium-ene cyclization reaction. This method gave both *syn* and *anti* diastereomers **53, 54** in the ratio ranging from 56:44 to 95:5 (*Scheme 3.2.13*).

Hoveyda and coworkers reported an highly stereoselective method for the synthesis of *cis*-2,6-disubstituted-4-methylene tetrahydropyrans using a Brønsted acid-catalysed reaction of



Scheme 3.2.13.

homoallyl enol ethers.[21] An enol ether **55** was reacted with a catalytic (0.01 mol%) amount of TfOH to afford the desired tetrahydropyran **56** and its regioisomers **57, 58** (*Scheme 3.2.14*).



Scheme 3.2.14.

3.3. Present Work

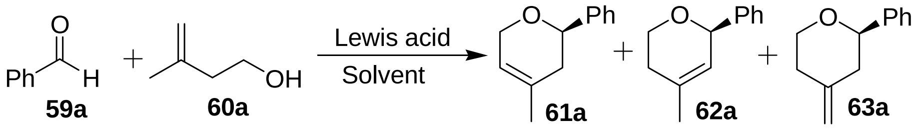
In our previous work, we have reported that simple homoallylic alcohol[22] and homopropargyl alcohol[15] reacts with aldehyde in arene to give 4-aryltetrahydropyran and 4-aryldihydropyran respectively under Prins-Friedel-Crafts reaction conditions. Loh and coworkers have demonstrated the synthesis of 4-methylene tetrahydropyrans from aldehydes and homoallylic alcohols with a 1,1- disubstituted terminal alkene via (2,5)-oxonium-ene cyclization reaction.[20] It is important to note that the disubstitution at the double bond is essential for this oxonium-ene type cyclization. In this chapter we studied the oxonium-ene reaction of aldehydes with a series of alcohols having a 1,1-disubstituted terminal alkene.

Initially, we started our investigation by treating 3-methyl-but-3-en-1-ol with benzaldehyde and boron trifluoride etherate in benzene at room temperature, which led to the formation of 4-methyl-2-phenyl-3,6-dihydro-2*H*-pyran as a major product and its exocyclic isomer 4-methylene-2-phenyl tetrahydropyran as a minor product with a ratio of 89:11 in 78% overall yield. These products cannot be separated by using conventional TLC and column chromatography methods. So the major isomer was isolated in 62% yield using TLC impregnated with $AgNO_3$. A similar type of condensation reaction between ketones and homoallylic alcohols catalyzed by $Hg(OTf)_2$ or BF_3 in acetone at -20 °C was reported by Nishizawa and coworkers, but the reaction ends up with a mixture of 6-membered ether alcohol, bis ether and olefins.[23] In our conditions we have not isolated any alcohol or bis ether products.

To improve the regioselectivity, the reaction was performed with other Lewis acids such as $InCl_3$, $In(OTf)_3$ and $Bi(OTf)_3$ and in different solvents (*Table 3.3.1*). Reaction of $InCl_3$ in CH_2Cl_2 gave three isomeric products **61a**, **62a** and **63a** with a ratio of 50:15:35 and 64% overall yield, but the reaction failed in CH_3CN. On the other hand reaction with $In(OTf)_3$ in CH_2Cl_2 gave only two isomers **61a** and **63a** with a ratio of 67: 33 and 72% overall yield, but no reaction in CH_3CN. Similarly reaction with $Bi(OTf)_3$ in CH_2Cl_2 produced **61a**, **62a** and **63a** with a ratio of 48:26:26

and overall 56% yield. Boron trifluoride etherate worked in CH_2Cl_2, toluene and benzene solvents, but benzene is the best solvent among these in terms of selectivity and yield.

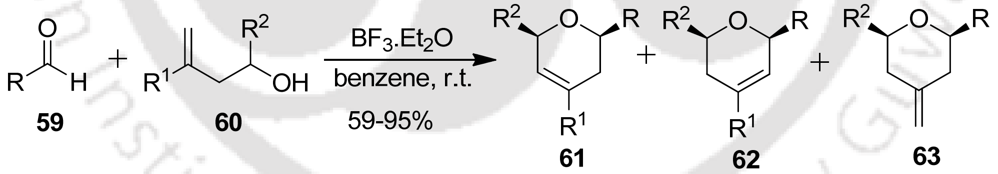
Table 3.3.1. Synthesis of dihydro- and tetrahydropyrans with different Lewis acids and solvents



Entry	Lewis acid (eqiv)	Solvent	(61a: 62a: 63a)[a]	Yield[b]
1	$InCl_3$ (0.2)	CH_2Cl_2	50:15:35	64
2	$In(OTf)_3$ (0.1)	CH_3CN	------	----
3	$In(OTf)_3$ (0.1)	CH_2Cl_2	67:00:33	72
4	$Bi(OTf)_3$ (0.1)	CH_2Cl_2	48:26:26	56
5	$BF_3.Et_2O$ (1)	CH_2Cl_2	75:00:25	68
6	$BF_3.Et_2O$ (1)	Toluene	82:00:18	70
7	$BF_3.Et_2O$ (1)	Benzene	89:00:11	78

[a] Ratios are on the basis of ^{1}HNMR. [b]Yields are isolated yield.

The boron trifluoride etherate mediated oxonium-ene reaction is generalized as shown in (*scheme 3.3.1*).



Scheme 3.3.1

The scope of the reaction was investigated by using different types of aldehydes and alcohols (*Table 3.3.2*) and it was observed that the reaction of aromatic aldehydes **59a–g** with methyl substituted alcohol **60a–g** gave endocyclic compounds **61a–g** as the major product with a minor exocyclic product **63a–g**, whereas the aliphatic aldehydes (entries **59h, i**) gave two isomeric endocyclic products with ratios 75:25 and 80:20, respectively. Conjugated aromatic aldehyde **59j** gave as a major endocyclic isomer **61j** with a minor exocyclic isomer **63j**. On the other hand, nitro-substituted conjugated aromatic aldehyde **59k** gave only endocyclic isomer **61k**. Reaction of phenyl substituted alcohols **60l**, **m** and **60o** with aromatic and conjugated aromatic aldehydes

Table 3.3.2. Synthesis of 4-alkyl/aryl dihydropyrans and 4-methylene tetrahydropyrans

Entry	Aldehyde **59**	Alcohol **60**		Time/h	Product ratio[a]			%Yield[b]
	R=	R^1	R^2		**61**	**62**	**63**	
a	C_6H_5	Me	H	0.5	89	-	11	62[b]
b	*p*-ClC_6H_4	Me	H	0.5	92	-	8	69[b]
c	*m*-$NO_2C_6H_4$	Me	H	0.5	86	-	14	72[b]
d	*p*-$MeO_2CC_6H_4$	Me	H	0.5	86	-	14	64[b]
e	*p*-$OTsC_6H_4$	Me	H	0.5	90	-	10	64[b]
f	*p*-MeC_6H_4	Me	H	0.5	91	-	9	68[b]
g	*p*-$MeOC_6H_4$	Me	H	0.5	83	-	17	59[b]
h	C_6H_{13}	Me	H	0.5	75	25	-	64[c]
i	$C_6H_5CH_2$	Me	H	0.5	80	20	-	78[c]
j	$C_6H_5CH{=}CH$	Me	H	0.5	86	-	14	66[b]
k	*p*-$NO_2C_6H_4CH{=}CH$	Me	H	0.5	100	-	-	95[d]
l	*p*-BrC_6H_4	Ph	H	0.5	100	-	-	78[d]
m	$MeOC_6H_4$	Ph	H	0.5	100	-	-	69[d]
n	C_6H_{13}	Ph	H	0.5	75	25	-	80[c]
o	$C_6H_5CH{=}CH$	Ph	H	0.5	100	-		72[d]
p	*o*-ClC_6H_4	Me	*p*-$MeO_2CC_6H_4$	3	-	-	100	75[d,f]
q	*p*-$MeOC_6H_4$	Me	*p*-$MeO_2CC_6H_4$	3	-	-	100	70[d,f]
r	C_6H_5	Me	*p*-$MeO_2CC_6H_4$	3	-	-	100	72[d,f]
s	*p*-BrC_6H_4	Me	*p*-$MeO_2CC_6H_4$	3	-	-	100	76[d,f]
t	*p*-MeC_6H_4	Me	*o*-ClC_6H_4	3	-	-	100	75[d,f]
u	*m*-$NO_2C_6H_4$	Me	*o*-ClC_6H_4	3	-	-	100	80[d,f]
v	C_6H_{13}	Me	*p*-$MeO_2CC_6H_4$	3	35	-	65	81[e,f]

[a]Ratios are on the basis of crude ^{1}HNMR. [b]Yield refers to isolated yield of the major isomer by $AgNO_3$ imprgnated TLC. [c]Overall yield of the both the isomers in the case of inseparable isomers. [d]Isolated yield of product by conventional column chromatography. [e]Overall yield of both the regio isomers that could be isolated by $AgNO_3$ imprgnated TLC in the ratio(28:53). The compounds are characterized by ^{1}H, ^{13}C NMR, Mass and X-ray analysis. [f]The de is 100% on the basis of crude ^{1}HNMR.

.

59l-o gave single endocyclic isomers **61l-o**. But the reaction with aliphatic aldehyde **59n** gave two endocyclic isomers **61n** and **62n** with a ratio of 75:25. The structure of the compounds was determined by NMR and X-ray analysis (*Figure 3.3.1*) and comparison with authentic samples.[15]

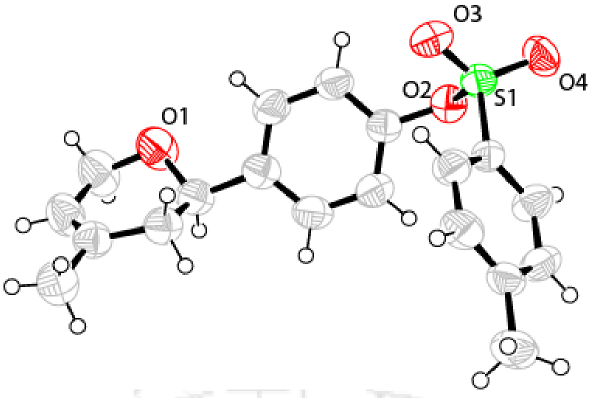


Figure 3.3.1. ORTEP diagram of Toluene 4-sulfonic acid 4-(4-methyl-3,6-dihydro-2*H*-pyran-2-yl) phenyl ester (**61e**)

In contrast to the above, the reaction of alcohols **60p–u** with a aromatic substitution at the C-1 position gave only exocyclic *cis*-products **63p–u** in good yields and excellent diastereoselectivity. But the reaction of alcohol **60v** with aliphatic aldehyde **59v** gave endocyclic **61v** and exocyclic **63v** with a ratio 35:65 (*Table 3.3.2*). The major isomers in the case of mixture of endocyclic and exocyclic isomers were separated by using AgNO$_3$ impregnated thin layer chromatography. However, the major isomers in the case of two endocyclic isomeric mixture could not be separated from its minor isomer. The diastereoselectivity of compounds **63p–v** was determined from the crude ^{1}H NMR and it was found that only *cis* diastereomer is formed. The *cis*-configuration of the 2,6-disubstituted 4-methylene tetrahydropyrans was confirmed from NOE and the coupling constants of the two peaks at C-2 (J = 11.6 and 2.4 Hz) and C-6 (J = 11.2 and 2.3 Hz) as shown in (*Figure 3.4.2*).

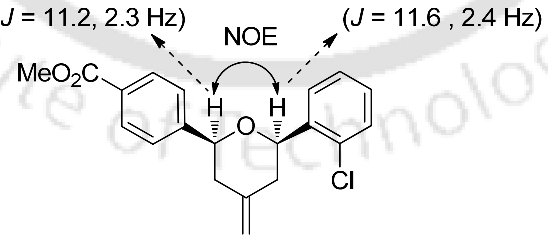
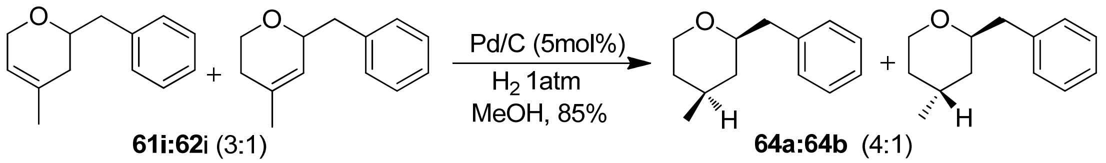


Figure 3.3.2. Coupling constants and NOE of compound **63p**

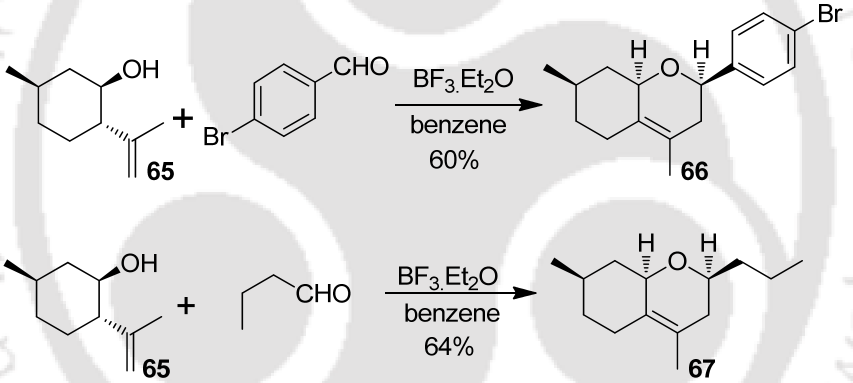
The formation of two isomeric endocyclic compounds in the case of aliphatic aldehydes is further confirmed by hydrogenation with hydrogen on palladium charcoal. Both the isomers gave the diastereomeric mixture of same tetrahydropyran **64a** and **64b** in the ratio 4:1.



Scheme 3.3.2.

The formation of mainly endocyclic compounds instead of the exocyclic compounds is due to the higher stability of the endocyclic compounds compared to the exocyclic one as demonstrated by Gil-Av and Shabtai[24] as well as by Turner and Garner.[25] The formation of major 2,6-disubstituted exocyclic products in the case of alcohols **60p-v** may be attributed to the presence of two substituents at 2 and 6 positions which makes them more stable.

The scope of the reaction was extended to chiral cyclic alcohols. Thus the reaction of 2-isopropenyl-5-methylcyclo-hexanol **65** with bromobenzaldehyde gave bicyclic 2-(4-bromophenyl)-4,7-dimethyl-3,5,6,7,8,8a-hexa-hydro-2*H*-chromene **66** in 60% yield. Similarly,



Scheme 3.3.3. *Synthesis of chromenes*

butyraldehyde gave dihydropyran **67** in 64% yield (*Scheme 3.3.3*). The structure of the compounds was determined by NOE and X-ray analysis (*Figure 3.3.3*).[26]

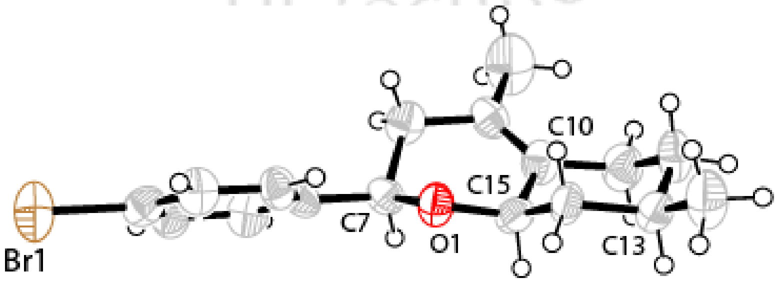
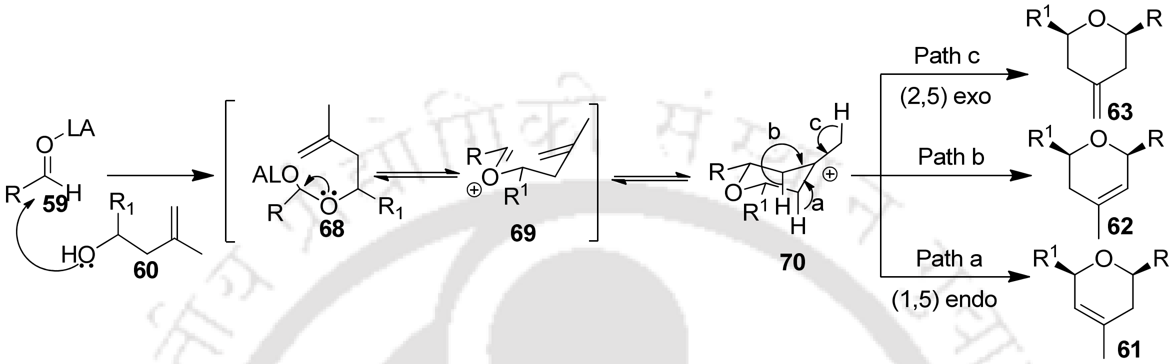


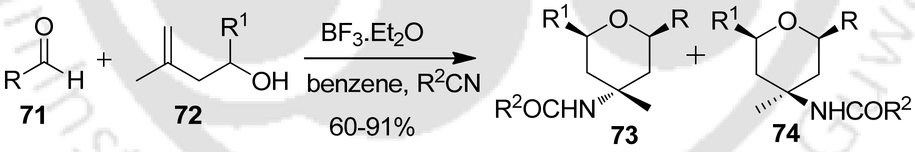
Figure 3.3.3. *ORTEP diagram of 2-(4-Bromophenyl)-4,7-dimethyl-3,5,6,7,8,8a-hexahydro-2H-chromene **(66)***

The mechanism of the reaction can be explained considering the oxonium-ene cyclization. The aldehyde is activated by Lewis acid for nucleophilic attack by homoallylic alcohol to form acetal **68**, which after decomposition gives oxocarbenium ion **69**. Oxocarbenium ion **69** after cyclization gives carbocation **70**, which after subsequent proton elimination forms three different products (*Scheme 3.3.4*).



Scheme 3.3.4.

The cationic oxonium-ene reaction was confirmed by trapping the carbocation **69** (*Scheme 3.3.5*) with nitrile nucleophiles to give the corresponding 4-amidotetrahydropyrans. The reaction for the synthesis of 4-amidotetrahydropyrans is generalized by employing different aldehydes and nucleophiles and the results are summarized in (*Table 3.3.3*).



Scheme 3.3.5.

It was observed that all the aldehydes yielded two inseparable diastereomers with different ratios except *m*-nitrobenzaldehyde**71j**, which produces only the major isomer. The aromatic aldehyde having electron-donating groups in the ring is not a good substrate **71d** for this reaction. The diastereomeric ratio was determined from crude ^{1}H NMR spectra. The structure and stereochemistry of the major isomer was determined from single crystal X-ray analysis (*Figure 3.3.4*).[26]

The formation of axial isomer as major product can be explained from the mechanism of the reaction (*Scheme 3.3.6*). The methyl group occupies a pseudo equatorial position to form the more favored intermediate **77**. The cation **77** is then attacked by the nitrile nucleophile from axial

Table 3.3.3. Synthesis of 4-amidotetrahydropyrans

Entry	Aldehyde (**71**)	Alcohol (**72**)	Nitrile (**73**)	Product ratio(**74:75**)[b]	%Yield[a]
a	*m*-$NO_2C_6H_4$	H	Me	69:31	82
b	C_6H_5	H	Me	67:33	91
c	*p*-BrC_6H_4	H	Me	60:40	95
d	*P*-MeC_6H_4	H	Me	67:33	67
e	*n*-C_2H_5	H	Me	80:20	89
f	$(CH_3)_2CHCH_2$	H	Me	78:22	92
g	$C_6H_5CH_2$	H	Me	79:21	80
h	$C_6H_5CH{=}CH$	H	Me	71:29	74
i	C_6H_5	H	Ph	75:25	70
j	*m*-$NO_2C_6H_4$	H	Ph	100:00	72
k	*n*-C_3H_7	H	Ph	75:25	65
l	*o*-ClC_6H_4	H	Ph	60:40	78
m	*n*-C_3H_7	H	$CHCl_2$	71:29	60
n	*m*-$NO_2C_6H_4$	H	$CHCl_2$	78:22	73
o	*m*-$NO_2C_6H_4$	H	$CH_2{=}CHCH_2$	67:33	92
p	C_6H_5	*p*-$MeO_2CC_6H_4$	Me	60:40	84
q	*P*-MeC_6H_4	*p*-$MeO_2CC_6H_4$	Me	50:50	78
r	*n*-C_3H_7	*p*-$MeO_2CC_6H_4$	Me	60:40	90

[a]Yield refers to isolated yield. The compounds are characterized by ^1H, ^{13}C NMR, Mass and X-ray analysis. [b]Ratios are on the basis of crude ^1H NMR.

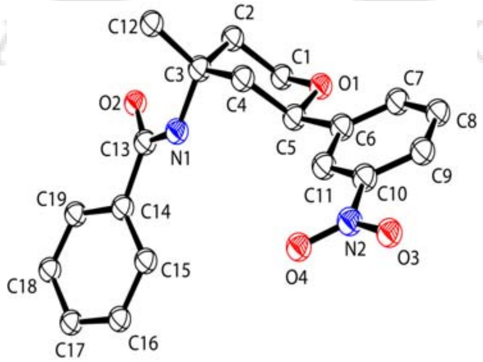
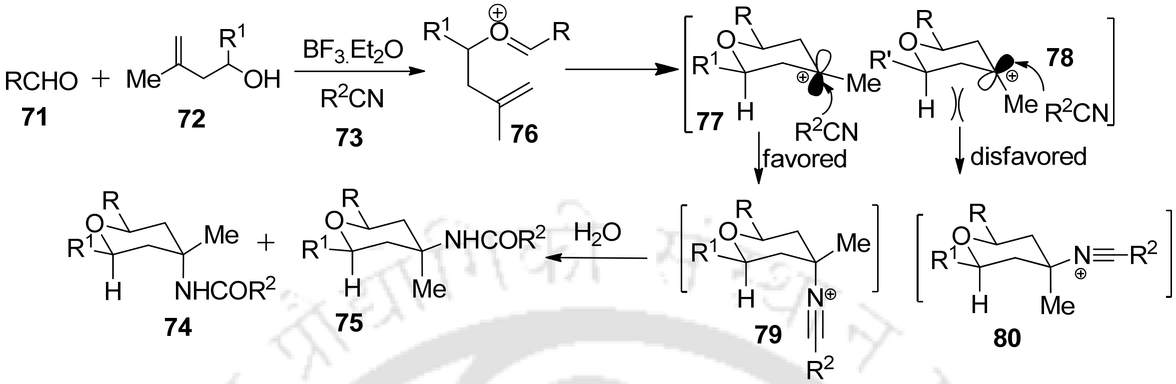


Figure 3.3.4. *ORTEP diagram of N-[4-Methyl-2-(3-nitrophenyl)-tetrahydropyran-4-yl]-benzamide**(74j)***

site to give species **79**, which after hydrolysis gives the major product **74**, whereas the less favoured species **78** gives the minor product **75**.



Scheme 3.3.6. Mechanism of formation of major axial isomer.

Conclusion:

In conclusion, we have developed an efficient and diastereoselective method for the synthesis of 4-alkyl/aryl dihydro- and 4-methylene tetrahydropyrans in good yields. The method is also suitable for chromene synthesis. The stepwise mechanism of intramolecular oxonium-ene reaction has been studied by trapping the in situ generated carbocation with nitrile nucleophile. Hence the method can be used to synthesize 4-amido tetrahydropyrans.

3.4. Experimental Section

3.4.1 Instrumentation and Characterization

As described in chapter 2 section 2.6.1.

3.4.2. Synthesis of Substituted Homoallylic Alcohols 60l, 60p, and 60t: The alcohols **60l**, **60p**, and **60t** were synthesized according to the literature procedure[27] and the analyses were consistent with the literature.[27]

3.4.3. General procedure for the Synthesis of 3,6-Dihydropyrans and 4-Methylene tetrahydropyrans: To a stirring solution of aldehyde (1.0 equiv) and boron trifluoride etherate (1.0 equiv) in benzene (2 mL) at room temperature was added homoallyl alcohol (1.1 equiv) in benzene (2 mL) drop by drop over 5 min. The reaction mixture was stirred at the same temperature for 45 min. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was quenched with saturated sodium bicarbonate solution, extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product. This was purified by either column chromatography or preparative TLC impregnated with silver nitrate to furnish the title compounds.

Synthesis of 4-Methyl-2-phenyl-3,6-dihydro-2*H* pyran: To a stirring solution of benzaldehyde (106 mg, 1.0 mmol) and boron trifluoride etherate (141 mg, 1.0 mmol) in benzene (2 mL) at room temperature was added 3-methyl-3-butene-1-ol (95 mg, 1.1 mmol) in benzene (2 mL) drop by drop over 5 min. The reaction mixture was stirred at the same temperature for 45 min. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was quenched with saturated sodium bicarbonate solution. The product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product. This was purified by preparative TLC impregnated with silver nitrate to furnish the 4-methyl-2-phenyl-3,6-dihydro-2*H* pyran (136 mg, 78%) as an oily liquid.

3.4.4. Separation of Alkene Regio-isomeric Mixture by Using Preparative TLC Impregnated with $AgNO_3$: A slurry was prepared from 60 g of TLC silica gel (SRL) containing 13% $CaSO_4 \cdot 1/2H_2O$ as binder with 5% methanol in ethyl acetate (120 mL). Four thin glass plates of 21X 11cm were coated uniformly with the slurry. The chromatoplates were allowed to dry for an hour at room temperature and then the plates were dipped into a silver nitrate solution (5 gm in 75 mL of water) chamber for 60−70 min. The plates were allowed to dry in a hot oven at 100 °C for an hour, the lower portion of the plates changed to gray color, indicating the impregnation of silver nitrate. The regioisomeric mixture dissolved in an adequate amount of ethyl acetate was applied to the plates, which was then developed in hexane-ethyl acetate solvent system. The plates were taken out from the solvent chamber and dried at room temperature for 15 min and then kept in the iodine chamber. A yellow colored band appeared after a few minutes. The bands were eluted with ethyl acetate and the solvent was evaporated in rotary vapor to give the title compounds.

3.4.5. Procedure for the Hydrogenation of Dihydropyrans 61i and 62i:

After two vacuum/H_2 cycles to replace air inside reaction vessel with hydrogen, the mixture of the substrate (188 mg, 1.0 mmol), 10% Pd/C (55 mg, 0.05 mmol), in MeOH (5 mL) was vigorously stirred at room temperature under hydrogen pressure (1 atm) for 24 h. The reaction mixture was filtered using celite pad and the filtrate was concentrated and to leave the crude product. This was further purified by column chromatography to obtain the tetrahydropyrans 64a and 64b (161mg, 85%) as a oily liquid

3.4.6. General Procedure for the Synthesis of 4-Amidotetrahydropyrans 74 and 75: To a mixture of aldehyde (1.0 equiv), nitrile (2.0 equiv) and boron trifluoride etherate (1.0 equiv) in benzene (2 mL) at room temperature was added homoallyl alcohol (1.1 equiv) in benzene (2 mL) drop by drop over 5 min. The reaction mixture was stirred at the same temperature for half an hour. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was quenched with saturated sodium bicarbonate solution. The product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product. This was further purified by column chromatography to give the desired 4-amidotetrahydropyrans.

Synthesis of N-[4-methyl-2-(3-nitrophenyl)-tetrahydropyran-4-yl]-acetamide: To a stirring solution of 3-nitrobenzaldehyde (151 mg, 1.0 mmol) with acetonitrile (82 mg, 2 mmol) and boron trifluoride etherate (141 mg, 1.0 mmol) in benzene (2 mL) at room temperature was added 3-methyl-3-butene-1-ol (95 mg, 1.1 mmol) in benzene (2 mL) drop by drop over 5 min. The reaction mixture was stirred at the same temperature for half an hour. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was quenched with saturated sodium bicarbonate solution. The product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product. This was further purified by column chromatography to furnish *N*-[4-methyl-2-(3- nitrophenyl)-tetrahydropyran-4-yl]-acetamide.

3.5. References and Notes

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26) The crystallographic data for compounds **61e**, **66** and **74j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 765896, 765895 and 801332, respectively.

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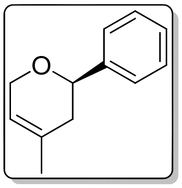
3.5 Spectral Data

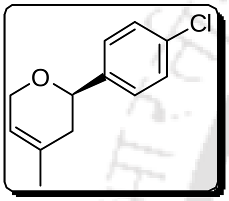
3.5.1. Spectral Data of Dihydro- and Tetrahydropyrans

4-Methyl-2-phenyl-3,6-dihydro-2*H*-pyran (61a):



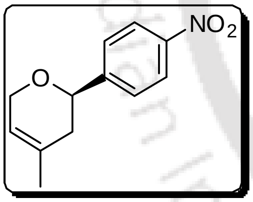
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.76 (s, 3 H, -CH_3), 2.06-2.14 (m, 1 H), 2.26-2.37 (m, 1 H), 4.33 (bs, 2 H), 4.54 (dd, *J* = 10.4 and 3.2 Hz, 1 H), 5.51 (t, *J* = 1.2 Hz, 1 H), 7.26-7.31 (m, 2 H, ArH), 7.34-7.41 (m, 3 H, ArH); ^{13}**CNMR** (100 MHz, $CDCl_3$): δ 23.1, 37.9, 66.6, 76.0, 120.0, 126.0, 127.6, 128.6, 132.2, 142.8; **IR**: 2924, 1604, 1496, 1451, 1383, 1245, 1123, 1092, 1040, 864, 756, 699 cm^{-1}. **Anal. Calcd** for $C_{12}H_{14}O$: C 82.72, H 8.10. Found: C 82.84, H 8.02.

2-(4-Chlorophenyl)-4-methyl-3,6-dihydro-2*H*-pyran (61b):



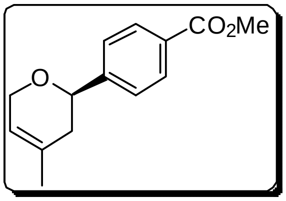
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.74 (s, 3 H, -CH_3), 2.04-2.10 (m, 1 H), 2.18-2.26 (m, 1 H), 4.28-4.33 (m, 2 H), 4.48 (dd, *J* = 10.4 and 3.6 Hz, 1 H), 5.48 (t, *J* = 1.6 Hz, 1 H), 7.26-7.34 (m, 4 H, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 23.1, 37.8, 66.6, 75.2, 120.0, 127.4, 128.6, 131.9, 133.2, 141.4; **IR**: 2925, 1598, 1493, 1436, 1123, 1089, 1043, 948, 824 cm^{-1}.**HRMS** (APCI)*m*/*z* calcd for $C_{12}H_{13}ClO$: $(M+H)^+$ 209.0733, Found 209.0729.

4-Methyl-2-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran (61c):



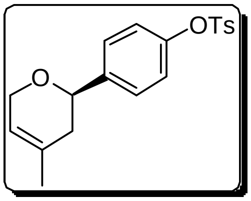
Yellow color liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.77 (s, 3 H, -CH_3), 2.14-2.23 (m, 1 H), 2.24-2.30 (m, 1 H), 4.30- 4.35 (m, 2 H), 4.63 (dd, *J* = 10.0 and 4.4 Hz, 1 H), 5.52 (t, *J* = 1.6 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H, ArH), 7.72 (d, *J* = 7.6 Hz, 1 H, ArH), 8.13 (dd, *J* = 8.4 and 1.2 Hz, 1 H, ArH), 8.27 (s, 1 H, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 23.0, 37.6, 66.6, 74.6, 120.0, 121.0, 122.5, 122.6, 129.5, 131.6, 132.1, 145.0; **IR**: 2929, 2853, 1530, 1445, 1348, 1122, 1098, 1042, 812, 737, 686 cm^{-1}. **Anal. Calcd** for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39. Found: C 65.65, H 6.10, 6.32.

Methyl 4-(4-methyl-3,6-dihydro-2*H*-pyran-2-yl)benzoate (61d):



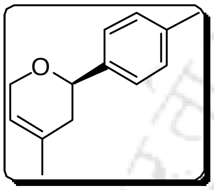
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.75 (s, 3 H, -CH_3), 2.08-2.15 (m, 1 H), 2.19-2.23 (m, 1 H), 3.90 (s, 3 H, CH_3), 4.30-4.34 (m, 2 H), 4.58 (dd, *J* = 10.0 and 3.6 Hz, 1 H), 5.50 (t, *J* = 1.6 Hz, 1 H), 7.45 (d, *J* = 8.4, 2 H, ArH), 8.02 (d, *J* = 8.0, 2 H, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 23.1, 37.8, 52.2, 66.6, 75.4, 120.0, 125.8, 129.3, 129.9, 131.9, 148.0, 167.2; **IR**: 2952, 2857, 1738, 1614, 1436, 1280, 1112, 1043, 1018, 854, 768, 705 cm^{-1}. **HRMS** (APCI) *m*/*z* calcd for $C_{14}H_{16}O_3$: $(M+H)^+$ 233.1178, Found 233.1187.

4-(4-Methyl-3,6-dihydro-2*H*-pyran-2-yl)phenyl 4-methylbenzenesulfonate (61e):



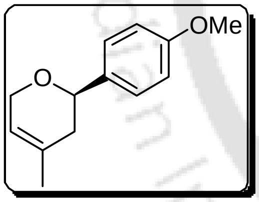
Yellowish solid, mp 80–82 °C; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.73 (s, 3 H, $-CH_3$), 2.02-2.10 (m, 1 H), 2.16-2.24 (m, 1 H), 2.43 (s, 3 H, $-CH_3$), 4.24-4.31 (m, 2 H), 4.48 (dd, *J* = 10.0 and 2.8 Hz, 1 H), 5.48 (t, *J* = 1.6 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 2 H, ArH), 7.29 (d, *J* = 7.6 Hz, 4 H, ArH), 7.68 (d, *J* = 6.8 Hz, 2 H, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.9, 23.0, 37.8, 66.6, 75.1, 119.9, 122.4, 127.2, 128.7, 129.9, 131.9, 132.4, 141.8, 145.5, 148.9; **IR**: 2929, 2911, 2824, 1597, 1503, 1372, 1197, 1154, 1119, 1093, 865, 744, 659 cm^{-1}. **HRMS** (APCI) *m*/*z* calcd for $C_{19}H_{20}O_4S$: $(M+H)^+$ 345.1161, Found 345.1169.

4-Methyl-2-(*p*-tolyl)-3,6-dihydro-2*H*-pyran (61f):



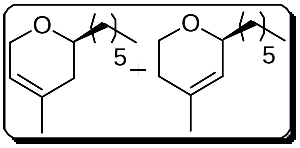
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.73 (s, 3 H, $-CH_3$), 2.02-2.11 (m, 1 H), 2.22-2.30 (m, 1 H), 2.33 (s, 3 H, $-CH_3$), 4.28-4.32 (m, 2 H), 4.48 (dd, *J* = 10.4 and 3.2 Hz, 1 H), 5.48 (t, *J* = 1.6 Hz, 1 H), 7.15 (d, *J* = 7.6, 2 H, ArH), 7.26 (d, *J* = 8.0 Hz, 2 H, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.3, 23.1, 37.8, 66.6, 75.8, 120.0, 126.0, 129.2, 132.3, 137.2, 139.8; **IR**: 3016, 2922, 1610, 1493, 1444, 1382, 1167, 1122, 1091, 1042, 1020, 946, 813 cm^{-1}. **Anal. Calcd** for $C_{13}H_{16}O$: C 82.94, H 8.57. Found: C 83.15, H, 8.49.

2-(4-Methoxyphenyl)-4-methyl-3,6-dihydro-2*H*-pyran (61g):



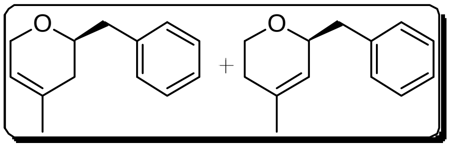
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.74 (s, 3 H, $-CH_3$), 2.03-2.09 (m, 1 H), 2.27-2.35 (m, 1 H), 3.80 (s, 3H, CH_3), 4.27-4.30 (m, 2 H), 4.47 (dd, *J* = 10.4 and 3.6Hz,1H), 5.48 (t, *J* = 1.6 Hz, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H, ArH), 7.30 (d, *J* = 8.8 Hz, 2 H, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 23.1, 37.7, 55.5, 66.6, 75.6, 113.9, 120.0, 127.4, 132.3, 134.9, 159.2; **IR**: 2929, 2836, 1614, 1248, 1175, 1109, 1035, 828, 779 cm^{-1}. **HRMS** (APCI) *m*/*z* calcd for $C_{13}H_{16}O_2$: $(M+H)^+$ 205.1229, Found 205.1235.

2-Hexyl-4-methyl-3,6-dihydro-2*H*-pyran and 6-Hexyl-4-methyl-3,6-dihydro-2*H*-pyran (61h and 62h; 75:25):

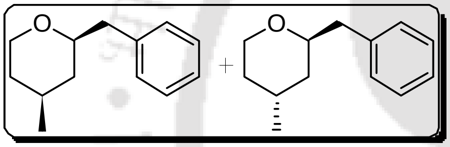


Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.89-0.96 (m, 3 H, $-CH_3$), 1.33-1.65 (m, 8 H, $-CH_2-$), 1.69 (s, 3 H, $-CH_3$), 1.72-1.78 (m, 2 H, $-CH_2-$), 1.79-1.87 (m, 1 H), 1.88-1.99 (m, 1 H), 3.42-3.50 (m, 0.75 H), 3.62 (ddd, *J* = 10.0 and 4.0 Hz, 0.25 H), 3.95-4.00 (m, 0.50 H), 4.04-4.18 (m, 1.50 H), 5.32 (d, *J* = 3.2 Hz, 0.25 H), 5.40 (dd, *J* = 1.6 and 1.2 Hz, 0.75 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 23.2, 25.5, 25.7, 29.6, 30.3, 32.0, 35.9, 36.1, 36.2, 66.1, 74.0, 74.3, 120.0, 124.4, 132.1; **IR**: 2956, 2928, 2856, 1654, 1458, 1380, 1166, 1139, 1020, 886, 831, 779 cm^{-1}. **Anal. Calcd** for $C_{12}H_{22}O$: C 79.06, H 12.16. Found: C 80.12, H 12.22.

2-Benzyl-4-methyl-3,6-dihydro-2*H*-pyran and 6-Benzyl-4-methyl-3,6-dihydro-2*H*-pyran (61i and 62i; 80:20):

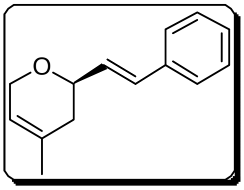


Colorless liquid; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.65 (s, 2.25 H), 1.68 (s, 0.75 H), 1.73- 1.80 (m, 1 H), 1.95-2.05 (m, 0.75 H), 2.10-2.23 (m, 0.75 H), 2.68 (dd, *J* = 9.6 and 6.4 Hz, 0.25 H), 2.72 (dd, *J* = 13.6 and 6.4 Hz, 0.75 H), 2.89 (dd, *J* = 12.8 and 7.2 Hz, 0.25 H), 2.96 (dd, *J* = 13.6 and 6.8 Hz, 1 H), 3.58-3.64 (m, 0.25 H), 3.68-3.75 (m, 0.75 H), 3.96-4.00 (m, 0.50 H), 4.05-4.25 (m, 1.50 H), 5.33 (brs, 0.25 H), 5.38 (br s, 0.75 H), 7.19-7.25 (m, 3 H), 7.27-7.31 (m, 2 H); ^{13}**C NMR** for **3i** (100 MHz, CDCl$_3$): δ 23.2, 35.7, 42.6, 66.2, 74.8, 119.9, 126.4, 126.5, 129.5, 131.8, 138.7 (major **3i**); **IR**: 3027, 2926, 2853, 1629, 1495, 1382, 1153, 1120, 1085, 1030, 858, 779 cm^{-1}. **Anal. Calcd** for $C_{13}H_{16}0$: C 82.94, H 8.57. Found: C 83.15, H, 8.68. this isomeric mixture, the mixture **6i** and **7i** was hydrogenated in the presence of H_2 and Pd on Charcoal (20% W/W) in MeOH at 28 °C for 24 h to afford the corresponding hydrogenated product as a mixture of two diastereomers at C-4 (4 : 1 ratio; identity of isomers not determined).



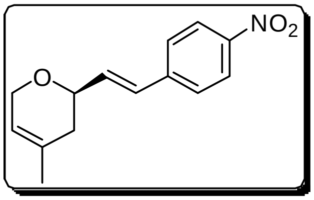
^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.90 (d, *J* = 6.4 Hz, 2.40 H), 1.01 (d, *J* = 6.8 Hz, 0.60 H), 1.15-1.27 (m, 1.60 H), 1.31-1.38 (m, 0.40 H), 1.48-1.68 (m, 2.40 H), 1.75-1.83 (m, 0.60 H), 2.63 (dd, *J* = 13.6 and 6.4 Hz, 0.80 H), 2.72 (dd, *J* = 14.0 and 6.0 Hz, 0.20 H), 2.89 (dd, *J* = 13.6 and 6.4 Hz, 0.80 H), 2.96 (dd, *J* = 14.0 and 7.2 Hz, 1 H), 3.35-3.50 (m, 1.60 H), 3.58-3.86 (m, 0.40 H), 3.95-4.00 (m, 0.80 H), 4.08-4.15 (m, 0.20 H), 7.18-7.23 (m, 3 H), 7.26-7.30 (m, 2 H); ^{13}**C NMR** for major only (100 MHz, CDCl$_3$): δ 22.5, 30.5, 34.8, 40.2, 43.3, 68.4, 78.7, 126.3, 128.4, 129.6, 138.9. **IR**: 2950, 2925, 2840, 1604, 1494, 1454, 1377, 1174, 1090, 1030, 749, 699 cm^{-1}. **Anal. Calcd** for $C_{13}H_{18}O$: C 82.06, H 9.53. Found: C 82.18, H 9.48.

(*E*)-4-Methyl-2-styryl-3,6-dihydro-2*H*-pyran (61j):



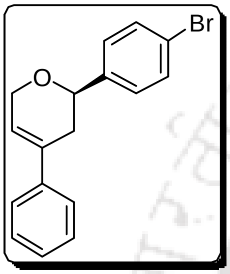
Yellow color liquid; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.73 (s, 3 H, -CH$_3$), 1.95-2.03 (m, 1 H), 2.12-2.40 (m, 1 H), 4.14- 4.21 (m, 1 H), 4.22-4.25 (m, 2 H), 5.46 (bs, 1 H), 6.28 (dd, *J* = 16.0, and 6.0 Hz, 1 H), 6.64 (d, *J* = 16.0 Hz, 1 H), 7.20-7.26 (m, 1 H), 7.28-7.31 (m, 2 H), 7.36-7.42 (m, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 23.2, 36.0, 65.9, 74.2, 119.9, 126.7, 127.8, 128.7, 130.1, 130.7, 131.7, 137.1; **IR**: 2929, 2852, 1599, 1449, 1382, 1132, 1028, 996, 747, 693 cm^{-1}. **Anal. Calcd** for $C_{14}H_{16}O$: C 83.96, H 8.05. Found: C 84.19, H 7.96.

(*E*)-4-Methyl-2-(4-nitrostyryl)-3,6-dihydro-2*H*-pyran (61k):



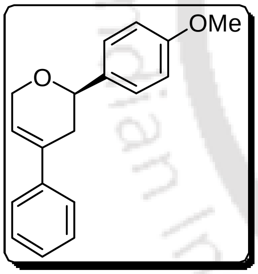
Yellow color liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.75 (s, 3 H, -CH_3), 1.90-2.10 (m, 1 H), 2.13-2.21 (m, 1 H), 4.20- 4.27 (m, 2 H), 5.44-5.50 (m, 1 H), 6.47 (dd, J = 16.0, and 5.2 Hz, 1 H), 6.72 (d, J = 16.0 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 2 H), 8.17 (d, J = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 23.1, 35.8, 66.0, 73.6, 119.9, 124.1, 127.1, 128.0, 131.4, 135.1, 143.6, 147.0; **IR**: 2961, 2931, 2826, 1596, 1516, 1342, 1133, 1110, 1071, 1012, 970, 855, 746, 690 cm^{-1}. **HRMS** (APCI) *m/z* calcd for $C_{14}H_{15}NO_3$: $(M+H)^+$ 246.1142, Found 246.1133.

2-(4-Bromophenyl)-4-phenyl-3,6-dihydro-2*H*-pyran (61l):



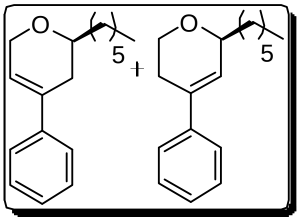
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.62-2.67 (m, 2 H), 4.52-4.56 (m, 2 H), 4.64 (t, J = 6.8 Hz, 1 H), 6.28 (t, J = 2.0 Hz, 1 H), 7.26-7.41 (m, 7 H), 7.50 (d, J = 8.4 Hz, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 35.0, 66.9, 75.4, 121.6, 122.4, 124.9, 127.7, 127.9, 128.7, 131.8, 134.4, 140.1, 141.6; **IR**: 3060, 2926, 2851, 1650, 1489, 1447, 1375, 1267, 1127, 1071, 1010, 820, 753, 697 cm^{-1}. **Anal. Calcd** for $C_{17}H_{15}BrO$: C 64.78, H 4.80.Found: C 64.85, H 4.70.

2-(4-Methoxyphenyl)-4-phenyl-3,6-dihydro-2*H*-pyran (61m):



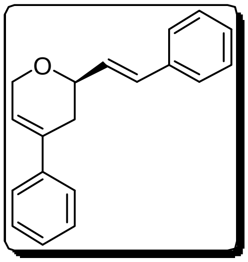
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.60-2.65 (m, 1 H), 2.67-2.76 (m, 1 H), 3.78 (s, 3 H), 4.50-4.54(m, 2 H), 4.62 (dd, J = 10.0 and 3.6 Hz, 1 H), 6.20 (d, J = 2.4 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 2 H), 7.26 (t, J = 7.2 Hz, 1 H), 7.31-7.42 (m, 6 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 34.9, 55.5, 67.0, 75.8, 114.1, 122.4, 124.5, 124.9, 127.5, 128.7, 134.6, 134.7, 140.2, 159.3; **IR**: 2929, 2836, 1613, 1514, 1446, 1249, 1176, 1124, 1033, 830, 751, 697 cm^{-1}. **Anal. Calcd** for $C_{18}H_{18}O_2$: C 81.17, H 6.81. Found: C 81.29, H 6.87.

2-Hexyl-4-phenyl-3,6-dihydro-2*H*-pyran (61n) and 6-Hexyl-4-phenyl-3,6-dihydro-2*H*-pyran (62n) (61n:62n = 75:25):



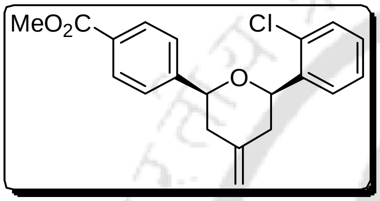
Colorless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.86–0.98 (m, 3 H), 1.24-1.40 (m, 7 H), 1.41-1.72 (m, 3 H), 2.20-2.24 (m, 0.25 H), 2.29-2.42 (m, 0.75 H), 2.60-2.66 (m, 0.25 H), 3.55-3.62 (m, 0.75 H), 3.75 (ddd, J = 10.8, and 3.6 Hz, 0.25 H), 4.10-4.25 (m, 1 H), 4.29-4.43 (m, 2 H), 6.04 (s, 0.25 H), 6.12 (s, 0.75 H), 7.20-7.60 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.2, 14.3, 22.7, 22.8, 22.9, 24.2, 25.7, 28.7, 28.9, 29.1, 29.3, 29.6, 31.1, 31.8, 32.0, 33.2, 36.2, 66.5, 74.2, 122.6, 125.0, 127.4, 128.6, 134.4, 140.6, 144.1, 155.6; **IR**: 3027, 2955, 2857, 1643, 1458, 1376, 1267, 1171, 1092, 1031, 749, 696 cm^{-1}. **Anal. Calcd** for $C_{17}H_{24}O$: C 83.55, H 9.90. Found: C 83.67, H 9.82.

(*E*)-4-Phenyl-2-styryl-3,6-dihydro-2*H*-pyran (61o):



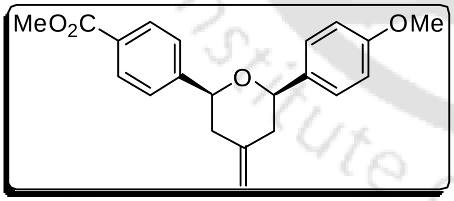
Pale yellow color liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.51-2.62 (m, 2 H), 4.30-4.36 (m, 1 H), 4.41-4.52 (m, 2 H), 6.15-6.17 (m, 1 H), 6.36 (dd, *J* = 16.0 and 6.0 Hz, 1 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 7.22-7.36 (m, 6 H), 7.40-7.43 (m, 4 H), **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 33.2, 66.3, 74.3, 122.4, 124.9, 126.7, 127.6, 127.9, 128.7, 128.8, 129.8, 131.0, 134.0, 136.9, 140.2; **IR**: 3027, 2926, 2851, 1599, 1495, 1448, 1374, 1269, 1132, 1073, 1027, 967, 750, 694 cm^{-1}. **Anal. Calcd** for $C_{19}H_{18}O$: C 86.99, H 6.92. Found: C 87.18, H 6.87.

Methyl-4-((2*S,6*R**)-6-(2-chlorophenyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)benzoate (63p):**



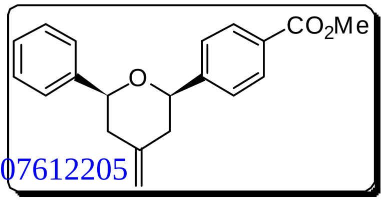
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.15 (t, *J* = 12.0 Hz, 1 H), 2.33 (t, *J* = 12.0 Hz, 1 H), 2.58 (d, *J* = 13.6 Hz, 1 H), 2.76 (d, *J* = 13.2 Hz, 1 H), 3.92 (s, 3 H), 4.64 (dd, *J* = 11.6 and 1.6 Hz, 1 H), 4.86 (dd, *J* = 11.2 and 2.4 Hz, 1 H), 4.94 (d, *J* = 1.6 Hz, 1 H), 4.97 (d, *J* = 1.6 Hz, 1 H), 7.15 (dt, *J* = 8.0 and 1.6 Hz, 1 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 7.53 (dd, *J* = 8.4 and 2.0 Hz, 3 H), 7.72 (dd, *J* = 8.0 and 1.6 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 41.4, 42.9, 52.3, 79.9, 80.4, 110.3, 121.7, 125.9, 127.7, 128.1, 129.1, 130.0, 132.8, 141.7, 143.4, 147.6, 167.2; **IR**: 2926, 2851, 1724, 1610, 1436, 1277, 1110, 1081, 1020, 895, 753, 703 cm^{-1}. **Anal. Calcd** for $C_{19}H_{17}ClO_3$: C 70.07, H 5.59. Found: C 70.25, H 5.50.

Methyl-4-((2S*,6R*)-6-(4-methoxyphenyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)benzoate (63q):



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.29 (t, *J* = 12.4 Hz, 1 H), 2.37 (t, *J* = 12.0 Hz, 1 H), 2.50-2.57 (m, 2 H), 3.81 (s, 3 H), 3.91 (s, 3 H), 4.48 (dd, *J* = 11.2 and 2.4 Hz, 1 H), 4.57 (dd, *J* = 11.6 and 2.4 Hz, 1 H), 4.90 (s, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 42.9, 43.1, 52.3, 55.5, 80.3, 80.6, 109.8, 114.0, 125.9, 127.4, 129.4, 129.9, 134.7, 144.2, 147.8, 159.3, 167.2; **IR**: 3026, 2853, 1723, 1614, 1434, 1278, 1249, 1110, 1079, 1034, 827, 771, 703 cm^{-1}. **Anal. Calcd** for $C_{21}H_{22}O_4$: C 74.54, H 6.55. Found: C 74.65, H 6.48.

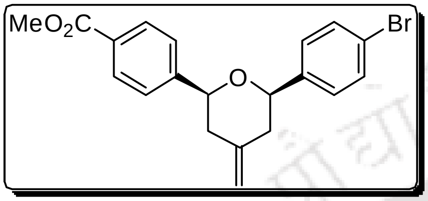
Methyl-4-((2*R,6*S**)-4-methylene-6-phenyltetrahydro-2*H*-pyran-2-yl)benzoate (63r):**



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.27-2.40 (m, 2 H), 2.53-2.59 (m, 2 H), 3.91 (s, 3H), 4.52-4.61 (m, 2 H), 4.92 (s, 2 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.38 (t, *J* = 7.2 Hz, 2 H), 7.46 (d, *J*

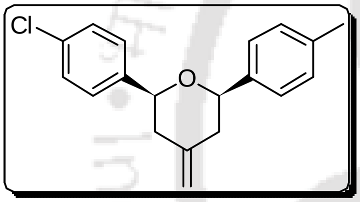
= 7.6 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 29.9, 43.1, 52.3, 80.3, 80.9, 110.0, 125.9, 126.0, 127.8, 128.6, 129.4, 129.9, 142.4, 144.0, 147.8, 167.2; **IR**: 2925, 2851, 1722, 1610, 1434, 1277, 1110, 1072, 755, 699 cm^{-1}. **Anal. Calcd** for $C_{20}H_{20}O_3$: C 77.90, H 6.54. Found: C 78.05, H 6.42.

Methyl4-((2*S,6*R**)-6-(4-bromophenyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)benzoate (63s):**



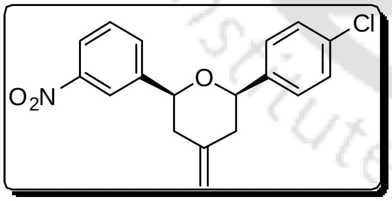
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.26-2.34 (m, 2 H), 2.50-2.59 (m, 2 H), 3.92 (s, 3 H), 4.50 (d, *J* = 11.2 Hz, 1 H), 4.98 (d, *J* = 12.0 Hz, 1 H), 4.92 (s, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.48-7.53 (m, 4 H), 8.03 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 42.9 (2C), 52.3, 80.1, 80.3, 110.3, 121.6, 125.9, 127.8, 129.5, 130.0, 131.7, 141.4, 143.5, 147.5, 167.1; **IR**: 2925, 2852, 1722, 1612, 1434, 1278, 1110, 1071, 767, 704 cm^{-1}. **Anal. Calcd** for $C_{20}H_{19}BrO_3$: C 62.03, H 4.95. Found: C 62.15, H 4.86

(2*S,6*R**)-2-(4-Chlorophenyl)-4-methylene-6-(*p*-tolyl)tetrahydro-2*H*-pyran (63t):**



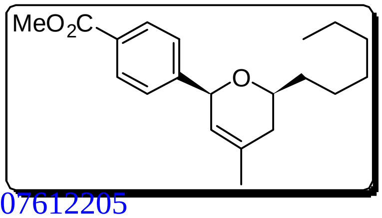
Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.24-2.37 (m, 2 H), 2.34 (s, 3 H), 2.48-2.53 (m, 2 H), 4.45-4.50 (m, 2 H), 4.88 (s, 2 H), 7.16 (d, *J* = 7.6 Hz, 2 H), 7.29-7.34 (m, 4 H), 7.37 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 21.4, 43.0, 43.1, 80.0, 80.7, 109.7, 126.0, 127.4, 128.6, 129.2, 133.2, 137.4, 139.5, 141.3, 144.3; **IR**: 3027, 2922, 2852, 1647, 1490, 1085, 1059, 809, 758 cm^{-1}. **Anal. Calcd** for $C_{19}H_{19}ClO$: C 76.37, H 6.41. Found: C 76.55, H 6.32.

(2*R,6*S**)-2-(4-Chlorophenyl)-4-methylene-6-(3-nitrophenyl)tetrahydro-2*H*-pyran (63u):**



Semisolid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.27-2.38 (m, 2 H), 2.52-2.63 (m, 2 H), 4.53 (d, *J* = 10.0 Hz, 1 H), 4.63 (d, *J* = 10.0 Hz, 1 H), 4.96 (s, 2 H), 7.34-7.40 (m, 4 H), 7.54(t, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.31 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 42.7 (2C), 79.6, 80.3, 110.7, 121.1, 122.8, 127.4, 128.8, 129.6, 132.2, 133.6, 140.5, 142.9, 144.5, 148.5; **IR**: 3076, 2925, 2853, 1651, 1529, 1492, 1349, 1089, 1072, 806, 772, 737 cm^{-1}. **Anal. Calcd** for $C_{18}H_{16}ClNO_3$: C 65.56, H 4.89, N 4.25. Found: C 65.48, H 4.75, N 4.34.

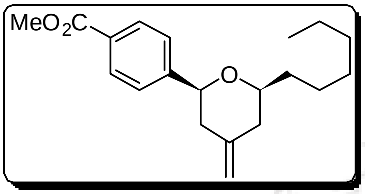
Methyl-4-((2*S,6*S**)-6-hexyl-4-methyl-5,6-dihydro-2*H*-pyran-2-yl)benzoate (61v):**



Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.88 (t, *J* = 7.4 Hz, 3 H), 1.27-1.37 (m, 6 H), 1.40-1.51 (m, 2 H), 1.55-1.63 (m, 2 H), 1.74 (s, 3 H), 2.00-2.20 (m, 2 H), 3.91(s, 3 H), 4.20-4.28 (m, 1 H), 4.63 (dd, *J* = 10.0 and 4.4 Hz, 1 H), 5.42 (brs, 1

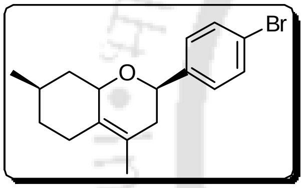
H), 7.46 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3, 22.9, 23.1, 25.3, 29.7, 32.1, 36.1, 38.2, 52.2, 75.4, 75.6, 124.5, 125.8, 129.2, 129.9, 132.1, 148.6, 167.3; **IR**: 2950, 2928, 2828, 1726, 1684, 1614, 1435, 1377, 1277, 1175, 1109, 1019, 851, 767, 704 cm^{-1}. **Anal. Calcd** for $C_{20}H_{28}O_3$: C 75.91, H 8.92. Found: C 76.12, H 8.85.

Methyl-4-((2*S,6*S**)-6-hexyl-4-methylenetetrahydro-2*H*-pyran-2-yl)benzoate (63v):**



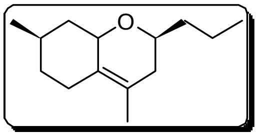
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.88 (t, *J* = 6.8 Hz, 3 H), 1.25-1.35 (m, 6 H), 1.38-1.72 (m, 4 H), 2.02 (t, *J* = 12.8, 1 H), 2.17 (t, *J* = 8.8, 1 H), 2.30 (d, *J* = 13.2, 1 H), 2.47 (d, *J* = 12.8, 1 H), 3.40-3.48 (m, 1 H), 3.91 (s, 3 H), 4.37 (dd, *J* = 11.6 and 2.0 Hz, 1 H), 4.81 (brs, 2 H), 7.45 (d, *J* = 8.4, 1 H), 8.01 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3, 22.8, 25.6, 29.6, 32.0, 36.5, 40.7, 43.0, 52.3, 79.1, 79.7, 109.2, 125.9, 129.3, 129.9, 144.7, 148.1, 167.3; **IR**: 2929, 2856, 2365, 1725, 1643, 1434, 1277, 1110, 1080, 1017, 891, 705, cm^{-1}. **Anal. Calcd** for $C_{20}H_{28}O_3$: C 75.91, H 8.92. Found: C 76.08, H 8.83.

(2*R,7*R**)-2-(4-Bromophenyl)-4,7-dimethyl-3,5,6,7,8,8a-hexahydro-2*H*-chromene (66):**



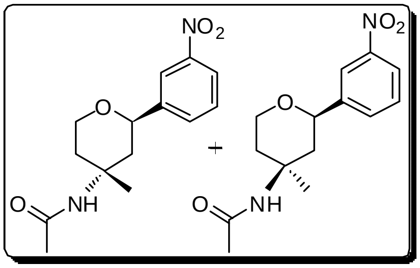
Colorless solid, mp 73-75 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.84-0.97 (m, 1 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 1.07 (q, *J* = 11.6 Hz, 1 H), 1.58-1.80 (m, 3 H), 1.68 (3 H), 1.98-2.05 (m, 1 H), 2.08-2.14 (m, 1 H), 2.22-2.28 (m, 1 H), 2.71-2.75 (m, 1 H), 4.11-4.15 (m, 1 H), 4.49 (dd, *J* = 10.8 and 2.8Hz, 1H), 7.25 (d, *J* = 8.4Hz, 2H), 7.45 (d, *J* = 8.0Hz,2H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 18.4, 22.3, 26.7, 31.2, 35.2, 39.6, 43.0, 74.7, 76.5, 121.2, 122.0, 127.9, 131.6, 131.7, 142.3; **IR**: 2951, 2882, 1401, 1265, 1114, 1087, 1010, 823, 738 cm^{-1}. **HRMS** (APCI) *m*/*z* calcd for $C_{17}H_{21}BrO$: $(M+H)^+$ 321.0854, Found 321.0863. **Specific rotation** [*α*]25 D = +121° (*C* = 0.4, $CHCl_3$).

(2*S,7*R**)-4,7-Dimethyl-2-propyl-3,5,6,7,8,8a-hexahydro-2*H*-chromene (67):**



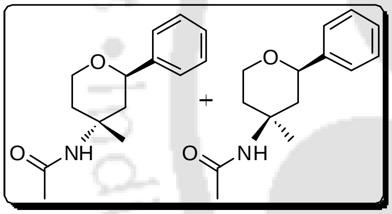
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.84-0.97 (m, 6 H), 1.32-1.49 (m, 4 H), 1.50-1.60 (m, 3 H), 1.64 (s, 3 H), 1.65-1.70 (m, 1 H), 1.74 (q, *J* = 2.4 Hz, 1 H), 1.78 (q, *J* = 2.4 Hz, 1 H), 1.94-2.06 (m, 3 H), 2.66-2.72 (m, 1 H), 3.40-3.48 (m, 1 H), 3.91-3.95 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.3, 18.4, 19.0, 22.2, 26.7, 31.2, 35.3, 37.8, 38.3, 43.1, 73.1, 75.9, 122.2, 131.5; **IR**: 2926, 2871, 1457, 1379, 1126, 1103, 1080, 1020, 872 cm^{-1}. **Anal. Calcd** for $C_{14}H_{24}O$: C 80.71, H 11.61. Found: C 80.86, H 11.51. **Specific rotation** [*α*]25 D : +52°(*C* = 0.2, $CHCl_3$).

N-((2*R,4*R**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)acetamide (74a) & N-((2*R**,4*S**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)acetamide (75a) (69:31):**



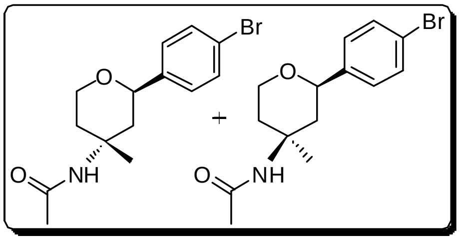
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 2.1 H), 1.65 (s, 0.9 H), 1.66-1.74 (m, 1 H), 1.79-1.90 (m, 1 H), 1.93 (s, 0.9 H), 1.96-2.10 (m, 1 H), 2.06 (s, 2.1 H), 2.33-2.36 (m, 0.3 H), 2.66-2.72 (m, 0.7 H), 3.74-3.85 (m, 1 H), 4.03-4.13 (m, 1 H), 4.56 (d, *J* = 11.6 Hz, 0.3 H), 4.61 (d,, *J* = 11.6 Hz, 0.7 H), 5.52 (s, 0.3 H), 5.60 (s, 0.7 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.23 (s, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.8, 24.3, 24.4, 27.7, 36.0, 36.5, 43.5, 44.5, 52.0, 63.9, 64.4, 73.8, 74.7, 120.7, 122.2, 122.4, 129.3, 132.1, 144.5, 144.8, 148.1, 170.1, 170.9; **IR**: 3298, 3079, 2966, 2928, 2865, 1651, 1531, 1439, 1350, 1259, 1158, 1097, 1052, 967, 908, 848, 737, 697, 684 cm^{-1}. **Anal. Calcd** for $C_{14}H_{18}N_2O_4$: C 60.42, H 6.52, N 10.07. Found: C 60.56, H 6.61, N 10.15.

N-((2*R,4*R**)-4-methyl-2-phenyltetrahydro-2*H*-pyran-4-yl)acetamide (74b) & N-((2*R**,4*S**)-4-methyl-2-phenyltetrahydro-2*H*-pyran-4-yl)acetamide (75b) (67:33):**



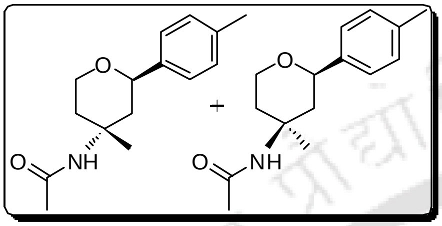
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.42 (s, 2 H), 1.51 (dd, *J* = 14.0 and 11.6 Hz, 0.67 H), 1.63 (s, 1 H), 1.67 (dd, *J* = 13.6 and 4.8 Hz, 0.33 H), 1.82 (t, *J* = 12.4 Hz, 0.33 H), 1.90 (s, 1 H), 1.94-1.98 (m, 0.67 H), 2.03 (s, 2 H), 2.13-2.21 (m, 1 H), 2.45 (dt, *J* = 14.0 and 1.6 Hz, 1H), 3.70-3.75 (m, 0.33 H), 3.77 (dt, *J* = 14.4 and 2.0 Hz, 0.67 H), 4.99 (dd, *J* = 12.4 and 4.8 Hz, 0.67 H), 4.03-4.10 (m, 0.33 H), 4.46 (dd, dt, *J* = 11.6 and 2.0 Hz, 0.33 H), 4.48 (dd, *J* = 12.0 and 2.0 Hz, 0.67 H), 5.47 (brs, 0.33 H), 5.51 (brs, 0.67 H), 7.24-7.38 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.7, 24.2, 27.7, 29.4, 29.6, 35.8, 36.7, 43.6, 44.8, 51.9, 63.8, 64.4, 74.9, 75.9, 125.8, 127.4, 128.2, 142.1, 142.2, 169.8, 170.5; **IR**: 3444, 3060, 2967, 2930, 2857, 1650, 1540, 1448, 1286, 1156, 1093, 1050, 963, 861, 751, 699 cm^{-1}. **Anal. Calcd** for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00. Found: C 72.25, H 8.15, N 6.12.

N-((2*R,4*R**)-2-(4-bromophenyl)-4-methyltetrahydro-2*H*-pyran-4-yl)acetamide (74c) & N-((2*R**,4*S**)-2-(4-bromophenyl)-4-methyltetrahydro-2*H*-pyran-4-yl)acetamide (75c) (60:40):**



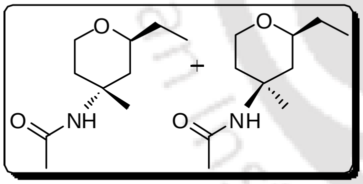
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.42 (s, 1.80 H), 1.62 (s, 1.20 H), 1.64-1.69 (m, 0.60 H), 1.70-1.80 (m, 0.40 H), 1.92 (s, 1.20 H), 1.96-2.08 (m, 1 H), 2.04 (s, 1.80 H), 2.17-2.23 (m, 1 H), 2.53 (d, *J* = 14.4 1 H), 3,77 (t, *J* = 12.4 Hz, 0.60 H), 3.90 (t, *J* = 5.6 Hz, 0.40 H), 4.01 (dd, *J* = 12.4 and 4.8 Hz, 0.60 H), 4.04-4.13 (m, 0.40H), 4.44 (d, *J* = 11.6Hz, 1H), 5.24 (brs, 0.60H), 5.31 (brs, 0.40 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.44 (*J* = 8.0 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 21.7, 24.5, 27.8, 29.6, 36.3, 36.8, 43.6, 44.8, 52.1, 59.9, 63.9, 64.5, 74.4, 75.3, 121.1, 127.6, 131.4, 141.3, 141.5, 169.9, 170.6; **IR**: 3307, 2966, 2859, 1651, 1553, 1402, 1373, 1094, 1010, 820, 733 cm^{-1}. **Anal. Calcd** for C$_{14}$H$_{18}$BrNO$_2$: C 53.86, H 5.81, N 4.49. Found: C 54.02, H 5.72, N 4.65.

N-((2*R,4*R**)-4-methyl-2-(*p*-tolyl)tetrahydro-2*H*-pyran-4-yl)acetamide (74d) & N-((2*R**,4*S**)-4-methyl-2-(*p*-tolyl)tetrahydro-2*H*-pyran-4-yl)acetamide (75d) (67:33):**



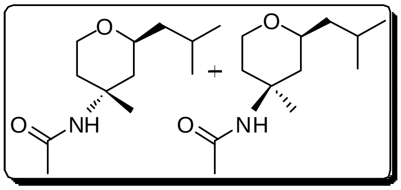
Semisolid; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.40 (s, 2 H), 1.49 (dd, J = 14.0 and 12.0 Hz, 0.67 H), 1.61 (s, 1 H), 1.64 (dd, J = 13.2 and 4.8 Hz, 0.33 H), 1.81 (t, J = 12.0 Hz, 0.33 H), 1.90 (s, 1 H), 1.92-1.98 (m, 0.67 H), 2.02 (s, 2 H), 2.12-2.20 (m, 1 H), 2.32(s, 0.67 H), 2.36-2.42 (m, 1 H), 3.68-3.79 (m, 1 H), 3.97 (dd, 3.99 (dd, J = 12.0 and 4.4Hz, 0.67 H), 4.02-4.11 (m, 0.33H), 4.42-4.47 (m, 1 H), 5.54 (brs, 0.33 H), 5.62 (brs, 0.67 H), 7.12 (d, J = 7.6 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 21.2, 21.9, 24.5, 24.6, 27.9, 36.1, 37.1, 44.0, 45.1, 52.2, 64.0, 64.6, 75.0, 75.9, 125.9, 129.1, 137.2, 139.3, 170.3; **IR**: 3446, 2961, 2859, 1650, 1550, 1373, 1094, 1053, 1023, 812, 768 cm^{-1}. **Anal. Calcd** for C$_{15}$H$_{21}$NO$_2$: C 72.84, H 8.56, N 5.66. Found: C 72.71, H 8.48, N 5.72.

N-((2*S,4*R**)-2-ethyl-4-methyltetrahydro-2*H*-pyran-4-yl)acetamide (74e) & N-((2*S**,4*S**)-2-ethyl-4-methyltetrahydro-2*H*-pyran-4-yl)acetamide (75e) (80:20):**



Semisolid; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.93 (t, J = 7.6 Hz, 3 H), 1.20 (dd, J = 14.8 and 14.0 Hz, 1 H), 1.39 (s, 2.4 H), 1.42-1.56 (m, 2.40 H), 1.51 (s, 0.60 H), 1.78-1.91 (m, 0.60 H), 1.93 (s, 0.60 H), 1.98 (s, 2.4 H), 2.00-2.05 (m, 0.40 H), 2.09-2.16 (m, 1.60 H), 3.29-3.36 (m, 1 H), 3.51-3.60 (m, 1 H), 3.83 (ddd, J = 12.0, 4.8 and 1.2 Hz, 0.80 H), 3.90 (ddd, J = 12.4, 5.2 and 1.6 Hz, 0.20 H), 5.37 (brs, 0.80 H), 5.47 (brs, 0.20 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 9.9, 21.9, 24.4, 27.9, 28.9, 29.2, 29.7, 36.2, 37.4, 41.8, 42.8, 51.8, 63.5, 64.1, 74.1, 75.1, 170.2; **IR**: 3308, 2961, 2930, 2856, 1651, 1549, 1372, 1289, 1146, 1073, 1037, 964, 758 cm^{-1}. **Anal. Calcd** for C$_{10}$H$_{19}$NO$_2$: C 64.83, H 10.34, N 7.56. Found: C 64.92, H 10.39, N 7.45.

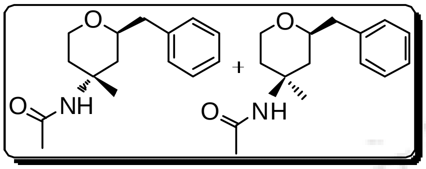
N-((2*S,4*R**)-2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-yl)acetamide (74f) & N-((2*S**,4*S**)-2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-yl)acetamide (75f) (78:22):**



Semisolid; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.89 (d, J = 6.4 Hz, 6 H), 1.10-1.26 (m, 2 H), 1.38 (s, 3 H), 1.41-1.56 (m, 2 H), 1.78 (quint., J = 6.8, 1 H), 1.98 (s, 3 H), 2.06-2.16 (m, 2 H), 3.42-3.49 (m, 1 H), 3.55 (dt, J = 12.0, 4.8 and 2.0 Hz, 1 H), 3.82 (dd, J = 11.6 and 4.4 Hz, 1 H), 5.33 (brs, 0.78 H), 5.53 (brs, 0.22 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ

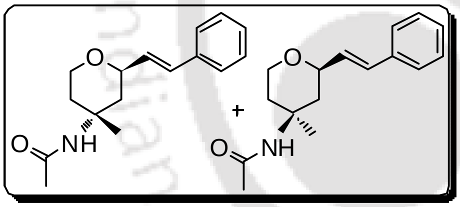
22.3, 23.3, 24.3, 24.4, 27.9, 36.3, 42.4, 45.2, 51.8, 63.5, 71.0, 170.2 (major); **IR**: 3307, 2958, 2928, 2870, 1652, 1549, 1372, 1288, 1115, 1088, 1043, 964, 758, 604; cm^{-1}. **Anal. Calcd** for $C_{12}H_{23}NO_2$: C 67.57, H 10.87, N 6.57.Found: C 67.66, H 10.75, N 6.49.

N-((2*R,4*R**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)acetamide (74g) & N-((2*R**,4*S*)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)acetamide (75g) (79:21):**



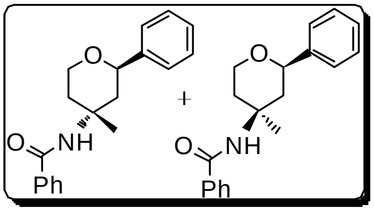
Colorless solid, mp 86-88 °C; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.36 (s, 2.37 H), 1.44 (s, 0.63 H), 1.49 (dd, *J* = 14.0 and 4.8 Hz, 2 H), 1.87 (d, *J* = 1.6 Hz, 0.63 H), 1.91 (d, *J* = 1.2 Hz, 2.37 H), 1.93-2.03 (m, 0.42 H), 2.08-2.18 (m, 1.58 H), 2.65 (dd, *J* = 13.6, and 4.8 Hz, 1 H), 2.81 (dd, *J* = 14.0, and 7.2 Hz, 1 H), 3.52 (dt, *J* = 12.0 and 1.6 Hz, 1 H), 3.61-3.67 (m, 1 H), 3.80 (dd, *J* = 12.0, and 4.8 Hz, 0.79 H), 3.85-3.99 (m, 0.21 H), 5.45 (s, 0.79 H), 5.57 (s, 0.21H), 7.13-7.40 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 24.4, 27.8, 35.8, 42.0, 42.5, 51.7, 63.6, 73.6, 126.3, 128.3, 129.4, 138.5, 170.2 (major); **IR**: 3310, 2926, 2856, 1650, 1551, 1439, 1371, 1101, 1031, cm^{-1}. **Anal. Calcd** for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66. Found: C 72.75, H 8.42, N 5.81.

N-((2*R,4*R**)-4-methyl-2-((E)-styryl)tetrahydro-2*H*-pyran-4-yl)acetamide (74h) & N-((2*R**,4*S**)-4-methyl-2-((E)-styryl)tetrahydro-2*H*-pyran-4-yl)acetamide (75h) (71:29):**



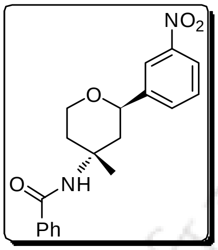
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.38 (dd, *J* = 11.6 and 2.4 Hz, 0.70 H), 1.42 (s, 2.10 H), 1.55 (s, 0.90 H), 1.60 (dd, *J* = 12.8, and 4.8 Hz, 0.30 H), 1.72-1.97 (m, 1 H), 1.94 (s, 0.90 H), 2.02 (s, 2.10 H), 2.08-2.14 (m, 1 H), 2.32-2.38 (m, 1 H), 3.63-3.74 (m, 1 H), 3.93 (dd, *J* = 12.0 and 4.0 Hz, 0.70 H), 3.98 (dd, *J* = 12.0 and 5.2 Hz, 0.30 H), 4.08-4.17 (m, 1 H), 5.47 (s, 0.70 H), 5.53 (s, 0.30 H), 6.15 (dd, *J* = 16.0, and 5.6 Hz, 1 H), 6.60 (d, *J* = 15.6 Hz, 0.30 H), 6.62 (d, *J* = 16.0 Hz, 0.70 H), 7.20-7.40 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 22.0, 24.5, 27.7, 29.5, 35.8, 36.5, 41.8, 42.5, 51.8 (2C), 63.4, 63.9, 73.1, 74.1, 126.4 (2C), 127.6, 128.0, 128.5, 128.9, 129.5, 129.6, 130.4, 130.5, 136.5, 136.7 170.2, 170.8; **IR**: 3318, 2963, 2856, 1651, 1547, 1447, 1372, 1107, 1085, 966, 746, 694 cm^{-1}. **Anal. Calcd** for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40. Found: C 74.28, H 8.25, N 5.24.

N-((2*R,4*R**)-4-methyl-2-phenyltetrahydro-2*H*-pyran-4-yl)benzamide (74i) & N-((2*R**,4*S**)-4-methyl-2-phenyltetrahydro-2*H*-pyran-4-yl)benzamide (75i) (75:25):**



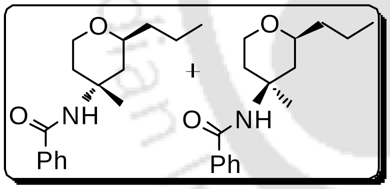
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.54 (s, 2.25 H), 1.62 (dd, *J* = 14.0 and 12.4 Hz, 1 H), 1.75 (s, 0.75 H), 1.76-1.82 (m, 0.75 H), 1.94 (t, *J* = 11.6 Hz, 0.25 H), 2.09 (dd, *J* = 7.6 and 3.2 Hz, 0.75 H), 2.25-2.35 (m, 0.50 H), 2.64 (dt, *J* = 14.4 and 2.0 Hz, 0.75 H), 3.76-3.97 (m, 1 H), 3.97-4.14 (m, 1 H), 4.56 (dd, *J* = 11.6 and 1.6 Hz, 0.75 H), 4.70 dd, *J* = 11.2 and 2.0 Hz, 0.25 H), 6.00 (brs, 1 H), 7.23-7.53 (m, 8 H), 7.66 (d, *J* = 7.2 Hz, 1 H), 7.77 (d, *J* = 7.2Hz,1H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 24.3, 24.4, 27.7, 36.0, 36.5, 43.5, 44.5, 52.0, 63.9, 64.4, 73.8, 74.7, 120.7, 122.2, 122.4, 129.3, 132.1, 144.5, 144.8, 148.1, 170.1, 170.9; **IR**: 3298, 3079, 2966, 2928, 2865, 1651, 1531, 1439, 1350, 1259, 1158, 1097, 1052, 967, 908, 848, 737, 697, 684 cm^{-1}. **Anal. Calcd** for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74. Found: C 77.45, H 7.12, N 4.66.

N-((2*R,4*R**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)benzamide (74j):**



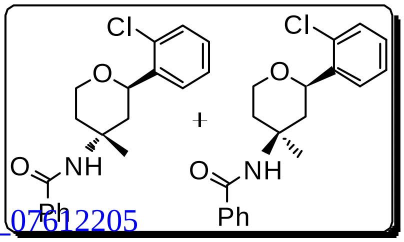
Solid, mp 153-155 °C; **^{1}H NMR** (400 MHz, CDCl$_3$): *δ* 1.51-1.60 (m, 1 H), 1.56 (s, 3H), 1.84 (ddd, *J* = 13.2 and 5.2Hz, 1H), 2.15-2.20 (m, 1 H), 2.91 (dt, *J* = 14.0 and 2.0Hz, 1H), 3.92 (dt, *J* = 12.4 and 1.6 Hz, 1 H), 4.12 (dd, *J* = 12.0 and 4.0 Hz, 1 H), 4.67 (d, *J* = 9.2 Hz, 1 H), 6.00 (brs, 1 H), 7.40-7.55 (m, 4 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.26 (s, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 27.9, 37.0, 43.4, 52.6, 64.0, 74.2, 120.9, 122.5, 126.9, 128.8, 129.4, 131.7, 132.2, 135.7, 144.6, 148.4, 167.9; **IR**: 3326, 2927, 2858, 1644, 1530, 1350, 1097, 1051, 736, 715, 695 cm^{-1}. **Anal. Calcd** for $C_{19}H_{20}N_2O_4$: C 67.05, H 5.92, N 8.23. Found: C 66.87, H 5.81, N 8.37.

N-((2*S,4*R**)-4-methyl-2-propyltetrahydro-2*H*-pyran-4-yl)benzamide (74k) & N-((2*S**,4*S**)-4-methyl-2-propyltetrahydro-2*H*-pyran-4-yl)benzamide (75k) (75:25):**



Semisolid; **^{1}H NMR** (400 MHz, CDCl$_3$): *δ* 0.88 (t, *J* = 6.8 Hz, 2.25 H), 0.95 (t, *J* = 6.8 Hz, 0.75 H), 1.20-1.38 (m, 2 H), 1.45-1.52 (m, 1 H), 1.48 (s, 2.25 H), 1.54-1.65 (m, 1 H), 1.61 (s, 0.75 H), 1.83-1.92 (m, 1 H), 1.98-2.03 (m, 1 H), 2.06-2.15 (m, 1 H), 2.19-2.30 (m, 2 H), 3.43-3.50 (m, 1 H), 3.54-3.65 (m, 1 H), 3.70-3.81 (m, 0.75 H), 3.85 (dd, *J* = 16.4 and 4.4 Hz, 0.75 H), 3.91 (dd, *J* = 12.0 and 4.4 Hz, 0.25 H), 4.07 (dd, *J* = 13.2 and 7.2 Hz, 0.25 H), 5.92 (brs, 0.75 H), 6.00 (brs, 0.25 H), 7.35-7.48 (m, 3 H), 7.67-7.71 (m, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 14.2, 18.7, 27.9, 36.5, 37.5, 38.3, 38.4, 38.5, 38.7, 42.3, 43.3, 44.7, 52.2, 63.7, 64.1, 72.7, 72.9, 73.5, 126.8, 128.5, 128.6, 131.3, 135.8, 167.5; **IR**: 3322, 2957, 2930, 2870, 1645, 1539, 1314, 1286, 1110, 1075, 1048, 714, 693 cm^{-1}. **Anal. Calcd** for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36. Found: C 73.38, H 9.06, N 5.29.

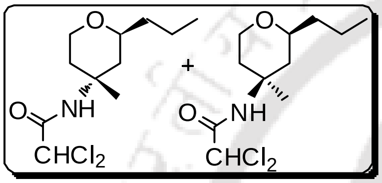
N-((2*R,4*R**)-2-(2-chlorophenyl)-4-methyltetrahydro-2*H*-pyran-4-yl)benzamide (74l) & N-((2*R**,4*S**)-2-(2-chlorophenyl)-4-methyltetrahydro-2*H*-pyran-4-yl)benzamide (75l) (60:40):**



Colorless solid, mp 105-107 °C**;** **^{1}H NMR** (400 MHz, CDCl$_3$): *δ* 1.46 (dd, *J* = 14.4 and 11.6 Hz, 1 H), 1.54 (s, 1.80 H), 1.76 (ddd, *J* = 13.2 and 4.8 Hz, 1 H), 1.77 (s, 1.20 H), 2.15-2.20 (m, 1 H), 2.37-2.44 (m, 1 H), 2.65 (d, *J* = 14.4 Hz, 1 H), 3.80-3.89

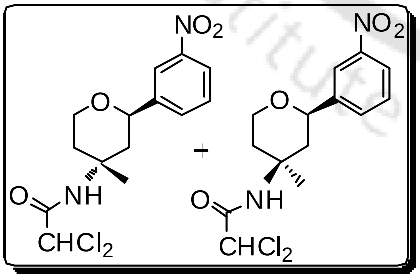
(m, 1 H), 3.99-4.18 (m, 1 H), 4.93 (d, *J* = 11.6 Hz, 0.4 H), 5.00 (d, *J* = 11.2 Hz, 0.60 H), 5.98 (brs, 0.40 H), 6.07 (brs, 0.60 H), 7.19-7.34 (m, 3 H), 7.39-7.59 (m, 4 H), 7.67-7.71 (m, 1 H), 7.78-7.81 (m, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.9, 27.8, 29.8, 31.7, 35.1, 37.1, 38.5, 43.8, 44.4, 45.4, 52.7, 52.8, 64.4, 64.8, 65.0, 68.1, 72.3, 73.1, 126.8, 127.1, 127.3, 127.3, 127.5, 128.4, 128.7, 128.9, 129.3, 131.2, 131.4, 131.6, 135.6, 135.8, 139.7, 139.9, 167.0, 167.4; **IR**: 3333, 2963, 2859, 1645, 1531, 1441, 1374, 1094, 1048, 753, 709 cm^{-1}. **Anal. Calcd** for $C_{19}H_{20}ClNO_2$: C 69.19, H 6.11, N 4.25. Found: C 69.30, H 6.17, N 4.15.

2,2-Dichloro-N-((2*S,4*R**)-4-methyl-2-propyltetrahydro-2*H*-pyran-4-yl)acetamide (74m) & 2,2-Dichloro-N-((2*S**,4*S**)-4-methyl-2-propyltetrahydro-2*H*-pyran-4-yl)acetamide (75m) (71:29):**



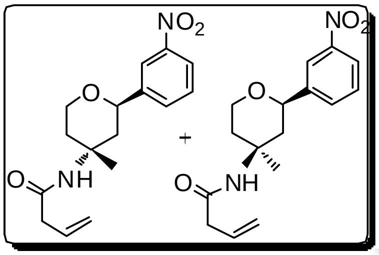
Semisolid; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.28 (dd, *J* = 14.0 and 12.0 Hz, 1 H), 1.35-1.52 (m, 4 H), 1.42 (s, 2.1 H), 1.55 (s, 0.90 H), 1.61 (ddd, *J* = 13.6, 8.8 and 4.8 Hz, 0.70 H), 1.78-1.91 (m, 0.30 H), 1.99 (dd, *J* = 14.4 and 12.4 Hz, 0.60 H), 2.13 (dd, *J* = 14.4 and 12.4 Hz, 1.40 H), 3.36-3.44 (m, 1 H), 3.56 (t, *J* = 12.4 Hz, 1 H), 3.87 (dd, *J* = 12.0 and 4.8 Hz, 0.70 H), 3.93 (dd, *J* = 12.0 and 4.0 Hz, 0.30 H), 5.82 (s, 0.30 H), 5.84 (s, 0.70 H), 6.22 (s, 0.70 H), 6.28 (s, 0.30 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.1, 18.7, 21.5, 27.3, 36.1, 36.8, 38.2, 38.4, 41.8, 42.6, 52.9, 53.1, 63.4, 64.0, 67.1, 67.3, 72.7, 73.4, 163.5; **IR**: 3297, 2961, 2933, 2872, 1682, 1557, 1450, 1346, 1144, 1113, 1079, 1008, 814, 658 cm^{-1}. **Anal. Calcd** for $C_{11}H_{19}Cl_2NO_2$: C 49.26, H 7.14, N 5.22.Found: C 9.43, H 7.02, N 5.16.

2,2-Dichloro-N-((2*R,4*R**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)acetamide (74n) & 2,2-Dichloro-N-((2*R**,4*S**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)acetamide (75n) (78:22):**



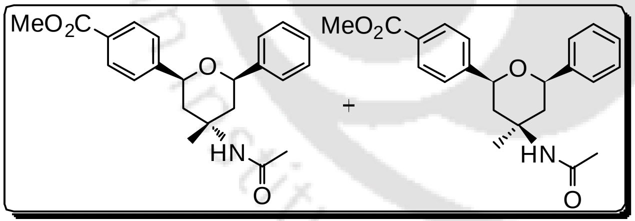
Semisolid; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.33 (s, 0.60 H), 1.42-1.60 (m, 1 H), 1.47 (s, 2.4 H), 1.75-1.90 (m, 1 H), 2.07-2.14 (m, 1 H), 2.32-2.37 (m, 0.2 H), 2.72 (dd, *J* = 14.4 and 1.6 Hz, 0.8 H), 3.82 (dt, *J* = 12.4 and 2.0 Hz, 0.8 H), 3.97-4.04 (m, 0.2 H), 4.06-4.20 (m, 1 H), 4.57 (d, *J* = 11.6 Hz, 0.8 H), 4.83 (d, *J* = 11.6 Hz, 0.20 H), 5.82 (s, 0.2 H), 5.92 (s, 0.8 H), 6.37 (brs, 1 H), 7.48-7.53 (m, 1 H), 7.64-7.70 (m, 1 H), 8.10-8.15 (m, 1 H), 8.24 (m, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 27.3, 29.8, 31.7, 36.5, 38.4, 42.9, 46.6, 53.1, 63.8, 64.2, 67.3, 68.0, 74.1, 74.8, 120.9, 121.0, 122.3, 122.6, 129.0, 129.5, 132.1, 144.3, 148.4, 163.9; **IR**: 3305, 2966, 2867, 1682, 1530, 1476, 1351, 1096, 1051, 811, 737, 716 cm^{-1}. **Anal. Calcd** for $C_{14}H_{16}Cl_2N_2O_4$: C 48.43, H 4.64, N 8.07. Found: C 48.26, H 4.71, N 8.15.

N-((2*R,4*R**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)but-3-enamide (74o) & N-((2*R**,4*S**)-4-methyl-2-(3-nitrophenyl)tetrahydro-2*H*-pyran-4-yl)but-3-enamide (75o) (67:33):**



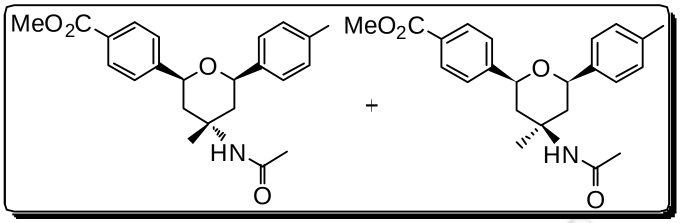
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.38- 1.50 (m, 1 H), 1.43 (s, 2 H), 1.65 (s, 1 H), 1.71 (ddd, *J* = 13.6, 8.4and 5.2 Hz, 0.67 H), 1.80 (t, *J* = 12.4 Hz, 0.33 H), 1.89 (d, *J* = 12.4 Hz, 0.33 H), 2.04 (d, *J* = 14.0 Hz, 0.67 H), 2.33 (dd, *J* = 13.2 and 2.4 Hz, 0.33 H), 2.71(dt, *J* = 14.0 and 2.0 Hz, 0.67 H), 2.93 (dt, *J* = 7.2 and 1.2 Hz, 0.66 H), 3.06 (dt, *J* = 7.2 and 1.2 Hz, 1.34 H), 3.64 (t, *J* = 15.2 Hz, 0.33 H), 3.77 (tt, *J* = 12.4 and 3.2 Hz, 0.67 H), 4.05 (dd, *J* = 12.0 and 4.0 Hz, 0.67 H), 4.11 (dd, *J* = 11.6 and 4.8 Hz, 0.33 H), 4.45-4.59 (m, 1 H), 5.16-5.23 (m, 1 H), 5.25-5.32 (m, 1 H), 5.55 (s, 0.33 H), 5.60 (s, 0.67 H), 5.89 (ddd, *J* = 10.0, 7.2 and 2.8 Hz, 0.33 H), 6.00 (ddd, *J* = 9.6, 7.2 and 3.2 Hz, 0.67 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 8.23 (m, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.8, 27.7, 36.2, 36.5, 42.3, 42.5, 43.3, 44.5, 48.2, 52.0, 63.8, 64.4, 73.8, 74.7, 119.2, 120.7, 122.2, 122.3, 129.2, 129.3, 131.5, 131.8, 132.0, 144.5, 144.7, 148.1, 170.3, 171.0; **IR**: 3394, 3310, 2927, 2863, 1650, 1531, 1350, 1097, 1052, 735, 683 cm^{-1}. **Anal. Calcd** for $C_{16}H_{20}N_2O_4$: C 63.14, H 6.62, N 9.20. Found: C 63.32, H 6.50, N 9.32.

Methyl-4-((2*S,4*R**,6*R**)-4-acetamido-4-methyl-6-phenyltetrahydro-2*H*-pyran-2-yl)benzoate (74p) & Methyl-4-((2*S**,4*S**,6*R**)-4-acetamido-4-methyl-6-phenyltetrahydro-2*H*-pyran-2-yl)benzoate (75p) (60:40):**



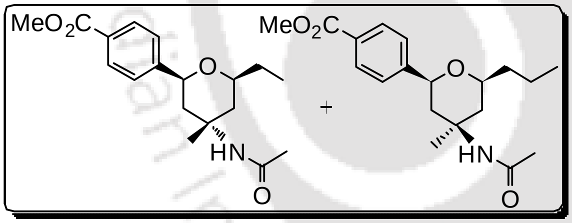
Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.45 (s, 1.8 H), 1.77 (s, 1.2 H), 1.91 (s, 1.2 H), 2.11 (s, 1.8 H), 2.20 (dm, *J* = 13.6 Hz, 1 H), 2.35 (dm, *J* = 12.8 Hz, 1 H), 2.43 (dm, *J* = 14.4 Hz, 1 H), 2.68 (dm, *J* = 14.0 Hz, 1 H), 3.91 (s, 3 H), 4.72-4.83 (m, 2 H), 5.32 (s, 0.4 H), 5.39 (s, 0.6 H), 7.28-7.31 (m, 1 H), 7.34-7.39 (m, 2 H), 7.43 (d, *J* = 7.2 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.0 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 22.5, 24.5, 24.8, 27.8, 43.4, 43.9, 44.4, 44.6, 52.2, 53.0, 53.1, 74.8, 75.2, 75.5, 76.0, 125.8, 125.9, 127.6, 127.7, 128.4, 129.0, 129.1, 129.6, 129.7, 141.9, 142.1, 147.5, 147.8, 167.2, 167.3, 170.3, 171.1; **IR**: 3368, 3060, 2926, 1718, 1657, 1543, 1371, 1280, 1112, 1091, 754, 700 cm^{-1}. **Anal. Calcd** for $C_{22}H_{25}NO_4$: C 71.91, H 6.86, N 3.81. Found: C 72.05, H 6.94, N 3.72.

Methyl-4-((2*S,4*R**,6*R**)-4-acetamido-4-methyl-6-(*p*-tolyl)tetrahydro-2*H*-pyran-2-yl)benzoate (74q) & Methyl-4-((2*S**,4*S**,6*)-4-acetamido-4-methyl-6-(*p*-tolyl)tetrahydro-2*H*-pyran-2-yl)benzoate (75q) (50:50):**



Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 1.5 H), 1.48 (dd, J = 11.6 and 2.0 Hz, 1 H), 1.59 (dd, J = 12.0 and 2.4 Hz, 1 H), 1.75 (s, 1.5 H), 1.80–1.86 (m, 0.5 H), 1.90 (s, 1.5 H), 2.10 (s, 1.5 H), 2.20 (dm, J = 13.2 Hz, 0.5 H), 2.34 (s, 1.5 H), 2.34 (s, 1.5 H), 2.38 (dm, J = 12.0 Hz, 0.5 H), 2.70 (dm, J = 14.0 Hz, 0.5 H), 3.90 (s, 3 H), 4.67-4.82 (m, 2 H), 5.43 (s, 0.50 H), 5.59 (s, 0.50 H), 7.15-7.18 (m, 2 H), 7.30-7.33 (m, 2 H), 7.48-7.50 (m, 2 H), 7.99-8.00 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.2, 22.4, 24.4, 24.6, 27.8, 43.3, 44.1, 44.6, 44.7, 52.1, 52.8, 52.9, 74.8, 75.1, 75.5, 75.9, 125.7, 125.8, 125.9, 129.1, 129.6, 129.7, 137.2, 137.3, 239.0, 139.2, 147.6, 147.9, 167.1, 169.8, 170.6; **IR**: 3305, 2951, 2924, 2861, 1721, 1656, 1547, 1436, 1280, 1111, 1089, 759 cm^{-1}. **Anal. Calcd** for $C_{23}H_{27}NO_4$: C 72.42, H 7.13, N 3.67.Found: C 72.31, H 7.29, N 3.61.

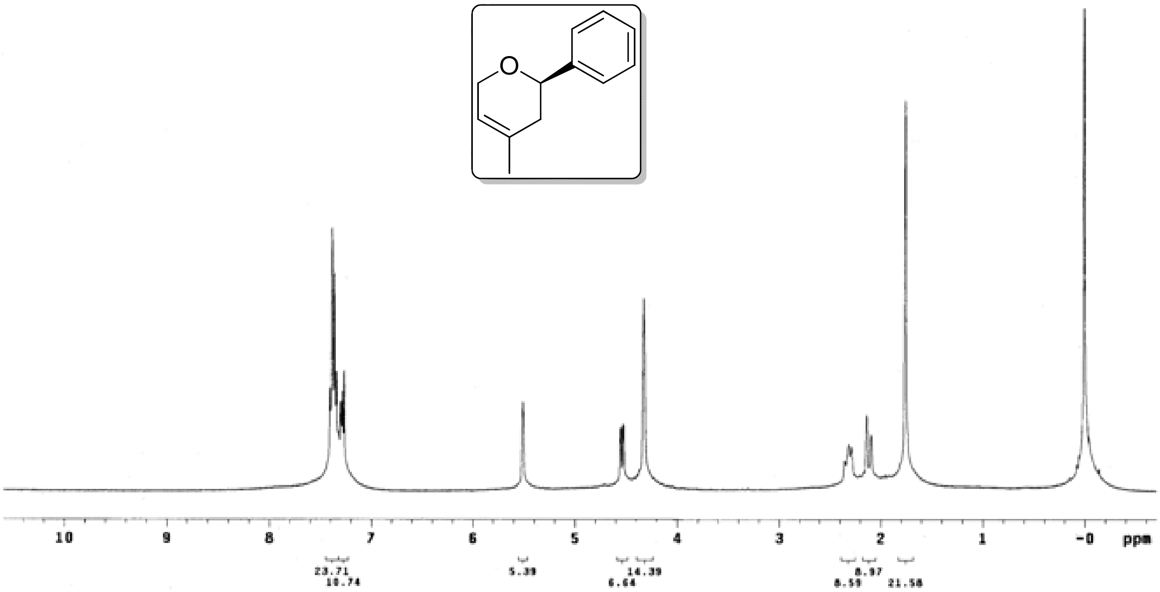
Methyl-4-((2*S,4*R**,6*S**)-4-acetamido-4-methyl-6-propyltetrahydro-2*H*-pyran-2-yl)benzoate (74r) & Methyl-4-((2*S**,4*S**,6*S**)-4-acetamido-6-ethyl-4-methyltetrahydro-2*H*-pyran-2-yl)benzoate (75r) (60:40):**

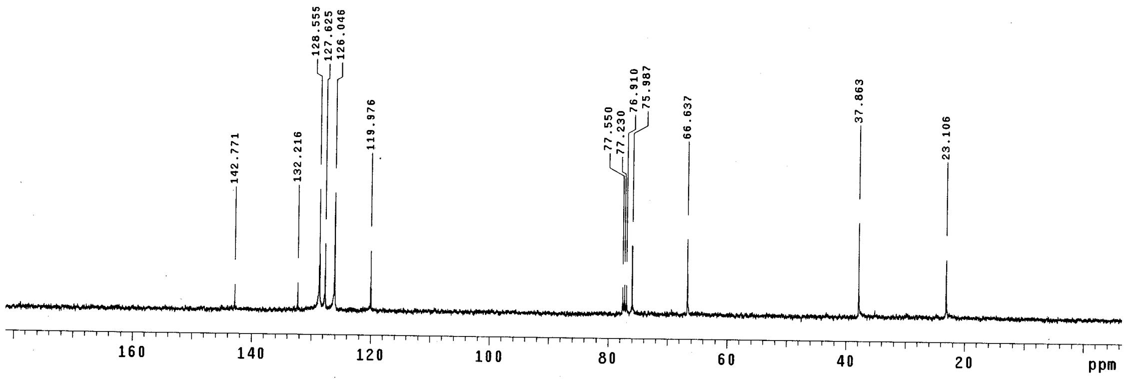


Semisolid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.90-0.99 (m, 3 H), 1.25 (s, 1.2 H), 127-1.38 (m, 1 H), 1.41 (s, 1.8 H), 1.43-1.52 (m, 1 H), 1.54-1.69 (m, 2 H), 1.93 (s, 1.2 H), 1.98 (dm, (dm, J = 12.8 Hz, 0.40 H), 2.04 (s, 1.80 H), 2.11 (dm, J = 14.0 Hz, 0.60 H), 2.24-2.33 (m, 2 H), 2.63 (dm, J = 14.0Hz, 1H), 3.61-3.72(m, 1 H), 3.90 (s, 3 H), 4.54 (d, J = 12.0 Hz, 0.40 H), 4.59 (d, J = 11.2 Hz, 0.60 H), 5.58-5.75 (brm, 1 H), 7.42 (d, J = 8.0 Hz, 2 H), 7.98 (d, J = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 13.8, 14.2, 14.3, 18.4, 18.8, 22.6, 24.5, 24.7, 27.9, 29.8, 36.2, 38.2, 38.4, 42.3, 42.6, 43.2, 44.7, 52.2, 52.9, 53.0, 73.0, 73.7, 74.3, 75.0, 125.8, 125.8, 129.0, 129.1, 129.7, 147.9, 148.1, 167.3, 170.1, 170.7, 177.9; **IR**: 3368, 2960, 1718, 1657, 1543, 1436, 1280, 1112, 1091, 754, 700 cm^{-1}. **Anal. Calcd** for $C_{19}H_{27}NO_4$: C 68.44, H 8.16, N 4.20. Found: C 68.38, H 8.25, N 4.31

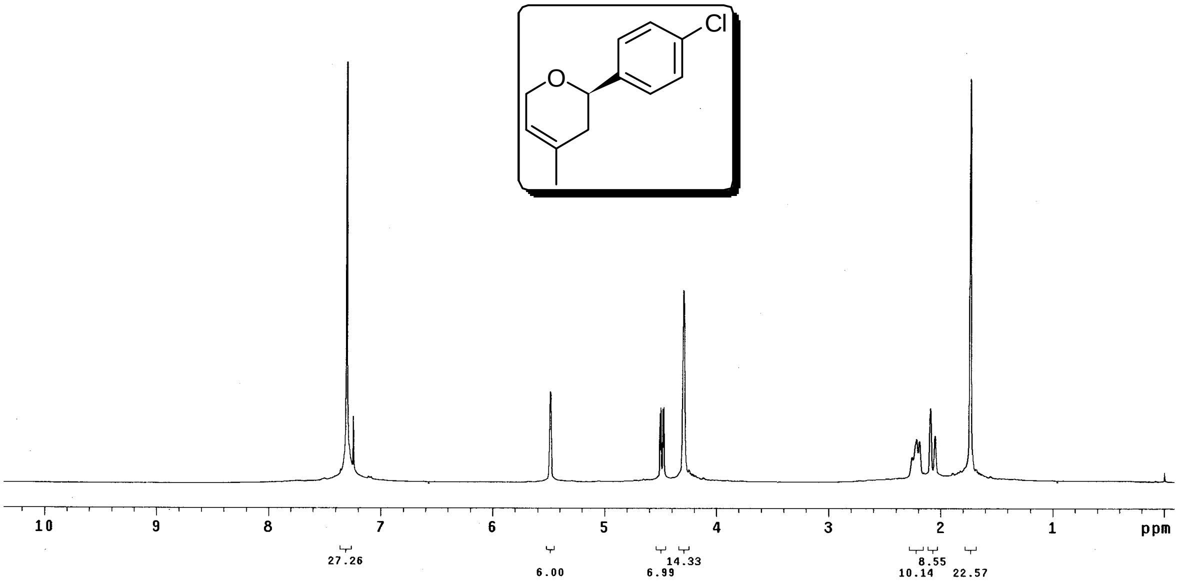
3.6. Selected Spectra of Dihydro- and Tettrahydropyrans

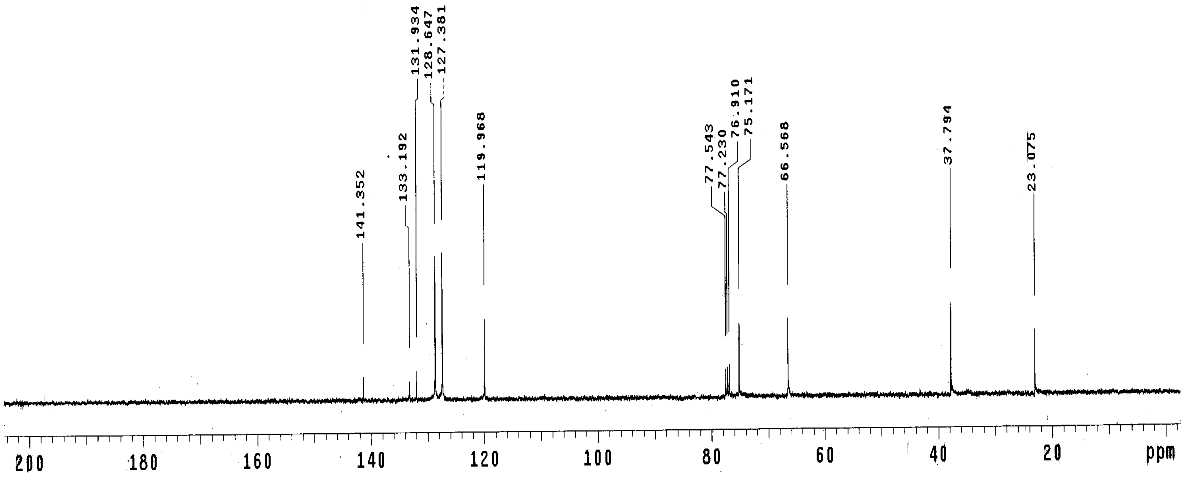
^{1}H and ^{13}C NMR spectra of **4-Methyl-2-phenyl-3,6-dihydro-*2H*-pyran:**



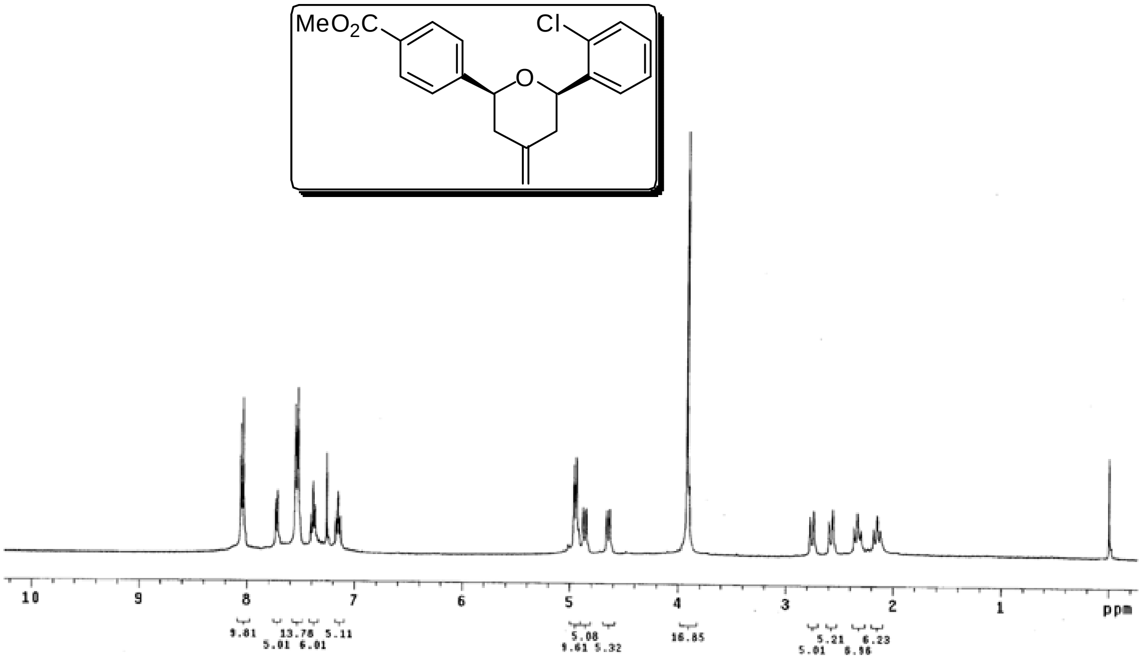


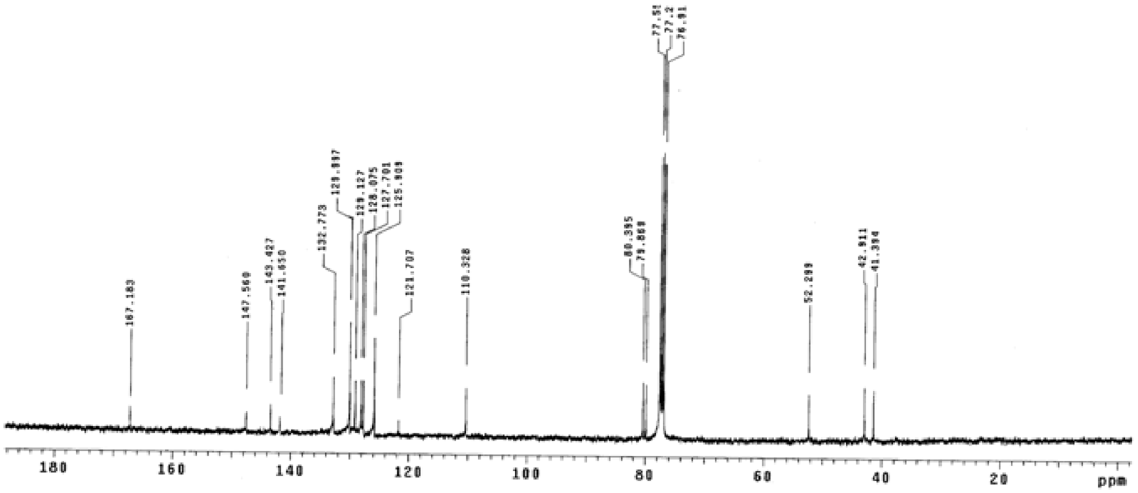
^{1}H and ^{13}C NMR spectra of **2-(4-Chlorophenyl)-4-methyl-3,6-dihydro-*2H*-pyran:**



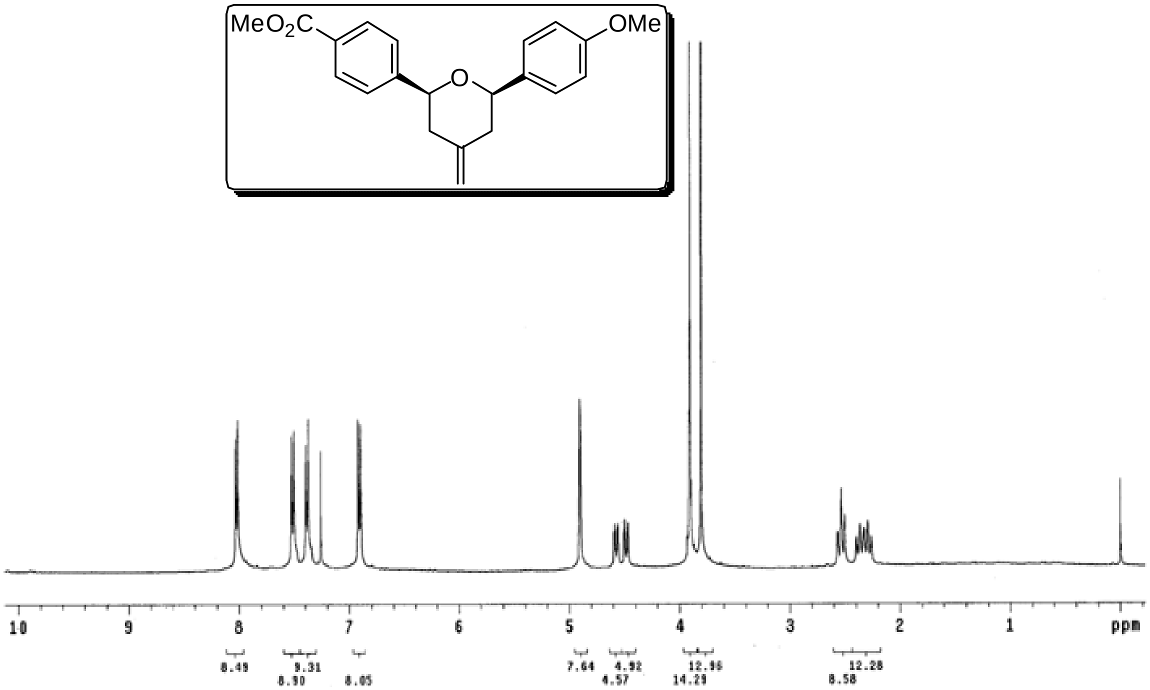


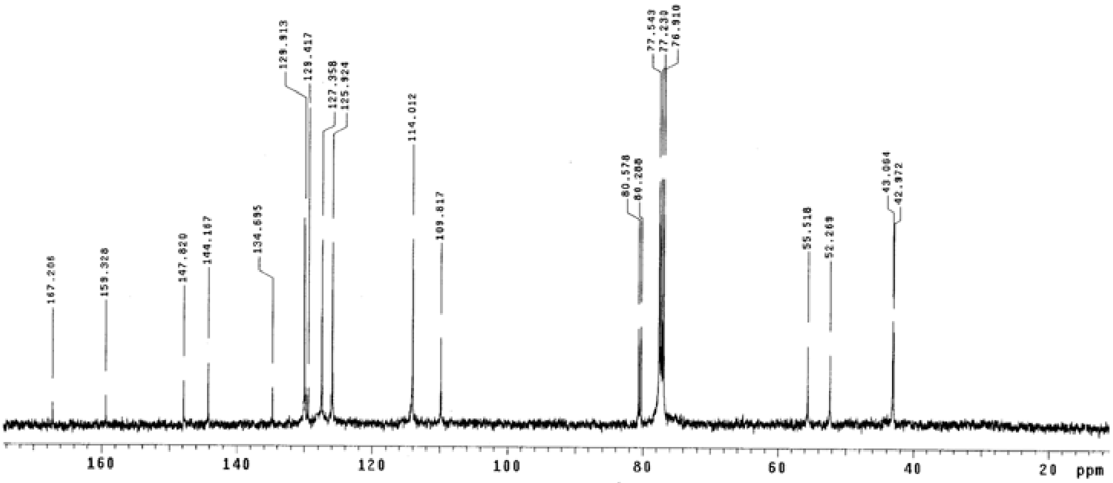
^{1}H and ^{13}C NMR spectra of **Methyl 4-((2*S**,6*R**)-6-(2-chlorophenyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)benzoate:**



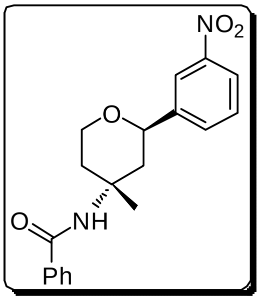


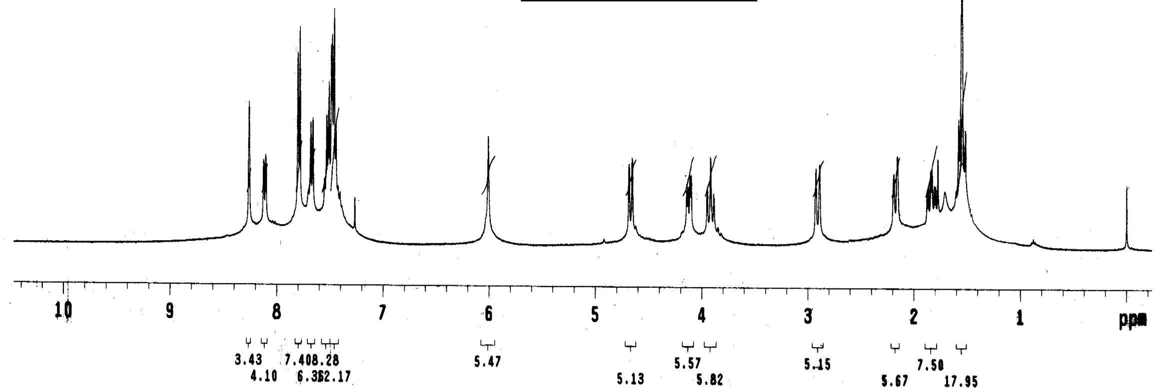
^{1}H and ^{13}C NMR spectra of **Methyl 4-((2*S**,6*R**)-6-(4-methoxyphenyl)-4-methylene-tetrahydro-*2H*-pyran-2-yl)benzoate:**

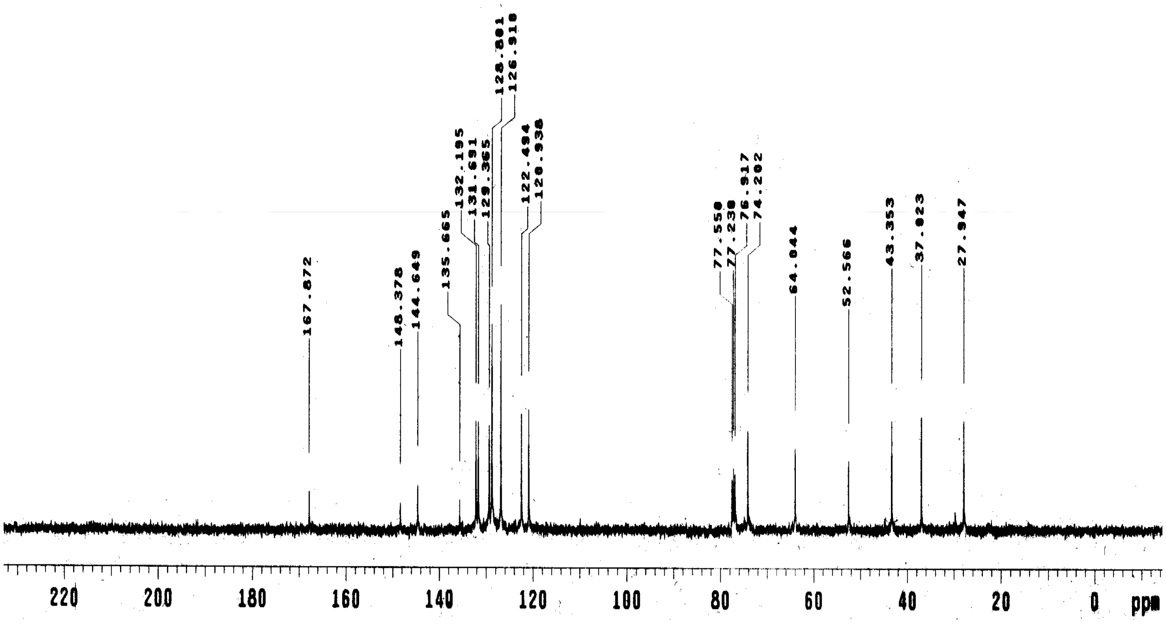




^{1}H and ^{13}C NMR spectra of **N-((2*R**,4*R**)-4-methyl-2-(3-nitrophenyl)tetrahydro-*2H*-pyran-4-yl)benzamide:**







3.7. Crystal Parameters

The crystal parameters of compound **61e**

Parameters	**61e** CCDC 765896
Formula	$C_{19}H_{20}O_4S$
Formula weight	344.41
T/K	296(2)
Crystal system	Triclinic
Space group	P (1)
a/Å	9.8247(5)
b/Å	11.1954(6)
c/Å	16.1562(9)
α/º	101.883 (3)
β/º	95.733 (3)
γ/º	91.650 (3)
V/Å^3	1728.04(16)
Z	4
Abs. Coeff./mm^{-1}	0.207
Abs. Correction	Multi-Scan
GOF on F^2	1.007
Final *R* indices	$R1 = 0.0514$
[$I > 2\sigma(I)$]	$wR2 = 0.1409$
R indices [all data]	$R1 = 0.0798$
	$wR2 = 0.1578$

The crystal parameters of compound **66**

Parameters	**66** CCDC 765895
Formula	$C_{17}H_{21}BrO$
Formula weight	321.24
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)
a/Å	4.7575 (2)
b/Å	9.8672(4)
c/Å	16.6178(6)
α/°	90.00
β/°	92.210 (2)
γ/°	90.00
V/Å^3	779.51(5)
Z	2
Abs. Coeff./mm^{-1}	2.628
Abs. Correction	Multi-Scan
GOF on F^2	1.077
Final R indices	$R1 = 0.0525$
[$I > 2\sigma(I)$]	$wR2 = 0.1308$
R indices [all data]	$R1 = 0.0605$
	$wR2 = 0.1449$

The crystal parameters of compound **74j**

Parameters	**74j**-CCDC 765895
Formula	$C_{19}H_{20}N_2O_4$
Formula weight	340.37
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/n
a/Å	11.6207(12)
b/Å	19.274(2)
c/Å	16.3163(15)
α/°	90.00
β/°	100.451(7)
γ/°	90.00
V/Å^3	3593.8(6)
Z	8
Abs. Coeff./mm^{-1}	0.089
Abs. Correction	Multi-Scan
GOF on F^2	1.003
Final R indices	$R1 = 0.0522$
[$I > 2\sigma$(I)]	$wR2 = 0.1180$
R indices [all data]	$R1 = 0.0988$
	$wR2 = 0.1411$

CHAPTER 4

Stereoselective Synthesis of Substituted Tetrahydrothiopyrans

4.1. Importance and Applications of Tetrahydrothiopyrans

Tetrahydrothiopyrans, analogues of tetrahydropyrans, are important structural units in biologically active molecules.[1] Some tetrahydrothiopyrans are found in petroleum products.[2] The sulfur analogues of mono- and oligosaccharides **1**, **2** are found to be potential glycosidase enzyme inhibitors.[3] The tetrahydriothiopyran ring also plays a key role in the biological activities of a number of pharmaceutical agents such as thiathromboxane **3** and dithiathromboxane A2 **4**.[4] Apart from these, the tetrahydrothiopyrans can be transformed into a variety of structures through simple reactions, such as hydrogenolysis, oxidation, and olefination.[5]

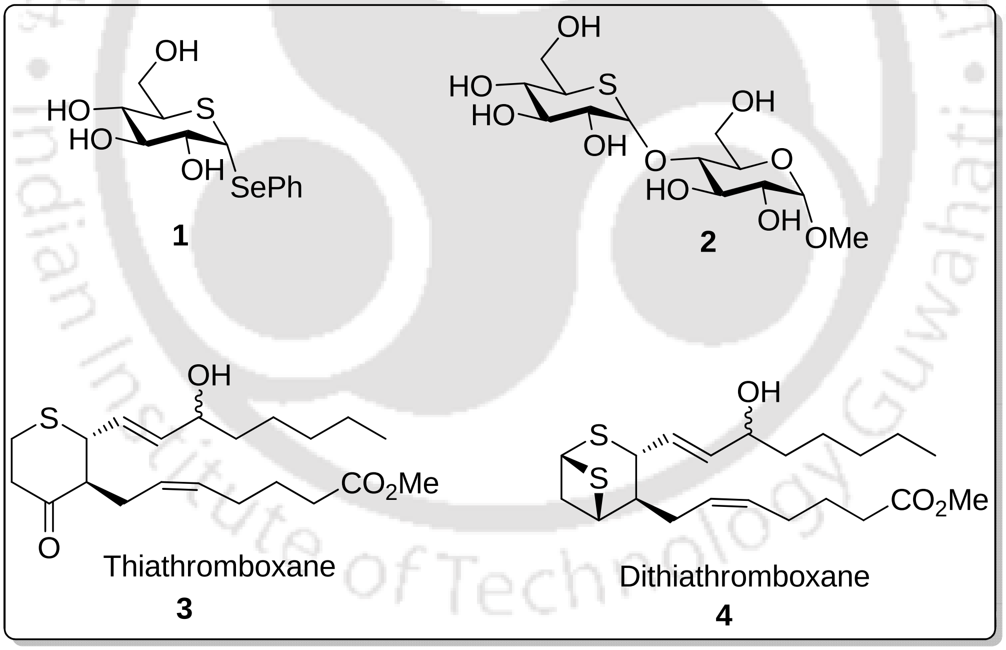
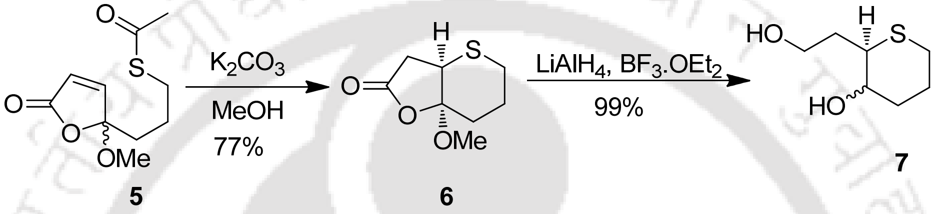


Figure 4.1. Some important biological active molecules containing tetrahydrothiopyran as a substructure.

4.2. An Overview of Relevant Synthetic Methods

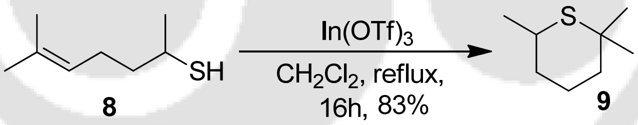
Tetrahydrothiopyrans are less frequently encountered in nature. Thus, a very few methods have been developed for their synthesis such as double-conjugate addition of sulfide to divinyl ketone, hydrothiolation of nonactivated olefins, ring-opening of epoxides by molecular thiolates, and thia-Prins cyclization. Amongst, thia-Prins cyclization has received considerable attention and showed significant progress in the synthesis of tetrahydrothiopyrans, which is already discussed in chapter 1, Section (1.3.6).

Gómez devised a method for stereoselective synthesis of 2,3-disubstituted tetrahydrothiopyrans (*Scheme 4.2.1*). The treatment of thioacetate **5** with potassium carbonate in methanol at 0 °C gives bicyclic lactone **6**, which on subsequent reduction with $LiAlH_4$ produces diastereoisomeric mixture of *cis* and *trans* 2,3-tetrahydrothiopyran diols **7**.[6]



Scheme 4.2.1.

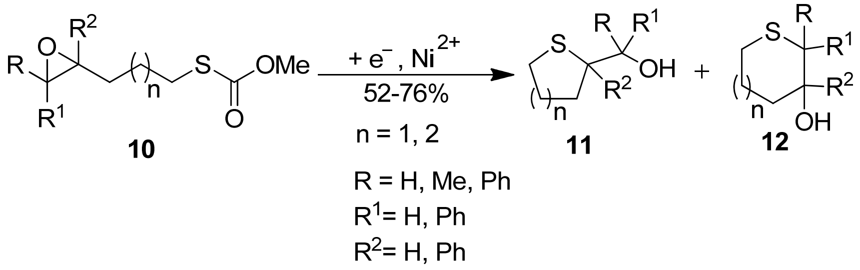
Dunach has described the intramolecular hydrothiolation of non-activated olefins **8** catalyzed by indium(III) trifluoromethanesulfonate to obtain tetrahydrothiopyrans **9**. The reaction is highly regioselective and the addition occurs in a Markovnikov’s fashion (*Scheme 4.2.2*).[7]



Scheme 4.2.2.

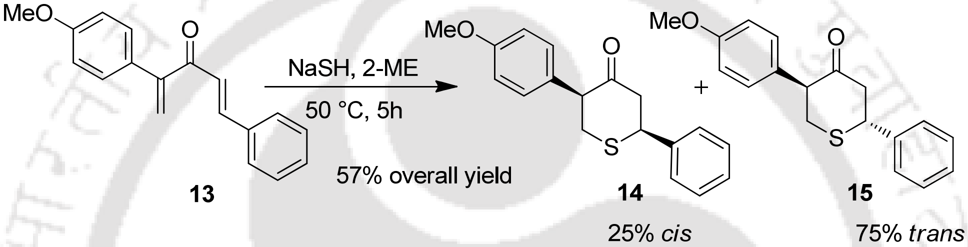
Ozaki *et al*. described the regioselective synthesis of the five-, six- and seven membered cyclic sulfides **11**, **12** through an intramolecular ring opening reaction of epoxide **10** by in situ generated thiolate ion, which is generated by selective catalytic electroreduction of the thioacetate group by a nickel(II) complex on substrate **10** (*Scheme 4.2.3*).[8]

Tetrahydrothiopyran-4-ones with aromatic substituents at 3,6 positions can be prepared by double-conjugate addition of the sulfide to the dienones **13** (*Scheme 4.2.7*). This method



Scheme 4.2.3.

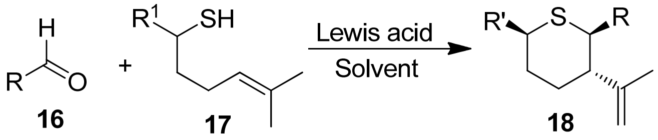
produces tetrhydrothiopyran-4-ones in moderate yields with good diastereoselectivity ranging from 75:25 to 90:10 and *trans* isomer **15** as major product.[9]



Scheme 4.2.4.

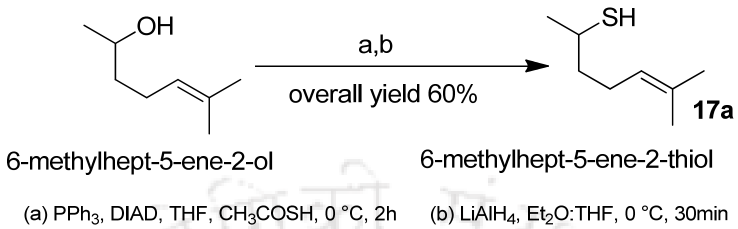
4.3. Present Work

In our previous chapter we have demonstrated a methodology for the synthesis of dihydro- and tetrahydro pyrans by using (1,5) and (2,5)-oxonium-ene reactions, respectively.[10] On the other hand, our group and Loh's group have independently developed methods for the synthesis of highly substituted tetrahydropyrans from the reaction of aldehydes with alkene bearing an hydroxyl group at γ-position via intramolecular (3,5)-oxonium-ene reaction promoted by lewis acid catalysts.[11] Taking clues from the Lewis acid catalyzed intramolecular oxonium-ene reactions we envisioned that it would be possible to synthesize highly substituted tetrahydrothiopyrans from the reaction of aldehydes with olefinic compounds having a thiol group at its γ-position mediated by Lewis acid (*Scheme 4.3.1*).



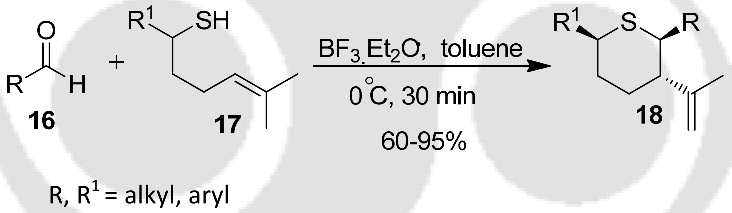
Scheme 4.3.1.

On that account, a known compound 6-methylhept-5-ene-2-thiol was prepared from the readily available 6-methylhept-5-ene-2-ol in good yield following the literature procedures (*Scheme 4.3.2*),[12] which was used as a model substrate to optimize the reaction conditions.



Scheme 4.3.2. Synthesis of thiols from alcohols

Thus, the reaction of 6-methylhept-5-ene-2-thiol **17a** with benzaldehyde **16a** in the presence of boron trifluoride etherate in toluene afforded 3-Isopropenyl-6-methyl-2-phenyl-tetrahydro-thiopyran **18a** in 86% yield with good diastereoselectivity. $BF_3{\cdot}OEt_2$ was found to be the most effective Lewis acid for this reaction as several other non-halogenated Lewis acids such as TMSOTf, $In(OTf)_3$, $Bi(OTf)_3$ and $Sc(OTf)_3$ were found to be less effective. The reaction is generalized as shown in (*scheme 4.3.3*).



Scheme 4.3.3.

In order to prove its general applicability, thiols **17k** and **17r** were synthesized similar to that of **17a** and their reactivity with a variety of alkyl and aryl aldehydes was investigated and the results are summarized in (*Table 4.3.1*). It was observed that the reaction holds good for both lectron-withdrawing as well as electron-donating groups on the aromatic ring of the aromatic aldehydes.

The reaction is diastereoselective as determined from the ^{1}H and ^{13}C NMR spectrum of the crude product and in all the cases, the substituents at 2 and 3 are *trans*, whereas substituents at 2 and 6 are in *cis* position. The structure of the compounds was determined by ^{1}H NMR and NOE experiments (*Figure 4.3.1*). The strong NOE between H-2 and H-6 protons of **18b** indicates that they are in *cis* position. The coupling constant between H-2 and H-3 was found to be 11.2 Hz, which indicates that protons H-2 and H-3 are *trans* and therefore the propenyl group and aryl groups are in *trans*-position. Finally the structure of **18b** was confirmed by X-ray crystallographic analysis (*Figure 4.3.2*).

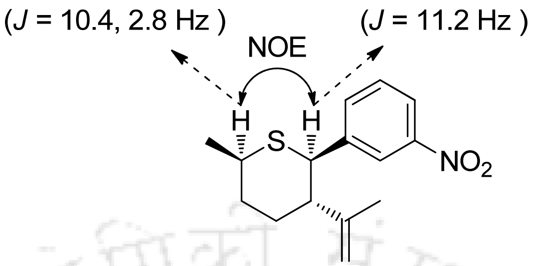


***Figure 4.3.1*:** Coupling constants and NOE of compound **18b**

It was observed that the aromatic aldehydes having electron-withdrawing groups gave better yields compared to aromatic aldehydes having electron-donating groups. This might be due to the increase in electrophilicity of the thiocarbenium ion (species **20**, *Scheme 4.3.4*), caused by the electron withdrawing character of the aryl ring, which in turn is attacked by the double bond effectively. On the other hand, the electron donating groups on the aromatic ring decreases the electrophilicity of the thiocarbenium ion. Further, the reaction with aliphatic aldehydes also gave good yields. Interestingly, electron rich aromatic aldehyde, 3,4,5-trimethoxybenzaldehyde (entry **g** and **p**) gave tricyclic compounds **18g** and **18p**, whereas phenylacetaldehyde (entry **j** and **m**) resulted benzothiochromenes **18j** and **18m**. It is evident from the above two results that the reaction proceeds through a stepwise manner via carbocation intermediate but not in a concerted fashion. The structure of **18m** was confirmed by X-ray crystallographic analysis.[13] The reaction is very fast and within 30 min all the starting materials are consumed to give the products. This may be attributed to the extra stability imparted by the sulfur d-orbital.

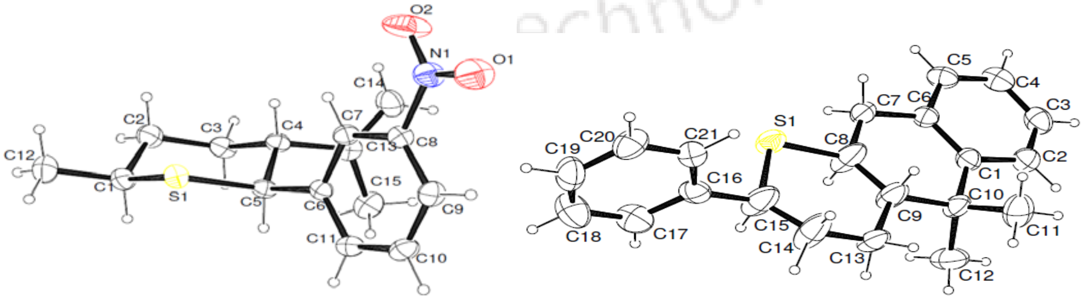
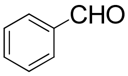
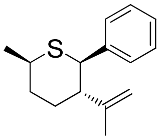
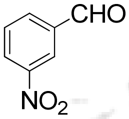
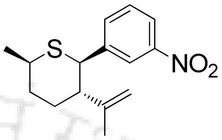
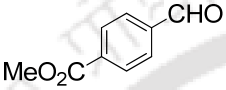
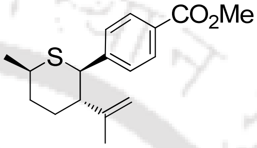
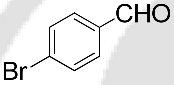
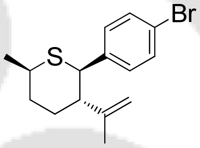
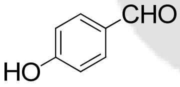
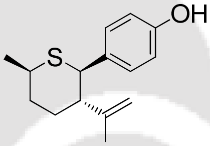
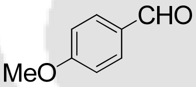
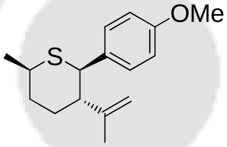
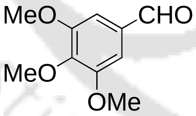
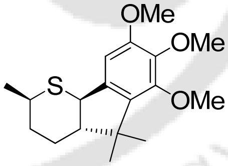
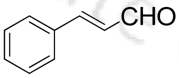
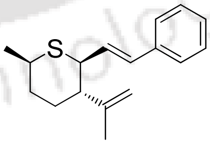
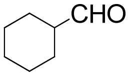
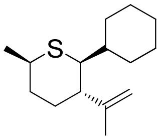
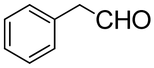
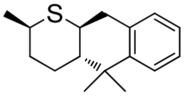
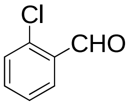
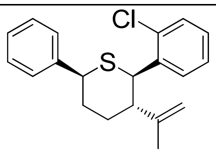
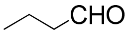
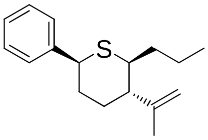
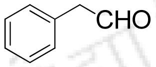
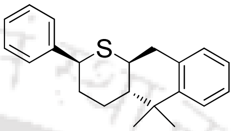
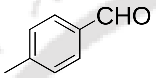
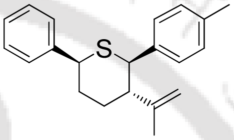
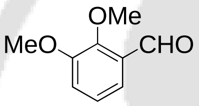
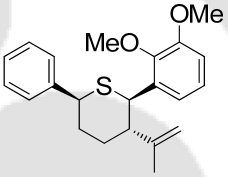
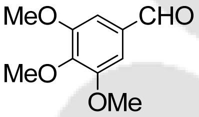
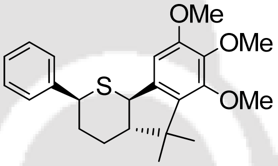
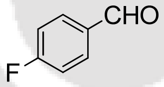
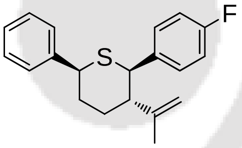
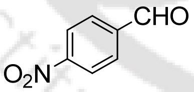
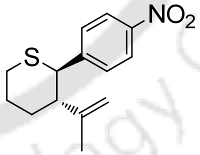


***Figure 4.3.2*:** ORTEP diagrams of compounds **18b** and **18m**

Table 4.3.1. Synthesis of Tetrahydrothiopyrans

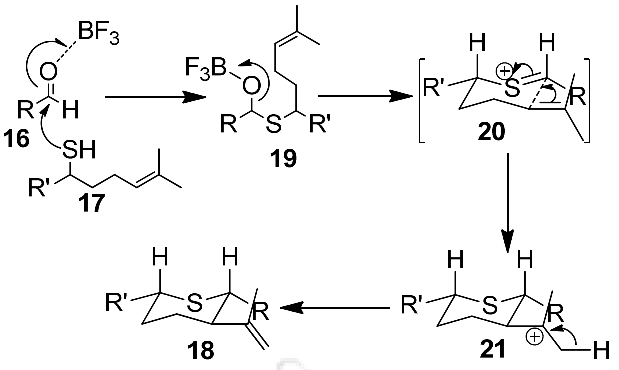
Entry	Aldehyde **16**	Thiol **17** R^1	Product **18**	Yield (%)[a]
a		Me		86
b		Me		90
c		Me		95
d		Me		94
e		Me		75
f		Me		81
g		Me		60
h		Me		92
i		Me		85
j		Me		65

Continued………….

Entry	Aldehyde **16**	Thiol **17** R^1	Product **18**	Yield (%)[a]
k		Ph		73
l		Ph		75
m		Ph		64
n		Ph		78
o		Ph		72
p		Ph		78
q		Ph		85
r		H		91

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

The mechanism of the reaction can be explained as follows. Lewis acid activates the carbonyl group of aldehyde **16** to facilitate the nucleophilic attack by thiol **17** to give the acetal **19**, which immediately converted to thionium ion **20**. This thionium ion **20** after cyclization provides carbocation **21**, which after elimination of proton gives tetrahydrothiopyrans **18**.



Scheme 4.3.4: *Mechanism of (3,5)-thionium-ene reaction*

Conclusion:

We have developed boron trifluoride etherate mediated (3,5)-thionium-ene cyclization, which provides a versatile approach to synthesize polysubstituted tetrahydrothiopyrans in good yields with excellent diastereoselectivity. Further we have investigated the stepwise mechanism of the developed (3,5)-thionium-ene cyclization reaction by trapping the in situ generated carbocation with electron rich aromatic ring. The present approach is very mild and convenient, and is expected to find useful applications in synthesis of S-heterocycles.

4.4. Experimental section

4.4.1. Instrumentation and Characterization

As described in chapter 2 section 2.6.1

4.4.2. Synthesis of Thiols: The thiols **17a**, **17k** and **17r** were synthesized according to the literature preocedures.[12] The compound **17a** is known, and the analyses were consistent with the literature.[12]

4.4.3. General procedure for the synthesis of Tetrahydrothiopyrans 18a-18r:

6-Methyl-hept-5-ene-2-thiol (1.2 equiv) in 2 mL of toluene was added dropwise to a stirring mixture of benzaldehyde (1.0 equiv), boron trifluoride etherate (1.0 equiv), and toluene (2 mL) at 0 °C. Then the stirring was continued at the same temperature for 30 min and then poured into saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with ethyl acetate and then washed with brine and water. The organic layers were collected, dried over Na_2SO_4, filtered and concentrated. Then the resultant crude residue was purified by column chromatography over silica gel (petroleum ether/EtOAc; 98:2) to give the title compounds **18a-18r**.

Synthesis of 3-isopropenyl-6-methyl-2-phenyl-tetrahydrothiopyran

(18a, Table 4.3.1): 6-Methyl-hept-5-ene-2-thiol (86 mg, 0.6 mmol) in 2 mL of toluene was added dropwise to a stirring mixture of benzaldehyde (53 mg, 0.5mmol), boron trifluoride etherate (63 μL, 0.5 mmol), and toluene (2 mL) at 0 °C. Then the stirring was continued at the same temperature for 30 min and then poured into saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with ethyl acetate and then washed with brine and water. The organic layers were collected, dried over Na2SO4, filtered and concentrated. Then the resultant crude residue was purified by column chromatography over silica gel (petroleum ether/EtOAc; 98:2) to give 3-Isopropenyl-6-methyl-2-phenyl-tetrahydro-thiopyran **18a** (100 mg, 86%) as a pale yellow liquid.

4.5. References and Notes

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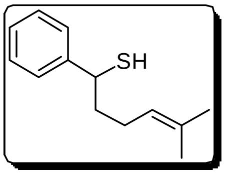
11) (a) Saha, P.; Bhunia. A.; Saikia, A. K. *Org. Biomol. Chem.* **2012**, *10*, 2470-2481. (b) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669-2672.
12) Stach, D.; Zheng, Y. F.; Perez, A. L.; Oehlschlager, A. C. *J. Med. Chem.* **1997**, *40*, 201-209.
13) The crystallographic data for compounds **18b** and **18m** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication nos. CCDC 848785 and 848786

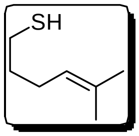
4.6. Spectral Data

5-Methyl-1-phenylhex-4-ene-1-thiol 17k:



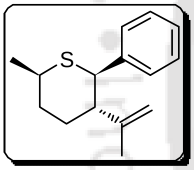
Pale yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.53 (s, 3 H), 1.68 (s, 3 H), 1.90 (d, *J* = 5.2 Hz, 1 H), 1.93-2.05 (m, 4 H), 3.97 (dt, *J* = 7.2 and 5.2 Hz, 1 H), 5.07 (t, *J* = 6.8 Hz, 1 H), 7.20-7.25 (m, 2 H), 7.29-7.35 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.9, 25.9, 26.4, 39.8, 43.6, 123.2, 127.0, 127.2, 128.7, 132.6, 144.8; **IR** (KBr, Neat): 3027, 2929, 1601, 1493, 1453, 1252, 1167, 1072, 758 cm^{-1}. **HRMS** (APCI) cald. for $C_{13}H_{18}S$ $(M+H)^+$ requires 207.1202; found 207.1202.

5-Methylhex-4-ene-1-thiol 17r:



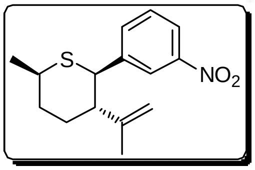
Pale yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.2 Hz, 1 H), 1.62 (s, 3 H), 1.64 (t, *J* = 7.2 Hz, 2 H), 1.69 (s, 3 H), 2.06-2.11 (m, 2 H), 2.52 (q, *J* = 7.2, 2 H), 5.08 (t, *J* = 7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.9, 24.3, 25.9, 26.8, 34.3, 123.4, 132.5; **IR** (KBr, Neat): 2924, 2853, 1646, 1458, 1377, 1267, 1152, 748 cm^{-1}. **HRMS** (APCI) cald. for $C_7H_{14}S$ $(M+H)^+$ requires 131.0889; found 131.0891.

(2*R,3*S**,6*R**)-6-Methyl-2-phenyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18a):**



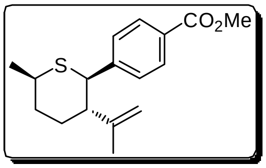
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.55-1.60 (m, 2 H), 1.91-2.00 (m, 1 H), 2.10 (dt, *J* = 10.4 and 2.8 Hz, 1 H), 2.63 (dt, *J* = 14.0 and 2.8 Hz, 1 H), 2.97-3.06 (m, 1 H), 3.90 (d, *J* = 10.8 Hz, 1 H), 4.56 (t, *J* = 1.2 Hz, 1 H), 4.59 (s, 1 H), 7.17-7.22 (m, 1 H), 7.23-7.28 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.2, 33.8, 37.2, 39.8, 51.0, 51.5, 112.3, 127.3, 128.3, 128.4, 140.8, 147.5; **IR** (KBr, Neat): 2960, 2922, 1644, 1450, 1374, 1159, 1070, 888 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{20}S$ $(M+H)^+$ requires 233.1358; found 233.1350.

(2*R,3*S**,6*R**)-6-Methyl-2-(3-nitrophenyl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18b):**



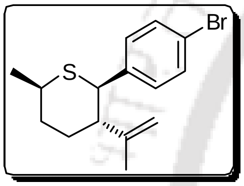
Pale Yellow crystalline solid, mp 100-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.52-1.65 (m, 2 H), 1.95-2.05 (m, 1 H), 2.09-2.19 (m, 1 H), 2.63 (dt, *J* = 10.4 and 2.8 Hz, 1 H), 2.97-3.06 (m, 1 H), 3.99 (d, *J* = 11.2 Hz, 1 H), 4.57- 4.61 (m, 2 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 8.07 (d, *J* = 7.2 Hz, 1 H), 8.16 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.1, 33.4, 37.0, 40.0, 50.1, 51.5, 113.1, 122.4, 123.4, 129.3, 134.6, 143.1, 146.6, 148.3; **IR** (KBr, Neat): 2963, 2924, 1639, 1529, 1448, 1350, 1267, 1098, 891 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{19}NO_2S$ $(M+H)^+$ requires 278.1209; found 278.1223.

Methyl-4-((2*R,3*S**,6*R**)-6-methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran-2-yl)benzoate (18c):**



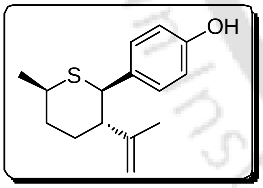
Pale yellow Crystalline solid, mp 58-60 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.4 Hz, 3 H), 1.47 (s, 3 H), 1.53-1.64 (m, 2 H), 1.92-2.00 (m, 1 H), 2.07-2.17 (m, 1 H), 2.63 (dt, *J* = 14.0 and 2.8 Hz, 1 H), 2.98-3.06 (m, 1 H), 3.89 (s, 3 H), 3.96 (d, *J* = 10.8 Hz, 1 H), 4.54-4.58 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 21.1, 33.6, 37.1, 39.9, 50.8, 51.5, 52.1, 112.6, 128.4, 129.1, 129.8, 146.1, 147.0, 167.0; IR (KBr, Neat): 2954, 2923, 1722, 1610, 1435, 1375, 1279, 1112, 1019, 752 cm^{-1}**.** **HRMS** (APCI) cald. for $C_{17}H_{22}O_2S$ $(M+H)^+$ requires 291.1413; found 291.1406.

(2*R,3*S**,6*R**)-2-(4-Bromophenyl)-6-methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18d):**



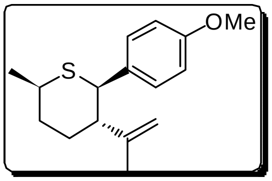
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (d, *J* = 7.2 Hz, 3 H), 1.48 (s, 3 H), 1.50-1.60 (m, 2 H), 1.90-1.97 (m, 1 H), 2.08-2.12 (m, 1 H), 2.56 (dt, *J* = 11.2 and 2.8 Hz, 1 H), 2.96-3.05 (m, 1 H), 3.86 (d, *J* = 10.8 Hz, 1 H), 4.57-4.59 (m, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.1, 33.7, 37.1, 39.9, 50.3, 51.6, 112.6, 121.0, 130.0, 131.6, 139.9, 147.1; **IR** (KBr, Neat): 2960, 2922, 1644, 1448, 1374, 1074, 1010, 890, 771 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{19}BrS$ $(M+H)^+$ requires 311.0464; found 311.0464.

4-((2*R,3*S**,6*R**)-6-Methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran-2-yl)phenol (18e):**



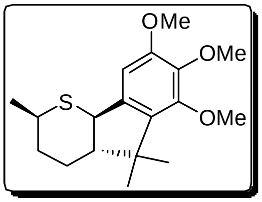
Brownish liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.53-1.59 (m, 2 H), 1.89-1.96 (m, 1 H), 2.06-2.11 (m, 1 H), 2.57 (dt, *J* = 11.2 and 2.8 Hz, 1 H), 2.97-3.05 (m, 1 H), 3.84 (d, *J* = 10.8 Hz, 1 H), 4.56-4.60 (m, 2 H), 6.71 (d, *J* = 8.4 Hz, 2 H), 7.13 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.2, 33.8, 37.2, 40.1, 50.4, 51.7, 112.3, 115.5, 129.5, 132.7, 147.7, 154.9; **IR** (KBr, Neat): 3453, 2956, 2867, 1637, 1467, 1335, 1114, 1028, 738 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{20}OS$ $(M+H)^+$ requires 249.1308; found 249.1301.

(2*R,3*S**,6*R**)-2-(4-Methoxyphenyl)-6-methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18f):**



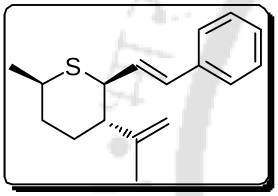
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.51-1.59 (m, 2 H), 1.89-1.96 (m, 1 H), 2.04-2.11 (m, 1 H), 2.89 (dt, *J* = 10.8 and 2.8 Hz, 1 H), 2.97-3.05 (m, 1 H), 3.77 (s, 3 H), 3.87 (d, *J* = 10.8 Hz, 1 H), 4.57-4.60 (m, 2 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.2, 33.9, 37.2, 39.9, 50.2, 51.7, 55.2, 112.2, 113.8, 129.3, 132.9, 147.7, 158.7; **IR** (KBr, Neat): 2922, 2836, 1644, 1450, 1301, 1247, 1176, 1037, 811 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{22}OS$ $(M+H)^+$ requires 263.1464; found 263.1469.

(2*R,4a*S**,9b*R**)-6,7,8-Trimethoxy-2,5,5-trimethyl-2,3,4,4a,5,9b-hexahydroindeno[1,2-b]thiopyran (18g):**



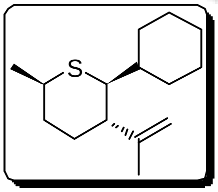
Pale yellow liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3 H), 1.42 (s, 3H), 1.45-1.56 (m, 2 H), 1.81-1.92 (m, 2 H), 2.16-2.21 (m, 1 H), 2.97-3.05 (m, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.89 (dd, *J* = 10.8 and 1.2 Hz, 1 H), 3.92 (s, 3 H), 6.51 (d, *J* = 1.2 Hz, 1 H); ^{13}**C NMR** (100 Hz, $CDCl_3$): δ 21.1, 21.5, 25.5, 26.4, 37.6, 39.9, 45.3, 50.1, 56.2, 60.4, 60.7, 60.9, 101.9, 135.6, 136.9, 141.7, 150.7, 153.1; **IR** (KBr, Neat): 2960, 2923, 1639, 1448, 1374, 1261, 1172, 1034, 786 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{26}O_3S$ $(M+H)^+$ requires 323.1675; found 323.1687.

(2*S,3*S**,6*R**)-6-Methyl-3-(prop-1-en-2-yl)-2-((*E*)-styryl)tetrahydro-2*H*-thiopyran (18h):**



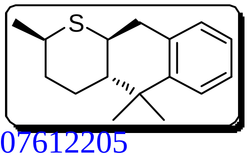
Colourless liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.20 (d, *J* = 6.4 Hz, 3 H), 1.47 (ddd, *J* = 11.2, 10.8 and 10.0 Hz, 1 H), 1.55-1.67 (m, 1 H), 1.63 (s, 3 H), 1.83 (dt, *J* = 10.0 and 2.8 Hz, 1 H), 2.02-2.08 (m, 1 H), 2.27 (dt, *J* = 11.2 and 2.8 Hz, 1 H), 2.92-2.98 (m, 1 H), 3.57 (t, *J* = 10.0 Hz, 1 H), 4.70-4.80 (m, 2 H), 6.99 (dd, *J* = 15.6 and 8.8 Hz, 1 H), 6.51(d, *J* = 15.6 Hz, 1 H), 7.18-7.22 (m, 2 H), 7.25-7.33 (m, 3 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 19.7, 21.3, 32.9, 36.9, 38.7, 48.0, 52.2, 112.1, 126.5, 127.6, 128.6, 128.9, 132.0, 137.1, 147.9; **IR** (KBr, Neat): 2960, 2922, 1644, 1448, 1374, 1159, 1028, 890 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}S$ $(M+H)^+$ requires 259.1515; found 259.1518.

(2*S,3*S**,6*R**)-2-Cyclohexyl-6-methyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18i):**



Pale yellow liquid; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.10-1.26 (m, 2 H), 1.20 (d, *J* = 6.8 Hz, 3 H), 1.33-1.58 (m, 6 H), 1.63 (s, 3 H), 1.67-1.78 (m, 6 H), 1.94-2.00 (m, 1 H), 2.36 (dt, *J* = 11.2 and 2.8 Hz, 1 H), 2.75-2.81 (m, 2 H), 4.75 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 18.9, 21.8, 26.7 (2C), 26.9, 27.1, 32.4, 34.0, 37.3, 38.3, 39.4, 49.6, 52.3, 112.0, 148.3; **IR** (KBr, Neat): 2923, 2852, 1639, 1448, 1371, 1267, 889 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}S$ $(M+H)^+$ requires 239.1828; found 239.1828.

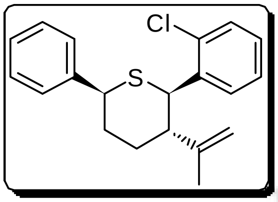
(2*R,4a*S**,10a*S**)-2,5,5-Trimethyl-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[g]thiochromene (18j):**



Light yellow solid, mp 83-85 °C; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.12 (s, 3 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 1.37 (s, 3 H), 1.41-1.51 (m, 1 H), 1.55 (dt, *J* = 11.2 and 2.4 Hz, 1 H), 2.05- 2.15 (m, 3 H), 2.76 (dd, *J* = 16.0 and 12.0

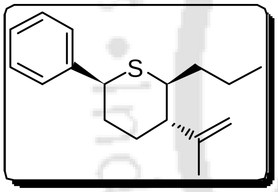
Hz, 1 H), 2.86-2.94 (m, 2 H), 3.18 (ddd, *J* = 11.6, 5.2 and 4.8 Hz, 1 H), 7.00 (d, *J* = 8.0, 1 H), 7.10 (t, *J* = 7.2, 1 H), 7.18 (t, *J* = 7.2, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 21.4, 27.5, 27.9, 28.6, 36.9, 37.6, 38.0, 38.7, 48.5, 125.7, 126.5, 127.2, 128.4, 133.5, 146.1; **IR** (KBr, Neat): 2962, 2884, 1633, 1491, 1447, 1364, 1291, 1174, 1034, 764, 730 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{22}S$ $(M+H)^+$ requires 247.1515; found 247.1526.

(2*R,3*S**,6*S**)-2-(2-Chlorophenyl)-6-phenyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran**



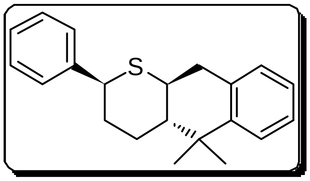
(18k): Colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.59 (s, 3 H), 1.70-1.84 (m, 1 H), 2.10-2.23 (m, 2 H), 2.30-2.37 (m, 1 H), 2.83 (dt, *J* = 13.6 and 2.8 Hz, 1 H), 4.15 (dd, *J* = 11.6 and 2.4 Hz, 1 H), 4.60 (s, 1 H), 4.67 (s, 1 H), 4.69 (d, *J* = 12.0 Hz, 1 H), 7.10-7.15 (m, 1 H), 7.18-7.25 (m, 2 H), 7.28-7.32 (m, 3 H), 7.37-7.40 (m, 2 H), 7.45 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 34.1, 35.8, 46.8, 49.5, 51.1, 112.5, 127.0, 127.5, 127.6, 128.4, 128.7, 129.4, 129.7, 133.8, 137.7, 141.5, 147.0; **IR** (KBr, Neat): 2928, 2857, 1645, 1442, 1376, 888 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{21}ClS$ $(M+H)^+$ requires 329.1125; found 329.1134.

(2*S,3*S**,6*S**)-6-Phenyl-3-(prop-1-en-2-yl)-2-propyltetrahydro-2*H*-thiopyran (18l):**

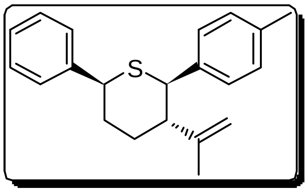


Brownish liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 3 H), 1.23-1.33 (m, 2 H), 1.54- 1.67 (m, 2 H), 1.69 (s, 3 H), 1.88-1.96 (m, 2 H), 1.98-2.05 (m, 1 H), 2.16-2.26 (m, 2 H), 2.97 (dt, *J* = 10.0 and 2.8 Hz, 1 H), 3.89 (dd, *J* = 11.6 and 2.0 Hz, 1 H), 4.79 (brs, 2 H), 7.21-7.25 (m, 1 H), 7.28-7.33 (m, 2 H), 7.34-7.37 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 19.5, 19.8, 33.9, 35.4, 35.6, 46.5, 48.1, 52.4, 112.2, 127.5, 127.6, 128.7, 142.5, 148.1; **IR** (KBr, Neat): 2957, 2927, 1634, 1452, 1376, 1186, 1076, 756 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{24}S$ $(M+H)^+$ requires 261.1671; found 261.1678.

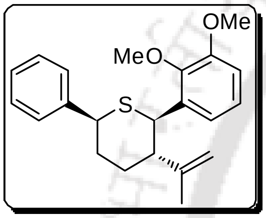
(2*S,4a*S**,10a*S**)-5,5-Dimethyl-2-phenyl-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[g]thiochromene (18m):**



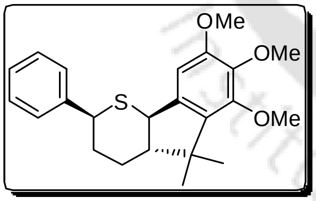
Colorless solid, mp 113-115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17 (s, 3 H), 1.42 (s, 3 H), 1.43-1.51 (m, 1 H), 1.71 (dt, *J* = 11.6 and 3.2 Hz, 1 H), 2.07 (dq, *J* = 12.8 and 2.4 Hz, 1 H), 2.20-2.27 (m, 1 H), 2.31-2.37 (m, 1 H), 2.80 (dd, *J* = 16.0 and 11.6 Hz, 1 H), 2.93 (dd, *J* = 16.4 and 5.2 Hz, 1 H), 3.35 (ddd, *J* = 11.6, 5.6 and 5.2 Hz, 1 H), 3.99 (dd, *J* = 11.6 and 2.4 Hz, 1 H), 7.01 (d, *J* = 7.6, 1 H), 7.10 (t, *J* = 7.6, 1 H), 7.19 (t, *J* = 8.0, 1 H), 7.24-7.28 (m, 1 H), 7.33 (t, *J* = 7.2 Hz, 2 H), 7.38 (d, *J* = 7.6, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.6, 28.3, 28.6, 36.1, 36.6, 38.1, 39.9, 47.7, 48.5, 125.8, 126.5, 127.3, 127.6, 127.7, 128.4, 128.8, 133.5, 142.1, 146.1; **IR** (KBr, Neat): 2965, 2926, 1634, 1446, 1365, 1188, 1080, 965 cm^{-1}. **HRMS** (APCI) cald. for $C_{21}H_{24}S$ $(M+H)^+$ requires 309.1671; found 309.1681.



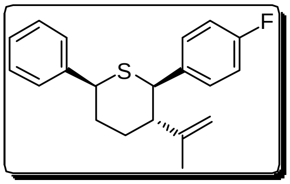
(2*R,3*S**,6*S**)-6-Phenyl-3-(prop-1-en-2-yl)-2-(*p*-tolyl)tetrahydro-2*H*-thiopyran (18n):** Brownish color solid, mp 118-120 °C; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.54 (s, 3 H), 1.68-1.79 (m, 1 H), 2.00-2.15 (m, 2 H), 2.19 (dd, *J* = 12.4 and 2.8 Hz, 1 H), 2.29 (s, 3 H), 2.77 (dt, *J* = 11.2 and 2.8 Hz, 1 H), 4.06 (d, *J* = 12.4 Hz, 1 H), 4.10 (dd, *J* = 12.0 and 2.8 Hz, 1 H), 4.61 (s, 1 H), 4.66 (s, 1 H), 7.07 (d, *J* = 7.6 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 2 H), 7.38 (d, *J* = 7.2 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 20.4, 21.3, 34.1, 35.5, 50.3, 51.4, 52.5, 112.5, 127.7 (2C), 128.3, 128.7, 129.2, 136.8, 137.1, 141.4, 147.3; **IR** (KBr, Neat): 2926, 2855, 1643, 1452, 1375, 1282, 1030, 753 cm^{-1}. **HRMS** (APCI) cald. for $C_{21}H_{24}S$ (M+H)$^+$ requires 309.1671; found 309.1675.



(2*R,3*S**,6*S**)-2-(2,3-Dimethoxyphenyl)-6-phenyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18o):** yellow color solid, mp 96-98 °C; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.57 (s, 3 H), 1.70-1.80 (m, 2 H), 2.10-2.20 (m, 2 H), 2.28-2.40 (m, 1 H), 2.75 (dt, *J* = 11.6 and 2.8 Hz, 1 H), 3.83 (s, 3 H), 3.92 (s, 3 H), 4.14 (d, *J* = 11.6 Hz, 1 H), 4.56 (s, 1 H), 4.65 (s, 1 H), 4.72 (d, *J* = 11.2 Hz, 1 H), 6.74-6.78 (m, 1 H), 6.98-7.02 (m, 2 H), 7.22 (t, *J* = 6.8 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.39 (d, *J* = 7.6 Hz, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 20.2, 34.3, 36.1, 43.1, 49.6, 51.1, 55.8, 61.6, 111.0, 112.1, 120.6, 124.1, 127.5, 127.7, 128.7, 134.1, 142.0, 146.8, 147.6, 152.6; **IR** (KBr, Neat): 2930, 2853, 1642, 1478, 1376, 1272, 1087, 1060, 1007, 888, 758 cm^{-1}. **HRMS** (APCI) cald. for $C_{22}H_{26}O_2S$ (M+H)$^+$ requires 355.1726; found 355.1733.



(2*S,4a*S**,9b*R**)-6,7,8-Trimethoxy-5,5-dimethyl-2-phenyl-2,3,4,4a,5,9b-hexahydroindeno[1,2-b]thiopyran (18p):** Colorless solid, mp 108-110 °C; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.06 (s, 3 H), 1.47 (s, 3 H), 1.99-2.14 (m, 4 H), 2.35-2.40 (m, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 3.93 (s, 3 H), 4.07 (dd, *J* = 11.6 and 3.6 Hz, 1 H), 4.09 (d, *J* = 10.6 Hz, 1 H), 6.52 (s, 1 H), 7.24-7.29 (m, 1 H), 7.32-7.36 (m, 2 H), 7.39-7.42 (m, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 21.2, 25.8, 26.4, 36.3, 45.5, 49.6, 51.0, 56.2, 60.4, 60.8, 61.0, 101.9, 127.5 (2C), 128.7, 135.6, 136.7, 141.9, 142.2, 150.8, 153.2; **IR** (KBr, Neat): 2932, 2866, 1602, 1470, 1410, 1335, 1113, 1096, 1027, 736, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{28}O_3S$ (M+H)$^+$ requires 385.1832; found 385.1843.

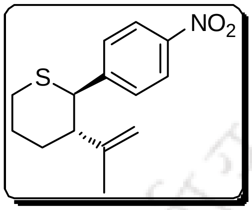


(2*R,3*S**,6*S**)-2-(4-Fluorophenyl)-6-phenyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18q):**

Brownish liquid; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.53 (s, 3 H), 1.73 (dq, *J* = 12.8 and 2.8 Hz, 1 H), 2.08-2.15 (m, 1 H), 2.19 (dd, *J* = 12.8 and 2.8 Hz, 1 H), 2.30 (dq, *J* = 13.2 and 2.7 Hz, 1 H), 2.72 (dt, *J* = 12.0

and 3.2 Hz, 1 H), 4.05 (d, *J* = 11.2 Hz, 1 H), 4.09 (dd, *J* = 11.6 and 2.0 Hz, 1 H), 4.62 (s, 1 H), 4.65 (s, 1 H), 6.95 (t, *J* = 8.8 Hz, 2 H), 7.23-7.33 (m, 5 H), 7.37 (d, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.4, 34.1, 35.5, 49.7, 51.4, 51.8, 112.7, 115.3 (d, *J* = 21.3 Hz), 127.6 (2C), 128.8, 129.9 (d, *J* = 7.6 Hz), 136.2, 141.6, 147.3, 162.0 (d, *J* = 244.8 Hz); 19F NMR (376 MHz, $CDCl_3/C_6F_6$): δ 46.58-46.63 (m, -F); **IR** (KBr, Neat): 2927, 2851, 1639, 1451, 1375, 1222, 1157, 836, 755, 697 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{21}FS$ $(M+H)^+$ requires 313.1421; found 313.1434.

(2*R,3*S**)-2-(4-Nitrophenyl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (18r):**



Pale yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.49 (s, 3 H), 1.56 (ddd, *J* = 13.2, 12.0 and 3.2 Hz, 1 H), 1.86 (qt, *J* = 13.2, and 3.2 Hz, 1 H), 1.98 (dd, *J* = 14.0, and 2.8 Hz, 1 H), 2.18 (dt, *J* = 14.0 and 2.8 Hz, 1 H), 2.65-2.72 (m, 2 H), 2.89 (ddd, *J* = 12.8, 10.8 and 2.8 Hz, 1 H), 3.93 (d, *J* = 10.8 Hz 1 H), 4.56 (s, 1 H), 4.58 (s, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 8.14 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 28.0, 31.2, 33.0, 49.8, 52.1, 113.0, 123.7, 129.3, 146.8, 147.1, 148.7; **IR** (KBr, Neat): 2928, 2852, 1644, 1598, 1520, 1346, 1287, 1110, 1074, 853, 738 cm^{-1}. **HRMS** (APCI) cald. For $C_{14}H_{17}NO_2S$ $(M+H)^+$ requires 264.1053; found 264.1066.

4.7. Selected Spectra of Tetrahydrothiopyrans

^{1}H and ^{13}C NMR spectra of **(2*R**,3*S**,6*R**)-6-Methyl-2-phenyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran**

```
somu_sene_7

exp1  s2pul

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file            exp   spin          not used
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sw           6389.8   pw90            19.700
at            1.998   alfa            20.000
np            25528          FLAGS
fb         not used   il                   n
bs                4   in                   n
d1            1.000   dp                   y
nt               32   hs                  nn
ct               32        PROCESSING
    TRANSMITTER       lb                0.10
tn               H1   fn               65536
sfrq        399.853          DISPLAY
tof           362.8   sp              -359.0
tpwr             57   wp              4105.9
pw            9.850   rfl              795.6
     DECOUPLER        rfp                  0
dn              C13   rp               112.8
dof               0   lp               -87.7
dm              nnn            PLOT
dmm               c   wc                 250
dpwr             50   sc                   0
dmf           15900   vs                  48
                      th                   6
                      nm   cdc   ph
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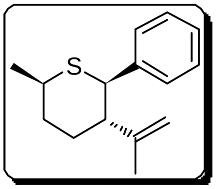

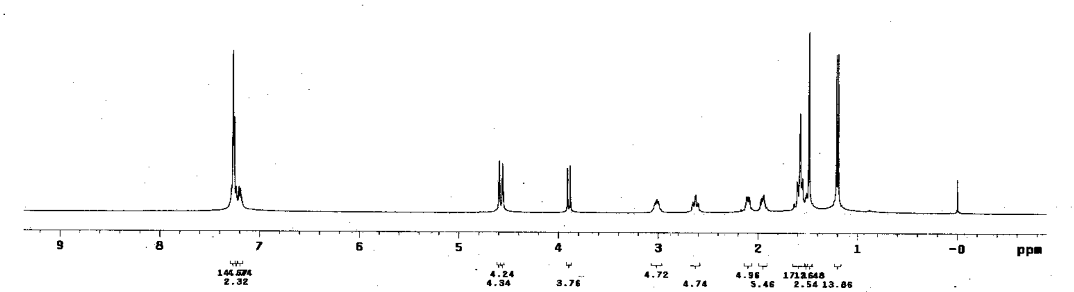

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 _7

s2pul

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file            exp   spin          not used
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sw          25125.6   pw90            18.600
at            1.199   alfa            20.000
np            60270          FLAGS
fb            13800   il                   n
bs               12   in                   n
d1            1.000   dp                   y
nt             3000   hs                  nn
ct              276        PROCESSING
    TRANSMITTER       lb                2.00
tn              C13   fn               65536
sfrq        100.554          DISPLAY
tof          1536.3   sp              -946.7
tpwr             61   wp             17993.7
pw            9.300   rfl             9239.1
     DECOUPLER        rfp             7764.9
dn               H1   rp               -73.0
dof               0   lp              -290.8
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dmm               w   wc                 250
dpwr             42   sc                   0
dmf            8900   vs                  16
                      th                   3
                      nm   no   ph
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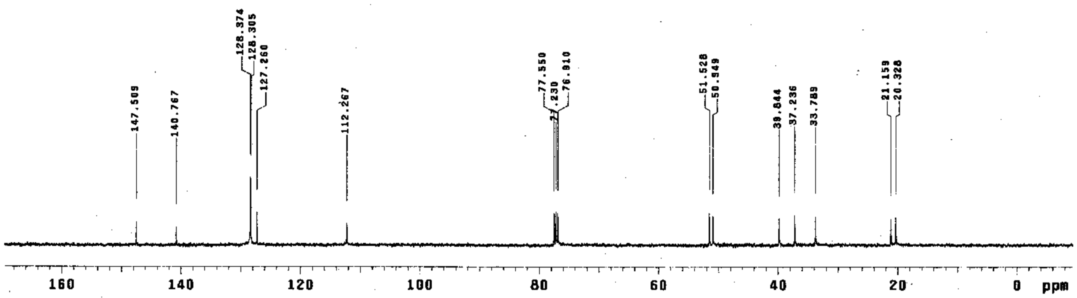

^{1}H and ^{13}C NMR spectra of **(2*R***,3*S**,6*S**)-2-(2-Chlorophenyl)-6-phenyl-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran**

```
somu_sene_16

exp1  std1h

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solvent      CDC13  gain        not used
file           exp  spin        not used
   ACQUISITION      hst            0.008
sw          6006.0  pw90          19.700
at           1.995  alfa          20.000
np           23964         FLAGS
fb        not used  il                 n
bs               4  in                 n
d1           1.000  dp                 y
nt              32  hs                nn
ct              32        PROCESSING
   TRANSMITTER      fn          not used
tn              H1          DISPLAY
sfrq       399.853  sp            -485.0
tof              0  wp            4443.2
tpwr            57  rfl            966.4
pw           7.000  rfp                0
    DECOUPLER       rp             112.9
dn             C13  lp             -75.5
dof              0           PLOT
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dmm              c  sc                 0
dpwr            50  vs                47
dmf          15900  th                 9
                    nm  cdc  ph
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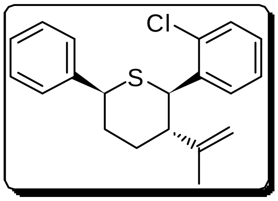

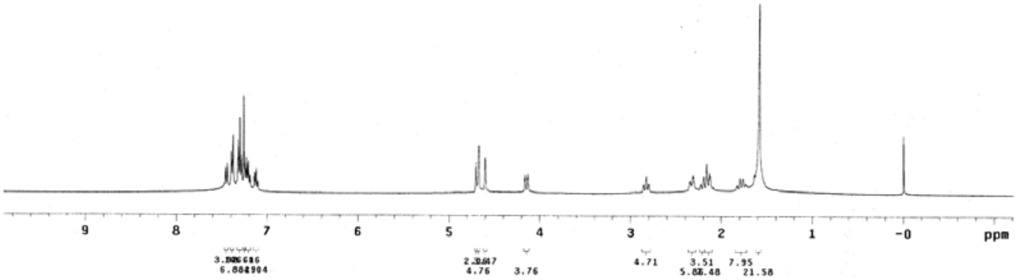

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some_sene_16

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file           exp  spin        not used
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at           1.199  alfa          20.000
np           60270         FLAGS
fb           13800  il                 n
bs              12  in                 n
d1           1.000  dp                 y
nt            3000  hs                nn
ct             540        PROCESSING
   TRANSMITTER      lb              2.00
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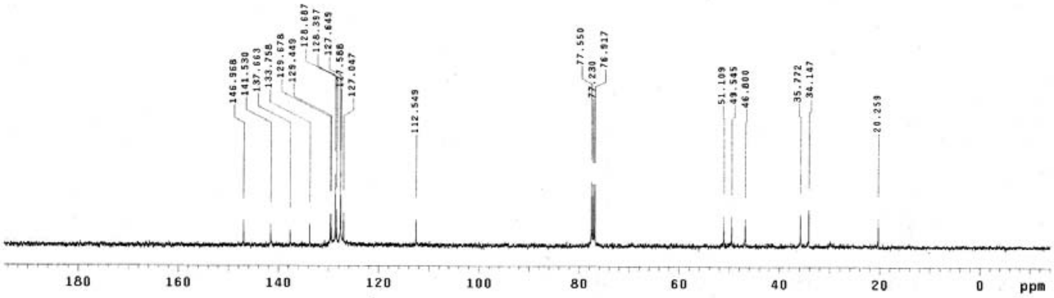

^{1}H and ^{13}C NMR spectra of **(2*R**,4a*S**,9b*R**)-6,7,8-Trimethoxy-2,5,5-trimethyl-2,3,4,4a,5,9b-hexahydroindeno[1,2-b]thiopyran**

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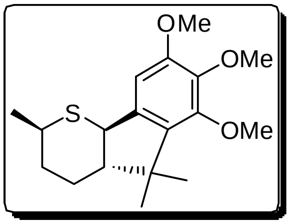

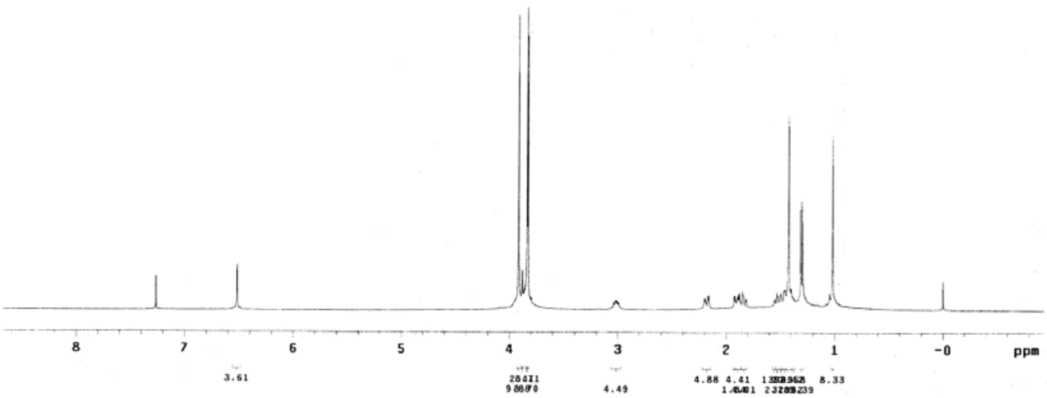

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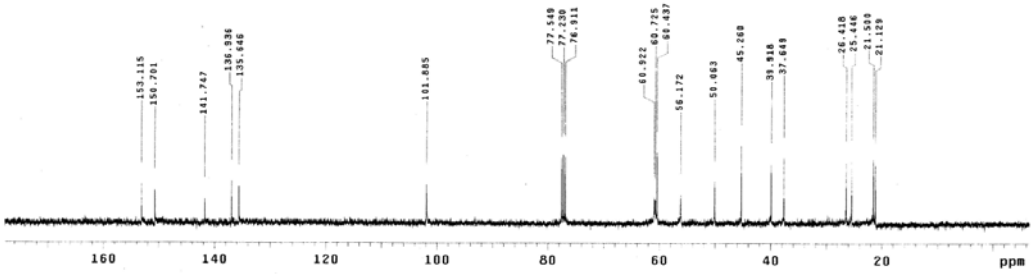

^{1}H and ^{13}C NMR spectra of **(2*S**,4a*S**,10a*S**)-5,5-Dimethyl-2-phenyl-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[g]thiochromene**

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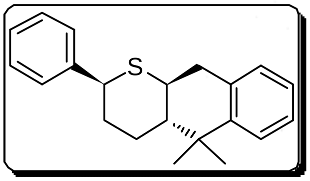

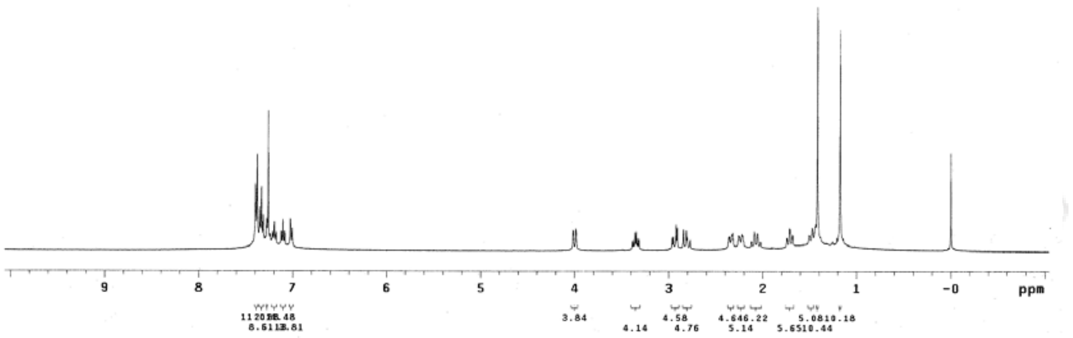

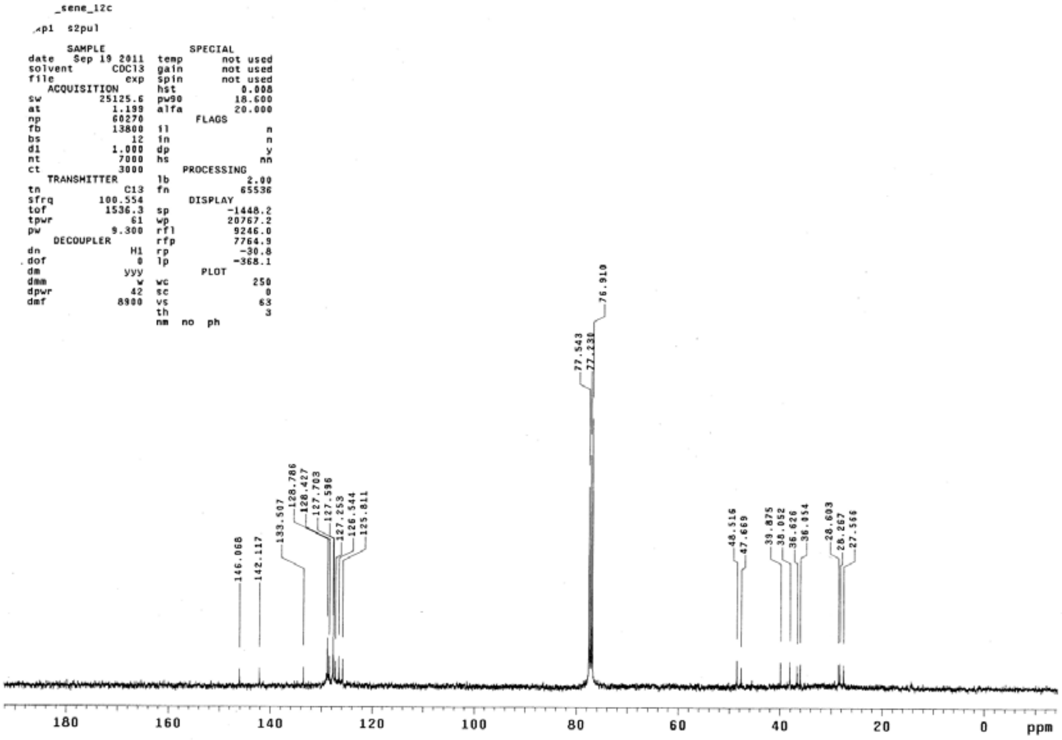

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                     th                3
                     nm   no   ph
```

4.8. Crystal Parameters

The crystal parameters of compound **18b**

parameters	CCDC 848785
Formula	$C_{15}H_{19}NO_2S$
Formula weight	277.37
T/K	296(2)
Crystal system	Triclinic
Space group	P -1
a/Å	7.4612(3)
b/Å	9.3954(3)
c/Å	11.6354(5)
α/º	77.585(2)
β/º	84.603(3)
γ/º	69.277(2)
V/Å^3	744.90(5)
Z	2
Abs. Coeff./mm^{-1}	0.215
Abs. Correction	Multi-scan
GOF on F^2	1.029
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0452$
	$wR2 = 0.1179$
R indices [all data]	$R1 = 0.0685$
	$wR2 = 0.1256$

The crystal parameters of compound **18m**

parameters	CCDC 848786
Formula	$C_{21}H_{24}S$
Formula weight	308.48
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/n
a/Å	9.953(3)
b/Å	22.576(5)
c/Å	23.586(6)
α/º	90.00
β/º	97.836(18)
γ/º	90.00
V/Å^3	5250(2)
Z	4
Abs. Coeff./mm^{-1}	0.180
Abs. Correction	Multi-scan
GOF on F^2	1.035
Final R indices [$I > 2\sigma$(I)]	$R1$ = 0.0775
	$wR2$ = 0.2011
R indices [all data]	$R1$ = 0.1370
	$wR2$ = 0.2468

CHAPTER 5

Stereoselective Synthesis of 2,3-Disubstituted Tetrahydroquinolines

5.1. Structure and Nomenclature

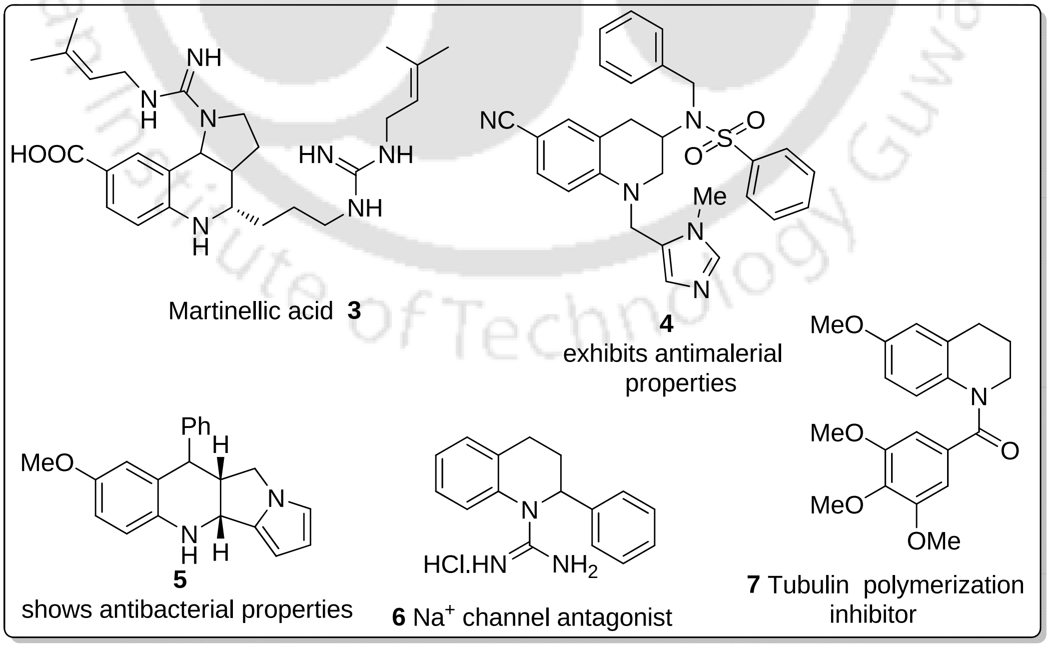
The name “tetrahydoquinoline” denotes mainly two structural units namely 1,2,3,4-tetrahydroquinoline **1** and 5,6,7,8-tetrahydroquinoline **2**. This chapter mainly deals with the 1,2,3,4- tetrahydroquinolines **1** (*Figure 5.1*).

1,2,3,4-tetrahydroquinoline **1**   5,6,7,8-tetrahydroquinoline **2**

Figure 5.1.

5.2. Importance and Application of Tetrahydroquinolines

The tetrahydroquinoline scaffold is prevalent in the fields of pharmacologically active agents and natural products. Particularly 1,2,3,4-tetrahydoquinoline derivatives are used as antidepressants,[1a] antiulcer,[1b] antibacterial,[1c] antimalerial[1d] agents as shown in (*Figure 5.2*).



Martinellic acid **3**

4 exhibits antimalerial properties

5 shows antibacterial properties

6 Na$^+$ channel antagonist

7 Tubulin polymerization inhibitor

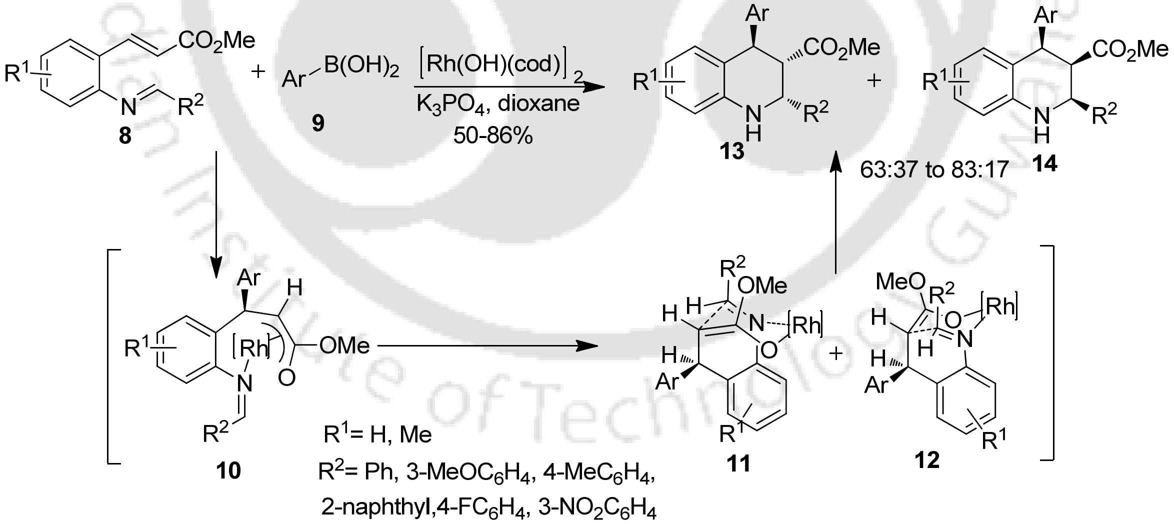
Figure5.2. *some biologically active tetrahydroquinolones*

Some tetrahydroquinolines are recognized as Na^+ channel antagonist **7**,[2] few other as tubulin polymerization inhibitors **6**, and corrosion inhibiters.[3] Besides, these pharmaceutical applications, tetrahydroquinoline derivatives are also used as pestisides,[4] and antioxidants,[5] Moreover, these are the precursor units for the substituted quinolines.[6]

5.3. Relevant Methods for the Synthesis of Tetrahydoquinolines

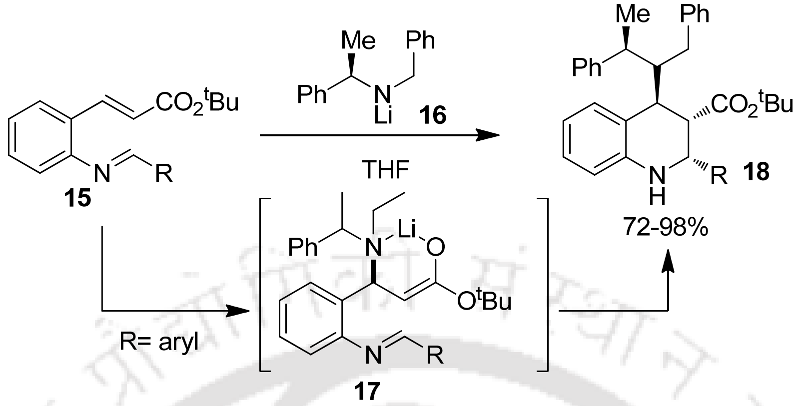
Several methods have been developed for the syntheis of 1,2,3,4-tetrahydroquinolines which include intramocelular aza-Michael addition, aza-Diels-alder reaction, Povarov reaction, intramolecular hydroamination and reduction of quinolines. Amomg them, here we discuss a few methods, where imine or N-acylinium are involved in the cyclization for the synthesis of tetrahydroquinilines with various degree of substitutions.

Youn and co-workers developed a rhodium-catalyzed domino conjugate addition-Mannich cyclization reaction sequence for the synthesis of 2,3,4-trisubstituted-1,2,3,4-tetrahydroquinolines. Firstly, in the presence of $[Rh(OH)(cod)]_2$ complex, conjugate addition of boronic acid **9** takes place on the unsaturated ester **8** to give (oxa-π-allyl)rhodium(I) intermediate **10**, followed by cyclization with the imine through the transition states **11** & **12** to afford diastereomeric mixtures of the tetrahydroquinolines **13** & **14** in good yields (*Scheme 5.3.1*).[7]



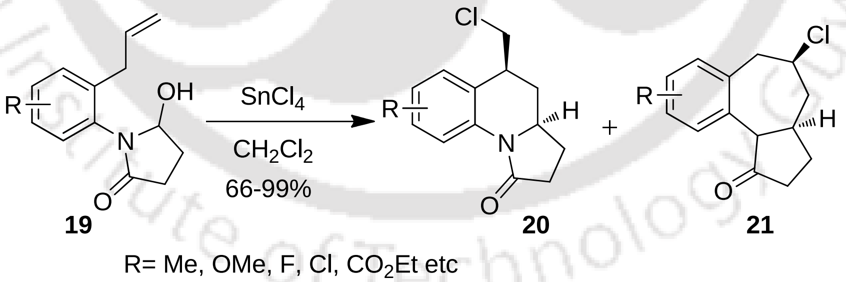
Scheme 5.3.1.

In a similar fashion, Davies has developed a potential method for the construction of chiral 4-amino-1,2,3,4-tetrahydroquinolines substituted at C-2 and C-3. The reaction was initiated with the conjugate addition of (R)-N-benzyl- N-(R-methylbenzyl)amide **16** onto an unsaturated ester **15** having an imine group at its ortho position to produce enolate intermediate **17**, which underwent cyclization with the imine to deliver trisubstituted tetrahydroquinoline nucleus **18** with excellent diastereoselectivity (*Scheme 5.3.2*).[8]



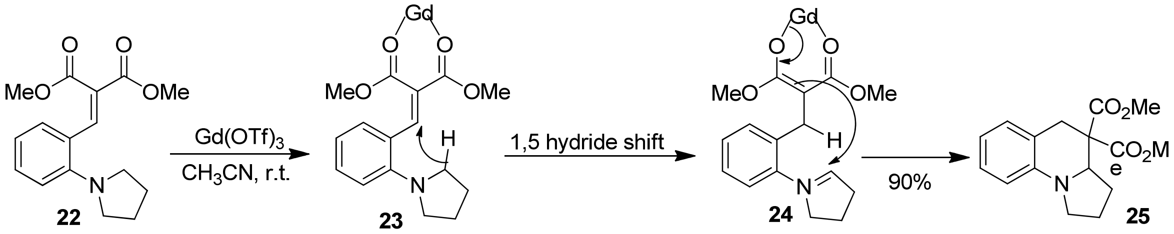
Scheme 5.3.2.

Hong and coworkers have developed an N-acylinium ion mediated cyclization promoted by $SnCl_4$ for the synthesis of pyrroloquinoline derivatives. 1-(2-Allylphenyl)-5-hydroxypyrrolidin-2-one **19** on treated with $SnCl_4$ in CH_2Cl_2 solvent gave pyrroloquinoline derivatives **20** in high yields along with small amounts of pyrrolobenzazepine derivatives **21**. The reaction proceeds through an N-acyliminium ion intermediate involving a 7-endo-trig cyclization, followed by a cationic rearrangement (*Scheme 5.3.3*).[9]



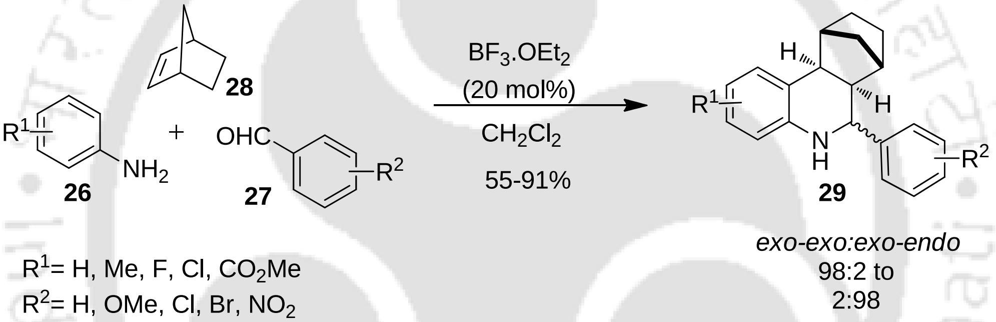
Scheme 5.3.3.

Siedel and coworkers reported the synthesis of polycyclic tetrahydroquinolines. In this process catalytic amount of $Gd(OTf)_3$ promoted the 1,5 hydride ion shift from a C-H bond adjacent to tertiary amine group to alkylidene malonates **23** to generate dipolar intermediate **24**, which underwent cyclization to furnish polycyclic tetrahydoquinoline **25**. This protocol allowed the synthesis of a large number of simple and fused tetrahydroquinolines based on the nature of substituents on the nitrogen atom (*Scheme 5.3.4*).[10]



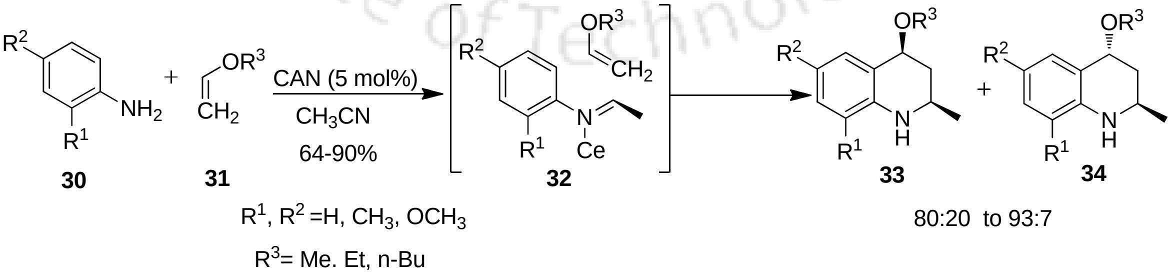
Scheme 5.3.4.

Batey and co-workers demonstrated a facile method for the synthesis of tetrahydroquinolines using $BF_3.Et_2O$ catalyzed aza-Diels-Alder reaction. The three-component reaction between arylamines **26**, arylaldehydes **27**, and norbornene **28** in the presence of 20 mol % of $BF_3.Et_2O$ in dichloromethane gave the corresponding tetrahydroquinoline derivatives **29** in moderate yields with good diastereoselectivity (*Scheme 5.3.5*).[11]



Scheme 5.3.5.

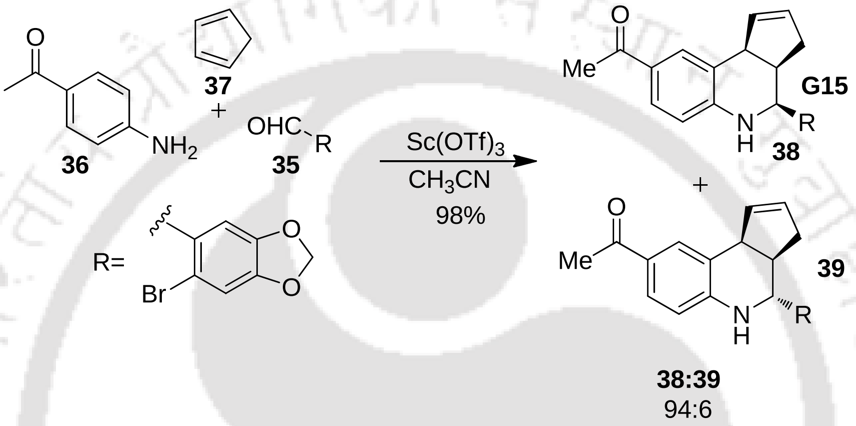
The reaction between arylamines and enol ethers in the presence of a catalytic amount of CAN (5 mol %) afforded tetrahydroquinoline derivatives in moderate to good yields. The arylamines**30** reacted with one equivalent of enol ethers **31** to give the corresponding N-arylimines **32**, which



Scheme 5.3.6.

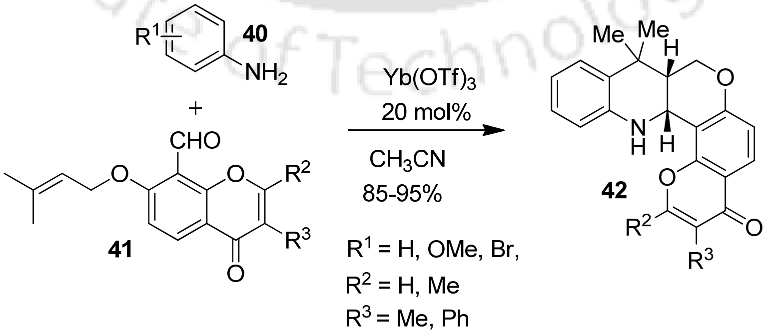
underwent [4+2] cycloaddition with another equivalent of the enol ether in the presence of CAN to afford tetrahydroquinolines **33** & **34** as a diastereomeric mixture (*Scheme 5.3.6*).[12]

Estrogen receptors **G-15** was synthesized in excellent yields and diastereoselectivities using a simple Sc(OTf)$_3$ catalyzed Povarov reaction. The reaction between 6-bromopiperonal **35**, arylamine **36**, and cyclopentadiene **37** in the presence of 10 mol % of Sc(OTf)$_3$ in acetonitrile afforded tetrahydroquinoline **38** (**G-15**) in nearly quantitative yield with a diastereomeric ratio of 94:6 (*Scheme 5.3.7*).[13]



Scheme 5.3.7.

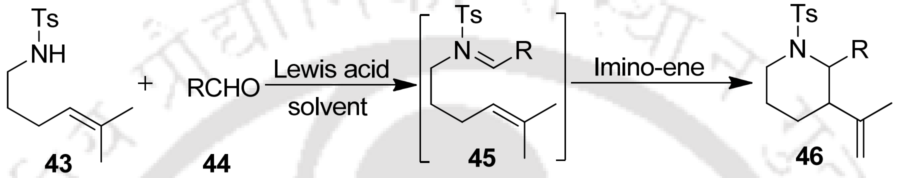
Nagaiah and co-workers recently reported the synthesis of *cis*-fused tetrahydrochromeno[4,3-b]quinolines. The compounds were synthesized via an intramolecular [4+2] imino-Diels–Alder reaction between the in situ-generated imine from arylamines **40** and the 7-O-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones **41** in the presence of a catalytic amount of Yb(OTf)$_3$. The reaction was completely diastereoselective and afforded exclusively the *cis* fused isomers **42** in excellent yields (*Scheme 5.3.8*).[14]



Scheme 5.3.8.

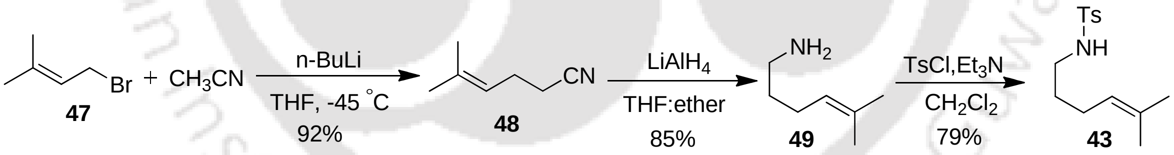
5.4. Present Work

Previously, we have developed few methods for the synthesis of tetrahydropyrans and thiotetrahydropyrans by using oxonium- and thionium-ene reactions, respectively.[15] Given the success of these developments, we envisioned that, the reaction of 4-methyl-N-(5-methylhex-4-en-1-yl)benzenesulfonamide **43** with aldehydes **44** in the presence of Lewis acid would provide the access to 2,3-disubstituted piperidines **46** via an intramolecular imino-ene cyclization as a key step as shown in (*Scheme 5.4.1*).



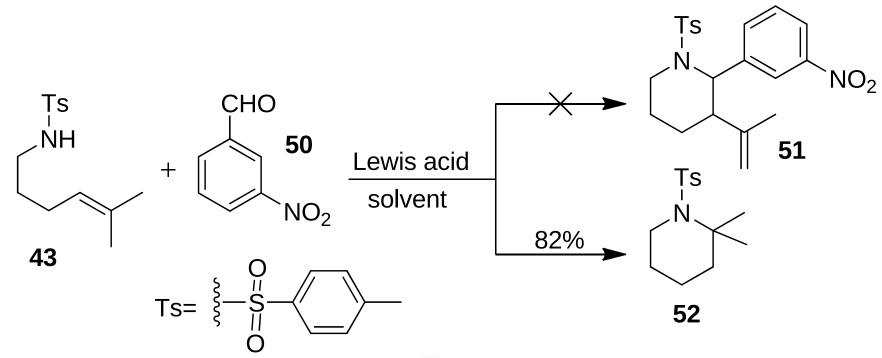
Scheme 5.4.1.

Within this context, the synthesis of 4-methyl-N-(5-methylhex-4-en-1-l)benzenesulfon-amide began with the substitution reaction between prenyl bromide **47** and acetonitrile, followed by reduction with $LiAlH_4$ and tosylation to obtain the requisite compound **43** in 54% overall yield (*Scheme 5.4.2*).



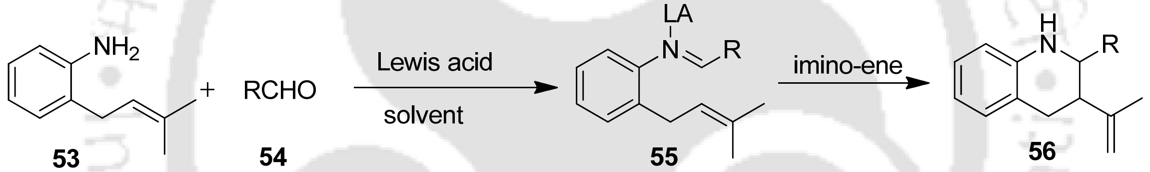
Scheme 5.4.2.

The reaction of 4-methyl-N-(5-methylhex-4-en-1-yl)benzenesulfonamide **43** with *m*-nitrobenzaldehyde **50** in the presence of boron trifluoride etherate in dichloromethane as solvent at room temperature only furnished self cyclized product **52** and no aldehyde coupled product **51** was observed. Further, we performed the reaction with various lewis acids such as $In(OTf)_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, TMSOTf, $FeCl_3$ in different solvents like CH_2Cl_2 and benzene. However, in contradiction to our hypothesis, the reaction gave only self cyclized product in all the cases, whose structure was confirmed by ^{1}H NMR (*Scheme 5.4.3*).



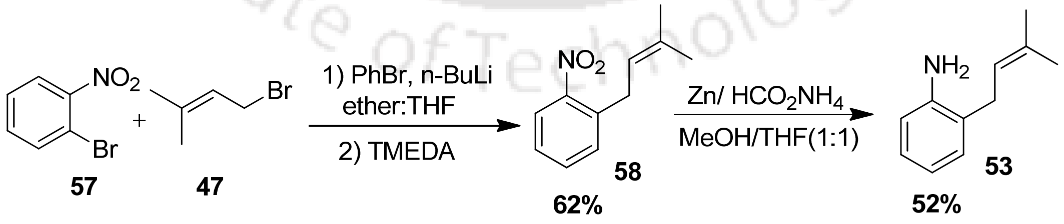
Scheme 5.4.3.

Thus, these results drew our attention to speculate the utility of free aromatic amines **53** to produce imines **55** with aldehydes **54** as reaction intermediates, that would be activated by lewis acid for the facile attack of alkene to afford corresponding imino-ene products **56** (*Scheme 5.4.4*).



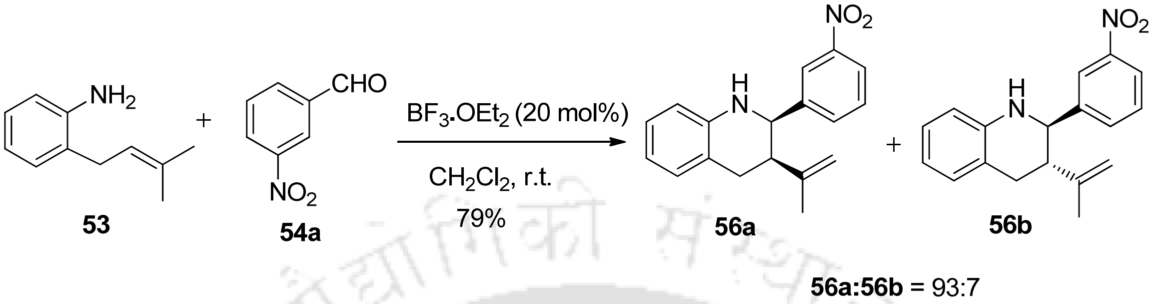
Scheme 5.4.4.

To examine this hypothesis, a known compound **53** was synthesized bearing an allylic group at ortho to amine functionality through the synthetic sequence following literature procedures as shown in (*Scheme 5.4.5*), and, was used as a model substrate to verify the success of the reaction.



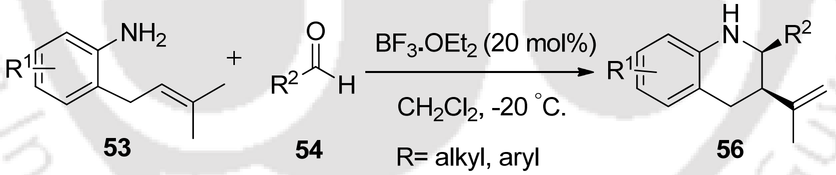
Scheme 5.4.5.

In an initial attempt, arylamine **53** was reacted with *m*-NO$_2$-benzaldehyde **54a** in the presence of boron trifluoride etherate at room temperature, which gave the desired product as a mixture of isomers **56a** & **56b**, in the ratio of 93:7. Both, major and minor isomers were separated by column chromatography and the products were characterized by NMR and X-ray analysis (*Scheme5.4.6*).



Scheme 5.4.6

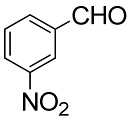
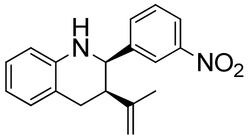
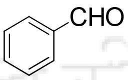
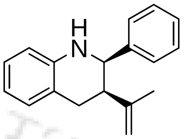
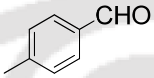
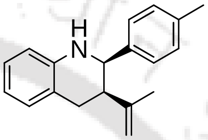
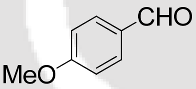
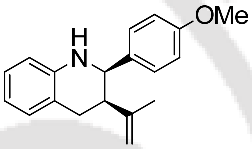
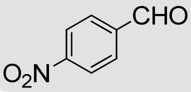
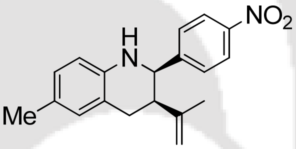
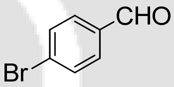
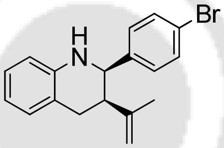
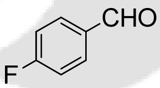
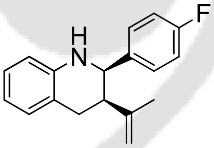
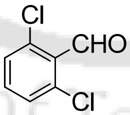
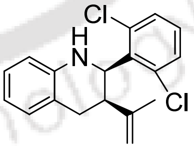
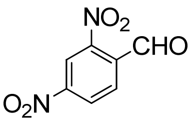
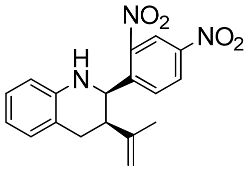
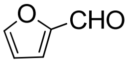
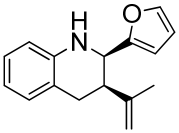
To improve the diastereoselectivity, the reaction was performed at -20 ˚C. To our delight, only a single diastereomer was detected in the crude reaction mixture. Therefore, it is noteworthy to mention that the temperature has a significant influence on the diastereoselectivity of the reaction. It has also been investigated that dichloromethane is the suitable solvent for the reaction as compared to the other solvents, such as THF and toluene. Having established the optimized reaction conditions, the scope of the reaction were then explored using a wide variety of aromatic, heteroaromatic and aliphatic aldehydes as shown in the (*Scheme 5.4.7* & *Table 5.4.1.*).



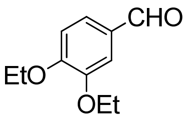
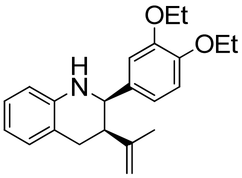
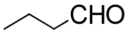
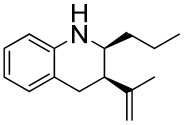
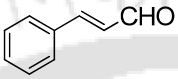
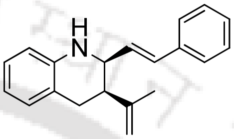
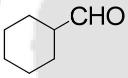
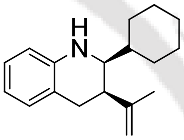
Scheme 5.4.7

In the case of aromatic aldehydes, substitution on the aromatic ring has substantial effect on the yield of the reaction. Aromatic aldehydes with electron withdrawing substituents on the ring gave good yields compared to the aromatic aldehydes with elecrtron donating groups on the ring. Among all the aromatic aldehydes outlined in the (*Table 5.4.1*), 2,6-dichloro benzaldehyde was observed to be best substrate for this reaction. On the other hand, the reactions of electron rich aromatic aldehydes e.g. diethoxy benzaldehyde, aliphatic aldehydes e.g. butanal, cyclohexane carboxaldehyde were unsuccessful to yield the desired tetrahydroquinolines. It is presumed to be the instability of the N-arylaldimine **59,** which is formed during the course of reaction.

Table 5.4.1. *Synthesis of 2,3 disubstituted tetrahydroquinolines*

Entry	Amine (**53**) R^1=	Aldehyde (**54**) R^2=	Product (**56**)	Yield^a(%)
a	H			84
b	H			75
c	H			73
d	H			64
e	Me			84
f	H			77
g	H			75
h	H			95
i	H			81
j	H			70

Continued………………

Entry	Amine (**53**) R^1=	Aldehyde (**54**) R^2=	Product (**56**)	Yield^a(%)
k	H			0
l	H			0
m	H			0
n	H			0

^{a}Yields refer to isolated yields. Compounds are characterized by ^{1}H, ^{13}C NMR, IR, and mass spectroscopy

Moreover, in all the cases studied, 2,3 disubstituted tetrahydoquinolines **56a-56j** were obtained in high purity without any side product, with a high degree of diastereoselectivity as determined from the ^{1}H and ^{13}C NMR spectrum of the crude product products. The stereochemistry of the 2,3-disubstituted tetrahydroquinolines was established by COSY experiments and ^{1}H NMR coupling constant values. The coupling constants of H-2 and H-3 protons of major isomer are in the range of 2.8-4.0 Hz, which indicates the *cis* relationship of the substitutions. Furthermore, the *cis* geometry of the substitution was unambiguously confirmed with single-crystal X-ray diffraction analysis of the compound (**56e**) as shown in (*Figure 5.4.1*).[16]

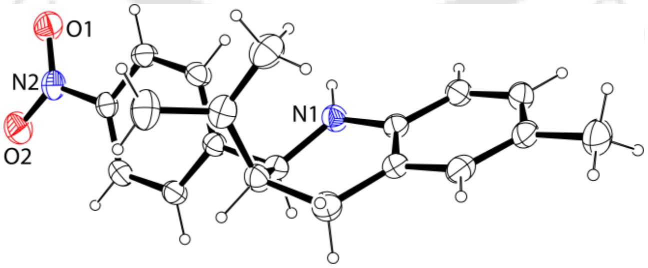
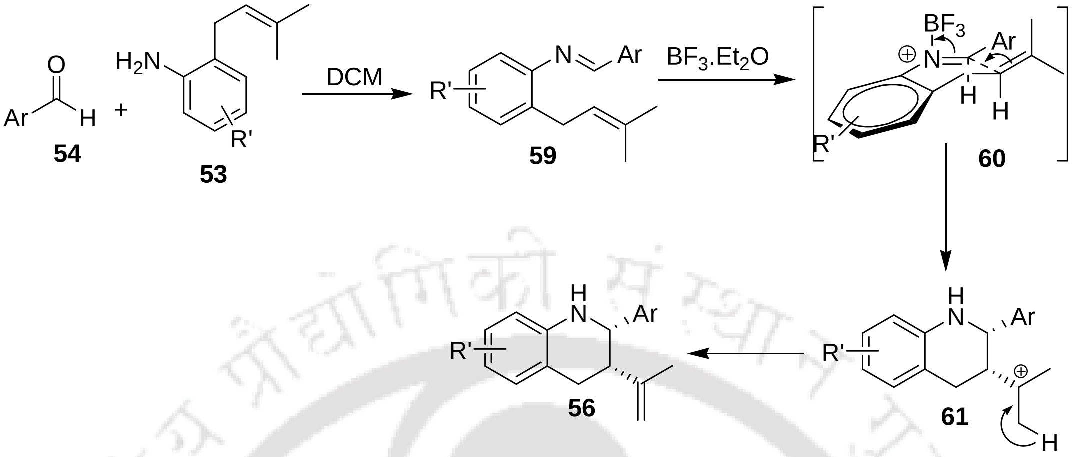


Figure 5.4.1. *ORTEP diagram of 6-methyl-2-(4-nitrophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline* (**56e**)

The mechanism of the reaction can be explained as follows. Aldehyde on reaction with amine forms an imine **59,** which is activated by Lewis acid to undergo the nucleophilic attack by alkene to produce a cationic intermediate **61** via transition state **60.** Thus, the intermediate **61** eliminates a proton to furnish tetrahydoquinolines **56**.



Scheme 8: Plausible mechanism of intramolecular aza-ene reaction

Conclusion:

In conclusion, we have developed a mild and an efficient method for the synthesis of 2,3 disubstituted 1,2,3,4-tetrahydroquinolines from aldehydes and 2-allyl anilines. The method is highly diastereoselective and it requires only a catalytic amount of Lewis acid. Further this method can be used in the synthesis of functionalized quinolines.

5.5. Experimental Section

5.5.1. Instrumentation and Characterization

As described in chapter 2 section 2.6.1

5.5.2. Synthesis of 5-methylhex-4-en-1-amine: The starting material amine **49** is a known compound and was synthesized following the literature procedures.[17]

5.5.3. Procedure for the Synthesis of 4-Methyl-N-(5-methylhex-4-en-1-yl)benzenesulfonamide (43): In an oven dried 10 mL round-bottomed flaskk equipped with magnetic stir bar, was loaded with *p*-toluenesulfonyl chloride (190 mg, 1 mmol) in CH_2Cl_2 (5 mL) followed by Et_3N (150mg, 1.5 mmol) was added. Then amine **49** (113mg, 1 mmol) was added. The progress of the reaction was checked by TLC. After completion of the reaction, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and organic layer was washed with 1.0M HCl (5 mL) and saturated NaCl solution (2×5 mL) and dried over anhydrous $CaCl_2$. Then it was dried in vaccuo and purified by column chromatography (SiO_2, hexanes:ethyl acetate), to give the title compound 4-methyl-N-(5-methylhex-4-en-1-yl)benzenesulfonamide **43** as a colorless oil (79%).

5.5.4. General Procedure for the Alkylation of Bromonitrobenzene: An oven-dried round-bottomed flask equipped with a magnetic stir bar, rubber septum under a nitrogen atmosphere, was charged with bromobenzene (1.2 mL, 11.5 mmol) and ethyl ether (10 mL). The solution was cooled in an ice bath and stirred at 0 °C for 5 min. A 1.5 M solution of butyllithium in hexane (10 mL, 15 mmol) was then added to the 0 °C ether solution over a period of 10 min via a syringe with a positive nitrogen pressure. After the addition was completed, the stirring was continued for 20 min at 0 °C the resulting solution was diluted to 50 mL with dry THF under nitrogen and the solution cooled to -78 °C (ethanol/liquid N_2). 1-bromo-2-nitrobenzene (2.0 g, 10 mmol) dissolved in THF (5 mL) was added drop wise via a syringe. After 5 min prenyl bromide (0.6 mL, 5.2 mmol) was added all at once, followed by TMEDA (1.5 mL, 10 mmol). The solution was kept at -78 °C for 3 h. After the reaction was quenched with saturated NH_4Cl (20 mL), the aqueous phase was extracted with ether (3×20 mL). The combined ethereal fractions were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes:ethyl acetate), yielding 1-(3-methylbut-2-en-1-yl)-2-nitrobenzene **58** as a brown oil (62%).

5.5.5. Procedure for the synthesis of 2-(3-methylbut-2-en-1-yl)aniline: To a suspension of 1-(3-methylbut-2-en-1-yl)-2-nitrobenzene **58** (5 mmol) and ammonium formate (40 mmol) in a 1:1 mixture of MeOH and THF (30 mL) was added zinc dust (40 mmol) at the room temperature. Stirring was continued at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through celite. The organic layer was evaporated and the residue was dissolved in ether and washed with brine solution to remove ammonium formate. The organic layer after drying and evaporation gave the desired 2-(3-methylbut-2-en-1-yl)aniline **53** as a pale yellow color liquid in 52% yield.

5.5.6. General Procedure for the Synthesis of Tetrahydroquinolines 56a-56j: An oven-dried round-bottomed flask was charged with the aldehyde (1.0 equiv), and dichloromethane (2 mL) and the resulting solution was cooled to -20 °C. To this solution was added aniline (1.0 equiv) in 2 mL of CH_2Cl_2 all at once. The mixture was stirred at the same temperature for 5 min. To this stirring solution was added boron tifluoride etherate (0.2 eqiv). After being stirred at room temperature for 1 hour, the mixture was poured into saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with ethyl acetate and then washed with brine and water. The organic layers were collected, dried over Na_2SO_4, filtered, and concentrated. Then the resultant crude residue was purified by column chromatography over silica gel (petroleum ether/ EtOAc) to afford the title compounds.

Synthesis of 1,2,3,4-Tetrahydro-2-phenyl-3-(prop-1-en-2-yl)quinoline 56b: An oven-dried round-bottomed flask was charged with the benzaaldehyde (106 mg, 1.0 mmol), and dichloromethane (2 mL) and the resulting solution was cooled to -20 °C. To this solution was added 2-(3-methylbut-2-en-1-yl)aniline (161mg, 1.0 mmol) in 2 mL of CH_2Cl_2 all at once. The mixture was stirred at the same temperature for 5 min. To this stirring solution was added boron tifluoride etherate (25 μL, 0.2 mmol). After being stirred at room temperature for 1 hour, the mixture was poured into saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with ethyl acetate and then washed with brine and water. The organic layers were collected, dried over Na_2SO_4, filtered, and concentrated. Then the resultant crude residue was purified by column chromatography over silica gel (petroleum ether/ EtOAc 97:3) to afford the (2*R*,3*R*)-1,2,3,4-Tetrahydro-2-phenyl-3-(prop-1-en-2-yl)quinoline **56b** (187mg, 75%) as a white color solid.

5.6. References

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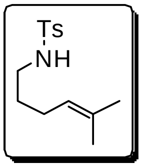
16) The crystallographic data for compounds **56e** has been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication nos. CCDC 873455.
17) (a) Tietze, L. F.; Bratz, M. *Synthesis* **1989**, 439-442.

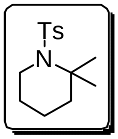
5.7. Spectral Data

5-Methyl-N-tosylhex-4-en-1-amine (43):



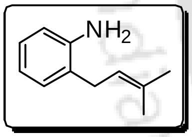
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.48 (t, *J* = 7.2 Hz, 2 H), 1.53 (s, 3 H), 1.65 (s, 3 H), 1.95 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3 H), 292 (q, *J* = 7.2 Hz, 2H), 4.76 (t, *J* = 5.6 Hz, 1 H), 2.74 (tt, *J* = 7.2 and 1.3 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 8.0 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.8, 21.7, 25.2, 25.8, 29.8, 43.1, 123.2, 127.3, 129.9, 132.9, 137.2, 143.5; **IR**: 3400, 2935, 2868, 1599, 1456, 1322, 1156, 1092, 708, 549 cm^{-1}; **Anal. Calcd** for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.82; H, 7.96; N, 5.20; S, 11.92.

2,2-Dimethyl-1-tosylpiperidine (52):



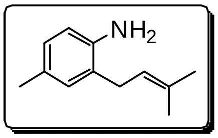
Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27(s, 6H), 1.45 (t, *J* = 5.6 Hz, 2 H), 1.56-1.62 (m, 4 H), 2.40 (s, 3 H), 3.50 (t, *J* = 4.8 Hz, 2 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 7.67(d, *J* = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.6, 21.5, 26.3 (3C), 41.4, 43.8, 58.0, 127.0, 129.5, 140.5, 142.7; **IR**: 2935, 2868, 1596, 1321, 1155, 1092, 816, 677 cm^{-1}; **Anal. Calcd** for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: 62.85; H, 7.97; N, 5.23; S, 11.96.

2-(3-Methylbut-2-enyl)benzenamine (53a):



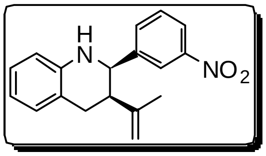
Light yellow color liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.75 (s, 6H), 3.23 (d, *J* = 7.2 Hz, 1 H), 5.23 (tt, *J* = 7.2 and 1.2 Hz, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 6.71-6.77 (m, 1 H), 7.02-7.06 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.8, 25.7, 30.8, 115.6, 118.8, 121.8, 126.0, 127.1, 129.5, 133.5, 144.5; **IR**: 3406, 2916, 1653, 1607, 1493, 1375, 1264, 747 , 700 cm^{-1}; **Anal. Calcd** for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.89; H, 9.36; N, 8.71.

4-Methyl-2-(3-methylbut-2-enyl)benzenamine (53e):



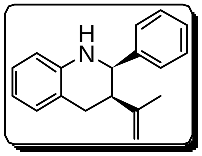
Light yellow color liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 6 H), 2.23 (s, 3 H), 3.20 (d, *J* = 6.8 Hz, 2 H), 5.22 (tt, *J* = 6.8 and 1.2 Hz 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 20.6, 25.8, 31.0, 115.9, 122.1, 126.2, 127.6, 128.0, 130.3, 133.4, 142.1; **IR**: 3406, 3057, 2915, 1606, 1493, 1321, 1265, 893, 746, 700 cm^{-1}; **Anal. Calcd** for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.26; H, 9.75; N, 7.94.

(2*R,3*R**)-2-(3-Nitrophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline** (56a):



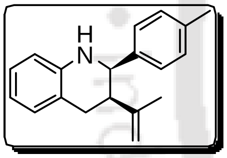
Red color solid, mp 73-75 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.78 (s, 3 H), 2.64 (dd, *J* = 16.4 and 10.8 Hz, 1 H), 2.74 (dd, *J* = 16.4 and 4.0 Hz, 1 H), 2.88 (dt, *J* = 10.8 and 4.0 Hz, 1 H), 4.36 (brs, 1 H), 4.44 (brs, 1 H), 4.81 (brs, 2 H), 6.62 (d, *J* = 8.0 Hz, 1 H), 6.70 (t, *J* = 6.8 Hz, 1 H), 7.02 (d, *J* = 7.2 Hz, 1 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.96 (s, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 23.1, 28.0, 43.6, 57.1, 113.6 (2C), 117.7, 120.2, 122.3, 122.5, 127.6, 128.8, 129.7, 133.5, 143.3, 143.9, 144.7, 147.8; **IR**: 2926, 2853, 1608, 1531, 1493, 1350, 1265, 740, 704 cm^{-1}; **HRMS** (APCI) *m/z* calcd for $C_{18}H_{18}N_2O_2$ (M+H)$^+$ requires 295.1441, found 295.1435.

(2*R,3*R**)-2-Phenyl-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56b):**



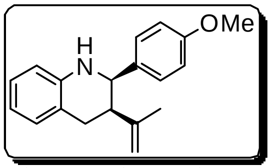
White color solid, mp 58-60 ˚C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.69 (s, 3 H), 2.69 (dd, *J* = 16.0 and 5.2 Hz, 1 H), 2.76 (dd, *J* = 16.0 and 10.8 Hz, 1 H), 2.84-2.90 (m, 1 H), 4.42 (brs, 2 H), 4.68 (brs, 1 H), 4.77 (t, *J* = 1.2 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 6.67 (t, *J* = 7.6 Hz, 1 H), 7.00-7.10 (m, 2 H), 7.12-7.15 (m, 2 H), 7.21-7.25 (m, 3 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 22.9, 28.3, 43.8, 57.9, 112.8, 113.4, 117.0, 120.7, 127.2, 127.3, 127.5, 127.9, 129.6, 142.7, 144.1, 144.8; **IR**: 2917, 1607, 1492, 1451, 1265, 1156, 746, 700 cm^{-1}; **HRMS** (APCI) *m/z* calcd for $C_{18}H_{19}N$ (M+H)$^+$ requires 250.1590, found 250.1586.

(2*R,3*R**)-3-(Prop-1-en-2-yl)-2-(*p*-tolyl)-1,2,3,4-tetrahydroquinoline (56c):**



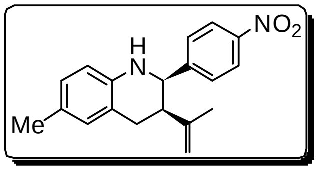
White color solid, mp 65-67°C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.70 (s, 3 H), 2.30 (s, 3 H), 2.69 (dd, *J* = 15.6 and 4.8 Hz, 1 H), 2.75 (dd, *J* = 15.6 and 10.4 Hz, 1 H), 2.82-2.87 (m, 1 H), 4.37 (brs, 1 H), 4.44 (brs, 1 H), 4.63 (d, *J* = 3.6 Hz, 1 H), 4.77 (t, *J* = 1.2 Hz, 1 H), 6.56 (d, *J* = 8.0 Hz, 1 H), 6.66 (t, *J* = 7.2 Hz, 1 H), 7.00-7.10 (m, 6 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.3, 23.0, 28.3, 43.9, 57.7, 112.7, 113.5, 117.0, 120.8, 127.3, 127.4, 128.6, 129.6, 136.8, 139.8, 144.2, 145.0; **IR**: 2920, 2854, 1606, 1492, 1438, 1265, 1154, 744 cm^{-1}; **HRMS** (APCI) *m/z* calcd for $C_{19}H_{21}N$ (M+H)$^+$ requires 264.1747, found 264.1738.

(2*R,3*R**)-2-(4-Methoxyphenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56d):**



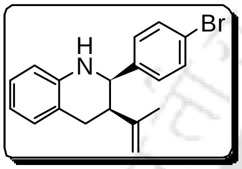
Semisolid; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.69 (s, 3 H), 2.68 (dd, *J* = 16.0 and 4.8 Hz, 1 H), 2.74 (dd, *J* = 16.0 and 10.4 Hz, 1 H), 2.81-2.84 (m, 1 H), 3.76 (s, 3 H), 4.36 (brs, 1 H), 4.44 (brs, 1 H), 4.62 (d, *J* = 2.8 Hz, 1 H), 4.78 (s, 1 H), 6.56 (d, *J* = 8.0 Hz, 1 H), 6.65 (t, *J* = 7.2 Hz, 1 H), 6.75-6.77 (m, 2 H), 7.00-7.10 (m, 4 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 22.9, 28.3, 43.9, 55.3, 57.3, 112.8, 113.2, 113.4, 117.0, 120.7, 127.3, 128.5, 129.6, 134.9, 144.2, 145.0, 158.8; **IR**: 2923, 2851, 1607, 1494, 1246, 1073, 1035, 830, 745 cm^{-1}; **HRMS** (APCI) *m/z* calcd for $C_{19}H_{21}NO$ (M+H)$^+$ requires 280.1696, found 280.1686.

(2*R,3*R**)-6-Methyl-2-(4-nitrophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56e):**



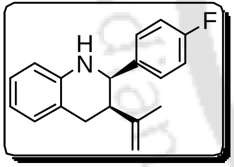
Red color solid, mp. 96-98 °C; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.76 (s, 3 H), 2.26 (s, 3 H), 2.62 (dd, *J* = 15.6 and 10.8 Hz, 1 H), 2.69 (dd, *J* = 15.6 and 4.8 Hz, 1 H), 2.86-2.91 (m, 1 H), 4.33 (brs, 1 H), 4.38 (brs, 1 H), 4.77 (d, *J* = 3.6 Hz, 1 H), 4.80 (s, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 6.85 (s, 1 H), 6.89 ((d, *J* = 8.4 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 8.08 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 20.6, 23.1, 28.0, 43.8, 57.4, 113.5, 113.7, 123.0, 124.5, 126.9, 128.2, 128.3, 130.2, 140.9, 143.9, 147.2, 150.4; **IR**: 2918, 1617, 1509, 1343, 1107, 804 750 cm^{-1}; **HRMS** (APCI) *m/z* calcd for C$_{19}$H$_{20}$N$_2$O$_2$ (M+H)$^+$ requires 309.1598, found 309.1660.

(2*R,3*R**)-2-(4-Bromophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56f):**



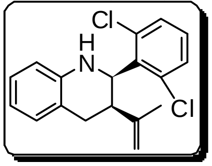
Brown color semisolid; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.70 (s, 3 H), 2.67 (d, *J* = 7.6 Hz, 2 H), 2.79-2.84 (m, 1 H), 4.35 (brs, 1 H), 4.41 (brs, 1 H), 4.60 (d, *J* = 4.0 Hz, 1 H), 4.79 (t, *J* = 1.2 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 6.66 (t, *J* = 7.6 Hz, 1 H), 6.97-7.06 (m, 4 H), 7.30 -7.34 (m, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 23.0, 28.1, 43.7, 57.3, 113.2, 113.5, 117.3, 120.5, 121.1, 127.4, 129.2, 129.7, 131.0, 141.7, 143.8, 144.4; **IR**: 2919, 1605, 1485, 1265, 896, 825, 746 cm^{-1}; **HRMS** (APCI) *m/z* calcd for C$_{18}$H$_{18}$BrN (M+H)$^+$ requires 318.0811, found 318.0823.

(2*R,3*R**)-2-(4-Fluorophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56g):**



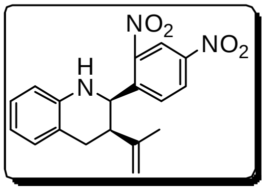
Colourless liquid; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.63 (s, 3 H), 2.63 (d, *J* = 8.0 Hz, 1 H), 2.74-2.79 (m, 1 H), 4.31 (brs, 1 H), 4.34 (brs, 1 H), 4.59 (s, 1 H), 4.72 (s, 1 H), 6.50 (d, *J* = 7.6 Hz, 1 H), 6.60 (t, *J* = 7.6 Hz, 1 H), 6.82-6.86 (m, 2 H), 6.93-6.98 (m, 2 H), 7.00-7.04 (m, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 22.9, 28.1, 43.8, 57.2, 113.0, 113.5, 114.7 (d, *J* = 21.3 Hz), 117.2, 120.5, 127.4, 128.9 (d, *J* = 7.5 Hz), 129.6, 138.4, 143.9, 144.6, 162.1 (d, *J* = 244.3 Hz); **^{19}F NMR** (376 MHz, CDCl$_3$/C$_6$F$_6$): δ 45.82-45.90 (m, -F); **IR**: 2922, 2853, 1605, 1223, 1157, 839, 746 cm^{-1}; **HRMS** (APCI) *m/z* calcd for C$_{18}$H$_{18}$FN (M+H)$^+$ requires 268.1496, found 268.1501.

(2*R,3*R**)-2-(2,6-Dichlorophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56h):**



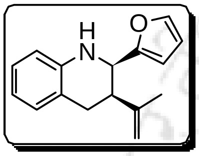
Colorless semisolid; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.62 (s, 3 H), 2.92-3.07 (m, 3 H), 4.33 (brs, 1 H), 4.35 (brs, 1 H), 4.70 (s, 1 H), 5.55 (t, *J* = 3.6 Hz, 1 H), 6.50 (d, *J* = 8.0 Hz, 1 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 7.00-7.05 (m, 2 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 23.0, 32.3, 43.4, 57.2, 114.0, 114.4, 117.4, 121.4, 127.0, 128.5, 129.3, 130.0, 136.1, 136.3, 144.4, 145.5; **IR**: 2920, 1608, 1588, 1483, 1266, 888, 780, 745 cm^{-1}; **HRMS** (APCI) *m/z* calcd for C$_{18}$H$_{17}$Cl$_2$N (M+H)$^+$ requires 318.0811, found 318.0823.

(2*R,3*R**)-2-(2,4-Dinitrophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56i):**



Red color solid, mp 95-97 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.69 (s, 3 H), 2.61 (dd, *J* = 16.4 and 10.8 Hz, 1 H), 2.76 (dd, *J* = 16.4 and 4.0 Hz, 1 H), 2.88 (dt, *J* = 10.8 and 4.4 Hz, 1 H), 4.15 (brs, 1 H), 4.47 (d, *J* = 3.6 Hz, 1 H), 4.77 (t, *J* = 1.2 Hz, 1 H), 5.75 (t, *J* = 4.0 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 7.6 Hz, 1 H), 7.03 (d, *J* = 7.2 Hz, 1 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 8.30 (d, *J* = 8.8 Hz, 1 H), 8.61 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 28.6, 42.9, 52.6, 113.9, 114.8, 118.2, 119.4, 120.0, 126.3, 127.8, 129.8, 131.7, 142.8, 143.8, 144.6, 146.8, 149.3; **IR**: 2922, 2850, 1606, 1588, 1530, 1494, 1349, 1265, 747 cm^{-1}; **HRMS** (APCI) *m/z* calcd for $C_{18}H_{17}N_3O_4$ $(M+H)^+$ requires 340.1292, found 340.1287.

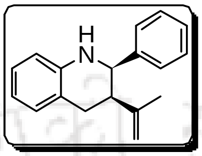
(2*R,3*R**)-2-(Furan-2-yl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline (56j):**

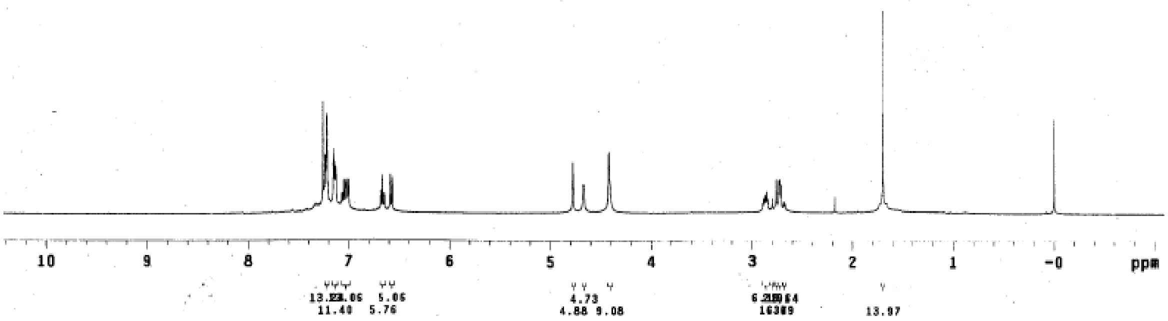


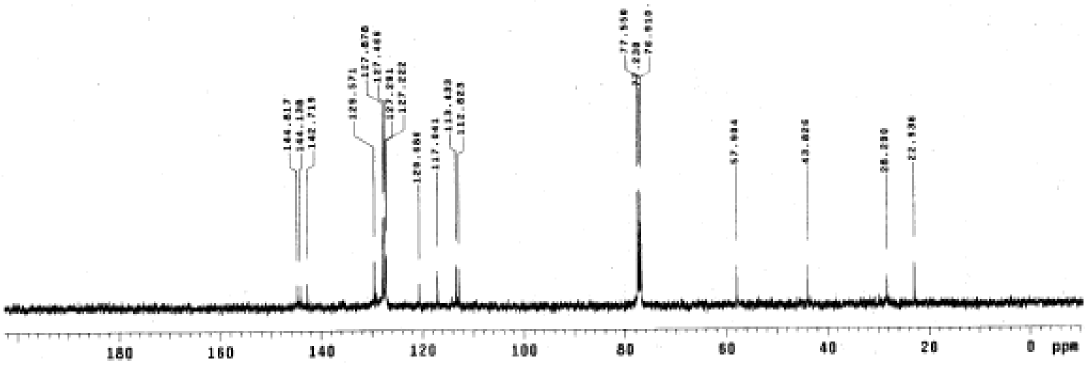
White color solid, mp 63-65 ˚C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.76 (s, 3 H), 2.76 (dd, *J* = 15.2 and 4.0 Hz, 1 H), 2.85 (dt, *J* = 11.2 and 3.6 Hz, 1 H), 2.88 (dd, *J* = 15.2 and 11.2 Hz, 1 H), 4.31 (brs, 1 H), 4.64 (brs,1 H), 4.74 (d, *J* = 3.6 Hz, 1 H), 3.82 (brs,1 H), 6.04 (d, *J* = 2.8 Hz, 1 H), 6.25 (dd, *J* = 3.2 and 1.6 Hz, 1 H), 6.54 (d, *J* = 7.2 Hz, 1 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.98-7.00 (m, 2 H), 7.27 (s, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.3, 28.3, 42.6, 52.2, 106.6, 110.3, 111.9, 114.7, 120.9, 127.2, 129.5, 141.4, 143.1, 145.0, 156.0; **IR**: 2966, 2919, 1607, 1493, 1263, 1144, 1011, 894, 743 cm^{-1}; **HRMS** (APCI) *m/z* calcd for $C_{16}H_{17}NO$ $(M+H)^+$ requires 240.1383, found 240.1387.

5.8. Selected Spectra of Tetrahydroquinolines

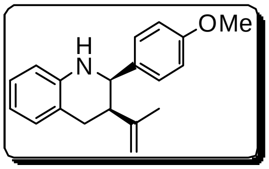
^{1}H and ^{13}C NMR spectra of **(2*R***,3*R***)-2-Phenyl-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline**

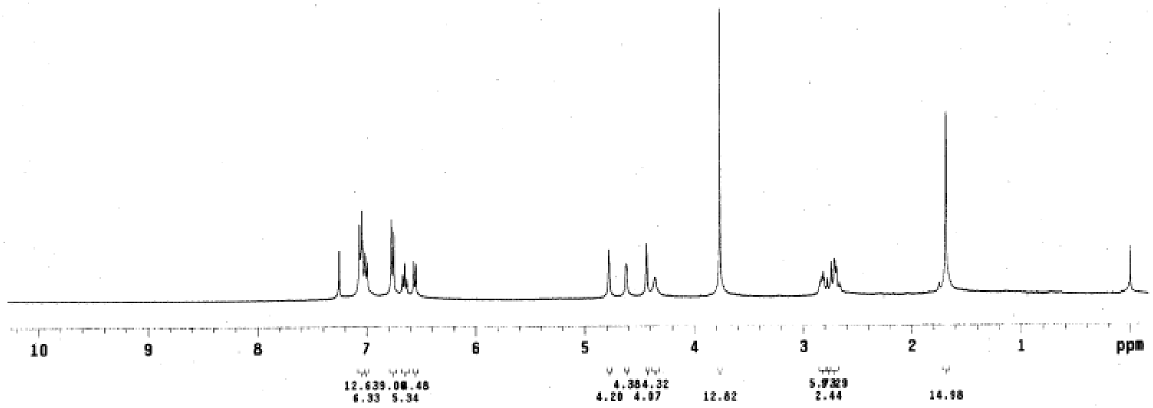


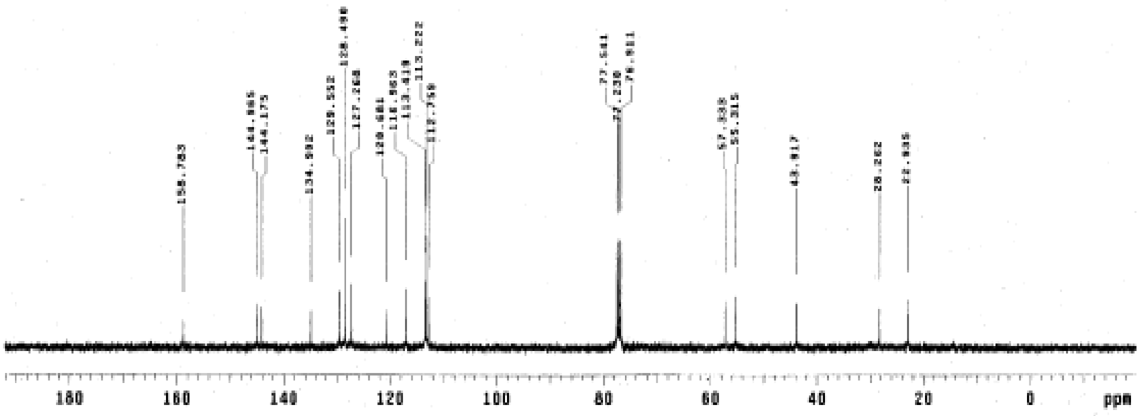




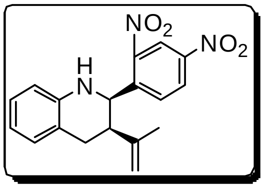
^{1}H and ^{13}C NMR spectra of **(2*R***,3*R***)-2-(4-Methoxyphenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline**

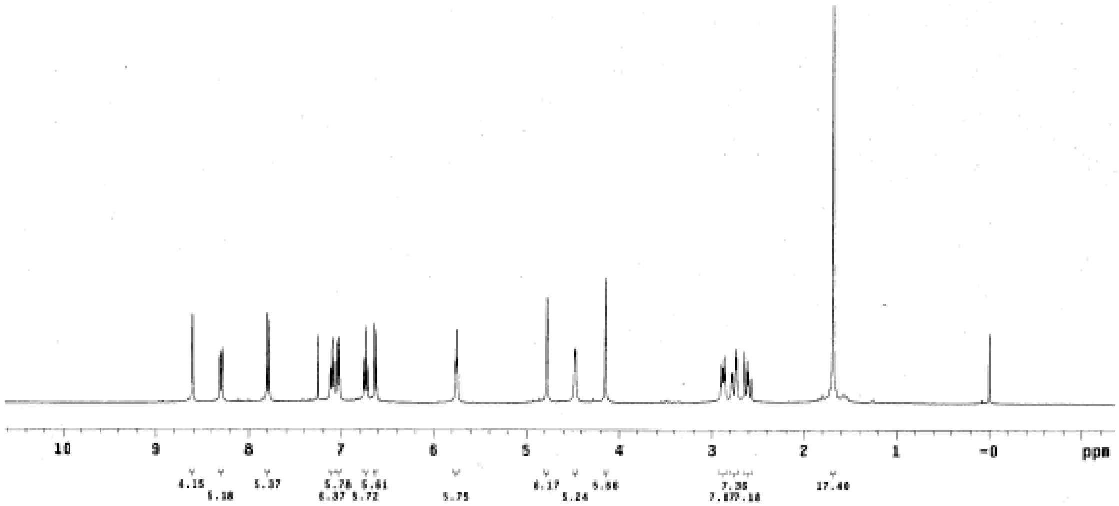


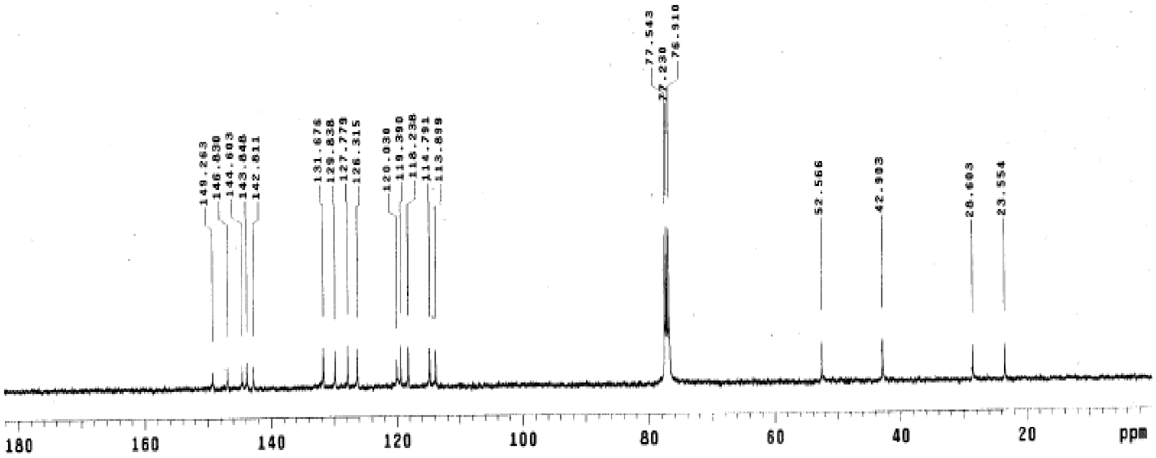




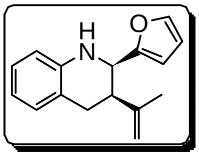
^{1}H and ^{13}C NMR spectra of **(2*R**,3*R**)-2-(2,4-Dinitrophenyl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline**

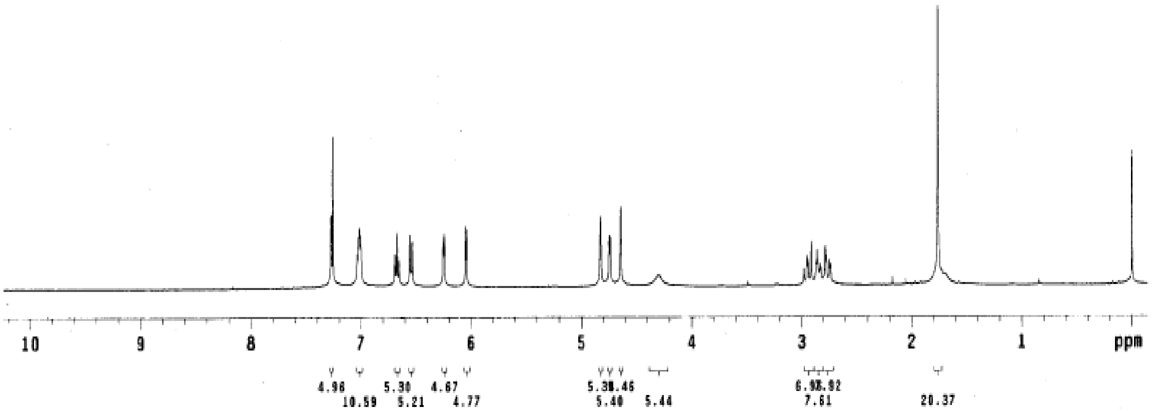


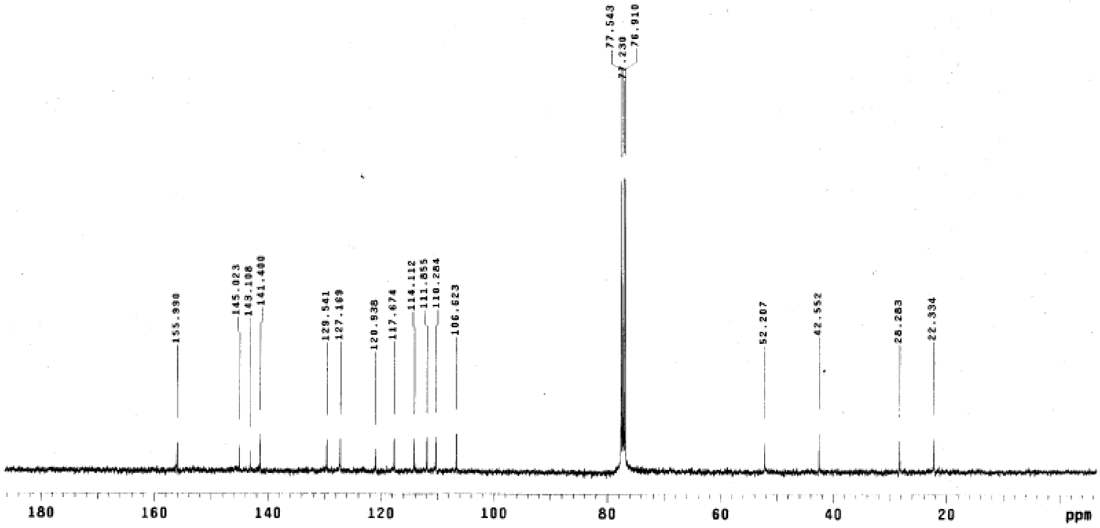




^{1}H and ^{13}C NMR spectra of **(2*R**,3*R**)-2-(Furan-2-yl)-3-(prop-1-en-2-yl)-1,2,3,4-tetrahydroquinoline**







5.9. Crystal Parameters

The crystal parameters of compound **56e**

Crystal Parameters	**56e**-CCDC 873455
Formula	$C_{19}H_{20}N_2O_2$
Formula weight	308.37
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	9.9116(5)
b/Å	12.0140(6)
c/Å	14.6057(7)
α/°	85.877(3)
β/°	76.735(3)
γ/°	76.366(3)
V/Å^3	1644.82(14)
Z	4
Abs. Coeff./mm^{-1}	0.082
Abs. Correction	Multi-Scan
GOF on F^2	0.946
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0445 $wR2$ = 0.1248
R indices [all data]	$R1$ = 0.0687 $wR2$ = 0.1477

Publication List

1. "Titanium tetrafluoride: An efficient Lewis acid and fluorinating agent for stereoselective synthesis of 4-fluorotetrahydropyrans" **Bondalapati**, **S**.; Reddy, U.C.; Kundu D. S.; Saikia A. K. *J. Fluor. Chem.* **2010**, *131*, 320-324.
2. "An Efficient Synthesis of 2,3-dihydropyran and 4-methylene tetrahydropyran via Oxonium-Ene Cyclization Reaction" **Bondalapati**, **S**.; Reddy, U. C.; Saha, P.; Saikia, A. K. *Org. Biomol. Chem*. **2011**, *9*, 3428-3438.
3. "Axial-selectivity in Prins Cyclization Reaction: Synthesis of 4-Iodotetrahydropyrans" Saikia, A. K.; **Bondalapati**, **S**.; Indukuri, K.: Gogoi, P. *Chem. Lett*. **2011**, 1176-1178.
4. "Diastereoselective Synthesis of Substituted Tetrahydrothiopyrans via Thionium-Ene Cyclization Reaction" **Bondalapati**, **S**.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2012**, *77*, 2608-2612.
5. "Diastereoselective Synthesis of Substituted Tetrahydoquinolines via Aza-Ene Cyclization Reaction" **Bondalapati**, **S**.; Indukuri, K.; Kotipalli, T.; Saikia, A. K. (*Communicated*).
6. "A Stereoselective One-Pot, Three-Component Synthesis of 4-Aryltetrahydropyrans via Prins-Friedel-Crafts Reaction" Reddy, U. C.; **Bondalapati**, **S**.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605-2608.
7. "Stereoselective Synthesis of 2,6-Disubstituted-4-Aryltetrahydropyrans Using Sakurai–Hosomi–Prins–Friedel–Crafts Reaction" Reddy, U. C.; **Bondalapati**, **S**.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, 1625–1629.
8. "A Novel Synthesis of Oxabicyclo-[3.3.1]-nonanone via (3,5)-Oxonium-Ene Reaction" Saha, P.; Reddy, U. C.; **Bondalapati**, **S**.; Saikia A. K. *Org. Lett.* **2010,** *12*, 1824-1826.
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