

Synthesis of Alkenols and Their Use in Construction of Oxygen Heterocycles

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Submitted by

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February 2016**



**DEDICATED
TO
MY FAMILY MEMBERS**



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled “**Synthesis of Alkenols and Their Use in Construction of Oxygen Heterocycles**” is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Prof. 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.

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CERTIFICATE

This is to certify that Ms. **Sabera Sultana** has been working under my supervision since July 2011 as a regular registered Ph.D. student. I am forwarding her thesis entitled “**Synthesis of Alkenols and Their Use in Construction of Oxygen Heterocycles**” being submitted for the Ph.D. (Science) degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

10th February, 2016
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Sabera Sultana

LIST OF ABBREVIATIONS**Synthetic**

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Bn	Benzyl
Bz	Benzoyl
Bu	Butyl
Cy	Cyclohexyl
DBMP	2,6-di- <i>tert</i> -but-4-methylpyridine
DCM	Dichloromethane
DIBAL	Diisobutylaluminiumhydride
DIPT	<i>N, N</i> -Diisopropyltryptamine
DMAP	4-Dimethylaminopyridine
DMF	<i>N, N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DNBA	Dinitrobenzenesulfonic acid
DTMBP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
LA	Lewis acid
LAH	Lithiumaluminium hydride
LDA	Lithiumdiisopropyl amine
MS	Molecular sieves
MsOH	Methanesulfonic acid
NMM	<i>N</i> -Methylmorpholine
Ph	Phenyl
Pr	Propyl
<i>p</i> -TSA	<i>p</i> -Toluenesulfonic acid
RCM	Ring closing metathesis
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	<i>p</i> -Toluenesulfonyl

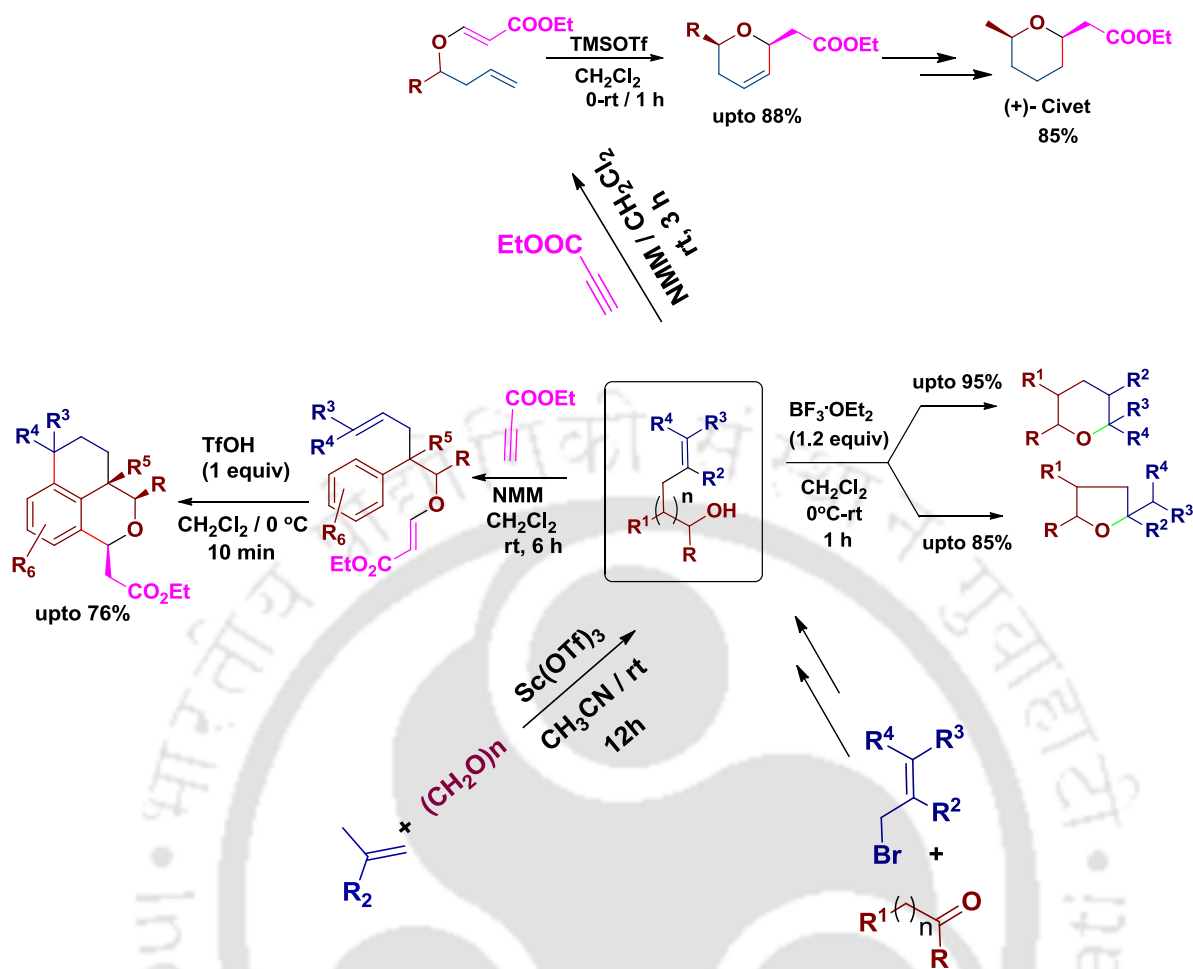
Analytical/Spectroscopic

Å	Angstrom
APSI	Atmospheric-pressure chemical ionization
Cm	Centimetre
Δ	Chemical shift
°C	Degree Celsius
CCDC	Cambridge crystallographic data centre
dr	Diastereomeric ratio
DEPT	Distortionless Enhancement of Polarisation Transfer
DFT	Density Function Theory
ee	Enantiomeric excess
ESI	Electrospray ionization
FTIR	Fourier transform infrared
gm	Gram
HRMS	High Resolution Mass Spectrometry
HMQC	Heteronuclear Multiple-Quantum Correlation
IR	Infrared
M	Molar
ml	Milliliter
m/z	Mass to charge ratio
mp	Melting point
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Pmm	Parts per million
rt	Room temperature
TLC	Thin Layer Chromatography
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplet
brs	Broad signal
Hz	Hertz

Abstract

The thesis entitled “Synthesis of Alkenols and their Use in Construction of Oxygen Heterocycles” is focused on acid catalyzed synthesis of alkenols and their utilization for the synthesis of oxygen bearing heterocycles such as dihydropyrans, tetrahydropyrans, tetrahydrofurans and isochromanes.

In synthetic organic chemistry, alkenols are considered as versatile intermediates due to their high reactivity. They are used as precursors for the synthesis of various *O*-heterocyclic compounds having synthetic and pharmaceutical importance. There are various reports for the synthesis of alkenols such as Barbier, Grignard, Hosomi-Sakurai and carbonyl-ene reactions. Among these methods, carbonyl-ene reactions have attracted much attention due to its ability to form C-C bond in presence of Lewis acids, high product yields and its usefulness in the synthesis of natural products and biologically active compounds. Oxygen containing heterocycles, especially five and six membered heterocycles are widely distributed in nature in various forms. They are also used as building blocks for the synthesis of numerous natural products and biologically active compounds starting from antibiotics to vitamins. To synthesize this class of heterocycles, many strategies have been developed over the years. The most widely used methods are the Prins cyclization, Hetero-Diels–Alder (HDA) reaction, oxonium-ene cyclization, intramolecular Michael addition, ring-closing metathesis, hydroalkoxylation of alkenols, oxa-Pictet-Spengler cyclization, Friedel–Crafts type intramolecular reaction and Baylis-Hillman reaction. These methods have their own advantages and disadvantages. Therefore, development of new and efficient methods is imperative especially to address the issue of diastereoselectivity. Thus in an attempt to overcome the limitations of the earlier methods, herein, we have reported few methodologies based on Prins cyclization, intramolecular oxonium-ene reaction, hydroalkoxylation of alkenols and oxa Pictet-Spengler reaction for the synthesis of highly diastereoselective *O*-heterocycles and its application towards natural product synthesis (Scheme 1).



Scheme 1: Thesis overview

In summary, the whole thesis is focused on the synthesis of alkenols and their use in various biologically important dihydropyrans, tetrahydropyrans, tetrahydrofurans and hexahydrobenzo[*de*]isochromanes. These newly developed methodologies and the synthesized novel compounds are expected to be widely used in synthetic organic chemistry and pharmaceutical industries.

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CHAPTER 1

Introduction to Alkenols and Oxygen Heterocyclic Compounds



CHAPTER 1

Introduction to Alkenols and Oxygen Heterocyclic Compounds

1.1. Background

Heterocyclic compound is an organic compound in which the carbon ring includes at least one atom in addition to carbon (S, O, N etc.). The chemistry of heterocyclic compounds is the largest branch in the organic chemistry with more than half of the existed compounds coming under this category. Among all the heterocycles, oxygen containing heterocyclic compounds play a vital role as these are widely spread in various forms throughout the nature. Oxygen heterocyclic compounds having five and six membered rings are the building blocks of numerous natural products from antibiotics to vitamins. These are also the key components of pharmaceutical chemistry and therefore, they have been a fruitful source of inspiration for the design of structural analogues to be used as pharmacological tools as well as new drugs. In the construction of oxygen heterocyclic compounds, alkenols play an important role. Many strategies have been developed for the synthesis of oxygen heterocyclic compounds using alkenols as precursor.

This thesis is intended to provide an insight into the importance and synthetic routes for the synthesis of alkenols, five and six membered cyclic ethers viz. tetrahydrofurans, tetrahydropyrans and tetrahydropyran fused with benzene ring (viz. isochromanes) and their application in natural product synthesis.

1.2. Importance of Alkenols

Alkenols are important building blocks in organic synthesis particularly for the synthesis of various oxygen heterocyclic compounds of synthetic and pharmaceutical importance.¹ The alkene functionality of homoallylic alcohols can be readily transformed into a wide variety of functional groups such as aldehydes (*via* ozonolysis), δ -lactones (*via* a facile hydroformylation), epoxides, other olefinic compounds (*via* cross-olefin metathesis) and they also act as substrates for Prins cyclization and intramolecular oxonium-ene reaction that provides oxygenated heterocycles.² Furthermore, they are also featured widely in many natural products as well as in many fruits and vegetables which provides flavors

and fragrances to them. Alkenols are also constituents of some biologically active molecules such as Lasonolide A (1), isolated from Caribbean marine sponge, *Forcepia*

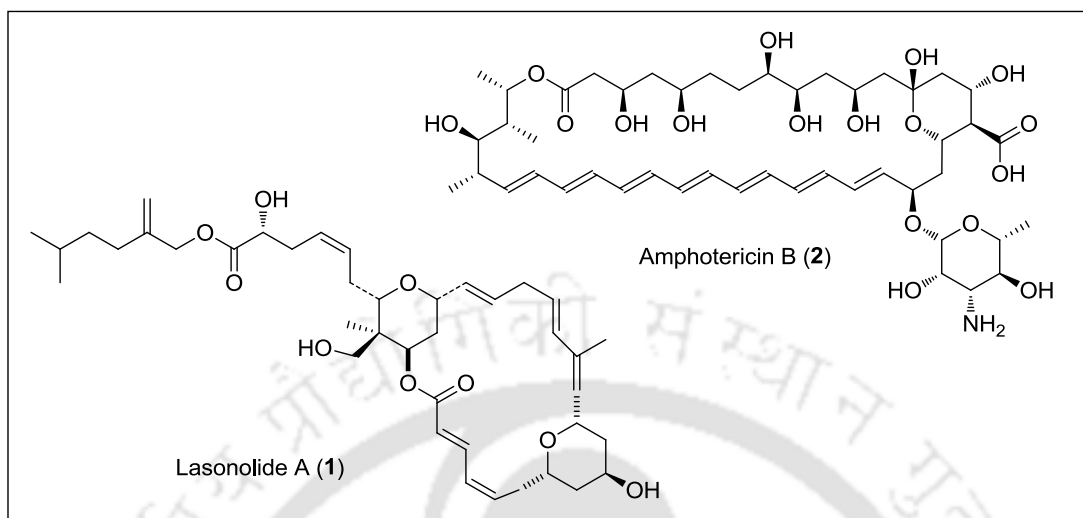


Figure 1.2.1. Bioactive molecules containing alkenols

sp. Which shows high biological activity as an antitumor agent,³ polyhydroxylated natural products *e.g.* Amphotericin B (2), extracted from *Streptomyces nodosus*, a filamentous bacterium, used for fungal infections⁴ (Figure 1.2.1).

1.3. Importance of Oxygen Heterocyclic Compounds

Five and six membered oxygen containing heterocycles possess significant biological properties. Among them dihydropyrans, tetrahydropyrans, tetrahydrofurans and isochromanes are widely spread in natural products or biologically active molecules. For example, Martiriol (3), a dihydropyran unit containing biological active molecule, isolated from the red algae of the genus *Laurencia*, shows potent activity against various tumour cell lines.⁵ Salinomycin (4), a dihydropyran containing polyether isolated from a culture broth of *Streptomyces albus* which has been shown to possess interesting antibacterial and anticoccidial properties.⁶ Laulimalide (5) is a structurally novel cancer therapeutic lead, recently isolated in trace quantities from pacific marine sponges.⁷ Aspergillide C (6) constitute a novel class of dihydropyran containing 14-membered macrolides, isolated along with its structurally related aspergillides A and B by Kusumi *et al.* from the marine-derived fungus *Aspergillus ostianus* strain 01F313, cultured in a medium composed of bromine modified artificial sea water (Figure 1.3.1).⁸

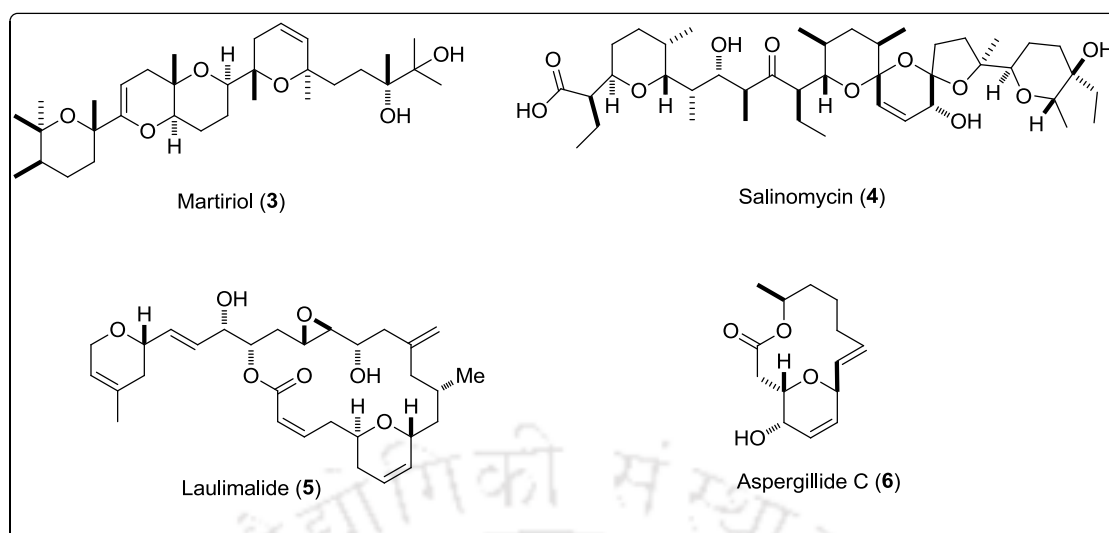


Figure 1.3.1. Bioactive molecules containing dihydropyran ring

Tetrahydropyran units are also widely spread among biologically active natural products such as polyether antibiotics, marine toxins and pheromones.⁹ For example, (-)-Centrolobine (7) was isolated from the heart-wood of the tree *Centrolobium tomentosum*, whereas its enantiomer (+)-centrolobine occurs in the closely related species *Centrolobium robustum*. Both enantiomers have antibiotic and anti-fungal activities.¹⁰

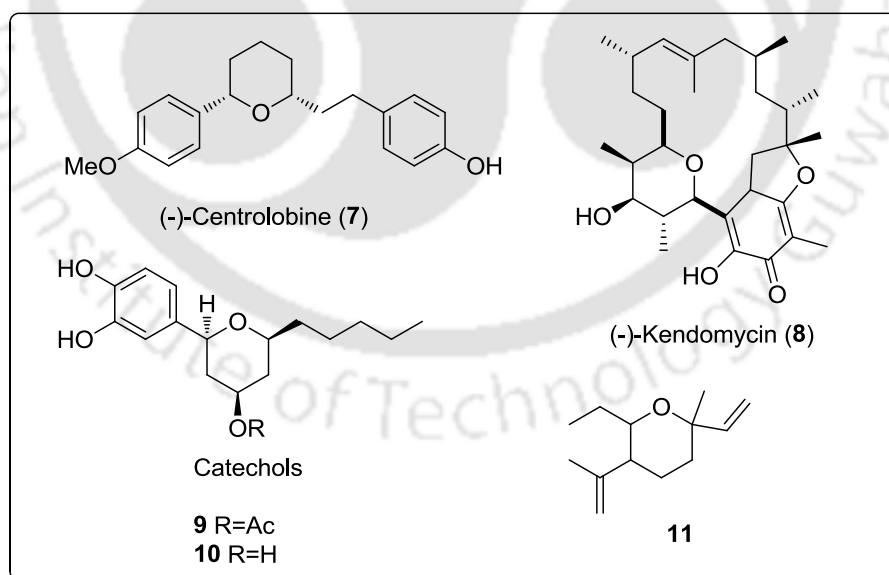


Figure 1.3.2. Bioactive molecules containing tetrahydropyran ring

Tetrahydropyran containing macrocycle, (-)-kendomycin (8) has a diverse and fascinating pharmacological profile. It was isolated in 1996 from *streptomyces* bacteria

and exhibits potent antagonism of the endothelin receptor agonism.¹¹ Catechols (**9**) and (**10**) isolated from the extracts of *Plectranthus sylvestris* (labiateae), a plant found in the woody hills in East Africa are potent antioxidants and possesses anti-inflammatory properties.¹² An alkyl substituted tetrahydropyran **11** are also used as aroma and flavouring agents for pharmaceuticals, cosmetics and food stuffs (Figure 1.3.2).¹³

The furan nucleus is also found in a large number of biologically active compounds. For example, the 16 membered macrodiolide pamamycin-607 (**12**) isolated from *streptomyces alboniger* and *S. aurantiacus* shows potent activity against gram-positive bacteria as well as against phytopathogenic fungi.¹⁴ The mycotoxin citreoviridine (**13**), isolated from *Penicillium citreoviride* is a potent inhibitor of the soluble mitochondrial ATPase.¹⁵ The muscarine (**14**), a furan containing biologically active alkaloid is the major toxic principle found in the well-known mushroom *Amanita muscaria* (Fly agaric).¹⁶

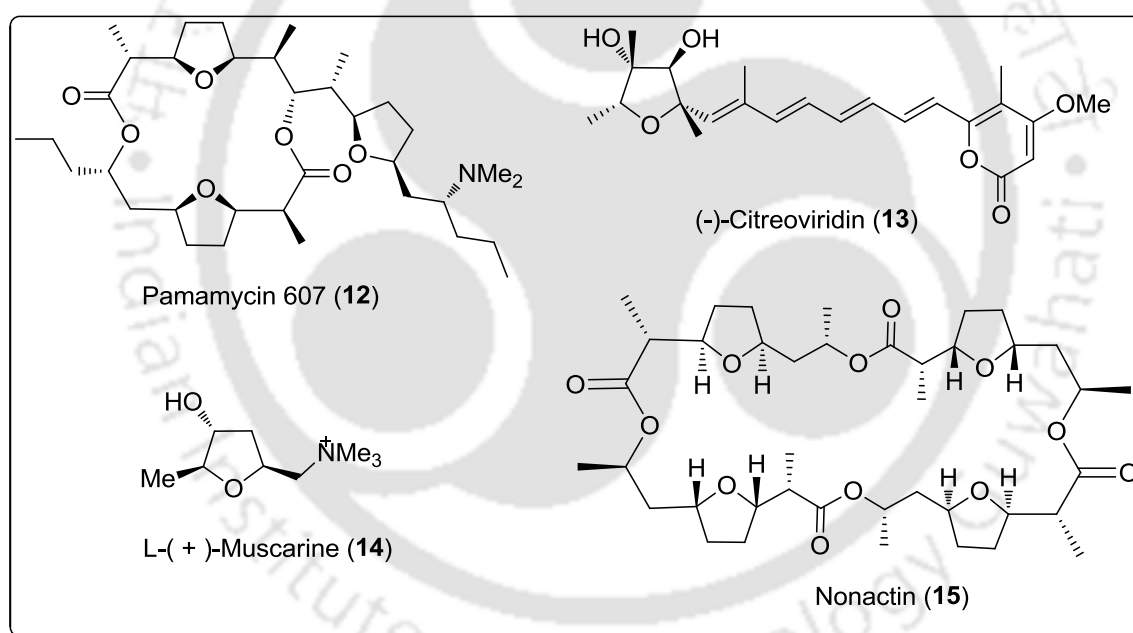


Figure 1.3.3. Bioactive molecules containing tetrahydrofuran ring

Muscarine acts as a selective agonist of the neurotransmitter acetylcholine on smooth muscles of the gastrointestinal tract, eye exocrine glands and heart.¹⁷ Nonactin (**15**), an ionophoric macrolide antibiotic isolated from a variety of *Streptomyces* cultures has been shown to possess antitumor activity both against mammalian cell lines *in vitro* and against Crocker sarcoma 180 in studies with mice¹⁸ (Figure 1.3.3).

Another important class of cyclic ethers are isochromanes in which a pyran ring fused with a benzene ring is present. The isochromane fragment is the core of various natural compounds, which exhibit a wide variety of pharmacological activities which are promising for the treatment of migraines, Parkinson's disease and schizophrenia respectively.¹⁹ Penidicitrinin B (**16**) isolated from *Penicillium citrinum* strains, containing C-1 phenyl substituted isochromane ring possesses antioxidant properties.²⁰

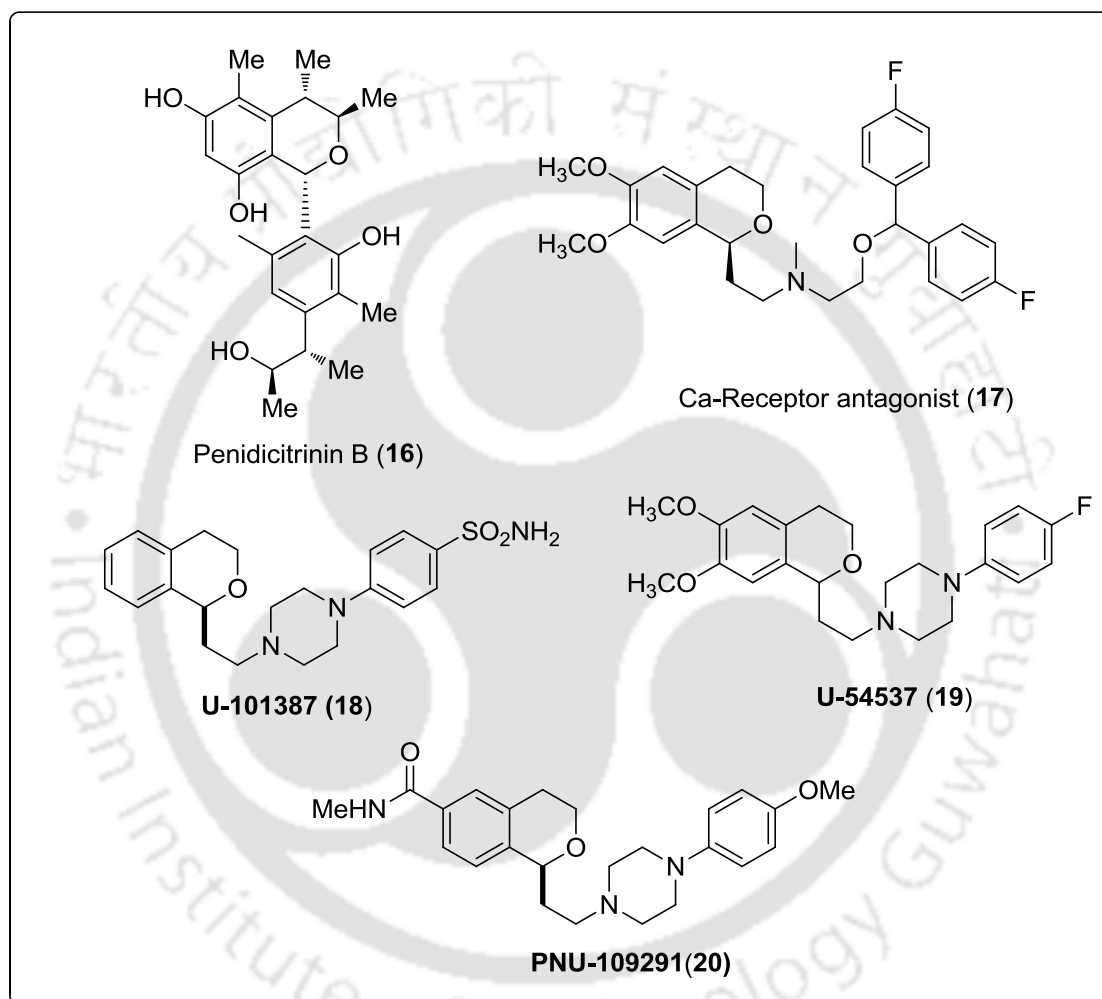


Figure 1.3.4. Bioactive molecules containing isochromane rings

Similarly, a wide spread 1-Aryl-6,7-dimethoxyisochromanes shows a wide range of biological activities such as analgesic, muscle relaxant, anti-depressant, anti-inflammatory, anti-histaminic, anti-coagulant, hypotensive with peripheral and central activities, and are adrenergic antagonists.²¹ Biologically active compound **17** containing a isochromane ring shows affinity towards Ca-receptors.²² Sonopiprazole U-101387 (**18**)

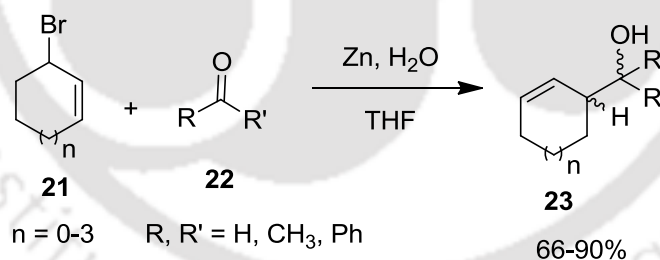
which exhibits high affinity for the D₄ receptor potentially useful for treatment of schizophrenia. A series of dimethoxyisochromanes *e.g.* U-54537 (**19**) have activity to lower blood pressure presumably by both peripheral and central α -adrenoreceptor blockade.²³ PNU-109291 (**20**) containing isochromane ring is selective 5-HT_{1D} receptor agonist with anti-migraine potential, like sumatriptan (Figure 1.3.4).²²

1.4. An Overview for the Synthesis of Alkenols

The most widely used methods for alkenols are Barbier, Grignard, Hosomi–Sakurai and carbonyl-ene reactions. A brief summary of these reactions are discussed below.

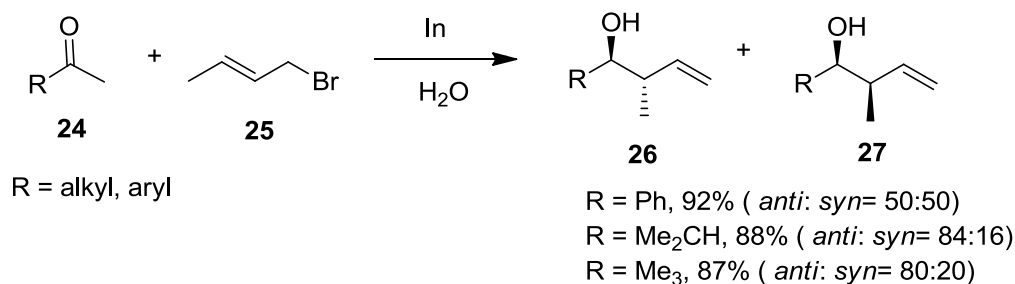
1.4.1. Barbier reaction

Barbier reaction is a C-C bond forming reaction involving the reaction between an alkyl halide and a carbonyl compound in the presence of metals like zinc, indium and tin. Breton *et al.* have reported zinc-mediated aqueous Barbier reaction of cyclic allylic bromide **21** with various aldehydes and ketones **22** to afford homoallylic alcohols **23** (Scheme 1.4.1.1). Both aromatic aldehydes and ketones afforded adducts in good yields (66–90%) with good diastereoselectivities. Aliphatic aldehydes also reacted well under these conditions, but in case of aliphatic ketones products were obtained in less yields.²⁴

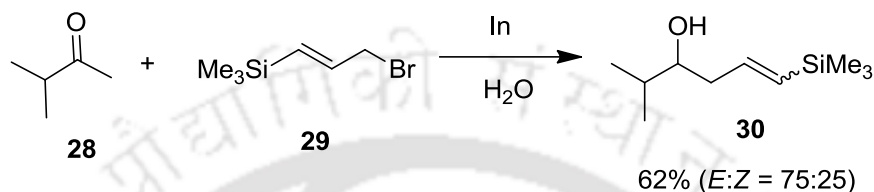


Scheme 1.4.1.1

Isaac *et al.* found that in the coupling of aldehyde **24** with crotyl bromide **25** mediated by indium in water (Scheme 1.4.1.2), the reaction was γ -regioselective and gave a mixture of *anti* **26** and *syn* **27** isomer. To make the reaction regioselective, they have coupled the aldehyde **28** with trimethylsilylpropenylbromide **29** giving a mixture of *E*- and *Z*-vinylsilanes **30** (Scheme 1.4.1.3).²⁵



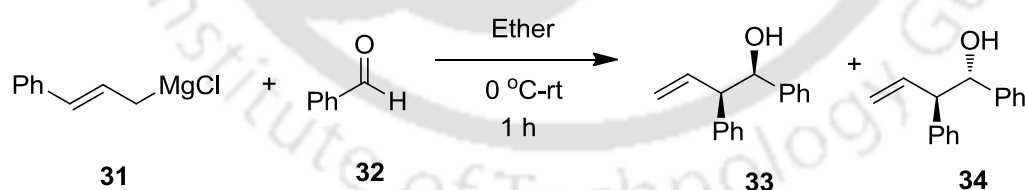
Scheme 1.4.1.2



Scheme 1.4.1.3

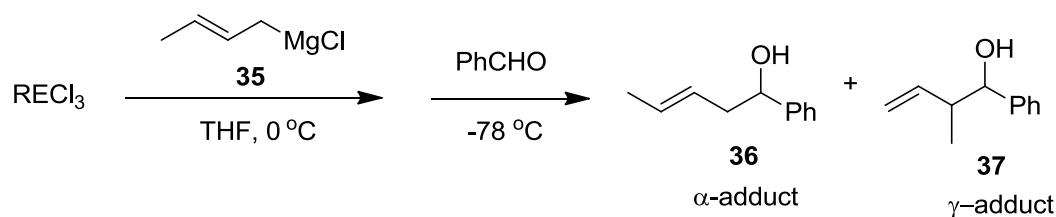
1.4.2. Grignard reaction

The Grignard reagent (RMgX) was named after Victor Grignard (1871-1935; Nobel Prize, shared with Paul Sabatier, 1912) and is probably the single most important organometallic reagent used in the laboratory synthesis of organic compounds. Grignard reaction has become important carbon-carbon bond forming reactions in organic synthesis. Coxon *et al.* have reported a reaction between 3-phenylpropen-1-yl magnesium chloride **31** with benzaldehyde **32** to give a mixture of homoallylic alcohols **33/34** with 7:3 ratio of *syn* and *anti* isomer (Scheme 1.4.2.1).²⁶



Scheme 1.4.2.1

A regioselective allylation reaction using crotyl Grignard reagent–lanthanide salt is described by Matsukawa group. Regioselectivity depends on the lanthanide salts: α -product was predominantly produced with light rare earth elements such as La, Ce, Pr, Nd, whereas γ -product was formed when heavy rare earth elements were used (Scheme 1.4.2.2).²⁷

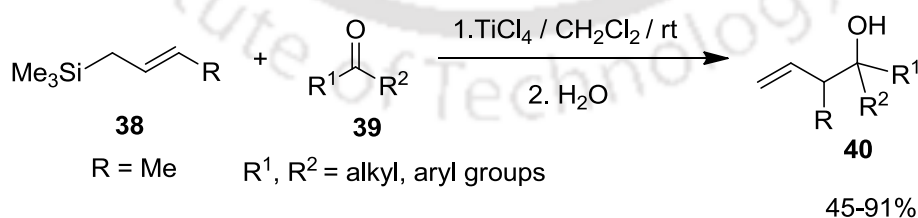


RE	yield (%)	$\alpha(\text{cis/trans}): \gamma$	RE	yield	$\alpha(\text{cis/trans}): \gamma$
Sc	89	4:9	Yb	88	1:99
La	93	80(25/75):20	Lu	91	24(16/84):76
Ce	94	86(13/87):14	Tm	91	27(17/83):73
Nd	98	89(8/92):11	Gd	96	64(4/96):36

Scheme 1.4.2.2

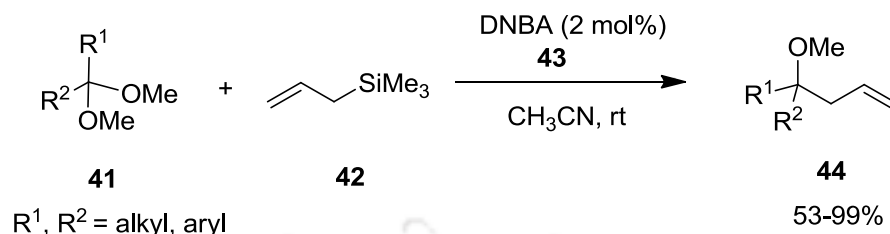
1.4.3. Hosomi–Sakurai reaction

Hosomi–Sakurai reaction is the chemical reaction of carbon electrophiles (such as ketone) with allylic silanes catalyzed by strong Lewis acids. It is named after the chemists Akira Hosomi and Hideki Sakurai. Strong Lewis acids such as titanium tetrachloride, boron trifluoride, tin tetrachloride and $\text{AlCl}(\text{Et})_2$ are all effective promoters of the Hosomi reaction. The reaction is a type of electrophilic allyl shift with formation of an intermediate β -silyl carbocation. Driving force is the stabilization of the carbocation by the β -silicon effect. The synthetic utility of this reaction is displayed by the regiospecific transformation of the allylic group to a carbonyl function (Scheme 1.4.3.1).²⁸



Scheme 1.4.3.1

List *et al.* have reported the synthesis of homoallylic ethers **44** in good yields via Hosomi–Sakurai reaction between acetals **41** and allyltrimethylsilane **42** in the presence of a catalytic amount of dinitrobenzenesulfonic acid (DNBA) **43** (Scheme 1.4.3.2).²



Scheme 1.4.3.2

1.4.4. Carbonyl-ene reaction

An ene reaction can be broadly classified as the reaction of an alkene bearing an allylic hydrogen (the ene) with a double or triple bond known as the enophile. These reactions are accompanied by migration of the double bond and a 1,5-hydrogen shift. These enophiles include alkenes, alkynes, allenes, carbonyls, imines and main-group double bonds. If the reaction involves an ene and carbonyl compounds as enophiles then it is referred to as carbonyl-ene reaction. The frontier-orbital interaction occurring in an ene reaction is between the HOMO of the ene and the LUMO of the enophile (Figure 1.4.4.1). The HOMO of the ene results from the combination of the pi-bonding orbital in the vinyl moiety and the C-H bonding orbital for the allylic H. From a mechanistic perspective, thermal ene reactions proceed in a concerted manner through a cyclic transition state and acid catalyzed carbonyl-ene reaction proceed through stepwise mechanism involving carbocation intermediates are considered to be a subset of Prins

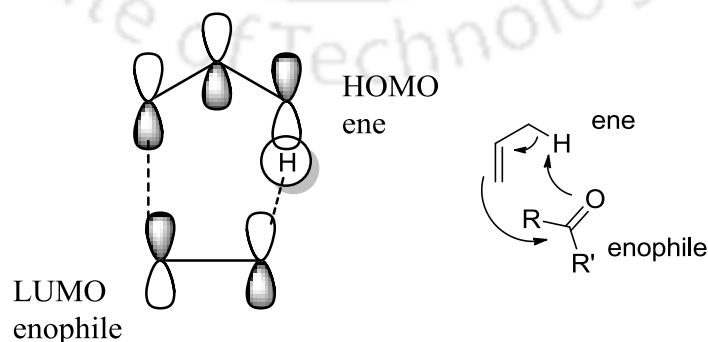
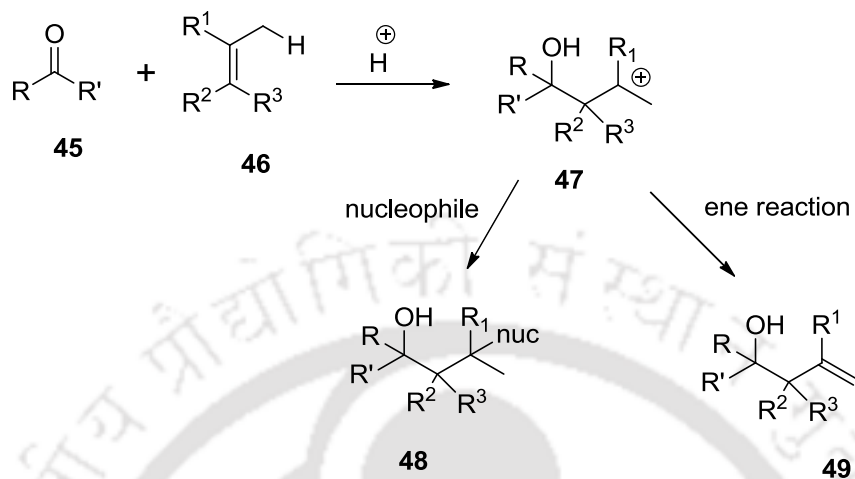


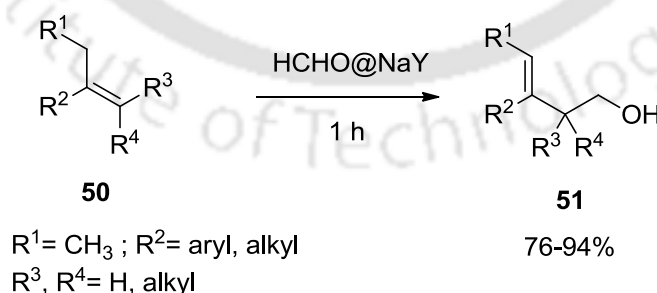
Figure 1.4.4.1. HOMO-LUMO interaction of ene reaction

reaction. In the Prins reaction, the carbocation intermediate **47** is either quenched by another nucleophile to give **48** or loses the allylic proton to form an ene-type product **49** (Scheme 1.4.4.1).³⁰



Scheme 1.4.4.1

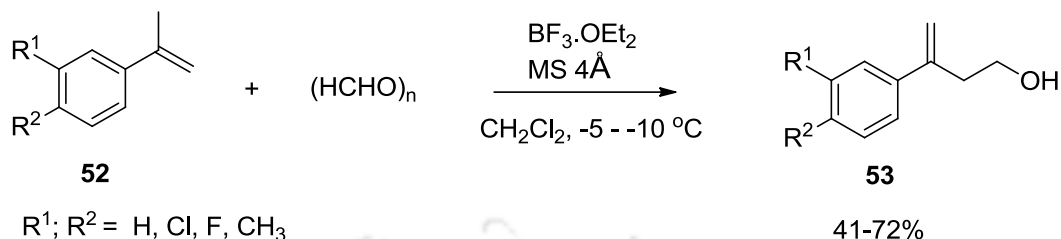
Makoto Onaka *et al.* have reported the synthesis of primary homoallylic alcohols **51** via carbonyl-ene reaction using zeolite-encapsulated formaldehyde and alkene **50** in good yields. In this reaction condition trisubstituted and cyclic olefins gives corresponding ene products in good yields but with low selectivity. In this case substrate to substrate reaction condition changes, in some cases they used 0 °C or -20 °C or room temperature and also they used different solvents *e.g.* cyclohexane or cyclohexane/ hexane or hexane (Scheme 1.4.4.2).³¹



Scheme 1.4.4.2

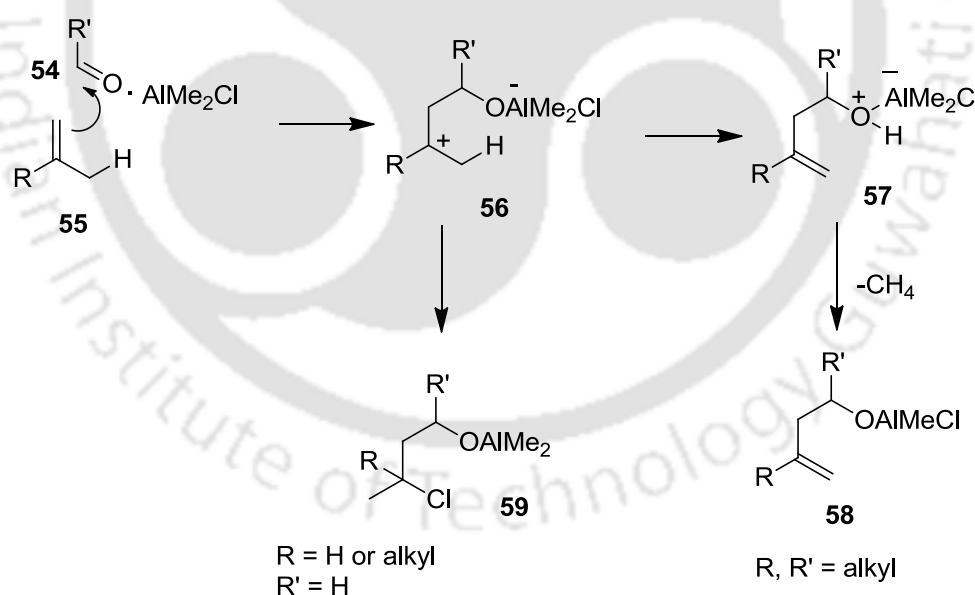
Makoto Onaka *et al.* have also reported a method for synthesis of primary homoallylic alcohols **53** via carbonyl-ene reaction of α -methylstyrenes **52** with paraformaldehyde

using a combination of boron trifluoride etherate and molecular sieves 4Å (Scheme 1.4.4.3). The reaction gives moderate to good yields but this system is not applicable with an electron-donating group.³²



Scheme 1.4.4.3

Dimethylaluminium chloride catalyzed ene reaction has been reported by Sinder *et al.* between aldehydes **54** and alkenes **55** with improved yields (16-93%) of ene adducts from formaldehyde. Me_2AlCl acts as a mild Lewis acid and a proton scavenger. The alcohol- Me_2AlCl complex **56** formed in the reaction decomposes rapidly to give methane and a non basic aluminium alkoxide **58** which does not undergo side reactions. Formation of a

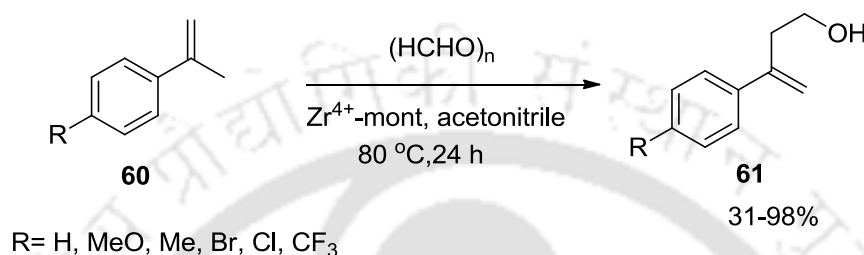


Scheme 1.4.4.4

chloro alcohol **59** as a byproduct is observed when the carbenium ion is secondary (Scheme 1.4.4.4). However, in presence of excess Me_2AlCl , the chloro alcohol is unstable, forming ene-adduct in case of cyclic alkenes and a complex mixture. They also

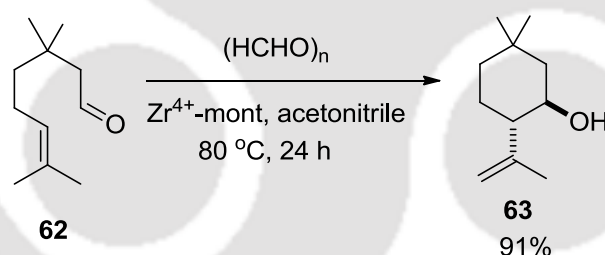
did the reaction with formaldehyde using Me_2AlCl to give good yields of ene adducts (70-80%) with chloro alcohols as byproducts.³³

Sakae Uemura *et al.* have reported the synthesis of homoallylic alcohols **61** via carbonyl-ene reactions between α -methylstyrenes **60** and paraformaldehyde catalyzed by zirconium-montmorillonite in acetonitrile at 80 °C (Scheme 1.4.4.5). No side products are formed in this reaction conditions and also the catalyst is recovered. The reaction is highly



Scheme 1.4.4.5

stereoselective in case of intramolecular cyclization of citronellal **62** to afford isopulegol **63** in high yields (Scheme 1.4.4.6).³⁴



Scheme 1.4.4.6

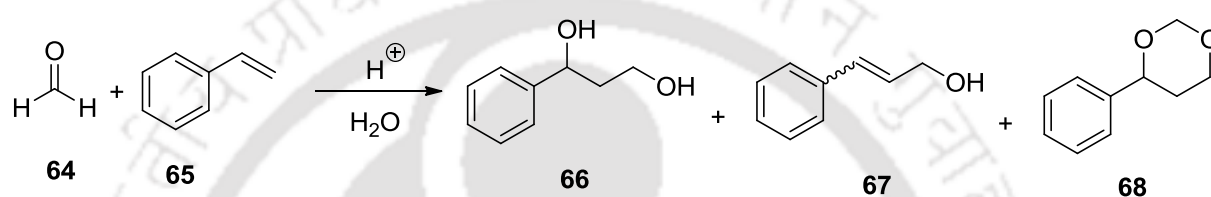
1.5. An Overview for the Synthesis of Dihydropyrans, Tetrahydropyrans, Tetrahydrofurans and Isochromanes

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

Therefore, development of new and efficient methods is imperative especially to address the issue of diastereoselectivity.

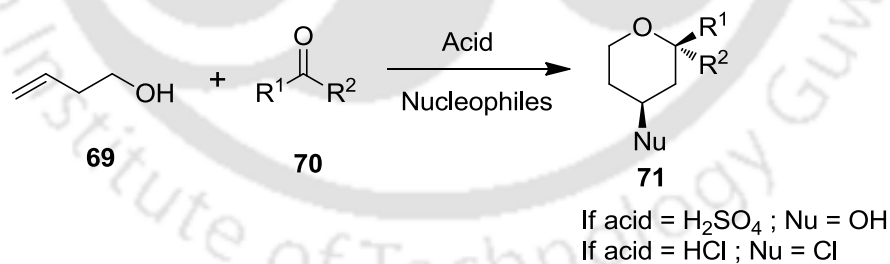
1.5.1. Prins cyclization reaction

The Prins reaction is one of the fundamental methods for C-C bond formation, first reported by H. J. Prins in the year 1919. In his initial studies, H. J. Prins performed the reaction of formaldehyde **64** and styrene **65** in aqueous acidic medium, resulting in a mixture of products such as diol **66**, unsaturated alcohol **67** and 1,3-dioxane **68** (Scheme 1.5.1.1).³⁵



Scheme 1.5.1.1

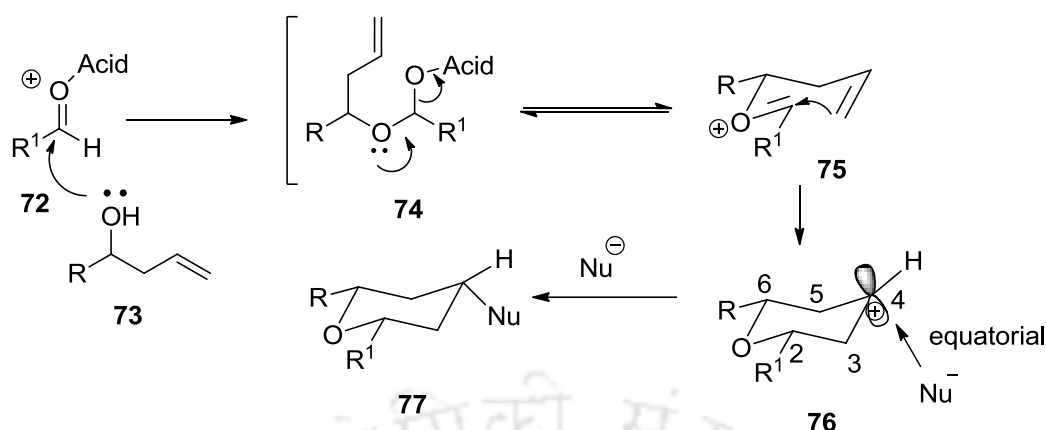
In 1955, Hanschke has further developed Prins reaction for the selective synthesis of tetrahydropyran (THP) rings **71** by combining 3-buten-1-ol **69** with a variety of aldehydes or ketones **70** in the presence of acid, called Prins cyclization reaction (Scheme 1.5.1.2).³⁶



Scheme 1.5.1.2

In most of the cases the Prins cyclization reaction is highly diastereoselective and give 2,4,6-substituted tetrahydropyrans with all equatorial substitutions. The diastereoselectivity was explained as follows.³⁷

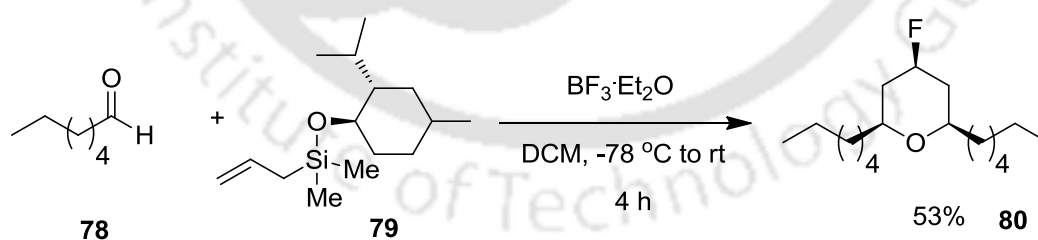
Homoallylic alcohol **73** reacts with aldehyde **72** in the presence of acid to generate an oxocarbenium ion **75** as a key intermediate, which undergoes 6-endo-trig-cyclization to



Scheme 1.5.1.3. Mechanism of the Prins cyclization reaction

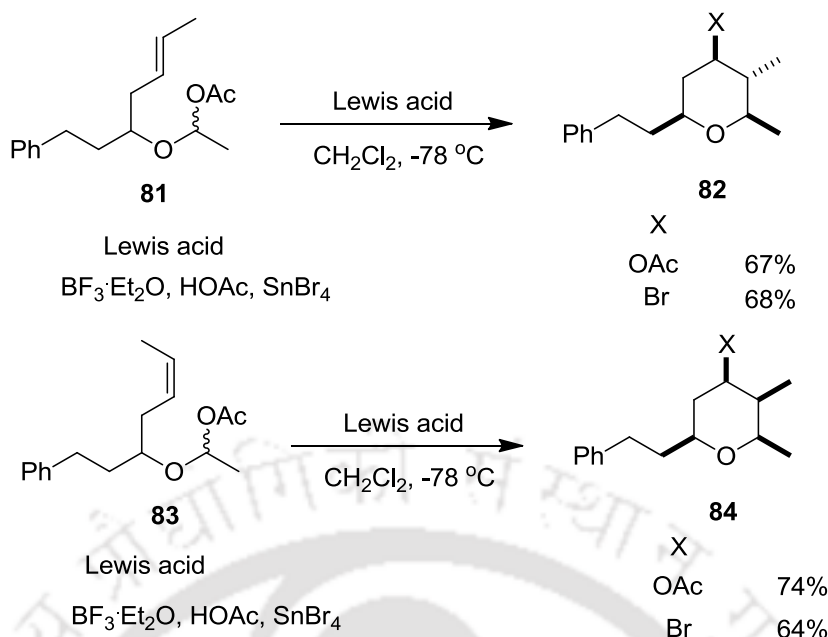
give more stable tetrahydropyranyl cation **76**. According to Alder's DFT calculations, carbocation **76** in its chair conformation is stabilized by stereoelectronic effects. The C2-C3 and C5-C6 σ^* and σ orbital overlap both the equatorial lone pair of the oxygen atom and the vacant p orbital at C4. Optimal overlap is reached when the hydrogen atom at C4 is pseudo-axial. This stabilization favors equatorial attack by the nucleophile to give tetrahydropyran **77** (Scheme 1.5.1.3).

Chan and co-workers have reported the synthesis of symmetrical *cis* 4-fluorotetrahydropyrans **80** from the reaction of two equivalents of aldehyde **78** and alkoxyallylsilane **79** catalyzed by boron trifluoride etherate at -78°C (Scheme 1.5.1.4).³⁸

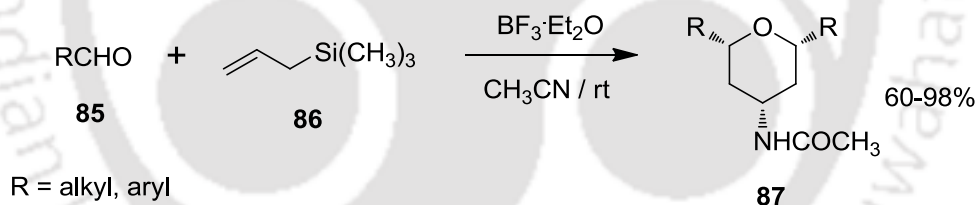


Scheme 1.5.1.4

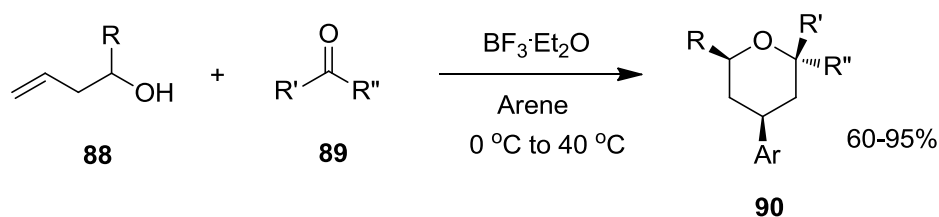
A highly substituted tetrahydropyran was reported by Rychnovsky group by treatment of α -acetoxy ether **81** and **83** with Lewis acid. Here alkene geometries dictate the product configurations, with *E*-alkenes **81** leading to equatorial substituents **82** and *Z*-alkenes **83** leading to axial substituents **84** (Scheme 1.5.1.5).³⁹

**Scheme 1.5.1.5**

Saikia and co-workers have reported the synthesis of 4-amidotetrahydropyrans **87** from the reaction of aldehydes **85** with allylsilane **86** in acetonitrile mediated by boron trifluoride etherate in good yields and high stereoselectivity (Scheme 1.5.1.6).⁴⁰

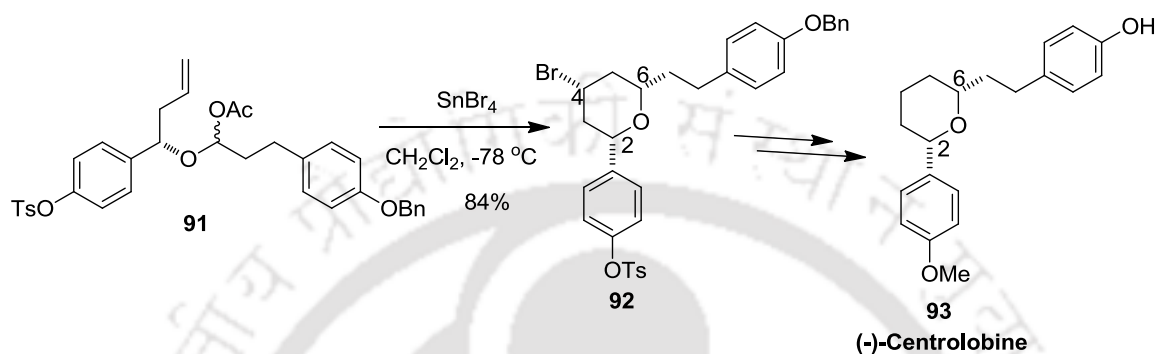
**Scheme 1.5.1.6**

Saikia and co-workers have reported a diastereoselective one-pot, three-component Prins-Friedel-Crafts reaction for the synthesis of 4-aryltetrahydropyran derivatives **90** from the

**Scheme 1.5.1.7**

reaction of carbonyl compounds **89** with homoallylic alcohols **88** in presence of boron trifluoride etherate (*Scheme 1.5.1.7*).⁴¹

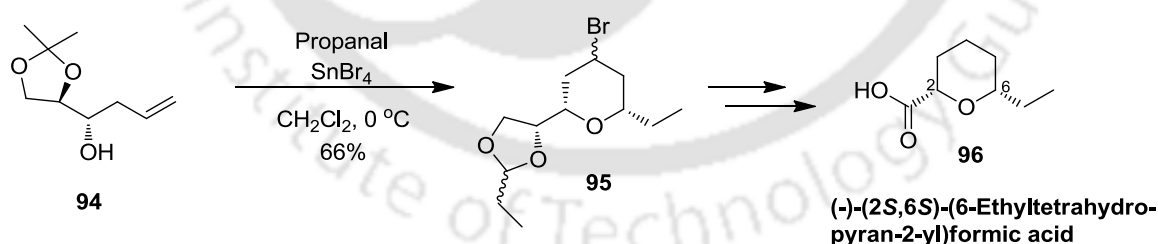
Synthesis of (-)-centrolobine **93**, an antibiotic isolated from the heartwood of *Centrolobium robustum* was reported by Rychnovsky groups via Prins cyclization between enantiopure α -acetoxy ether **91** in the presence of SnBr_4 . The initially formed 4-



Scheme 1.5.1.8

bromo-tetrahydropyran **92** has been converted to (-)-centrolobine **93** via consecutive steps (*Scheme 1.5.1.8*).⁴²

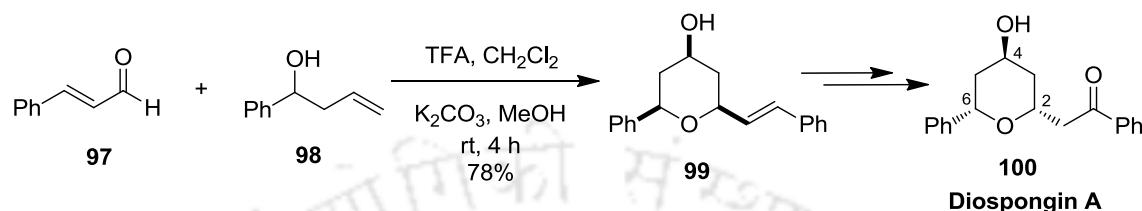
($\pm$)-*Cis*-(6-ethyltetrahydropyran-2-yl)formic acid is a novel class of non-steroidal analgesic compound. Vasconcellos and co-workers described the enantioselective synthesis of (-)-(2*S*,6*S*)-(6-ethyl-tetrahydropyran-2-yl)-formic acid **96** in five steps with



Scheme 1.5.1.9

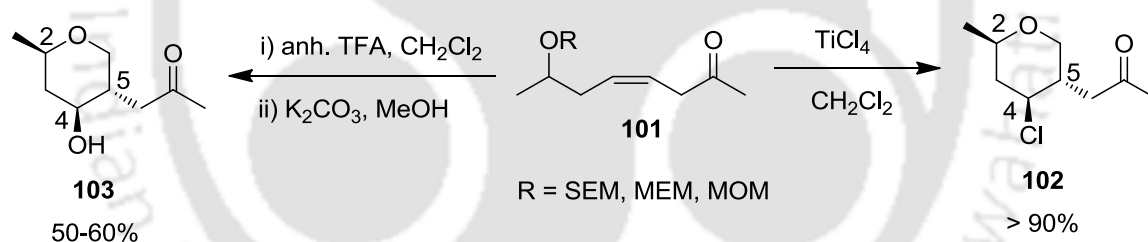
30% overall yield (87% ee) from the commercial chiral template (*R*)-2,3-isopropylideneglyceraldehyde **94**. An efficient Prins cyclization reaction of **94** with propanal mediated by SnBr_4 resulted in a mixture of four diastereomers of **95** (*Scheme 1.5.1.9*). Reduction of the latter, followed by oxidative cleavage of diol, led to the levo enantiomer of **96** in 87% ee.⁴³

Yadav *et al.* developed a concise and efficient total synthesis of diospongins A **100** which is active against osteoporosis, using Prins cyclization and enzymatic kinetic resolution as key steps. 2,4,6-*cis*-trisubstituted tetrahydropyran ring **99** was achieved *via* Prins reaction of cinnamaldehyde **97** and homoallylic alcohol **98** catalyzed by triflic acid (Scheme 1.5.1.10).⁴⁴



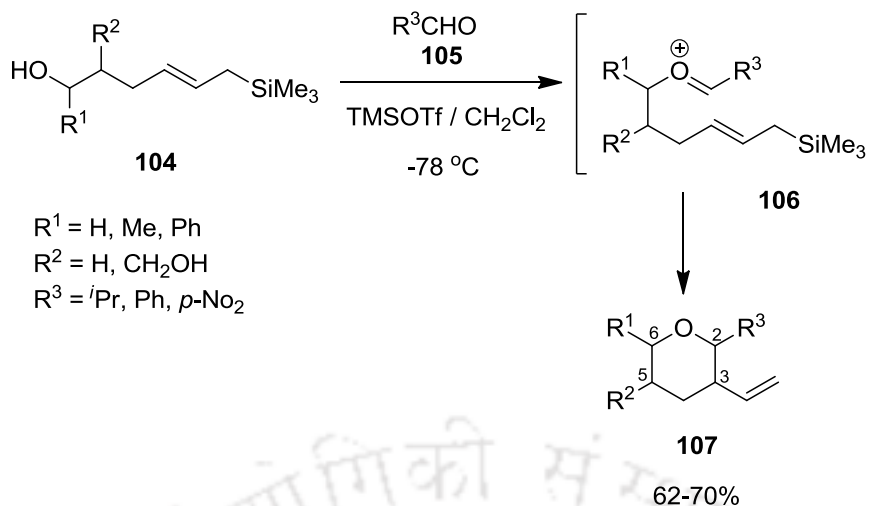
Scheme 1.5.1.10

Willis and co-workers have reported a Prins type cyclization of homoallylic acetals **101** for the synthesis of 2,4,5-trisubstituted tetrahydropyrans **102** and **103**. The reaction is versatile and by varying the acid (TiCl₄ or TFA) different C-4 substituted tetrahydropyrans were obtained (Scheme 1.5.1.11).⁴⁵



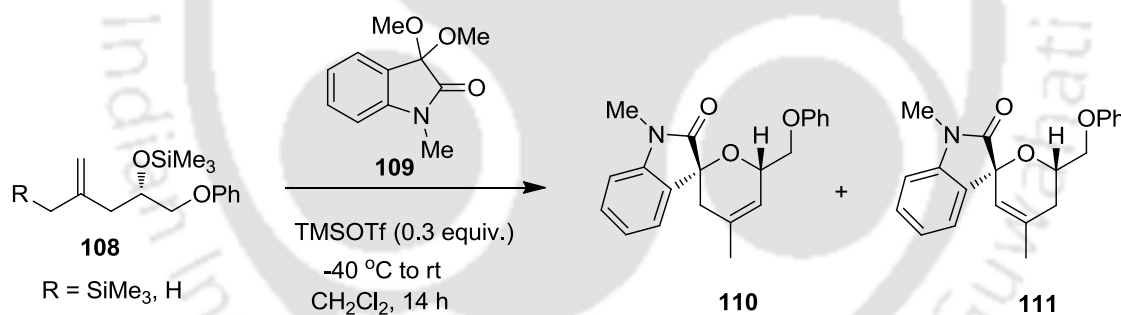
Scheme 1.5.1.11

Szabó and co-workers have reported a methodology for the synthesis of 2,3,5,6-substituted tetrahydropyrans **107** from the reaction of functionalized allylsilanes **104** and aldehydes **105** mediated by TMSOTf in dichloromethane at -78 °C with excellent stereoselectivity (Scheme 1.5.1.12). According to DFT calculations, the high stereoselectivity arises from electronically induced steric effects occurring in the key-intermediate of the cyclization.⁴⁶



Scheme 1.5.1.12

Porco, Jr. and co-workers have reported the synthesis of spirocyclic oxindole pyrans having 4-methyl substituted dihydropyran unit **110/111**. These spirocyclic compounds are prepared from the reaction of homoallylic alcohols **108** with isatin ketals **109** in the presence of trimethylsilyl trifluoromethanesulfonate (Scheme 1.5.1.13).⁴⁷

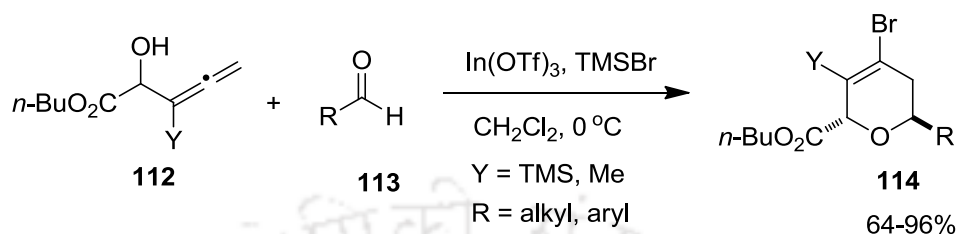


Entry	R	Additive	Yield
1	$SiMe_3$	DBMP (0.1 equiv.)	110 = 38%, 111 = 19%
2	H	DBMP (0.1 equiv.)	110 = 46%, 111 = 20%
3	H	None	110 = 58%, 111 = 24%

Scheme 1.5.1.13

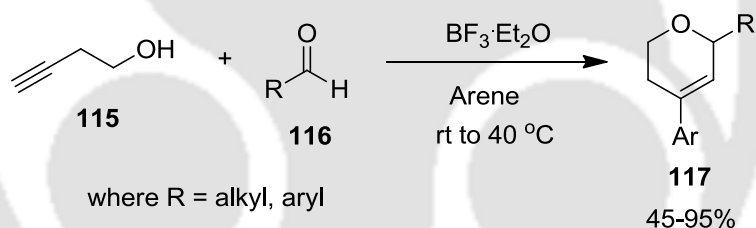
Loh and co-workers have reported the synthesis of 2,6-*trans* dihydropyrans from the reaction of allenic alcohols **112** and aldehydes **113** in the presence of indium triflate in

good yields (Scheme 1.5.1.14). However, a good diastereoselectivity was obtained by using bulky-silicon substituted allenic alcohols under the same condition. The reason of high *trans* diastereoselectivity is due to the anomeric effect as well as lone pair stabilization of the δ^+ of the oxo-carbenium intermediate by the ester group.⁴⁸



Scheme 1.5.1.14

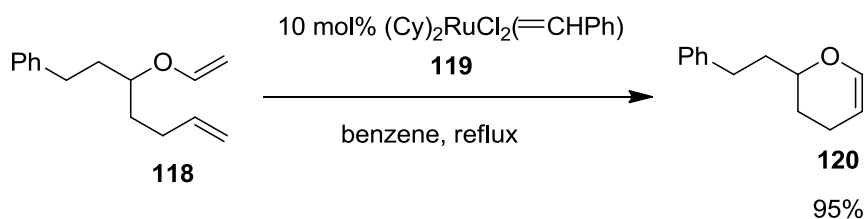
Saikia and co-workers have reported the synthesis of 4-aryl-5,6-dihydro-2H-pyrans **117** from the reaction of carbonyl compounds **116** with homopropargyl alcohol **115** in arenes mediated by boron trifluoride etherate by using alkyne-Prins-Friedel-Crafts reaction (Scheme 1.5.1.15).⁴⁹



Scheme 1.5.1.15

1.5.2. Olefin metathesis

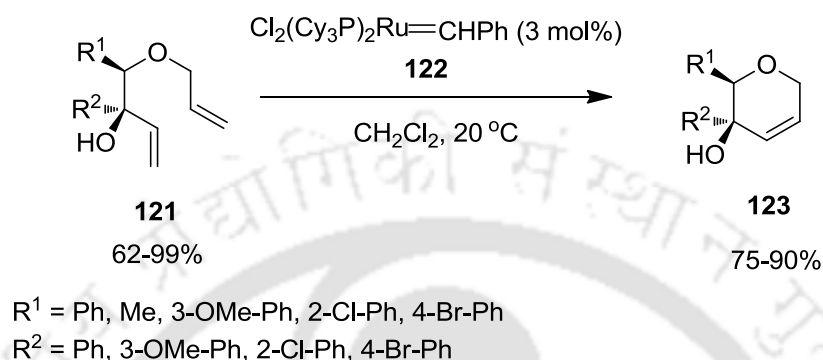
Sturino *et al.* have reported the synthesis of dihydropyrans **120** by ring closing metathesis (RCM) of acyclic vinyl ethers **118** with Grubb's catalyst **119** (Scheme 1.5.2.1).⁵⁰ They



Scheme 1.5.2.1

found that vinyl ethers are excellent substrate for the ring closing metathesis (RCM) with ruthenium based catalysts.

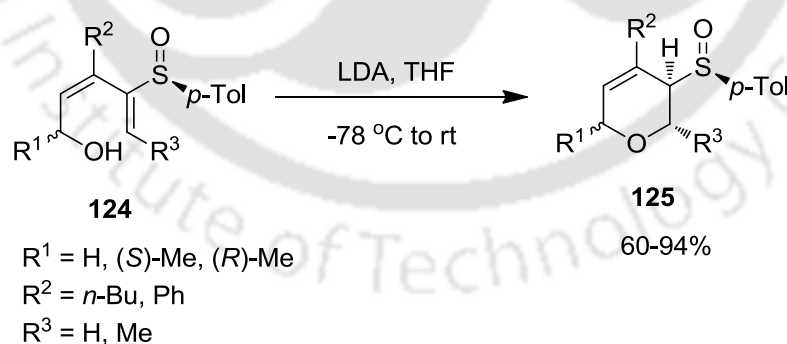
Schmidt *et al.* have reported a highly diastereoselective synthesis of enantiomerically pure dihydropyrans **123** from enantiomerically pure (*R*)-hydroxy ketones **121** via ring closing olefin metathesis step (Scheme 1.5.2.2).⁵¹



Scheme 1.5.2.2

1.5.3. Base promoted cyclization of sulfinyl dienols

de la Pradilla *et al.* have developed a highly selective base-promoted intramolecular cyclization of 2-sulfinyl dienols **124** at -78°C to afford allylic sulfinyl dihydropyrans **125**. This strategy allows for creation of two asymmetric centres within a synthetically useful dihydropyran framework in an experiment manner (Scheme 1.5.3.1).⁵²

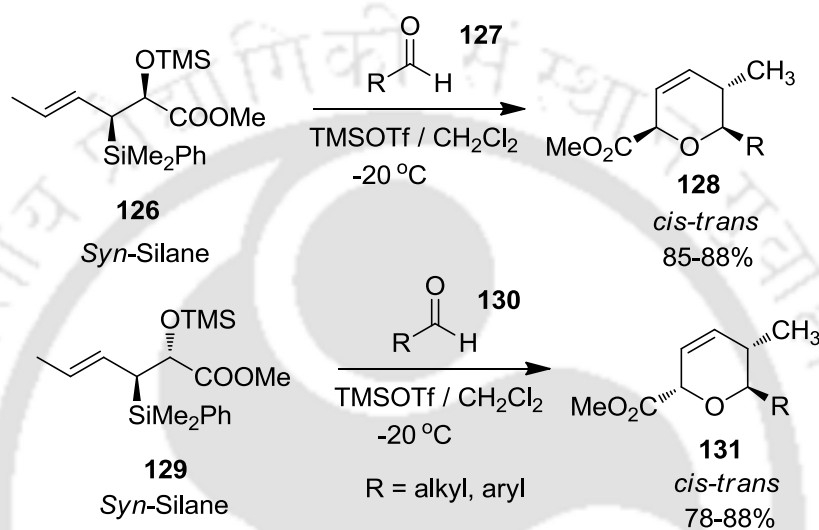


Scheme 1.5.3.1

1.5.4. [4+2] annulations of crotylsilanes

Panek *et al.* have developed an efficient method to synthesize stereochemically well-defined *cis*-2,6- and the complementary *trans*-2,6-dihydropyrans **128/131** from silanes

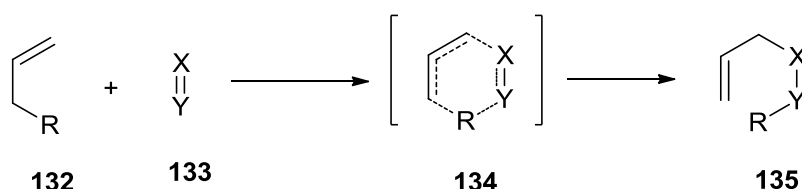
126 or **129** and aldehydes **127** or **130** catalyzed by TMSOTf (0.1 eqvt.) in dichloromethane. These experiments underscore the important role of the silicon-bearing centre as a dominant stereocontrol element in these heterocyclizations. The cyclization of *syn*-silane **126** produced the *cis-trans* substituted dihydropyrans **128** with *trans-trans* substituted dihydropyrans as minor diastereomers; meanwhile the cyclization of anti-silane **129** provided *trans-trans* substituted dihydropyrans **131** as the major isomers with all *cis* dihydropyrans as minor products (*Scheme 1.5.4.1*).⁵³



Scheme 1.5.4.1

1.5.5. Oxonium-ene reaction

As discussed above the reaction of an alkene bearing an allylic hydrogen (the ene) with another alkene (enophile) to produce a new alkene is known as ene-reaction (*Scheme 1.5.5.1*). 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.⁵⁴ Ene cyclization that involves the oxonium ion as the enophile component, is called oxonium-ene cyclization reaction.

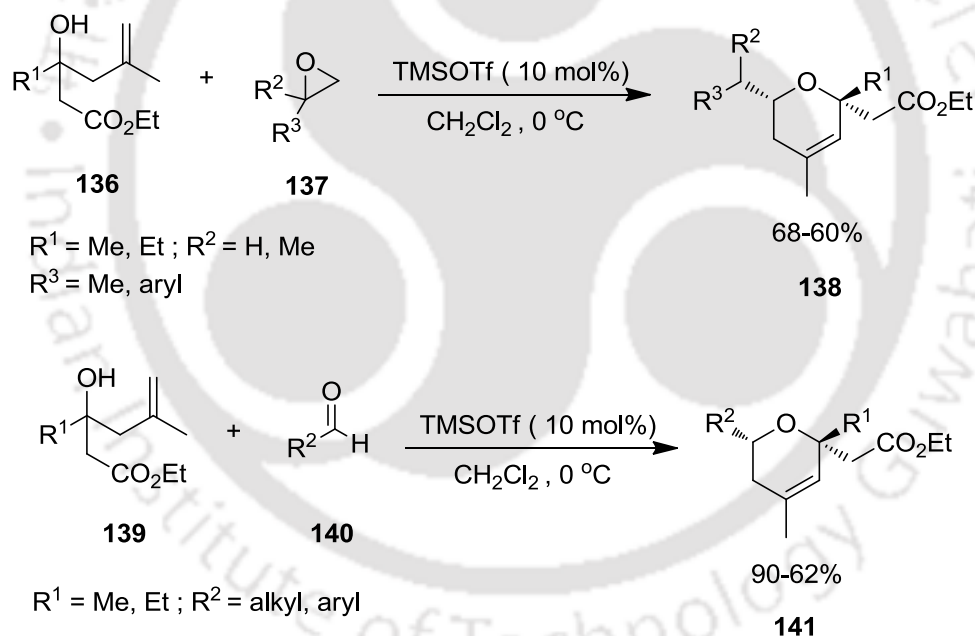


R = H or metal

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

Scheme 1.5.5.1.

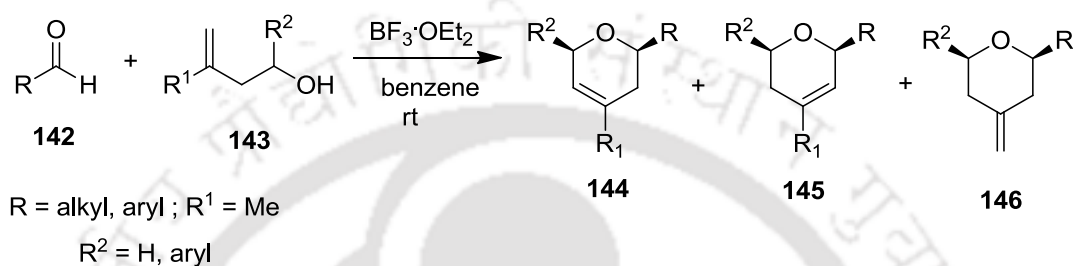
Saikia and co-workers have reported a highly diastereo- and regioselective synthesis of substituted dihydropyrans **138** and **141** between the reaction of epoxides **137** or aldehydes **140** and enote **136** or **139** via oxonium-ene reaction catalyzed by 10 mol % of TMSOTf under mild conditions. The formation of single regioisomer of this reaction supports the concerted mechanism (Scheme 1.5.5.2).⁵⁵



Scheme 1.5.5.2

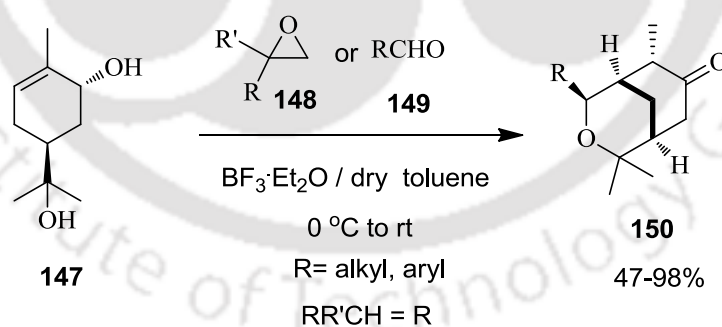
Saikia and co-workers have also reported a diastereoselective methodology for the synthesis of dihydropyrans from 1,1-disubstituted homolallylic alcohols **143** and aldehydes **142** via oxonium-ene cyclization reaction mediated by boron trifluoride etherate. The reaction of aromatic aldehydes with methyl substituted alcohols (R¹ = Me and R² = H) gave endo cyclic compound **144** as the major product with a minor exocyclic

product **146** whereas the aliphatic aldehydes with methyl substituted alcohols ($R^1 = \text{Me}$ and $R^2 = \text{H}$) gave two isomeric endocyclic **144/145** with a ratio of 3:1. Reaction of phenyl substituted alcohols ($R^1 = \text{Ph}$ and $R^2 = \text{H}$) with aromatic aldehydes gave single endocyclic isomer **144** but with aliphatic aldehydes it gave two isomeric endocyclic **144/145** with a ratio of 3:1. The reaction of alcohols with substitution at C-1 position and aromatic aldehydes gave only exocyclic *cis*-product **146** in good yields but with aliphatic aldehydes it gave **144/145** with 3.5:6.5 (Scheme 1.5.5.3).⁵⁶



Scheme 1.5.5.3

Saikia and co-workers have reported the synthesis of oxabicyclo[3.3.1]nonanone **150** via (3,5)-oxonium-ene reaction from the reaction of epoxides **148** or aldehydes **149** with commercially available *trans*-*p*-menth-6-ene-2,8-diol **147** mediated by boron trifluoride etherate in good yields (50-98%) (Scheme 1.5.5.4).⁵⁷

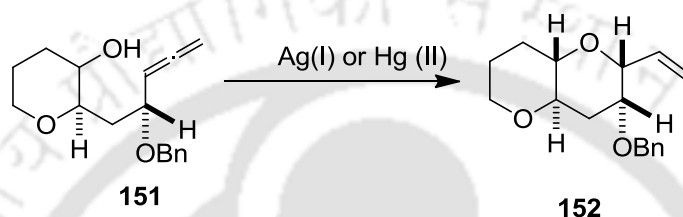


Scheme 1.5.5.4

1.5.6. Hydroalkoxylation of alkenols

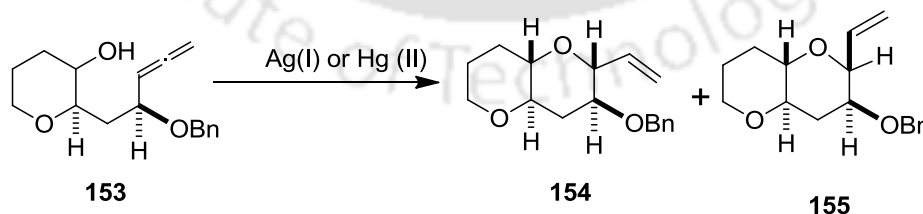
Intramolecular hydroalkoxylation of alkenols are also found importance in the synthesis of various five and six membered oxygen heterocyclic compounds. Mori and co-workers have reported the synthesis of fused tetrahydropyrans via intramolecular

hydroalkoxylation of δ -hydroxy allenes installed on a tetrahydropyran template **151** catalyzed by silver(I)- and mercury(II) (*Scheme 1.5.6.1*). Cyclization of simple allenes with AgClO_4 (1.2 eqvt.) in dichloroethane at 50 °C for 20h afforded bis-tetrahydropyran **152** in 88% yield where as with AgNO_3 (4.0 eqvt.) in dioxane/ H_2O at 80 °C observed yield was 40% . The reactions with AgBF_4 and AgOTf were also effective in affording the product in moderate yields and the reaction with $\text{Hg}(\text{OTf})_2$ caused significant decomposition of the reaction mixture even with a catalytic amount at a lower temperature (0 °C).⁵⁸



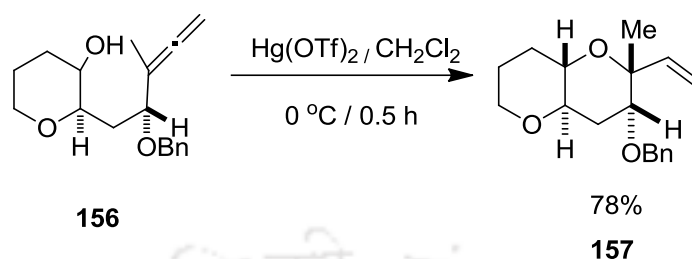
Scheme 1.5.6.1

The hydroalkoxylation of the diastereomeric δ -hydroxy allene **153** was also examined and found that cyclization was also promoted by silver salts, but the yields were generally low and a mixture of diastereoisomers were formed. Treatment of **153** with AgClO_4 or AgBF_4 led to inseparable 8:1 mixtures of isomers **154** and **155** in 42% or 32% combined yields, respectively. Diastereomeric ratio increased to 49:1 when AgOTf was employed. In contrast to the silver(I)-mediated reactions, the mercury(II)-catalyzed hydroalkoxylation showed the opposite diastereoselectivity to afford a 1:2 mixture of products in 59% yield (*Scheme 1.5.6.2*).⁵⁸



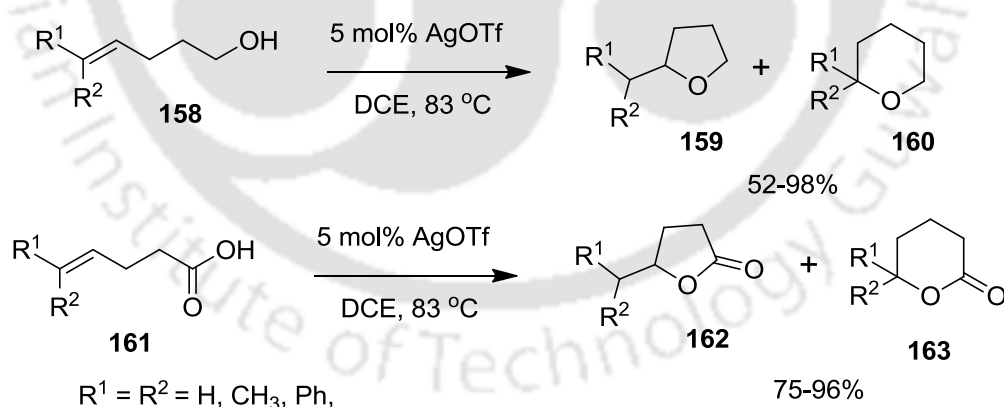
Scheme 1.5.6.2

The cyclization of methyl-substituted allenes **156** at the internal allenic carbon atom was achieved more effectively with a catalytic amount of mercuric triflate rather than with silver salts (*Scheme 1.5.6.3*).⁵⁸



Scheme 1.5.6.3

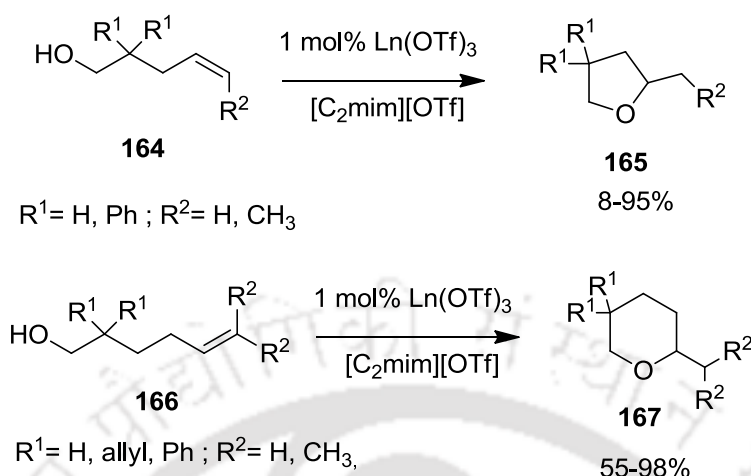
Chaun and co-workers have reported a methodology for the synthesis of cyclic ethers **159/160** or lactones **162/163** via intramolecular hydroalkoxylation and hydroacyloxylation of inert olefins **158** or **161** catalyzed by 5 mol % silver(I) triflate giving good to excellent yields (*Scheme 1.5.6.4*). The use of a terminal monosubstituted olefin gave a mixture of the 5-exo and 6-endo cyclic products with the 5-exo product significantly favored. However, the 6-endo cyclic ethers were found to be the sole products for terminal di-substituted alkenes and a γ -hydroxyl alkene with a phenyl substitution at the terminus.⁵⁹



Scheme 1.5.6.4

Marks and co-workers have reported the synthesis of substituted tetrahydrofurans **165** and pyrans **167** via intramolecular hydroalkoxylation of alkenols **164** and **166** catalyzed by $\text{Ln}(\text{OTf})_3$ in imidazolium-based ionic liquids (*Scheme 1.5.6.5*). The relative ordering of catalytic activity was found in the order $\text{Yb}^{3+} > \text{Sm}^{3+} > \text{La}^{3+}$. They have also done the

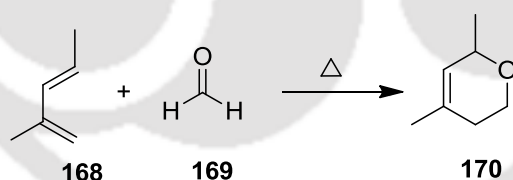
kinetic study of the reaction and found the reaction as first-order dependence on $[\text{Ln}^{3+}]$ and $[\text{substrate}]$.⁶⁰



Scheme 1.5.6.6

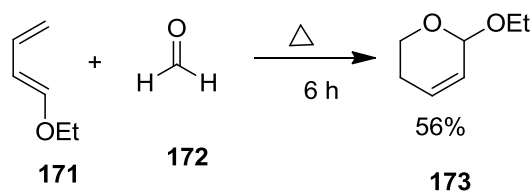
1.5.7. Hetero-Diels-Alder (HAD) reaction

Hetero Diels-Alder (HDA) reaction was first reported by Gresham and Steadman in 1951. In their report they have prepared 2,4-dimethyl-5,6-dihydro-1,2-pyran **170** by reacting methylpentadiene **168** with formaldehyde **169** (Scheme 1.5.7.1).⁶¹ This was an unusual reaction as in this case formaldehyde was acting as a dienophile.



Scheme 1.5.7.1

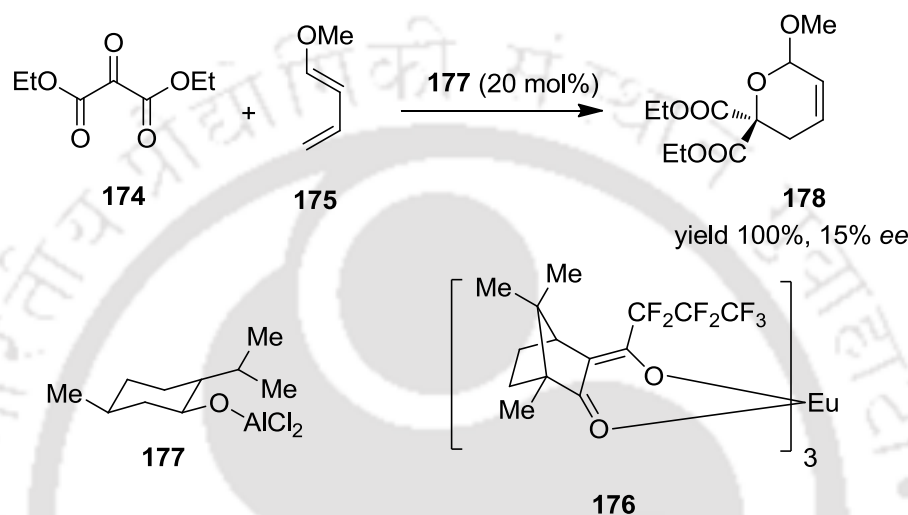
In 1962 Kubler found that an electron donating group, usually alkoxy group on the 1-position of a diene **171** provides sufficient activation to permit the Diels-Alder reaction



Scheme 1.5.7.2

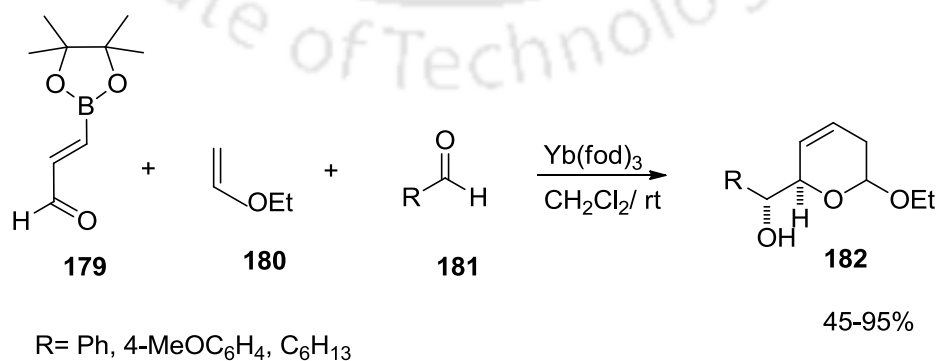
with paraformaldehyde **172**, to give 2-alkoxy-5,6-dihydro-2*H*-pyrans **173** (Scheme 1.5.7.2).⁶²

Jankowski *et al.* have reported the enantioselective HDA reaction using chiral lanthanide catalysts **176** and methoxyaluminium catalyst **177** between ketomalonate **174** and 1-methoxy-1,3-butadiene **175**. The reaction gave 100 % yield of **178** with 15% ee (Scheme 1.5.7.3).⁶³



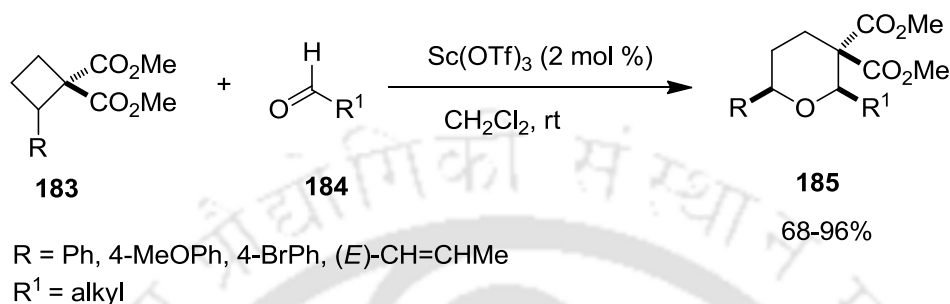
Scheme 1.5.7.3

Carreaux *et al.* have developed a strategy for the preparation of α -hydroxyalkyl dihydropyrans **182** using an approach based on a tandem hetero [4+2]/allylboration reaction. The reaction begins with the [4+2] cycloaddition of (2*E*)-3-borylacrolein **179** with ethyl vinyl ether **180** followed by the addition of aldehyde **181** catalyzed by Yb(fod)₃ (Scheme 1.5.7.4).⁶⁴



Scheme 1.5.7.4

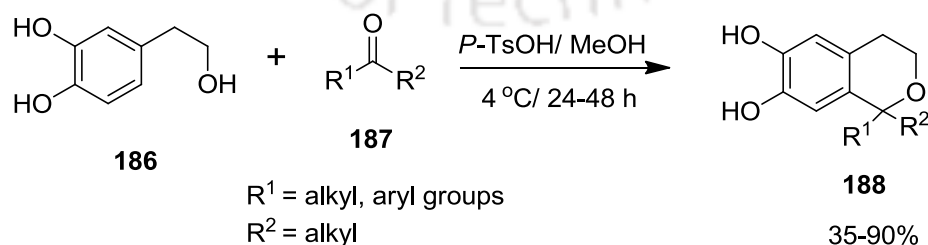
Johnson *et al.* have reported the synthesis of *cis*-2,6-disubstituted tetrahydropyrans **185** via HDA reaction between malonate derived cyclobutanes **183** and aldehydes **184** catalyzed by $\text{Sc}(\text{OTf})_3$ with 2 mol % in dichloromethane at room temperature (Scheme 1.5.7.5).⁶⁵ The resulting THP products are of interest because of their prevalence in biologically relevant and structurally interesting molecules.



Scheme 1.5.7.5

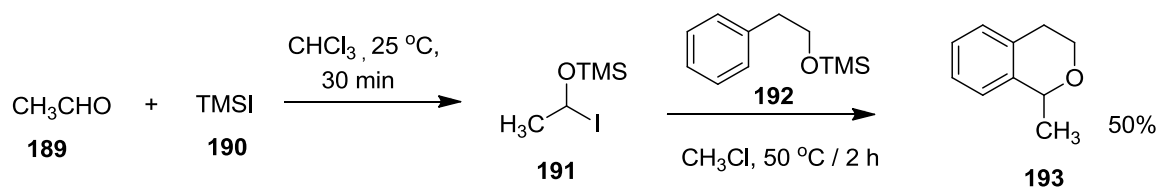
1.5.8. Oxa-Pictet-Spengler reaction

In 1922 Wünsch and Zott reported oxa-Pictet-Spengler reaction. In this reaction, a compound such as a 2-arylethanol reacts with an aldehyde or a ketone, as such or in masked form, to give an aromatic compound with a newly formed pyranic ring. Later, it was modified by many scientist. Guiso and co-workers have developed a method for the synthesis of substituted isochromanes **188** via oxa-Pictet Spengler reaction between 2-(3,4-dihydroxy)phenylethanol **186** and carbonylic compounds **187** using *p*-toluenesulfonic acid as a catalyst in methanol at 4 °C (Scheme 1.5.8.1). In these reactions it was found that aldehydes react faster than ketones and those aromatic aldehydes gave higher yields than their aliphatic counterparts. No side product was observed in this reaction condition.⁶⁶

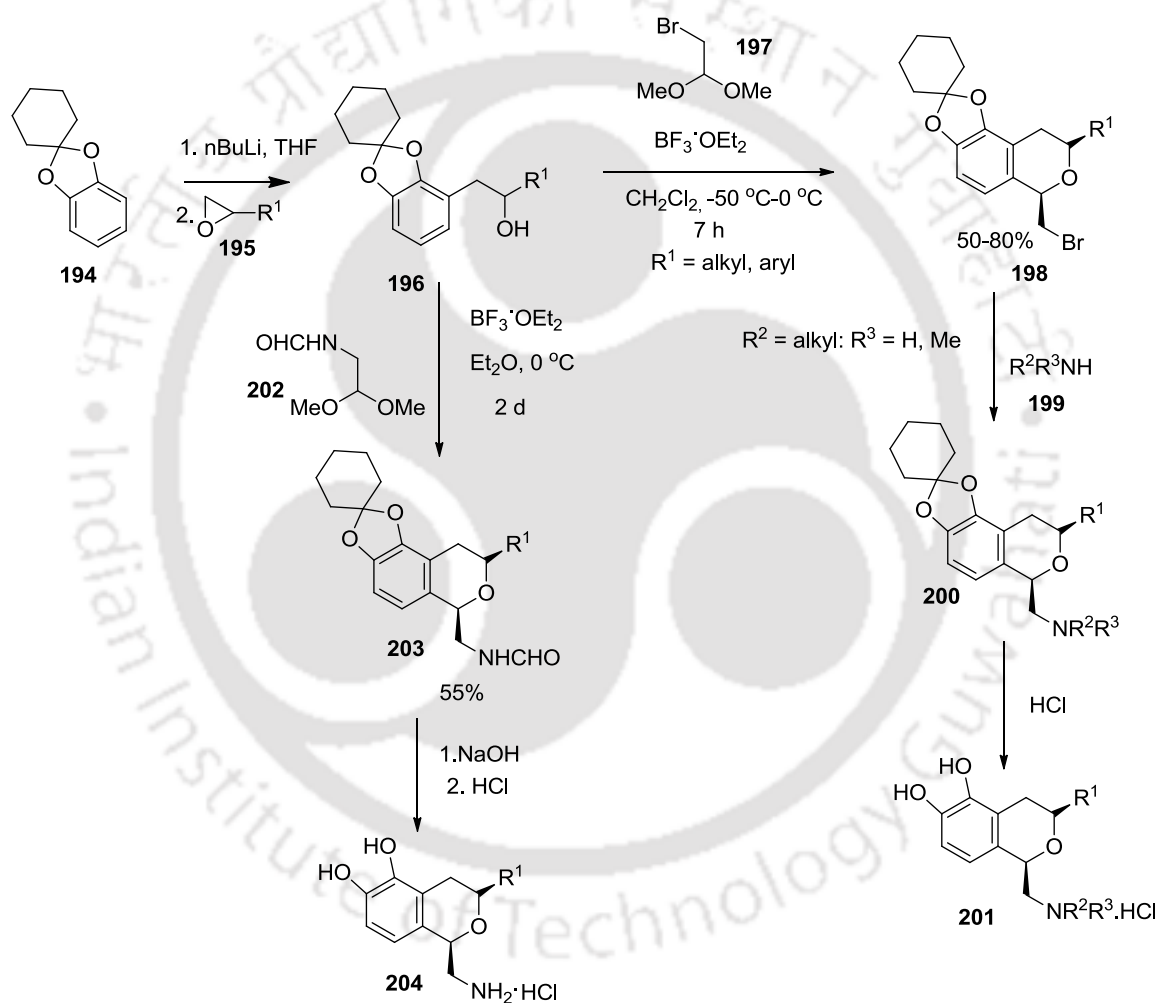


Scheme 1.5.8.1

Jung *et al.* have reported the synthesis of isochromane **193** by using protected β -phenethyl alcohol **192** and TMSI adduct of acetaldehyde **191** in chloroform at 50 °C *via* oxa-Pictet-Spengler and Friedel–Crafts reaction (Scheme 1.5.8.2).⁶⁷



Scheme 1.5.8.2



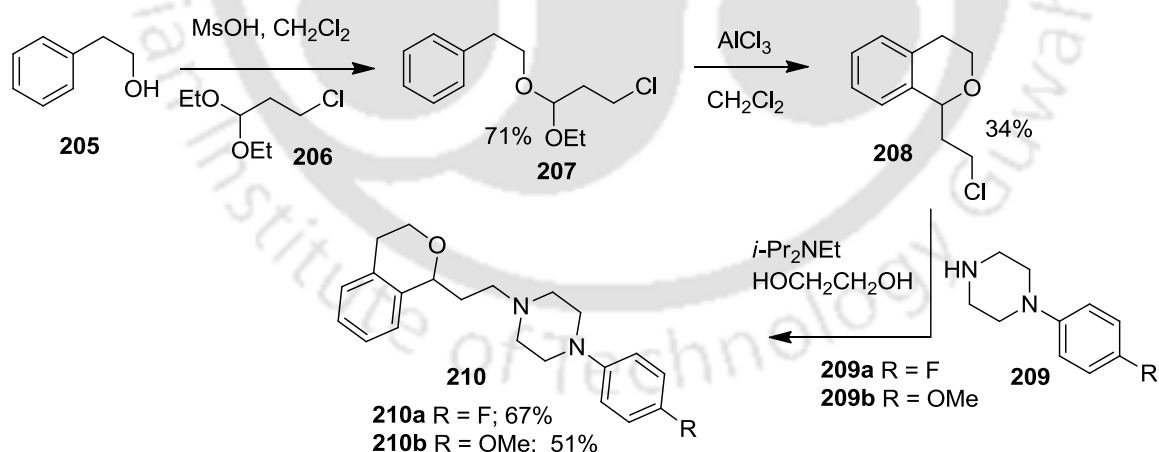
Scheme 1.5.8.3

Michael and co-workers have reported the synthesis of 1,3-*cis* substituted isochromanes *via* oxa-Pictet–Spengler reaction. They treated protected phenylethyl alcohol **196**, which was prepared *via* ring opening of epoxide **195** by the compound **194**, with

bromoacetaldehyde dimethyl acetal **197** and with *N*-formyl aminoacetal **211** under boron trifluoride etherate to furnish **198** and **203**. Treatment of **198** with substituted amine **199** followed by hydrolysis (HCl/ethanol) gave catecholamine hydrochloride salt **201**. Similarly, hydrolysis of **203** with sodium hydroxide followed by HCl/ethanol hydrolysis gave catecholamine hydrochloride salt **204** in good yields (Scheme 1.5.8.3).⁶⁸

1.5.9. Intramolecular oxa-Pictet–Spengler cyclization

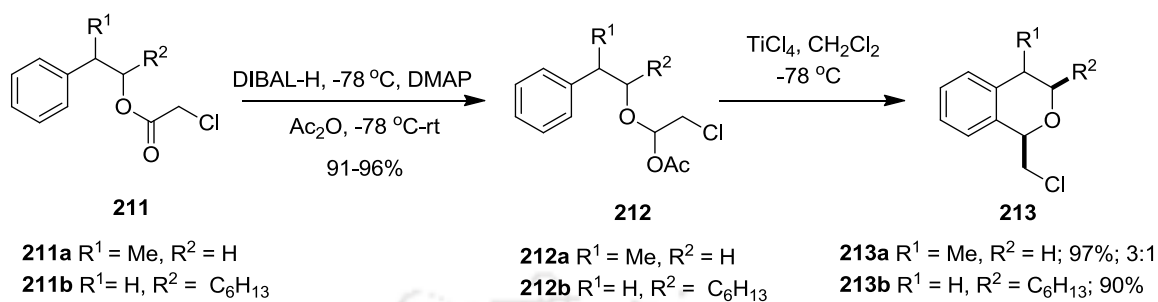
The intramolecular versions of the oxa-Pictet–Spengler cyclization comprise reactions in which the carbonyl component is attached to the β -aryl-ethanol in the form of a mixed acetal, vinyl ether, α -acetoxy ether or halomethyl ether. Through this intramolecular oxa-Pictet–Spengler cyclization some natural compounds were synthesized such as **210a** and **210b** which exhibit an increased preference for the D₄ over the D₂ receptor, while retaining significant binding to other CNS receptors. The synthesis of these compounds were started with β -phenethyl alcohol **205** which was reacted with chloroacetal **206** to give mixed acetal **207**, this was isolated and subjected to an oxa-Pictet–Spengler cyclization to isochromane **208** with aluminum chloride as the Lewis acid promoter. Displacement of the halogen with different aryl piperazines (**209a** and **209b**) gave final products **210** in good yields (Scheme 1.5.9.1).⁶⁹



Scheme 1.5.9.1

Rychnovsky *et al.* have reported the synthesis of 1,3-*cis*-isochromanes from chloroacetate **211b**, derived from a β -substituted β -phenylethyl alcohol, furnished exclusively 1,3-*cis*-isochromanes **213b** in 90% yield through the intermediacy of **212b**. However, in the

example involving the α -substituted congener **211a**, the same transformation from mixed acetal **212a** furnished 97% of **213a** as a 3:1 diastereomeric mixture (Scheme 1.5.9.2).⁷⁰



Scheme 1.5.9.2

1.6. References

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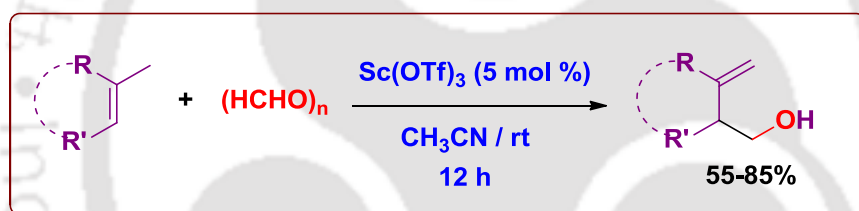
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CHAPTER 2

Scandium(III) triflate Catalyzed Synthesis of Primary Homoallylic Alcohols via Carbonyl-Ene Reaction



Tetrahedron Lett. **2013**, 54, 1576.

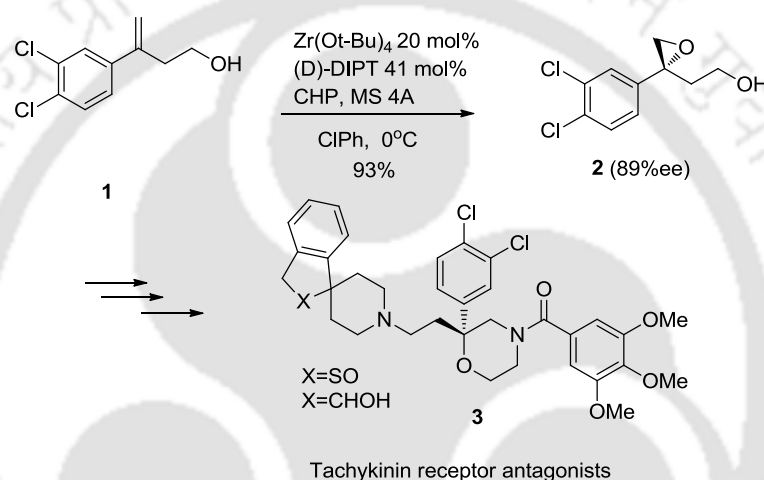




Scandium(III) triflate Catalyzed Synthesis of Primary Homoallylic Alcohols via Carbonyl-Ene Reaction

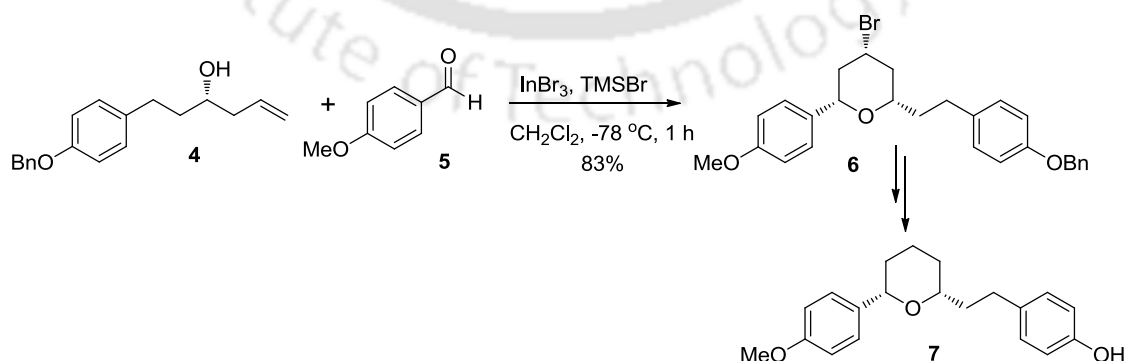
2.1. Importance and Applications of Alkenols (viz. Homoallylic Alcohols)

Alkenols containing hydroxy group on the β -carbon of the allylic group *e.g.* homoallylic alcohols are important building blocks in organic synthesis¹ and also key precursors in the synthesis of many biologically active compounds. For example, the chiral epoxide **2** generated from 1-(3,4-dichlorophenyl)but-3-en-1-ol **1** via Sharpless epoxidation is a key intermediate for the synthesis of Tachykinin receptor antagonists **3** (Scheme 2.1.1).²



Scheme 2.1.1

In 2005, Loh used chiral homoallylic alcohol (S)-1-(4-(benzyloxy)phenyl)hex-5-en-3-ol **4** for the total synthesis of (-)-centrolobine **7** (Scheme 2.1.2).³

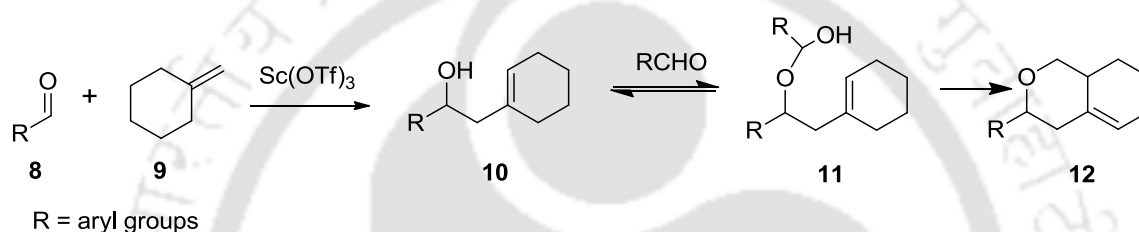


Scheme 2.1.2

2.2. Literature Review on Synthesis of Homoallylic Alcohols

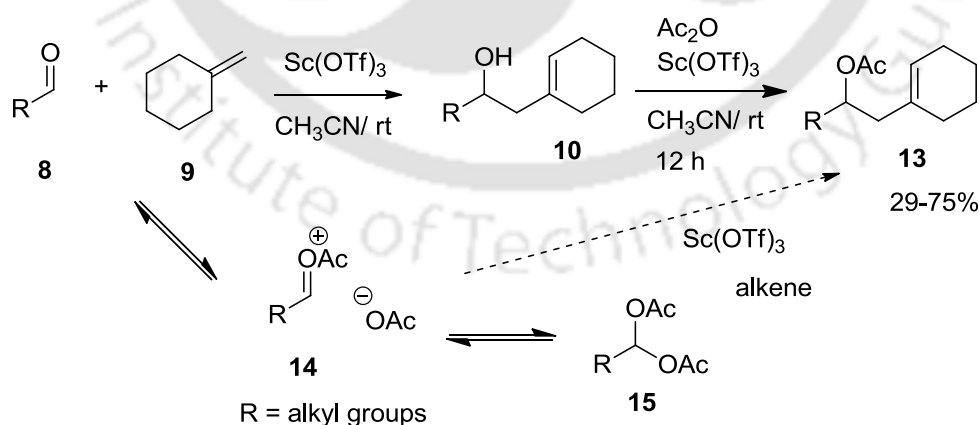
Review of literature reveals that several strategies have been developed for the synthesis of homoallylic alcohols *via* carbonyl-ene reaction which we already discussed in the introductory part (chapter 1).

Varinder. K. Agarwal and his group have also reported the synthesis of homoallylic alcohols **13** *via* carbonyl-ene reaction between aldehydes **8** and methylene cyclohexane **9** catalyzed by scandium triflate. Initially, they noticed that two aldehyde groups had incorporated in this reaction condition and produced pyran **12** as a product (Scheme 2.2.1).



Scheme 2.2.1

In order to inhibit the incorporation of the second aldehyde, they trapped the alcohol **10** by acylation giving **13** at moderate yields. Aliphatic aldehydes were unreactive in this reaction conditions and gave diacetates **15** (Scheme 2.2.2).⁴



Scheme 2.2.2

From a survey on synthesis of homoallylic alcohols, we had come to a conclusion that most of the methods reported so far suffer from drawbacks such as formation of Prins

cyclized products and requirement of reaction conditions which are difficult to achieve like very low temperature. However, the methods involving mild reaction conditions and atom economic with no other side products are always attractive.

2.3. Our Strategy and Objective

Following the literature reports, we have developed an efficient methodology for the synthesis of primary homoallylic alcohols *via* carbonyl-ene reaction from the reaction of paraformaldehyde with olefins catalyzed by scandium trifluoromethanesulfonate (Scheme 2.3.1).



Scheme 2.3.1. Synthesis of primary homoallylic alcohols

2.4. Results and Discussions

2.4.1. Optimization studies

To start with, we had chosen paraformaldehyde and prop-1-en-2-ylbenzene as model substrates for our optimization studies and the results are summarized in Table 2.4.1.1. The reaction carried out by using $\text{Sc}(\text{OTf})_3$ (5 mol %) as Lewis acid in acetonitrile at room temperature and the product 3-phenylbut-3-en-1-ol **18a** was obtained in a good yield (71%). The catalytic activity of $\text{Sc}(\text{OTf})_3$ was also studied with different quantities such as 5, 10 and 20 mol %, and 5 mol % was found to be the best. Change of solvent to dichloromethane decreased the yield to 40%. The reaction was also checked by the addition of additive such as molecular sieves but no improvement of yield was observed. The reaction was also optimized with other Lewis acids such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$, InCl_3 , $\text{In}(\text{OTf})_3$, $\text{Zn}(\text{OTf})_2$, AlCl_3 , TMSOTf , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{Ce}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$, $\text{Bi}(\text{OTf})_3$ and $\text{Cu}(\text{OTf})_2$. Lewis acids $\text{BF}_3 \cdot \text{Et}_2\text{O}$, InCl_3 , $\text{In}(\text{OTf})_3$, TMSOTf and $\text{Bi}(\text{OTf})_3$ provided 1,3-dioxane **19a**. However, in case of AlCl_3 and $\text{Ce}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ the desired product was obtained in 27% and 22% yields respectively. On the other hand, Lewis acids $\text{Zn}(\text{OTf})_2$,

$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{Cu}(\text{OTf})_2$ failed to give any product. Therefore, 5 mol% of scandium triflate in acetonitrile was found to be the best combination for the synthesis of homoallylic alcohols.

Table 2.4.1.1. Optimization of the reaction

$\text{16a} + (\text{HCHO})_n \xrightarrow[\text{Solvent / rt, 12 h}]{\text{Lewis acid}} \text{18a} + \text{19a}$

Entry	Lewis acid (Equiv.)	Solvent	Product	Yield (%) ^a
1	$\text{Sc}(\text{OTf})_3$ (5 mol%)	CH_3CN	18a	71
2	$\text{Sc}(\text{OTf})_3$ (10 mol%)	CH_3CN	18a	67
3	$\text{Sc}(\text{OTf})_3$ (20 mol%)	CH_3CN	18a	63
4	$\text{Sc}(\text{OTf})_3$ (5 mol%)	CH_3CN	18a	61 ^b
5	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1equiv.)	CH_3CN	19a	75
6	InCl_3 (1 equiv.)	CH_3CN	19a	20
7	$\text{In}(\text{OTf})_3$ (10 mol%)	CH_3CN	19a	79
8	$\text{Zn}(\text{OTf})_2$ (10 mol%)	CH_3CN	----	----
9	AlCl_3 (1equiv.)	CH_3CN	18a	27
10	TMSOTf (10 mol%)	CH_3CN	19a	81
11	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1 equiv.)	CH_3CN	---	----
12	$\text{Ce}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ (10 mol%)	CH_3CN	18a	22
13	$\text{Sc}(\text{OTf})_3$ (5 mol%)	CH_2Cl_2	18a	40
14	$\text{Bi}(\text{OTf})_3$ (10mol%)	CH_3CN	19a	83
15	$\text{Cu}(\text{OTf})_2$ (10mol%)	CH_3CN	---	----

^aYields refer to isolated yield. ^bwith MS 4A. The compounds are characterized by IR, ^1H , ^{13}C NMR and comparison with known compounds.

2.4.2. Substrate scope of the reaction

With the optimized condition in hand, the scope of the reaction was investigated by using different types of olefins (Table 2.4.2.1). It was found that the reaction proceeds smoothly

Table 2.4.2.1. Synthesis of homoallylic alcohols

Entry	Alkene 16	Product 18	Yield (%) ^a
a			71
b			78
c			73
d		 18da:18db = 2:3	70 ^b
e			55
f		 18fa:18fb = 1:1	85 ^b
g			71
h			65
i		 18ia:18ib = 3:2 (24%) 18ic = 46%	70 ^b
j			81
k			0

^aYields refer to isolated yield. The compounds are characterized by IR, ¹H, ¹³C NMR, and elemental analysis.

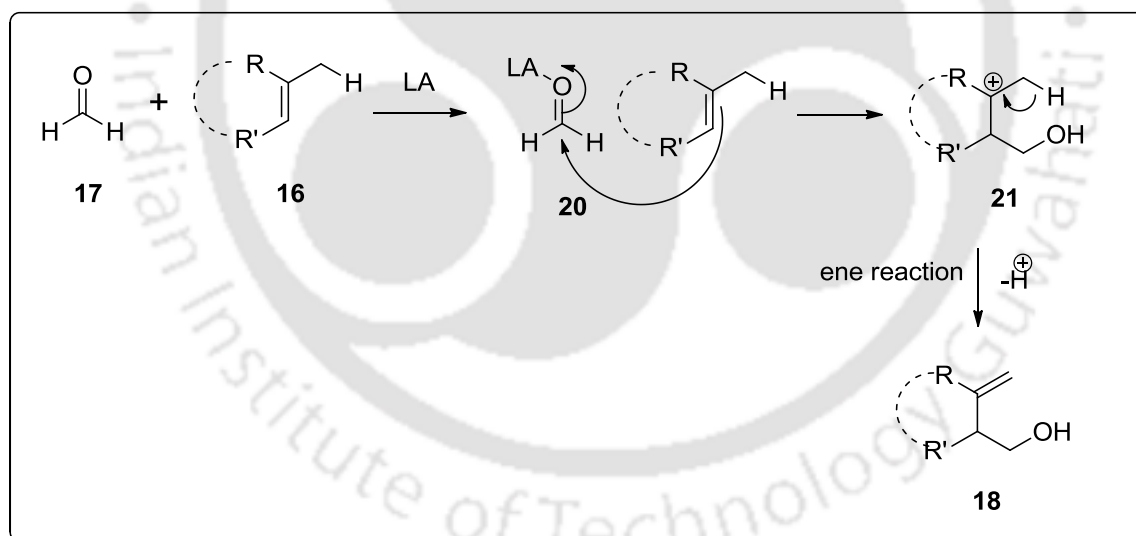
^bRatio is determined by ¹H and ¹³C NMR.

with terminal and internal olefins in good yields without giving any 1,3-dioxanes. The aromatic terminal alkenes such as α -methylstyrenes **16a-c** and methylene cyclohexane

16e gave single products **18a-c** and **18e** (yield 55-78%) respectively. On the other hand, the aliphatic terminal alkene **16i** gave three isomeric products **18ia-ic** of which **18ia** and **18ib** are inseparable geometric (*E,Z*) isomers in a ratio of 3:2 (yield 24%) and a regioisomer **18ic** (yield 46%). All other internal olefins except **16d** and **16f** provided their corresponding products as single isomer. Alkene **16d** yielded two inseparable regioisomers **18da** and **18db** in a ratio of 2:3 (yield 70%) and Compound **16f** gave two inseparable diastereomers **18fa** and **18fb** in a ratio of 1:1 (yield 85%). The olefin having strong electron-withdrawing group **16k** on the aromatic ring failed to give product. This may be attributed due to the destabilization of carbocation **21** formed during the reaction (Scheme 2.4.3.1).

2.4.3. Plausible mechanism of the reaction

Based on literature reports,⁵ a mechanism of the reaction is proposed. First Lewis acid activates the carbonyl group of the paraformaldehyde **17** followed by olefin attack leads to the formation of carbocation intermediate **21**, which after loses the allylic proton to form ene product **18**.



Scheme 2.4.3.1. Mechanism of the carbonyl ene reaction

2.5. Conclusion

In conclusion, we have developed a methodology for the synthesis of primary homoallylic alcohols from alkenes and paraformaldehyde catalyzed by scandium trifluoromethanesulfonate in good yields. The reaction is mild and the groups such as acetate, bromide and sulfide are unaffected under the reaction conditions.

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 GF254 (0.25 mm). ^1H NMR spectra were recorded in CDCl_3 on a Varian AS 400 (400 MHz) spectrometer using TMS as internal standard. The ^{13}C spectra were obtained on a Varian 400 spectrometer operating at 100 MHz. IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer. Elemental analysis was performed on Perkin Elmer 2400 series II CHNS analyser.

2.6.2. General procedure for the synthesis of homoallylic alcohols (18a-k):

To a mixture of paraformaldehyde (1.0 equiv.) and $\text{Sc}(\text{OTf})_3$ (5 mol%) in acetonitrile (3 mL) was added alkene (1.0 equiv.). The reaction mixture was stirred at room temperature for the specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with water and the product was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product which was purified by column chromatography over silica gel to furnish the title compounds.

2.6.3. Synthesis of 3-phenyl-but-3-en-1-ol (18a):

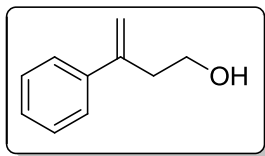
To a mixture of paraformaldehyde (120 mg, 4.0 mmol) and $\text{Sc}(\text{OTf})_3$ (98 mg, 5 mol%) in acetonitrile (3 mL) was added alkene (472 mg, 4.0 mmol). The reaction mixture was stirred at room temperature for 12h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (EtOAc:Hexane, 1:9) as eluents. After completion of the reaction, the reaction mixture was treated with water and the product was extracted with ethyl acetate (2x 10 mL). The organic layer was washed with brine (5 mL). The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product, which was

purified by column chromatography (10% ethyl acetate/hexane) over silica gel to furnish the product (420 mg, 71%) as colorless oil.



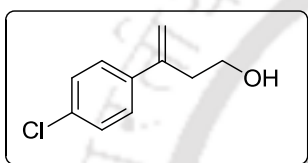
2.7. Charactererization Data

3-phenyl-but-3-en-1-ol (18a):



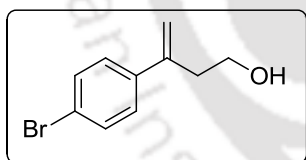
Colorless oil (420 mg, 71%); ^1H NMR (400 MHz, CDCl_3): δ 2.79 (t, $J = 6.4$ Hz, 2 H), 3.73 (t, $J = 6.4$ Hz, 2 H), 5.17 (d, $J = 1.2$ Hz, 1 H), 5.42 (d, $J = 1.2$ Hz, 1 H), 7.26-7.43 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3): δ 38.7, 61.2, 114.7, 126.3, 127.3, 128.6, 140.6, 145.0; IR: 3402, 2927, 2865, 1626, 1445, 1040, 703 cm^{-1} ; Anal. Calcd. For $\text{C}_{10}\text{H}_{12}\text{O}$: C, 81.04; H, 8.16. Found: C, 81.16; H, 8.09.

3-(4-Chlorophenyl)but-3-en-1-ol (18b):



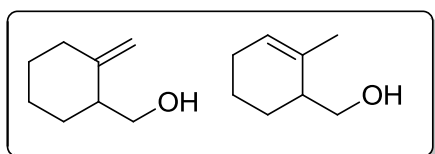
Colorless oil (142 mg, 78%); ^1H NMR (400 MHz, CDCl_3): δ 2.76 (t, $J = 6.4$ Hz, 2 H), 3.73 (t, $J = 6.4$ Hz, 2 H), 5.18 (d, $J = 1.2$ Hz, 1 H), 5.40 (d, $J = 1.2$ Hz, 1 H), 7.30 (d, $J = 8.8$ Hz, 2 H), 7.35 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 38.6, 61.1, 115.2, 127.6, 128.7, 133.7, 139.1, 143.9; IR: 3417, 2927, 1629, 1490, 1099, 1048, 834 cm^{-1} ; Anal. Calcd. For $\text{C}_{10}\text{H}_{11}\text{ClO}$: C, 65.76; H, 6.07. Found: C, 65.65; H, 6.16.

3-(4-Bromophenyl)but-3-en-1-ol (18c):



Colorless oil (166 mg, 73%); ^1H NMR (400 MHz, CDCl_3): δ 2.68 (t, $J = 6.4$ Hz, 2 H), 3.64 (t, $J = 6.4$ Hz, 2 H), 5.10 (s, 1 H), 5.33 (s, 1 H), 7.20 (d, $J = 8.4$ Hz, 2 H), 7.38 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 38.6, 61.1, 115.3, 121.9, 128.0, 131.7, 139.6, 144.1; IR: 3422, 2923, 1642, 1456, 1087, 749 cm^{-1} ; Anal. Calcd. For $\text{C}_{10}\text{H}_{11}\text{BrO}$: C, 52.89; H, 4.88. Found: C, 52.80; H, 5.00.

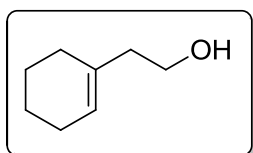
(2-Methylenecyclohexyl)methanol (18da) and (2-Methylcyclohex-2-en-1-yl)methanol (18db): (18da:18db = 2:3):



Colorless oil (88 mg, 70%); ^1H NMR (400 MHz, CDCl_3): δ 1.23-1.37 (m, 3 H), 1.45-1.67 (m, 1 H), 1.68 (s, 3 H), 1.69-2.40 (m, 3 H), 3.54-3.79 (m, 2 H), 4.64 (s, 1 H for **18da**), 4.76 (s, 1 H for **18da**),

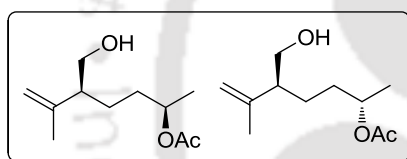
5.44 (t, $J = 1.6$ Hz, 1 H for **18db**); ^{13}C NMR (100 MHz, CDCl_3): δ 19.9, 22.3, 24.2, 25.6, 26.0, 28.5, 29.6, 34.6, 41.8, 45.8, 64.2, 64.6, 107.6, 125.7, 133.2, 149.9; IR: 3425, 2924, 1640, 1453, 1089, 803 cm^{-1} . Anal. Calcd. For $\text{C}_8\text{H}_{14}\text{O}$: C, 76.14; H, 11.18. Found: C, 76.04; H, 11.27.

2-(Cyclohex-1-en-1-yl)ethanol (**18e**):



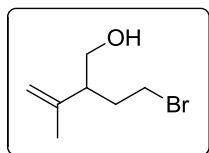
Colorless oil (69 mg, 55%); ^1H NMR (400 MHz, CDCl_3): δ 1.24-1.29 (m, 2 H), 1.47-1.74 (m, 6 H), 1.92-2.05 (2 H), 2.21 (t, $J = 6.0$ Hz, 1 H), 3.66 (t, $J = 6.0$ Hz, 2 H), 5.53 (brs, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.5, 23.1, 25.5, 28.2, 41.3, 65.7, 124.6, 134.2; IR: 3403, 2930, 2863, 1648, 1448, 1090, 674 cm^{-1} ; Anal. Calcd. For $\text{C}_8\text{H}_{14}\text{O}$: C, 76.14; H, 11.18. Found: C, 76.25; H, 11.02.

5-(Hydroxymethyl)-6-methylhept-6-en-2-yl acetate (**18f**, 1:1 diastereomeric mixture determined by ^{13}C NMR):



Colorless oil (183 mg, 85%); ^1H NMR (400 MHz, CDCl_3): δ 1.16 (d, $J = 6.4$ Hz, 3 H), 1.21-1.44 (m, 4 H), 1.63 (s, 3 H), 1.98 (s, 3 H), 2.16-2.24 (m, 1 H), 3.42-3.51 (m, 2 H), 4.78 (s, 1 H), 4.69-4.90 (m, 1 H), 4.91 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.8, 18.9, 20.0, 20.1, 21.4, 24.9, 25.1, 33.6, 33.7, 49.7, 50.0, 64.2, 70.9, 71.2, 114.1, 144.7, 171.0; IR: 3437, 2929, 2866, 1727, 1646, 1451, 1376, 1253, 1038, 894 cm^{-1} ; Anal. Calcd. For $\text{C}_{11}\text{H}_{20}\text{O}_3$: C, 65.97; H, 10.07. Found: C, 65.84; H, 10.16.

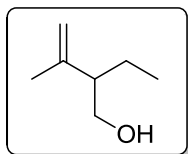
2-(2-Bromoethyl)-3-methylbut-3-en-1-ol (**18g**):



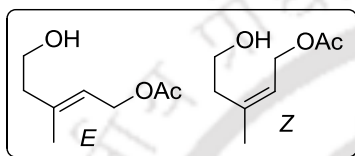
Colorless oil (158 mg, 71%); ^1H NMR (400 MHz, CDCl_3): δ 1.71 (s, 3 H), 1.90-1.97 (m, 2 H), 2.49-2.56 (m, 1 H), 3.30-3.36 (m, 2 H), 3.40-3.46 (m, 2 H), 3.57 (d, $J = 6.4$ Hz, 1 H), 4.88 (s, 1 H), 5.00 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.4, 31.5, 32.5, 48.2, 63.9, 114.7, 143.5; IR: 3417, 2926, 2863, 1643, 1444, 1253, 1042, 897 cm^{-1} ; Anal. Calcd. For $\text{C}_7\text{H}_{13}\text{BrO}$: C, 43.54; H, 6.79. Found: C, 43.69; H, 6.72.

2-Ethyl-3-methylbut-3-en-1-ol (18h):

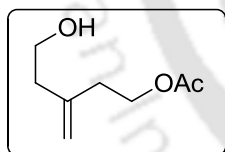
Solid, m.pt. 97-101 °C; Colorless oil (84 mg, 65%); ^1H NMR (400 MHz, CDCl_3): δ 0.83 (t, $J = 7.6$ Hz, 3 H), 1.26-1.42 (m, 2 H), 1.63 (s, 3 H), 2.12-2.18 (m, 1 H), 3.44-3.51 (m, 3 H), 4.78 (s, 1 H), 4.90 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.9, 18.9, 22.3, 52.0, 64.0, 113.9, 145.2; IR: 3423, 2924, 2863, 1644, 1455, 1260, 1100, 1043, 802 cm^{-1} ; Anal. Calcd. For $\text{C}_7\text{H}_{14}\text{O}$: C, 73.63; H, 12.36. Found: C, 73.75; H, 12.45.

**(E,Z)-6-Hydroxy-4-methylhex-3-en-1-yl acetate (18ia:18ib, 3:2):**

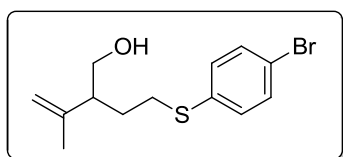
Colorless oil (35 mg, 24%); ^1H NMR (400 MHz, CDCl_3): δ 1.71 (s, 3 H, E), 2.02 (s, 6 H, E, Z), 2.03 (s, 3 H, Z), 2.71-2.37 (m, 4 H, E, Z), 3.68-3.73 (m, 4 H, E, Z), 4.17 (t, $J = 6.8$ Hz, 2 H, E), 4.58 (d, $J = 7.2$ Hz, 2 H, Z), 4.91 (brs, 1 H, E), 5.40 (t, $J = 6.8$ Hz, 1 H, Z); ^{13}C NMR (100 MHz, CDCl_3): δ 21.1, 21.2, 35.1, 39.5, 60.4, 60.6, 61.3, 62.9, 114.0, 121.4, 138.6, 142.3, 171.3; IR: 3419, 2923, 2851, 1732, 1631, 1458, 1254, 1093, 1045, 671 cm^{-1} ; Anal. Calcd. For $\text{C}_8\text{H}_{14}\text{O}_3$: C, 60.74; H, 8.92. Found: C, 60.65; H, 9.05.

**6-Hydroxy-4-methylenehexyl acetate (18ic):**

Colorless oil (66 mg, 46%); ^1H NMR (400 MHz, CDCl_3): δ 1.51-1.55 (m, 2 H), 1.73-1.81 (m, 2 H), 2.02 (s, 3 H), 3.85-3.89 (m, 2 H), 4.18 (t, $J = 7.2$ Hz, 2 H), 4.81 (d, $J = 6.8$ Hz, 1 H), 4.85 (d, $J = 6.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.5, 21.2, 35.7, 38.5, 60.4, 62.8, 109.2, 142.3, 171.2; IR: 3428, 2925, 2856, 1739, 1652, 1462, 1241, 1160, 1030, 839, 674 cm^{-1} ; Anal. Calcd. For $\text{C}_8\text{H}_{14}\text{O}_3$: C, 60.74; H, 8.92. Found: C, 60.62; H, 9.12.

**2-(2-((4-Bromophenyl)thio)ethyl)-3-methylbut-3-en-1-ol (18j):**

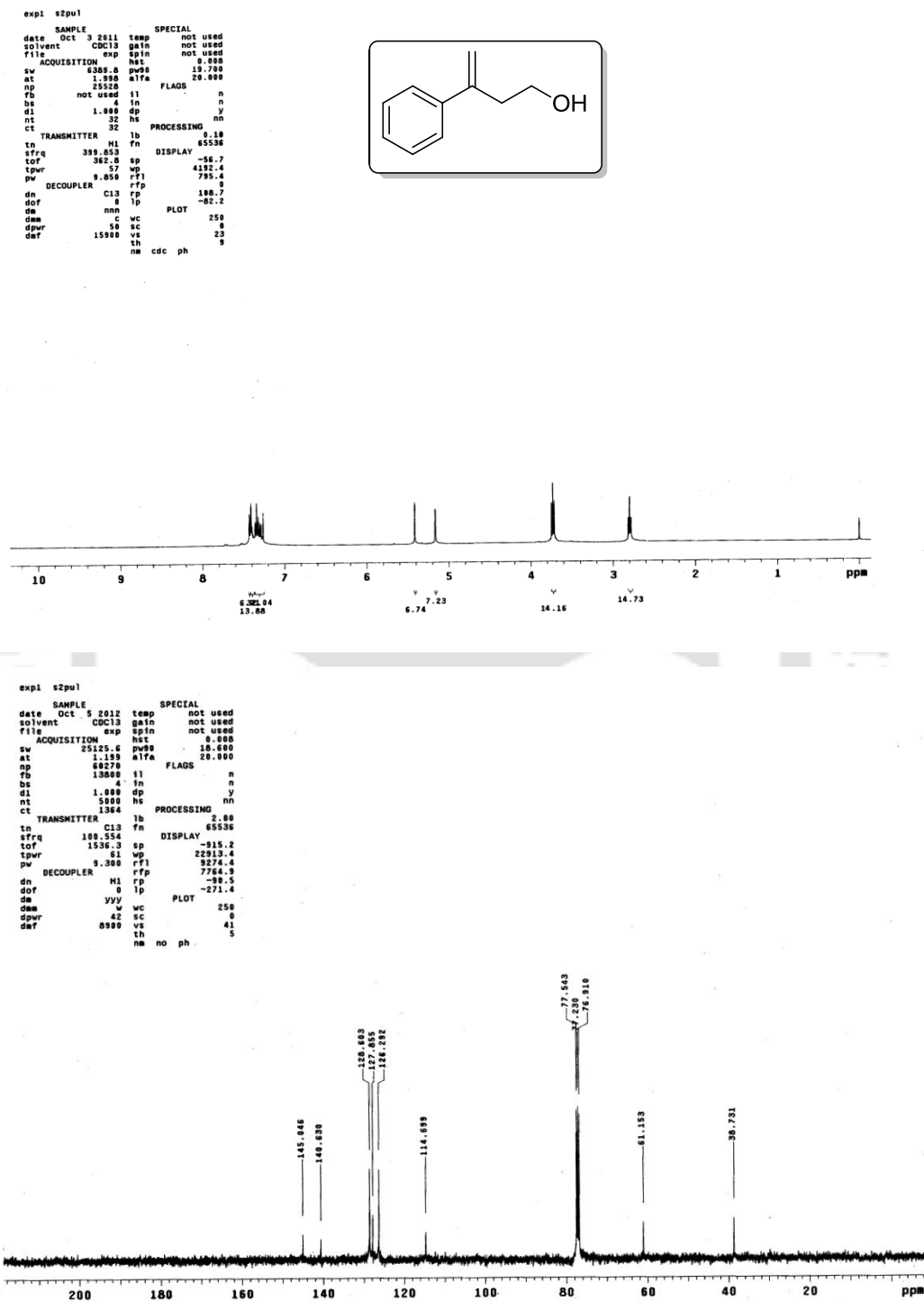
Colorless oil (243 mg, 81%); ^1H NMR (400 MHz, CDCl_3): δ 1.50-1.68 (m, 2 H), 1.60 (s, 3 H), 2.34-2.39 (m, 1 H), 2.70-2.76 (m, 1 H), 2.80-2.88 (m, 1 H), 3.44 (d, $J = 6.8$ Hz, 2 H), 4.77 (t, $J = 0.8$ Hz, 1 H), 4.90 (t, $J = 1.6$ Hz, 1 H), 7.11 (d, $J = 8.8$ Hz, 2 H), 7.314.77 (t, $J = 8.8$ Hz, 2 H); ^{13}C NMR (100 MHz,



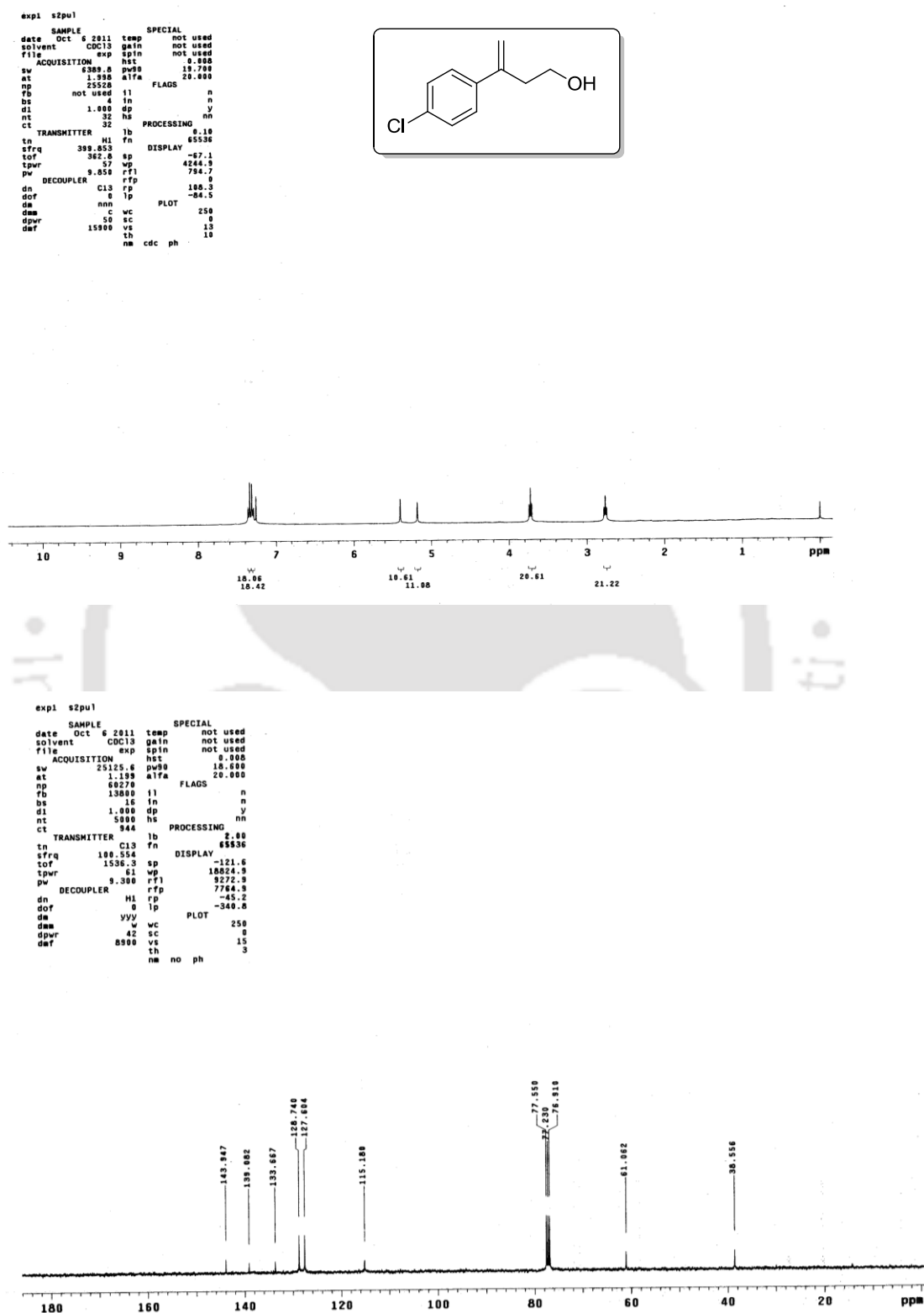
CDCl₃): δ 19.3, 28.8, 31.7, 49.0, 64.1, 114.7, 119.9, 130.9, 132.1, 135.9, 144.0; IR: 3408, 2925, 2854, 1643, 1470, 1091, 1040, 809 cm⁻¹; Anal. Calcd. For C₁₃H₁₇BrOS: C, 51.83; H, 5.69. Found: C, 51.94; H, 5.63.



2.8. Representative Spectra

 ^1H and ^{13}C NMR of 3-phenyl-but-3-en-1-ol (18a):

^1H and ^{13}C NMR of 3-(4-Chlorophenyl)but-3-en-1-ol, (18b):

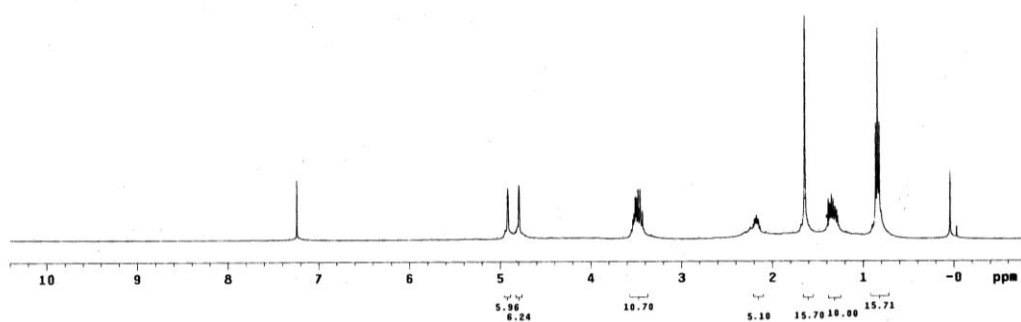
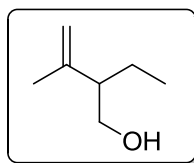


^1H and ^{13}C NMR of 2-Ethyl-3-methylbut-3-en-1-ol, (18h):

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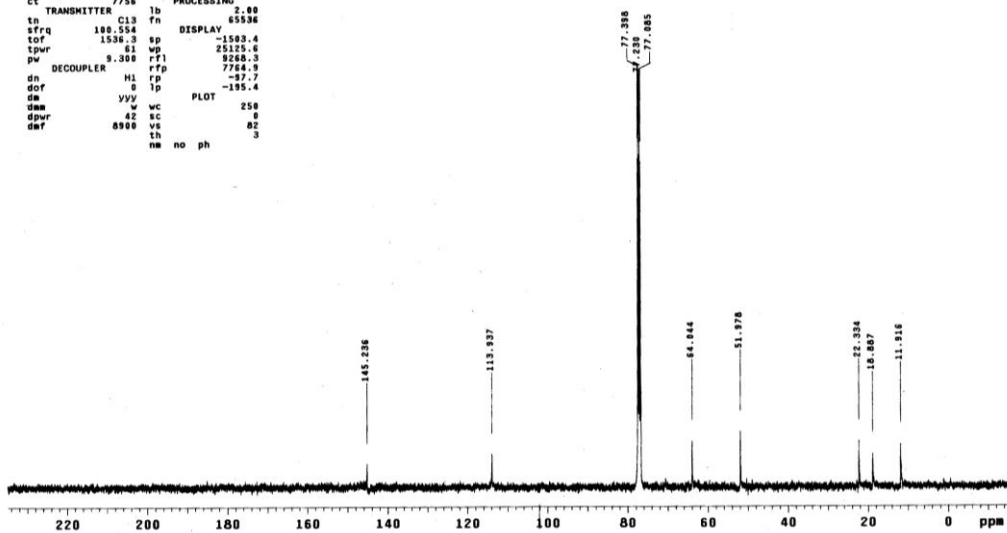
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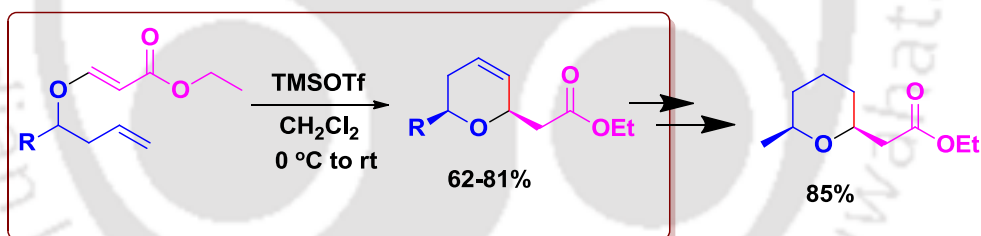


2.9. References

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CHAPTER 3

Diastereoselective Synthesis of Dihydropyrans via Prins Cyclization of Enol Ethers: Total Asymmetric Synthesis of (+)-Civet Cat Compound



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Diastereoselective Synthesis of Dihydropyrans via Prins Cyclization of Enol Ethers: Total Asymmetric Synthesis of (+)-Civet Cat Compound

3.1. Importance and Applications

Dihydropyrans are important structural motifs that are found within many biologically active natural products.¹ Swinholide A (**1**) and Swinholide J (**2**), are biologically active dihydropyrans, isolated from the red sea marine sponge *Theonella swinhoei*. Swinholide A (**1**) displays impressive biological properties including antifungal activity and potent cytotoxicity against a number of tumor cells. Swinholide J (**2**) shows potent antiproliferative activity against KB cells, with an IC_{50} comparable to that of the parent compound (IC_{50} 1.2 nM against KB cells) (Figure 3.1.1)².

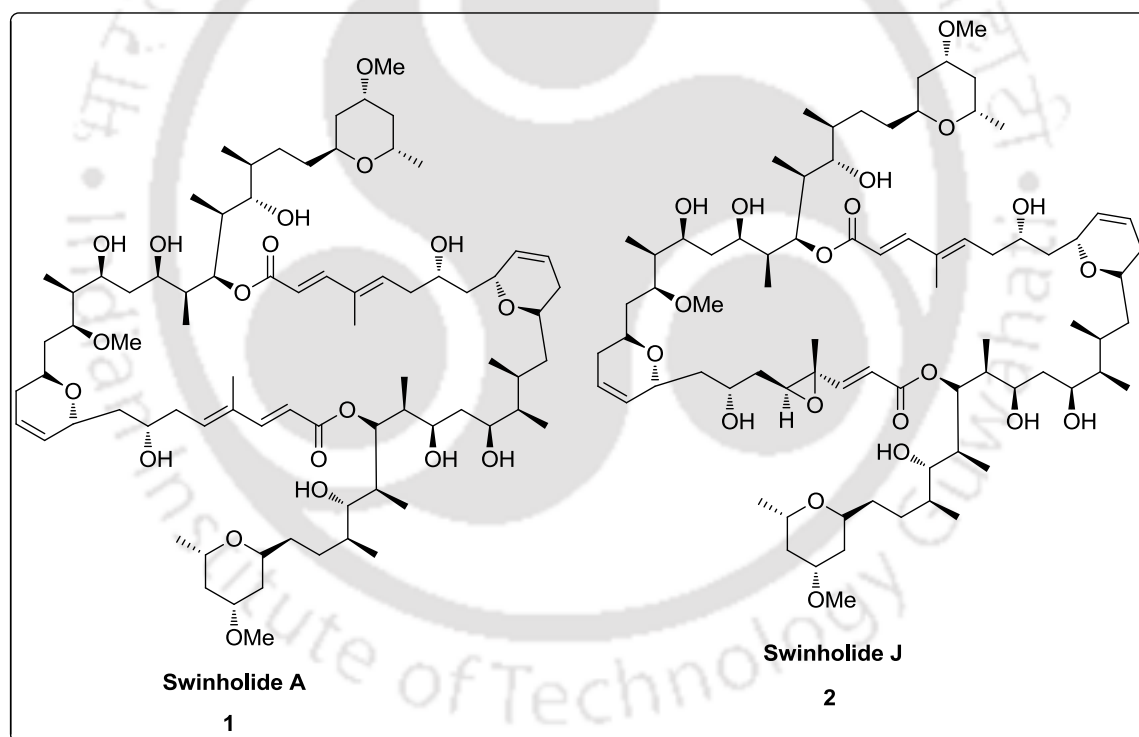


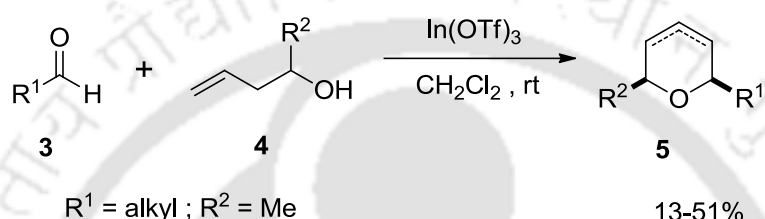
Figure 3.1.1. Biologically active cyclic ethers

3.2. An Overview of Relevant Synthetic Methods

Review of literature reveals that dihydropyrans are generally prepared by hetero Diels-Alder reactions, olefin metathesis, Prins cyclization or base-promoted cyclizations of

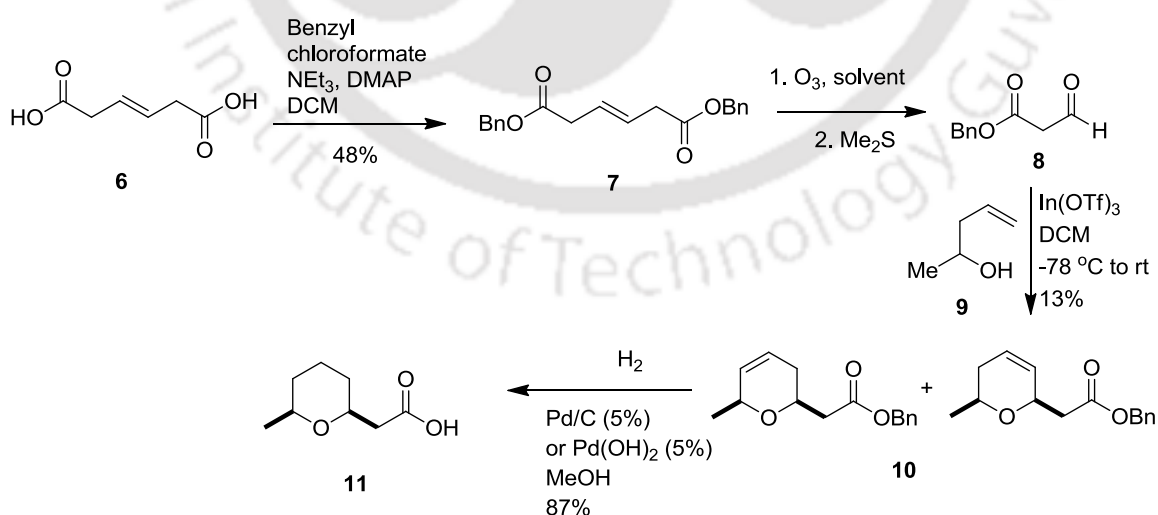
sulfinyl dienols. Among these, Prins cyclization is the most convenient methodology because it provides the desired product in a single step and it is also useful in natural product synthesis, usually Lewis acid is used for this reaction and in most of the cases, the product is 4-hydroxy tetrahydropyrans.

Adrian P. Dobbs and co-workers have reported the diastereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans **5** via Prins reaction. In this case, they used aldehydes **3** and homoallylic alcohols **4** and the reaction is catalyzed by indium(III) trifluoromethanesulfonate. However, the yield of the reaction is low and the reaction is



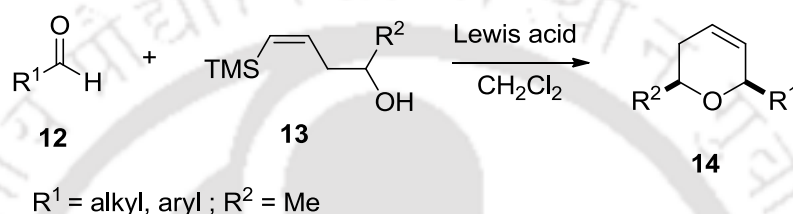
Scheme 3.2.1

not regioselective. It gives mixture of inseparable dihydropyrans **5** (Scheme 3.2.1). The dihydropyrans are obtained in the racemic form. They applied this methodology for the synthesis of natural product ($\pm$)-Civet **11** as shown in Scheme 3.2.2. Overall yield of the reaction is very less, only 2.2%. From this method, they obtained Civet as an oil.³

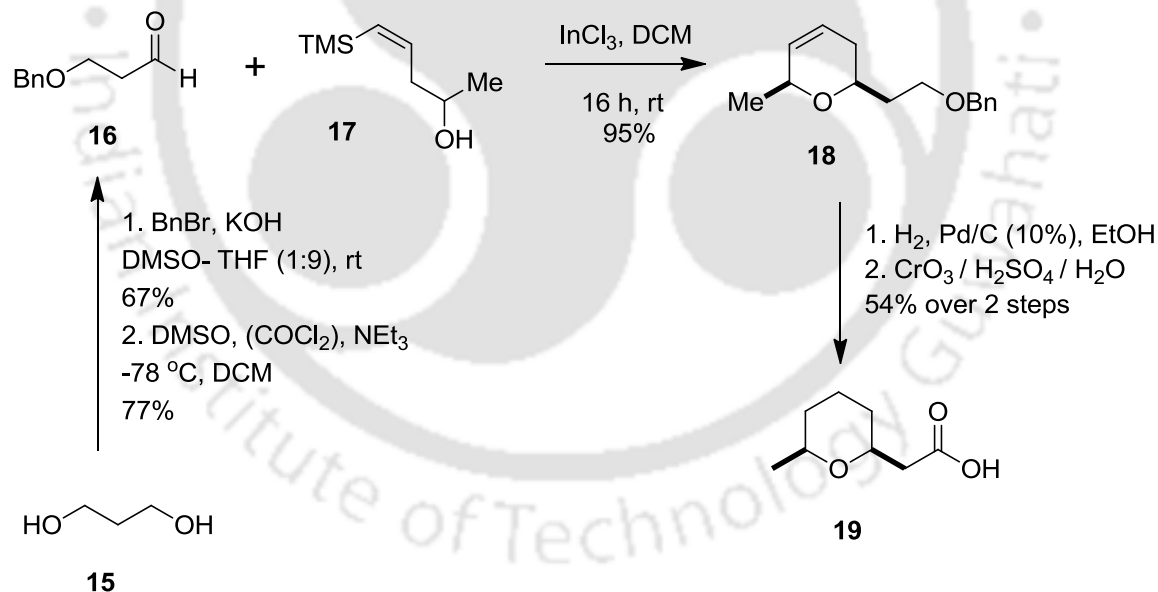


Scheme 3.2.2

To make the reaction regioselective, Dobbs and coworkers extended their work via silyl-Prins reaction by introducing a silicon moiety to the olefin component **13** which via β -effect generated dihydropyran **14** with complete regioselectivity. A random screening revealed that many Lewis acids are capable of promoting the silyl-Prins reaction *e.g.* $\text{BF}_3 \cdot \text{OEt}_2$ (-78°C , yield 90 %), TMSOTf (-78°C , yield 86 %) and InCl_3 (rt, yield 88 %) proving to be the most successful protocol (Scheme 3.2.3). They repeated the synthesis of Civet using this silyl Prins methodology as shown in Scheme 3.2.4. Unlike Civet obtained earlier as an oil, here they obtained Civet as crystal.³



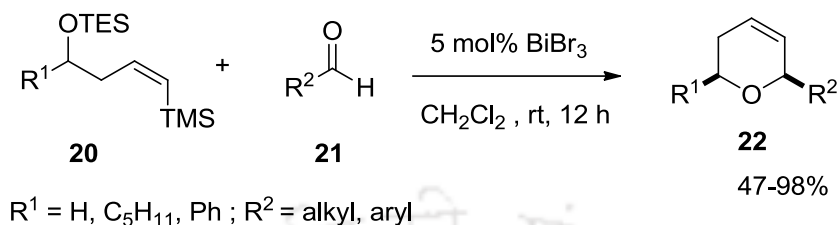
Scheme 3.2.3



Scheme 3.2.4

Hinkle and co-workers have also reported a tandem silyl-Prins reaction between δ -triethylsilyloxyvinyltrimethylsilanes **20** and a variety of aldehydes **21** to afford *cis*-2,6-disubstituted dihydropyrans **22** using 5 mol% of BiBr_3 in dichloromethane (Scheme

3.2.5). The diastereoselectivities in the crude products were significantly affected by aldehyde substitution, with electron-rich aldehydes providing 2-3:1 (*cis:trans*) and neutral (or electron poor) aldehydes affording $dr \geq 19:1$ (*cis:trans*).⁴



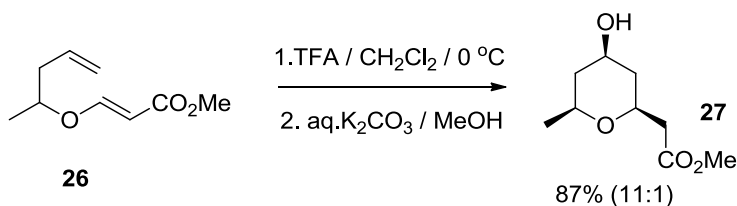
Scheme 3.2.5

A stannyl-Prins cyclization was reported by Furman and coworkers for stereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans **25**. The reaction of vinylstannanes **23** with aldehydes **24** in the presence of TMSOTf afforded *cis*-2,6-disubstituted dihydropyrans **25** in good yields with excellent stereoselectivity (Scheme 3.2.6). Although the dihydropyrans were obtained in the racemic form, the use of optically pure vinylstannane afforded optically pure 2,6-disubstituted dihydropyrans.⁵



Scheme 3.2.6

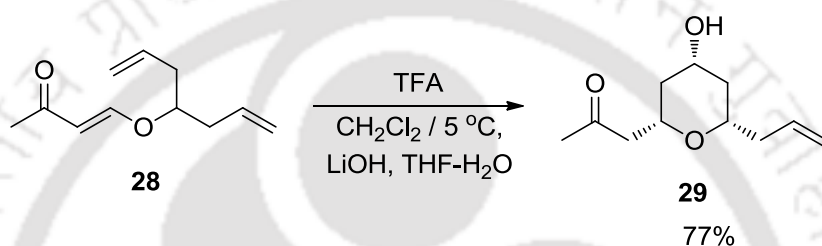
In 1987, one more variation has been reported in Prins cyclization by Fráter and Nussbaumer by using enol ether **26** as the source of the oxocarbenium ion. They



Scheme 3.2.7

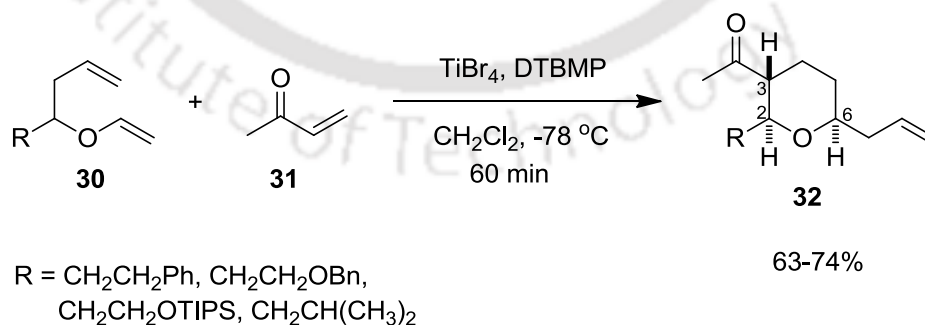
catalyzed the reaction by using TFA and the reaction afforded C-4 hydroxy substituted tetrahydropyran ring **27** as a diastereomic mixture (*Scheme 3.2.7*).⁶

Another example of using enol ether as the source of the oxocarbenium ion intermediate was reported by Kozmin for the synthesis of 4-hydroxy tetrahydrofuran **29**. The cyclization of enol-ether **28** was promoted by trifluoroacetic acid. The resulting trifluoroacetate was hydrolyzed using LiOH to afford the *cis*-tetrahydropyran **29** in high yield. The reaction proved to be efficient in the construction of the three stereogenic centers and only one isomer was observed (*Scheme 3.2.8*).⁷



Scheme 3.2.8

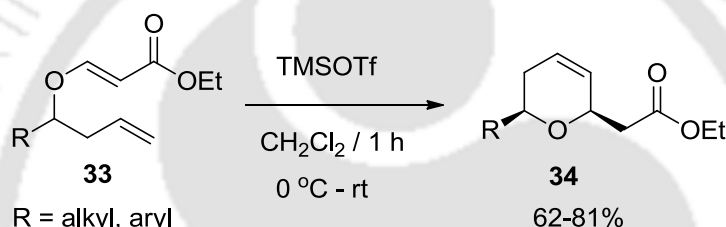
Rychnovsky and co-workers have reported the synthesis of 2,3,6-trisubstituted tetrahydropyrans **32** from a Mukaiyama-Michael cascade reaction of homoallylic enol ethers **30** and 3-butene-2-one **31** promoted by TiBr₄ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (*Scheme 3.2.9*). The resulting tetrahydropyrans **32** are obtained in high yields and as a single diastereomer.⁸



Scheme 3.2.9

3.3. Our Strategy and Objective

In spite of several methods available in the literature for the synthesis of dihydropyrans, most of the procedures suffer from major drawbacks such as multistep synthesis of starting material, low yield and lack of regioselectivity. As such there is still much interest in the development of new methodologies for the synthesis of dihydropyrans. Our interest in developing newer methods for the synthesis of substituted dihydropyrans led us towards Prins enol-ether cyclization. Although there are reports of Prins cyclization of enol-ether for the synthesis of tetrahydropyrans, no reports have been found for dihydropyran synthesis. We now present here an efficient method for the stereo- and regio-selective synthesis of dihydropyrans using Prins enol-ether cyclization reaction



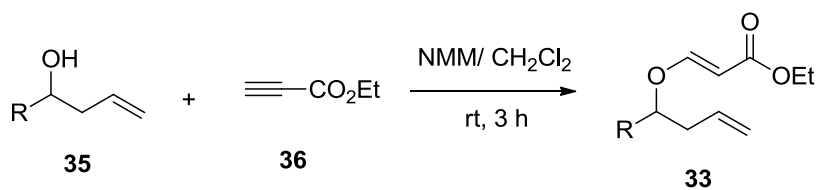
Scheme 3.3.1

from enol ethers mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf). Thus, the reaction of enol ethers **33** in dichloromethane mediated by TMSOTf gave dihydropyrans **34** in good yields (Scheme 3.3.1).

3.4. Results and Discussions

3.4.1. Preparation of enol ethers

The enol ethers **33** were synthesized from alkenols **35** and ethylpropiolate **36** in presence of *N*-methylmorpholine (NMM) in dichloromethane at room temperature (Scheme 3.4.1.1).⁹



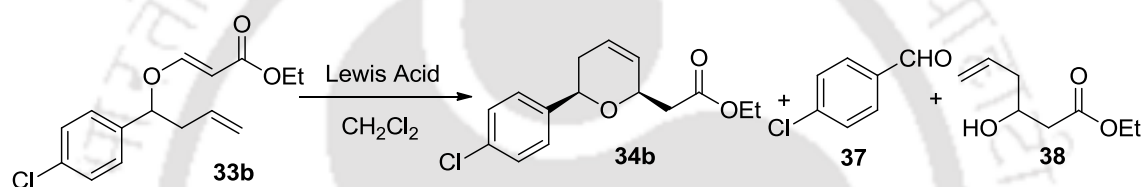
Scheme 3.4.1.1

The yield was upto 93%. The structures of all compounds were determined from IR, ^1H , ^{13}C NMR and mass spectrometry.

3.4.2. Optimization studies

To determine the optimum reaction conditions, the enol ether (*E*)-ethyl 3-((1-(4-chlorophenyl)but-3-en-1-yl)oxy)acrylate **33b** was chosen as model substrate. Initially, this was treated with different Lewis acids and solvents. The results are summarized in Table 3.4.2.1. It was observed that the reaction with $\text{BF}_3 \cdot \text{OEt}_2$ in dichloromethane at room temperature gave desired product **34b** with 25% yield, along with 4-chlorobenzaldehyde **37** and alcohol **38**¹⁰ as side products where as TMSOTf produced 66 % of desired product

Table 3.4.2.1. Optimization of the reaction

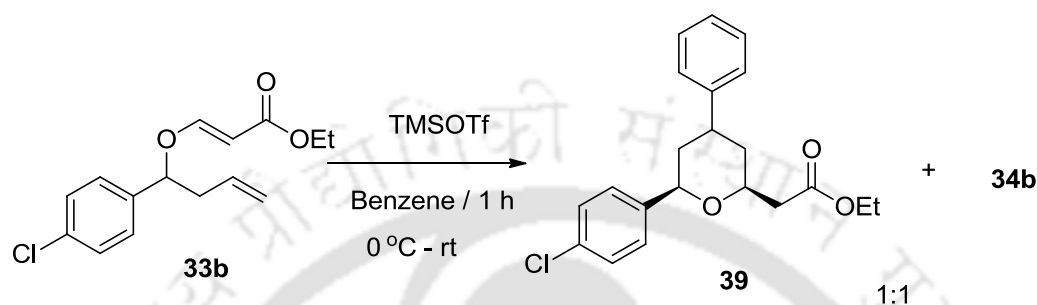


Entry	Lewis acid	Temp.	Solvents	Products (% yield) ^a			
1	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	0 °C- rt	CH_2Cl_2	34 (25)	37 (21)	38 (19)	33b (31)
2	FeCl_3	0 °C-rt	CH_2Cl_2	--	37 (26)	38 (16)	33b (44)
3	$\text{Sc}(\text{OTf})_3$	0 °C-rt	CH_2Cl_2	--	37 (30)	38 (27)	33b (23)
4	$\text{In}(\text{OTf})_3$	0 °C-rt	CH_2Cl_2	--	--	--	33b (90)
5	InCl_3	0 °C-rt	CH_2Cl_2	--	--	--	33b (94)
6	$\text{Bi}(\text{OTf})_3$	0 °C - rt	CH_2Cl_2	--	37 (33)	38 (28)	33b (26)
7	TMSOTf	0 °C-rt	CH_2Cl_2	34 (66)	trace	trace	--
8	TMSOTf	rt	CH_2Cl_2	34 (64)	trace	trace	--
9	TMSOTf	-20 °C	CH_2Cl_2	34 (54)	trace	trace	33b (35)
10	TMSOTf	0 °C- rt	CH_3CN	--	--	--	33b (95)

^aYields refer to isolated yield. The compounds are characterized by IR, NMR and Mass spectrometry.

34b in the same solvent and temperature with trace amount of side products. With FeCl_3 , $\text{Sc}(\text{OTf})_3$ and $\text{Bi}(\text{OTf})_3$, no desired product was observed instead generated the aldehyde **37** and alcohol **38**. In case of $\text{In}(\text{OTf})_3$ and InCl_3 only starting material **33b** was recovered. Under the optimization of the reaction with TMSOTf at low temperature (-20

$^{\circ}\text{C}$), only 54% yield was observed. The reaction was also performed in acetonitrile and benzene. While there was no reaction in acetonitrile, 4-phenyl tetrahydropyran **39** was observed along with dihydropyran **34b** in a ratio of 1:1 in 76% yield in benzene as inseparable mixture (*Scheme 3.4.2.1*). So, TMSOTf (1.0 equiv) in dichloromethane at 0°C -rt was found to be the best reaction conditions.



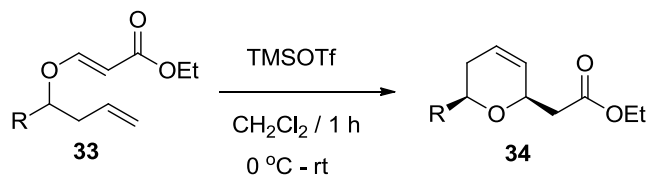
Scheme 3.4.2.1

3.4.3. Substrate scope of the reaction

Having the optimized condition in hand, we explored the scope of the reaction with various substituted enol ethers. The results are outlined in the *Table 3.4.3.1*. The reaction gives only 5,6-dihydropyran in all cases as single diastereomer **34**, which was confirmed by ^1H and ^{13}C NMR spectroscopy. The reaction works well for both aromatic and aliphatic substituents and gave good yields (60-81%). However, the reaction failed to give product with substrate having highly electron withdrawing group such as nitro group on the aromatic ring **33h**. This might be due to the destabilization of oxocarbenium ion **42** formed during the reaction (*Scheme 3.4.5.1*). On the other hand, tolyl group gave the desired product **34m** with 30% yield with a crossover product 2,6-diethylcarboxylate dihydropyran **34m'** in 33% yield, which was formed from the reaction of aldehyde **47** and alcohol **38**, which in turn was formed from rearrangement of carbocation **42** (*Scheme 3.4.6.1*).

3.4.4. Stereochemistry of the dihydropyrans

The stereochemistry of all compounds was determined from NOESY experiment of compound **34j**. We observed a strong NOE between C-2 and C-6 hydrogens which-

Table 3.4.3.1. Synthesis of dihydropyrans *via* Prins cyclization of enol ether

Entry	Substrate R =	Product 34	% Yield ^a
a	Ph		60
b	4-Cl-Ph		66
c	2-Cl-Ph		67
d	4-Br-Ph		69
e	3-Br-Ph		72
f	4-MeO ₂ C-Ph		64
g	2-Naphthyl		62
h	4-NO ₂ -Ph		0
i	PhCH ₂		64
j	(CH ₃) ₂ CHCH ₂		81
k	<i>n</i> -C ₆ H ₁₃		79
l	<i>cyclo</i> -C ₆ H ₁₁		66
m	4-Me-Ph		30
			33

^aYields refer to isolated yield. The compounds are characterized by IR, NMR and Mass spectrometry.

confirms that these two hydrogens are *cis* to each other (Figure 3.4.4.1).

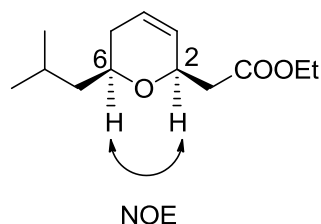
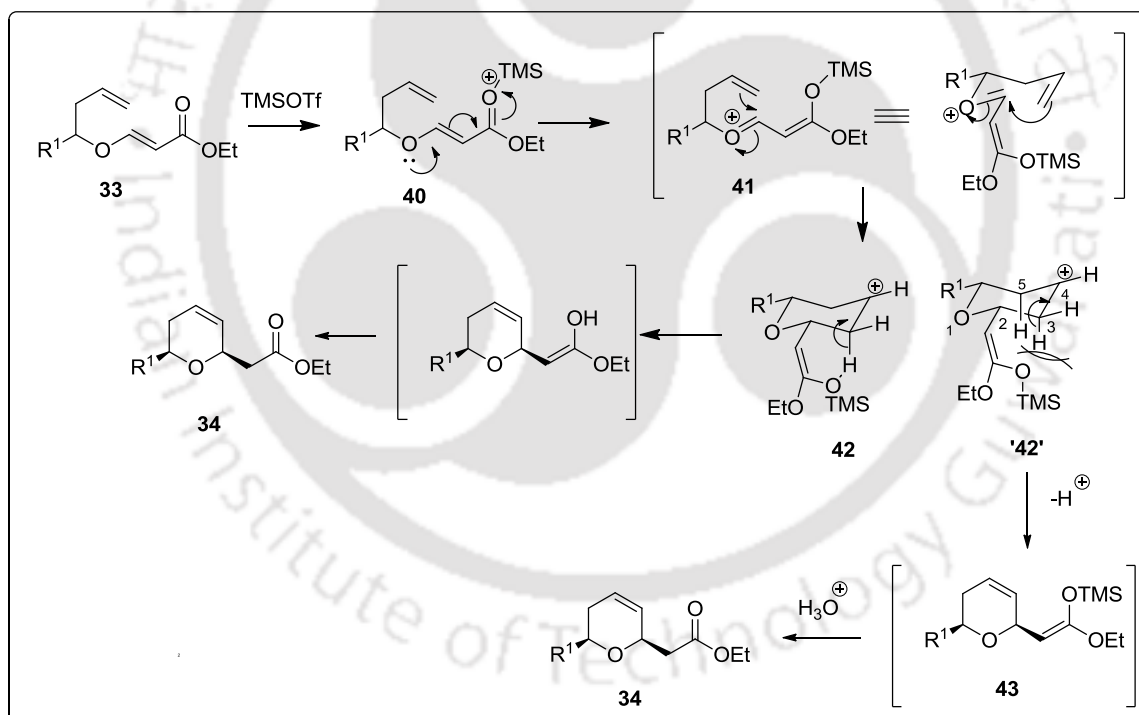


Figure 3.4.4.1. NOE of Ethyl-2-(6-isobutyl-5,6-dihydro-2H-pyran-2-yl)acetate

3.4.5. Plausible mechanism for the synthesis of 5,6-dihydropyrans

On the basis of our results, we proposed a mechanism for explaining the regioselectivity of the reaction (Scheme 3.4.5.1). It involves the Lewis acid activation of the carbonyl group of the ester functionality of enol ether **33** leading to the formation of oxocarbenium



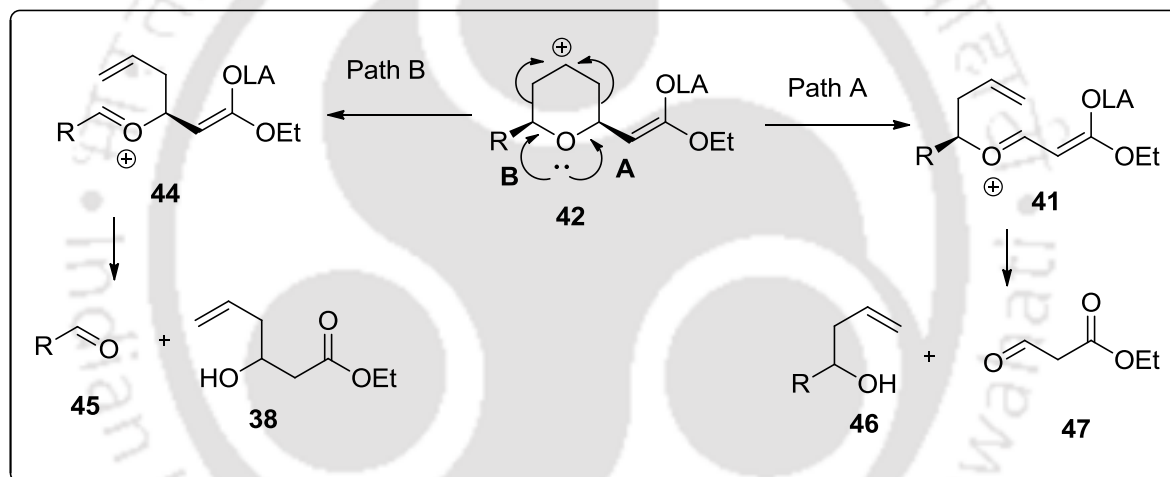
Scheme 3.4.5.1. Proposed mechanism of the reaction

ion **41**, which after Prins cyclization forms tetrahydropyranyl cation **42**. The side-chain enolate abstracts a proton from C-3 of the tetrahydropyranyl carbocation **42**, which is acidic in nature because of the presence of a positive charge in the α -position, via a second six-membered cyclic transition state to form the 3,4-double bond in final

compound **34**.¹¹ Another possibility is that the bulky equatorial silyl-enol ether and axial hydrogen at C-3 of carbocation **42'** experiences a steric constraint. To release this steric constraint, the axial hydrogen at C-3 eliminates to give the selective elimination product **34**.¹²

3.4.6. Explanation for the synthesis of side products

The formation of aldehydes **37** and alcohols **38** is rationalized by the following mechanism (Scheme 3.4.6.1). The tetrahydropyranyl cation **42** undergoes [3,3] oxonia-cope rearrangement in two different pathways **A** and **B** to give aldehydes **45** and **47** and alcohols **38** and **46**, respectively. The aldehyde **47** and alcohol **38** reacts under these reaction conditions to give product **34m'** (Table 3.4.3.1).



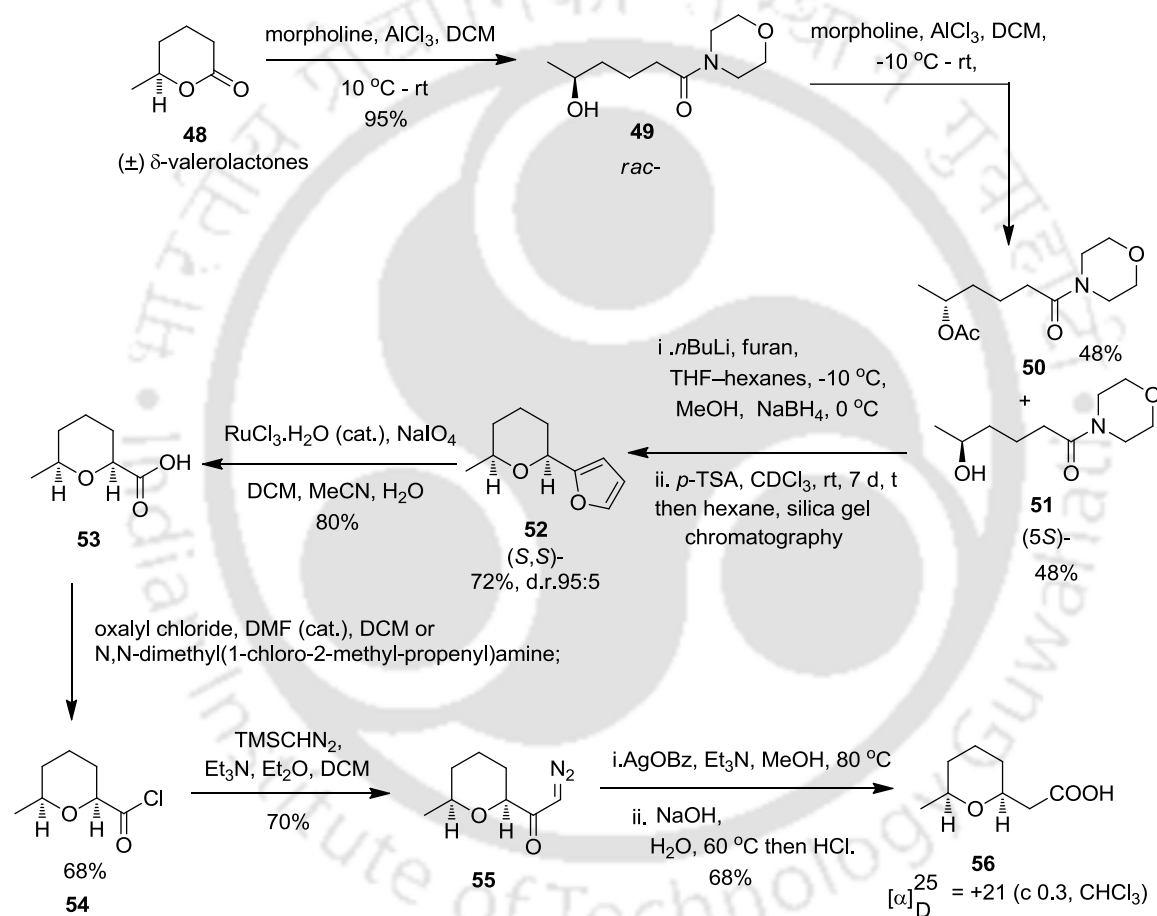
Scheme 3.4.6.1

3.5. Total Asymmetric Synthesis of (+)-Civet Cat Compound

Civet or *cis*-6-methyltetrahydropyran-2-yl acetic acid, was isolated from the glandular secretions of the civet cat by Maurer in 1979. This compound is used as fragrances for perfumery industry.¹³

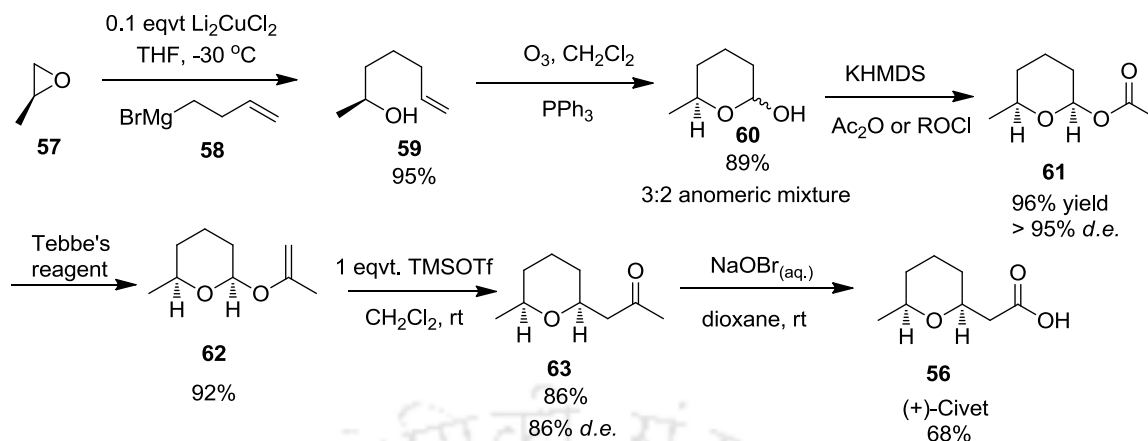
3.5.1. Literature review

In literature, numerous methods have been reported for the synthesis of ($\pm$)-civet but only some methods are there for asymmetric synthesis of (+)-civet. Matthew O'Brien *et al.* have described the asymmetric synthesis of (+)-civet **56** by starting the reaction with δ -valerolactone **48** followed by nine steps synthesis as shown in *scheme 3.5.1.1* affording (+)-civet cat compound **56** in 68% as colourless oil with specific rotation $[\alpha]_D^{20} +21$ (c 0.3, CHCl₃).¹⁴



Scheme 3.5.1.1

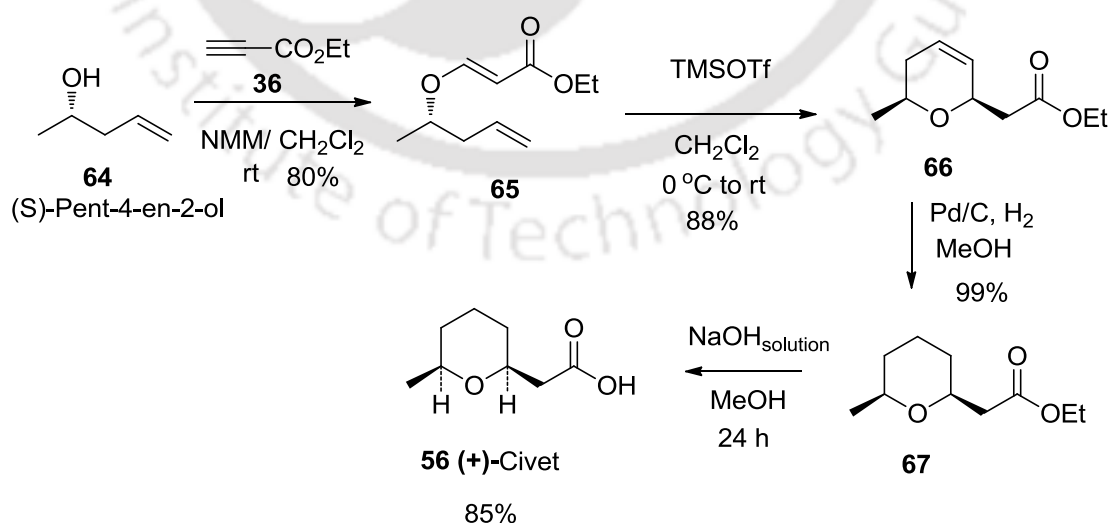
There is another report for asymmetric synthesis of (+)-civet described by Ley *et al.* The reaction started with ring-opening of (-)-(*S*)-propylene oxide **57** with butenyl Grignard reagent **58** (1.2 equiv.) followed by five steps synthesis giving (+)-civet cat compound **56** in 68% as a colourless oil with specific rotation $[\alpha]_D^{20} +20.5$ (c 1.23, CHCl₃) (*Scheme 3.5.1.2*).¹⁵



Scheme 3.5.1.2

3.5.2. Our strategy

Here, we have utilized our methodology for the total asymmetric synthesis of (+)-civet cat compound. We have accomplished the total synthesis of the same natural product only in four steps. We started the synthesis with (2*S*)-pent-4-en-2-ol as shown in Scheme 3.5.2.1. (2*S*)-Pent-4-en-2-ol **64** was reacted with ethyl propiolate **36** in the presence of *N*-methyl morpholine in dichloromethane to give enol ether **65** in 80% yield. Prins cyclization of the enol ether **65** and subsequent hydrogenation with palladium charcoal gave tetrahydropyran **67**, which was then hydrolyzed with aqueous methanolic sodium hydroxide solution to give the civet **56** in 85% yield and 17 % yield over four steps. The



Scheme 3.5.2.1. Short synthesis of (+)-Civet

specific rotation of the synthesized civet was found to be $[\alpha]_D^{20} +22.4$ (c 0.25, CHCl_3), Lit.¹⁵ $[\alpha]_D^{20} +22.0$ (c 1.23, CHCl_3), Lit.^{16a} $[\alpha]_D^{20} +26.0$ (c 0.18, CHCl_3), Lit.¹⁴ $[\alpha]_D^{20} +21.0$ (c 0.3, CHCl_3), Lit.^{16b} $[\alpha]_D^{20} +21.9$ (c 1.108, CHCl_3). The ^1H and ^{13}C NMR data were found in good agreement with the previously reported civet.¹⁵ The good agreement of the specific rotation with the reported data indicates that under these reaction conditions the product does not undergo racemization.¹⁷

3.6. Conclusion

In conclusion, we have developed a methodology for the synthesis of dihydropyran from enol ether using Prins cyclization reaction. The reaction is diastereo- and regioselective and gives good yield. The utility of this methodology was demonstrated by a short asymmetric synthesis of a natural product (+)-civet in good yield.

3.7. Experimental Section

3.7.1. 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 (60-10 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm).

^1H NMR spectra were recorded in CDCl_3 on 400 MHz NMR spectrometer using TMS as internal standard. The ^{13}C NMR spectra were recorded at 150 and 100 MHz using CDCl_3 as internal standard. IR spectra were recorded on FT-IR spectrometer. The HRMS data were measured with Waters QTOF-Premier, LC Ms/Ms system.

Chiral (S)-pent-4-ene-2-ol was purchased from Sigma Aldrich Chemicals Pvt.

3.7.2. General Procedure for preparation of enol ethers (33a-m and 65):

To a solution of homoallylic alcohol (2.0 mmol) in dichloromethane (3 mL), *N*-methyl morpholine (2.0 mmol) and ethyl propiolate (2.0 mmol) were added. The reaction mixture

was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction the solvent was removed on a rotary evaporator and diluted with water (5 mL). The product was extracted with ethyl acetate (3x10 mL), and the combined organic layers were washed with brine (3 mL) and finally dried over anhydrous Na_2SO_4 . The solvent was removed under rotary evaporator and the crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents

3.7.3. Synthesis of (E)-ethyl 3-((1-phenylbut-3-en-1-yl)oxy)acrylate (33a) :

To a solution of 1-phenylbut-3-en-1-ol (0.296 mg, 2.0 mmol) in dichloromethane (3 mL), *N*-methyl morpholine (0.22 mL, 2 mmol) and ethyl propiolate (0.2 mL, 2.0 mmol) were added. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction the solvent was removed on a rotary evaporator and diluted with water (5 mL). The product was extracted with ethyl acetate (3x10 mL), and the combined organic layers were washed with brine (3 mL) and finally dried over anhydrous Na_2SO_4 . The solvent was removed under rotary evaporator and the crude product was purified on silica gel column chromatography using ethyl acetate and hexane (EtOAc:hexane, 1:9) as eluents to give **33a** (235 mg, 84%) as a Pale yellow oil.

3.7.4. General Procedure for the synthesis of substituted dihydropyrans (34a-m and 66):

To a solution of enol ether (1.0 mmol) in dry dichloromethane (2 mL) at 0 °C was added trimethylsilyl trifluoromethane sulfonate (1.0 mmol) under N_2 atmosphere. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for 1h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (EtOAc:Hexane, 1:9) as eluents. After completion of the reaction, the solvent was removed on rotary evaporator and quenched with saturated solution of NaHCO_3 . The product was extracted with ethyl acetate and then washed with brine solution. The organic layer was dried (Na_2SO_4) and evaporated to give the crude product, which was purified by short column chromatography over silica gel to give the title compound.

3.7.5. Synthesis of ethyl-2-(6-phenyl-5,6-dihydro-2H-pyran-2-yl) acetate (34a):

To a solution of (*E*)-ethyl-3-((1-phenylbut-3-en-1-yl)oxy)acrylate **33a** (246 mg, 1.0 mmol) in dry dichloromethane (2 ml) at 0 °C was added trimethylsilyl trifluoromethane sulfonate (0.18 ml, 1.0 mmol) under N₂ atmosphere. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for 1h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (EtOAc:Hexane, 1:9) as eluents. After completion of the reaction, the solvent was removed on rotary evaporator and quenched with saturated solution of NaHCO₃. The product was extracted with ethyl acetate and then washed with brine solution. The organic layer was dried (Na₂SO₄) and evaporated to give the crude product, which was purified by short column chromatography over silica gel (EtOAc:Hexane, 1:9) to give **34a** (147 mg, 60%) as a colourless oil.

3.7.6. Ethyl 2-((2*S*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yl)acetate (67)

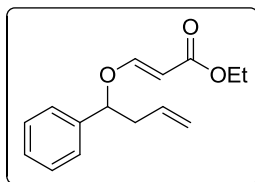
The dihydropyran **66** (0.184 g) was dissolved in dry methanol (1.5 ml), followed by the addition of Pd/C catalyst (10 mol %, 0.018 g) under nitrogen. This stirring mixture was then fitted with a 3-way tap connected to a H₂ balloon. After evacuating the remaining N₂ and flushing the reaction mixture with hydrogen three times, the mixture was left to stir with hydrogen blowing under the surface at room temperature overnight. The next day the crude mixture was filtered through a cake of celite and the filtered solution was concentrated in vacuo to yield the product **67** (184 mg, 99%) as a clear oil.

3.7.7. 2-((2*S*,6*S*)-6-Methyltetrahydro-2*H*-pyran-2-yl)acetic acid, (+)-Civet (56) :

To a solution of Ethyl 2-((2*S*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yl)acetate **67** (0.186 g, 1mmol) in 2 mL methanol was added 4 mL of a 2.5 M aq. solution of NaOH and stirred at room temperature for 24h and then acidified with 4N HCl. The aq. Phase was extracted with CH₂Cl₂ (2x100 mL) after saturation with NaCl. The combined organic extracts were dried (Na₂SO₄) and evaporated to give the product **56** (134 mg, 85%) as a colorless gummy.

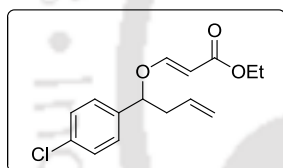
3.8. Charactererization Data

(*E*)-Ethyl-3-(1-phenyl-3-buten-1-yl)oxy-2-propenoate (33a):



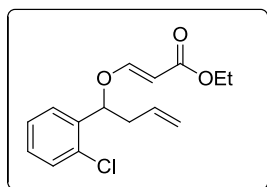
Pale yellow oil, (238 mg, 97%); ^1H NMR (400 MHz, CDCl_3): δ 7.42 (d, $J = 12.5$ Hz, 1 H), 7.26-7.15 (m, 5H), 5.67-5.57 (m, 1 H), 5.13 (d, $J = 12.5$ Hz, 1 H), 5.00-4.96 (m, 2 H), 4.78 (dd, $J = 7.5$, 5.7 Hz, 1 H), 4.03-3.95 (m, 2 H), 2.63-2.55 (m, 1 H), 2.47-2.40 (m, 1 H), 1.10 (qd, $J = 7.1$, 1.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.5, 161.2, 139.4, 132.8, 128.5, 128.1, 126.0, 118.1, 98.4, 83.7, 59.5, 41.6, 14.1; IR (KBr, neat): 3084, 3037, 2978, 2943, 2908, 1713, 1643, 1625, 1496, 1455, 1367, 1326, 1284, 1196, 1132, 1044, 997, 961, 920, 832, 761, 703 cm^{-1} ; HRMS calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 269.1148, found 269.1139.

(*E*)-Ethyl-3-((1-(4-chlorophenyl)but-3-en-1-yl)oxy)acrylate (33b):



Pale yellow oil, (235 mg, 84%); ^1H NMR (400 MHz, CDCl_3): δ 1.23 (t, $J = 7.2$ Hz, 3 H), 2.48-2.55 (m, 1 H), 2.64-2.71 (m, 1 H), 4.11 (q, $J = 7.2$ Hz, 2 H), 4.87 (t, $J = 6.0$ Hz, 1 H), 5.06-5.10 (m, 2 H), 5.19 (d, $J = 12.8$ Hz, 1 H), 5.64-5.75 (m, 1 H), 7.21 (d, $J = 8.4$ Hz, 2 H), 7.34 (d, $J = 8.4$ Hz, 2 H), 7.48 (d, $J = 12.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 41.7, 59.7, 83.0, 98.8, 118.6, 127.6, 128.9, 132.5, 134.0, 138.1, 161.0, 167.4; IR (KBr, Neat): 2983, 2935, 1710, 1634, 1487, 1368, 1132, 1043, 829, 744 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{18}\text{ClO}_3$ ($\text{M}+\text{H}$) $^+$ requires 281.0939; found 281.0949.

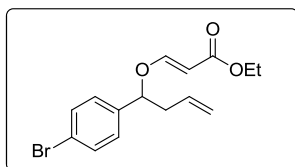
(*E*)-Ethyl 3-((1-(2-chlorophenyl)but-3-en-1-yl)oxy)acrylate (33c):



Pale yellow oil, (232 mg, 83%); ^1H NMR (400 MHz, CDCl_3): δ 1.15 (t, $J = 7.2$ Hz, 3 H), 2.53 (dd, $J = 6.8$ and 5.6 Hz, 2 H), 4.06 (q, $J = 7.2$ Hz, 2 H), 5.02-5.06 (m, 2 H), 5.09 (d, $J = 12.4$ Hz, 1 H), 5.30 (t, $J = 6.0$ Hz, 1 H), 5.68-5.79 (m, 1 H), 7.14-7.32 (m, 4 H), 7.43 (d, $J = 12.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 40.2, 59.7, 79.7, 98.7, 118.5, 127.2, 127.4, 129.3, 129.4, 129.6, 132.7, 137.2, 161.1, 167.5; IR

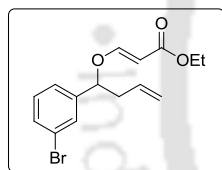
(KBr, Neat): 2983, 2939, 1710, 1633, 1470, 1320, 1132, 1043, 830, 755 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{15}\text{H}_{18}\text{ClO}_3$ ($\text{M}+\text{H}$)⁺ requires 281.0939; found 281.0949.

(E)-Ethyl 3-((1-(4-bromophenyl)but-3-en-1-yl)oxy)acrylate (33d):



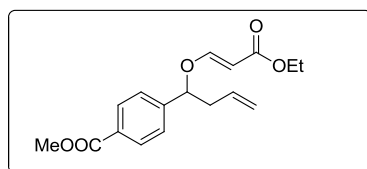
Colorless oil, (288 mg, 89%); ^1H NMR (400 MHz, CDCl_3): δ 1.23 (t, $J = 7.2$ Hz, 3 H), 2.48-2.55 (m, 1 H), 2.63-2.70 (m, 1 H), 4.01-4.16 (m, 2 H), 4.85 (t, $J = 7.2$ Hz, 1 H), 5.06-5.11 (m, 2 H), 5.18 (d, $J = 12.8$ Hz, 1 H), 5.64-5.75 (m, 1 H), 7.14 (d, $J = 8.4$ Hz, 2 H), 7.47 (d, $J = 12.8$ Hz, 1 H), 7.49 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 41.7, 59.8, 83.0, 98.9, 118.7, 122.2, 127.9, 131.9, 132.5, 138.6, 161.0, 167.5; IR (KBr, Neat): 2983, 2940, 1712, 1632, 1480, 1132, 1055, 828, 743 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{15}\text{H}_{18}\text{BrO}_3$ ($\text{M}+\text{H}$)⁺ requires 325.0434; found 325.0442.

(E)-Ethyl 3-((1-(3-bromophenyl)but-3-en-1-yl)oxy)acrylate (33e):



Colorless oil, (278 mg, 86%); ^1H NMR (400 MHz, CDCl_3): δ 1.22 (t, $J = 7.2$ Hz, 3 H), 2.51-2.59 (m, 1 H), 2.66-2.73 (m, 1 H), 4.06-4.15 (m, 2 H), 4.96 (dd, $J = 7.2$ and 5.6 Hz, 1 H), 5.05-5.10 (m, 2 H), 5.19 (d, $J = 12.8$ Hz, 1 H), 5.63-5.75 (m, 1 H), 7.35 (d, $J = 8.4$ Hz, 2 H), 7.51 (d, $J = 12.8$ Hz, 1 H), 8.04 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 41.7, 59.8, 82.9, 98.9, 118.8, 122.8, 124.8, 129.1, 130.3, 131.4, 132.4, 141.9, 161.0, 167.5; IR (KBr, Neat): 2982, 2937, 1707, 1634, 1471, 1194, 1043, 831, 742 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{15}\text{H}_{18}\text{BrO}_3$ ($\text{M}+\text{H}$)⁺ requires 325.0434; found 325.0442.

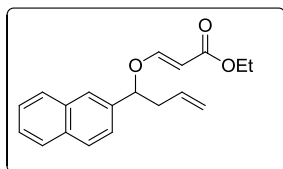
(E)-Methyl 4-(1-((3-ethoxy-3-oxoprop-1-en-1-yl)oxy)but-3-en-1-yl)benzoate (33f):



Pale yellow oil, (273 mg, 90%); ^1H NMR (400 MHz, CDCl_3): δ 1.22 (t, $J = 7.2$ Hz, 3 H), 2.51-2.59 (m, 1 H), 2.66-2.73 (m, 1 H), 3.91 (s, 3 H), 4.06-4.15 (m, 2 H), 4.96 (dd, $J = 7.2$ and 5.6 Hz, 1 H), 5.05-5.10 (m, 2 H), 5.19 (d, $J = 12.8$ Hz, 1 H), 5.63-5.75 (m, 1 H), 7.35 (d, $J = 8.4$ Hz, 2 H), 7.51 (d, $J = 12.8$ Hz, 1 H), 8.04 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 41.8, 52.3, 59.9, 83.2, 99.1, 118.9, 126.3, 130.1, 130.2, 132.5, 144.7, 161.1, 166.7, 167.6; IR (KBr, Neat):

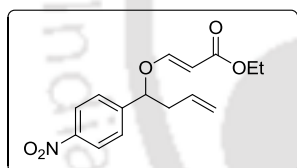
2985, 1720, 1635, 1445, 1282, 1129, 1044, 829, 770 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{17}\text{H}_{21}\text{O}_5$ ($\text{M}+\text{H}$)⁺ requires 305.1384; found 305.1397.

(E)-Ethyl 3-((1-(naphthalen-2-yl)but-3-en-1-yl)oxy)acrylate (33g):



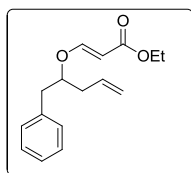
Colorless oil, (230 mg, 78%); ^1H NMR (400 MHz, CDCl_3): δ 1.18 (t, $J = 7.2$ Hz, 3 H), 2.57-2.65 (m, 1 H), 2.73-2.79 (m, 1 H), 4.01-4.13 (m, 2 H), 5.01-5.12 (m, 3 H), 5.24 (d, $J = 12.4$ Hz, 1 H), 5.68-5.79 (m, 1 H), 7.37 (dd, $J = 8.8$ and 1.6 Hz, 1 H), 7.46-7.51 (m, 2 H), 7.53 (d, $J = 12.4$ Hz, 1 H), 7.70 (s, 1 H), 7.80-7.85 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 41.8, 59.8, 84.1, 98.8, 118.5, 123.8, 125.7, 126.4, 126.5, 127.9, 128.1, 128.9, 133.0, 133.2, 133.3, 137.0, 161.4, 167.8; IR (KBr, Neat): 2981, 2934, 1706, 1633, 1324, 1130, 1045, 824, 749 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{19}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$)⁺ requires 297.1485; found 297.1500.

(E)-Ethyl 3-((1-(4-nitrophenyl)but-3-en-1-yl)oxy)acrylate (33h):



Colorless solid, m.pt. 109-110 $^{\circ}\text{C}$ (238 mg, 82%); ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 2.56-2.61 (m, 1 H), 2.67-2.72 (m, 1 H), 4.07-4.14 (m, 2 H), 5.04 (t, $J = 6.8$ Hz, 1 H), 5.05-5.11 (m, 2 H), 5.20 (d, $J = 12.8$ Hz, 1 H), 5.68-5.75 (m, 1 H), 7.46 (d, $J = 8.4$ Hz, 2 H), 7.59 (d, $J = 12.8$ Hz, 1 H), 8.24 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 41.6, 60.0, 82.4, 99.4, 119.4, 124.0, 127.1, 131.9, 146.8, 147.8, 166.1, 167.3; IR (KBr, Neat): 2983, 2929, 1711, 1615, 1524, 1341, 1189, 1132, 1042, 848, 745 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{15}\text{H}_{17}\text{NO}_5$ ($\text{M}+\text{H}$)⁺ requires 292.1179; found 292.1178.

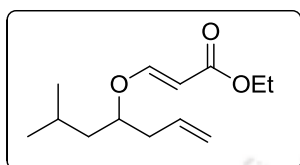
(E)-Ethyl 3-((1-phenylpent-4-en-2-yl)oxy)acrylate (33i):



Colorless oil, (236 mg, 91%); ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 2.37 (t, $J = 7.2$ Hz, 2 H), 2.86-2.95 (m, 2 H), 4.10-4.19 (m, 3 H), 5.09-5.17 (m, 2 H), 5.24 (d, $J = 12.4$ Hz, 1 H), 5.75-5.82 (m, 1 H), 7.17 (d, $J = 6.8$ Hz, 2 H), 7.23-7.31 (m, 3 H), 7.41 (d, $J = 12.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 38.2, 40.3, 59.8, 83.9, 97.6, 118.8, 126.9,

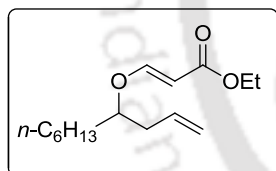
128.7, 129.6, 133.1, 137.1, 162.2, 168.1; IR (KBr, Neat): 2982, 2933, 1703, 1641, 1322, 1132, 1025, 832, 701 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{16}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$)⁺ requires 261.1485; found 261.1489.

(E)-Ethyl 3-((6-methylhept-1-en-4-yl)oxy)acrylate (33j):



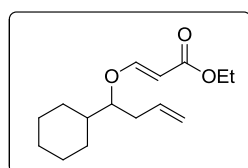
Pale yellow oil, (164 mg, 73%); ^1H NMR (400 MHz, CDCl_3): δ 0.87 (d, J = 6.4 Hz, 3 H), 0.89 (d, J = 6.4 Hz, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.28-1.34 (m, 1 H), 1.51-1.58 (m, 1 H), 1.62-1.72 (m, 1 H), 2.31 (t, J = 5.6 Hz, 2 H), 3.95-4.01 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.05-5.11 (m, 2 H), 5.21 (d, J = 12.4 Hz, 1 H), 5.66-5.77 (m, 1 H), 7.48 (d, J = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 21.7, 22.7, 24.1, 38.8, 42.6, 59.1, 81.1, 96.8, 118.0, 132.8, 162.0, 167.5; IR (KBr, Neat): 2955, 1711, 1633, 1463, 1376, 1207, 1130, 1043, 832, 742 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_3$ ($\text{M}+\text{H}$)⁺ requires 227.1642; found 227.1658.

(E)-Ethyl-3-(1-decen-4-yl)oxy-2-propenoate (33k):



Pale yellow oil, (167 mg, 66%); ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, 12.4 Hz, 1 H), 5.76-5.66 (m, 1 H), 5.19 (d, J = 12.4 Hz, 1 H), 5.08-5.03 (m, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.88 (dddd or app. quint, J = 6.1 Hz, 1 H), 2.34-2.26 (m, 2 H), 1.59-1.48 (m, 2 H), 1.38-1.20 (m, 11 H), 0.83 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.0, 162.3, 133.0, 118.1, 96.9, 83.3, 59.5, 38.5, 33.7, 31.5, 29.0, 25.0, 22.4, 14.2, 13.9; IR (KBr, Neat): 3084, 2931, 2860, 1708, 1643, 1619, 1466, 1372, 1326, 1284, 1202, 1132, 1049, 996, 955, 920, 832, 744, 726 cm^{-1} ; HRMS calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ 277.1774, found 277.1787.

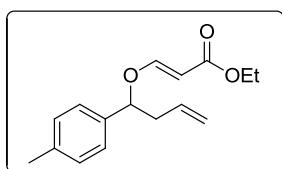
(E)-Ethyl 3-((1-cyclohexylbut-3-en-1-yl)oxy)acrylate (33l):



Pale yellow oil, (179 mg, 71%); ^1H NMR (400 MHz, CDCl_3): δ 0.90-1.07 (m, 3 H), 1.10-1.27 (m, 6 H), 1.49-1.69 (m, 5 H), 1.76-2.10 (m, 1 H), 2.22-2.28 (m, 1 H), 4.08 (q, J = 7.2 Hz, 2 H), 4.14-4.21 (m, 1 H), 5.00-5.07 (m, 2 H), 5.15 (d, J = 12.8 Hz, 1 H), 5.63-5.81 (m, 1 H), 7.41 (d, J = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ

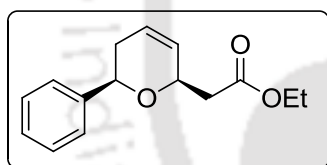
14.4, 26.0, 26.1, 26.4, 28.1, 28.9, 35.9, 41.4, 59.6, 88.5, 96.7, 118.1, 133.7, 163.5, 169.4; IR (KBr, Neat): 2928, 2856, 1711, 1632, 1450, 1244, 1132, 1042, 832, 743 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_3$ ($\text{M}+\text{H}$)⁺ requires 253.1798; found 253.1798.

(E)-Ethyl 3-((1-(p-tolyl)but-3-en-1-yl)oxy)acrylate (33m):



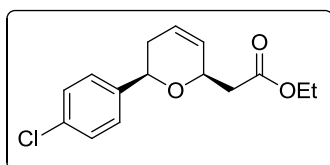
Pale yellow oil, (241 mg, 93%); ^1H NMR (400 MHz, CDCl_3): δ 1.18 (t, $J = 7.2$ Hz, 3 H), 2.30 (s, 3 H), 2.46-2.54 (m, 1 H), 2.63-2.71 (m, 1 H), 4.02-4.10 (m, 2 H), 4.84 (dd, $J = 7.2$ and 6.4 Hz, 1 H), 5.04-5.10 (m, 2 H), 5.21 (d, $J = 12.8$ Hz, 1 H), 5.65-5.78 (m, 1 H), 7.00-7.18 (m, 4 H), 7.50 (d, $J = 12.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 21.0, 41.7, 59.5, 83.3, 98.3, 118.0, 126.1, 129.3, 133.1, 136.5, 137.9, 161.3, 167.5; IR (KBr, Neat): 2983, 2932, 1709, 1635, 1452, 1318, 1132, 819, 750 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{16}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$)⁺ requires 261.1485; found 261.1480.

Ethyl-2-(6-phenyl-5,6-dihydro-2H-pyran-2-yl) acetate (34a) :



Colorless oil (147 mg, 60%) ; ^1H NMR (400 MHz, CDCl_3): δ 1.26 (t, $J = 7.2$ Hz, 3 H), 2.25-2.29 (m, 2 H), 2.55 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.68 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 4.16 (dq, $J = 7.2$ and 2.4 Hz, 2 H), 4.64 (dd, $J = 8.8$ and 5.2 Hz, 1 H), 4.73-4.78 (m, 1 H), 5.76 (ddd, $J = 9.6$, 3.6, and 1.6 Hz, 1 H), 5.76 (ddd, $J = 9.6$, 4.8, and 2.4 Hz, 1 H), 7.23-7.29 (m, 2 H), 7.31-7.42 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 32.9, 40.9, 60.7, 72.5, 75.7, 125.8, 127.5, 128.5, 128.7, 129.0, 142.6, 171.3; IR (KBr, Neat): 2921, 2847, 1730, 1602, 1453, 1382, 1285, 1172, 1070, 1026, 752, 696 cm^{-1} ; HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$)⁺ requires 247.1329; found 247.1332.

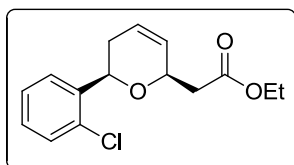
Ethyl-2-(6-(4-chlorophenyl)-5,6-dihydro-2H-pyran-2-yl)acetate (34b):



Colorless oil (184 mg, 66%); ^1H NMR (400 MHz, CDCl_3): δ 1.26 (t, $J = 7.2$ Hz, 3 H), 2.20-2.25 (m, 2 H), 2.54 (dd, $J = 15.2$ and 7.5 Hz, 1 H), 2.67 (dd, $J = 15.2$ and 7.5 Hz, 1 H), 4.14-4.20 (m, 2 H), 4.61 (dd, $J = 8.8$ and 5.2 Hz, 1 H), 4.72-4.80 (m, 1 H), 5.74-5.79 (m, 1 H), 5.91-5.96 (m, 1 H), 7.22-7.35 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 32.9, 40.9, 60.7, 72.5, 74.9, 125.6, 127.2, 128.6, 129.1, 133.1,

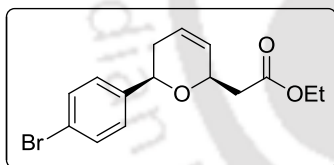
141.2, 171.2; IR (KBr, Neat): 2981, 2925, 1735, 1655, 1492, 1393, 1166, 1163, 1085, 1030, 823 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{15}\text{H}_{17}\text{ClO}_3$ ($\text{M}+\text{H}$)⁺ requires 281.0939; found 281.0949.

Ethyl-2-(6-(2-chlorophenyl)-5,6-dihydro-2H-pyran-2-yl)acetate (34c):



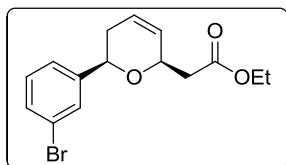
Colorless oil (187 mg, 67%); ^1H NMR (400 MHz, CDCl_3): δ 1.26 (t, $J = 7.2$ Hz, 3 H), 2.40-2.50 (m, 2 H), 2.56 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.68 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 4.11-4.22 (m, 2 H), 4.74-4.84 (m, 1 H), 4.98 (dd, $J = 10.4$ and 3.2 Hz, 1 H), 5.75-5.79 (m, 1 H), 5.92-5.98 (m, 1 H), 7.19 (t, $J = 7.6$ Hz, 1 H), 7.27 (d, $J = 7.6$ Hz, 1 H), 7.30 (d, $J = 7.6$ Hz, 1 H), 7.57 (d, $J = 7.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 31.4, 41.0, 60.7, 72.6, 72.7, 125.9, 127.2, 127.3, 128.5, 128.8, 129.2, 131.6, 140.4, 171.2; IR (KBr, Neat): 2979, 2925, 1735, 1585, 1473, 1380, 1172, 1079, 1037, 756 cm^{-1} . HRMS (ESI) cald. for $\text{C}_{15}\text{H}_{17}\text{ClNaO}_3$ ($\text{M}+\text{Na}$)⁺ requires 303.0758; found 303.0756.

Ethyl-2-(6-(4-bromoophenyl)-5,6-dihydro-2H-pyran-2-yl)acetate (34d):



Colorless oil (223 mg, 69%); ^1H NMR (400 MHz, CDCl_3): δ 1.27 (t, $J = 7.2$ Hz, 3 H), 2.20-2.27 (m, 2 H), 2.54 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.67 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 4.11-4.21 (m, 2 H), 4.60 (dd, $J = 8.4$ and 4.8 Hz, 1 H), 4.72-4.79 (m, 1 H), 5.74-5.79 (m, 1 H), 5.90-5.96 (m, 1 H), 7.23 (d, $J = 8.4$ Hz, 2 H), 7.45 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 32.9, 40.9, 60.7, 72.5, 75.0, 121.3, 125.6, 127.6, 129.1, 131.5, 141.7, 171.2; IR (KBr, Neat): 2923, 2850, 1733, 1647, 1483, 1382, 1169, 1077, 1023, 678 cm^{-1} . HRMS (ESI) cald. for $\text{C}_{15}\text{H}_{17}\text{BrNaO}_3$ ($\text{M}+\text{Na}$)⁺ requires 347.0253; found 347.0251 (major), 349.0207 (minor).

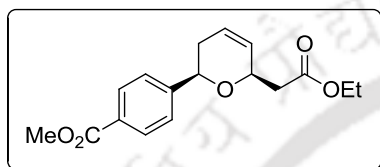
Ethyl-2-(6-(3-bromoophenyl)-5,6-dihydro-2H-pyran-2-yl)acetate (34e):



Colorless oil (233 mg, 72%); ^1H NMR (400 MHz, CDCl_3): δ 1.28 (t, $J = 7.2$ Hz, 3 H), 2.21-2.27 (m, 2 H), 2.54 (dd, $J = 14.8$ and 6.0 Hz, 1 H), 2.67 (dd, $J = 14.8$ and 7.6 Hz, 1 H), 4.12-4.22 (m, 2 H), 4.61 (dd, $J = 9.2$ and 5.2 Hz, 1 H), 4.71-

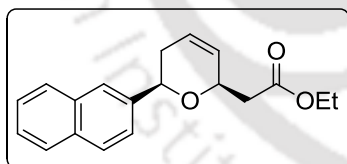
4.79 (m, 1 H), 5.74-5.79 (m, 1 H), 5.90-5.96 (m, 1 H), 7.19 (t, $J = 7.6$ Hz, 1 H), 7.26 (d, $J = 7.6$ Hz, 1 H), 7.38 (d, $J = 7.6$ Hz, 1 H), 7.53 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 32.7, 40.8, 60.7, 72.4, 74.7, 122.5, 124.3, 125.4, 128.8, 128.9, 129.9, 130.4, 144.9, 171.1; IR (KBr, Neat): 2923, 2850, 1733, 1569, 1381, 1170, 1078, 1029, 781, 695 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{17}\text{BrNaO}_3$ ($\text{M}+\text{Na}$) $^+$ requires 347.0253; found 347.0251 (major), 349.0207 (minor).

Methyl-4-(6-(2-ethoxy-2-oxoethyl)-3,6-dihydro-2H-pyran-2-yl)benzoate (34f):



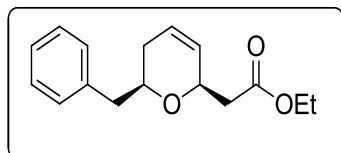
Colorless liquid, (194 mg, 64%); ^1H NMR (400 MHz, CDCl_3): δ 1.28 (t, $J = 7.2$ Hz, 3 H), 2.21-2.30 (m, 2 H), 2.56 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.69 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 3.91 (s, 3 H), 4.11-4.23 (m, 2 H), 4.70 (dd, $J = 10.0$ and 4.0 Hz, 1 H), 4.74-4.80 (m, 1 H), 5.75-5.80 (m, 1 H), 5.93-5.98 (m, 1 H), 7.43 (d, $J = 8.0$ Hz, 2 H), 7.99 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 32.8, 40.8, 52.2, 60.7, 72.4, 75.1, 125.5, 125.6, 129.0, 129.1, 129.7, 147.7, 167.1, 171.2; IR (KBr, Neat): 2945, 2850, 1727, 1617, 1438, 1382, 1174, 1105, 1025, 764, 702 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_5$ ($\text{M}+\text{H}$) $^+$ requires 305.1384; found 305.1394.

Ethyl 2-(6-(naphthalen-1-yl)-5,6-dihydro-2H-pyran-2-yl)acetate (34g):



Colorless oil (183 mg, 62%); ^1H NMR (400 MHz, CDCl_3): δ 1.27 (t, $J = 7.2$ Hz, 3 H), 2.31-2.37 (m, 2 H), 2.58 (dd, $J = 14.8$ and 6.4 Hz, 1 H), 2.73 (dd, $J = 14.8$ and 7.6 Hz, 1 H), 4.12-4.21 (m, 2 H), 4.77-4.90 (m, 2 H), 5.78-5.82 (m, 1 H), 5.94-6.0 (m, 1 H), 7.41-7.64 (m, 3 H), 7.79-7.98 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 32.9, 41.0, 60.7, 72.6, 75.8, 124.3, 124.4, 125.8 (2C), 126.2, 127.8, 128.2 (2C), 129.1, 133.0, 133.5, 140.1, 171.3; IR (KBr, Neat): 2945, 2850, 1727, 1617, 1438, 1382, 1174, 1105, 1025, 764, 702 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{20}\text{NaO}_3$ ($\text{M}+\text{Na}$) $^+$ requires 319.1305; found 319.1317.

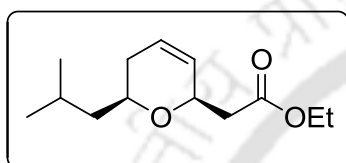
Ethyl-2-(6-benzyl-5,6-dihydro-2H-pyran-2-yl)acetate (34i):



Colorless oil (166 mg, 64%); ^1H NMR (400 MHz, CDCl_3): δ 1.24 (t, $J = 7.2$ Hz, 3 H), 1.86-1.99 (m, 1 H), 2.00-2.07 (m,

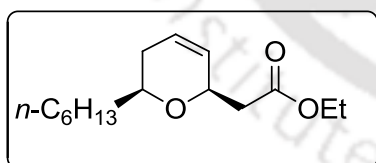
1 H), 2.45 (dd, $J = 14.8$ and 6.0 Hz, 1 H), 2.55 (dd, $J = 14.8$ and 8.0 Hz, 1 H), 2.68 (dd, $J = 14.0$ and 6.4 Hz, 1 H), 2.93 (dd, $J = 14.0$ and 6.8 Hz, 1 H), 3.77-3.80 (m, 1 H), 4.07-4.18 (m, 2 H), 4.50-4.55 (m, 1 H), 5.62-5.66 (m, 1 H), 5.78-5.83 (m, 1 H), 7.17-7.29 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 30.7, 41.0, 42.4, 60.6, 72.0, 75.0, 125.7, 126.3, 128.3, 128.9, 129.7, 138.7, 171.3; IR (KBr, Neat): 2923, 2848, 1734, 1596, 1376, 1170, 1085, 1033, 741, 696 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{16}\text{H}_{20}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 261.1485; found 261.1489.

Ethyl 2-(6-isobutyl-5,6-dihydro-2H-pyran-2-yl)acetate (34j):

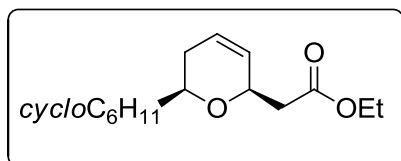


Colorless oil (183 mg, 81%); ^1H NMR (400 MHz, CDCl_3): δ 0.84 (d, $J = 6.4$ Hz, 3 H), 0.85 (d, $J = 6.4$ Hz, 3 H), 1.21 (t, $J = 7.2$ Hz, 3 H), 1.42-1.48 (m, 1 H), 1.72-1.80 (m, 1 H), 1.86-1.94 (m, 2 H), 1.95-2.00 (m, 1 H), 2.39 (dd, $J = 15.2$ and 6.0 Hz, 1 H), 2.50 (dd, $J = 15.2$ and 8.0 Hz, 1 H), 3.55-3.60 (m, 1 H), 4.11 (q, $J = 7.2$ Hz, 2 H), 4.47-4.52 (m, 1 H), 5.58-5.62 (m, 1 H), 5.77-5.81 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 22.5, 23.2, 24.6, 31.5, 40.9, 45.0, 60.5, 71.9, 72.5, 126.0, 129.0, 171.3; IR (KBr, Neat): 2955, 2917, 1738, 1650, 1465, 1375, 1171, 1084, 1035, 685 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{13}\text{H}_{22}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 227.1642; found 227.1633.

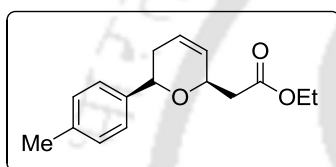
Ethyl 2-(6-hexyl-5,6-dihydro-2H-pyran-2-yl)acetate (34k):



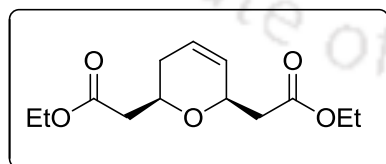
Colorless oil (200 mg, 79%); ^1H NMR (400 MHz, CDCl_3): δ 0.84 (d, $J = 6.4$ Hz, 3 H), 1.20-1.30 (m, 9 H), 1.34-1.42 (m, 2 H), 1.48-1.53 (m, 2 H), 1.88-1.94 (m, 2 H), 2.39 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.52 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 3.37-3.52 (m, 1 H), 4.12 (q, $J = 7.2$ Hz, 2 H), 4.45-4.52 (m, 1 H), 5.58-5.64 (m, 1 H), 5.77-5.82 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 14.3, 22.6, 25.4, 29.3, 31.1, 31.9, 36.0, 40.8, 60.5, 71.8, 74.2, 125.8, 128.9, 171.3; IR (KBr, Neat): 2956, 2928, 1738, 1653, 1466, 1395, 1164, 1081, 1031, 685 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{15}\text{H}_{26}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 255.1955; found 255.1943.

Ethyl 2-(6-cyclohexyl-5,6-dihydro-2H-pyran-2-yl)acetate (34l):

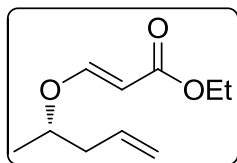
Colorless oil (166 mg, 66%); ^1H NMR (400 MHz, CDCl_3): δ 0.85-0.98 (m, 2 H), 1.08-1.20 (m, 2 H), 1.23 (t, $J = 7.2$ Hz, 3 H), 1.28-1.38 (m, 2 H), 1.58-1.70 (m, 4 H), 1.91-2.98 (m, 3 H), 2.39 (dd, $J = 14.8$ and 6.0 Hz, 1 H), 2.50 (dd, $J = 14.8$ and 8.0 Hz, 1 H), 3.18-3.24 (m, 1 H), 4.11 (q, $J = 7.2$ Hz, 2 H), 4.42-4.50 (m, 1 H), 5.58-5.63 (m, 1 H), 5.78-5.84 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 26.1, 26.3, 26.8, 28.6 (2C), 29.3, 41.0, 42.9, 60.6, 72.2, 78.5, 126.2, 129.0, 171.5; IR (KBr, Neat): 2925, 2852, 1731, 1447, 1287, 1174, 1080, 1033, 853, 682 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 253.1797; found 253.1795.

Ethyl 2-(6-(*p*-tolyl)-5,6-dihydro-2H-pyran-2-yl)acetate (34m):

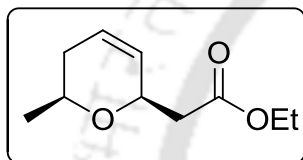
Colorless oil (78 mg, 30%); ^1H NMR (400 MHz, CDCl_3): δ 1.27 (t, $J = 7.2$ Hz, 3 H), 2.24-2.31 (m, 2 H), 2.34 (s, 3 H), 2.54 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.68 (dd, $J = 15.2$ and 7.2 Hz, 1 H), 4.17 (q, $J = 7.2$ Hz, 2 H), 4.61 (dd, $J = 10.0$ and 4.0 Hz, 1 H), 4.70-4.78 (m, 1 H), 5.75-5.79 (m, 1 H), 5.91-5.97 (m, 1 H), 7.14 (d, $J = 7.6$ Hz, 2 H), 7.25 (d, $J = 7.6$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 21.3, 32.9, 40.9, 60.7, 72.5, 75.6, 125.8, 125.9, 129.0, 129.1, 137.2, 139.7, 171.3; IR (KBr, Neat): 2924, 2857, 1733, 1591, 1455, 1280, 1172, 1074, 1030, 810, 678 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{20}\text{NaO}_3$ ($\text{M}+\text{Na}$) $^+$ requires 283.1305; found 283.1301.

Diethyl 2,2'-(3,6-dihydro-2H-pyran-2,6-diyl)diacetate (34m'):

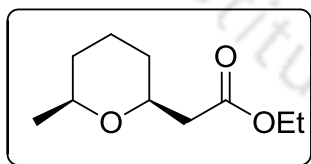
Colorless oil (84 mg, 33%); ^1H NMR (400 MHz, CDCl_3): δ 1.26 (t, $J = 7.2$ Hz, 3 H), 1.27 (t, $J = 7.2$ Hz, 3 H), 2.02-2.08 (m, 2 H), 2.45-2.63 (m, 4 H), 4.02-4.10 (m, 1 H), 4.15 (q, $J = 7.2$ Hz, 4 H), 4.60-4.64 (m, 1 H), 5.64-5.69 (m, 1 H), 5.58-5.88 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4 (2C), 30.5, 40.7, 41.2, 60.8 (2C), 70.8, 72.0, 125.3, 128.8, 171.5, 171.7; IR (KBr, Neat): 2980, 2924, 1733, 1579, 1378, 1286, 1166, 1081, 1031, 810, 680 cm^{-1} . HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{20}\text{NaO}_5$ ($\text{M}+\text{Na}$) $^+$ requires 279.1203; found 279.1210.

(S,E)-Ethyl 3-(pent-4-en-2-yloxy)acrylate (65):

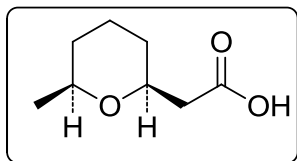
Colorless oil; (147 mg, 80%); ^1H NMR (400 MHz, CDCl_3): δ 1.15 (d, $J = 6.0$ Hz, 3 H), 1.18 (t, $J = 7.2$ Hz, 3 H), 2.18-2.24 (m, 1 H), 2.28-2.36 (m, 1 H), 3.98-4.10 (m, 3 H), 5.00-5.10 (m, 2 H), 5.15 (d, $J = 12.4$ Hz, 1 H), 5.62-5.71 (m, 1 H), 7.44 (d, $J = 12.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 19.2, 40.2, 59.2, 78.4, 97.1, 117.9, 132.9, 161.4, 167.5; IR (KBr, Neat): 2982, 2934, 1709, 1634, 1454, 1378, 1130, 1050, 832, 740 cm^{-1} ; HRMS (APCI) cald. for $\text{C}_{10}\text{H}_{16}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 185.1172; found 185.1179. $[\alpha]_{\text{D}}^{20}$ -8.2 (c 1.00, CH_2Cl_2).

Ethyl 2-(2R,6S)-6-methyl-5,6-dihydro-2H-pyran-2-yl)acetate (66):

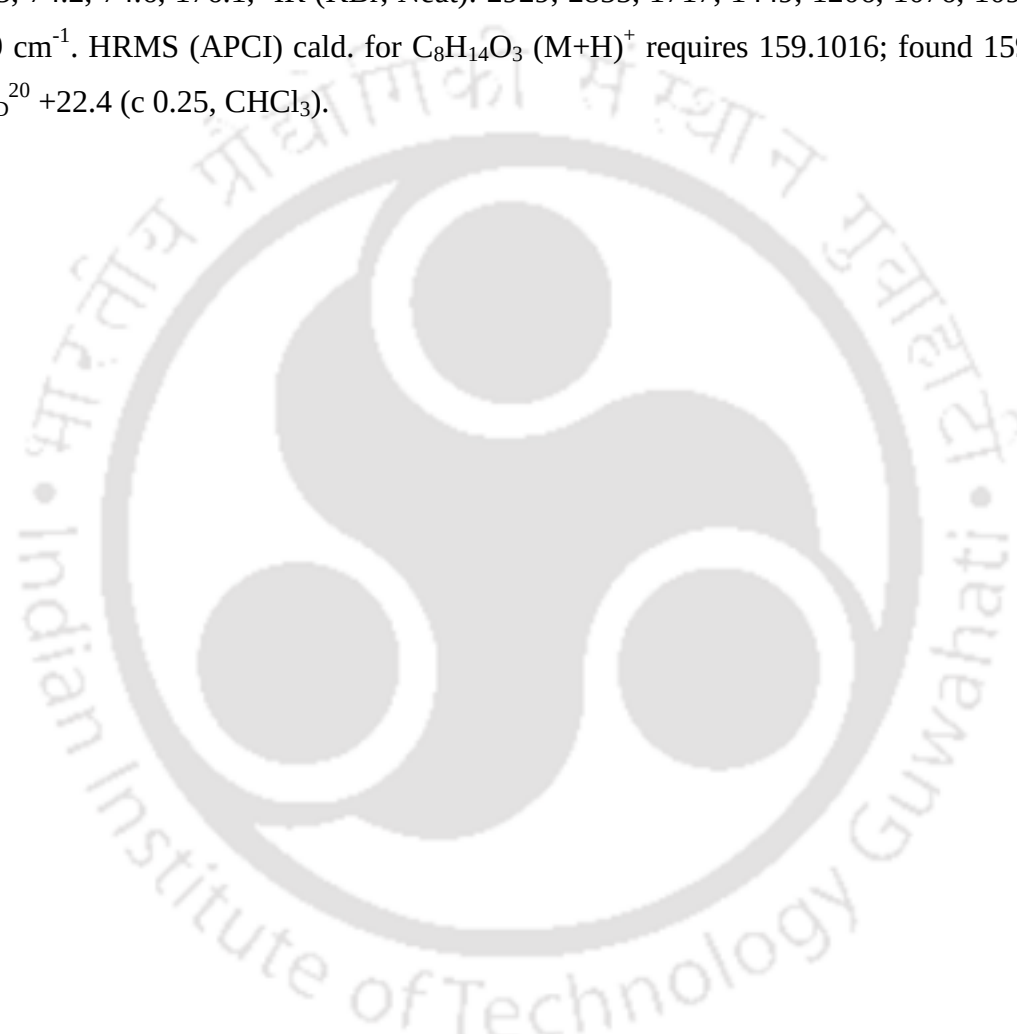
Colorless oil (161 mg, 88%); ^1H NMR (400 MHz, CDCl_3): δ 1.19 (d, $J = 6.0$ Hz, 3 H), 1.24 (t, $J = 7.2$ Hz, 3 H), 1.90-1.95 (m, 2 H), 2.40 (dd, $J = 15.2$ and 6.4 Hz, 1 H), 2.55 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 3.64-3.73 (m, 1 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 4.50-4.56 (m, 1 H), 5.60-5.65 (m, 1 H), 5.77-5.83 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 21.7, 32.8, 40.9, 60.7, 70.4, 71.8, 125.9, 128.9, 171.4; IR (KBr, Neat): 2984, 1721, 1621, 1462, 1372, 1249, 1178, 1097, 1027, 858, 748 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{10}\text{H}_{16}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 185.1172; found 185.1181. $[\alpha]_{\text{D}}^{20}$ +3.7 (c 0.70, CH_2Cl_2).

Ethyl 2-((2S,6S)-6-methyltetrahydro-2H-pyran-2-yl)acetate (67):

Colorless oil (184 mg, 99%); ^1H NMR (400 MHz, CDCl_3): δ 1.09 (d, $J = 6.4$ Hz, 3 H), 1.11-1.17 (m, 1 H), 1.24 (t, $J = 7.2$ Hz, 3 H), 1.40-1.65 (m, 4 H), 1.72-1.79 (m, 1 H), 2.32 (dd, $J = 15.2$ and 5.6 Hz, 1 H), 2.49 (dd, $J = 15.2$ and 7.6 Hz, 1 H), 3.37-3.44 (m, 1 H), 3.68-3.75 (m, 1 H), 4.09 (q, $J = 7.2$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.4, 17.0, 17.9, 25.4, 27.4, 35.2, 53.8, 67.6, 67.8, 165.0; IR (KBr, Neat): 2923, 1730, 1636, 1457, 1371, 1257, 1091, 802 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{10}\text{H}_{18}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 187.1329; found 187.1329. $[\alpha]_{\text{D}}^{20}$ +17.0 (c 0.50, CHCl_3), Lit.¹⁸ $[\alpha]_{\text{D}}^{20}$ +16.43 (c 0.30, CHCl_3).

2-((2S,6S)-6-Methyltetrahydro-2H-pyran-2-yl)acetic acid, (+)-Civet (56):

Colorless gum (134 mg, 85%); ^1H NMR (400 MHz, CDCl_3): δ 1.15 (d, $J = 6.0$ Hz, 3 H), 1.17-1.28 (m, 1 H), 1.45-1.63 (m, 4 H), 1.77-1.84 (m, 1 H), 2.45 (dd, $J = 15.6$ and 5.2 Hz, 1 H), 2.55 (dd, $J = 15.6$ and 7.6 Hz, 1 H), 3.46-3.54 (m, 1 H), 3.70-3.78 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.2, 23.4, 31.0, 32.9, 41.5, 74.2, 74.6, 176.1; IR (KBr, Neat): 2929, 2855, 1717, 1449, 1206, 1076, 1097, 860, 799 cm^{-1} . HRMS (APCI) cald. for $\text{C}_8\text{H}_{14}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 159.1016; found 159.1016. $[\alpha]_{\text{D}}^{20} +22.4$ (c 0.25, CHCl_3).

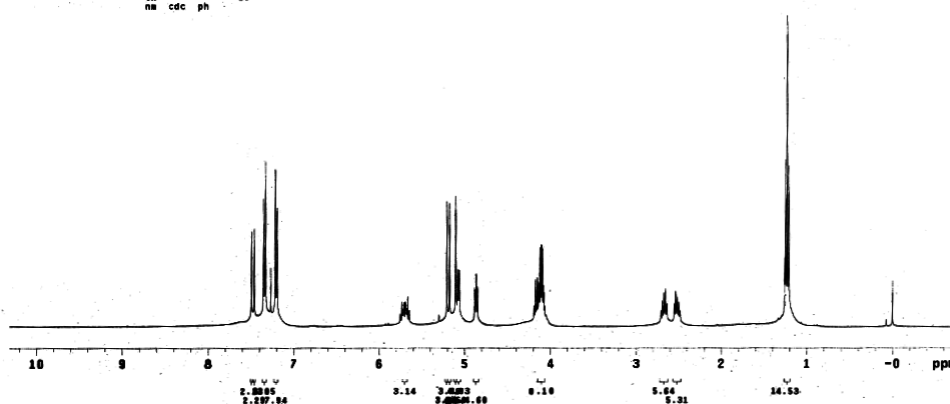
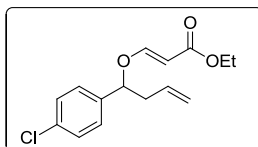


3.9. Representative Spectra:

^1H and ^{13}C NMR of (*E*)-Ethyl 3-((1-(4-chlorophenyl)but-3-en-1-yl)oxy)acrylate, (33b):

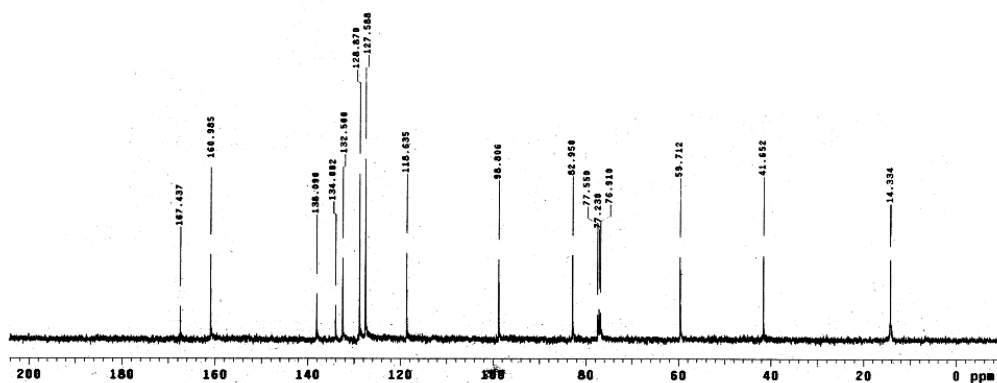
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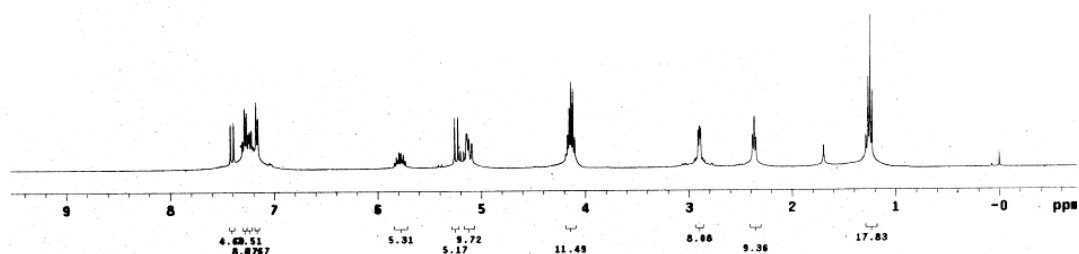
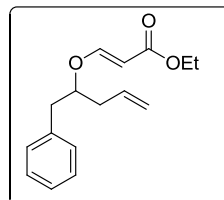


^1H and ^{13}C NMR of (*E*)-Ethyl 3-((1-phenylpent-4-en-2-yl)oxy)acrylate, (33i):

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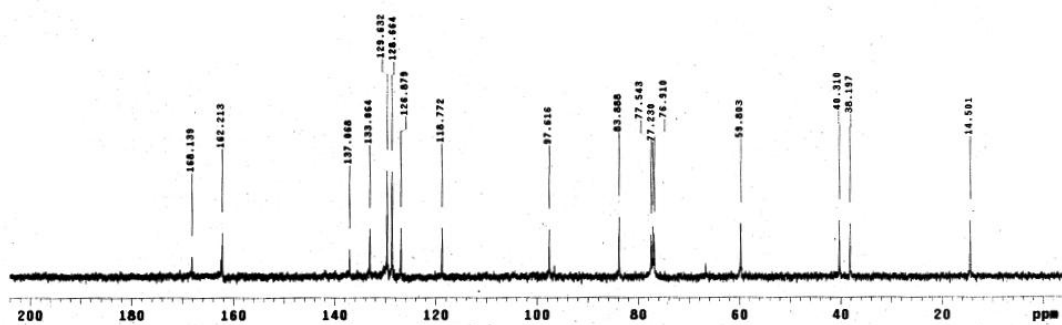
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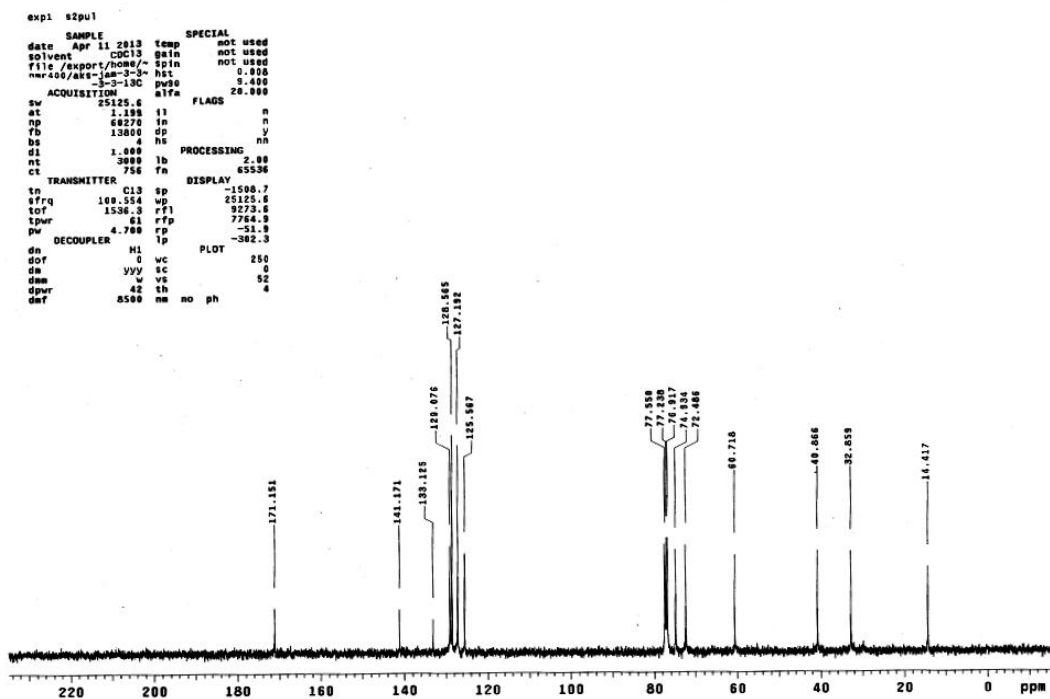
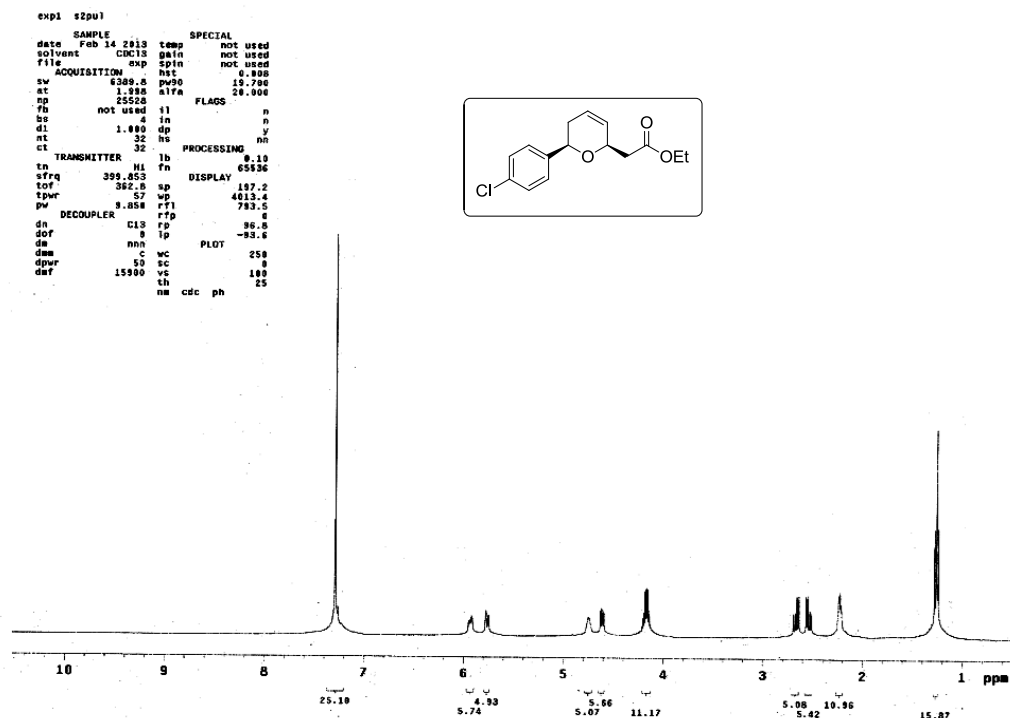
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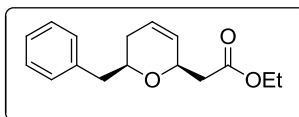
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^1H and ^{13}C NMR of Ethyl-2-(6-(4-chlorophenyl)-5,6-dihydro-2H-pyran-2-yl)acetate, (34b):



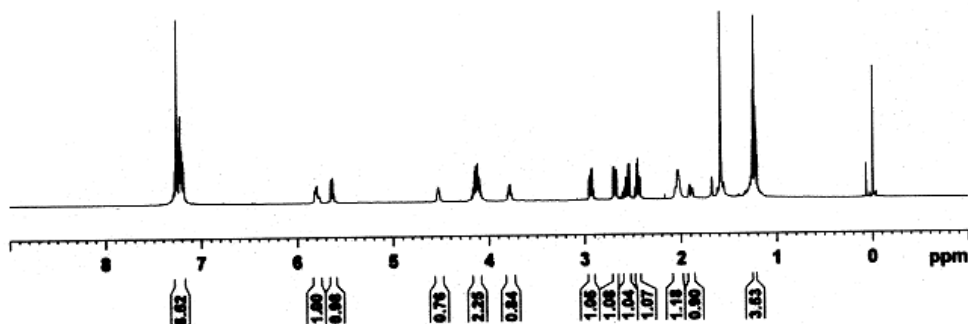
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 PROCNO 1

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 PULPROG zg30
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 Sample Volume 20.888

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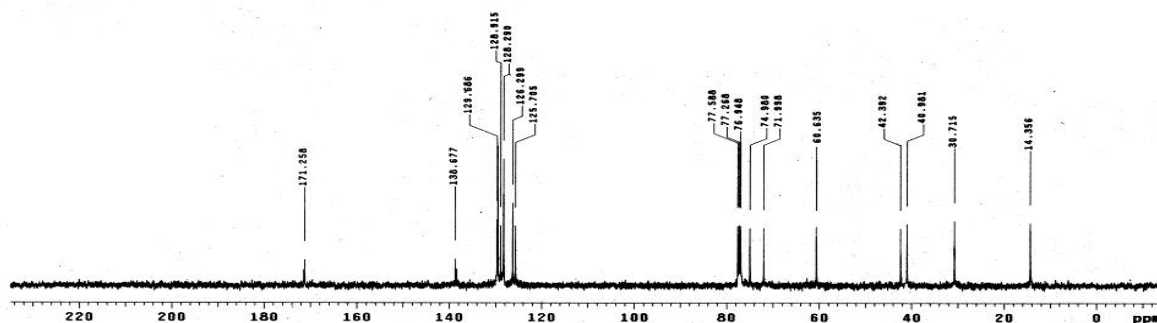
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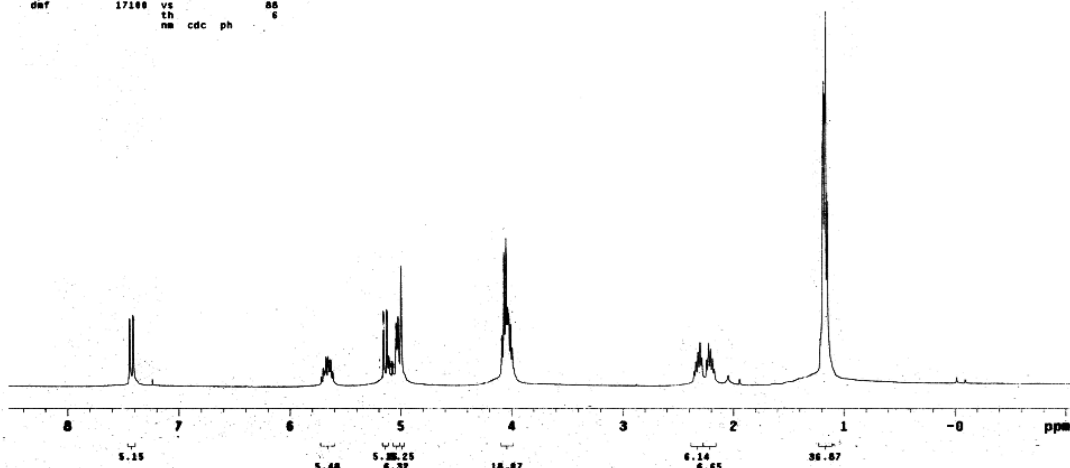
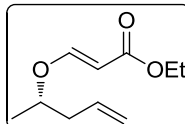


^1H and ^{13}C NMR of (S,E)-Ethyl 3-(pent-4-en-2-yloxy)acrylate, (65):

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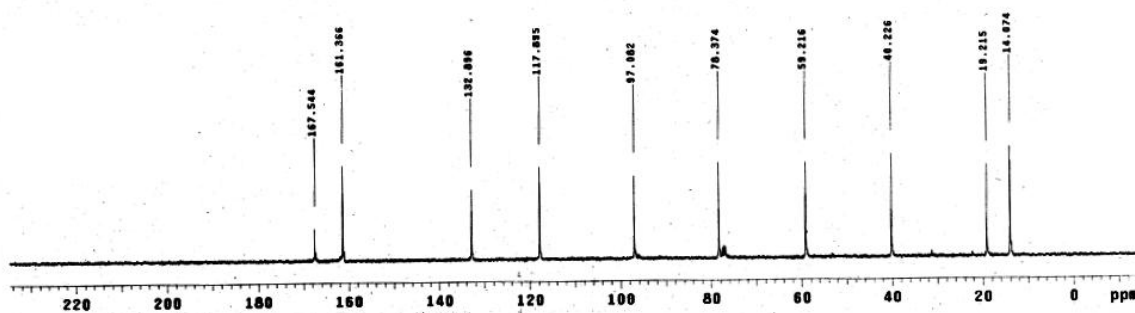
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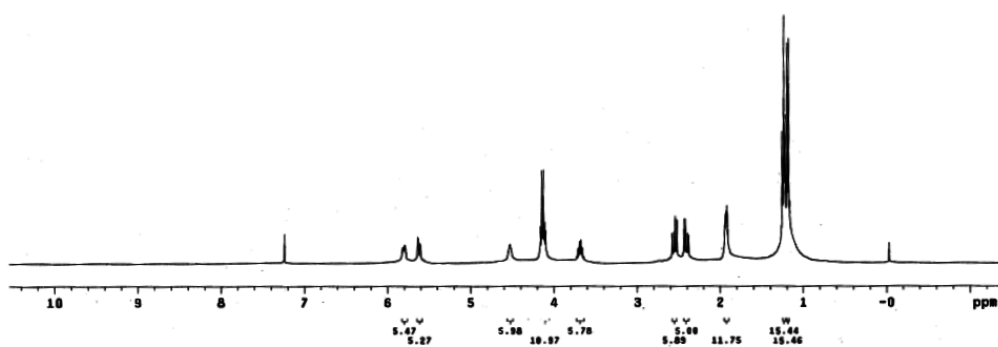
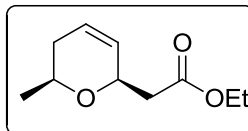
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^1H and ^{13}C NMR of Ethyl 2-(2*R*,6*S*)-6-methyl-5,6-dihydro-2*H*-pyran-2-yl)acetate, (66):

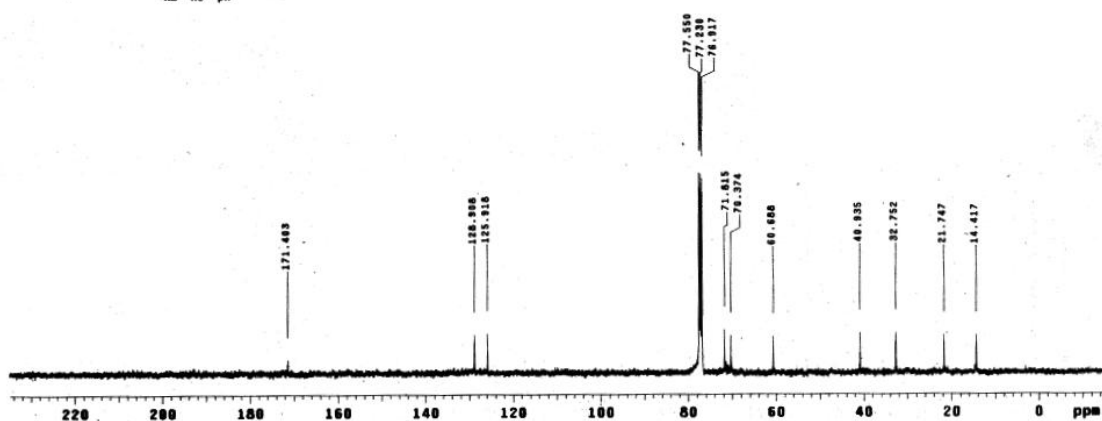
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pw 4.780 rfp 7784.9
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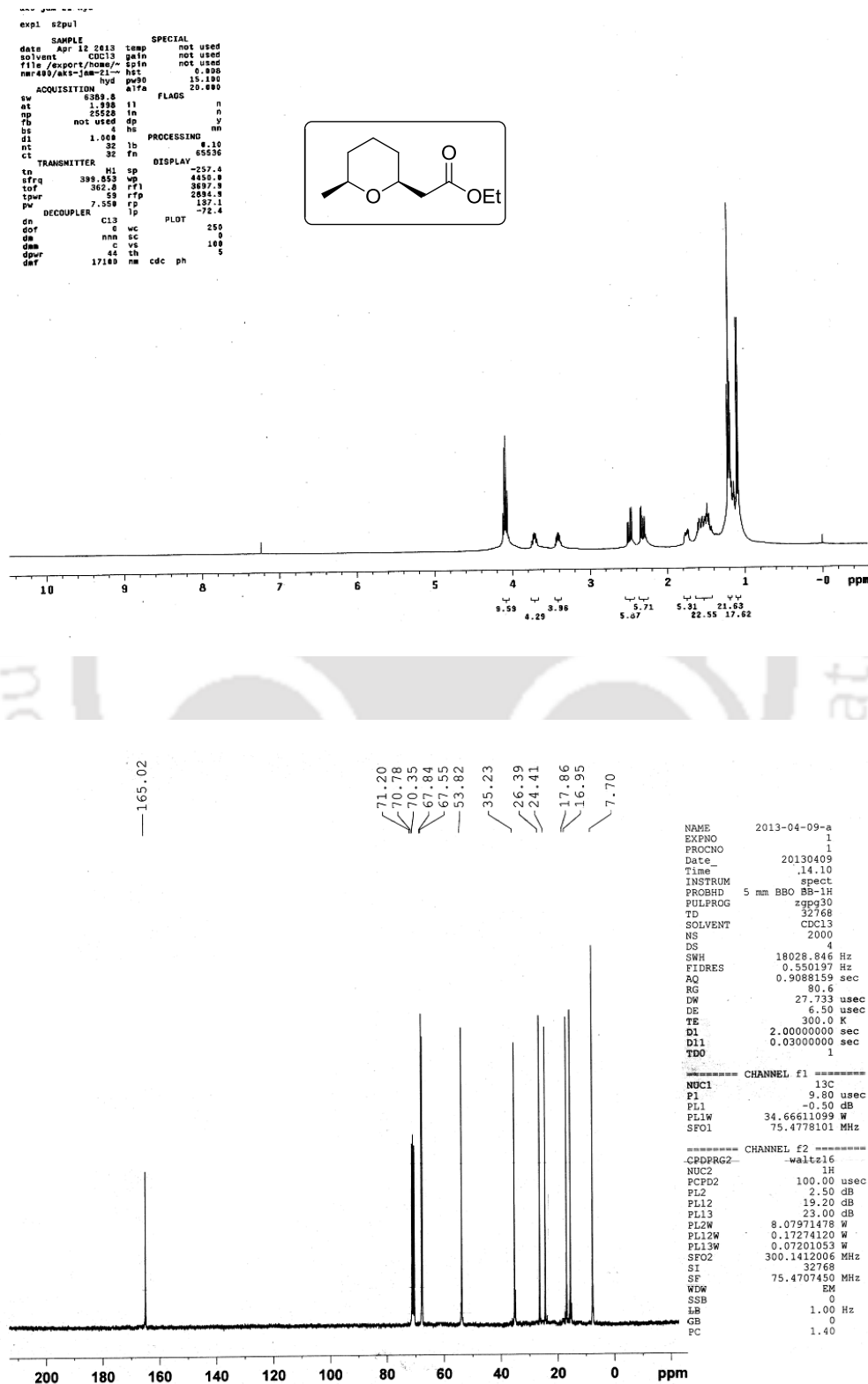


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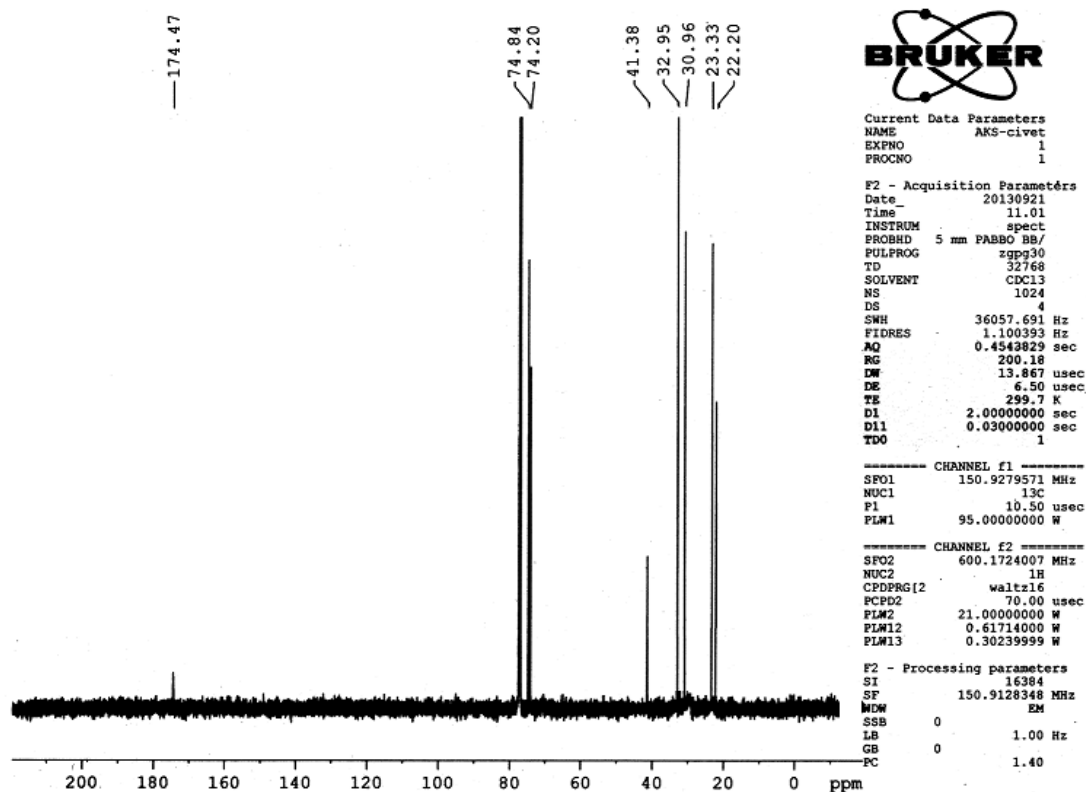
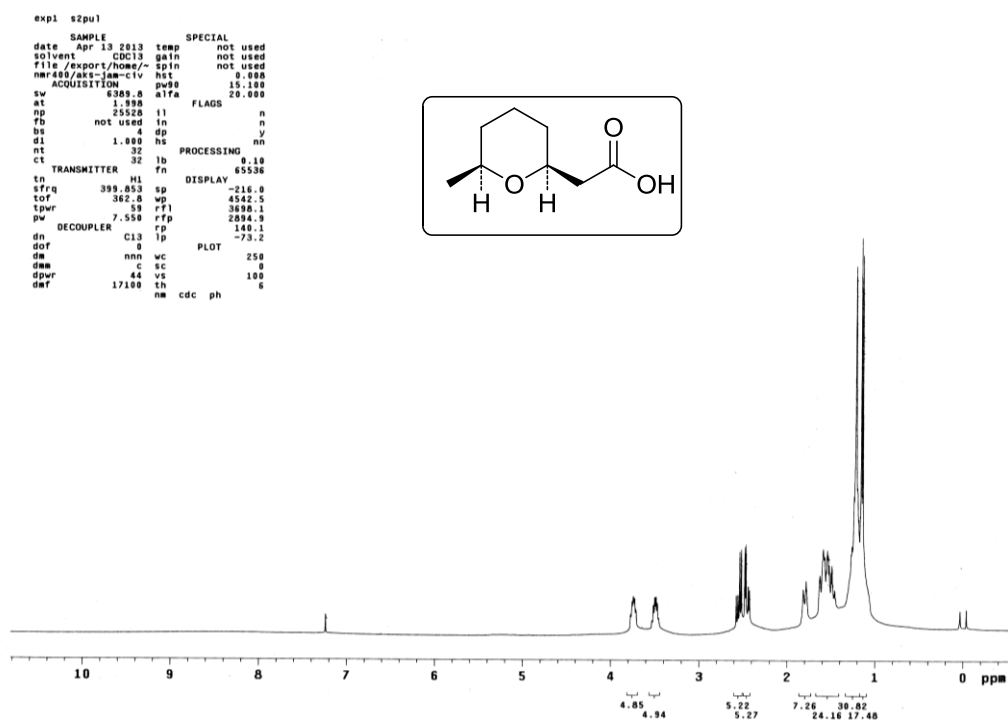
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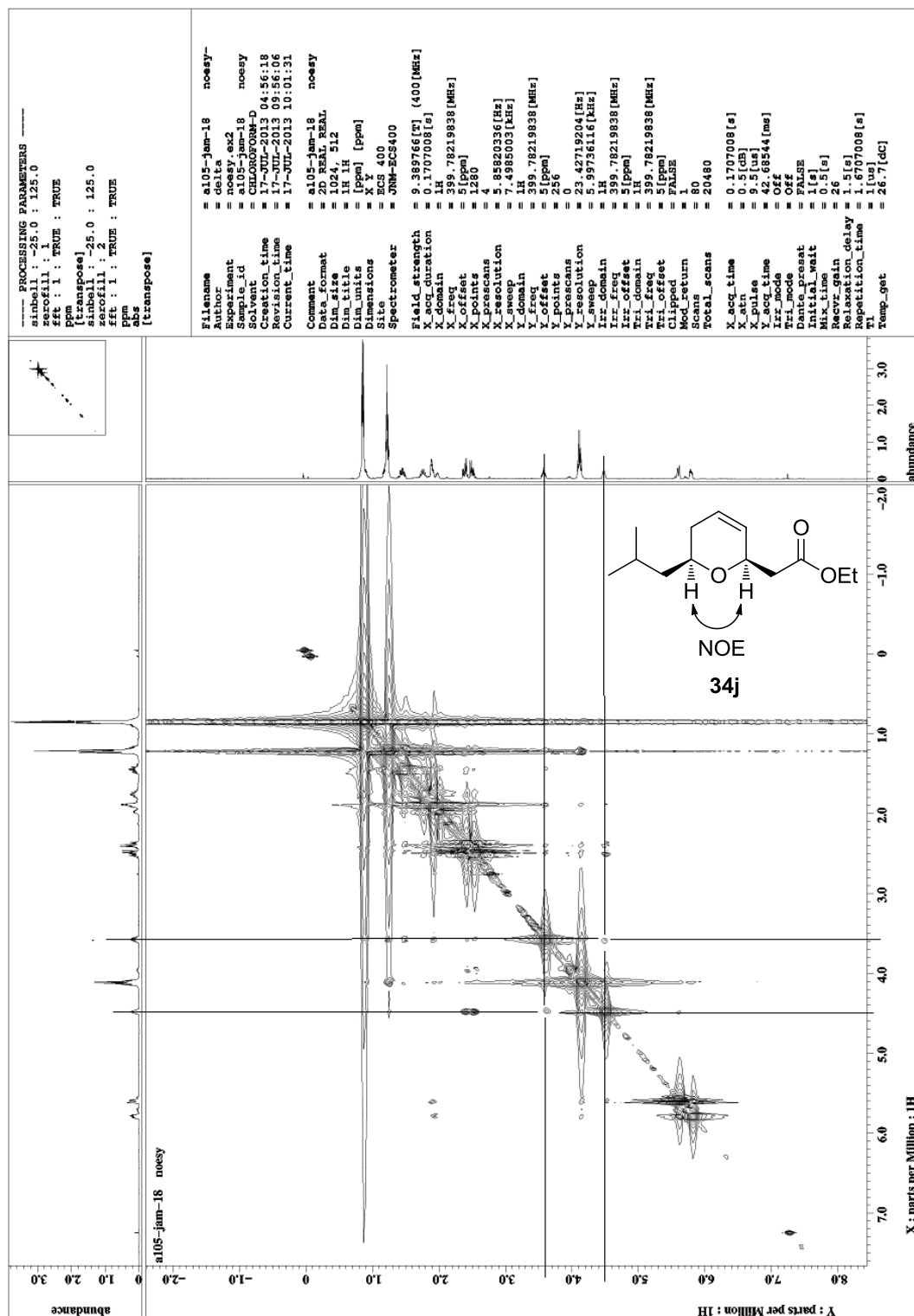
^1H and ^{13}C NMR of Ethyl 2-((2S,6S)-6-methyltetrahydro-2H-pyran-2-yl)acetate, (67):



^1H and ^{13}C NMR of 2-((2S,6S)-6-Methyltetrahydro-2H-pyran-2-yl)acetic acid, (+)-Civet, (56):



NOE spectra of Ethyl 2-(6-isobutyl-5,6-dihydro-2H-pyran-2-yl)acetate, (34j):



3.10. References

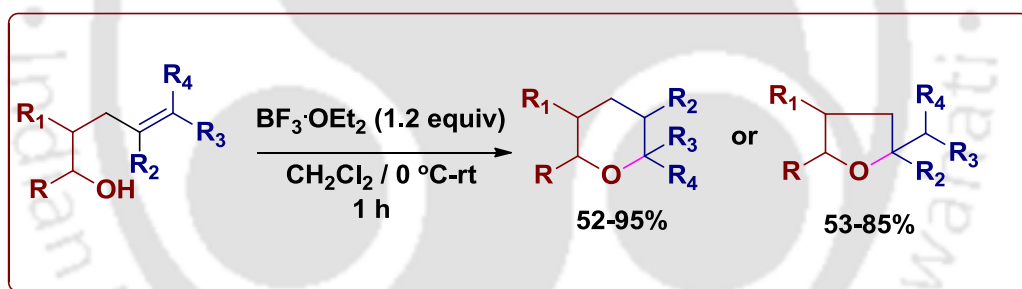
- 1) (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (d) Li, C.-J.; Zhang, W.-C. *Tetrahedron* **2000**, *56*, 2403. (e) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421. (f) Pham, M.; Allatabakhsh, A.; Minehan, T. G. *J. Org. Chem.* **2008**, *73*, 741.
- 2) (a) Paterson, Ian.; Yeung, K.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (b) Marino, S. D.; Festa, C.; D'Auria, M. V.; Cresteil, T.; Cecile Debitus.; Zampella, A. *Mar. Drugs* **2011**, *9*, 1133.
- 3) Chio, F. K.; Warne, J.; Gough, D.; Penny, M.; Green, S.; Coles, S. J.; Hursthouse, M. B.; Jones, P.; Hassall, L.; McGuire, T. M.; Dobbs, A. P. *Tetrahedron* **2011**, *67*, 5107.
- 4) Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071.
- 5) Dziedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678.
- 6) Nussbaumer, C.; Fräter, G. *J. Org. Chem.* **1987**, *52*, 2096.
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- 8) Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 16044.
- 9) Nussbaumer, C.; Fräter, G. *J. Org. Chem.* **1987**, *52*, 2096.
- 10) Ema, T.; Moriya, H.; Kofukuda, T.; Ishida, T.; Maehara, K.; Utaka, M.; Sakai, T. *J. Org. Chem.* **2001**, *66*, 8682.
- 11) Jones, C. R.; Baruah, P. K.; Thompson, A. L.; Scheiner, S. *J. Am. Chem. Soc.* **2012**, *134*, 12064.
- 12) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543.
- 13) Maurer, A.; Thommen, W. *Helv. Chim. Acta.* **1979**, *62*, 44.
- 14) O'Brien, M.; Cahill, S.; Evans, L. A. *Chem. Commun.* **2008**, 5559.
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- 16) (a) Carreno, M. C.; Des, Mazery, R.; Urbano, A.; Colobert, F.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2006**, *61*, 11679. (b) Karlubíková, O.; Babjak, M.; Gracza, T. *Tetrahedron* **2011**, *67*, 4980.

- 17) (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, 4, 577. (b) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, 128, 13640.



CHAPTER 4

Synthesis of substituted tetrahydro-pyran and –furan via intramolecular hydroalkoxylation of alkenols



Asian J. Org. Chem. **2015**, 4, 1281.



Synthesis of Substituted Tetrahydro-pyran and -furan via Intramolecular Hydroalkoxylation of Alkenols

4.1. Importance and Applications

The tetrahydro-pyrans and -furans are important structural features in synthetic organic chemistry as they are core units of many biologically active molecules and natural products.¹ The polyether antibiotics, marine toxins and pheromones belong to such biologically active natural products.² The substituted tetrahydropyran and furan units are found in antibiotics such as FR-901464 **1** and X-206 **2** (Figure 4.1.1).³ The presence of ester group in the tetrahydropyran ring is important because a diverse functionalization can be achieved in the tetrahydropyran molecule.

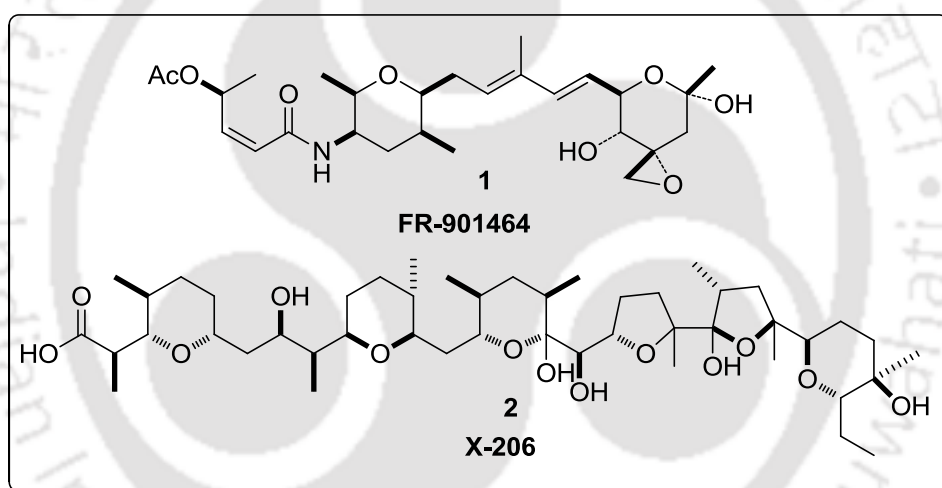


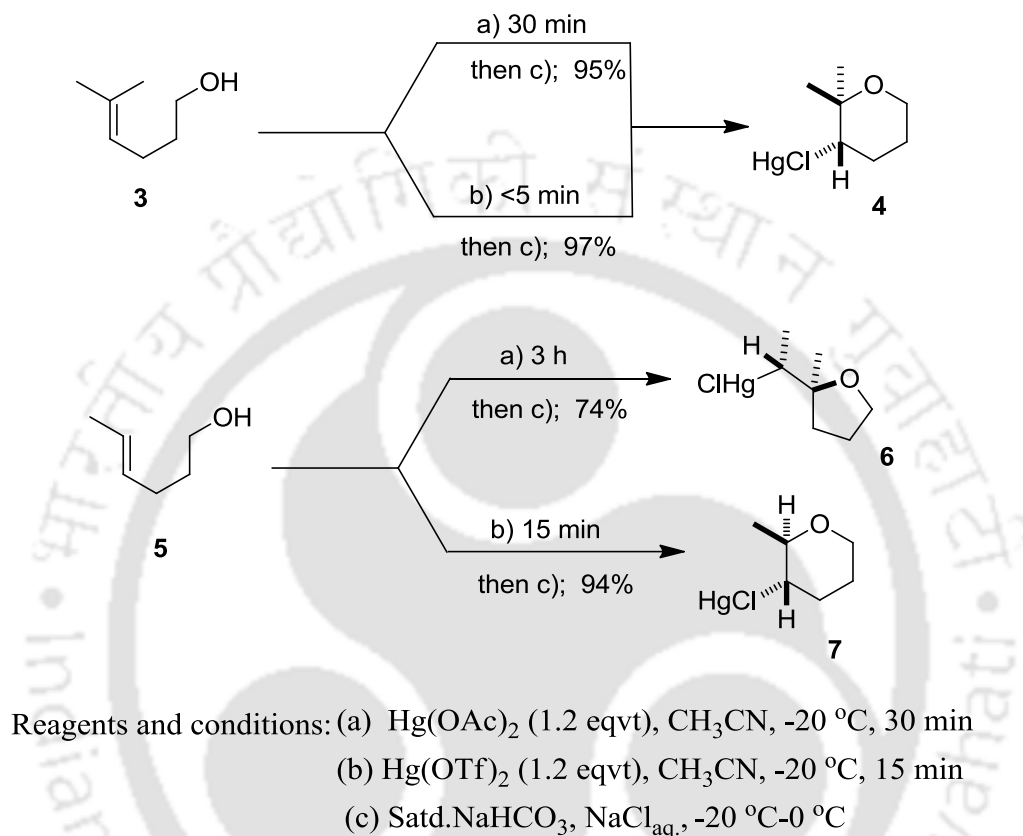
Figure 4.1.1. Some biologically important molecules containing tetrahydropyrans and furans as core units.

4.2. Literature Review on Synthesis of Tetrahydro-pyrans and -furans

Over the years many strategies have been developed for the synthesis of tetrahydro-pyrans and -furans, which include Prins cyclization, hetero-Diels-Alder reactions, manipulations of carbohydrates, intramolecular Michael reactions, oxonium-ene reaction, hydroalkoxylation of allenes, hydroalkoxylation of alkenols and other methods.⁴

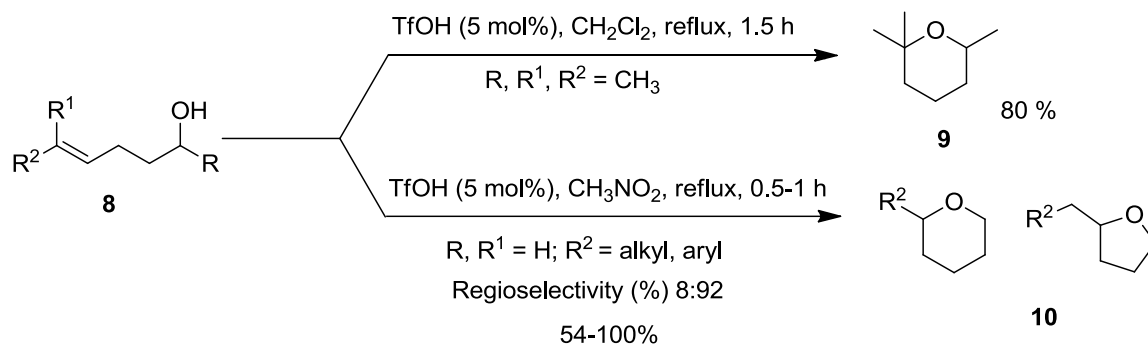
Sugihara and Nishizawa *et al.* described mercuric salts-mediated intramolecular oxymercuration of simple alkenols. They observed that use of mercuric triflate shortened

the reaction time in the Markovnikov-type cyclization of **3**. In addition, the intramolecular oxymercuration of **5** with mercuric triflate afforded **7** selectively *via* the 6-endo mode cyclization, whereas the 5-exo product **6** was produced with mercuric acetate (Scheme 4.2.1).⁵

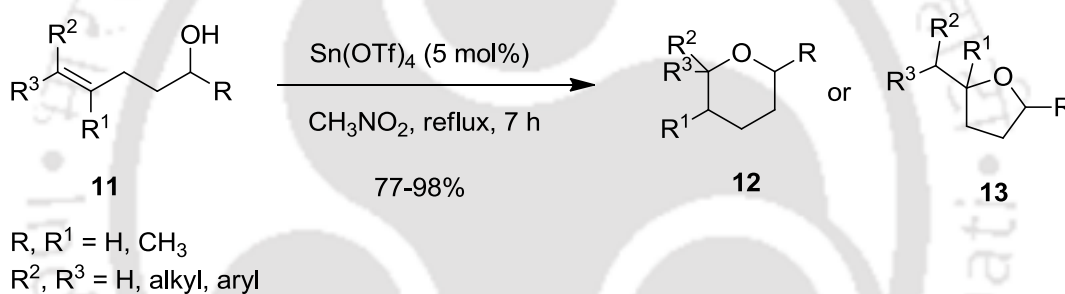


Scheme 4.2.1

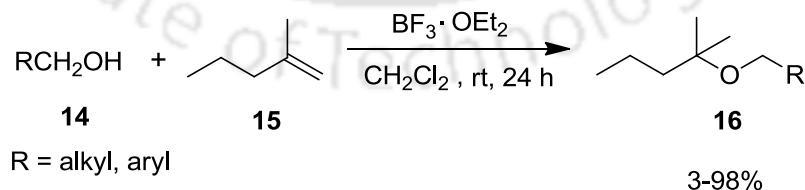
Duñach *et al.* demonstrated a method for the cyclization of alkenols catalyzed by triflic acid. They refluxed 6-methyl-5-hepten-2-ol **8** with catalytic amount of triflic acid (5 mol%) in dichloromethane and got a completely regioselective product **9** in 80%. In case of alkenols having internal disubstituted double bond **8** reaction was refluxed in nitromethane affording a mixture of tetrahydro-furan and -pyran derivatives **10** with tetrahydrofuran as the major isomer with 92% regioselectivity (Scheme 4.2.2).⁶

**Scheme 4.2.2**

Later, the same group showed that the use of stoichiometric amount of Tin(IV) trifluoromethanesulfonate as Lewis acid also effective for the cyclization of alkenols **11** to tetrahydro-pyrans **12** or -furans **13** in good yields (Scheme 4.2.3).⁷

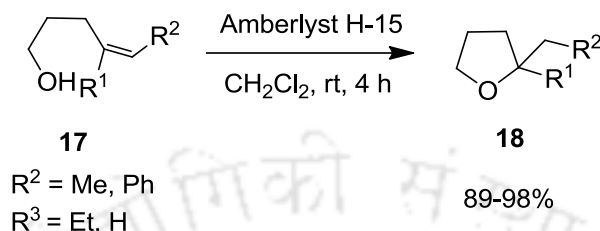
**Scheme 4.2.3**

Figadbre *et al.* described a chemoselective protection of primary hydroxyl groups via intermolecular hydroalkoxylation of alkenes **15** with primary alcohols **14** catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 4.2.4).⁸

**Scheme 4.2.4**

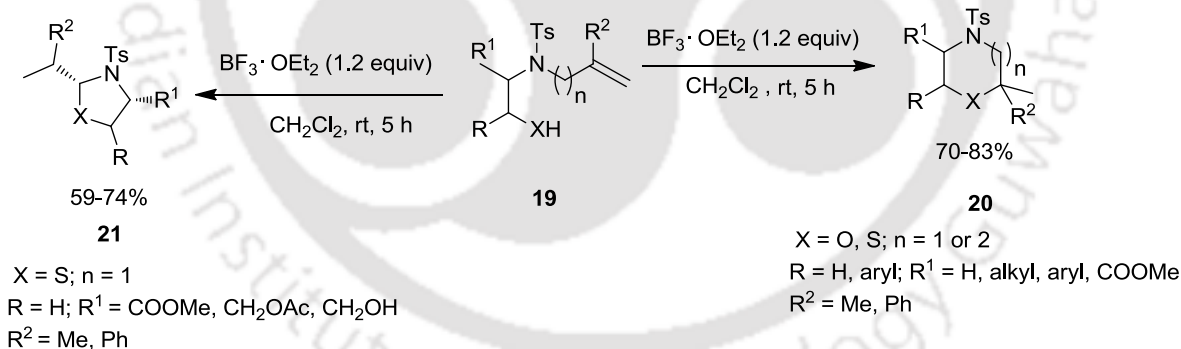
Later, the same group extended their work via intramolecular hydroalkoxylation reaction between non-activated γ,δ -unsaturated primary alcohols with Amberlyst H-15 in CH_2Cl_2

at room temperature (Scheme 4.2.5).⁹ In the case of primary alcohol possessing a trisubstituted double bond **17**, they observed a clean cyclization, in 4 hours at room temperature, leading to the corresponding tetrahydrofurans **18** in high yields. In this case secondary alcohols did not work.



Scheme 4.2.5

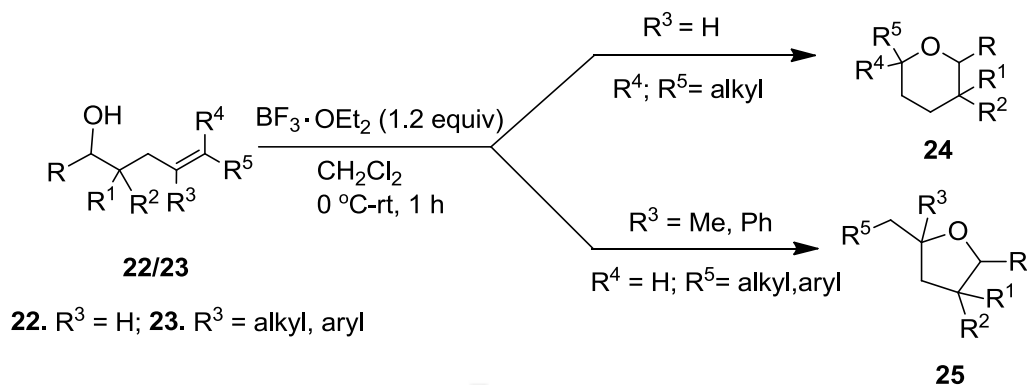
Intramolecular hydroalkoxylation/hydrothioalkoxylation of nitrogen-tethered alkenes and alcohols/thiols **8** mediated by boron trifluoride etherate reported by Saikia *et al.* leading to five-membered thiazolidine, six-membered 1,4-oxazines (morpholines) and tetrahydro-2H-1,4-thiazines (thiomorpholines) and sevenmembered 1,4-oxazepanes in good yields (Scheme 4.2.6).¹⁰



Scheme 4.2.6

4.3. Our Strategy and Objective

Following the above discussed literatures, we synthesized both substituted tetrahydro-furans and pyrans *via* intramolecular hydroalkoxylation of alkenols mediated by boron trifluoride etherate in good yields (Scheme 4.3.1).

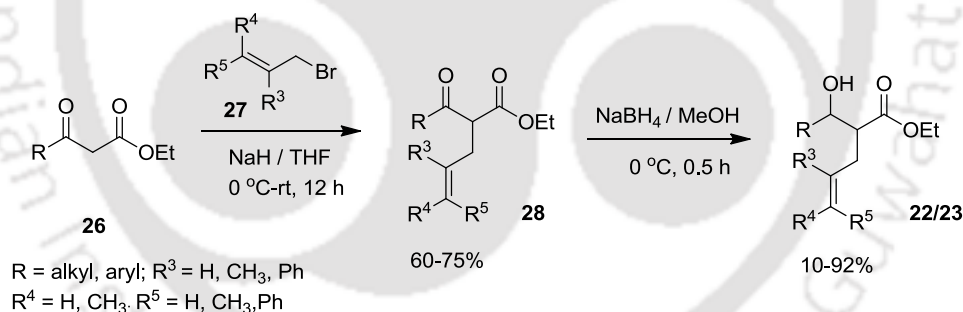


Scheme 4.3.1

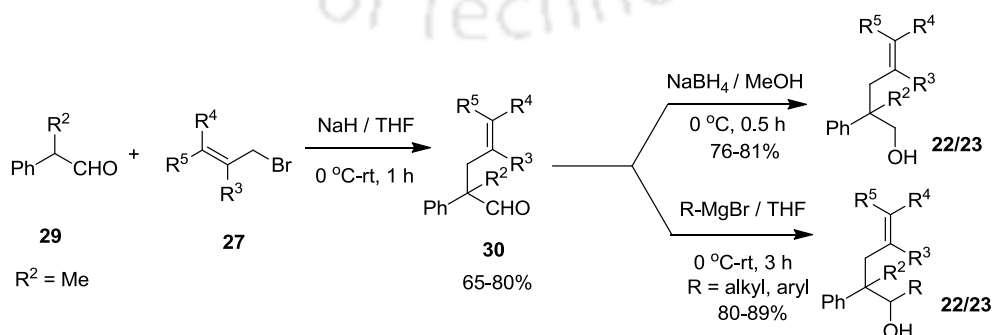
4.4. Results and Discussions

4.4.1. Preparation of alkenols

The starting alkenols **22/23** were prepared *via* allylation of carbonyl compounds **26/29** in presence of sodium hydride followed by sodium borohydride reduction (Scheme 4.4.1.1) and (Scheme 4.4.1.2). Substitution in alkenols were further achieved by Grignard reaction (Scheme 4.4.1.2).¹¹



Scheme 4.4.1.1

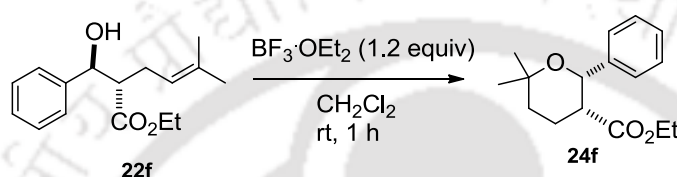


Scheme 4.4.1.2

4.4.2. Optimization studies

First we used alkenol (*S**)-ethyl 2-((*S**)-hydroxy(phenyl)methyl)-5-methylhex-4-enoate **22f** as a model substrate, which was treated with 1.2 equivalents of boron trifluoride etherate in dichloromethane at room temperature for 1h and (2*S**,3*R**)-ethyl 6,6-dimethyl-2-phenyltetrahydro-2*H*-pyran-3-carboxylate **24f** was obtained in 53% yield. The reaction was also performed in different Lewis and Brønsted acidic conditions, and the

Table 4.4.2.1. Optimization of the reaction



Entry	Reagent (equiv.)	Solvent	Time (h)	Yield (%) ^a
1	$\text{BF}_3 \cdot \text{OEt}_2$ (1.2)	CH_2Cl_2	1	53
2	$\text{BF}_3 \cdot \text{OEt}_2$ (0.5)	CH_2Cl_2	12	38
3	$\text{Zn}(\text{OTf})_2$ (0.2)	CH_2Cl_2	24	5
4	$\text{Cu}(\text{OTf})_2$ (0.2)	CH_2Cl_2	24	d
5	$\text{In}(\text{OTf})_3$ (0.2)	CH_2Cl_2	24	30
6	InCl_3 (0.2)	CH_2Cl_2	24	d
7	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.2)	CH_2Cl_2	24	d
8	FeCl_3 (1.2)	CH_2Cl_2	24	d
9	TfOH (1.2)	CH_2Cl_2	24	42
10	$\text{BF}_3 \cdot \text{OEt}_2$ (1.2)	Toluene	12	35
11	$\text{BF}_3 \cdot \text{OEt}_2$ (1.2)	CH_3CN	12	26
12	$\text{BF}_3 \cdot \text{OEt}_2$ (1.2)	THF	12	33

^a Yields refer to isolated yield. The compounds are characterized by IR, ^1H , ^{13}C NMR and comparison with known compounds. ^dNo reaction; starting material was recovered.

results are shown in *Table 4.4.2.1*. The reaction with 0.5 equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ furnished only 38% yield over 12h. Metal triflates such as zinc, copper and indium triflates were

also screened for the reaction. Out of these, only zinc and indium triflates gave the product in 5% and 30% yields, respectively. Similarly, metal salts InCl_3 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and FeCl_3 failed to give the desired product and in this case starting material was recovered in 98% yield. Brønsted acid such as triflic acid (TfOH) gave the corresponding product in 42% yield. The reaction was also screened in other solvents such as toluene, acetonitrile and THF which gave 35%, 26% and 33% yields, respectively. Therefore, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 at room temperature was found to be the best condition for this reaction.

4.4.3. Substrate scope of the reaction

With the optimized condition in hand, the reaction was generalized with various alkenols as exemplified in Table 4.4.3.1. It was found that alkenols, having alkyl substituted olefinic groups **22a-o** gave tetrahydropyrans **24a-o** in good yields (53-95%). The cases where starting materials were used as diastereomeric mixture such as **22a-d**, **22l** and **22o**, gave their corresponding products as diastereomeric products with different ratios and in most of the cases we got two separable diastereomeric products such as in the case of **22a-d** and **22l**. Only in case of substrate **22o**, we got two inseparable diastereomeric products **24o** in a ratio of 3:1 and 82% overall yield. However, substrates using as single diastereomer such as **22e-j** and **22m**, gave their corresponding tetrahydropyran as single diastereomeric products **24e-j** and **24m** in good yields (53-95%). It may be noted that from *cis* isomer as in case of **22e** and **22j**, we got only *trans* products **24e** and **24j** (75% and 95%) respectively, whereas from *trans* isomers as in case of **22f-i**, only *cis* products **24f-i** were obtained (53-72%). One drawback of this reaction is that substrate having methoxy group on the aromatic ring **22p** did not work.

4.4.4. Stereochemistry of the tetrahydropyrans

The structure and relative stereochemistry of tetrahydropyrans were determined from ^1H NMR and *J*-coupling analysis of compound **24e** and **24f**. In the ^1H NMR spectrum of **24e** the axial proton at C-2 (H_{2a}) shows a doublet with coupling constant 10.8 Hz at δ 4.72 ppm which indicates that the proton is in *trans* with the proton at C-3 whereas in case of **24f** the axial proton at C-2 (H_{2a}) shows a doublet with coupling constant 3.6 Hz at δ 4.91 ppm which indicates that the proton is coupled with neighboring equatorial proton at C-3 (H_{3e}) (Figure 4.4.4.1).

Table 4.4.3.1. Synthesis of tetrahydropyrans

$ \begin{array}{c} \text{R}^1 \text{---} \text{C}(\text{R}^2) \text{---} \text{CH}(\text{R}^3) \text{---} \text{CH}(\text{R}^4) \text{---} \text{OH} \\ \text{R} \\ \mathbf{22} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2 / \text{rt}]{\text{BF}_3 \cdot \text{OEt}_2 (1.2 \text{ equiv}), 1 \text{ h}} \begin{array}{c} \text{R}^1 \text{---} \text{C}(\text{R}^2) \text{---} \text{CH}(\text{R}^3) \text{---} \text{CH}(\text{R}^4) \text{---} \text{O} \\ \text{R} \\ \mathbf{24} \end{array} $			
Entry	Substrate 22	Product 24	Yield (%) ^a
a			24a/24a' :31/48
b			24b/24b' :25/52
c			24c/24c' :25/52
d			24d/24d' :3/76
e			75
f			53
g			56
h			58
i			72
j			95

Continue....

Entry	Substrate 22	Product 24	Yield (%) ^a
k			80
l			24l/24l' :35/56
m			60
n			63
o			82 ^b
p			0

^aYields refer to isolated yield. ^bInseparable diastereomer with a ratio of 3:1. The compounds are characterized by IR, NMR and mass spectrometry.

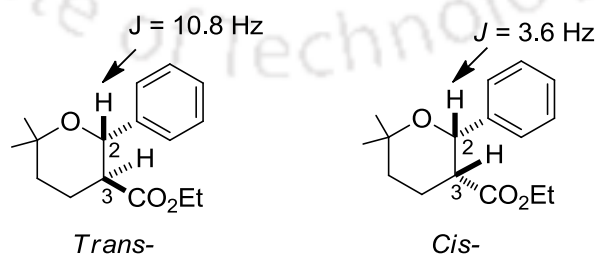


Figure 4.4.4.1. Coupling constants of *trans* and *cis* isomers of ethyl 6,6-dimethyl-2-phenyltetrahydro-2H-pyran-3-carboxylate

The stereochemistry of tetrahydropyran was further confirmed by X-ray crystallographic analysis of **24f** (Figure 4.4.4.2).

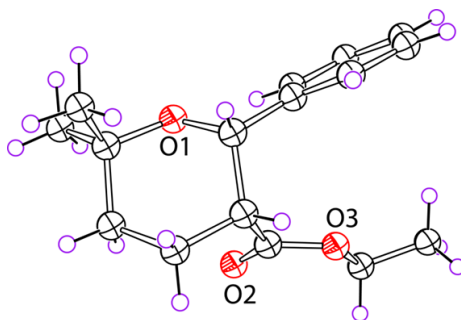


Figure 4.4.4.2. ORTEP diagram of (2S*,3R*)-Ethyl 6,6-dimethyl-2-phenyltetrahydro-2H-pyran-3-carboxylate

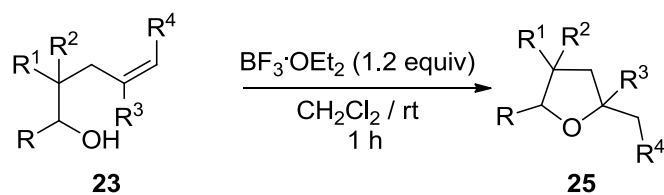
4.4.5. Synthesis of tetrahydrofurans

After a successful study on tetrahydropyrans, the scope of the methodology has been extended to a series of substituted tetrahydrofuran rings (Table 4.4.5.1). In this case, alkenol using as diastereomeric mixture **23q** gave two inseparable mixture of diastereomers **25q** in a ratio of 5:3 in 85% yield. However, alkenols having bulky phenyl group attached to double bond **23r** and **23s** are used as single diastereomer and provided their corresponding tetrahydrofurans as single diastereomer **25r** and **25s** in 58% and 53% yields, respectively. On the other hand, the primary alkenol **23t** gave two diastereomeric mixture **25t** in a ratio of 3:2 with overall 80% yield. It was observed that starting materials having different ratio of diastereomers gave different diastereomeric products in a different ratio. This might be due to the unequal reactivity of the two diastereomers.

4.4.6. Stereochemistry of the tetrahydrofurans

The relative stereochemistry of tetrahydrofuran was determined from NOESY experiment of **25r** (Figure 4.4.6.1). We observed a strong NOE between H2a and C-5 methyl hydrogens (1.58 ppm) and between H3a and C-5 methyl hydrogens (1.58 ppm), which confirms that all hydrogens at C-2, C-3 and C-5 methyl group are *cis* to each other.

Table 4.4.5.1. Synthesis of tetrahydrofurans



Entry	Substrate 23	Product 25	Yield (%) ^a
q			85 ^b
r			58
s			53
t			80 ^b

^aYield refers to isolated yield. ^bInseparable diastereomers with a ratio of 5:3 and 3:2, respectively. R is determined from ¹H NMR.

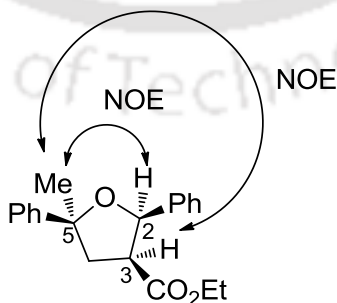
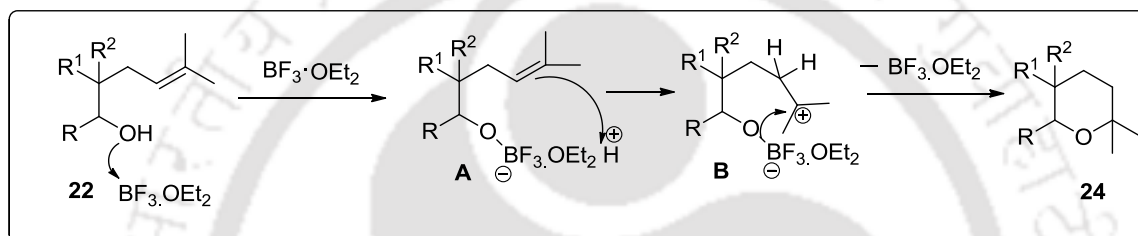


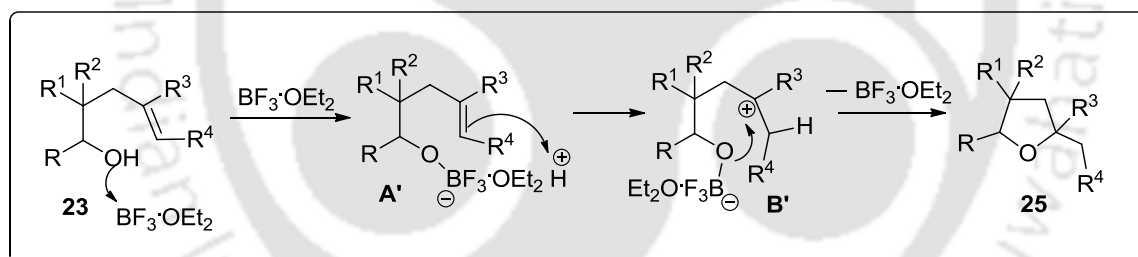
Figure 4.4.6.1. NOE of (2R*,3S*,5S*)-Ethyl 5-methyl-2,5-diphenyltetrahydrofuran-3-carboxylate

4.4.7. Mechanism of the reaction

Based on previous literature⁹, we explained the mechanism of the reaction as follows. The 5,5-disubstituted alkenol **22** reacts with boron trifluoride etherate to form intermediate **A**, an ion pair, of which the proton adds to the C-4 of the double bond via Markovnikov's rule to give more stable carbocation **B** (Scheme 4.4.7.1). The carbocation **B** is then attacked by alkoxide ion to form tetrahydropyran **24**. On the other hand, in case of terminal and 4,5-disubstituted alkenol **23**, proton adds to the C-5 of the double bond to generate most stable carbocation **B'** (Scheme 4.4.7.2), which is then attacked by alkoxide ion to give tetrahydrofuran **25**.



Scheme 4.4.7.1. Mechanism of the reaction



Scheme 4.4.7.2. Mechanism of the reaction

4.5. Conclusion

In conclusion, we have developed a mild and efficient method for the synthesis of substituted tetrahydro-pyrans and -furans via intramolecular cyclization reaction of alkenols in good yields. The reaction is highly atom economic and compatible to functional groups such as ester, chloro, and nitro groups.

4.6. Experimental Section

4.6.1. Instrumentation and characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in CDCl₃ with tetramethylsilane as the internal standard for ¹H (600 MHz and 400 MHz) or ¹³C (150 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic MoK α radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2 . All non-hydrogen atomic positions were located in different Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

4.6.2. General procedure for the synthesis of alkenols 22a-p/ 23q-t:

A solution of carbonyl compounds **26/29** (1.0 equiv) in dry THF was added to a stirred solution of sodium hydride (1.2 equiv) in dry THF under an inert atmosphere at 0 °C. After complete evolution of hydrogen gas, substituted allylbromide **27** (1.0 equiv) in dry THF was added drop wise for 10 min, and the reaction was stirred at room temperature. After completion of the reaction, brine solution was added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. The organic layer was further washed with brine solution. The organic layer was dried over Na₂SO₄ and concentrated in a rotary evaporator. The crude product thus obtained was subjected to column chromatography

over silica gel to give the corresponding product **28/30**. To an ice cooled solution of **28/30** (1.0 equiv) in methanol was added sodium borohydride (1.2 equiv) pinch wise and stirred as such for half an hour. After completion of the reaction, 1N HCl was added to make the solution acidic (p^H 6 or below) and the reaction mixture was extracted with ethyl acetate. The organic layer was further washed with brine solution. The organic layer was dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude product was subjected to column chromatography over silica gel to give the corresponding product **22/23**.

In some cases, substitution in alkenols were achieved by Grignard reaction. To an ice cooled solution of aldehyde **30** (1.0 equiv) in THF was added Grignard reagent (1.2 equiv) and stirred at room temperature for 3h. The reaction mixture was quenched with saturated aqueous NH_4Cl , and the mixture was extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give **22/23**.

4.6.3. General procedure for the synthesis of tetrahydropyrans and furans **24a-p/25q-t**:

To a solution of hydroxyalkenols **22/23** (1.0 equiv) in dry dichloromethane under N_2 atmosphere at 0 °C was added borontrifluoride etherate (1.2 equiv). The reaction mixture was stirred at room temperature for 1h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (49:1) as eluents. After completion of the reaction, the product was extracted with ethyl acetate and then washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude products, which were purified by column chromatography over silica gel to give the title compound **24/25**.

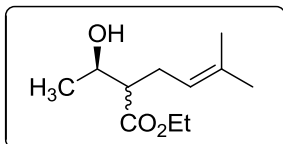
4.6.4. Synthesis of (2*S**,3*S**)-ethyl 2,6,6-trimethyltetrahydro-2*H*-pyran-3-carboxylate **24a** and (2*S**,3*R**)-ethyl 2,6,6-trimethyltetrahydro-2*H*-pyran-3-carboxylate **24a'**:

To a solution of ethyl 2-(*S*)-1-hydroxyethyl)-5-methylhex-4-enoate **22a** (100 mg, 0.5 mmol) in dry dichloromethane (1 mL) under N_2 atmosphere at 0 °C was added $BF_3 \cdot OEt_2$ (0.05mL, 0.6 mmol). The reaction mixture was stirred at room temperature for 1h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (49:1) as

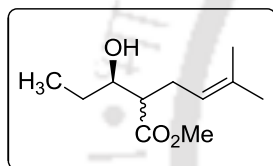
eluents. After completion of the reaction, the product was extracted with ethyl acetate (10 mL) and then washed with brine (5mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude products, which were purified by column chromatography over silica gel to give the title compound as colorless oil. **24a**: R_f (hexane/EtOAc 49:1) 0.60; yield 62 mg, 31%; **24a'**: R_f (hexane/EtOAc 49:1) 0.50; yield 96 mg, 48%.



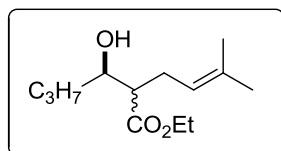
4.7. Charactererization Data

Ethyl 2-(1-hydroxyethyl)-5-methylhex-4-enoate (diastereomeric mixture, 2:3, (22a):

Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 156 mg, 78%; ^1H NMR (400 MHz, CDCl_3): δ 1.19-1.29 (m, 6 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 2.29-2.47 (m, 3 H), 2.51 (brs 0.5 H), 2.69 (brs, 0.5 H), 3.86-3.96 (m, 0.5 H), 3.98-4.06 (m, 0.5 H), 4.08-4.24 (m, 2 H), 5.04-5.14 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1(2C), 17.5(2C), 20.5, 21.1, 25.6(2C), 26.7, 27.7, 53.0, 53.1, 60.2, 60.3, 67.8, 67.9, 120.5, 121.1, 133.3, 133.6, 174.7, 175.0; IR (Neat): 3441, 2972, 2929, 1732, 1640, 1182, 1155 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{11}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 201.1485; found 201.1480.

Methyl 2-(1-hydroxypropyl)-5-methylhex-4-enoate (diastereomeric mixture, 1:1, (22b):

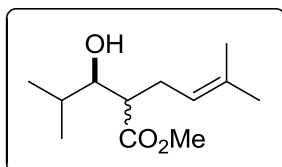
Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 166 mg, 78%; ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, $J = 7.6$ Hz, 3 H), 1.25 (t, $J = 7.2$ Hz, 1.5 H), 1.26 (t, $J = 7.2$ Hz, 1.5 H), 1.45-1.54 (m, 2 H), 1.61 (s, 1.5 H), 1.62 (s, 1.5 H), 1.69 (s, 3 H), 2.28-2.50 (m, 3 H), 2.67 (brs, 1 H), 3.56-3.64 (m, 0.5 H), 3.70-3.78 (m, 0.5 H), 4.08-4.22 (m, 2 H), 5.04-5.16 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 10.2, 10.3, 14.3(2C), 17.8(2C), 25.8, 26.1, 27.4(2C), 28.3, 28.6, 50.7, 51.2, 60.5(2C), 73.3, 73.4, 120.7, 121.3, 133.6, 134.1, 175.3, 175.5; IR (Neat): 3456, 2968, 2932, 1731, 1642, 1183, 1159 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{11}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ requires 201.1485; found 201.1483.

Ethyl 2-(1-hydroxybutyl)-5-methylhex-4-enoate (diastereomeric mixture, 2:1, (22c):

Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 205 mg, 90%; ^1H NMR (400 MHz, CDCl_3): δ 0.88-0.92 (m, 3 H), 1.21-1.26 (m, 3 H), 1.33-1.54 (m, 4 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 2.24-2.58 (m, 3 H), 3.61-3.69 (m, 1 H, major), 3.78-3.83 (m, 1 H, minor), 4.07-4.18 (m, 2 H), 5.04-5.10 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 19.7, 30.8, 34.4, 37.6, 53.5, 60.8, 74.6, 76.3, 127.2, 128.5, 128.6, 140.1, 171.2; IR (KBr,

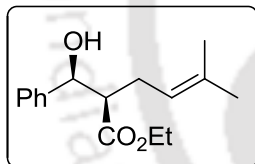
neat) 3528, 2924, 2855, 1598, 1496, 1330, 1159, 1020, 898, 701 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 229.1798, found 229.1794.

Methyl 2-(1-hydroxy-2-methylpropyl)-5-methylhex-4-enoate (diastereomeric mixture), 10:1, (22d):



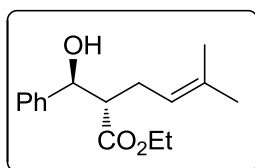
Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 205 mg, 90%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (d, $J = 6.8$ Hz, 3 H), 0.94 (d, $J = 6.8$ Hz, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 2.28-2.43 (m, 2 H), 2.54-2.62 (m, 2 H), 3.27-3.35 (m, 1 H, major), 3.50-3.54 (m, 1 H, minor), 3.65 (s, 3 H, minor), 3.67 (s, 3 H, major), 5.02-5.06 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 17.4, 17.8, 17.9, 19.7, 25.9, 26.0, 28.8, 29.9, 31.2, 32.4, 48.4, 49.1, 51.7, 76.9, 77.6, 120.6, 121.3, 133.5, 134.5, 176.1, 176.3; IR (KBr, neat) 3523, 2967, 2876, 1718, 1639, 1440, 1259, 1002, 770 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 215.1642, found 215.1640.

(R^*)-Ethyl 2-((S^*)-hydroxy(phenyl)methyl)-5-methylhex-4-enoate (22e):



Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 104 mg, 40%; ^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.2$ Hz, 3 H), 1.54 (s, 3 H), 1.64 (s, 3 H), 2.29 (ddd, $J = 14.4, 8.8$ and 5.8 Hz, 1 H), 2.46 (ddd, $J = 14.4, 8.8$ and 5.6 Hz, 1 H), 2.72 (ddd, $J = 10.4, 5.6$ and 4.4 Hz, 1 H), 3.03 (brs, 1H), 4.02 (q, $J = 7.2$ Hz, 2 H), 4.95 (d, $J = 5.6$ Hz, 1 H), 5.04 (t, $J = 6.8$ Hz, 1 H), 7.24-7.39 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 17.8, 25.9, 26.1, 53.3, 60.7, 74.2, 121.1, 126.4, 127.8, 128.4, 134.0, 141.7, 175.0; IR (Neat): 3460, 2979, 2930, 1728, 1453, 1375, 1180, 1026, 767, 701 cm^{-1} . HRMS (APCI) cald. for $\text{C}_{16}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$)⁺ requires 263.1642; found 263.1642.

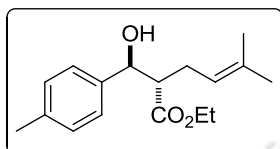
(S^*)-Ethyl 2-((S^*)-hydroxy(phenyl)methyl)-5-methylhex-4-enoate (22f):



Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 115 mg, 44%; ^1H NMR (400 MHz, CDCl_3): δ 1.18 (t, $J = 7.2$ Hz, 3 H), 1.50 (s, 3 H), 1.65 (s, 3 H), 2.05 (ddd, $J = 13.2, 7.6$ and 5.6 Hz, 1 H), 2.25 (ddd, $J = 14.8, 8.0$ and 6.8 Hz, 1 H), 2.75 (ddd, $J = 12.8, 8.8, 5.2$ Hz, 1 H), 3.16 (d, $J = 5.2$ Hz, 1 H), 4.11 (q, $J = 7.2$ Hz, 2 H), 4.80 (dd, $J = 6.4$ and 4.4

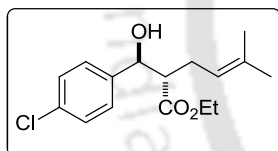
Hz, 1 H), 5.03 (dt, $J = 6.8$ and 1.2 Hz, 1 H), 7.26-7.37 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 17.8, 25.9, 28.4, 53.3, 60.7, 74.8, 120.2, 126.6, 128.0, 128.6, 134.3, 142.2, 175.2; IR (Neat): 3461, 2978, 2929, 1729, 1452, 1377, 1180, 1037, 766, 702 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_3$ ($\text{M}+1$) $^+$ requires 263.1642; found 263.1640.

(S*)-Ethyl 2-((S*)-hydroxy(*p*-tolyl)methyl)-5-methylhex-4-enoate (22g):



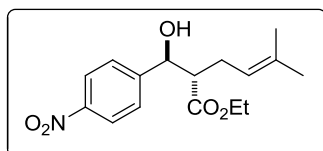
Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 82 mg, 30%; ^1H NMR (400 MHz, CDCl_3): δ 1.20 (t, $J = 7.2$ Hz, 3 H), 1.50 (s, 3 H), 1.65 (s, 3 H), 2.04-2.10 (m, 1 H), 2.21-2.29 (m, 1 H), 2.34 (s, 3 H), 2.72-2.78 (m, 1 H), 2.96 (brs, 1 H), 4.07-4.19 (m, 2 H), 4.77 (d, $J = 6.0$ Hz, 1 H), 5.03 (t, $J = 8.0$ Hz, 2 H), 7.22 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 17.8, 21.3, 25.9, 28.4, 53.3, 60.7, 74.8, 120.3, 126.5, 129.2, 134.2, 137.6, 139.2, 175.2; IR (KBr, neat) 3447, 2986, 1728, 1637, 1275, 1177, 1055, 768 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 277.1798, found 277.1788.

(S*)-Ethyl 2-((S*)-(4-chlorophenyl)(hydroxy)methyl)-5-methylhex-4-enoate (22h):



Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 59 mg, 20%; ^1H NMR (400 MHz, CDCl_3): δ 1.18 (t, $J = 7.2$ Hz, 3 H), 1.52 (s, 3 H), 1.66 (s, 3 H), 2.11-2.18 (m, 1 H), 2.22-2.30 (m, 1 H), 2.68-2.73 (m, 1 H), 3.23 (brs, 1 H), 4.05-4.16 (m, 2 H), 4.78 (d, $J = 6.0$ Hz, 1 H), 5.02 (t, $J = 7.2$ Hz, 1 H), 7.25 (d, $J = 8.8$ Hz, 2 H), 7.31 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 17.9, 26.0, 28.4, 53.0, 60.9, 74.0, 120.0, 127.9, 128.8, 133.7, 134.8, 140.9, 175.1; IR (KBr, neat) 3447, 2986, 1728, 1637, 1275, 1118, 1055, 768 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{22}\text{ClO}_3$ ($\text{M} + \text{H}$) $^+$ 297.1252, found 297.1245.

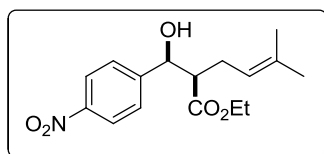
(S*)-Ethyl 2-((S*)-hydroxy(4-nitrophenyl)methyl)-5-methylhex-4-enoate (22i):



Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 246 mg, 80%; ^1H NMR (600 MHz, CDCl_3): δ 1.14 (t, $J = 7.2$ Hz, 3 H), 1.56 (s, 3 H), 1.68 (s, 3 H), 2.28-2.34 (m, 2 H), 3.75 (q, $J = 6.6$ Hz, 1 H), 3.69 (d, $J = 5.4$ Hz, 1 H), 4.04-4.18 (m, 2 H), 4.91 (t, $J = 7.2$ Hz, 1 H), 5.05 (t, $J = 6.6$ Hz, 1 H), 7.50 (d, $J = 8.4$ Hz, 2 H), 8.19 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 18.0, 26.0, 28.4, 52.5, 61.2, 73.4,

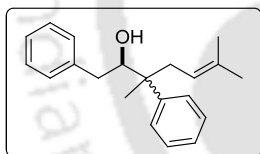
119.7, 123.8, 127.2, 135.4, 147.6, 150.0, 174.9; IR (KBr, neat) 3445, 2985, 1717, 1637, 1524, 1461, 1348, 1276, 1259, 913, 768 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ ($\text{M} + \text{H}$)⁺ 308.1492, found 308.1479.

(R*)-ethyl 2-((S*)-hydroxy(4-nitrophenyl)methyl)-5-methylhex-4-enoate (22j):



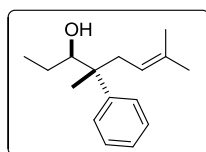
Colorless oil; R_f (hexane/EtOAc 9:1) 0.48; yield 31 mg, 10%; ^1H NMR (600 MHz, CDCl_3): δ 1.18 (t, $J = 7.2$ Hz, 3 H), 1.50 (s, 3 H), 1.69 (s, 3 H), 2.15-2.18 (m, 1 H), 2.41-2.48 (m, 1 H), 2.71-2.74 (m, 1 H), 3.48 (brs, 1 H), 4.06-4.13 (m, 2 H), 4.98 (t, $J = 7.2$ Hz, 1 H), 5.12 (d, $J = 3.6$ Hz, 1 H), 7.54 (d, $J = 8.4$ Hz, 2 H), 8.20 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.3, 18.0, 26.0, 28.4, 52.5, 61.1, 73.4, 119.7, 123.8, 127.3, 135.4, 147.6, 150.0, 174.8; IR (KBr, neat) 3444, 2987, 1714, 1640, 1524, 1461, 1348, 1276, 1260, 913, 767 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ ($\text{M} + \text{H}$)⁺ 308.1492, found 308.1487.

3,6-Dimethyl-1,3-diphenylhept-5-en-2-ol (diastereomeric mixture, 2:3, (22l):



Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 255 mg, 87%; ^1H NMR (600 MHz, CDCl_3): δ 1.46 (s, 3 H), 1.65 (s, 3 H), 1.67 (s, 3 H), 2.38-2.45 (m, 1 H), 2.55-2.62 (m, 2 H), 2.66-2.70 (m, 1 H), 2.90 (brs, 1 H, major), 2.93 (brs, 1 H, minor), 3.91 (dd, $J = 9.0$ and 1.2 Hz, 1 H, minor), 4.03 (d, $J = 9.6$ Hz, 1 H, major), 4.95 (t, $J = 7.2$ Hz, 1 H, major), 5.01 (t, $J = 4.2$ Hz, 1 H, minor), 7.14-7.17 (m, 1 H), 7.23-7.27 (m, 3 H), 7.30-7.35 (m, 3 H), 7.41-7.46 (m, 2 H), 7.50-7.52 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 17.8, 18.2, 18.3, 20.2, 26.1, 36.6, 37.8, 38.1, 38.6, 38.8, 46.5, 46.6, 80.4, 80.5, 120.8, 126.1, 126.2, 126.3, 126.4, 127.1, 127.8, 128.3, 128.4, 128.5, 128.6, 129.3, 129.4, 133.6, 140.1, 140.2, 141.9, 144.9, 145.5; IR (KBr, neat) 3475, 2968, 1638, 1449, 1275, 1110, 1068, 747 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{27}\text{O}$ ($\text{M} + \text{H}$)⁺ 295.2056, found 295.2045.

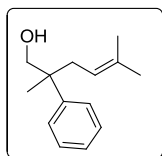
(3R*,4R*)-4,7-Dimethyl-4-phenyloct-6-en-3-ol (22m):



Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 185 mg, 80%; ^1H NMR (600 MHz, CDCl_3): δ 0.86 (t, $J = 7.2$ Hz, 3 H), 1.06-1.14 (m, 1 H), 1.21 (s, 3 H), 1.23-1.28 (m, 1 H), 1.58 (s, 6 H), 2.46 (d, $J = 7.2$ Hz,

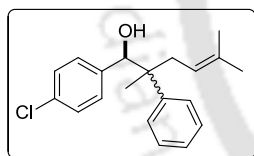
2 H), 3.54 (d, $J = 10.2$ Hz, 1 H), 4.83 (dd, $J = 7.2$ and 1.2 Hz, 1 H), 7.13-7.18 (m, 1 H), 7.27-7.34 (m, 4 H); ^{13}C NMR (150 MHz, CDCl_3): δ 11.2, 17.6, 18.0, 24.3, 25.5, 36.4, 46.1, 80.8, 120.3, 126.7, 127.0, 127.6, 132.8, 144.9; IR (KBr, neat) 3475, 2968, 1638, 1448, 1275, 1110, 1069, 748 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{25}\text{O}$ ($\text{M} + \text{H}$) $^+$ 233.1900, found 233.1898.

2,5-Dimethyl-2-phenylhex-4-en-1-ol (22n):



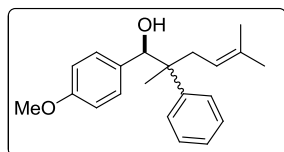
Colorless oil; R_f (hexane/EtOAc 9:1) 0.60; yield 165 mg, 81%; ^1H NMR (600 MHz, CDCl_3): δ 1.32 (s, 3 H), 1.59 (s, 3 H), 1.65 (s, 3 H), 2.35 (dd, $J = 14.4$ and 7.8 Hz, 1 H), 2.43 (dd, $J = 14.4$ and 6.6 Hz, 1 H), 3.60 (d, $J = 10.8$ Hz, 1 H), 3.75 (d, $J = 10.8$ Hz, 1 H), 4.96 (t, $J = 7.2$ Hz, 1 H), 7.23 (t, $J = 7.2$ Hz, 1 H), 7.33-7.38 (m, 4 H); ^{13}C NMR (150 MHz, CDCl_3): δ 18.2, 22.1, 26.1, 37.0, 44.1, 72.0, 120.2, 126.3, 127.0, 128.6, 133.9, 145.2; IR (KBr, neat) 3417, 2929, 1622, 1494, 1376, 1154, 1029, 775 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{21}\text{O}$ ($\text{M} + \text{H}$) $^+$ 205.1587, found 205.1590.

1-(4-Chlorophenyl)-2,5-dimethyl-2-phenylhex-4-en-1-ol (diastereomeric mixture,

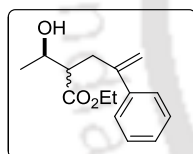


1:1, 22o):

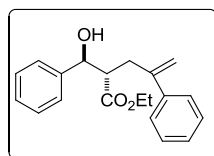
Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 279 mg, 89%; ^1H NMR (600 MHz, CDCl_3): δ 1.17 (s, 1.5 H), 1.28 (s, 1.5 H), 1.50 (s, 1.5 H), 1.55 (s, 1.5 H), 1.57 (s, 1.5 H), 1.59 (s, 1.5 H), 1.80-1.84 (m, 0.5 H), 2.09 (dd, $J = 6.0$ and 3.0 Hz, 0.5 H), 2.23 (dd, $J = 14.4$ and 8.4 Hz, 0.5 H), 2.48 (dd, $J = 15.0$ and 8.4 , 0.5 H), 2.62 (brs, 1 H), 4.71 (dd, $J = 6.6$ and 3.0 Hz, 1 H), 4.78 (t, $J = 6.0$ Hz, 0.5 H), 4.86 (t, $J = 6.6$ Hz, 0.5 H), 6.81 (d, $J = 8.4$ Hz, 1 H), 6.99 (d, $J = 8.4$ Hz, 1 H), 7.10 (d, $J = 8.4$ Hz, 1 H), 7.13-7.21 (m, 2 H), 7.23-7.29 (m, 2 H), 7.31 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 17.7, 17.8, 18.5, 18.8, 25.4, 34.8, 36.2, 46.5, 46.6, 80.8, 81.1, 119.4, 120.0, 125.8, 126.0, 126.8, 127.1, 127.4, 127.5, 127.7, 128.5, 128.9, 132.4, 132.7, 133.0, 133.2, 138.8, 139.1, 142.9, 143.1; IR (KBr, neat) 3475, 2984, 2880, 1639, 1492, 1276, 1260, 1091, 1033, 909, 746 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{24}\text{ClO}$ ($\text{M} + \text{H}$) $^+$ 315.1510, found 315.1512.

1-(4-Methoxyphenyl)-2,5-dimethyl-2-phenylhex-4-en-1-ol (diastereomeric mixture,**1:1, 22p):**Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 255 mg, 85%; ^1H NMR (600 MHz, CDCl_3): δ 1.19 (s, 3 H), 1.28 (s, 3 H), 1.51 (s, 3 H), 1.55 (s, 3 H), 1.58 (s, 3 H), 1.61 (s, 3 H), 1.69 (brs, 1

H), 1.88 (brs, 1 H), 2.24 (dd, $J = 14.4$ and 8.4 Hz, 1 H), 2.46 (dd, $J = 14.4$ and 7.8 Hz, 1 H), 2.66 (t, $J = 15.6$ Hz, 2 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.71 (s, 1 H), 4.73 (s, 1 H), 4.78 (t, $J = 6.6$ Hz, 1 H), 4.96 (t, $J = 6.0$ Hz, 1 H), 6.70 (d, $J = 8.4$ Hz, 2 H), 6.78 (d, $J = 7.8$ Hz, 2 H), 6.85 (d, $J = 8.4$ Hz, 2 H), 7.00 (d, $J = 7.8$ Hz, 2 H), 7.21 (d, $J = 8.4$ Hz, 3 H), 7.24-7.29 (m, 3 H), 7.31-7.36 (m, 4 H); ^{13}C NMR (150 MHz, CDCl_3): δ 18.4, 19.1, 20.1, 26.1, 35.1, 37.1, 47.4, 55.3, 55.4, 81.8, 82.2, 112.8, 113.0, 120.4, 120.9, 126.3, 126.5, 128.0, 128.1, 128.2, 128.3, 128.9, 129.3, 133.2, 144.1, 158.9; IR (KBr, neat) 3444, 3007, 1615, 1461, 1275, 1260, 1036, 913, 747 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{27}\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 311.2006, found 311.2001.

Ethyl 2-(1-hydroxyethyl)-4-phenylpent-4-enoate (diastereomeric mixture, 7:3, (23q):Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 213 mg, 86%; ^1H NMR (400 MHz, CDCl_3): δ 1.19-1.26 (m, 6 H), 2.44 (d, $J = 4.4$, 1 H, minor), 2.48-2.57 (m, 1 H), 2.60 (d, $J = 8.4$, 1 H, major), 2.83-2.96 (m, 2 H), 3.88-3.93 (m, 1 H, major), 3.97-4.02 (m, 1 H, minor), 4.05-4.12

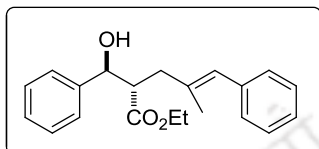
(m, 2 H), 5.11 (s, 1 H, minor), 5.15 (s, 1 H, major), 5.28 (s, 1 H, minor), 5.31 (s, 1 H, major), 7.28-7.39 (m, 5 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 20.5, 21.9, 33.7, 35.3, 51.1, 51.3, 60.7, 68.2, 68.3, 114.5, 115.0, 126.4, 127.8, 128.5, 140.6, 145.8, 146.3, 175.0; IR (KBr, neat) 3452, 2980, 1732, 1628, 1445, 1377, 1176, 1029, 903, 779, 709 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 249.1485, found 249.1487.

(S*)-Ethyl 2-((S*)-hydroxy(phenyl)methyl)-4-phenylpent-4-enoate (23r):Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 254 mg, 92%; ^1H NMR (400 MHz, CDCl_3): δ 1.12 (t, $J = 7.2$ Hz, 3 H), 2.63 (d, $J = 14.4$ and 4.2 Hz, 1 H), 2.81 (dd, $J = 13.8$ and 2.4 Hz, 1 H), 2.86-2.88 (m, 1 H), 3.03 (d, $J = 6.0$ Hz, 1 H), 4.01-4.05 (m, 2 H), 4.83 (t, $J = 6.0$ Hz, 1

H), 5.10 (s, 1 H), 5.27 (s, 1 H), 7.21 (d, $J = 7.2$ Hz, 2 H), 7.25-7.32 (m, 5 H), 7.33-7.36

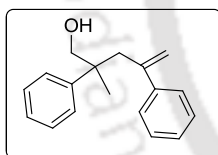
(m, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 35.8, 51.8, 60.8, 75.1, 115.1, 126.4, 126.5, 127.8, 128.2, 128.5, 128.7, 140.2, 142.0, 145.4, 174.9; IR (KBr, neat) 3424, 2967, 2826, 1728, 1446, 1379, 1179, 1024, 956, 764 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 311.1642, found 311.1645.

(E)-Ethyl 2-(hydroxy(phenyl)methyl)-4-methyl-5-phenylpent-4-enoate (23s):



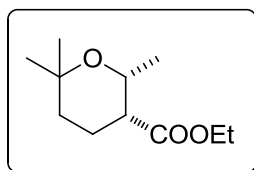
Pale yellow oil; R_f (hexane/EtOAc 9:1) 0.60; yield 213 mg, 66%; ^1H NMR (600 MHz, CDCl_3): δ 1.15 (t, $J = 7.2$ Hz, 3 H), 1.80 (s, 3 H), 2.18 (dd, $J = 13.2$ and 4.8 Hz, 1 H), 2.50 (dd, $J = 12.6$ and 11.4 Hz, 1 H), 3.04-3.08 (m, 1 H), 4.08-4.12 (m, 3 H), 4.85 (d, $J = 7.2$ Hz, 1 H), 6.28 (s, 1 H), 7.15-7.19 (m, 2 H), 7.27-7.32 (m, 4 H), 7.35-7.39 (m, 4 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 17.7, 41.3, 52.0, 60.9, 75.5, 126.4, 126.5, 127.7, 128.2, 128.8, 128.9, 135.2, 138.1, 142.2, 174.9; IR (KBr, neat) 3459, 2934, 2917, 1730, 1447, 1380, 1167, 1028, 950, 724 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 325.1798, found 325.1793.

2-Methyl-2,4-diphenylpent-4-en-1-ol (23t):



Colorless oil; R_f (hexane/EtOAc 97:1) 0.60; yield 192 mg, 76%; ^1H NMR (600 MHz, CDCl_3): δ 1.23 (s, 3 H), 2.87 (d, $J = 13.8$ Hz, 1 H), 2.92 (d, $J = 13.8$ Hz, 1 H), 3.51 (d, $J = 10.8$ Hz, 1 H), 3.70 (d, $J = 11.4$ Hz, 1 H), 4.85 (s, 1 H), 5.17 (s, 1 H), 7.16 (t, $J = 7.2$ Hz, 1 H), 7.19-7.28 (m, 7 H), 7.31 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 22.4, 44.2, 44.3, 71.1, 117.6, 126.4, 126.6, 126.9, 127.3, 128.4, 128.5, 143.4, 145.1, 146.0; IR (KBr, neat) 3417, 2928, 2875, 1622, 1494, 1445, 1376, 1154, 1030, 903, 775 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{21}\text{O}$ ($\text{M} + \text{H}$) $^+$ 253.1587, found 253.1588

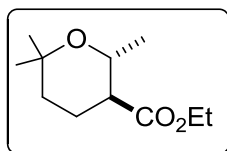
(2S*,3S*)-ethyl 2,6,6-trimethyltetrahydro-2H-pyran-3-carboxylate (24a) :



Colorless oil; R_f (hexane/ EtOAc 49:1) 0.60; yield 62 mg, 31%; ^1H NMR (400 MHz, CDCl_3): δ 1.19 (s, 3 H), 1.20 (d, $J = 5.6$ Hz, 3 H), 1.22 (s, 3 H), 1.24 (t, $J = 7.2$ Hz, 3 H), 1.79-2.00 (m, 4 H), 2.36-2.42 (m, 1 H), 3.86-3.92 (m, 1 H), 4.07-4.17 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 14.5, 20.4, 22.4, 24.8, 31.6, 31.7, 43.5, 60.1, 66.5, 72.2, 173.1;

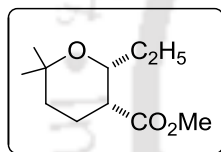
IR (KBr, neat) 2987, 1735, 1632, 1460, 1380, 1275, 1131, 1079, 750 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 201.1485 found 201.1480.

(2S*,3R*)-ethyl 2,6,6-trimethyltetrahydro-2H-pyran-3-carboxylate (24a') :



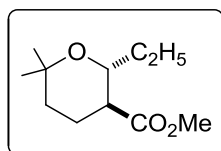
Colorless oil; R_f (hexane/EtOAc 49:1) 0.50; yield 96 mg, 48%; ^1H NMR (400 MHz, CDCl_3): δ 1.11 (d, $J = 6.4$ Hz, 3 H), 1.20 (s, 3 H), 1.23 (s, 3 H), 1.23 (t, $J = 7.2$ Hz, 3 H), 1.40 (ddd, $J = 12.8$, 5.2 and 4.8 Hz, 1 H), 1.50 (dt, $J = 13.2$, and 7.2 Hz, 1 H), 1.77-1.92 (m, 2 H), 2.05 (ddd, $J = 11.2$, 6.4 and 5.2 Hz, 1 H), 3.76-3.84 (m, 1 H), 4.11 (q, $J = 7.2$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 14.4, 20.9, 22.1, 24.3, 31.7, 35.2, 49.7, 60.5, 67.5, 71.9, 174.8; IR (KBr, neat) 2987, 1731, 1466, 1276, 1259, 1163, 1029, 770 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 201.1485 found 201.1481.

(2S*,3S*)-Methyl 2-ethyl-6,6-dimethyltetrahydro-2H-pyran-3-carboxylate (24b):

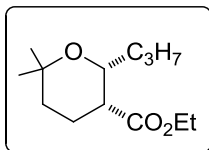


Colorless oil; R_f (hexane/EtOAc 49:1) 0.60; yield 50 mg, 25%; ^1H NMR (400 MHz, CDCl_3): δ 0.88 (t, $J = 7.2$ Hz, 3 H), 1.18 (s, 3 H), 1.20 (s, 3 H), 1.29-1.53 (m, 4 H), 1.76-1.93 (2 H), 2.13-2.21 (m, 1 H), 3.54-3.60 (m, 1 H), 3.64 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3): 9.8, 22.1, 24.5, 27.7, 31.6, 35.2, 47.7, 51.7, 71.6, 72.3, 175.4; IR (KBr, neat) 2975, 2875, 1738, 1638, 1459, 1275, 1260, 1131, 1079, 750 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 201.1485 found 201.1479.

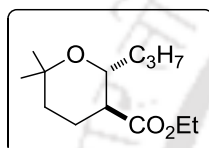
(2S*,3R*)-Methyl 2-ethyl-6,6-dimethyltetrahydro-2H-pyran-3-carboxylate (24b'):



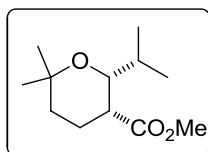
Colorless oil; R_f (hexane/EtOAc 49:1) 0.50; yield 104 mg, 52%; ^1H NMR (400 MHz, CDCl_3): δ 0.94 (t, $J = 7.2$ Hz, 3 H), 1.21 (s, 3 H), 1.25 (s, 3 H), 1.31 (dt, $J = 12.8$ and 3.6 Hz, 1 H), 1.49-1.57 (m, 2 H), 1.89 (dt, $J = 14.0$ and 6.6 Hz, 1 H), 1.92-2.05 (m, 2 H), 2.49-2.52 (m, 1 H), 3.55-3.60 (m, 1 H), 3.67 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3): 10.8, 22.2, 23.0, 27.3, 31.6, 31.8, 42.0, 51.2, 72.1, 72.4, 173.6; IR (KBr, neat) 2974, 2876, 1739, 1454, 1380, 1165, 1079, 970, 773 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 201.1485 found 201.1477.

(2S*,3S*)-Ethyl 6,6-dimethyl-2-propyltetrahydro-2H-pyran-3-carboxylate (24c):

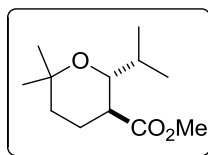
Colorless oil; R_f (hexane/EtOAc 49:1) 0.60; yield 57 mg, 25%; ^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, $J = 7.2$ Hz, 3 H), 1.20 (s, 3 H), 1.22 (s, 3 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.30-1.45 (m, 4 H), 1.49-1.56 (m, 2 H), 1.81-1.95 (m, 2 H), 2.12-2.20 (m, 1 H), 3.65-3.71 (m, 1 H), 4.13 (q, $J = 7.2$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 14.1, 14.5, 18.7, 22.1, 24.6, 31.7, 35.2, 36.9, 48.3, 60.4, 70.8, 71.6, 175.0; IR (KBr, neat) 2989, 1730, 1636, 1461, 1275, 1219, 1129, 1067, 767 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 229.1798 found 229.1794.

(2S*,3R*)-Ethyl 6,6-dimethyl-2-propyltetrahydro-2H-pyran-3-carboxylate (24c'):

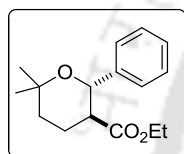
Colorless oil; R_f (hexane/EtOAc 49:1) 0.50; yield 118 mg, 52%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (t, $J = 7.2$ Hz, 3 H), 1.20 (s, 3 H), 1.24 (s, 3 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.30-1.37 (m, 1 H), 1.41-1.1.51 (m, 2 H), 1.52-1.57 (m, 2 H), 1.82-1.90 (dt, $J = 14.4$ and 4.4 Hz, 1 H), 1.92-2.04 (m, 2 H), 2.43-2.45 (m, 1 H), 3.65-3.71 (m, 1 H), 4.08-4.20 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 14.1, 14.5, 19.2, 22.2, 23.0, 31.7, 31.8, 36.4, 42.3, 59.9, 70.5, 72.0, 173.1; IR (KBr, neat) 2997, 1728, 1637, 1461, 1275, 1220, 1164, 1026, 768 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 229.1798 found 229.1796.

(2S*,3S*)-Methyl-2-isopropyl-6,6-dimethyltetrahydro-2H-pyran-3-carboxylate (24d):

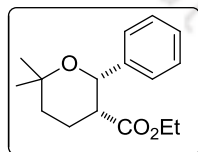
Colorless oil; R_f (hexane/EtOAc 49:1) 0.60; yield 11 mg, 3%; ^1H NMR (400 MHz, CDCl_3): δ 0.87 (d, $J = 6.4$ Hz, 3 H), 0.93 (d, $J = 6.4$ Hz, 3 H), 1.16 (s, 3 H), 1.22 (s, 3 H), 1.26-1.30 (m, 1 H), 1.74-1.84 (m, 2 H), 1.88-1.98 (m, 2 H), 2.63-2.66 (m, 1 H), 3.13 (dd, $J = 10.0$ and 2.4 Hz, 1 H), 3.65 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 19.0, 20.5, 22.1, 23.6, 31.2, 31.7, 31.8, 40.2, 51.3, 72.2, 77.6, 173.6; IR (KBr, neat) 2925, 2854, 1742, 1495, 1465, 1311, 1188, 1081, 969, 702 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 215.1642 found 215.1641.

(2S*,3R*)-Methyl-2-isopropyl-6,6-dimethyltetrahydro-2H-pyran-3-carboxylate**(24d')**:

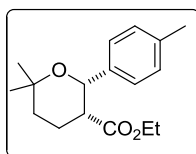
Colorless oil; R_f (hexane/EtOAc 49:1) 0.50; yield 173 mg, 76%; ^1H NMR (400 MHz, CDCl_3): δ 0.84 (d, $J = 6.8$ Hz, 3 H), 0.89 (d, $J = 6.8$ Hz, 3 H), 1.15 (s, 3 H), 1.17 (s, 3 H), 1.34 (ddd, $J = 13.2, 6.6$ and 3.6 Hz, 1 H), 1.47 (dt, $J = 12.0$ and 2.8 Hz, 1 H), 1.53-1.61 (m, 1 H), 1.76-1.93 (m, 2 H), 2.27-2.34 (m, 1 H), 3.53 (dd, $J = 10.4$ and 2.4 Hz, 1 H), 3.64 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 15.6, 19.8, 22.1, 24.8, 31.2, 31.5, 35.1, 45.3, 51.6, 71.2, 74.9, 175.7; IR (KBr, neat) 2975, 2869, 1740, 1435, 1380, 1131, 1038, 969, 889 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 215.1642 found 215.1640.

(2R*,3R*)-Ethyl 6,6-dimethyl-2-phenyltetrahydro-2H-pyran-3-carboxylate (24e):

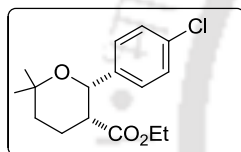
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 196 mg, 75%; ^1H NMR (400 MHz, CDCl_3): δ 0.97 (t, $J = 7.2$ Hz, 3 H), 1.30 (s, 3 H), 1.37 (s, 3 H), 1.62-1.67 (m, 2 H), 1.91-1.98 (m, 1 H), 2.02-2.14 (m, 1 H), 2.45-2.54 (m, 1 H), 3.90 (q, $J = 7.2$ Hz, 2 H), 4.72 (d, $J = 10.8$ Hz, 1 H), 7.23-7.35 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3): 14.1, 22.0, 24.5, 31.7, 35.2, 50.4, 60.3, 72.7, 74.8, 127.3, 128.1, 128.4, 141.2, 174.0; IR (KBr, neat) 2944, 2887, 1737, 1420, 1322, 1196, 1084, 983, 725 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 263.1642 found 263.1642.

(2S*,3R*)-Ethyl 6,6-dimethyl-2-phenyltetrahydro-2H-pyran-3-carboxylate (24f):

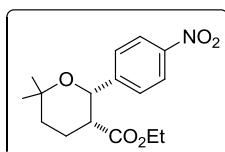
White solid, m.pt. 90-92 $^{\circ}\text{C}$; R_f (hexane/EtOAc 49:1) 0.42; yield 139 mg, 53%; ^1H NMR (400 MHz, CDCl_3): δ 0.85 (t, $J = 7.2$ Hz, 3 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.36-1.42 (m, 1 H), 2.02-2.12 (m, 2 H), 2.17 (ddd, $J = 12.0, 6.4$ and 5.6 Hz, 1 H), 2.77-2.80 (m, 1 H), 3.71-3.79 (m, 2 H), 4.91 (d, $J = 3.6$ Hz, 1 H), 7.18-7.36 (m, 5 H); ^{13}C NMR (150 MHz, CDCl_3): 14.0, 21.9, 23.0, 31.3, 31.7, 44.7, 59.7, 72.2, 72.7, 125.9, 127.1, 128.1, 141.7, 172.4; IR (KBr, neat) 2962, 2897, 1735, 1485, 1376, 1140, 1051, 724 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 263.1642 found 263.1637.

(2R*,3S*)-Ethyl 6,6-dimethyl-2-(*p*-tolyl)tetrahydro-2H-pyran-3-carboxylate (24g):

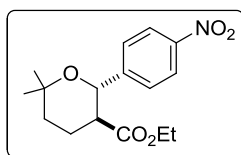
Pale yellow liquid; R_f (hexane/EtOAc 49:1) 0.50; yield 155 mg, 56%; ^1H NMR (400 MHz, CDCl_3): δ 1.10 (t, $J = 7.2$ Hz, 3 H), 1.28 (s, 3 H), 1.36 (s, 3 H), 1.56-1.64 (m, 2 H), 1.92-1.98 (m, 1 H), 2.05 (ddd, $J = 12.8, 4.8$ and 4.8 Hz, 1 H), 2.95 (s, 3 H), 2.45-2.53 (m, 1 H), 3.91 (q, $J = 7.2$ Hz, 2 H), 4.67 (d, $J = 10.4$ Hz, 1 H), 7.09 (d, $J = 8.4$ Hz, 2 H), 7.22 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.2, 21.5, 22.1, 24.6, 31.8, 35.2, 50.2, 60.3, 72.7, 74.5, 127.3, 129.1, 137.7, 138.2, 174.1; IR (KBr, neat) 2986, 2855, 1731, 1638, 1461, 1276, 1259, 1089, 770 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 277.1798 found 277.1787.

(2R*,3S*)-Ethyl 2-(4-chlorophenyl)-6,6-dimethyltetrahydro-2H-pyran-3-carboxylate (24h):

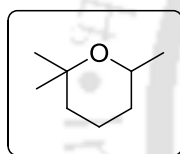
Colorless oil; R_f (hexane/EtOAc 49:1) 0.50; yield 172 mg, 58%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (t, $J = 7.2$ Hz, 3 H), 1.30 (s, 3 H), 1.37 (s, 3 H), 1.39-1.43 (m, 1 H), 2.04-2.08 (m, 2 H), 2.10-2.16 (m, 1 H), 2.75-2.79 (m, 1 H), 3.77-3.80 (m, 2 H), 4.88 (d, $J = 3.6$ Hz, 1 H), 7.25-7.31 (m, 4 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 22.0, 23.0, 31.3, 31.7, 44.6, 60.0, 71.7, 73.0, 127.5, 128.2, 132.8, 140.4, 172.2; IR (KBr, neat) 2986, 1731, 1639, 1461, 1276, 1259, 1089, 1040, 770 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{22}\text{ClO}_3$ ($\text{M} + \text{H}$) $^+$ 297.1252, found 279.1246.

(2R*,3S*)-Ethyl 6,6-dimethyl-2-(4-nitrophenyl)tetrahydro-2H-pyran-3-carboxylate (24i):

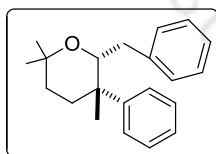
Pale yellow solid, mp 102-104 $^{\circ}\text{C}$; R_f (hexane/EtOAc 49:1) 0.40; yield 221 mg, 72 %; ^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, $J = 7.2$ Hz, 3 H), 1.30 (s, 3 H), 1.37 (s, 3 H), 1.41 (d, $J = 12.0$ Hz, 1 H), 2.04-2.11 (m, 3 H), 2.87 (s, 1 H), 3.73-3.80 (m, 2 H), 4.97 (s, 1 H), 7.53 (d, $J = 8.4$ Hz, 2 H), 8.15 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.0, 21.8, 23.0, 31.3, 31.5, 44.2, 60.0, 71.5, 73.2, 123.2, 126.8, 147.0, 149.5, 171.5; IR (KBr, neat) 2977, 1732, 1638, 1520, 1377, 1275, 1180, 1095, 1039, 767 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ ($\text{M} + \text{H}$) $^+$ 308.1492, found 308.1493.

(2R*,3R*)-Ethyl 6,6-dimethyl-2-(4-nitrophenyl)tetrahydro-2H-pyran-3-carboxylate (24j):

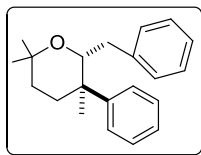
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 291 mg, 95%; ^1H NMR (600 MHz, CDCl_3): δ 1.03 (t, $J = 7.2$ Hz, 3 H), 1.32 (s, 3 H), 1.37 (s, 3 H), 1.62 (dd, $J = 13.2$ and 4.2 Hz, 1 H), 1.67 (d, $J = 13.2$ Hz, 1 H), 1.99 (dd, $J = 13.2$ and 3.0 Hz, 1 H), 2.04-2.10 (m, 1 H), 2.39-2.44 (m, 1 H), 3.90-3.98 (m, 2 H), 4.85 (d, $J = 10.2$ Hz, 1 H), 7.53 (d, $J = 8.4$ Hz, 2 H), 8.16 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.2, 22.0, 24.5, 31.6, 32.1, 35.0, 60.7, 73.2, 73.8, 123.7, 128.3, 147.8, 148.7, 173.5; IR (KBr, neat) 2927, 1730, 1604, 1523, 1374, 1172, 1071, 912, 746 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{22}\text{NO}_5$ ($\text{M} + \text{H}$) $^+$ 308.1492, found 308.1498.

2,2,6-Trimethyltetrahydro-2H-pyran (24k):

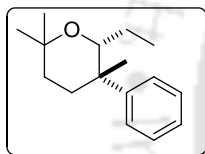
Colorless oil; R_f (hexane/EtOAc 49:1) 0.70; yield 102 mg, 80%; ^1H NMR (400 MHz, CDCl_3): δ 1.85 (d, $J = 6.0$ Hz, 3 H), 1.17 (s, 3 H), 1.18 (s, 3 H), 1.28-1.43 (m, 2 H), 1.49-1.53 (m, 1 H), 1.57-1.67 (m, 3 H), 3.60-3.68 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): 20.3, 22.1, 22.9, 32.1, 33.6, 36.2, 66.5, 71.8; IR (KBr, neat) 2968, 2930, 1461, 1378, 1088, 979, 890, 757 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_8\text{H}_{17}\text{O}$ ($\text{M} + \text{H}$) $^+$ 129.1274 found 129.1267.

(2S*,3R*)-2-Benzyl-2,6,6-trimethyl-3-phenyltetrahydro-2H-pyran (24l):

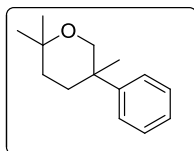
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.60; yield 102 mg, 35%; ^1H NMR (600 MHz, CDCl_3): δ 1.15 (s, 3 H), 1.29-1.34 (m, 1 H), 1.32 (s, 3 H), 1.40 (s, 3 H), 1.60 (ddd, $J = 13.2$, 4.2 and 3.6 Hz, 1 H), 1.69 (dt, $J = 13.8$ and 4.2 Hz, 1 H), 1.85 (ddd, $J = 13.8$, 4.2 and 3.6 Hz, 1 H), 2.59 (d, $J = 15.0$ Hz, 1 H), 2.77 (dd, $J = 15.0$ and 9.0 Hz, 1 H), 3.80 (d, $J = 10.2$ Hz, 1 H), 7.20-7.28 (m, 6 H), 7.36 (t, $J = 7.8$ Hz, 2 H), 7.82 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 22.6, 26.9, 31.1, 32.5, 37.5, 37.9, 40.3, 72.3, 81.3, 125.7, 125.8, 127.8, 128.1, 128.7, 129.0, 141.6, 145.9; IR (KBr, neat) 2973, 2928, 1637, 1275, 1080, 764 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{27}\text{O}$ ($\text{M} + \text{H}$) $^+$ 295.2056 found 295.2044.

(2S*,3S*)-2-Benzyl-2,6,6-trimethyl-3-phenyltetrahydro-2H-pyran (24l')

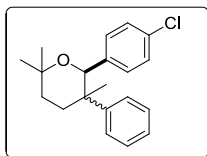
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 165 mg, 56%; ^1H NMR (600 MHz, CDCl_3): δ 1.17 (s, 3 H), 1.27 (s, 3 H), 1.38 (dt, J = 13.2 and 2.4 Hz, 1 H), 1.45 (s, 3 H), 1.50 (dt, J = 12.0 and 1.8 Hz, 1 H), 1.80 (dt, J = 13.8 and 4.2 Hz, 1 H), 2.12 (dt, J = 13.8 and 3.6 Hz, 1 H), 2.26 (d, J = 14.4 Hz, 1 H), 2.45 (dd, J = 15.6 and 9.6 Hz, 1 H), 4.15 (d, J = 15.6 Hz, 1 H), 7.07 (d, J = 7.2 Hz, 2 H), 7.11 (t, J = 7.2 Hz, 1 H), 7.16-7.23 (m, 3 H), 7.34 (t, J = 7.8 Hz, 2 H), 7.44 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): 15.9, 22.4, 31.9, 33.0, 36.9, 37.0, 40.9, 72.0, 78.0, 125.7, 126.2, 126.3, 128.0, 128.6, 129.0, 141.4, 148.4; IR (KBr, neat) 2972, 2927, 1635, 1450, 1260, 1029, 762 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{27}\text{O}$ ($\text{M} + \text{H}$) $^+$ 295.2056 found 295.2045.

(5S*,6R*)-6-ethyl-2,2,5-trimethyl-5-phenyltetrahydro-2H-pyran (24m)

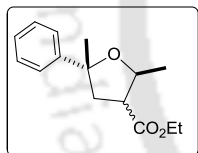
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.60; yield 140 mg, 60%; ^1H NMR (600 MHz, CDCl_3): δ 0.81 (t, J = 7.2 Hz, 3 H), 1.00-1.06 (m, 1 H), 1.13-1.21 (m, 1 H), 1.31 (s, 3 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.42 (dt, J = 13.8 and 3.6 Hz, 1 H), 1.46 (dt, J = 13.8 and 3.6 Hz, 1 H), 1.79 (dt, J = 13.8 and 4.2 Hz, 1 H), 2.13 (dt, J = 13.8 and 4.2 Hz, 1 H), 3.78 (d, J = 9.6 Hz, 1 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.33 (t, J = 7.2 Hz, 2 H), 7.40 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 11.7, 15.9, 22.6, 23.3, 32.0, 33.0, 36.8, 40.7, 71.8, 78.5, 126.0, 126.3, 128.4, 148.7; IR (KBr, neat) 2925, 2858, 1635, 1379, 1265, 1139, 1080, 1030, 951, 764 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{25}\text{O}$ ($\text{M} + \text{H}$) $^+$ 233.1900 found 233.1898.

2,2,5-Trimethyl-5-phenyltetrahydro-2H-pyran (24n)

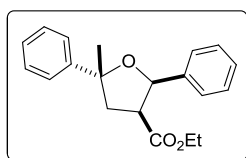
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.60; yield 129 mg, 63%; ^1H NMR (600 MHz, CDCl_3): δ 1.17 (s, 3 H), 1.26 (s, 3 H), 1.27 (s, 3 H), 1.35-1.40 (m, 1 H), 1.54-1.60 (m, 1 H), 1.76-1.80 (m, 1 H), 2.01-2.06 (m, 1 H), 3.61 (d, J = 12.0 Hz, 1 H), 3.94 (d, J = 11.4 Hz, 1 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.33 (t, J = 7.8 Hz, 2 H), 7.41 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): 25.8, 32.8 (2 C), 32.9 (2C), 37.1, 69.9, 71.0, 126.1, 126.3, 128.4, 147.6; IR (KBr,neat) 2971, 2930, 1602, 1367, 1225, 1103, 1078, 1030, 910, 699 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{21}\text{O}$ ($\text{M} + \text{H}$) $^+$ 205.1587 found 205.1588.

6-(4-Chlorophenyl)-2,2,5-trimethyl-5-phenyltetrahydro-2H-pyran (diastereomeric mixture, 3:1, 24o):

Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 257 mg, 82%; ^1H NMR (600 MHz, CDCl_3): δ 1.16 (s, 3 H), 1.22-1.27 (m, 1 H), 1.37 (s, 3 H, minor), 1.40 (s, 3 H, major), 1.41 (s, 3 H, minor), 1.43 (s, 3 H, major), 1.46-1.52 (m, 1 H, major), 1.57 (dd, $J = 13.8$ and 1.8 Hz, 1 H, minor), 1.78-1.82 (m, 1 H, minor), 1.86-1.96 (m, 1 H, major), 2.25-2.29 (m, 1 H, minor), 2.50 (t, $J = 13.8$ Hz, 1 H, major), 4.67 (s, 1 H, minor), 4.96 (s, 1 H, major), 6.66 (d, $J = 8.4$ Hz, 2 H), 6.98 (d, $J = 8.4$ Hz, 2 H), 7.07-7.13 (m, 1 H), 7.19-7.27 (m, 1 H), 7.27-7.54 (m, 2 H), 7.55 (d, $J = 7.1$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): 15.9, 22.3, 22.9, 27.5, 31.2, 31.9, 32.5, 32.6, 34.8, 37.0, 40.7, 41.6, 72.7, 73.3, 78.7, 81.3, 126.1, 126.5, 127.0, 127.1, 127.5, 127.6, 128.3, 128.8, 128.9, 130.1, 132.4, 132.7, 138.6, 138.7, 144.3, 146.7; IR (KBr, neat) 2987, 2856, 1637, 1458, 1376, 1277, 1219, 1087, 918, 770 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{24}\text{ClO}$ ($\text{M} + \text{H}$) $^+$ 315.1510 found 315.1513.

Ethyl 2,5-dimethyl-5-phenyltetrahydrofuran-3-carboxylate (diastereomeric mixture, 5:3, 25q):

Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 210 mg, 85%; ^1H NMR (600 MHz, CDCl_3): δ 1.15-1.19 (m, 3 H), 1.42 (d, $J = 6.0$ Hz, 3 H, minor), 1.43 (d, $J = 5.4$ Hz, 3 H, major), 1.53 (s, 3 H, major), 1.59 (d, $J = 15.6$ Hz, 3 H, minor), 2.42-2.65 (m, 2 H), 2.80 (q, $J = 9.0$ Hz, 1 H, minor), 2.97 (q, $J = 8.4$ Hz, 1 H, major), 4.03-4.07 (m, 1 H, minor), 4.11-4.17 (m, 2 H), 4.33-4.38 (m, 1 H, major), 7.22 (t, $J = 7.2$ Hz, 1 H), 7.32 (t, $J = 7.2$ Hz, 2 H), 7.37-7.44 (d, $J = 7.2$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 18.2, 20.5, 20.8, 31.0, 31.8, 41.4, 43.7, 44.9, 48.1, 51.3, 52.1, 60.7, 60.8, 74.8, 84.6, 124.7, 126.8, 128.3, 128.4, 128.5, 147.4, 148.2, 172.7, 172.9; IR (KBr, neat) 2986, 2871, 1737, 1446, 1375, 1188, 1028, 934, 765, 702 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{21}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 249.1485, found 249.1485.

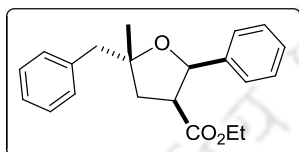
(2R*,3S*,5S*)-Ethyl 5-methyl-2,5-diphenyltetrahydrofuran-3-carboxylate (25r):

Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 180 mg, 58 %; ^1H NMR (400 MHz, CDCl_3): δ 0.81 (t, $J = 7.2$ Hz, 3 H), 1.58 (s, 3 H), 2.43 (dd, $J = 12.4$ and 4.8 Hz, 1 H), 2.68 (dd, $J = 11.6$ and 11.2

Hz, 1 H), 3.49-3.56 (m, 1 H), 3.60-3.67 (m, 1 H), 3.72 (q, $J = 7.2$ Hz, 1 H), 5.53 (d, $J = 8.8$ Hz, 1 H), 7.22-7.32 (m, 6 H), 7.39 (t, $J = 8.0$ Hz, 2 H), 7.56 (d, $J = 7.6$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 13.8, 28.7, 41.3, 50.5, 60.6, 81.2, 84.9, 125.0, 126.9, 127.2, 128.0, 128.1, 128.4, 139.5, 147.6, 171.7; IR (KBr, neat) 2977, 2928, 1732, 1446, 1379, 1179, 1024, 956, 764 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 311.1642 found 311.1641.

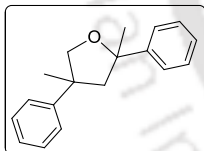
(2*R,3*S**,5*S**)-Ethyl-5-benzyl-5-methyl-2-phenyltetrahydrofuran-3-carboxylate**

(25s):



Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.60; yield 272 mg, 53%; ^1H NMR (600 MHz, CDCl_3): δ 1.24-1.29 (m, 5 H), 1.91 (s, 3 H), 2.79-2.83 (m, 1 H), 2.92-2.97 (m, 1 H), 3.01-3.06 (m, 1 H), 4.17-4.19 (m, 2 H), 4.68 (s, 1 H), 7.08-7.20 (m, 10 H); ^{13}C NMR (150 MHz, CDCl_3): δ 13.8, 29.9, 42.0, 51.6, 58.6, 60.8, 78.7, 82.3, 126.4, 126.5, 128.0, 128.1, 128.5, 135.4, 136.9, 144.4, 175.6; IR (KBr, neat) 2926, 1731, 1640, 1447, 1372, 1170, 1033, 802, 700 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 325.1798 found 325.1791.

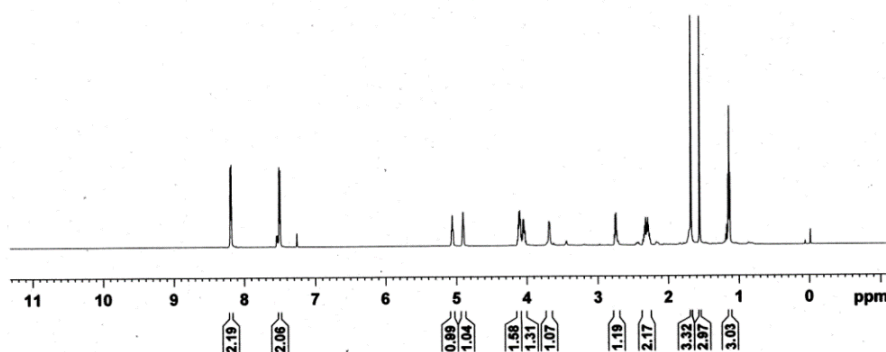
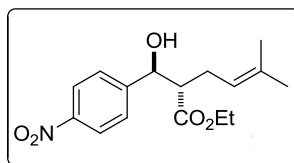
2,4-Dimethyl-2,4-diphenyltetrahydrofuran (diastereomeric mixture, 3:2, 25t):



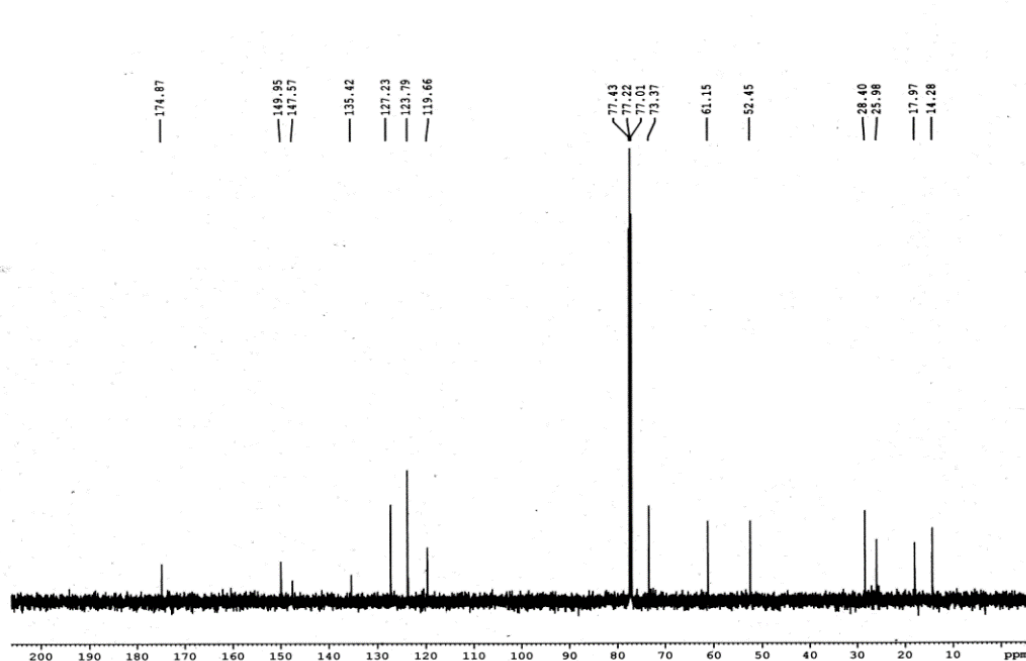
Pale yellow oil; R_f (hexane/EtOAc 49:1) 0.50; yield 202 mg, 80 %; ^1H NMR (600 MHz, CDCl_3): δ 1.20 (s, 3 H, major), 1.48 (s, 3 H, major), 1.62 (s, 3 H, minor), 1.67 (s, 3 H, minor), 2.45 (d, $J = 12.6$ Hz, 1 H, minor), 2.55 (s, 2 H, major), 2.69 (d, $J = 12.6$ Hz, 1 H, minor), 3.94 (d, $J = 8.4$ Hz, 1 H, minor), 4.03 (d, $J = 8.4$ Hz, 1 H, major), 4.07 (d, $J = 8.4$ Hz, 1 H, minor), 4.27 (d, $J = 9.0$ Hz, 1 H, major), 7.09 (t, $J = 7.8$ Hz, 1 H), 7.11-7.40 (m, 7 H), 7.49 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 28.7, 30.1, 31.8, 32.9, 48.6, 49.1, 53.8, 54.2, 78.0, 78.2, 84.9, 85.0, 124.6, 124.7, 126.0, 126.1, 126.2, 126.3, 126.4, 128.3, 128.4, 128.5, 128.6, 147.9, 148.4, 149.5, 149.7; IR (KBr, neat) 2971, 2930, 1601, 1450, 1382, 1137, 1030, 840 762 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{21}\text{O}$ ($\text{M} + \text{H}$) $^+$ 253.1587 found 253.1578.

4.8. Representative Spectra

^1H and ^{13}C NMR of (*S**)-Ethyl 2-((*S**)-hydroxy(4-nitrophenyl)methyl)-5-methylhex-4-enoate (22i):

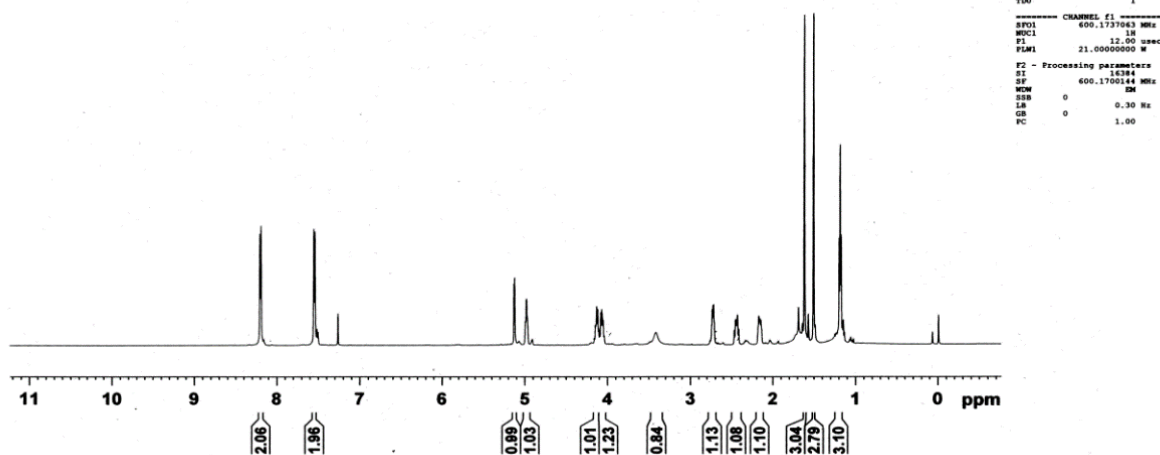
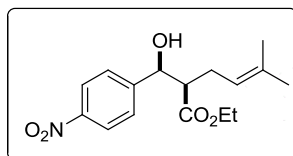


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PROCNO 1
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Date_ 20150728
Time 20.46
INSTRUM spect
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PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 2
DS 12019.230 Hz
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543829 sec
RG 65.24
LW 13.867 usec
DE 6.50 usec
TE 294.0 K
D1 2.0000000 sec
D11 0.0300000 sec
TD0 1
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NUC1 13C
P1 12.50 usec
PLW1 21.0000000 W
F2 - Processing parameters
SI 32768
SF 600.170145 MHz
WDW EM
SSB 0
GB 0
PC 1.00
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Current Data Parameters
NAME AKS-SS-NO2-ON-13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150728
Time 20.46
INSTRUM spect
PROBHD 5 mm F400 NMR/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 2
DS 36057.691 Hz
SWH 1.100393 Hz
FIDRES 0.4543829 sec
RG 65.24
LW 13.867 usec
DE 6.50 usec
TE 294.0 K
D1 2.0000000 sec
D11 0.0300000 sec
TD0 1
===== CHANNEL f1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.0000000 W
===== CHANNEL f2 =====
SFO2 600.170145 MHz
NUC2 13C
PCPD2 70.00 usec
PLW2 21.0000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W
F2 - Processing parameters
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SF 150.9128403 MHz
WDW EM
SSB 0
GB 0
PC 1.40
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^1H and ^{13}C NMR of (*R**)-ethyl 2-((*S**)-hydroxy(4-nitrophenyl)methyl)-5-methylhex-4-enoate (22j):

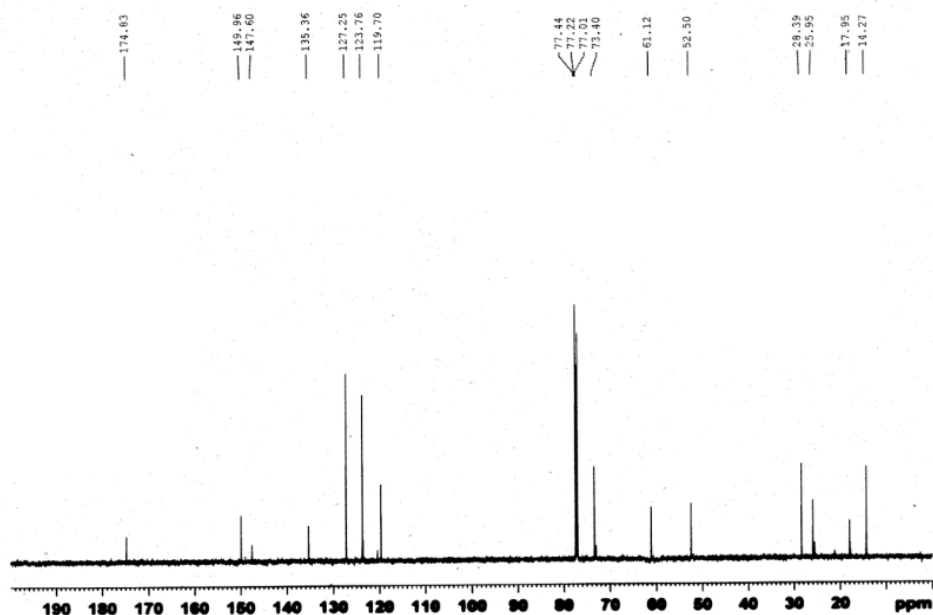


Current Data Parameters
NAME ARS-M02-02-08-18
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150703
Time 10:46
INSTRUM spect
PROBHD 5 mm F400 BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.364796 Hz
AQ 1.4821488 sec
RG 48.24
DM 41.000 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
D11 1

CHANNEL f1 -----
SFO1 600.137043 MHz
NUC1 1H
P1 12.00 usec
PLM1 21.0000000 W

F2 - Processing parameters
SI 16384
SF 600.1700144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME ARS-SE-M02-08-13C
EXPNO 1
PROCNO 1

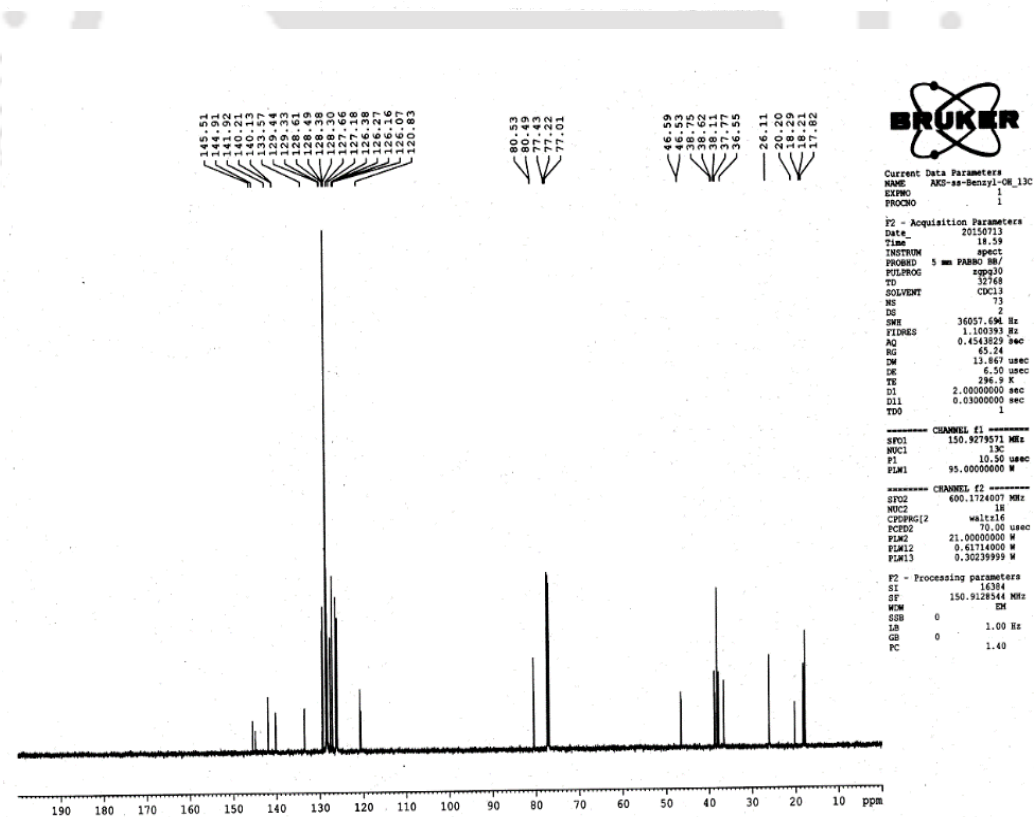
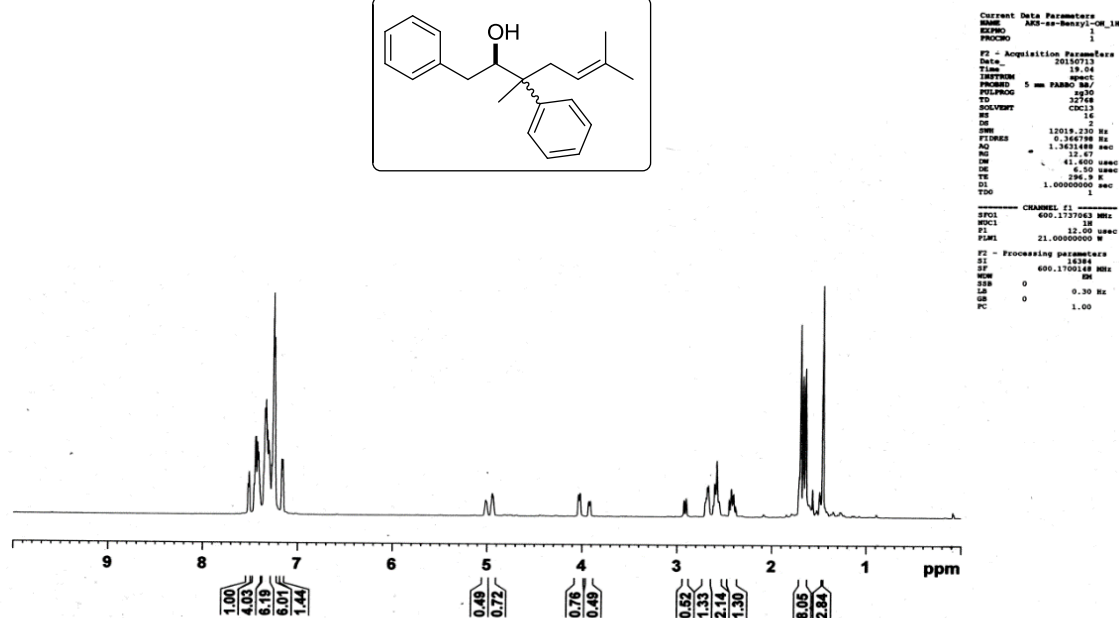
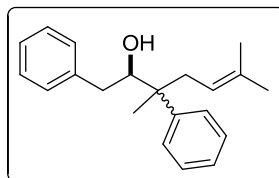
F2 - Acquisition Parameters
Date_ 20150709
Time 10:20
INSTRUM spect
PROBHD 5 mm F400 BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 58
DS 2
SWH 42613.637 Hz
FIDRES 1.300465 Hz
AQ 0.3844779 sec
RG 200.18
DM 11.733 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
D12 1

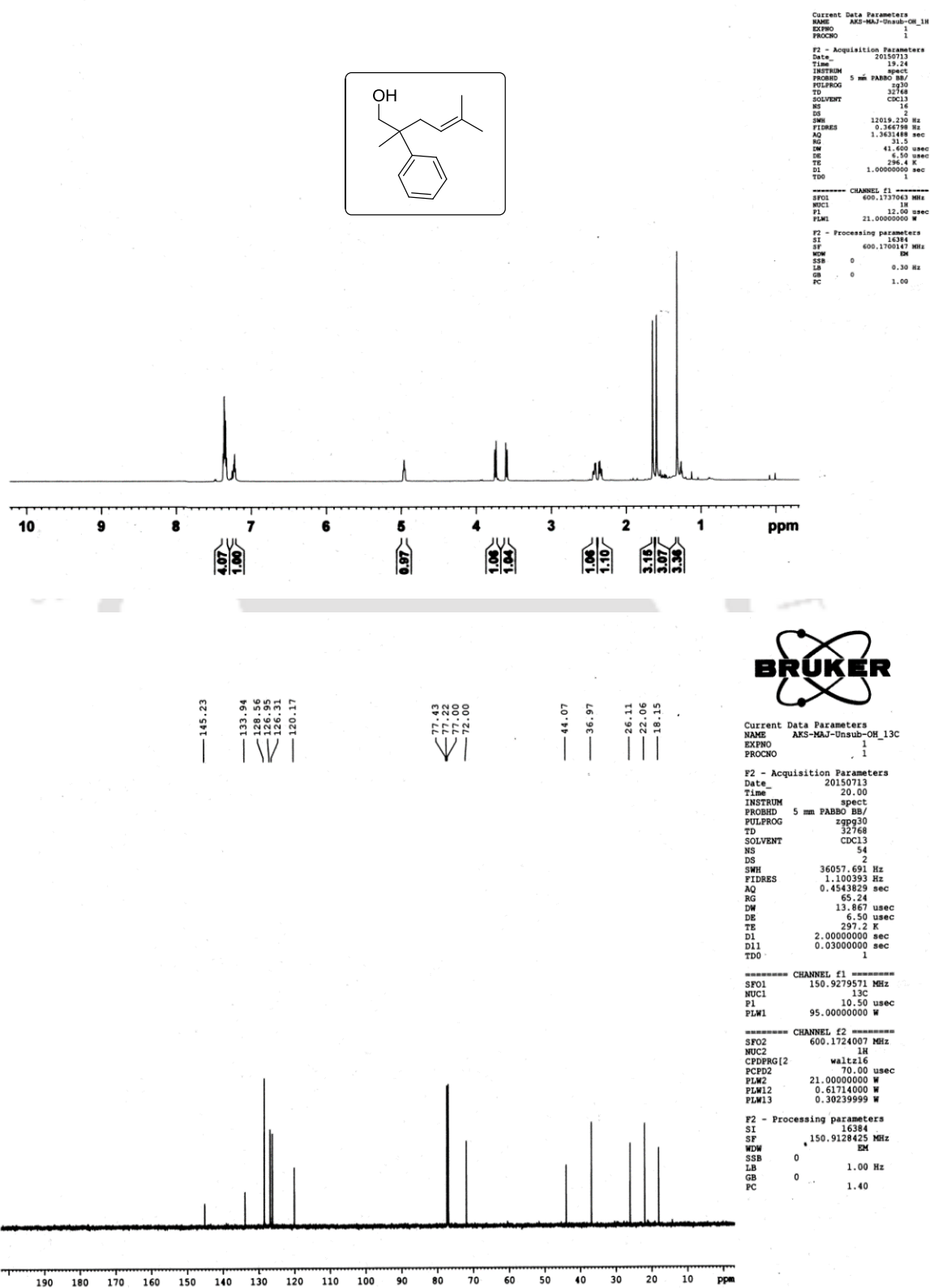
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NUC1 13C
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PLM1 95.0000000 W

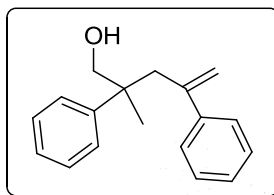
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NUC2 1H
CPDPRG2 waltz16
PCPDZ 70.00 usec
PLM2 21.0000000 W
PLM12 0.61714000 W
PLM13 0.30239999 W

F2 - Processing parameters
SI 16384
SF 150.9128390 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^1H and ^{13}C NMR of 3,6-Dimethyl-1,3-diphenylhept-5-en-2-ol (diastereomeric mixture, 2:3, 22l):



^1H and ^{13}C NMR of 2,5-Dimethyl-2-phenylhex-4-en-1-ol (22n):

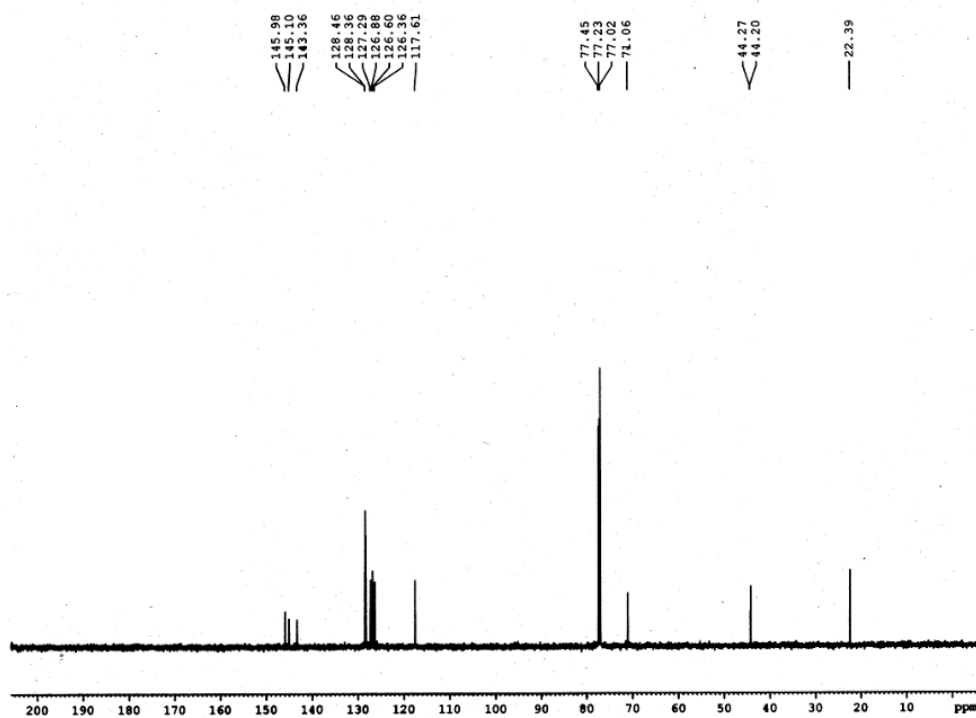
^1H and ^{13}C NMR of 2-Methyl-2,4-diphenylpent-4-en-1-ol (23t):

Current Data Parameters
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EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150724
Time 12.59
INSTRUM spect
PROBHD 5 mm PARBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 12019.219 Hz
FIDRES 0.366798 Hz
AQ 1.3631499 sec
RG 49.39
DW 41.609 usec
DE 6.50 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 600.177043 MHz
NUC1 1H
P1 12.00 usec
PLW1 21.00000000 W

F2 - Processing parameters
SI 16384
SF 600.176244 MHz
WDW EM
SSB 0
LB 0.39 Hz
GB 0
PC 1.00



Current Data Parameters
NAME AKS-MAJ-232-OH_13C
EXPNO 1
PROCNO 1

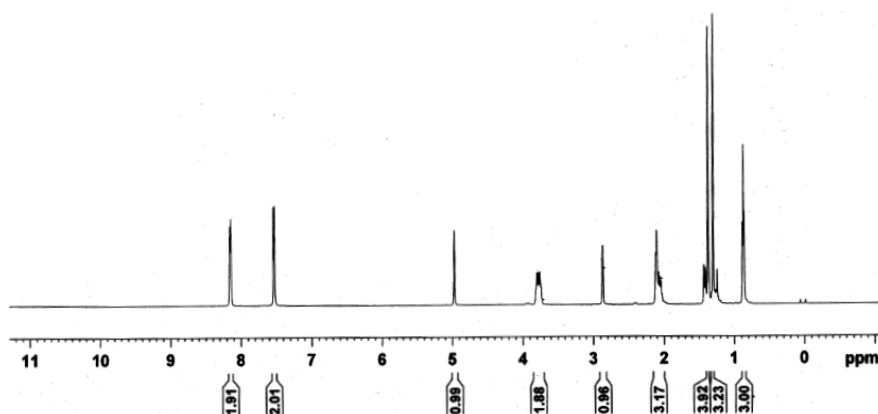
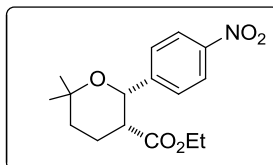
F2 - Acquisition Parameters
Date_ 20150724
Time 13.02
INSTRUM spect
PROBHD 5 mm PARBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 42613.637 Hz
FIDRES 1.300465 Hz
AQ 0.3844779 sec
RG 65.24
DW 11.733 usec
DE 6.50 usec
TE 293.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W

===== CHANNEL f2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W

F2 - Processing parameters
SI 16384
SF 150.9128422 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^1H and ^{13}C NMR of (2R*,3S*)-Ethyl 6,6-dimethyl-2-(4-nitrophenyl)tetrahydro-2H-pyran-3-carboxylate (24i):

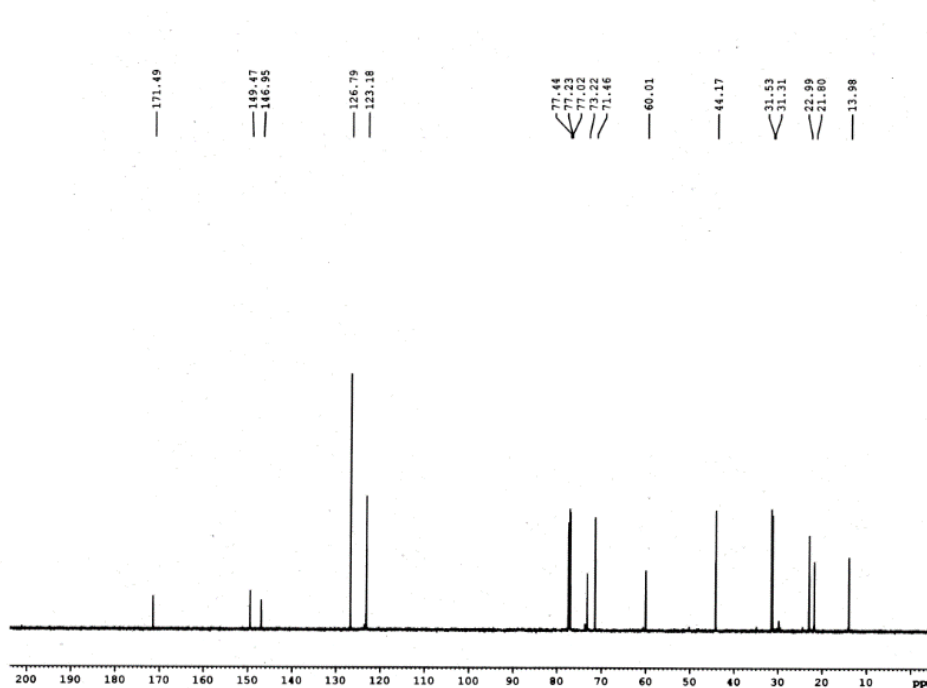


Current Data Parameters
NAME AKS_MAJ_NO2_1_F-1H
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.238 Hz
FIDRES 0.364398 Hz
AQ 1.261188 sec
RG 187.57
DW 14.480 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1

===== CHANNEL F1 =====
SFO1 600.137043 MHz
NUC1 1H
P1 12.00 usec
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F2 - Processing parameters
SI 16384
SF 600.137043 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



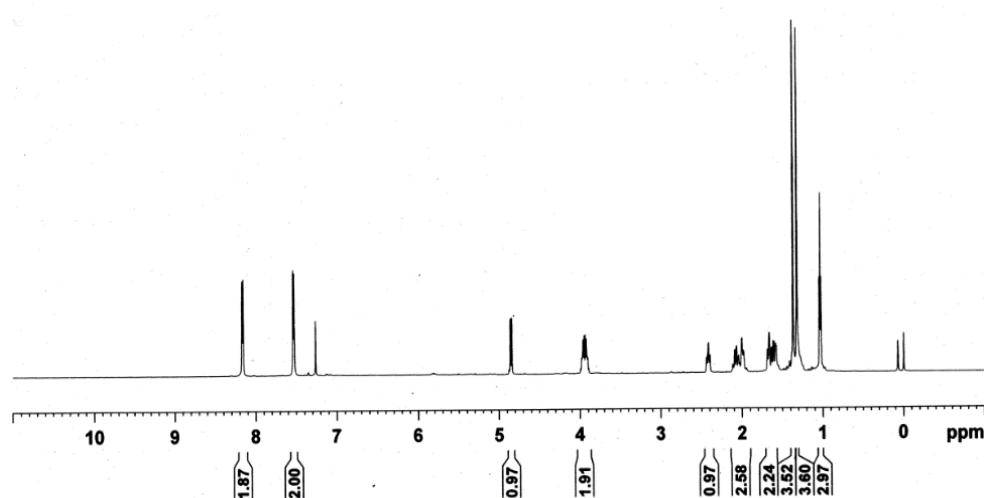
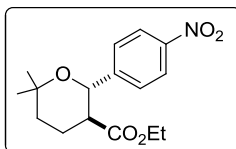
Current Data Parameters
NAME AKS_MAJ_NO2_1_F-13C
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 10:23
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 87
DS 2
SWH 42613.637 Hz
FIDRES 1.300465 Hz
AQ 0.3844775 sec
RG 65.24
DW 11.733 usec
DE 6.50 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL F1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W

===== CHANNEL F2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W

F2 - Processing parameters
SI 16384
SF 150.9128429 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

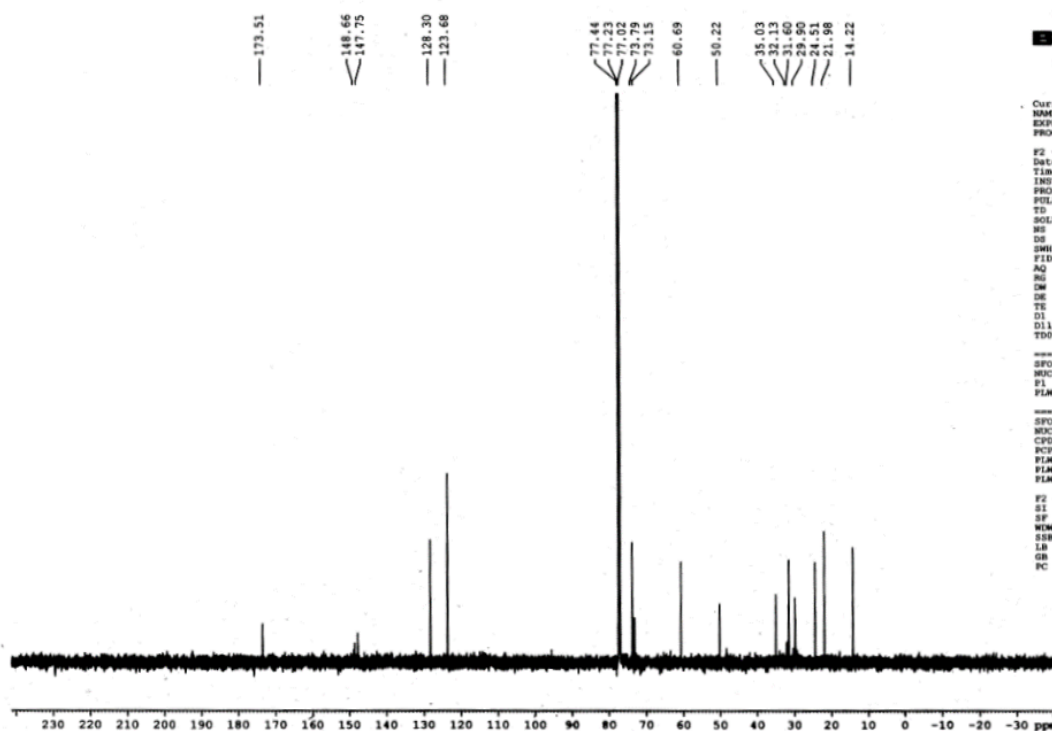
^1H and ^{13}C NMR of (2*R,3*R**)-Ethyl 6,6-dimethyl-2-(4-nitrophenyl)tetrahydro-2H-pyran-3-carboxylate (24j):**

Current Data Parameters
NAME ARS-KA3-NO2-0-F2-1H
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 14.05
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PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.364798 Hz
AQ 1.3631488 sec
RG 49.39
DM 41.600 usec
DE 6.50 usec
TE 296.6 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 600.1737063 MHz
NUC1 1H
P1 12.00 usec
PLW1 21.00000000 W

F2 - Processing parameters
SI 16384
SF 600.1700148 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME ARS-KA3-NO2-0-F2-13C
EXPNO 1
PROCNO 1

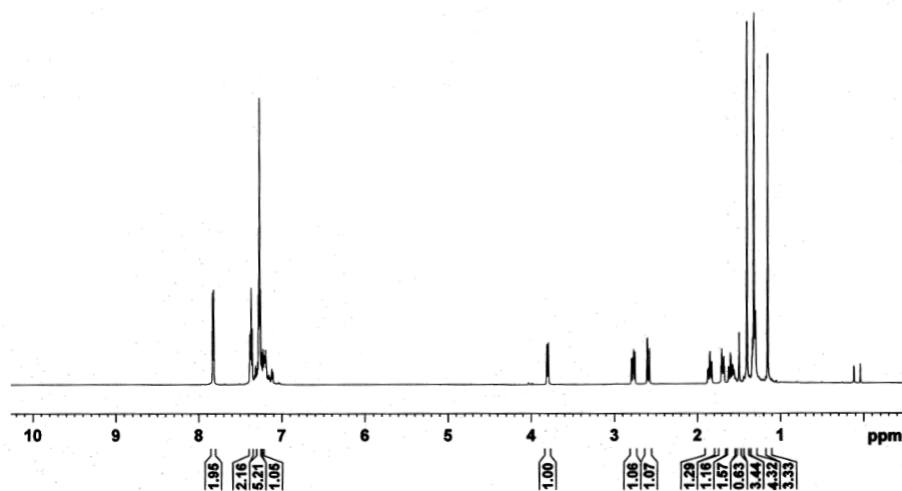
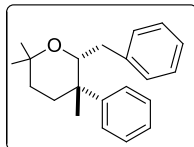
F2 - Acquisition Parameters
Date_ 20150709
Time 15.58
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 122
DS 2
SWH 47613.637 Hz
FIDRES 1.300465 Hz
AQ 0.3844779 sec
RG 65.24
DM 11.733 usec
DE 6.50 usec
TE 297.3 K
D1 2.00000000 sec
D11 0.01000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 150.9279971 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W

===== CHANNEL f2 =====
SFO2 600.1724087 MHz
NUC2 1H
CPCPRG2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.41714000 W
PLW13 0.30239999 W

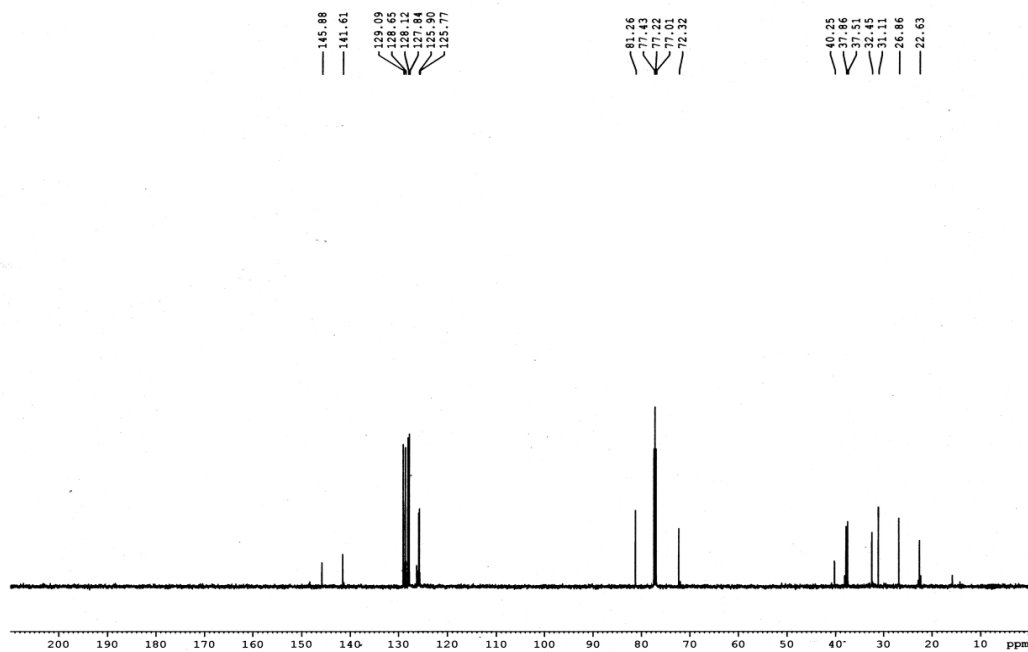
F2 - Processing parameters
SI 16384
SF 150.9128359 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^1H and ^{13}C NMR of (2*S**,3*R**)-2-Benzyl-2,6,6-trimethyl-3-phenyltetrahydro-2*H*-pyran (24l):



Current Data Parameters
NAME: 24l-04J-12-Benzyl-10-F-18
EXPNO: 1
PROCNO: 1
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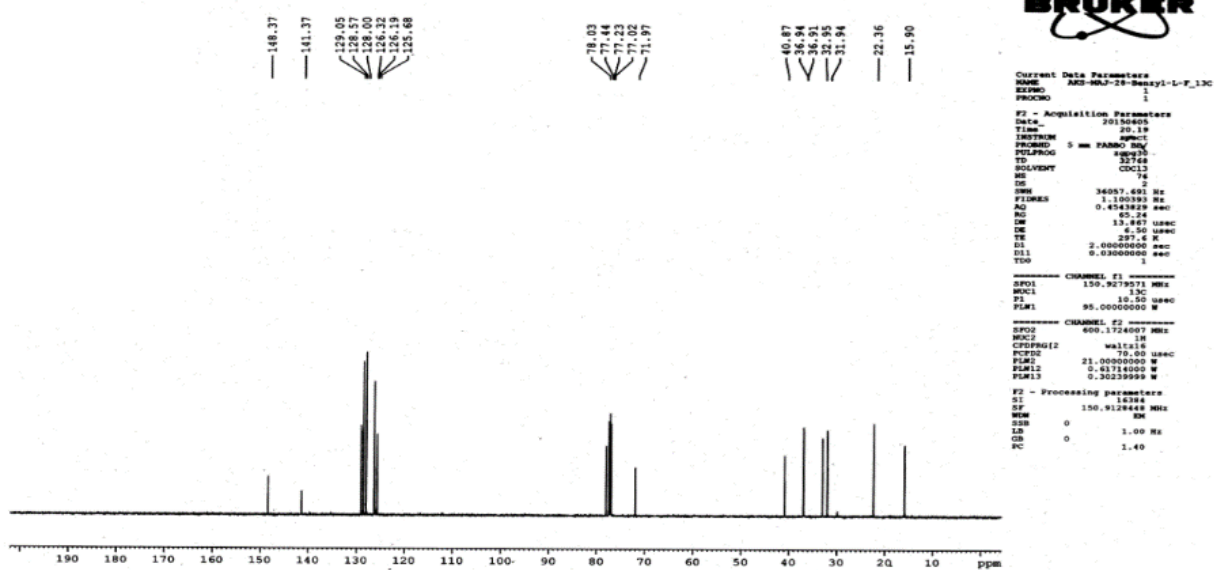
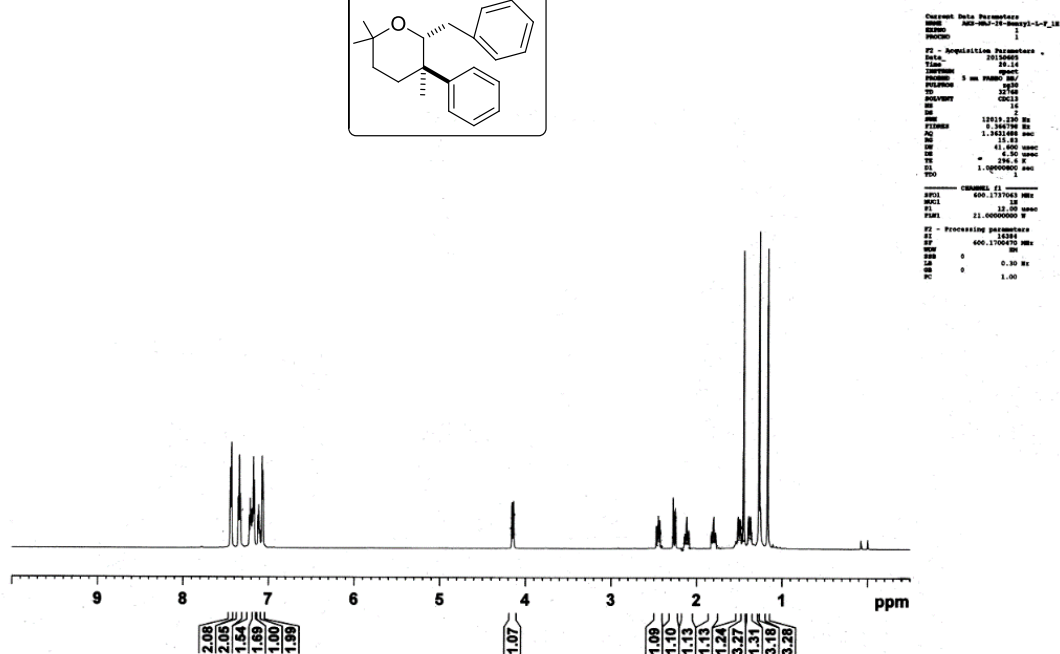
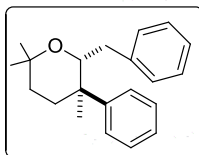
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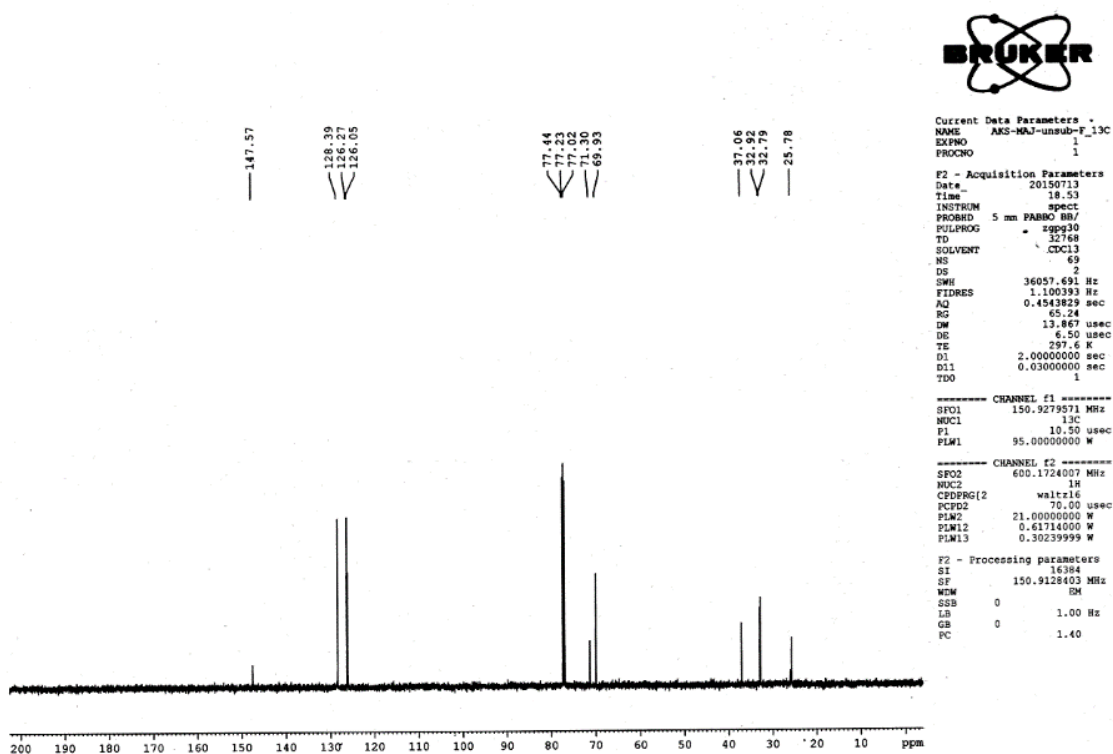
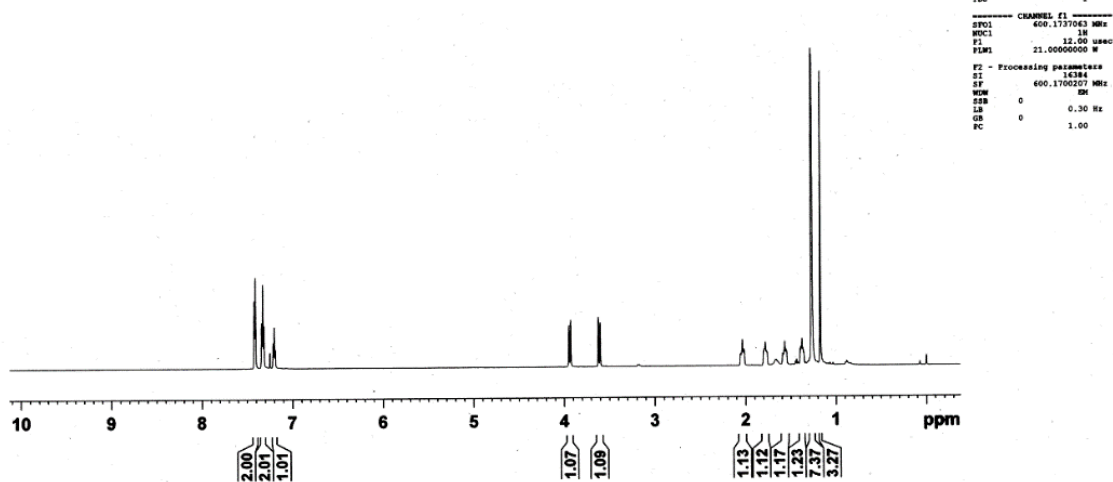
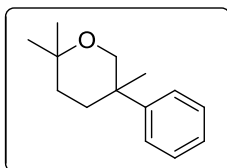


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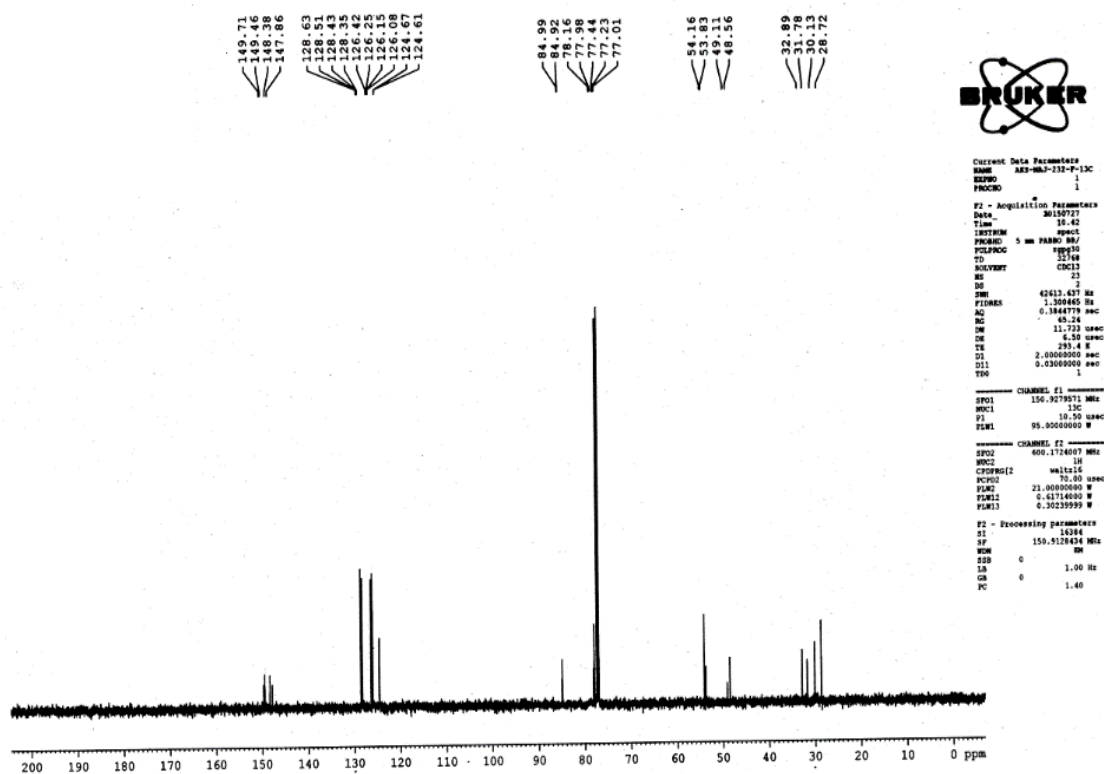
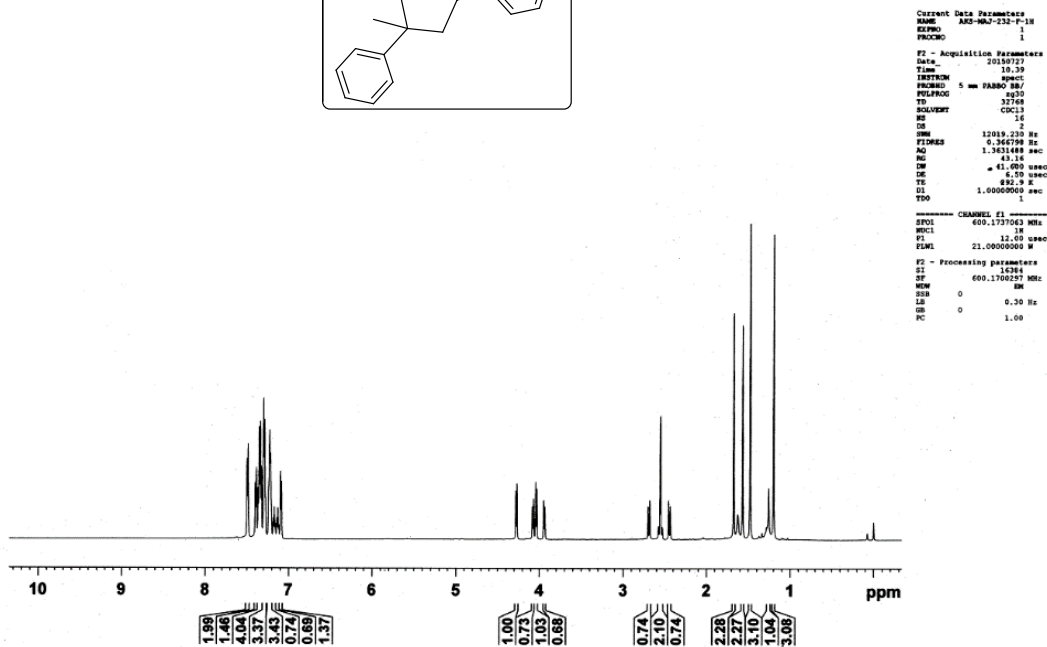
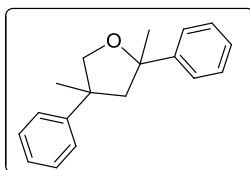
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WDW: EM
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LB: 0.30 Hz
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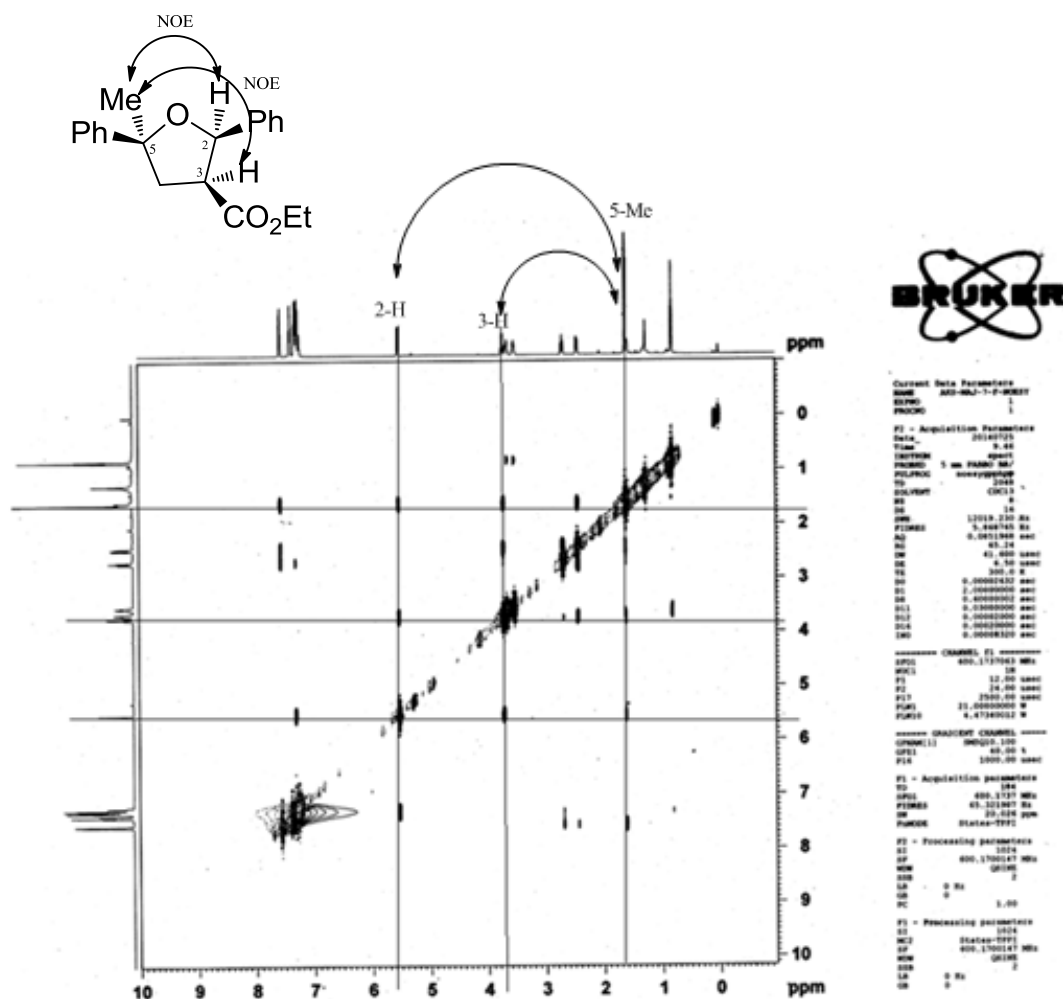


^1H and ^{13}C NMR of 2,2,5-Trimethyl-5-phenyltetrahydro-2H-pyran (24n):

^1H and ^{13}C NMR of 2,4-Dimethyl-2,4-diphenyltetrahydrofuran (diastereomeric mixture, 3:2, 25t):



NOE of (2R*,3S*,5S*)-Ethyl 5-methyl-2,5-diphenyltetrahydrofuran-3-carboxylate (25r):



4.9. The Crystal Parameters of Compound 24f

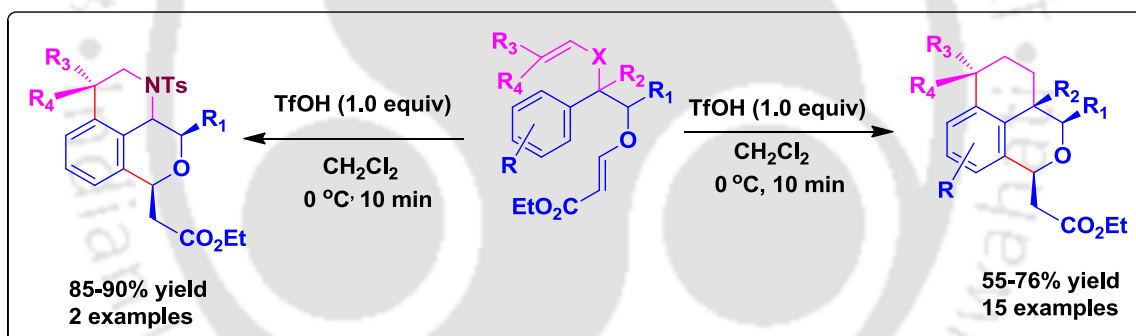
Crystal Parameters	CCDC 1404939
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Formula weight	262.34
<i>T</i> /K	296(2)
Crystal system	Triclinic
Space group	<i>P</i> -1
<i>a</i> /Å	7.8161(13)
<i>b</i> /Å	9.8520(16)
<i>c</i> /Å	10.4751(19)
α /°	94.483(13)
β /°	101.306(13)
γ /°	108.458(12)
<i>V</i> /Å ³	741.7 (2)
<i>Z</i>	2
Abs. Coeff./mm ⁻¹	0.080
Abs. Correction	None
GOF on <i>F</i> ²	1.012
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.1523 <i>wR</i> 2 = 0.4323
<i>R</i> indices [all data]	<i>R</i> 1 = 0.2070 <i>wR</i> 2 = 0.4061

4.10. References

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CHAPTER 5

Diastereoselective Synthesis of Substituted Hexahydrobenzo[de]isochromans and their Evaluation as Antileishmanial Activity



Org. Biomol. Chem. **2016**, 14, 970.



Diastereoselective Synthesis of Substituted Hexahydrobenzo[de]isochromanes and their Evaluation for Antileishmanial Activity

5.1. Importance and Applications

Pyran fused with a benzene ring (*e.g.* chromanes and isochromanes) are another important class of cyclic ethers as they are core units of many biologically active molecules and natural products.¹ Pseudodefectusin (**1**), an isochromane derivative isolated from the culture broth of *Aspergillus pseudodeflectus* exhibits cytotoxicity towards several human cancer cell lines, including those derived from the stomach (NUGC-3), cervix (HeLa-S3) and peripheral blood (HL-60). The related natural products ustusoranes C (**2**) and D (**3**), isolated from *Aspergillus ustus* 094102, shows activity against HCT116 human colon cancer cells.² Cyathusals B (**4**), isolated from the culture of the *basidiomycete* *Cyathus stercoreus*, exhibits antioxidative properties.³ Penicitrinols F (**5**) isolated from the marine-derived fungus *Penicillium citrinum*, shows antimicrobial activities.⁴

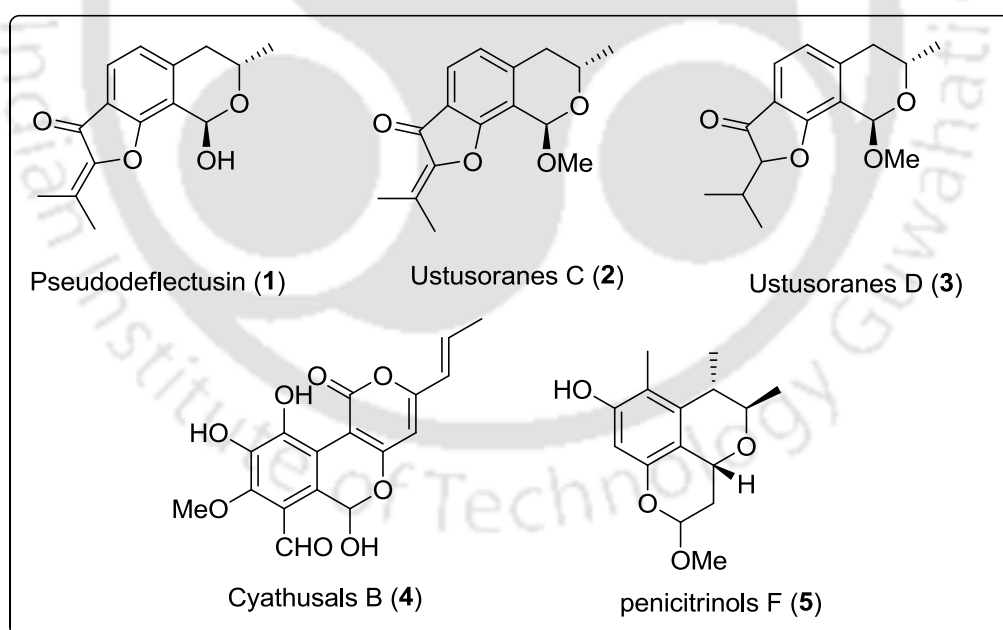


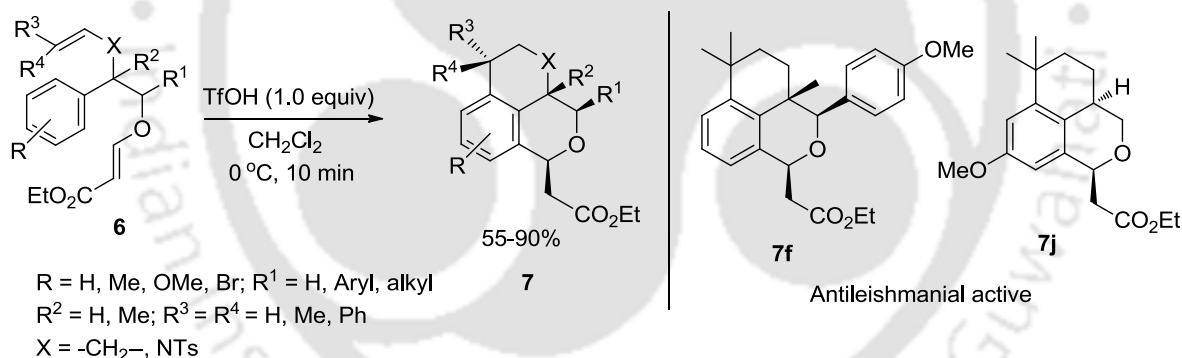
Figure 5.1.1. Biologically active compounds containing isochromane ring as core units.

5.2. Literature Review on Relevant Synthetic Methods

Owing to their wide range of biological activities, synthesis of substituted isochromanes have attracted the attention of the synthetic community and various methods have been developed for the functionalization of isochromane core in recent years, many of them we have already discussed in chapter 1. However, till now there is no literature on synthesis of hexahydrobenzo[de]isochromanes.

5.3. Our Strategy and Objective

In this chapter, we are going to present an efficient methodology for the synthesis of tricyclic compound hexahydrobenzo[de]isochromanes *via* Friedel Crafts and oxa-Pictet-Spengler type reaction from aryl and alkene substituted enol ethers catalyzed by triflic acid in good yields under mild conditions. This method is also extended for the synthesis of hexahydropyrano[3,4,5-*ij*]isoquinoline (Scheme 5.3.1). We have also studied the antileishmanial activity of some hexahydrobenzo[de]isochromanes.



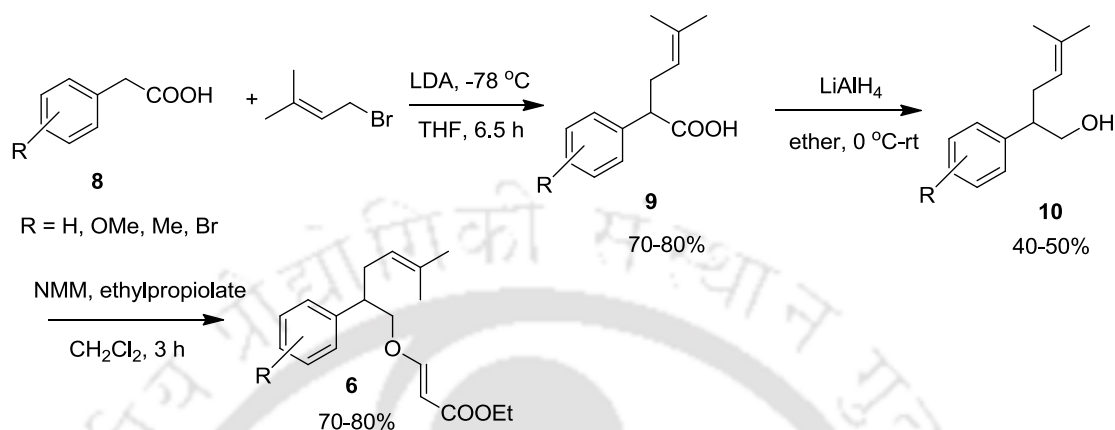
Scheme 5.3.1

5.4. Results and Discussions

5.4.1. Preparation of alkenols and enol ethers

We started our investigation with the preparation of alkenols **10** from 2-phenylacetic acid **8** and 1-bromo-3-methylbut-2-ene as shown in Scheme 5.4.1.1. The reaction of 2-phenylacetic acid **8** with 1-bromo-3-methylbut-2-ene in presence of LDA in THF at -78 °C afforded substituted 5-methyl-2-phenylhex-4-enoic acid **9**, which after reduction with lithiumaluminiumhydride ($LiAlH_4$) in ether gives alkenols **10** in good yields. The

alkenols **10** is then treated with ethyl propiolate in presence of NMM to give enol ethers **6** in 70-80% yields.⁵ The other enol ethers were synthesized from alkenols as already discussed in chapter 4 (Scheme 4.4.1.2). The structures of all compounds were determined from IR, ¹H, ¹³C NMR and mass spectrometry.



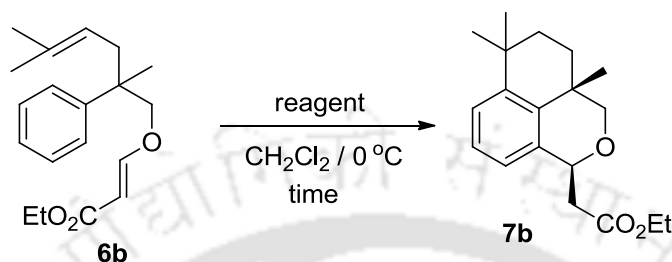
5.4.2. Optimization studies

To start with, we had chosen (*E*)-ethyl 3-((2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate **6b** as model substrate for our optimization studies and the results are summarized in Table 5.4.2.1. The effect solvents in enol-ether cyclization were already discussed in chapter 3 and dichloromethane was found to be a best solvent for this cyclization. So, in this case we optimized the reaction with various acids by taking dichloromethane as sole solvent. At first, we carried out the reaction by using triflic acid (TfOH) (1.0 equiv) in dichloromethane at 0 °C and the product ethyl 2-((1*S**,3*aS**)-3*a*,6,6-trimethyl-1,3,3*a*,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate **7b** was obtained in 75% yield. The catalytic activity of TfOH was also studied with 10 mol% and the desired product **7b** was obtained with the same yield (75%). The reaction was also performed with different Brønsted and Lewis acids. The reaction with 1.0 equivalent of BF₃·OEt₂, In(OTf)₃, Sc(OTf)₂ and InCl₃ didn't give any desired products and starting material was recovered in all the cases. On the other hand, TMSOTf, FeCl₃ and TsOH gave inseparable mixture of products. So, 10 mol% of triflic acid in dichloromethane was found to be best combination for the synthesis of hexahydrobenzo[de]isochromanes.

5.4.3. Substrate scope of the reaction

With the optimized condition in hand, the scope of the reaction was investigated by using different types of substrates having aliphatic and aromatic substituents at different

Table 5.4.2.1. Optimization of the reaction

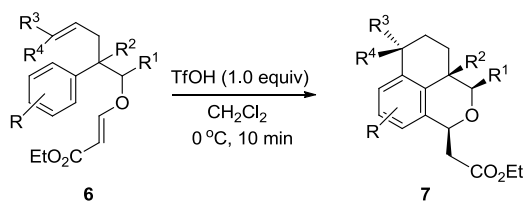


entry	reagent (equiv)	time/min	yield(%) ^b
1	BF ₃ ·OEt ₂ (1.0)	30	-- ^c
2	In(OTf) ₃ (1.0)	30	-- ^c
3	Sc(OTf) ₂ 1.0)	30	-- ^c
4	InCl ₃ (1.0)	30	-- ^c
5	TMSOTf (1.0)	30	-- ^d
6	FeCl ₃ (1.0)	30	-- ^d
7	<i>p</i> -TsOH (1.0)	30	-- ^d
8	TfOH (1.0)	10	75
9	TfOH (10 mol%)	10	75

^aReaction conditions: enol ether (1.0 mmol), solvent (2 mL) ^bYield refers to isolated yield. ^cNo reaction, starting material was recovered. ^dcomplex mixture.

positions of the enol ethers as summarized in Table 5.4.3.1. It was found that substrates having disubstitution at the 6-position of the enol ethers (**6a-j** and **6n**) gave their corresponding products (**7a-j** and **7n**) as single diastereomer in good yields (62-76%). However, in case where 6-position of the enol ethers were monosubstituted (**6k-l** and **6o**), the products (**7k-l** and **7o**) were obtained as diastereomeric mixture in different ratio in good yields (57-75%). In some cases, we also synthesized the tricyclic heterocyclic compounds having a substitution at the bridgehead position (**7b-g**, **7k-l** and **7n-o**) in good yields (57-76%). It was also observed that in case of para substituted substituent at C-3

Table 5.4.3.1. Synthesis of hexahydrobenzo[de]isochromanes



Sl.No.	Substrate 6	Product 7	Yield (%) ^a	d. r. ^b
a			76	—
b			75	—
c			65	—
d			76	—
e			68	—
f			75	—
g			55	—
h			71	—

Continue.....

Sl.No.	Substrate 6	Product 7	Yield (%) ^a	d. r. ^b
i			62	—
j			74	—
k			70	3:1
l			75	4:1
m			71	8:1
n			73	—
o			57	8:5

^aYields refer to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry.^bRatio is determined by ¹H NMR.

position of the product (**7d-7f**, **7l**), yield of the reaction was good but the yield was decreased in case of meta substituted substituent (**7g**, 55%). This is due to the steric hindrance of meta substituted substituent with bridgehead substituent at C-3a position.

5.4.4. Stereochemistry of the hexahydrobenzo[de]isochromanes

The stereochemistry of the compounds was determined by 2-D nuclear overhauser effect (NOESY). The compounds **7a**, **7h-j** and **7m** where there is no bridgehead methyl group, the correlation between the hydrogen at C3a-H and hydrogen at C1-H was determined by NOE experiment of compound **7i**. These hydrogens showed a strong NOE correlation, which confirms that these are in *cis* configuration and the positions of these hydrogens are determined from the DEPT and HMQC experiments. Similarly, the compounds **7b**, **7k** and **7o** having bridgehead substituents, the configuration between the substituents at C-1 and C-3a positions was determined by NOE experiment of the compound **7b** and these also showed a *cis* configuration. On the other hand, stereochemistry of the compounds **7c-g**, **7l** and **7n** having substitutions at 1, 3, 3a and 6 positions is determined by NOE experiments of **7d** and these also found to be *cis* configuration (Figure 5.4.4.1).

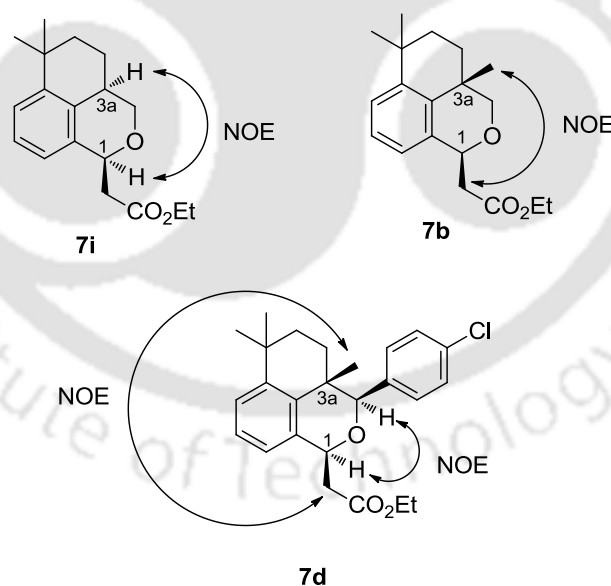


Figure 5.4.4.1. NOE of compounds **7i**, **7b** and **7d**

5.5. Synthesis of Pyranoisoquinoline

5.5.1. Importance of pyranoisoquinoline

Pyranoisoquinoline is the core unit of the tetracyclic alkaloids stephaxocanes. These are obtained from natural sources of China, Japan and Brazil. Five members of this family (stephaxocanidine, eletefine, excentricine, *N*-methylexcentricine and stephaxocanine) (Figure 5.5.1.1) were isolated from specimens of *Stephania cepharantha*, *Stephania excentrica* and *Cissampelos glaberrima*, all belonging to Menispermaceae family. These find applications in folk medicines. Some of them show potent inhibitory activity of the enzyme *acetylcholinesterase*, one of the most important therapeutic targets for the treatment of Alzheimer's disease.⁶

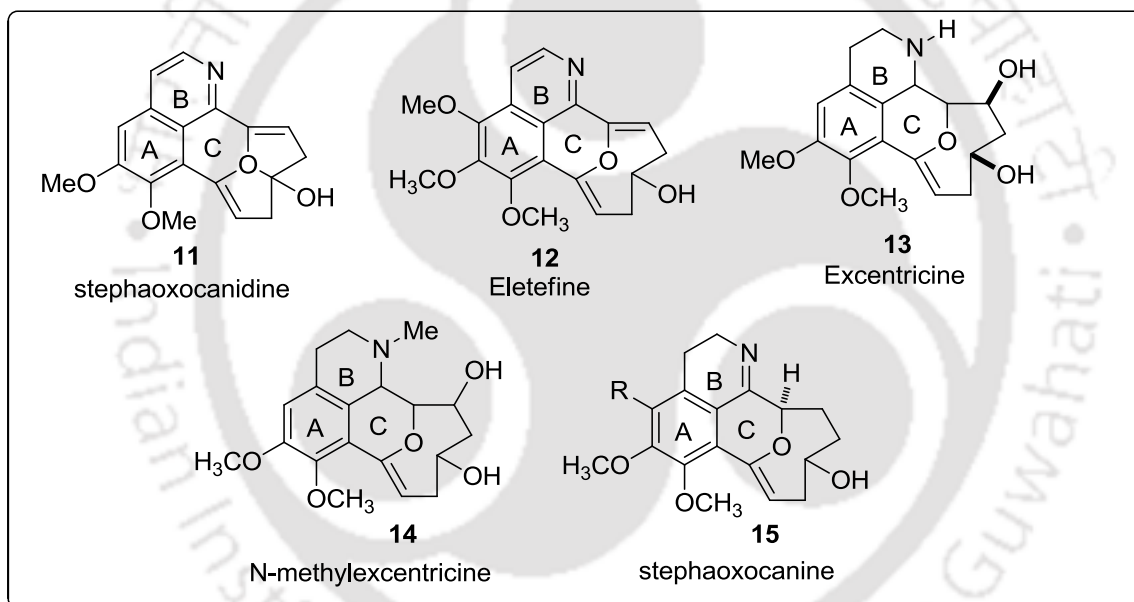
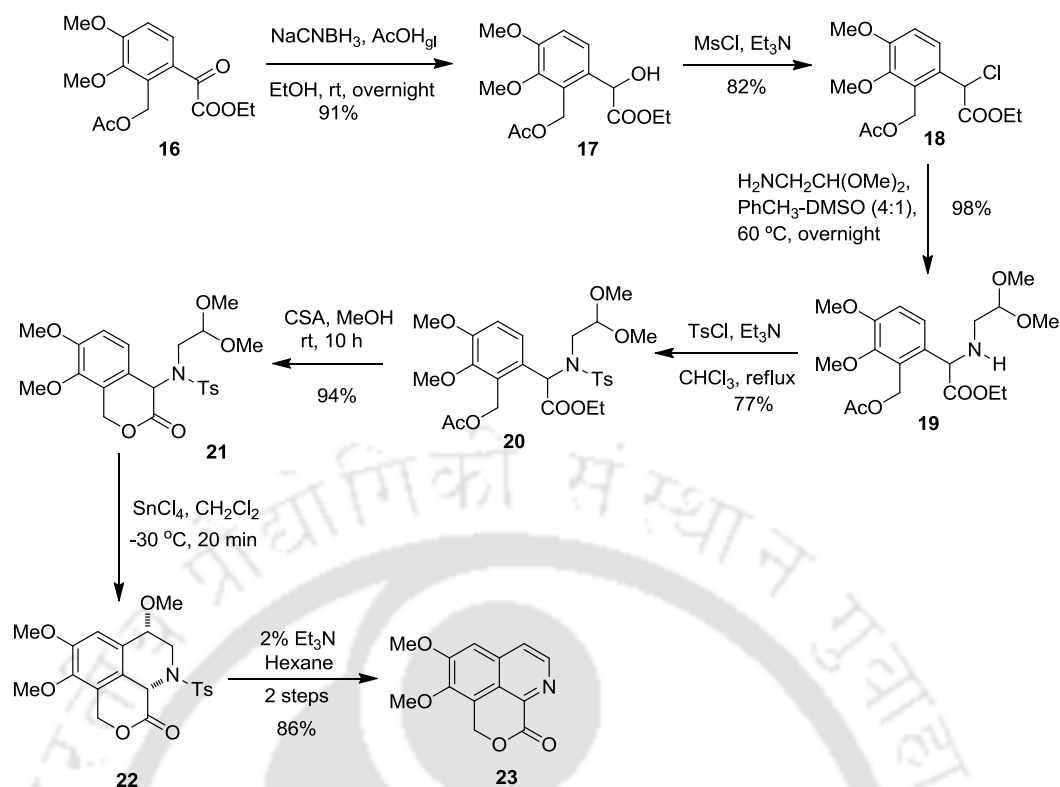


Figure 5.5.1.1. Some biologically important molecules containing pyranoisoquinoline ring as core units.

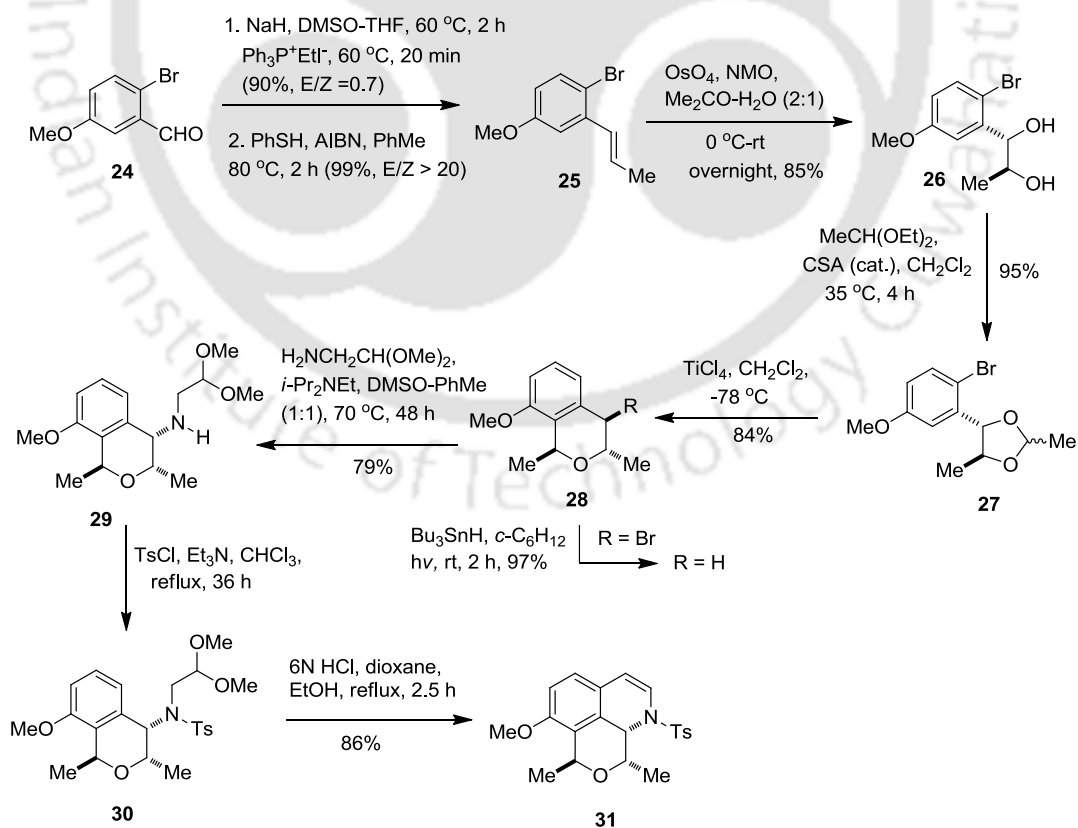
5.5.2. Literature review on synthesis of pyranoisoquinoline

Review of literature reveals that strategies developed for the synthesis of pyranoisoquinoline rings are limited.

Kaufman and co-workers have reported a methodology for the synthesis of pyranoisoquinoline ring **23** from tricarbonylic compound **16** followed by six steps synthesis giving the tricyclic compound **23** (Scheme 5.5.2.1).⁷



Scheme 5.5.2.1

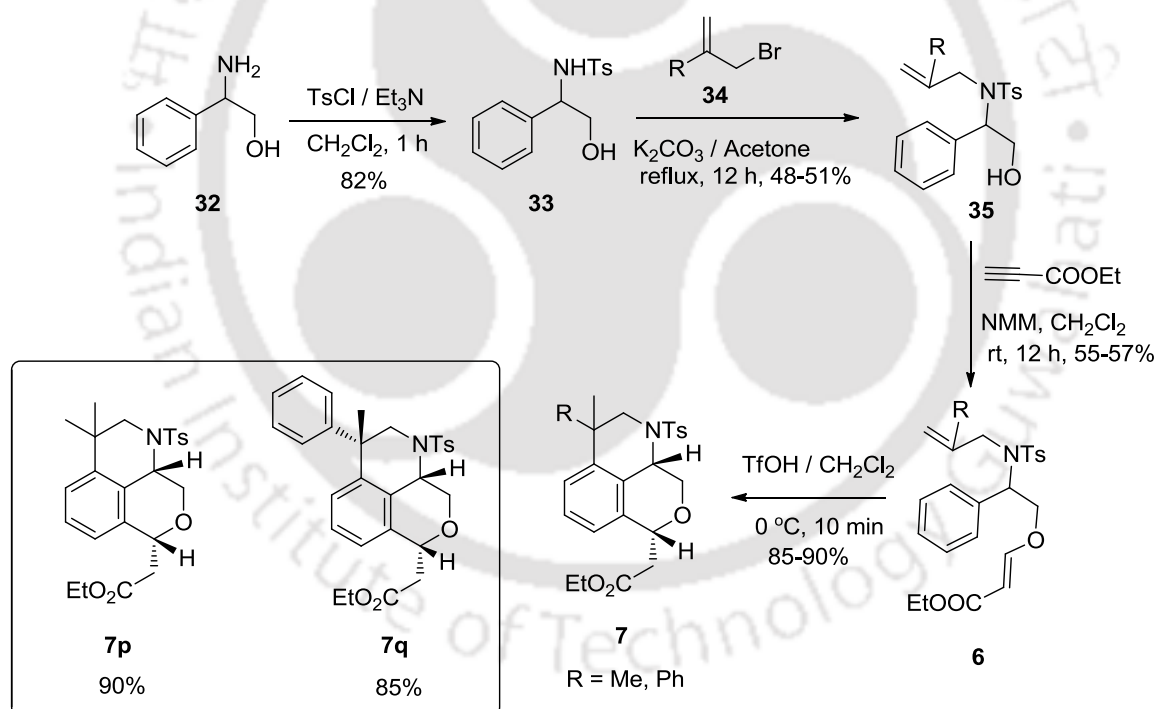


Scheme 5.5.2.2

The same group also described the synthesis of pyranoisoquinoline ring **31** from bromobenzaldehyde **24** followed by eight steps synthesis to afford tricyclic compound **31** in 86% (Scheme 5.5.2.2).⁸

5.5.3. Our strategy

Here, we have utilized our methodology for the synthesis of pyranoisoquinoline ring. We started the synthesis by tosylation of phenylglycinol **32** to give *N*-tosylated phenyl glycinol **33**, which on allylation with substituted allylbromide **34** gave alkenol **35**.⁹ The Michael addition reaction of **35** with ethylpropiolate in presence of NMM afforded enol ether **6**. Treatment of enol ether **6** with triflic acid in dichloromethane at 0 °C afforded hexahydropyrano[3,4,5-*ij*]isoquinoline **7** in good yields (85-90%). We have synthesized two hexahydropyrano[3,4,5-*ij*]isoquinoline **7p** (90%) and **7q** (85%) by varying the substituent at C-6 position of enol ether **6** (Scheme 5.5.3.1).



Scheme 5.5.3.1. Synthesis of hexahydropyrano[3,4,5-*ij*]isoquinoline

5.5.4. Stereochemistry of hexahydropyrano[3,4,5-*ij*]isoquinoline

The stereochemistry of **7p** and **7q** were determined by NOE experiment of **7q** (Figure 5.5.4.1.). In NOESY experiment, hydrogens at C-1, C-3a and methyl group at C-6

position showed characteristic correlation in NOE, which confirms that all these hydrogens are in *cis* configuration.

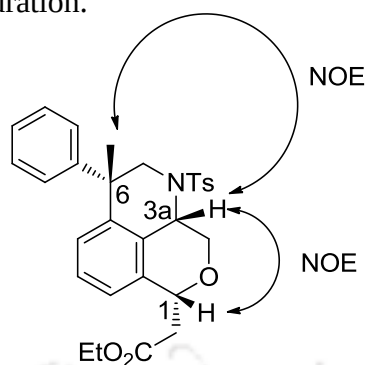
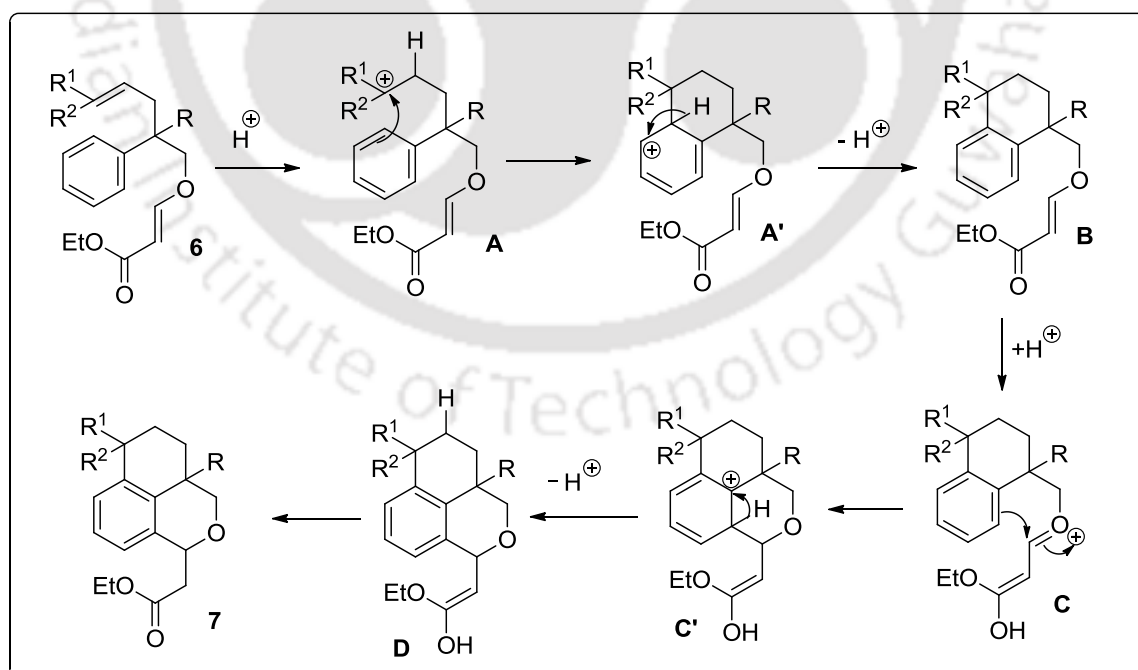


Figure 5.5.4.1. NOE of ethyl 2-((3*S*,7*R*,9*aS*)-3-methyl-3-phenyl-1-tosyl-1,2,3,7,9,9*a*-hexahydropyrano[3,4,5-*ij*]isoquinolin-7-yl)acetate

5.6. Plausible Mechanism of the Reaction

On the basis of our results, we proposed a mechanism in which both Friedel-Crafts and oxa Pictet-Spengler type reactions operating in tandem. The enol ether **6** reacts with acid to form carbocation **A**, which after Friedel-Crafts reaction and subsequent elimination and addition of protons give oxocarbenium ion **C**. The oxocarbenium ion **C** is then attacked



Scheme 5.6.1. Mechanism of the reaction

by aromatic ring via Pictet-Spengler type reaction to form hexahydrobenzo[de]isochromane **7** (Scheme 5.6.1).

5.7. Biological Studies

After the successful study of the methodology for the synthesis of tricyclic compounds we screened some of them against leishmania. Leishmania is a dimorphic protozoan parasite, which is responsible for the disease leishmaniasis.¹⁰ Due to the high toxicity, high cost and drug resistance of available drugs, there is a need of synthesizing and evaluating the antileishmanial activity of new compounds.¹¹ We have already studied the antileishmanial activity of few oxabicyclo[3.3.1]nonanones and found promising result for one of the compounds.¹² Encouraged by these results, we also screened some functional group containing tricyclic oxygen and nitrogen heterocycles fused with aromatic ring as these ring systems such as chromane and isochromane derivatives are reported to be biologically active. The three compounds **7f**, **7j** and **7p** were experimentally assessed for their anti-leishmanial activities. IC₅₀ values for these

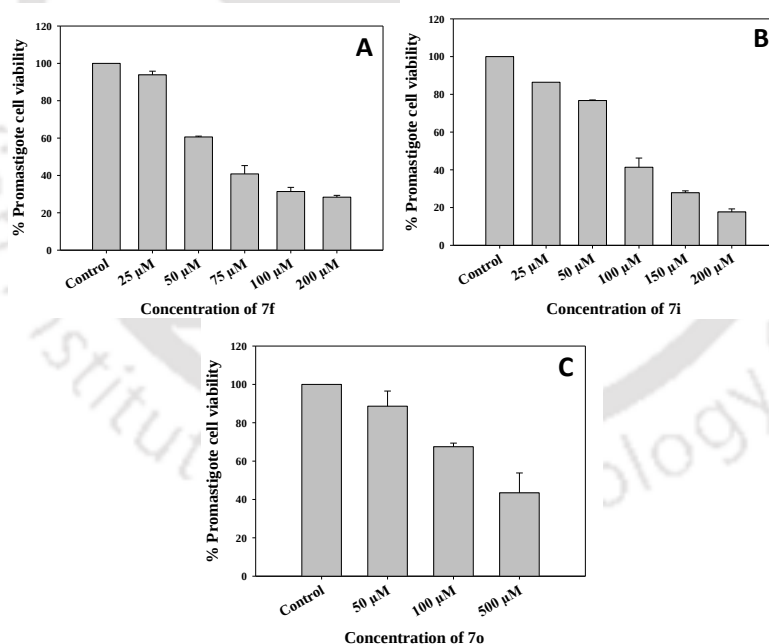


Figure 5.7.1. Antileishmanial effect of compounds **7f** (A), **7j** (B) and **7p**(C) on *Leishmania donovani* promastigote cells. The IC₅₀ values were found out to be 72.5 µM, 98.75 µM and 440 µM, respectively.

compounds were found out to be 72.5 μM , 98.75 μM and 440 μM respectively. So, the compounds **7f** and **7j** were found to be moderately effective against *Leishmania donovani* promastigotes with moderate IC_{50} values while compound **7p** was found to be least effective with a high IC_{50} value 440 μM (Figure 5.9.1). However, the known potentially active antileishmanials like miltefosine has an IC_{50} value of 25 μM . Thus, there is need for further improvement in the efficacy of these compounds. This provides a novel chemical space for further modification for development of highly effective antileishmanial compounds.

5.8. Conclusion

In conclusion, we have developed a mild and efficient method for the synthesis of tricyclic compound, hexahydrobenzo[de]isochromane via Friedel Crafts and oxa-Pictet-Spengler type reaction of enol ether in good yields. This methodology was successfully applied for the total synthesis of hexahydropyrano[3,4,5-*ij*]isoquinoline. The reaction is highly diastereoselective and compatible to functional groups such as ester, halides and ether. This methodology would provide a tool to synthesize tricyclic heterocyclic compounds having a functional group at the bridgehead position. Two of the hexahydrobenzo[de]isochromanes **7f** and **7h** are found to have antileishmanial activity with IC_{50} values 72.5 μM and 98.75 μM , respectively.

5.9. Experimental Section

5.9.1. Instrumentation and characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in CDCl_3 with tetramethylsilane as the internal standard for ^1H (600 MHz and 400 MHz) or ^{13}C (150 MHz and 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

5.9.2. General procedure for the synthesis of enol ethers 6a-q:

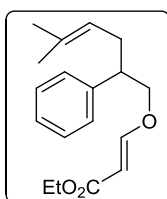
As described in reference 5 and also in Chapter 4 Section 4.6.2 .

5.9.3. General procedure for the synthesis of hexahydrobenzo[de]isochromanes and hexahydropyrano[3,4,5-ij]isoquinoline 7a-q:

To a solution of enol ether (1.0 mmol) in dry dichloromethane (1 mL) at 0 °C was added trifluoromethanesulfonic acid (10 mol%) under a N₂ atmosphere.. The reaction mixture was stirred for 10 minutes. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (EtOAc/hexane 24:1) as eluents. After the completion of the reaction, the solvent was removed on a rotary evaporator and quenched with a saturated solution of NaHCO₃ (2 mL). The product was extracted with ethyl acetate (10 mL) and then washed with brine solution (3 mL). The organic layer was dried (Na₂SO₄) and evaporated to give the crude product, which was purified by column chromatography over silica gel giving corresponding products **7a-q**.

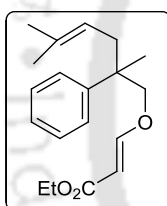
5.10. Characterization Data

(E)-Ethyl 3-((5-methyl-2-phenylhex-4-en-1-yl)oxy)acrylate (6a):



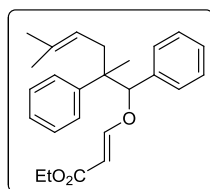
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.50; yield 225 mg, 78%; ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.54 (s, 3 H), 1.64 (s, 3 H), 2.26-2.33 (m, 1 H), 2.44-2.52 (m, 1 H), 3.01 (quintet, $J = 6.8$ Hz, 1 H), 3.96 (d, $J = 6.8$ Hz, 2 H), 4.14 (q, $J = 7.2$ Hz, 2 H), 5.03 (t, $J = 7.6$ Hz, 1 H), 5.17 (d, $J = 12.4$ Hz, 1 H), 7.18-7.21 (m, 2 H), 7.22-7.25 (m, 1 H), 7.28-7.32 (m, 2 H), 7.54 (d, $J = 13.2$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 17.9, 25.9, 31.1, 45.5, 59.9, 74.2, 96.6, 121.3, 126.9, 128.0, 128.6, 134.0, 141.8, 162.5, 168.0; IR (KBr, neat) 2980, 2928, 1712, 1632, 1454, 1319, 1220, 1136, 1041, 770, 692 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 289.1798 found 289.1799.

(E)-Ethyl 3-((2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (6b):



Pale yellow oil; R_f (hexane/EtOAc, 24:1) 0.50; yield 242 mg, 80%; ^1H NMR (600 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.35 (s, 3 H), 1.56 (s, 3 H), 1.63 (s, 3 H), 2.42 (d, $J = 7.2$ Hz, 2 H), 3.86 (d, $J = 9.6$ Hz, 1 H), 3.92 (d, $J = 9.6$ Hz, 1 H), 4.15 (q, $J = 7.2$ Hz, 2 H), 4.89 (t, $J = 7.2$ Hz, 1 H), 5.19 (d, $J = 12.6$ Hz, 1 H), 7.22 (t, $J = 8.4$ Hz, 1 H), 7.25-7.33 (m, 4 H), 7.57 (d, $J = 12.6$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.6, 18.2, 22.9, 26.1, 37.2, 42.4, 60.0, 78.3, 96.5, 119.5, 126.4, 126.5, 128.5, 134.6, 144.9, 162.8, 168.0; IR (KBr, neat) 2977, 1709, 1625, 1444, 1326, 1220, 1133, 1048, 760, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 303.1955 found 303.1956.

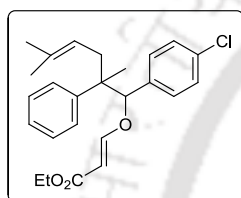
(E)-Ethyl 3-((2,5-dimethyl-1,2-diphenylhex-4-en-1-yl)oxy)acrylate (diastereomeric mixture, 4:3, 6c):



Pale yellow oil; R_f (hexane/EtOAc, 24:1) 0.50; yield 306 mg, 81%; ^1H NMR (600 MHz, CDCl_3): δ 1.18 (t, $J = 7.2$ Hz, 3 H, major), 1.98 (t, $J = 7.2$ Hz, 3 H, minor), 1.27 (s, 3 H, major), 1.29 (s, 3 H, minor), 1.56 (s, 3 H, major), 1.57 (s, 3 H, minor), 1.60 (s, 3 H), 2.45 (dd, $J = 14.4$ and 8.4 Hz, 2 H, minor), 2.61 (dd, $J = 14.4$ and 7.2 Hz, 2 H, major), 4.01-4.11 (m, 2 H), 4.81 (t, $J = 7.2$ Hz, 1 H, major), 4.87 (t, $J = 7.2$ Hz, 1 H, minor), 4.88 (s, 1 H, major), 4.95 (s, 1

H, minor), 5.11 (d, $J = 12.6$ Hz, 1 H, major), 5.15 (d, $J = 12.0$ Hz, 1 H, minor), 6.70 (d, $J = 7.8$ Hz, 2 H, minor), 6.81 (d, $J = 7.2$ Hz, 2 H, major), 7.08-7.26 (m, 8 H), 7.39 (d, $J = 12.0$ Hz, 1 H, major), 7.49 (d, $J = 12.0$ Hz, 1 H, minor); ^{13}C NMR (150 MHz, CDCl_3): δ 14.3, 14.5, 18.3, 18.4, 18.8, 20.9, 26.0, 26.1, 36.3, 36.4, 46.5, 47.0, 59.8, 59.9, 91.0, 91.6, 98.4, 98.6, 119.8, 120.2, 126.5, 126.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.18, 128.2, 128.4, 133.8, 134.3, 135.6, 136.8, 142.8, 161.8, 162.0, 168.0; IR (KBr, neat) 2981, 2929, 1712, 1642, 1446, 1368, 1220, 1130, 1045, 779 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{31}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 379.2268 found 379.2265.

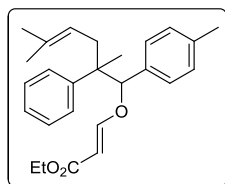
(E)-Ethyl-3-((1-(4-chlorophenyl)-2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (diastereomeric mixture, 3:2, 6d):



Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.50; yield 293 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 1.19 (t, $J = 7.2$ Hz, 3 H, major), 1.21 (t, $J = 7.2$ Hz, 3 H, minor), 1.26 (s, 3 H, major), 1.27 (s, 3 H, minor), 1.57 (s, 3 H, minor), 1.58 (s, 3 H, major), 1.60 (s, 3 H, minor), 1.61 (s, 3 H, major), 2.49 (dd, $J = 14.4$ and 8.4 Hz, 2 H, minor), 2.60 (dd, $J = 14.4$ and 7.8 Hz, 2 H, major), 4.02-4.12 (m, 2 H), 4.79 (t, $J = 7.2$ Hz, 1 H, minor), 4.84 (s, 1 H, major), 4.89 (t, $J = 7.2$ Hz, 1 H, major), 4.92 (s, 1 H, minor), 5.09 (d, $J = 12.6$ Hz, 1 H, major), 5.13 (d, $J = 12.6$ Hz, 1 H, minor), 6.59 (d, $J = 8.4$ Hz, 2 H, minor), 6.70 (d, $J = 8.4$ Hz, 2 H, major), 7.06 (d, $J = 8.4$ Hz, 1 H), 7.10-7.14 (m, 2 H), 7.19-7.27 (m, 1 H), 7.37 (d, $J = 12.6$ Hz, 1 H, major), 7.48 (d, $J = 12.6$ Hz, 1 H, minor); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 18.4, 18.5, 21.1, 26.0, 26.1, 36.1, 36.5, 46.5, 47.0, 59.9, 60.1, 90.2, 90.8, 98.8, 98.9, 119.6, 119.9, 126.7, 126.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.3, 129.2, 129.7, 133.8, 134.0, 134.6, 135.4, 142.2, 142.3, 161.5, 161.7, 167.8; IR (KBr, neat) 2980, 2927, 1709, 1628, 1624, 1445, 1377, 1220, 1130, 1046, 760, 699 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{30}\text{ClO}_3$ ($\text{M} + \text{H}$) $^+$ 413.1878 found 413.1861.

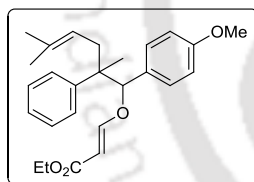
(E)-Ethyl-3-((2,5-dimethyl-2-phenyl-1-(p-tolyl)hex-4-en-1-yl)oxy)acrylate (diastereomeric mixture, 4:3, 6e):

Colorless oil; R_f (hexane/EtOAc 24:1) 0.48; yield 294 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 1.19 (t, $J = 7.2$ Hz, 3 H, minor), 1.21 (t, $J = 7.2$ Hz, 3 H, major), 1.28 (s, 3 H,



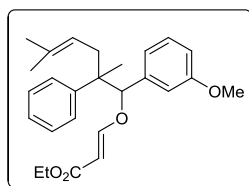
minor), 1.30 (s, 3 H, major), 1.57 (s, 3 H, minor), 1.58 (s, 3 H, major), 1.61 (s, 3 H), 2.25 (s, 3 H, major), 2.29 (s, 3 H, minor), 2.46 (dd, $J = 14.4$ and 8.4 Hz, 2 H, minor), 2.61-2.63 (m, 2 H, major), 4.04-4.10 (m, 2 H), 4.82 (t, $J = 7.2$ Hz, 1 H, major), 4.87 (s, 1 H, minor), 4.89 (t, $J = 7.2$ Hz, 1 H, minor), 4.93 (s, 1 H, major), 5.12 (d, $J = 12.0$ Hz, 1 H, minor), 5.16 (d, $J = 12.6$ Hz, 1 H, major), 6.61 (d, $J = 7.8$ Hz, 2 H, major), 6.71 (d, $J = 7.8$ Hz, 2 H, minor), 6.91 (d, $J = 7.8$ Hz, 2 H, minor), 6.98 (d, $J = 7.8$ Hz, 2 H, major), 7.15 (d, $J = 7.8$ Hz, 2 H), 7.20-7.36 (m, 1 H), 7.38 (d, $J = 12.6$ Hz, 1 H, major), 7.49 (d, $J = 12.6$ Hz, 1 H, minor); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 18.3, 18.4, 20.9, 21.2, 21.3, 26.0, 26.1, 36.3, 36.4, 46.5, 47.0, 59.8, 59.8, 91.0, 91.6, 98.3, 98.4, 119.9, 120.2, 126.4, 126.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.25, 128.3, 128.4, 128.5, 133.7, 133.8, 134.2, 137.5, 137.9, 142.8, 142.9, 161.9, 162.2, 168.0; IR (KBr, neat) 2978, 1707, 1622, 1444, 1220, 1130, 1038, 854, 758 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{33}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 393.2424 found 393.2425.

(E)-Ethyl 3-((1-(4-methoxyphenyl)-2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (diastomeric mixture, 3:2, 6f):



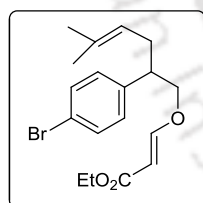
Colorless oil; R_f (hexane/EtOAc 24:1) 0.48; yield 238 mg, 70%; ^1H NMR (600 MHz, CDCl_3): δ 1.19 (t, $J = 7.2$ Hz, 3 H, major), 1.20 (t, $J = 7.2$ Hz, 3 H, minor), 1.26 (s, 3 H, minor), 1.29 (s, 3 H, major), 1.55 (s, 3 H, minor), 1.56 (s, 3 H, major), 1.60 (s, 3 H, major), 1.61 (s, 3 H, minor), 2.44 (dd, $J = 15.0$ and 8.4 Hz, 2 H, minor), 2.56-2.66 (m, 2 H, major), 3.73 (s, 3 H, major), 3.76 (s, 3 H, minor), 4.03-4.10 (m, 2 H), 4.82 (t, $J = 7.2$ Hz, 1 H, major), 4.83 (s, 1 H, minor), 4.88 (t, $J = 7.2$ Hz, 1 H, minor), 4.90 (s, 1 H, major), 5.10 (d, $J = 12.6$ Hz, 1 H, minor), 5.15 (d, $J = 12.6$ Hz, 1 H, major), 6.61 (d, $J = 7.2$ Hz, 4 H, major), 6.71 (d, $J = 7.8$ Hz, 4 H, minor), 6.13 (d, $J = 7.8$ Hz, 1 H), 7.19-7.26 (m, 3 H), 7.35-7.40 (m, 1 H), 7.38 (d, $J = 12.6$ Hz, 1 H, minor), 7.48 (d, $J = 12.6$ Hz, 1 H, major); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 18.2, 18.3, 18.4, 18.9, 20.9, 26.0, 26.1, 36.3, 36.3, 46.6, 47.0, 55.1, 55.2, 59.7, 59.8, 90.7, 91.3, 98.3, 98.4, 112.9, 113.1, 119.8, 120.2, 126.4, 126.5, 127.8, 127.9, 128.0, 128.1, 128.3, 128.8, 129.1, 129.2, 129.6, 133.7, 134.2, 142.7, 142.8, 159.1, 159.4, 161.9, 162.1, 168.0; IR (KBr, neat) 2980, 2930, 1708, 1641, 1622, 1514, 1445, 1376, 1220, 1176, 1037, 830, 763, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{NaO}_5$ ($\text{M} + \text{Na}$) $^+$ 431.2193 found 431.2180.

(E)-Ethyl 3-((1-(3-methoxyphenyl)-2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (diastereomeric mixture, 3 : 2, 6g).

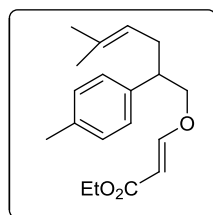


Colorless oil; R_f (hexane/EtOAc 24 : 1) 0.48; yield 199 mg, 49%; ^1H NMR (400 MHz, CDCl_3): δ 1.18–1.35 (m, 6 H), 1.57 (s, 6 H, major), 1.63 (s, 6H, minor), 2.47 (dd, $J = 16.0$ and 9.6 Hz, 1 H), 2.61 (d, $J = 4.0$ Hz, 1 H), 3.53 (s, 3 H, major), 3.56 (s, 3 H, minor), 4.04–4.17 (m, 2 H), 4.81 (t, $J = 7.2$ Hz, 1 H, major), 4.84 (s, 1 H, minor), 4.90 (t, $J = 7.2$ Hz, 1 H, minor), 4.92 (s, 1 H, major), 5.15 (d, $J = 12.6$ Hz, 1 H, minor), 5.16 (d, $J = 12.0$ Hz, 1 H, major), 6.10 (s, 1 H, major), 6.17 (s, 1 H, minor), 6.38 (d, $J = 8.0$ Hz, 1 H, major), 6.51 (d, $J = 8.0$ Hz, 1 H, minor), 6.69 (d, $J = 8.0$ Hz, 1 H), 6.75 (d, $J = 8.0$, 1 H), 7.03 (t, $J = 8.0$ Hz, 1 H), 7.10 (t, $J = 8.0$ Hz, 1 H, minor), 7.15 (d, $J = 8.0$ Hz, 1 H, major), 7.16–7.31 (m, 3 H), 7.41 (d, $J = 12$ Hz, 1 H, minor), 7.50 (d, $J = 12$ Hz, 1 H, major); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 14.5, 18.3, 18.4, 18.9, 21.2, 26.1, 26.2, 30.0, 36.5, 47.0, 58.2, 59.9, 60.0, 91.0, 91.4, 98.5, 98.6, 113.1, 113.4, 114.0, 114.3, 120.1, 120.4, 128.0, 128.2, 128.4, 133.9, 134.4, 138.3, 142.8, 142.8, 158.8, 159.0, 161.8, 162.1, 168.0. IR (KBr, neat) 2975, 2948, 1706, 1650, 1620, 1511, 1425, 1370, 1210, 1100, 1031, 755, 690 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{32}\text{NaO}_4$ ($\text{M} + \text{Na}$) $^+$ 431.2193 found 431.2195.

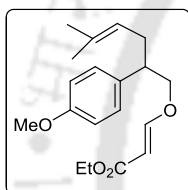
(E)-Ethyl 3-((2-(4-bromophenyl)-5-methylhex-4-en-1-yl)oxy)acrylate (6h):



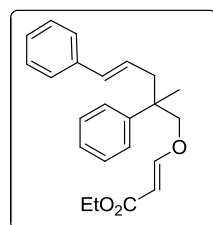
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 275 mg, 71%; ^1H NMR (600 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 2.26 (quint, $J = 7.2$ Hz, 1 H), 2.45 (quint, $J = 7.2$ Hz, 1 H), 2.95 (quint, $J = 7.2$ Hz, 1 H), 3.92–3.94 (m, 2 H), 4.14 (q, $J = 7.2$ Hz, 2 H), 4.98 (t, $J = 7.8$ Hz, 1 H), 5.16 (d, $J = 12.6$ Hz, 1 H), 7.06 (d, $J = 7.8$ Hz, 2 H), 7.42 (d, $J = 8.4$ Hz, 2 H), 7.52 (d, $J = 13.2$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 18.0, 25.9, 31.0, 45.1, 60.0, 73.9, 96.9, 120.8, 120.9, 129.8, 131.7, 134.4, 140.8, 162.3, 167.9; IR (KBr, neat) 2977, 2929, 1709, 1625, 1489, 1327, 1220, 1137, 1048, 821, 758, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{23}\text{BrO}_3$ ($\text{M} + \text{Na}$) $^+$ 389.0723 found 389.0726.

(E)-Ethyl 3-((5-methyl-2-(p-tolyl)hex-4-en-1-yl)oxy)acrylate (6i):

Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 211 mg, 70%; ^1H NMR (600 MHz, CDCl_3): δ 1.26 (t, $J = 7.2$ Hz, 3 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 2.29 (quint, $J = 7.2$ Hz, 1 H), 2.33 (s, 3 H), 2.48 (quint, $J = 7.2$ Hz, 1 H), 2.96 (quint, $J = 7.2$ Hz, 1 H), 3.95 (d, $J = 6.0$ Hz, 2 H), 4.15 (q, $J = 7.2$ Hz, 2 H), 5.04 (t, $J = 7.2$ Hz, 1 H), 5.18 (d, $J = 12.6$ Hz, 1 H), 7.08 (d, $J = 7.8$ Hz, 2 H), 7.12 (d, $J = 7.8$ Hz, 2 H), 7.56 (d, $J = 12.6$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 18.0, 21.2, 25.9, 31.1, 45.1, 59.9, 74.4, 96.6, 121.4, 127.8, 129.3, 133.8, 136.5, 138.7, 162.6, 168.0; IR (KBr, neat) 2977, 2928, 1710, 1625, 1447, 1325, 1219, 1136, 1048, 816, 768 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 303.1955 found 303.1952.

(E)-Ethyl 3-((2-(4-methoxyphenyl)-5-methylhex-4-en-1-yl)oxy)acrylate (6j):

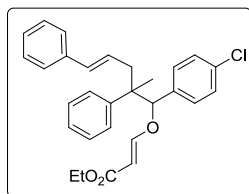
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 239 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.55 (s, 3 H), 1.65 (s, 3 H), 2.26 (quint, $J = 7.2$ Hz, 1 H), 2.46 (quint, $J = 7.2$ Hz, 1 H), 2.95 (quint, $J = 7.2$ Hz, 1 H), 3.79 (s, 3 H), 3.92 (d, $J = 6.0$ Hz, 2 H), 4.14 (q, $J = 7.2$ Hz, 2 H), 5.02 (t, $J = 7.2$ Hz, 1 H), 5.17 (d, $J = 12.6$ Hz, 1 H), 6.85 (d, $J = 8.4$ Hz, 2 H), 7.10 (d, $J = 8.4$ Hz, 2 H), 7.55 (d, $J = 12.6$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 18.0, 25.9, 31.2, 44.7, 55.4, 59.9, 74.5, 96.6, 114.1, 121.4, 128.9, 133.7, 133.8, 158.6, 162.6, 168.0; IR (KBr, neat) 2928, 1710, 1625, 1463, 1325, 1220, 1136, 1040, 829, 772 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 319.1904 found 319.1907.

(E)-Ethyl 3-(((E)-2-methyl-2,5-diphenylpent-4-en-1-yl)oxy)acrylate (6k):

Colorless oil; R_f (hexane/EtOAc 24:1) 0.48; yield 245 mg, 70%; ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 1.42 (s, 3 H), 2.59 (dd, $J = 14.0$ and 14.0 Hz, 1 H), 2.70 (dd, $J = 14.0$ and 6.8 Hz, 1 H), 3.93 (dd, $J = 12.8$ and 9.6 Hz, 2 H), 4.15 (q, $J = 7.2$ Hz, 2 H), 5.20 (d, $J = 12.8$ Hz, 1 H), 5.91 (quint, $J = 7.6$ Hz, 1 H), 6.38 (d, $J = 15.6$ Hz, 1 H), 7.16-7.20 (m, 1 H), 7.20-7.25 (m, 5 H), 7.27-7.36 (m, 4 H), 7.59 (d, $J = 13.2$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 22.9, 42.3, 42.5, 60.0, 78.4, 96.7, 125.7, 126.3, 126.5, 126.8, 127.4, 128.7, 133.5, 137.5, 144.3, 162.7, 168.0; IR (KBr, neat) 2975,

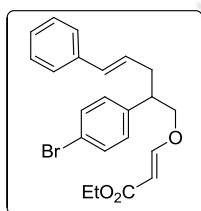
2928, 1707, 1629, 1455, 1399, 1210, 1132, 1040, 964, 770, 680 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{27}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 351.1955 found 351.1950.

(E)-Ethyl-3-(((E)-1-(4-chlorophenyl)-2-methyl-2,5-diphenylpent-4-en-1-yl)oxy)acrylate (diastereomeric ratio 2:1, 6l):



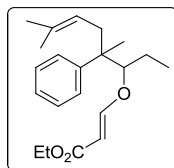
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 313 mg, 68%; ^1H NMR (400 MHz): δ 1.18-2.26 (m, 3 H, major & minor), 1.32 (s, 3 H, major), 1.34 (s, 3 H, minor), 2.56 (dd, $J = 14.0$ and 9.2 Hz, 1 H, minor), 2.71 (dd, $J = 14.4$ and 9.2 Hz, 1 H, major), 2.95 (ddd, $J = 13.6$, 5.6 and 4.8 Hz, 1 H, major & minor), 4.02-4.13 (m, 2 H, major & minor), 4.87 (s, 1 H, minor), 4.98 (s, 1 H, major), 5.12 (d, $J = 12.4$ Hz, 1 H, minor), 5.16 (d, $J = 12.4$ Hz, 1 H, major), 5.78-5.87 (m, 1 H, major), 5.89-5.95 (m, 1 H, minor), 6.40 (d, $J = 15.6$ Hz, 1 H, major & minor), 6.63 (d, $J = 8.8$ Hz, 2 H, major), 6.73 (d, $J = 8.8$ Hz, 2 H, minor), 7.07-7.19 (m, 12 H, major & minor), 7.39 (d, $J = 12.8$ Hz, 1 H, minor), 7.49 (d, $J = 12.4$ Hz, 1 H, major); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 18.6, 21.3, 41.3, 42.1, 46.4, 46.9, 59.9, 60.0, 90.4, 90.7, 98.9, 99.1, 125.8, 126.1, 126.2, 126.3, 126.9, 127.0, 127.2, 127.3, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 129.2, 129.7, 133.3, 133.7, 133.9, 135.1, 137.6, 141.8, 142.0, 161.3, 161.6, 167.7; IR (KBr, neat) 2979, 1707, 1642, 1492, 1321, 1220, 1131, 1048, 761, 686 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{30}\text{ClO}_3$ ($\text{M} + \text{H}$)⁺ 461.1878 found 461.1885.

(E)-Ethyl 3-(((E)-2-(4-bromophenyl)-5-phenylpent-4-en-1-yl)oxy)acrylate (6m):



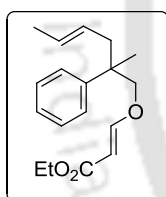
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 298 mg, 72%; ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.2$ Hz, 3 H), 2.54 (quint, $J = 7.2$ Hz, 1 H), 2.67 (quint, $J = 7.6$ Hz, 1 H), 3.11 (quint, $J = 7.2$ Hz, 1 H), 3.98 (d, $J = 6.0$ Hz, 2 H), 4.14 (q, $J = 7.2$ Hz, 2 H), 5.18 (d, $J = 12.8$ Hz, 1 H), 6.02 (quint, $J = 7.6$ Hz, 1 H), 6.38 (d, $J = 15.6$ Hz, 1 H), 7.10 (d, $J = 8.4$ Hz, 2 H), 7.18-7.21 (m, 1 H), 7.25-7.27 (m, 4 H), 7.45 (d, $J = 8.0$ Hz, 2 H), 7.54 (d, $J = 12.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 35.9, 45.0, 60.0, 73.8, 97.1, 121.1, 126.3, 126.7, 127.5, 128.7, 129.8, 131.9, 132.8, 137.3, 140.1, 162.2, 167.8; IR (KBr, neat) 2979, 2933, 1706, 1631, 1485, 1325, 1219, 1136, 1043, 963, 771, 683 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{24}\text{BrO}_3$ ($\text{M} + \text{H}$)⁺ 415.0903 found 415.0900.

(E)-Ethyl 3-((4,7-dimethyl-4-phenyloct-6-en-3-yl)oxy)acrylate (diaestereomeric ratio 3:1, 6n):



Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 270 mg, 82%; ^1H NMR (600 MHz, CDCl_3): δ 0.80 (t, $J = 7.2$ Hz, 3 H, major), 0.97 (t, $J = 7.2$ Hz, 3 H, minor), 1.24-1.30 (m, 6 H), 1.31-1.41 (m, 2 H), 1.51 (s, 3 H), 1.59 (s, 3 H), 2.41 (d, $J = 7.2$ Hz, 2 H, major), 2.53 (d, $J = 7.2$ Hz, 2 H, minor), 3.52 (d, $J = 9.6$ Hz, 1 H, minor), 3.90 (d, $J = 9.6$ Hz, 1 H, major), 4.16 (q, $J = 7.2$ Hz, 2 H), 4.71 (t, $J = 6.6$ Hz, 1 H, major), 4.85 (t, $J = 6.6$ Hz, 1 H, minor), 5.33 (d, $J = 12.0$ Hz, 1 H), 7.19-7.38 (m, 5 H, major, minor), 7.37 (d, $J = 7.8$ Hz, 1 H, minor) 7.55 (d, $J = 8.0$ Hz, 1 H, major); ^{13}C NMR (100 MHz, CDCl_3): δ 11.4, 11.9, 14.6, 18.25, 18.3, 19.5, 23.8, 24.7, 26.0, 26.1, 36.6, 37.8, 46.8, 59.8, 81.3, 95.5, 96.5, 119.8, 120.8, 126.2, 126.4, 127.2, 127.6, 128.3, 128.4, 134.1, 144.2, 165.3, 168.7; IR (KBr, neat) 2974, 2926, 1706, 1635, 1455, 1378, 1233, 1133, 1045, 814, 701 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{31}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 331.2268 found 331.2257.

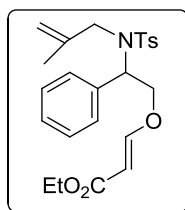
(E)-Ethyl 3-(((E)-2-methyl-2-phenylhex-4-en-1-yl)oxy)acrylate (6o):



Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 196 mg, 68%; ^1H NMR (400 MHz, CDCl_3): δ 1.28 (t, $J = 7.6$ Hz, 3 H), 1.33 (s, 3 H), 1.59 (d, $J = 6.8$ Hz, 3 H), 2.37 (dd, $J = 13.6$ and Hz, 1 H), 2.47 (dd, $J = 13.6$ and 7.6 Hz, 1 H), 3.84 (d, $J = 10$ Hz, 1 H), 3.90 (d, $J = 9.6$ Hz, 1 H), 4.14 (q, $J = 7.2$ Hz, 2 H), 5.11-5.5.16 (m, 1 H), 5.19 (d, $J = 12.4$ Hz, 1 H), 5.37-5.55 (m, 1 H), 7.18-7.24 (m, 1 H), 7.25-7.39 (m, 4 H), 7.56 (d, $J = 12.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 18.2, 22.8, 41.9, 42.1, 59.9, 78.3, 96.5, 126.4, 126.5, 126.8, 128.4, 128.5, 144.7, 162.8, 168.1; IR (KBr, neat) 2926, 1708, 1630, 1454, 1323, 1205, 1131, 1042, 964, 749, 701 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 289.1798 found 289.1790.

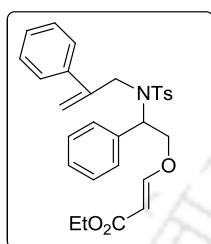
(E)-Ethyl-3-(2-(4-methyl-N-(2-methylallyl)phenylsulfonamido)-2-phenylethoxy)acrylate (6p):

Pale yellow oil; R_f (hexane/EtOAc 17:3) 0.40; yield 244 mg, 55%; ^1H NMR (400 MHz, CDCl_3): δ 1.28 (t, $J = 7.2$ Hz, 3 H), 1.56 (s, 3 H), 2.45 (s, 3 H), 3.35 (d, $J = 16.0$ Hz, 1 H), 3.84 (d, $J = 16.0$ Hz, 1 H), 4.14-4.19 (m, 3 H), 4.32-4.41 (m, 2 H), 4.77 (s, 1 H), 4.85 (s, 1 H), 5.20 (d, $J = 12.8$ Hz, 1 H), 7.02-7.04 (m, 2 H), 7.24-7.29 (m, 5H), 7.45 (d, $J =$



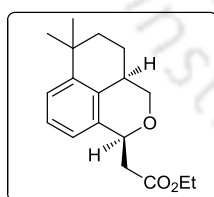
12.8 Hz, 1 H), 7.68 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 20.0, 21.7, 51.5, 59.4, 60.1, 69.6, 97.4, 114.7, 127.7, 128.6, 128.7, 128.8, 129.7, 134.7, 137.9, 142.3, 143.7, 161.4, 167.7; IR (KBr, neat) 2920, 1725, 1632, 1443, 1219, 1039, 928, 772, 680 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{30}\text{NO}_5\text{S}$ ($\text{M} + \text{H}$) $^+$ 444.1839 found 444.1839.

(E)-Ethyl-3-(2-(4-methyl-N-(2-phenylallyl)phenylsulfonamido)-2-phenylethoxy)acrylate (6q):



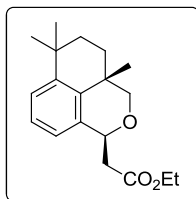
Pale yellow oil; R_f (hexane/EtOAc 17:3) 0.40; yield 288 mg, 57%; ^1H NMR (600 MHz, CDCl_3): δ 1.27 (t, $J = 7.2$ Hz, 3 H), 2.44 (s, 3 H), 3.92 (d, $J = 16.2$ Hz, 1 H), 4.06 (dd, $J = 10.2$ and 3.6 Hz, 1 H), 4.15 (q, $J = 7.2$ Hz, 2 H), 4.28 (dd, $J = 10.2$ and 1.8 Hz, 1 H), 4.39 (d, $J = 16.2$ Hz, 1 H), 5.05 (d, $J = 12.6$ Hz, 1 H), 5.11 (s, 1 H), 5.18 (t, $J = 7.2$ Hz, 1 H), 5.34 (s, 1 H), 6.99 (d, $J = 7.8$ Hz, 2 H), 7.20-7.32 (m, 12 H), 7.60 (d, $J = 8.4$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.6, 21.7, 49.6, 59.2, 60.1, 69.9, 97.4, 116.8, 126.8, 127.8, 128.3, 128.6 (2C), 128.7 (2C), 129.7, 134.6, 137.6, 138.7, 143.7, 144.5, 161.3, 167.7; IR (KBr, neat) 2931, 1707, 1632, 1332, 1145, 1042, 732 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{32}\text{NO}_5\text{S}$ ($\text{M} + \text{H}$) $^+$ 506.1996 found 506.2000.

Ethyl 2-((1S*,3aR*)-6,6-dimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7a):



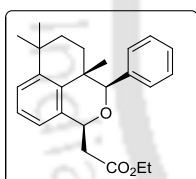
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 219 mg, 76%; ^1H NMR (400 MHz, CDCl_3): δ 1.23 (s, 3 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.36 (s, 3 H), 1.65-1.71 (m, 2 H), 1.74-1.77 (m, 2 H), 2.72 (dd, $J = 15.2$ and 9.2 Hz, 1 H), 2.88 (dd, $J = 15.2$ and 8.0 Hz, 1 H), 2.92 (dd, $J = 12.0$ and 7.2 Hz, 1 H), 3.36 (dd, $J = 11.2$ and 10.4 Hz, 1 H), 4.03 (dd, $J = 10.4$ and 4.8 Hz, 1 H), 4.19 (q, $J = 7.2$ Hz, 2 H), 5.31 (d, $J = 6.8$ Hz, 1 H), 6.87 (d, $J = 7.2$ Hz, 1 H), 6.17 (t, $J = 7.6$ Hz, 1 H), 7.24 (d, $J = 7.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 21.6, 31.9, 32.8, 34.5, 36.6, 38.3, 43.3, 60.5, 69.6, 74.1, 122.8, 125.2, 126.2, 133.8, 135.1, 145.8, 171.3; IR (KBr, neat) 2926, 2858, 1735, 1445, 1373, 1220, 1180, 1029, 855, 761 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 289.1798 found 289.1799.

Ethyl-2-((1S*,3aS*)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7b):



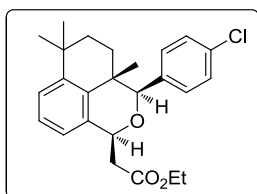
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 227 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 1.19 (s, 3 H), 1.29 (t, $J = 7.2$ Hz, 3 H), 1.33 (s, 3 H), 1.38 (dt, $J = 12.6$ and 3.6 Hz, 1 H), 1.40 (s, 3 H), 1.50 (dt, $J = 13.2$ and 3.0 Hz, 1 H), 1.63 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 2.11 (dt, $J = 14.4$ and 3.6 Hz, 1 H), 2.82 (dd, $J = 15.0$ and 9.6 Hz, 1 H), 2.94 (dd, $J = 15.0$ and 3.0 Hz, 1 H), 3.49 (d, $J = 10.8$, 1 H), 3.67 (d, $J = 10.8$, 1 H), 4.20-4.24 (m, 2 H), 5.32 (dd, $J = 9.6$ and 3.0 Hz, 1 H), 6.84 (d, $J = 7.2$ Hz, 1 H), 7.15 (t, $J = 7.8$ Hz, 1 H), 7.21 (d, $J = 7.8$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 27.1, 28.9, 32.4, 33.9, 34.0, 34.1, 34.6, 43.7, 60.8, 74.1, 75.3, 122.2, 125.9, 126.4, 134.6, 138.0, 144.3, 171.7; IR (KBr, neat) 2961, 2866, 1737, 1472, 1286, 1220, 1159, 1097, 1032, 765 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 303.1955 found 303.1955.

Ethyl-2-((1S*,3R*,3aS*)-3a,6,6-trimethyl-3-phenyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7c):



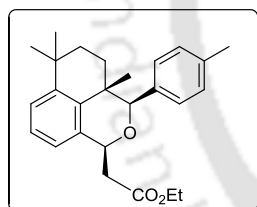
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 246 mg, 65%; ^1H NMR (600 MHz, CDCl_3): δ 1.15 (s, 3 H), 1.24 (s, 3 H), 1.28 (t, $J = 7.2$ Hz, 3 H), 1.31 (dt, $J = 15.0$ and 7.2 Hz, 1 H), 1.37 (s, 3 H), 1.55 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 1.68 (dt, $J = 13.8$ and 2.4 Hz, 1 H), 1.92 (dt, $J = 14.4$ and 2.4 Hz, 1 H), 2.93 (dd, $J = 14.4$ and 9.0 Hz, 1 H), 2.98 (dd, $J = 14.4$ and 3.6 Hz, 1 H), 4.16-4.20 (m, 1 H), 4.22-4.30 (m, 1 H), 4.52 (s, 1 H), 5.50 (dd, $J = 9.6$ and 4.2 Hz, 1 H), 6.91 (d, $J = 7.2$ Hz, 1 H), 7.20 (t, $J = 7.8$ Hz, 1 H), 7.26-7.29 (m, 2 H), 7.31 (t, $J = 7.8$ Hz, 2 H), 7.38 (d, $J = 7.2$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.2, 22.4, 29.7, 32.4, 33.8, 34.1, 34.3, 37.7, 44.3, 60.8, 74.7, 87.2, 122.4, 126.2, 126.5, 127.5, 128.2, 134.7, 135.6, 138.8, 139.0, 144.7, 171.6; IR (KBr, neat) 2960, 1717, 1622, 1447, 1369, 1220, 1123, 1094, 1029, 854, 165, 703 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{31}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 379.2268 found 379.2267.

Ethyl-2-((1S*,3R*,3aS*)-3-(4-chlorophenyl)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydro-benzo[de]isochroman-1-yl)acetate (7d):



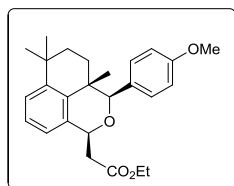
Colorless oil; R_f (hexane/EtOAc 24:1) 0.48; yield 313 mg, 76%; ^1H NMR (600 MHz, CDCl_3): δ 1.11 (s, 3 H), 1.23 (s, 3 H), 1.26-1.29 (m, 4 H), 1.37 (s, 3 H), 1.55 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 1.65 (dt, $J = 13.8$ and 2.4 Hz, 1 H), 1.92 (dt, $J = 13.8$ and 2.4 Hz, 1 H), 2.91 (dd, $J = 14.4$ and 9.0 Hz, 1 H), 2.98 (dd, $J = 14.4$ and 3.6 Hz, 1 H), 4.16-4.20 (m, 1 H), 4.22-4.26 (m, 1 H), 4.49 (s, 1 H), 5.49 (dd, $J = 9.6$ and 3.6 Hz, 1 H), 6.91 (d, $J = 7.8$ Hz, 1 H), 7.20 (t, $J = 7.8$ Hz, 1 H), 7.26-7.31 (m, 5 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 22.3, 29.7, 32.4, 33.8, 34.0, 34.3, 37.6, 44.2, 60.9, 74.8, 82.9, 122.4, 126.3, 126.6, 127.7, 129.5, 133.3, 134.5, 137.3, 138.7, 144.7, 171.5; IR (KBr, neat) 2929, 1734, 1448, 1375, 1220, 1168, 1088, 1028, 930, 771, 680 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{30}\text{ClO}_3$ ($\text{M} + \text{H}$) $^+$ 413.1878 found 413.1884.

Ethyl-2-((1S*,3R*,3aS*)-3a,6,6-trimethyl-3-(*p*-tolyl)-1,3,3a,4,5,6-hexahydro-benzo[de]iso-chroman-1-yl)acetate (7e):



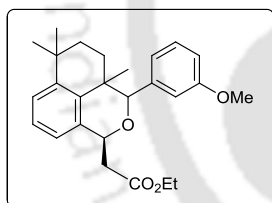
Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 267 mg, 68%; ^1H NMR (600 MHz, CDCl_3): δ 1.15 (s, 3 H), 1.23 (s, 3 H), 1.25-1.29 (m, 4 H), 1.37 (s, 3 H), 1.54 (dt, $J = 10.8$ and 3.0 Hz, 1 H), 1.66 (dt, $J = 12.0$ and 2.4 Hz, 1 H), 1.91 (dt, $J = 13.8$ and 1.8 Hz, 1 H), 2.35 (s, 3 H), 2.92 (dd, $J = 14.4$ and 9.0 Hz, 1 H), 2.97 (dd, $J = 14.4$ and 3.6 Hz, 1 H), 4.15-4.18 (m, 1 H), 4.19-4.25 (m, 1 H), 4.48 (s, 1 H), 5.49 (dd, $J = 9.0$ and 3.6 Hz, 1 H), 6.91 (d, $J = 7.8$ Hz, 1 H), 7.12 (d, $J = 7.2$ Hz, 2 H), 7.19 (t, $J = 7.8$ Hz, 1 H), 7.25-7.26 (m, 3 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 21.3, 22.4, 29.7, 32.4, 33.9, 34.1, 34.3, 37.7, 44.3, 60.8, 74.7, 83.3, 122.4, 126.2, 126.5, 128.1, 128.2, 134.7, 135.9, 137.1, 139.1, 144.7, 171.6; IR (KBr, neat) 2980, 2924, 1709, 1623, 1445, 1376, 1220, 1130, 1046, 944, 760, 699 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{33}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 393.2424 found 393.2427.

Ethyl-2-((1S*,3R*,3aS*)-3-(4-methoxyphenyl)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydro-benzo[de]isochroman-1-yl)acetate (7f):

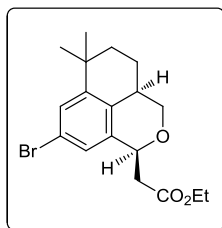


Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 306 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 1.14 (s, 3 H), 1.23 (s, 3 H), 1.23–1.29 (m, 4 H), 1.37 (s, 3 H), 1.54 (dt, $J = 13.8$ and 3.6 Hz, 1 H), 1.64 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 1.92 (dt, $J = 13.8$ and 3.6 Hz, 1 H), 2.92 (dd, $J = 14.4$ and 9.0 Hz, 1 H), 2.97 (dd, $J = 14.4$ and 3.6 Hz, 1 H), 3.81 (s, 3 H), 4.17 (dd, $J = 10.8$ and 7.2 Hz, 1 H), 4.24 (dd, $J = 10.8$ and 7.2 Hz, 1 H), 4.47 (s, 1 H), 5.49 (dd, $J = 9.0$ and 3.6 Hz, 1 H), 6.86 (d, $J = 6.6$ Hz, 2 H), 6.90 (d, $J = 7.8$ Hz, 1 H), 7.18 (t, $J = 7.8$ Hz, 1 H), 7.25 (d, $J = 7.8$ Hz, 1 H), 7.28 (d, $J = 9.0$ Hz, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.5, 22.3, 29.7, 32.4, 33.9, 34.0, 34.3, 37.7, 44.32, 55.42, 60.8, 74.7, 83.1, 113.0, 122.4, 126.2, 126.5, 129.2, 131.1, 134.7, 139.1, 144.7, 159.1, 171.6; IR (KBr, neat) 2960, 1735, 1613, 1514, 1370, 1220, 1123, 1035, 930, 759, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{32}\text{NaO}_4(\text{M} + \text{Na})^+$ 431.2193 found 431.2186.

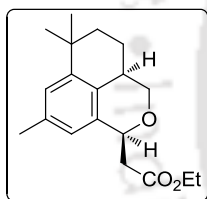
Ethyl-2-((1S*,3R*,3aS*)-3-(3-methoxyphenyl)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7g):



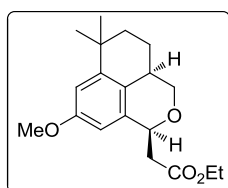
Pale yellow oil; R_f (hexane/EtOAc 24 : 1) 0.48; yield 224 mg, 55%; ^1H NMR (600 MHz, CDCl_3): δ 1.14 (s, 3 H), 1.23 (s, 3 H), 1.23–1.29 (m, 4 H), 1.37 (s, 3 H), 1.54 (dt, $J = 14.0$ and 4.0 Hz, 1 H), 1.64 (dt, $J = 14.0$ and 4.0 Hz, 1 H), 1.92 (dt, $J = 14.0$ and 4.0 Hz, 1 H), 2.92 (dd, $J = 18.0$ and 6.0 Hz, 1 H), 2.97 (dd, $J = 12.0$ and 6.0 Hz, 1 H), 3.81 (s, 3 H), 4.16–4.27 (m, 2 H), 4.47 (s, 1 H), 5.49 (dd, $J = 12.0$ and 6.0 Hz, 1 H), 6.86 (d, $J = 7.2$ Hz, 1 H), 6.91 (d, $J = 7.2$ Hz, 1 H), 6.95–6.96 (m, 2 H), 7.19 (t, $J = 7.2$ Hz, 1 H), 7.23 (t, $J = 8.0$ Hz, 1 H), 7.27–7.29 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.3, 22.9, 29.9, 32.2, 33.9, 34.0, 34.1, 37.7, 44.3, 55.5, 60.8, 74.8, 83.4, 112.7, 114.3, 120.9, 122.4, 126.2, 126.5, 128.4, 134.5, 139.5, 140.5, 144.7, 159.1, 171.6. IR (KBr, neat) 2952, 1729, 1610, 1530, 1365, 1218, 1120, 1030, 925, 765, 690 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{32}\text{NaO}_4(\text{M} + \text{Na})^+$ 431.2193 found 431.2197.

Ethyl-2-((1S*,3aR*)-8-bromo-6,6-dimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7h):

Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 260 mg, 71%; ^1H NMR (600 MHz, CDCl_3): δ 1.20 (s, 3 H), 1.23-1.29 (m, 4 H), 1.33 (s, 3 H), 1.66-1.69 (m, 1 H), 1.71- 1.76 (m, 2 H), 2.71 (dd, J = 15.6 and 9.0 Hz, 1 H), 2.80-2.85 (m, 2 H), 3.31 (t, J = 10.8 Hz, 1 H), 4.02 (dd, J = 10.8 and 4.8 Hz, 1 H), 4.17-4.20 (m, 2 H), 5.23 (dd, J = 9.0 and 3.0 Hz, 1 H), 7.0 (s, 1 H), 7.32 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 21.7, 32.1, 33.0, 35.1, 36.7, 38.4, 43.3, 60.9, 69.8, 73.9, 120.5, 125.1, 128.7, 133.2, 137.9, 147.8, 171.2; IR (KBr, neat) 2961, 1736, 1445, 1371, 1220, 1108, 1028, 931, 855, 761, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{23}\text{NaBrO}_3$ ($\text{M} + \text{Na}$) $^+$ 389.0723 found 389.0722.

Ethyl-2-((1S*,3aR*)-6,6,8-trimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7i):

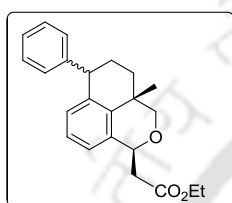
Colorless oil; R_f (hexane/EtOAc 24:1) 0.48; yield 187 mg, 62%; ^1H NMR (600 MHz, CDCl_3): δ 1.22 (s, 3 H), 1.23-1.28 (m, 4 H), 1.35 (s, 3 H), 1.65-1.70 (m, 1 H), 1.72-1.75 (m, 2 H), 2.30 (s, 3 H), 2.71 (dd, J = 15.0 and 9.6 Hz, 1 H), 2.85-2.88 (m, 2 H), 3.32 (t, J = 10.8 Hz, 1 H), 4.02 (dd, J = 10.8 and 4.2 Hz, 1 H), 4.20 (q, J = 7.2 Hz 2 H), 5.28 (dd, J = 10.2 and 7.2 Hz, 1 H), 6.70 (s, 1 H), 7.04 (s, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 21.6, 22.0, 32.3, 33.1, 34.7, 36.7, 38.7, 43.7, 60.8, 70.0, 74.4, 122.9, 126.3, 131.2, 135.4, 135.8, 145.0, 171.7; IR (KBr, neat) 2925, 2858, 1736, 1612, 1465, 1374, 1220, 1168, 1109, 1031, 856, 772 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 303.1955 found 303.1955.

Ethyl-2-((1S*,3aR*)-8-methoxy-6,6-dimethyl-1,3,3a,4,5,6-hexahydro-benzo[de]isochroman-1-yl)acetate (7j):

Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 235 mg, 74%; ^1H NMR (600 MHz, CDCl_3): δ 1.22 (s, 3 H), 1.22-1.29 (m, 4 H), 1.34 (s, 3 H), 1.62-1.67 (m, 1 H), 1.72- 1.75 (m, 2 H), 2.72 (t, J = 15.0 and 9.6 Hz, 1 H), 2.81-2.86 (m, 2 H), 3.31 (t, J = 10.2 Hz, 1

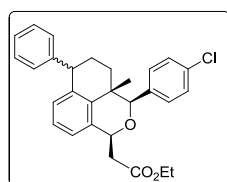
H), 3.77 (s, 3 H), 4.00 (dd, $J = 10.8$ and 4.8 Hz, 1 H), 4.20 (q, $J = 7.2$ Hz 2 H), 5.26 (dd, $J = 9.0$ and 3.0 Hz, 1 H), 6.41 (d, $J = 2.4$ Hz, 1 H), 6.77 (d, $J = 2.4$ Hz, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 22.0, 32.3, 33.0, 35.1, 36.4, 38.7, 43.6, 55.4, 60.9, 70.2, 74.4, 107.4, 111.6, 126.7, 136.8, 146.8, 158.2, 171.6; IR (KBr, neat) 2959, 2858, 1736, 1605, 1471, 1372, 1220, 1174, 1112, 1063, 854, 765 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_4(\text{M} + \text{H})^+$ 319.1904 found 319.1906.

Ethyl 2-((1*S,3*aS**)-3*a*-methyl-6-phenyl-1,3,3*a*,4,5,6-hexahydrobenzo[de]isochroman-1-yl)-acetate (diastereomeric mixture, 3:1, 7k):**



Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 245 mg, 70%; ^1H NMR (400 MHz, CDCl_3): δ 1.22-1.32 (m, 4 H), 1.40 (s, 3 H, minor), 1.49 (s, 3 H, major), 1.52-1.59 (m, 2 H), 1.81-1.86 (m, 1 H, minor), 2.13-2.20 (m, 1 H, major), 2.56-2.61 (m, 1 H, minor), 2.81-2.89 (m, 1 H, major), 2.94-3.00 (m, 1 H), 3.55 (d, $J = 10.4$ Hz, 1 H, major), 3.59 (d, $J = 10.8$ Hz, 1 H, minor), 3.72 (d, $J = 10.8$ Hz, 1 H, major), 3.74 (d, $J = 11.2$ Hz, 1 H, minor), 4.06 (t, $J = 9.2$ Hz, 1 H), 4.20-4.26 (m, 2 H), 5.35 (dd, $J = 9.0$ and 3.0 Hz, 1 H, major), 5.37 (dd, $J = 9.6$ and 6.6 Hz, 1 H, minor), 6.69-6.73 (m, 1 H), 6.88 (m, 1 H), 6.95 (d, $J = 6.8$ Hz, 1 H), 6.97-7.04 (m, 1 H), 7.15-7.25 (m, 3 H), 7.29-7.33 (m, 1 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.4, 14.7, 26.9, 27.5, 27.6, 27.8, 29.0, 32.0, 33.7, 43.3, 43.4, 43.5, 46.7, 59.5, 60.9, 74.2, 75.3, 75.6, 122.5, 122.6, 126.1, 126.3, 126.4, 128.5, 128.7, 128.7, 128.8, 128.9, 134.7, 137.9, 138.1, 139.5, 148.0, 148.6, 171.7; IR (KBr, neat) 2926, 1736, 1449, 1220, 1096, 772, 702 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{27}\text{O}_3(\text{M} + \text{H})^+$ 351.1955 found 351.1953.

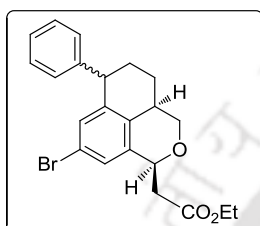
Ethyl-2-((1*S,3*R**,3*aS**)-3-(4-chlorophenyl)-3*a*-methyl-6-phenyl-1,3,3*a*,4,5,6-hexahydro-benzo[de]isochroman-1-yl)acetate (diastereomeric mixture, 4:1, 7l):**



Colorless oil; R_f (hexane/EtOAc 24:1) 0.48; yield 345 mg, 75%; ^1H NMR (600 MHz, CDCl_3): δ 1.20-1.30 (m, 6 H), 1.32-1.36 (m, 1 H), 1.64-1.80 (m, 1 H), 1.93-2.05 (m, 1 H), 2.08-2.12 (m, 1 H), 2.93-2.96 (m, 1 H), 3.00-3.06 (m, 1 H), 4.06-4.26 (m, 3 H), 4.55 (s, 1 H, major), 4.60 (s, 1 H, minor), 5.53 (dd, $J = 9.6$ and 3.6 Hz, 1 H, major), 5.57 (dd, $J = 9.0$ and 3.6 Hz, 1 H, minor), 6.77 (d, $J = 7.8$ Hz, 1 H, major), 6.82 (d, $J = 7.2$ Hz, 1 H, minor), 6.93 (d, $J = 7.8$ Hz, 1 H, major), 6.97 (d, $J = 7.8$ Hz, 1 H, minor), 7.04-7.10 (m, 1

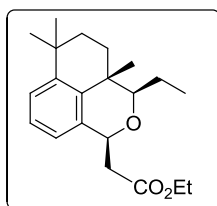
H), 7.18-7.33 (m, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.5, 22.2, 22.9, 27.1, 28.0, 29.0, 29.9, 32.1, 32.8, 37.4, 44.1, 46.6, 60.9, 74.8, 74.9, 82.9, 83.1, 122.8, 122.9, 126.4, 126.5, 127.7, 127.8, 128.5, 128.7, 128.8, 129.3, 129.5, 129.9, 133.4, 134.6, 137.2, 138.6, 140.1, 147.9, 171.5; IR (KBr, neat) 2979, 1733, 1444, 1371, 1220, 1036, 931, 854, 761, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{30}\text{ClO}_3$ ($\text{M} + \text{H}$) $^+$ 461.1878 found 461.1883.

Ethyl-2-((1*S,3*aR**)-8-bromo-6-phenyl-1,3,3*a*,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (diastereomeric mixture, 8:1, 7m):**



Pale yellow oil; R_f (hexane/EtOAc 24:1) 0.48; yield 294 mg, 71%; ^1H NMR (400 MHz, CDCl_3): δ 1.22-1.30 (m, 4 H), 1.59-1.63 (m, 1 H), 1.82-1.97 (m, 1 H), 2.21-2.31 (m, 1 H), 2.62-2.83 (m, 1 H), 2.87-3.06 (m, 2 H), 3.40 (dt, $J = 11.2$ and 10.4 Hz, 1 H), 4.00-4.06 (m, 1 H), 4.08-4.13 (m, 1 H), 4.19-4.24 (m, 2 H), 5.18-5.20 (m, 1 H, minor), 5.26-5.33 (m, 1 H, major), 6.87-6.96 (m, 2 H), 7.03-7.08 (s, 1 H), 7.15-7.22 (m, 2 H), 7.24-7.34 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.3, 14.4, 22.9, 25.1, 32.2, 33.6, 34.0, 35.4, 43.2, 43.8, 61.0, 69.8, 69.9, 73.8, 73.9, 120.3, 120.5, 125.6, 125.64, 126.5, 126.8, 128.6, 128.7, 128.9, 129.0, 131.0, 131.3, 131.6, 134.4, 137.8, 137.9, 139.5, 140.7, 146.6, 147.2, 171.1, 171.2; IR (KBr, neat) 2929, 1736, 1619, 1447, 1372, 1220, 1163, 1094, 768, 685 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{24}\text{BrO}_3$ ($\text{M} + \text{H}$) $^+$ 415.0903 found 415.0894.

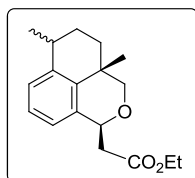
Ethyl-2-((1*S,3*R**,3*aS**)-3-ethyl-3*a*,6,6-trimethyl-1,3,3*a*,4,5,6-hexahydro-benzo[de]isochroman-1-yl)acetate (7n):**



Colorless oil, R_f (hexane/EtOAc 24:1) 0.48; yield 241 mg, 73%; ^1H NMR (600 MHz, CDCl_3): δ 1.04 (t, $J = 7.2$ Hz, 3 H), 1.17 (s, 3 H), 1.22-1.26 (m, 1 H), 1.29 (t, $J = 7.2$ Hz, 3 H), 1.31-1.35 (m, 1 H), 1.37 (s, 3 H), 1.41 (s, 3 H), 1.50-1.55 (m, 1 H), 1.58 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 1.71 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 2.06 (dt, $J = 13.8$ and 3.0 Hz, 1 H), 2.78 (dd, $J = 15.0$ and 9.6 Hz, 1 H), 2.93 (dd, $J = 15.6$ and 3.0 Hz, 1 H), 3.56 (dd, $J = 12.0$ and 3.6 Hz, 1 H), 4.16-4.30 (m, 2 H), 5.19 (dd, $J = 9.6$ and 3.0 Hz, 1 H), 6.82 (d, $J = 7.8$ Hz, 1 H), 7.12 (t, $J = 7.8$ Hz, 1 H), 7.20 (d, $J = 7.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 10.7, 14.3, 20.6, 28.5, 32.2, 33.9, 34.3, 34.6, 37.3, 43.5, 60.8, 61.5, 68.4, 82.3, 121.8, 125.8, 125.9, 134.7, 136.2, 145.1, 171.8; IR (KBr, neat)

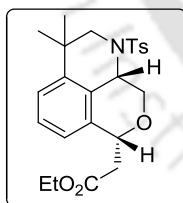
2927, 1738, 1637, 1372, 1220, 1127, 1038, 772 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{31}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 331.2268 found 331.2261.

Ethyl 2-((1S*,3aS*)-3a,6-dimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (diastereomeric ratio 8:5, 7o):

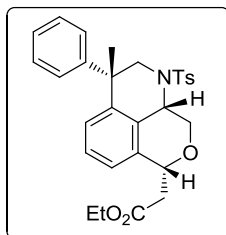


Colorless oil; R_f (hexane/EtOAc, 24:1) 0.48; yield 164 mg, 57%; ^1H NMR (600 MHz, CDCl_3): δ 1.23 (d, $J = 6.6$ Hz, 3 H, major), 1.24 (d, $J = 6.6$ Hz, 3 H, minor), 1.27-3.9 (m, 6 H), 1.41-1.45 (m, 1 H), 1.47-1.55 (m, 1 H), 1.58-1.652 (m, 1 H, major), 1.77-1.84 (m 1 H, minor), 1.98-2.05 (m, 1 H, major), 2.25-2.33 (m, 1 H, minor), 2.65 (dt, $J = 15.0$ and 3.0 Hz, 1 H, major), 2.80-3.00 (m, 2 H), 3.02-3.05 (m, 1 H, minor), 3.45-3.70 (2 H), 4.17-4.26 (m, 2 H), 5.28-5.32 (m, 1 H, minor), 5.47-5.51 (m, 1 H, major), 6.81-6.86 (m, 1 H), 7.04-7.14 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 19.7, 25.1, 30.9, 33.6, 35.4, 36.2, 41.7, 42.1, 43.1, 43.8, 47.1, 61.0, 69.7, 69.8, 72.7, 73.8, 73.9, 120.3, 120.5, 126.4, 126.7, 128.6, 128.7, 134.5, 134.8, 137.8, 137.9, 146.6, 147.2, 171.1; IR (KBr, neat) 2927, 2855, 1734, 1621, 1451, 1372, 1286, 1163, 1095, 1028, 805, 848, 702 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{25}\text{O}_3$ ($\text{M} + \text{H}$)⁺ 289.1798 found 289.1795.

Ethyl-2-((7R*,9aS*)-3,3-dimethyl-1-tosyl-1,2,3,7,9,9a-hexahydropyrano[3,4,5-ij]isoquinolin-7-yl)acetate (7p):



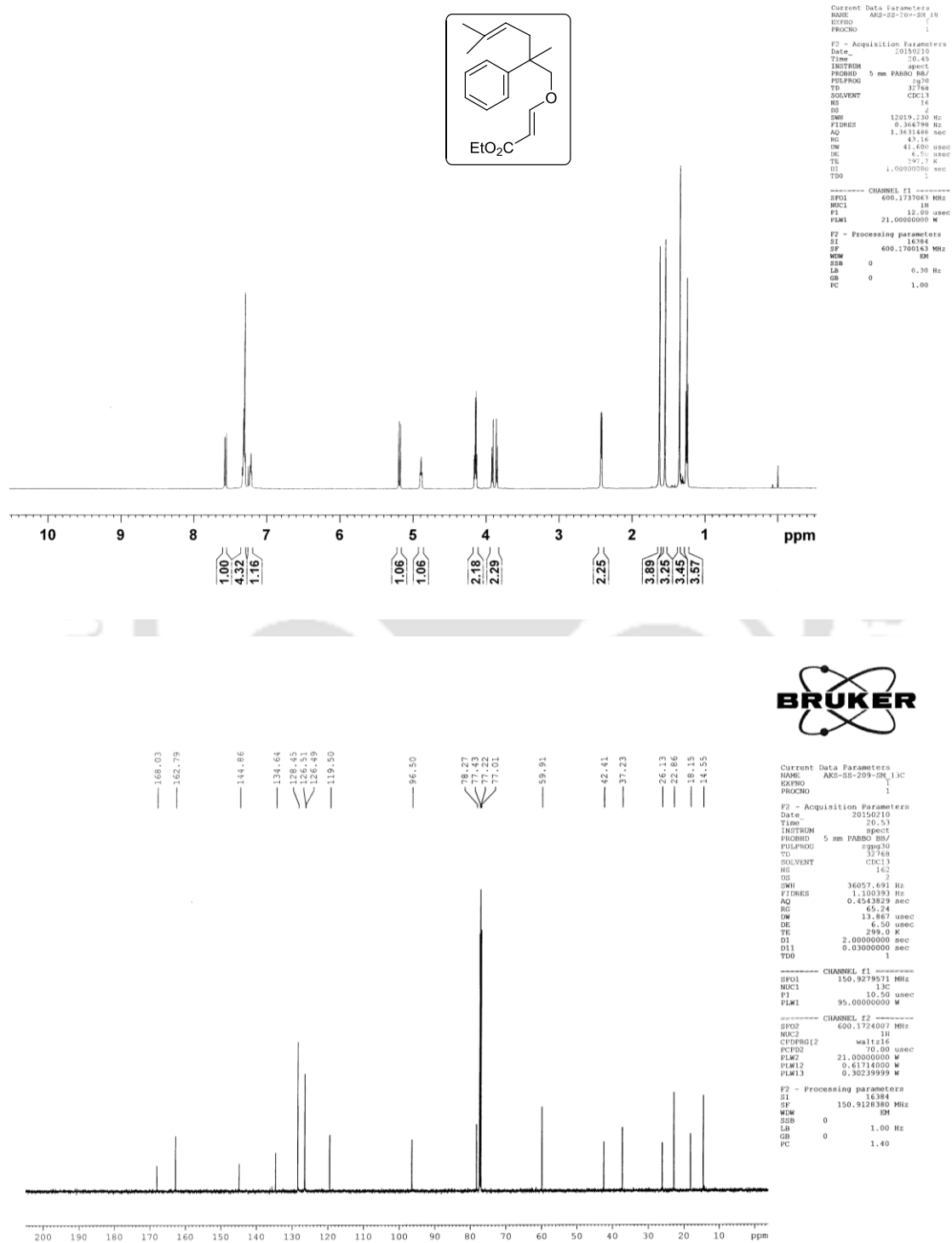
Pale yellow oil; R_f (hexane/EtOAc 17:3) 0.48; yield 399 mg, 90%; ^1H NMR (400 MHz, CDCl_3): δ 1.18 (s, 3 H), 1.22 (t, $J = 7.2$ Hz, 3 H), 1.35 (s, 3 H), 2.41 (s, 3 H), 2.66 (dd, $J = 15.6$ and 8.8 Hz, 1 H), 2.80 (dd, $J = 15.2$ and 3.2 Hz, 1 H), 3.16 (d, $J = 12.4$ Hz, 1 H), 3.41 (d, $J = 12.0$ Hz, 1 H), 3.54 (t, $J = 10.4$ Hz, 1 H), 4.15 (q, $J = 7.2$ Hz, 2 H), 4.34 (dd, $J = 9.6$ and 4.4 Hz, 1 H), 4.61 (dd, $J = 10.4$ and 4.0 Hz, 1 H), 5.22 (dd, $J = 8.8$ and 3.2 Hz, 1 H), 6.87-6.89 (m, 1 H), 7.18-7.22 (m, 2 H), 7.30 (d, $J = 7.6$ Hz, 2 H), 7.71 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 21.7, 27.3, 28.6, 36.0, 43.1, 53.9, 57.0, 61.0, 67.5, 74.0, 122.9, 123.9, 127.4, 127.6, 130.1, 135.5, 136.7, 143.4, 143.8, 171.1; IR (KBr, neat) 2971, 1734, 1447, 1337, 1220, 1160, 1103, 1036, 927, 771, 679 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{30}\text{NO}_5\text{S}$ ($\text{M} + \text{H}$)⁺ 444.1839 found 444.1839.

Ethyl-2-((3*S,7*R**,9*aS**)-3-methyl-3-phenyl-1-tosyl-1,2,3,7,9*a*-hexahydropyrano [3,4,5-*ij*]isoquinolin-7-yl)acetate (7q):**

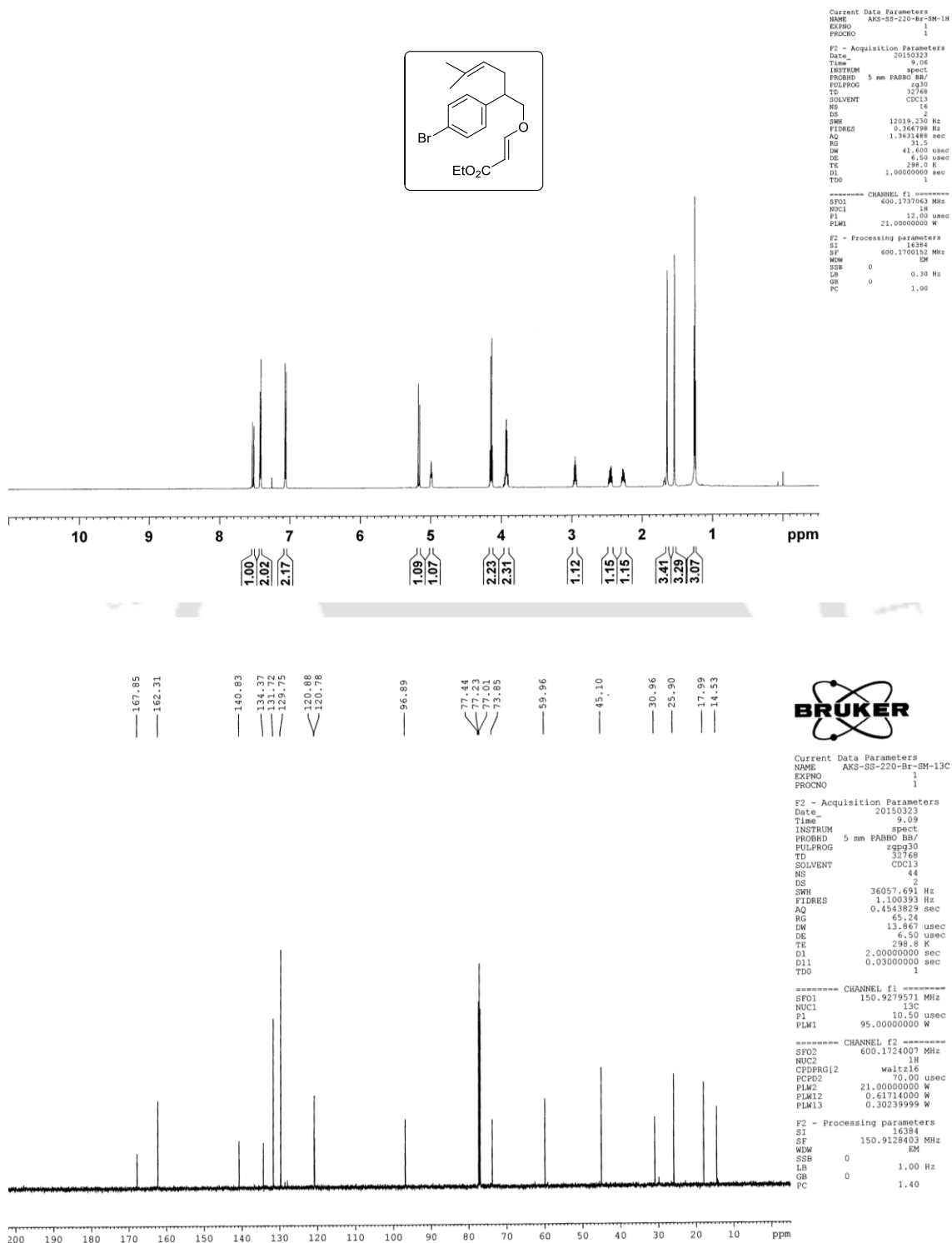
Pale yellow oil; R_f (hexane/ EtOAc 17:3) 0.48; yield 429 mg, 85%; ^1H NMR (400 MHz, CDCl_3): δ 1.27 (s, 3 H), 1.66 (s, 3 H), 2.40 (s, 3 H), 2.77 (dd, $J = 15.6$ and 8.4 Hz, 1 H), 2.86 (dd, $J = 15.6$ and 3.6 Hz, 1 H), 3.46 (d, $J = 13.2$ Hz, 1 H), 3.50 (d, $J = 10.2$ Hz, 1 H), 3.72 (d, $J = 12.6$ Hz, 1 H), 4.19 (q, $J = 7.2$ Hz, 2 H), 4.57 (dd, $J = 10.2$ and 4.2 Hz, 1 H), 4.69 (dd, $J = 10.2$ and 4.2 Hz, 1 H), 5.32 (dd, $J = 8.4$ and 3.6 Hz, 1 H), 6.80 ($J = 7.8$ Hz, 1 H), 6.94 (d, $J = 7.8$ Hz, 1 H), 7.11-7.15 (m, 3 H), 7.23 (d, $J = 8.4$ Hz, 2 H), 7.25 (d, $J = 7.2$ Hz, 1 H), 7.30 (t, $J = 7.2$ Hz, 2 H), 7.56 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.4, 21.7, 25.4, 43.2, 44.2, 53.2, 56.7, 61.0, 67.2, 74.0, 123.2, 126.8, 126.9, 127.3, 127.4, 127.8, 128.4, 129.9, 130.8, 135.5, 137.7, 142.6, 143.7, 145.8, 171.1; IR (KBr, neat) 2925, 2854, 1735, 1624, 1468, 1332, 1158, 1090, 1026, 830, 767 cm^{-1} ; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{32}\text{NO}_5\text{S}$ ($\text{M} + \text{H}$) $^+$ 506.1996 found 506.1994.

5.11. Representative Spectra

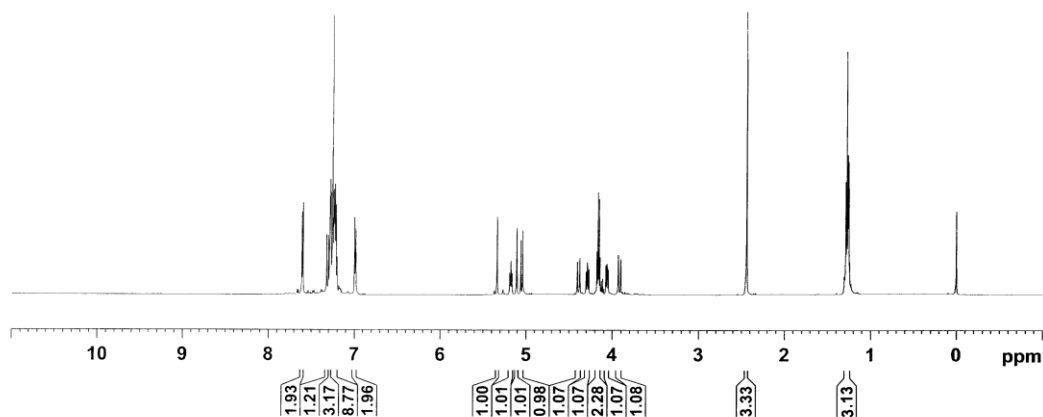
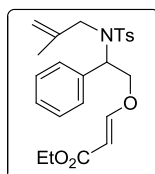
^1H and ^{13}C NMR of (*E*)-Ethyl 3-((2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (6b):



¹H and ¹³C NMR of (*E*)-Ethyl 3-((2-(4-bromophenyl)-5-methylhex-4-en-1-yl)oxy)acrylate (6h):



^1H and ^{13}C NMR of (*E*)-Ethyl 3-(2-(4-methyl-*N*-(2-methylallyl)phenyl)sulfonamido)-2-phenylethoxy)acrylate (6p):

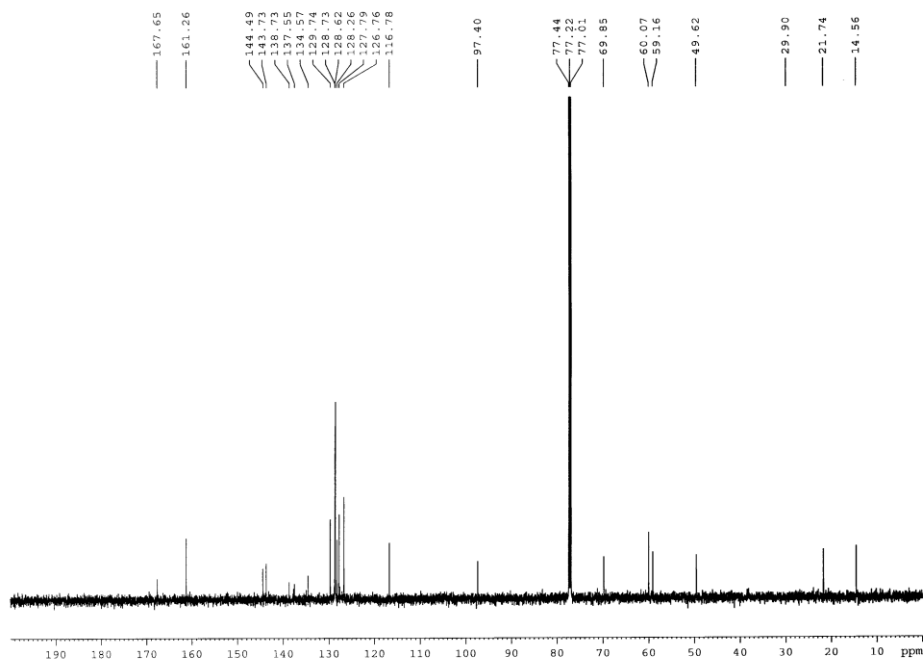


Current Data Parameters
NAME AKS-SS-235-SM-1H
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150501
Time_ 13.26
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.210 Hz
FIDRES 0.366798 Hz
AQ 1.361488 sec
RG 80.22
DM 41.600 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
TDO 1

===== CHANNEL f1 =====
SFO1 600.1737063 MHz
NUC1 1H
P1 12.00 usec
PLW1 21.00000000 W

F2 - Processing parameters
SI 16384
SF 600.1700145 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME AKS-SS-235-SM-13C
EXPNO 1
PROCNO 1

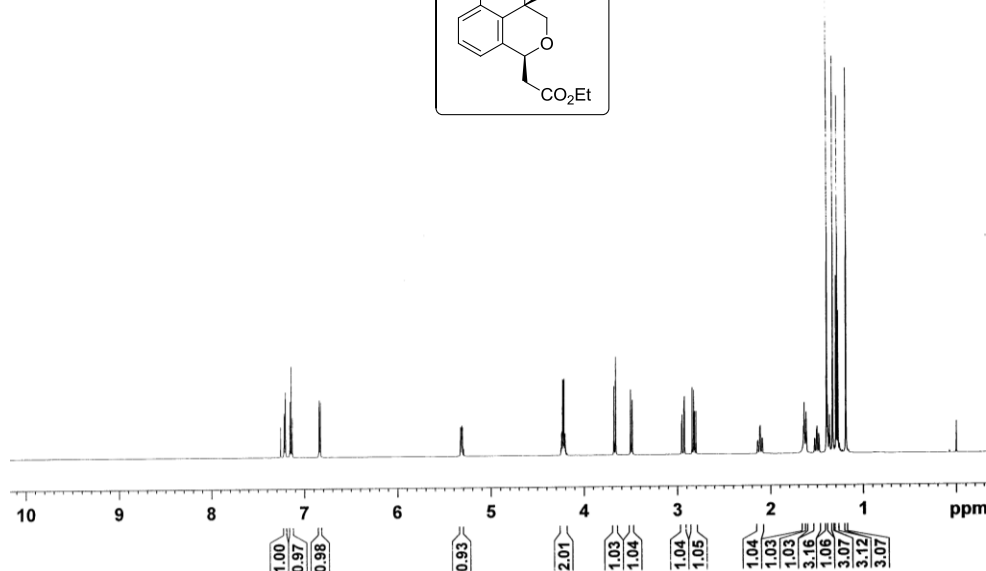
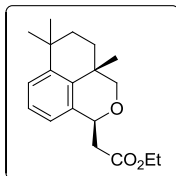
F2 - Acquisition Parameters
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Time_ 13.20
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 128
DS 2
SWH 16057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543823 sec
RG 200.18
DM 13.867 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1

===== CHANNEL f1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W

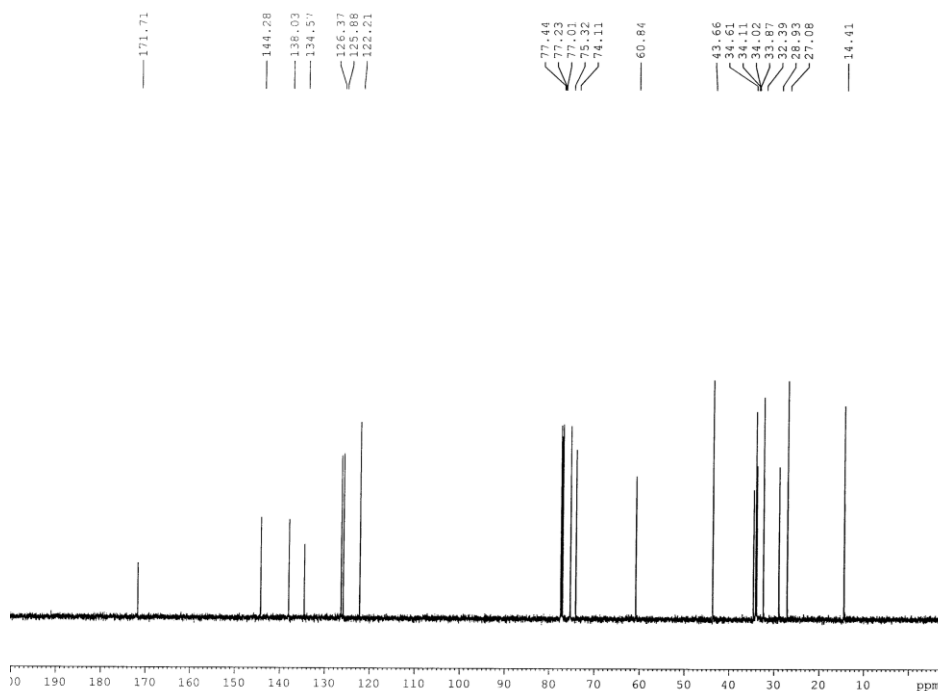
===== CHANNEL f2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG12 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.10239999 W

F2 - Processing parameters
SI 16384
SF 150.9183867 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^1H and ^{13}C NMR of Ethyl 2-((1S*,3aS*)-3a,6,6-trimethyl-1,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7b):

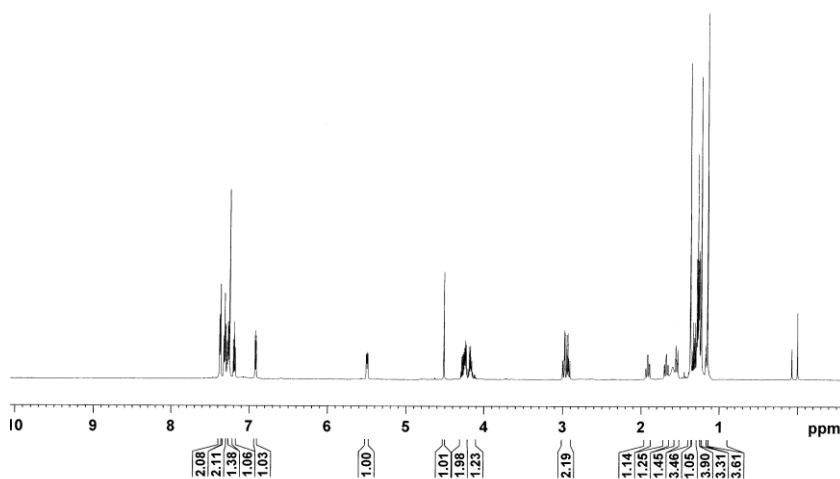
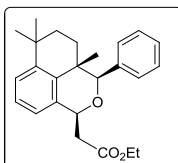


Current Data Parameters
NAME AKS-SS-209-13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date 20150210
Time 21.10
INSTRUM spect
PROBHD 5 mm PABBO BB
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543829 sec
RG 65.24
DW 13.867 usec
DE 6.50 usec
TE 299.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
===== CHANNEL f1 =====
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W
===== CHANNEL f2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
F2P2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W
F2 - Processing parameters
SI 16384
SF 150.9279571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Current Data Parameters
NAME AKS-SS-209-13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date 20150210
Time 21.10
INSTRUM spect
PROBHD 5 mm PABBO BB
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543829 sec
RG 65.24
DW 13.867 usec
DE 6.50 usec
TE 299.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
===== CHANNEL f1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W
===== CHANNEL f2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
F2P2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W
F2 - Processing parameters
SI 16384
SF 150.9279571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^1H and ^{13}C NMR of Ethyl 2-((1S*,3R*,3aS*)-3a,6,6-trimethyl-3-phenyl-1,3,3a,4,5,6-hexahydrobenzo[de]iso-chroman-1-yl)acetate (7c):



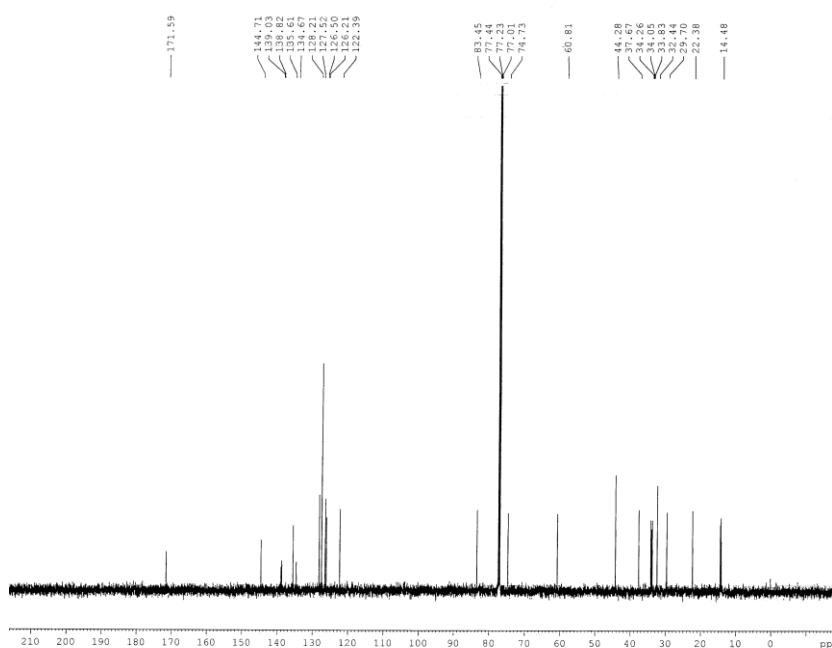
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Current Data Parameters
NAME  AR2-20-210-P-benz_1H
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date_  20160507
Time  16.11
INSTRUM  spect
PROBHD  5 mm F4001
PULPROG  zgpg30
TD  65536
SOLVENT  CDCl3
NS  16
DS  4
SWH  12019.230 Hz
FIDRES  0.366768 Hz
AQ  1.1621498 sec
RG  655.18
DM  41.600 usec
DE  6.40 usec
TE  299.0 K
SI  1.00000000 sec
TDO  1

===== CHANNEL f1 =====
NUC1  13C
P1  12.00 usec
PL1  0.00dB
===== CHANNEL f2 =====
NUC2  1H
P2  12.00 usec
PL2  0.00dB

F2 - Processing parameters
SI  65536
SF  400.1760171 MHz
WDW  EM
SSB  0
LB  0.30 Hz
GB  0
PC  1.00
  
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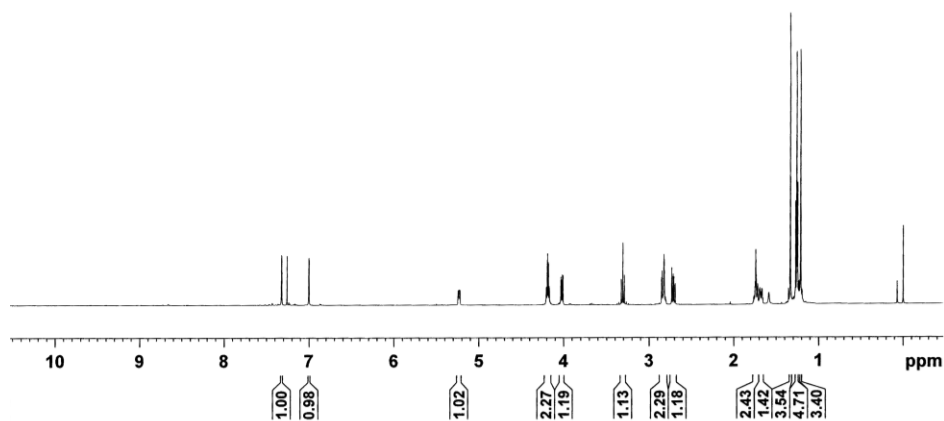
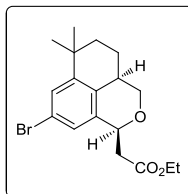
Current Data Parameters
NAME  AR2-20-210-P-benz_13C
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date_  20160507
Time  16.11
INSTRUM  spect
PROBHD  5 mm F4001
PULPROG  zgpg30
TD  65536
SOLVENT  CDCl3
NS  16
DS  4
SWH  34037.681 Hz
FIDRES  1.120393 Hz
AQ  0.4843823 sec
RG  655.18
DM  13.867 usec
DE  6.40 usec
TE  297.3 K
SI  2.50000000 sec
TDO  0.00000000 sec

===== CHANNEL f1 =====
NUC1  13C
P1  16.00 usec
PL1  0.00dB
===== CHANNEL f2 =====
NUC2  1H
P2  12.00 usec
PL2  0.00dB

F2 - Processing parameters
SI  16384
SF  150.9125000 MHz
WDW  EM
SSB  0
LB  1.00 Hz
GB  0
PC  1.40
  
```

¹H and ¹³C NMR of Ethyl 2-((1S*,3aR*)-8-bromo-6,6-dimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7h):

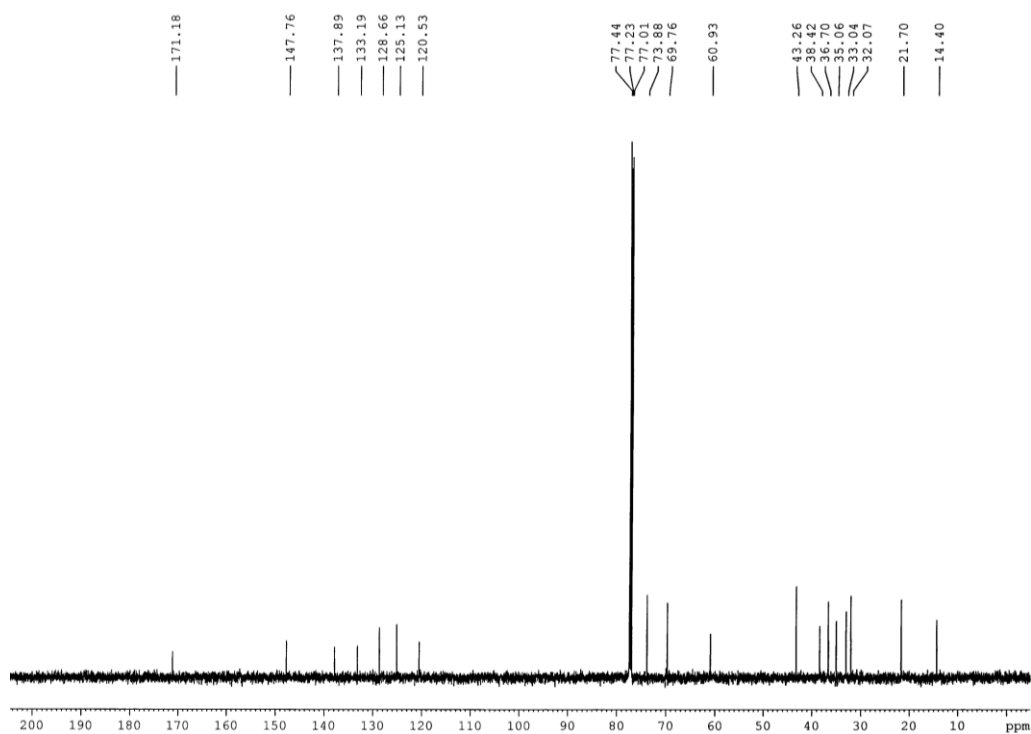


Current Data Parameters
NAME AKS-SS-220-Br-P-1H
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150323
Time 9.24
INSTRUM spect
PROBHD 5 mm F4BBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 1.353188 sec
RG 3.2
RW 41.600 usec
DE 6.50 usec
TE 297.8 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 600.1731063 MHz
NUC1 1H
P1 12.00 usec
PLW1 21.00000000 W

F2 - Processing parameters
SI 16384
SF 600.1700152 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME AKS-SS-220-Br-P-13C
EXPNO 1
PROCNO 1

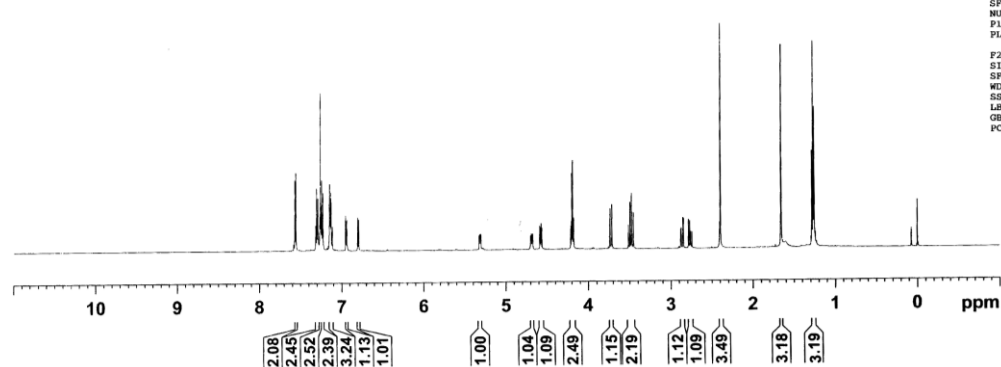
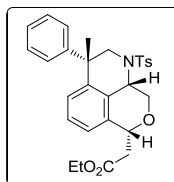
F2 - Acquisition Parameters
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Time 9.28
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PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 55
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543829 sec
RG 65.24
DW 13.867 usec
DE 6.50 usec
TE 298.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

===== CHANNEL f1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.00000000 W

===== CHANNEL f2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W

F2 - Processing parameters
SI 16384
SF 150.9128359 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^1H and ^{13}C NMR of Ethyl 2-((3*S,7*R**,9*aS**)-3-methyl-3-phenyl-1-tosyl-1,2,3,7,9,9*a*-hexahydropyrano[3,4,5-*ij*]isoquinolin-7-yl)acetate (7q):**

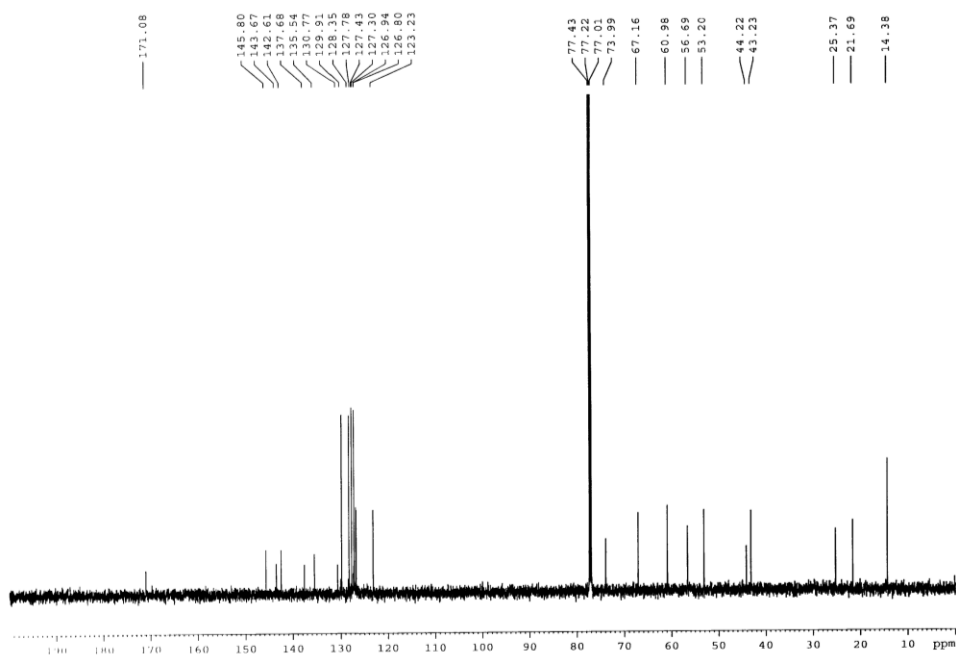


Current Data Parameters
NAME AKS-SS-235-F-1H
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150501
Time 13.06
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 1.361488 sec
RG 43.16
DW 41.600 usec
DE 6.50 usec
TE 297.2 K
D1 1.0000000 sec
TDO 1

===== CHANNEL f1 =====
SFO1 600.137063 MHz
NUC1 1H
P1 12.00 usec
PLW1 21.0000000 W

F2 - Processing parameters
SI 16384
SF 600.1700151 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



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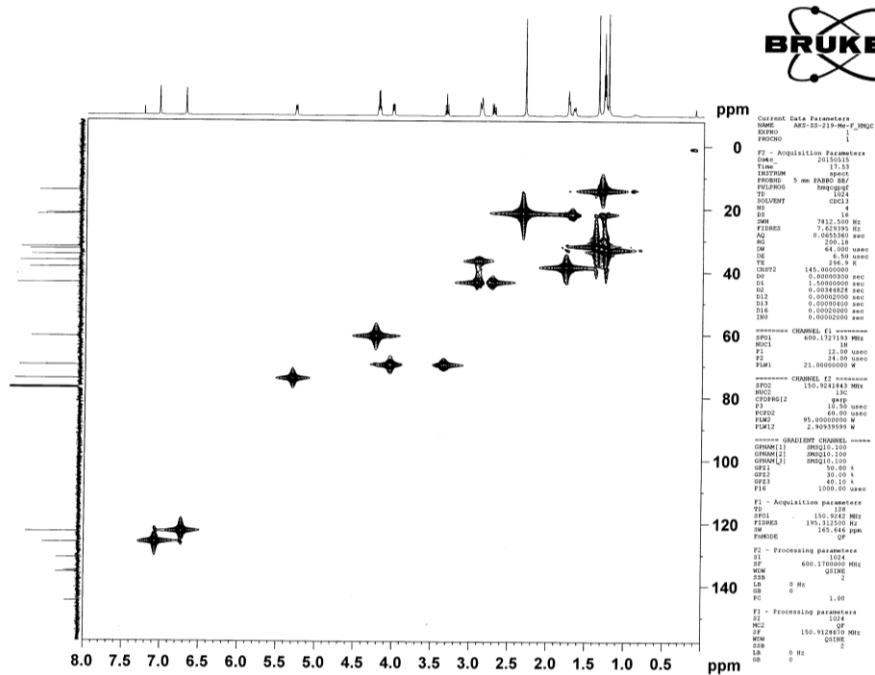
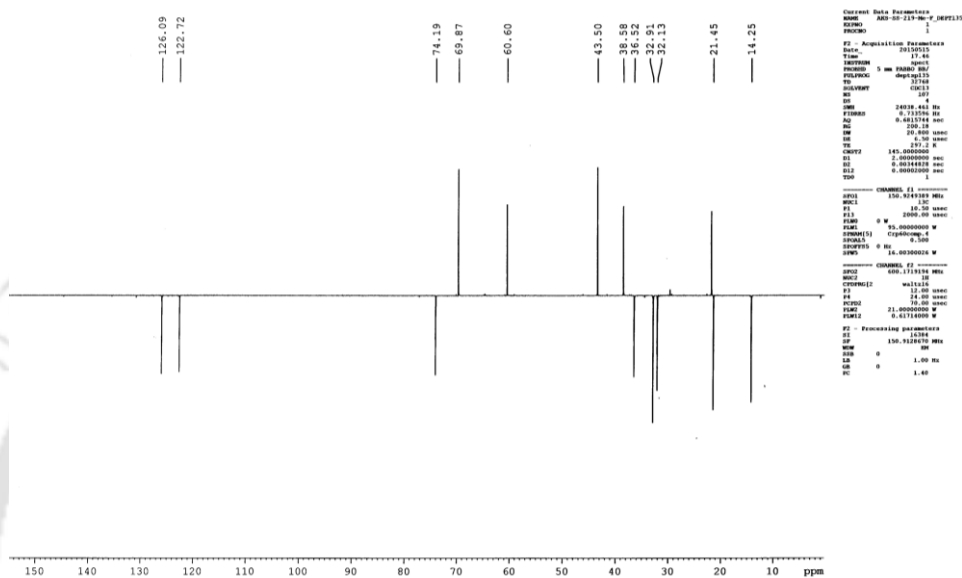
Current Data Parameters
NAME AKS-SS-235-F-13C
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150501
Time 13.12
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 117
DS 2
SWH 36057.691 Hz
FIDRES 1.100393 Hz
AQ 0.4543825 sec
RG 200.18
DW 13.867 usec
DE 6.50 usec
TE 298.2 K
D1 2.0000000 sec
D11 0.0300000 sec
TDO 1

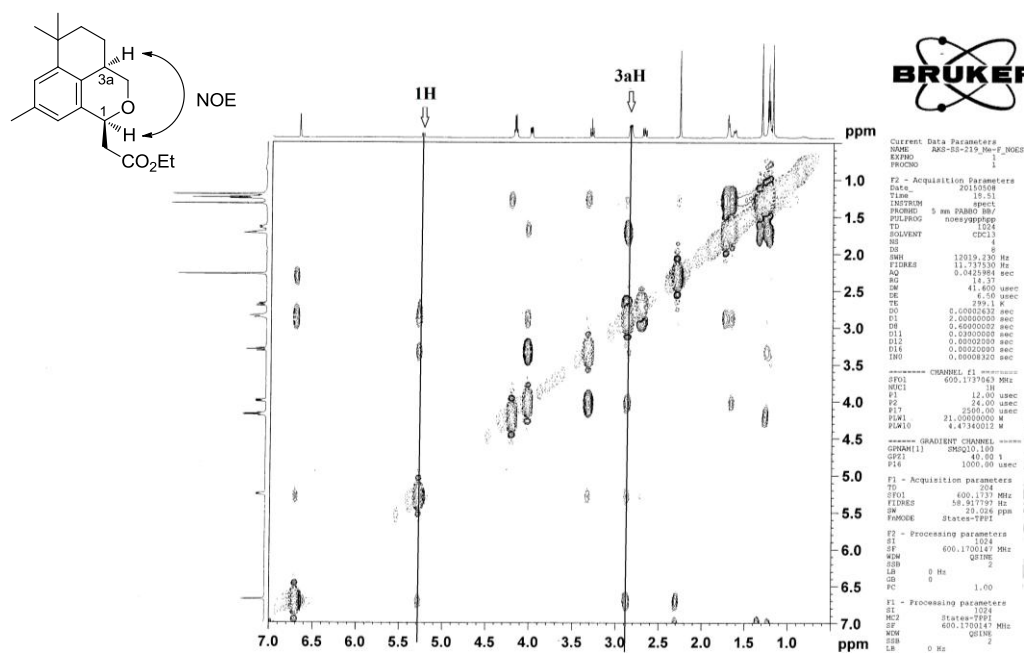
===== CHANNEL f1 =====
SFO1 150.9279571 MHz
NUC1 13C
P1 10.50 usec
PLW1 95.0000000 W

===== CHANNEL f2 =====
SFO2 600.1724007 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 70.00 usec
PLW2 21.0000000 W
PLW12 0.6171400 W
PLW13 0.30239995 W

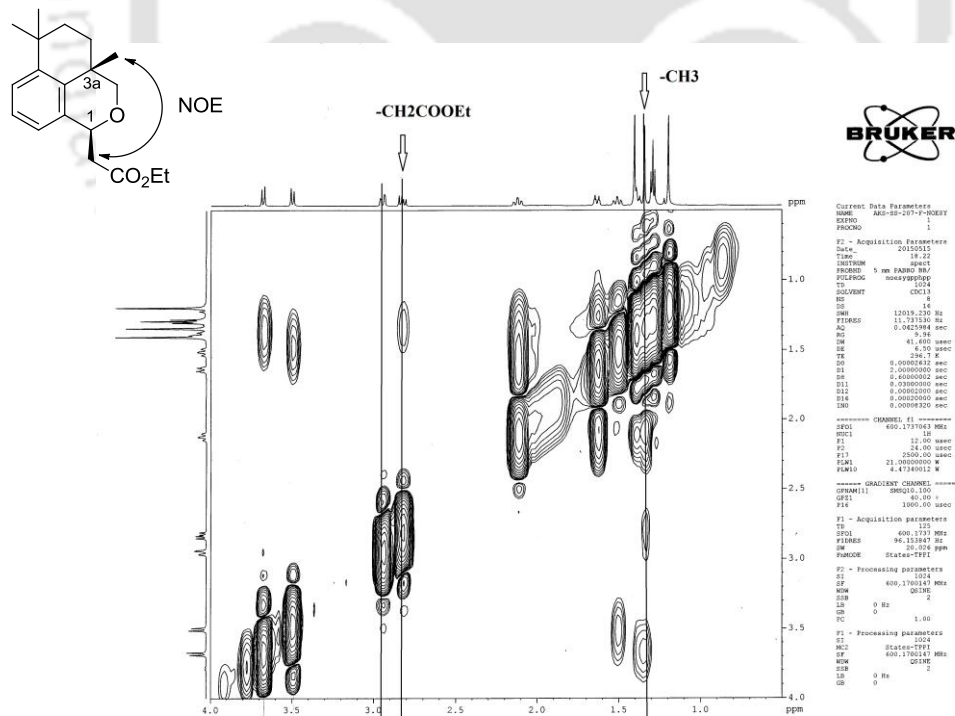
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LB 1.00 Hz
GB 0
PC 1.40



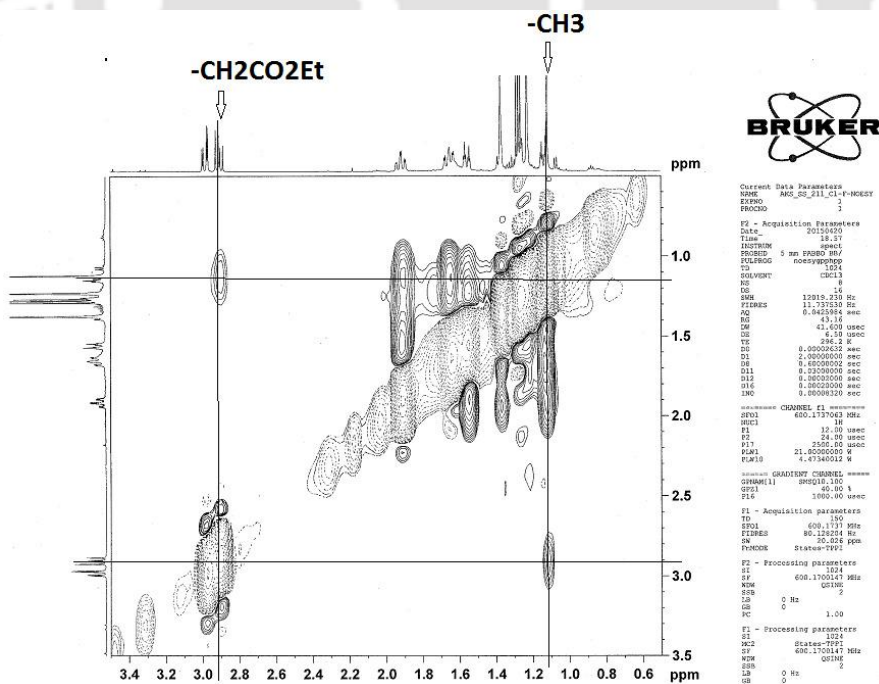
NOE Spectra



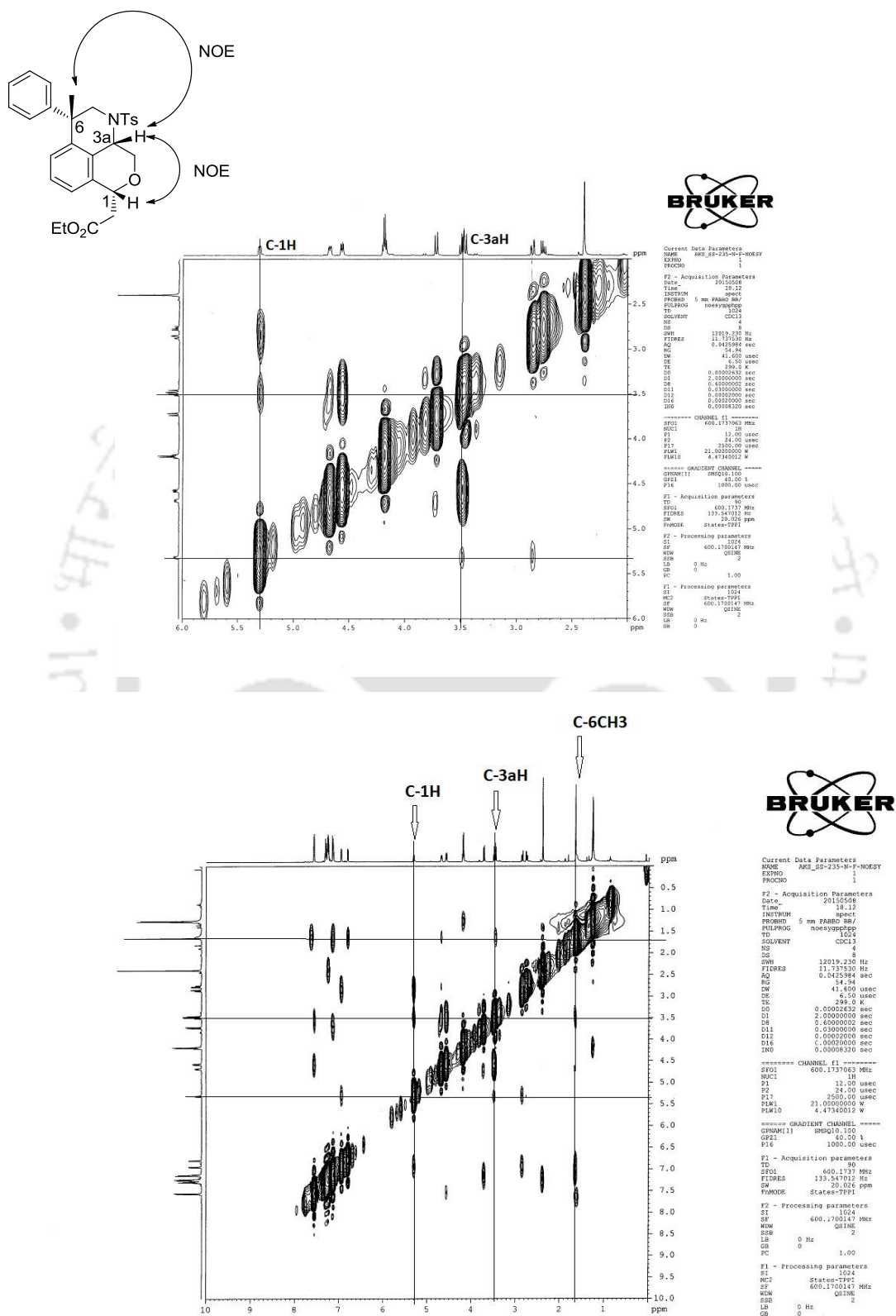
NOE spectrum of Ethyl-2-((1S*,3aS*)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydrobenzo[de]isochroman-1-yl)acetate (7b):



Chemical structure of compound **3a** is shown, which is a tricyclic molecule. It features a central benzene ring fused to two six-membered rings. One of these rings is substituted with a tert-butyl group and a methyl group. The other ring is substituted with an ethyl ester group (CO_2Et) and a 4-chlorophenyl group. Two NOE (Nuclear Overhauser Effect) correlations are indicated by curved arrows: one between the methyl group and the ethyl ester group, and another between the ethyl ester group and the 4-chlorophenyl group.



NOE spectra of Ethyl 2-((3*S,7*R**,9*aS**)-3-methyl-3-phenyl-1-tosyl-1,2,3,7,9,9*a*-hexahydropyrano[3,4,5-*ij*]isoquinolin-7-yl)acetate (7q):**



5.12. References

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- 12) (a) Saudagar, P.; Saha, P.; Saikia, A. K.; Dubey, V. K. *Eur. J. Pharma. Biopharma* **2013**, *85*, 569. (b) Saudagar, P.; Mudavath, L.; Saha, P.; Saikia, A. K.; Sundar, S.; Dubey, V. K. *Lett. Drug Design. Discovery* **2014**, *11*, 937.

List of Publications

1. "Scandium(III) triflate Catalyzed Synthesis of Primary Homoallylic Alcohols *via* Carbonyl-Ene Reaction" **Sultana, S.**; Bondalapati, S.; Indukuri, K.; Gogoi, P.; Saha, P.; Saikia A. K. *Tetrahedron Lett.* **2013**, 54, 1576.
2. "Diastereoselective Synthesis of Dihydropyrans *via* Prins Cyclization of Enol Ethers: Total Asymmetric Synthesis of (+)-Civet Cat Compound" **Sultana, S.**; Indukuri, K.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, 78, 12182.
3. "Synthesis of Substituted Tetrahydro-pyran and -furan *via* Intramolecular Hydroalkoxylation of Alkenols" **Sultana, S.**; Devi, N. R.; Saikia, A. K. *Asian J. Org. Chem.* **2015**, 4, 1281.
4. "Diastereoselective Synthesis of Substituted Hexahydrobenzo[*de*]isochromans and Evaluation of their Antileishmanial Activity" Saikia, A. K.; **Sultana, S.**; Devi, N. R.; Deka, M. J.; Tiwari, K.; Dubey, V. K. *Org. Biomol. Chem.* **2016**, 14, 970.
5. "Synthesis of Substituted Isochromans *via* Oxa-Pictet Spengler Reaction of Vinylogous Enol Esters" Sarkar, S.; **Sultana, S.**; Indukuri, K.; Unnavaa, R.; Saikia, A. K. *Synthesis* **2016** (doi: 10.1055/s-0035-1561581).
6. "Synthesis of Five-, Six-, and Seven-Membered 1,3- and 1,4- Heterocyclic Compounds *via* Intramolecular Hydroalkoxylation/ Hydrothioalkoxylation of Alkenols/Thioalkenols" Deka, M. J.; Indukuri, K.; **Sultana, S.**; Borah, M.; Saikia, A. K. *J. Org. Chem.* **2015**, 80, 4349.
7. "Diastereoselective Synthesis of Substituted Dihydropyrans *via* an oxonium-ene Cyclization Reaction" Saha, P.; Ghosh, P.; **Sultana, S.**; Saikia, A. K. *Org. Biomol. Chem.* **2012**, 10, 8730.
8. "Synthesis of 2,3-dihydro-4-pyranones from Epoxides *via* Intermolecular [4+2]-Cycloaddition Reaction" Indukuri, K.; Bondalapati, S.; **Sultana, S.**; Saikia, A. K. *RSC Adv.* **2012**, 29, 9398.