Newer Strategies for the Synthesis of Mono- and Bicyclic Oxygen Heterocycles

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

Doctor of Philosophy

Submitted by

Pipas Saha

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati 781039
August 2012

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Dedicated

To

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis entitled "*Newer Strategies for the Synthesis of Mono- and Bicyclic Oxygen Heterocycles*" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the supervision of Prof. Anil K. Saikia.

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

August, 2012
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Dr. Anil K. Saikia
Professor

CERTIFICATE

This is to certify that Mr. Pipas Saha has been working under my supervision since July 2008. I am forwarding his thesis entitled "***Newer Strategies for the Synthesis of Mono- and Bicyclic Oxygen Heterocycles***" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

August, 2012
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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I also take this opportunity to thank all of my Ph.D. batchmates (July, 08), the other research scholars in the chemistry department and all my IITG friends, who have shared their thoughts and views with me.

Finally, my deepest gratitude goes to my family for their unflagging love and support throughout my life. I feel deeply indebted to them for whatever I have achieved so far.

Pipas Saha

LIST OF ABBREVIATIONS

Ac	acetyl	NMR	nuclear magnetic resonance
AIBN	azobisisobutyronitrile	NOESY	nuclear overhauser enhancement spectroscopy
Bn	benzyl	ORTEP	oak ridge thermal ellipsoid plot
BOX	bisoxazoline	Ph	phenyl
Bz	benzoyl	PMA	phosphomolybdic acid
CCDC	cambridge crystallographic data centre	Pr	propyl
COSY	correlation spectroscopy	RCM	ring-closing metathesis
DBMP	2,6-di-*tert*-butyl-4-methylpyridine	r.t.	room temperature
DCE	1,1-dichloroethane	SEM	trimethylsilyl ethoxymethyl
DCM	dichloromethane	TBDMS	*tert*-butyldimethylsilyl
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine	TBDPS	*tert*-butyldiphenylsilyl
dr	diastereomeric ratio	THF	tetrahydrofuran
ee	enantiomeric excess	TLC	thin layer chromatography
HRMS	high resolution mass spectrometry	TFA	trifluoroacetic acid
IR	infrared	TMS	trimethylsilyl
LDA	lithium diisopropylamide	Tf	trifluoromethanesulfonyl
MEM	methoxyethoxymethyl	*p*-TsOH	*p*-toluenesulfonic acid
MOM	methoxymethyl	Ts	*p*-toluenesulfonyl
M.P.	melting point	XRD	x-ray diffraction
MS	molecular sieves	m/z	mass to charge ratio

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

s	singlet	td	triplet of doublets
d	doublet	m	multiplet
dd	doublet of doublets	brs	broad singlet
ddd	doublet of doublet of doublets	Hz	hertz
t	triplet	MHz	mega-hertz

Abstract

The thesis contains six chapters. The first chapter provides a brief introduction about mono- and bicyclic oxygen heterocycles and oxonium-ene cyclization reactions. Special emphasis has been given to six membered oxygen heterocycles and oxabicyclic compounds. The second chapter gives a description about the novel synthesis of oxabicyclo[3.3.1]nonanone via (3,5)-oxonium-ene reaction. The third chapter describes about the synthesis of oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans via (3,5)-oxonium-ene reaction. In the fourth chapter there is a description about the stereoselective synthesis of 6-oxabicyclo[3.2.1]octene via (3,5)-oxonium-ene reaction. The fifth chapter presents the synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans via (3,5)-oxonium-ene reaction. The sixth chapter describes about the diastereoselective synthesis of substituted dihydropyrans via oxonium-ene cyclization reaction.

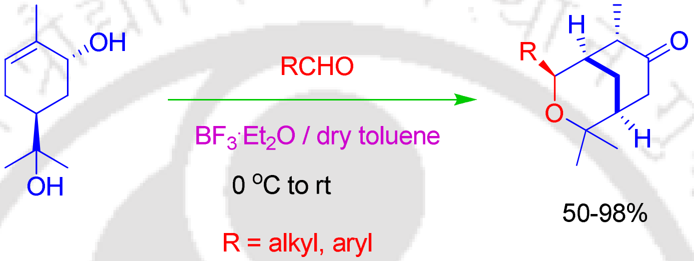
Chapter 1. Introduction to Mono- and Bicyclic Oxygen Heterocycles and Oxonium-Ene Cyclization Reactions

Heterocyclic compounds are widely distributed in nature and are essential to life. Almost all the drugs, most vitamins and many other natural products are heterocycles. They are 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. The six membered ring heterocycles of oxygen *i.e.*, dihydropyrans (DHPs) and tetrahydropyrans (THPs) are structural motifs of many biologically active natural products such as polyether antibiotics, marine toxins and pheromones. On the other hand oxabicyclic compounds are important due to their potential biological properties. Oxabicyclo[3.3.1]nonenes and selected derivatives are known to behave as estrogen receptor ligands.

The reaction of an alkene with an allylic hydrogen atom (the ene) with another alkene (enophile) to produce a new alkene is known as ene reaction. Ene cyclization that involves the oxonium ion as the enophile component, is called oxonium-ene cyclization reaction. There are three different types of oxonium-ene cyclization reactions, namely, (1,5), (2,5) and (3,5). Although (1,5) and (2,5) oxonium-ene-type cyclizations have been well studied, the (3,5)-oxonium-ene cyclization has not been investigated extensively.

Chapter 2: A Novel Synthesis of Oxabicyclo[3.3.1]nonanone via (3,5)-Oxonium-Ene Reaction

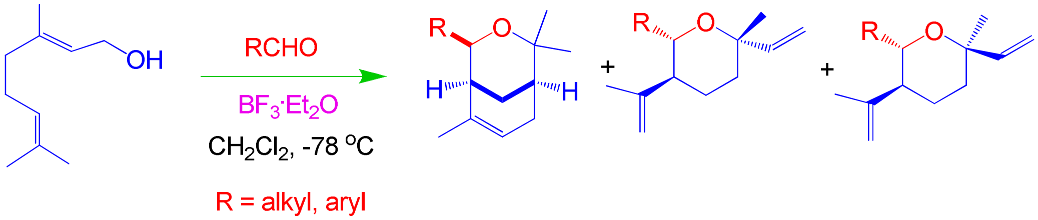
This chapter describes an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonanone via (3,5)-oxonium-ene reaction from the reaction of aldehydes or epoxides with commercially available *trans*-*p*-menth-6-ene-2,8-diol, mediated by boron trifluoride etherate (Scheme 1). The reaction is diastereoselective and a series of oxabicyclo[3.3.1]nonanones have been synthesized in good yields.



Scheme 1

Chapter 3: Synthesis of Oxabicyclo[3.3.1]nonenes and Substituted Tetrahydropyrans via (3,5)-Oxonium-Ene Reaction

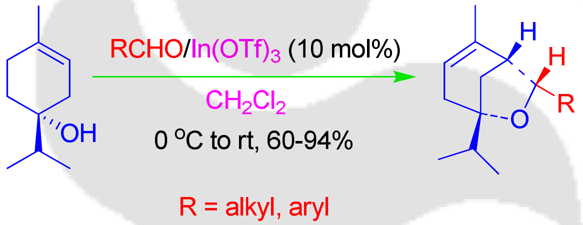
Oxabicyclo[3.3.1]nonenes and selected derivatives are known to behave as estrogen receptor ligands. On the other hand, tetrahydropyrans are found in many biologically active natural products and pharmaceuticals. Alkyl substituted tetrahydropyrans are used as aroma and flavouring substances for pharmaceuticals, cosmetics and food stuff. In this chapter an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans from the reaction of geraniol with aldehydes and epoxides promoted by boron trifluoride etherate is presented. The reaction can be generalized as shown in Scheme 2.



Scheme 2

Chapter 4: Stereoselective Synthesis of 6-Oxabicyclo[3.2.1]octene via (3,5)-Oxonium-Ene Reaction

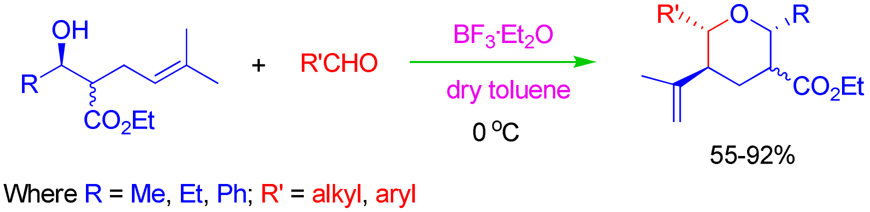
Oxabicyclo[3.2.1]octanes/octenes are important intermediate in organic synthesis for numerous organic transformations. Two different types of oxabicyclo[3.2.1]octane/octene are well known, one is 6-oxabicyclo[3.2.1]octane/octene and another one is 8-oxabicyclo[3.2.1]octane/octene. Although several strategies are developed for the synthesis of 8-oxabicyclo[3.2.1]octane/octene, methodology for the synthesis of 6-oxabicyclo[3.2.1]octane/octene are very limited in the literature. This chapter provides a stereoselective method for the synthesis of 6-oxabicyclo[3.2.1]octene via (3,5)-oxonium-ene reaction from the reaction of (-)-terpinen-4-ol with aldehyde or epoxide catalyzed by indium triflate (In(OTf)$_3$) in good yields (Scheme 3).



Scheme 3

Chapter 5: Synthesis of 2,3,5,6-Tetrasubstituted Tetrahydropyrans via (3,5)-Oxonium-Ene Reaction

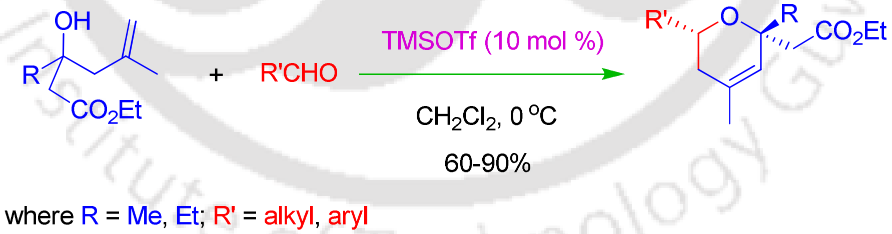
The tetrahydropyrans are important structural features in synthetic organic chemistry as they are core units of many biologically active molecules and natural products. The polyether antibiotics, marine toxins and pheromones belong to such biologically active natural products. The 2,3,5,6-tetrasubstituted tetrahydropyran units are found in antibiotics such as FR-901464 and X-206. The presence of ester group in the tetrahydropyran ring is important because a diverse functionalization could be achieved in the tetrahydropyran molecule. In this chapter an efficient methodology is presented for the synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans from the reaction of aldehydes and ethyl 2(1-hydroxyalkyl/hydroxy(phenyl)methyl)-5-methylhex-4-enoate using (3,5)-oxonium-ene reaction promoted by boron trifluoride etherate under mild conditions. The reaction is general and a series of substituted tetrahydropyrans have been synthesized in good yields (Scheme 4).



Scheme 4

Chapter 6: Diastereoselective Synthesis of Substituted Dihydropyrans via Oxonium-Ene Cyclization Reaction

Dihydropyrans are important intermediates for the synthesis of biologically active natural products such as ambruticin, phorboxazoles, leucascandrolide, kendomycin, neopeltolide, clavisolides and diospongins. The olefin functionality of dihydropyrans can be manipulated for the synthesis of polysubstittuted tetrahydropyrans. Substituted dihydropyrans are also used as a flavoring or aroma material for food and other products. The 4-methyl substituted dihydropyran unit is present in macrolide natural products laulimalide and okadaic acid. This chapter describes a methodology for the diastereoselective synthesis of substituted dihydropyrans from the reaction of aldehydes or epoxides and ethyl 3-alkyl-3-hydroxy-5-methylhex-5-enoate using oxonium-ene reaction catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) under mild conditions. The reaction can be generalized as shown in Scheme 5.



Scheme 5

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CHAPTER 1

Introduction to Mono- and Bicyclic Oxygen Heterocycles and Oxonium-Ene Cyclization Reactions

1.1 Introduction to Mono- and Bicyclic Oxygen Heterocycles

Heterocyclic compounds are widely distributed in nature and are essential to life. Almost all the drugs, most vitamins and many other natural products are heterocycles. They are 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. The six membered ring heterocycles of oxygen *i.e.*, dihydropyrans (DHPs) and tetrahydropyrans (THPs) are structural motifs of many biologically active natural products such as polyether antibiotics, marine toxins and pheromones.[1] Consequently a huge amount of effort has been directed towards developing ever more efficient method to synthesize them. For example, over the last ten years thousands of tetrahydropyran containing compounds have been entered into preclinical and clinical trials.[2] Alkyl substituted tetrahydropyrans such as **1** (Figure 1.1.1) are used as aroma and flavouring substances for pharmaceuticals, cosmetics and food stuff.[3] The macrocycle, (-)-Kendomycin **2** has a diverse and fascinating pharmacological profile. It was isolated in 1996 from

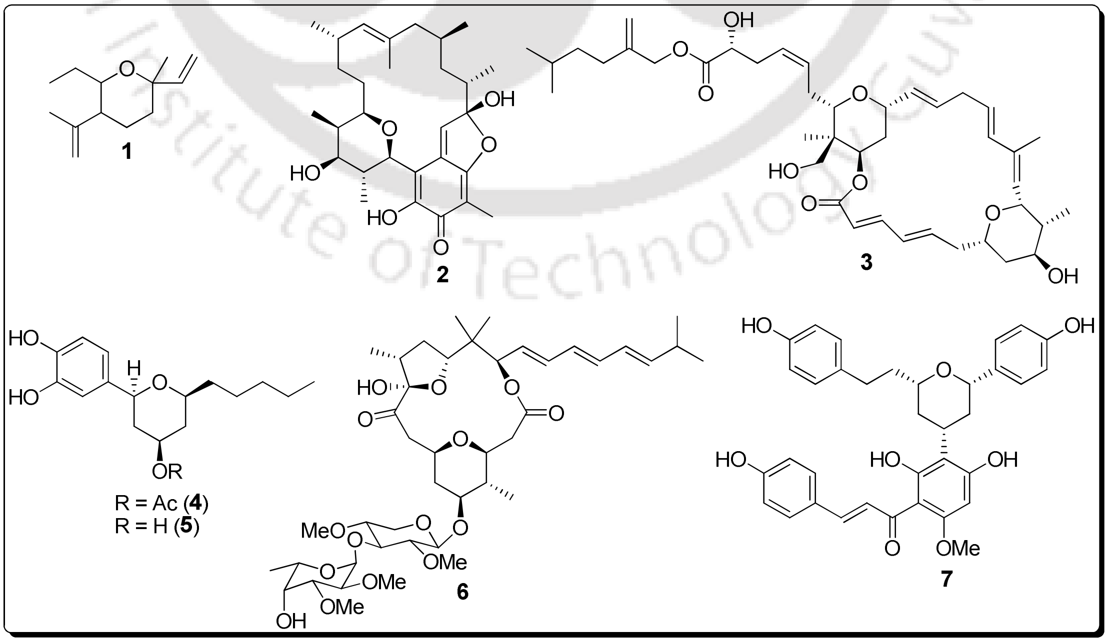
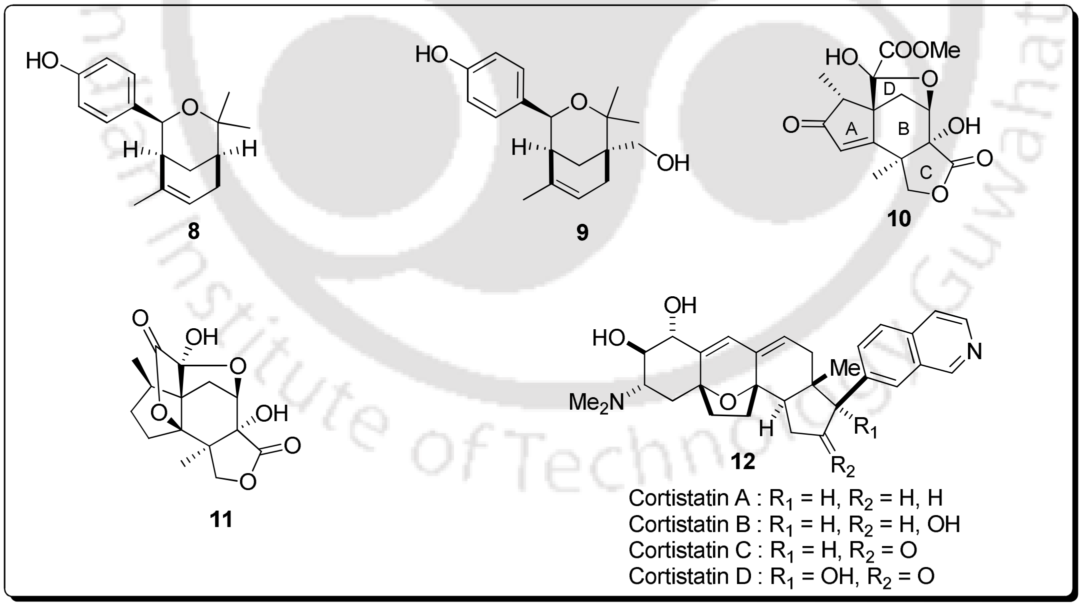


Figure 1.1.1. Some bioactive molecules containing tetrahydropyran ring

Streptomyces bacteria and exhibits potent antagonism of the endothelin receptor agonism.[4] Lasonolide A, **3** isolated from a shollow water Caribbean sponge, species *Forcepia* shows potent activity against A-549 human lung carcinoma.[5] Catechols **4** and **5** isolated from extracts of *Plectranthus* sylvestris (labiatae), a plant found in the woody hills in East Africa are potent antioxidants and posses anti-inflamatory properties. Polycavernoside A, **6** a potent marine toxin[6] isolated from the red algae *Polycavernosa tsudai* also has a tetrahydropyran moiety. Calyxin, a new family of natural products isolated from *Alpinia blepharocalyx* seeds, are used for the treatment of stomach disorders in Chinese medicine.[2h] Several of these natural products show interesting antiproliferative activity against carcinoma cells. Epicalyxin F, **7** is the most potent member of the class and showed ca. 1 *μ*M activity against human HT-1080 fibrosarcoma and murine 26-L5 carcinoma.

Oxabicyclic compounds are important due to their potential biological properties. Oxabicyclo[3.3.1]nonenes and selected derivatives (Figure 1.1.2, **8** & **9**) are known to behave as estrogen receptor ligands.[7] Oxabicyclo[3.2.1]octenes are important intermediate in organic synthesis for numerous organic transformations.[8] The 6- and 8-oxabicyclo[3.2.1]octane/octene skeleton are present in biologically active natural products



Cortistatin A : R_1 = H, R_2 = H, H
Cortistatin B : R_1 = H, R_2 = H, OH
Cortistatin C : R_1 = H, R_2 = O
Cortistatin D : R_1 = OH, R_2 = O

Figure 1.1.2. Biologically active oxabicyclic compounds

like Jiadifenin **10**, Jiadifenolide **11** and Cortistatin **12**.[9] Although there are various natural and synthetic oxabicyclic compounds, this thesis will discuss efficient methodologies for the synthesis of oxabicyclo[3.3.1]nonanones, oxabicyclo[3.3.1]nonenes and 6-oxabicyclo[3.2.1]octenes.

1.2 General Approaches for the Synthesis of Dihydro- and Tetrahydropyrans

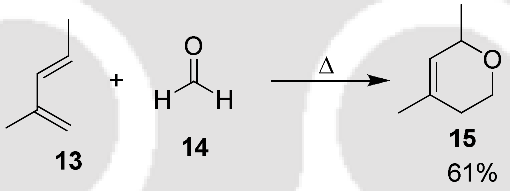
Dihydro- and Tetrahydropyrans are generally prepared by

i) Hetero Diels-Alder reaction
ii) Manipulation of carbohydrates
iii) Intramolecular Michael reactions
iv) Prins cyclization

A brief summary of different applications involving these four types of reactions are discussed below.

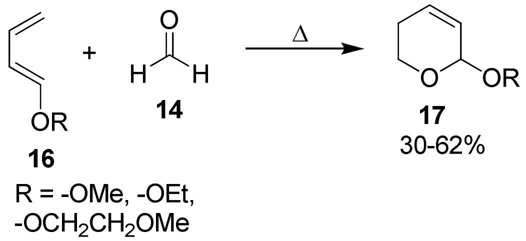
1.2.1 Hetero Diels-Alder Reaction

Hetero Diels-Alder reaction was first reported by Gresham and Steadman in 1951.[10] In their report they have prepared 2,4-dimethyl-5,6-dihydro-1,2-pyran **15** by reacting methylpentadiene **13** with formaldehyde **14** (Scheme 1.2.1.1). This was an unusal reaction as in this case formaldehyde was acting as a dienophile.



Scheme 1.2.1.1.

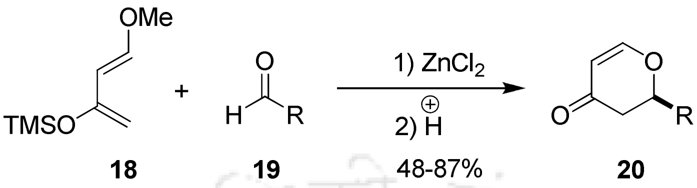
In 1962 kubler reported that an alkoxy group on the 1-position of a 1,3-alkadiene provides sufficient activation to permit the Diels-Alder reaction with paraformaldehyde.[11] The reaction products are 2-alkoxy-5,6-dihydro-2*H*-pyrans **17** (Scheme 1.2.1.2*)***.** Later on it has been established by others[12] that electron donating group on diene increase the reactivity and regioselectivity of hetero Diels-Alder reaction to produce substituted dihydropyrans



Scheme 1.2.1.2.

(DHPs) in good yields.

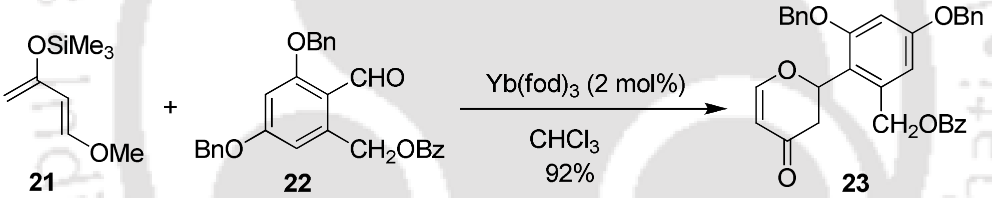
In 1982 Danishefsky reported the Lewis acid catalyzed hetero Diels-Alder reaction for the synthesis of substituted dihydropyrans (DHPs) in good yields (Scheme 1.2.1.3*)*.[13]



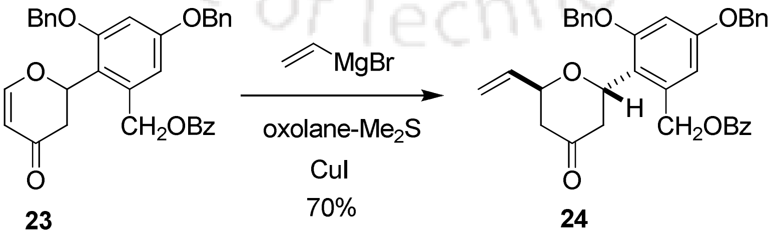
R = Et, Ph, CHNHCbz, CH_2SPh, CH_2OBn

Scheme 1.2.1.3.

Lewis acid catalyzed hetero Diels-Alder reaction of (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **21** with 6-benzoyloxymethyl-2,4-dibenzyloxy benzaldehyde **22** afforded 2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4*H*-pyran-4-one **23** in good yields (Scheme 1.2.1.4). The product **23** on treatment with vinylmagnesium bromide in oxolane-dimethylsulfide with cuprous iodide produces tetrahydropyrone **24** in 70% yield (Scheme 1.2.1.5*)*. The presence of vinyl group at the C-6 position of the tetrahydropyrone **24** increases its synthetic utility as the vinyl group is a precursor of hydroxymethyl function (*i.e.*, C-6 of the C-1 arylated D-glycosyl residue).[14]



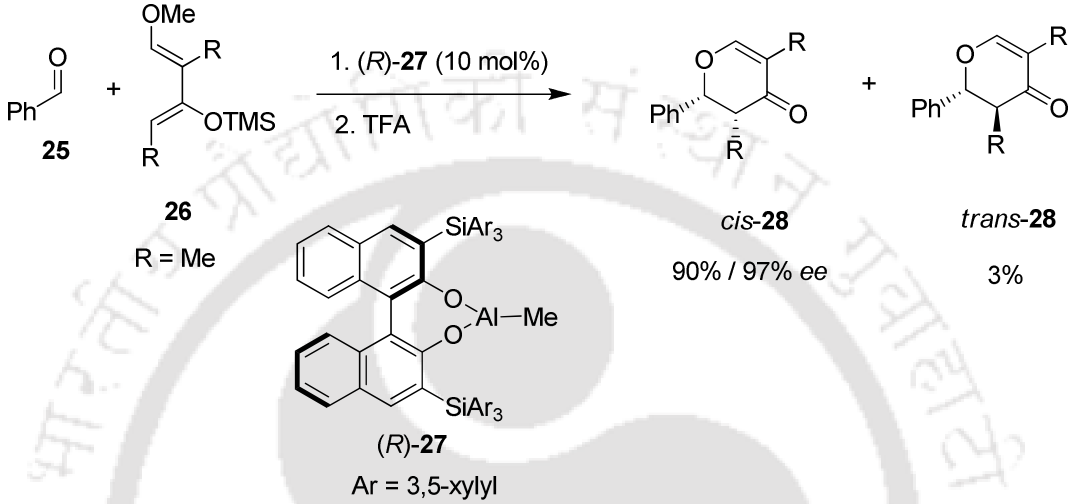
Scheme 1.2.1.4.



Scheme 1.2.1.5.

The first reliable and highly efficient chiral aluminium(III) catalyst for HDA reactions of aldehydes was reported by Yamamoto and co-workers.[15] The use of the chiral BINOL-

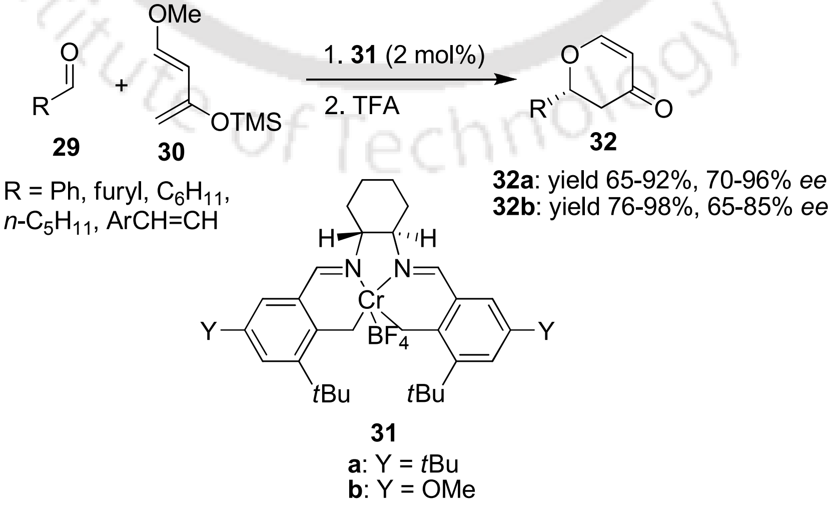
AlMe complex (*R*)-**27** was found to be highly effective for the HDA reaction of various aldehydes with activated dienes. For example, the reaction of benzaldehyde **25** with *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene **26**, affords *cis*-dihydropyrones *cis*-**28** as the major product in high yield with up to 97% *ee* (Scheme 1.2.1.6). The reaction proceeds well in nonpolar solvents such as toluene.



Scheme 1.2.1.6.

Different chiral transition- and lanthanide metal complexes can catalyze the HDA reaction of unactivated and activated aldehydes with especially activated dienes.[16]

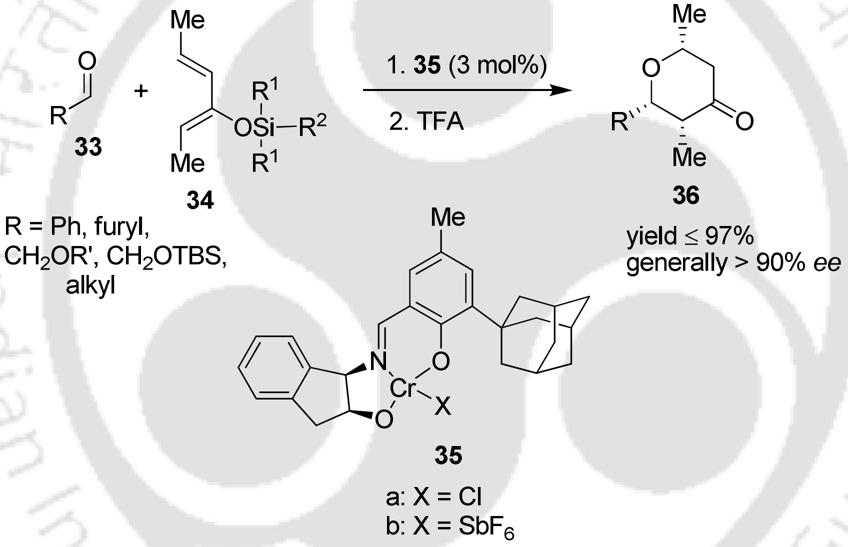
Jacobsen and co-workers[17] have shown that the chiral salen-chromium(III) complexes **31a** and **31b** can catalyze the HDA reaction of different aldehydes **29** containing aromatic, aliphatic and conjugated substituents with diene **30** (Scheme 1.2.1.7). The reaction proceeds



Scheme 1.2.1.7.

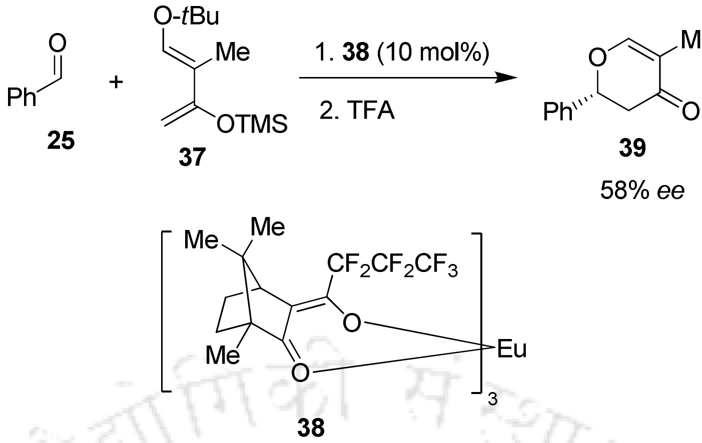
in good yield (up to 98%) and 62-93% *ee*. It was found that the presence of oven-dried powdered 4 Å molecular sieves (MS) led to an increased yield and enantioselectivity.

A more general catalytic enantioselective HDA reaction has also been achieved by Jacobsen and co-workers by the introduction of chiral tridentate Schiff base chromium(III) complexes **35** (Scheme 1.2.1.8).[18] These complexes, which are highly diastereo- and enantioselective catalysts for the reaction of unactivated aldehydes, can catalyze the reaction of less nucleophilic dienes bearing fewer than two oxygen substituents. The adamantly-substituted catalysts **35a** and **35b** gave the best results, and both aliphatic and aromatic aldehydes underwent HDA reactions. It was found that use of the hexafluoroantimonate chromium catalyst **35b** resulted in a faster and more enantioselective reaction and that the reaction can proceed without solvent.



Scheme 1.2.1.8.

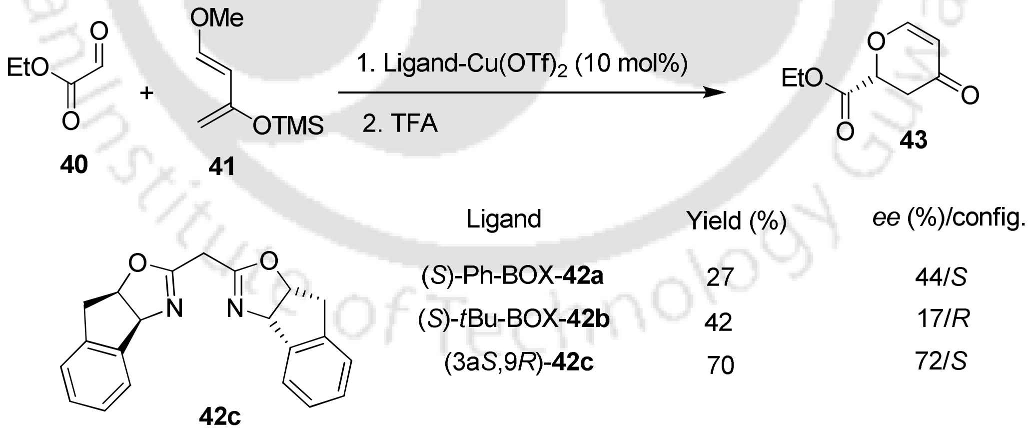
Danishefsky and co-workers were probably the first to observe that lanthanide complexes can catalyze the HDA reaction of aldehydes with activated dienes.[19] The reaction of benzaldehyde **25** with activated conjugated dienes such as **37** was found to be catalyzed by [Eu(hfc)$_3$] **38** (hfc = 3-(heptafluoropropylhydroxymethylene)camphorate) giving up to 58% *ee* (Scheme 1.2.1.9).



Scheme 1.2.1.9.

In 1995, it was demonstrated that chiral C_2-symmetric bisoxazoline-copper(II) complexes[20] are efficient catalysts for the HDA reactions.

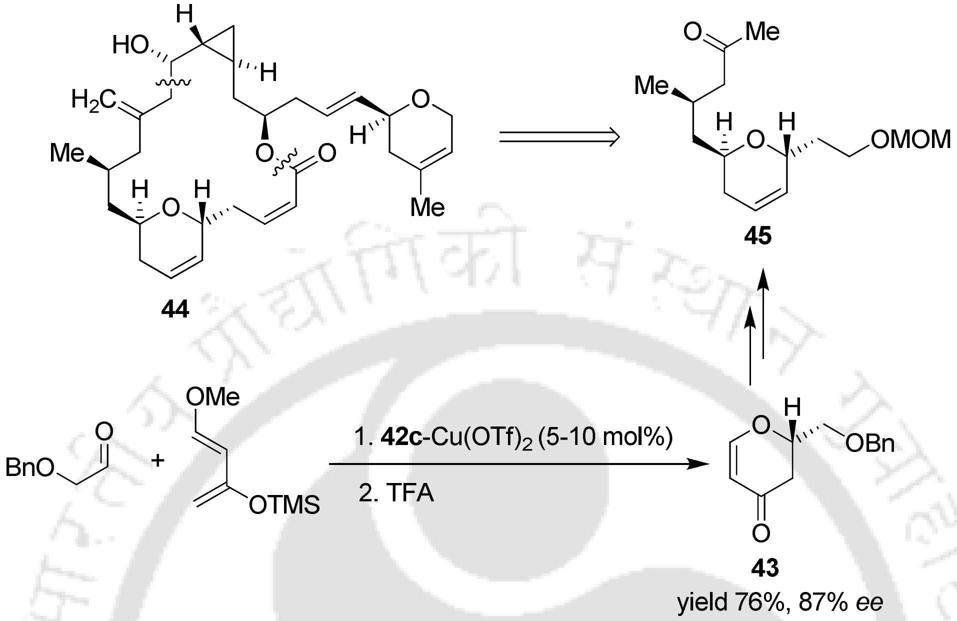
Ghosh *et al.* have investigated the HDA reaction catalyzed by chiral BOX-copper(II) complexes between ethyl glyoxylate **40** and Danishefsky's diene **41** by applying catalyst systems derived from $Cu(OTf)_2$ and ligands (*S*)-Ph-BOX (*S*)-**42a**, (*S*)-*t*Bu-BOX (*S*)-**42b**, and the conformationally constrained BOX ligand **42c** in order to compare the properties of the latter ligand with the two others (Scheme 1.2.1.10).[21] The HDA adduct **43** was obtained with a significant improvement compared with the two other catalysts.



Ligand	Yield (%)	*ee* (%)/config.
(*S*)-Ph-BOX-**42a**	27	44/*S*
(*S*)-*t*Bu-BOX-**42b**	42	17/*R*
(3a*S*,9*R*)-**42c**	70	72/*S*

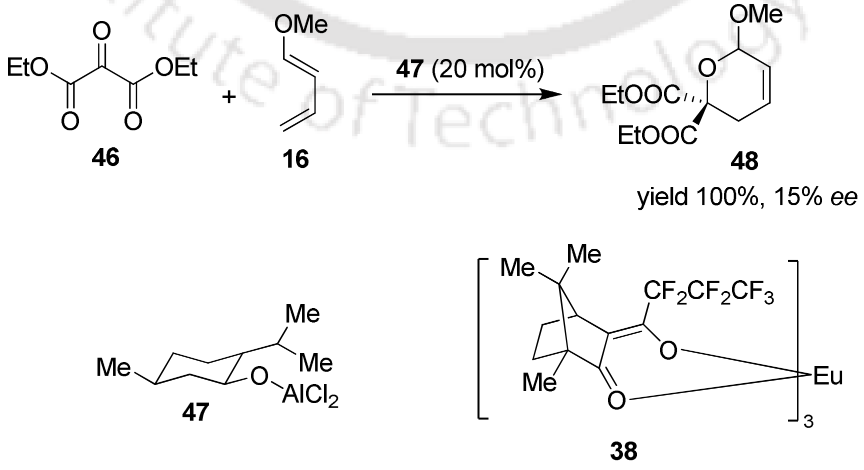
Scheme 1.2.1.10.

The methodology in Scheme 1.2.1.10 has been used for the synthesis of the C_3-C_{14} segment **45** of the antitumor agent laulimalide **44** (Scheme 1.2.1.11).[22] The constrained chiral BOX ligand **42c** in combination with $Cu(OTf)_2$ afforded dihydropyrane **43** by a HDA reaction in good yield and high enantiomeric excess, which was converted to the C_3-C_{14} segment **45** by a Ferrier type of rearrangement in several steps.



Scheme 1.2.1.11.

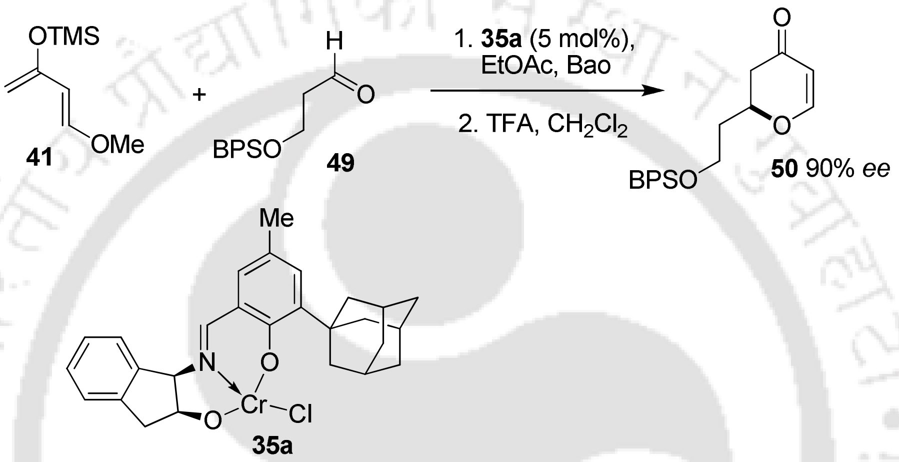
Ketones are generally less reactive than aldehydes. Therefore, the HDA reaction of ketones should be expected to be more difficult to achieve. This is well reflected in the few reported catalytic enantioselective HDA reactions of ketones compared with the many successful examples on the enantioselective reaction of aldehydes. Jankowski *et al.* have reported the reaction of Ketomalonate **46** with 1-methoxy-1,3-butadiene **16** using the menthoxyaluminium catalyst **47** and chiral lanthanide catalysts **38**. The highest enantio-



Scheme 1.2.1.12.

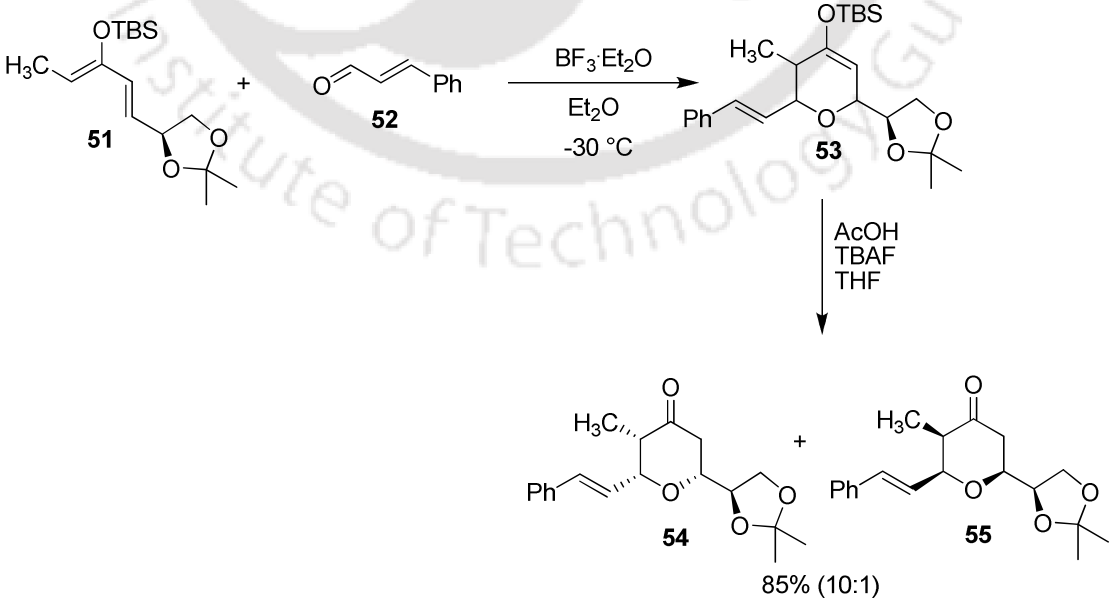
selectivity of 15% *ee* for the HDA adduct **48** was achieved by using **47** as the catalyst (Scheme 1.2.1.12).[23]

Paterson *et al.* have reported the synthesis 2,3-dihydro-*γ*-pyrone (**50**) via a HDA reaction between Danishefsky's diene **41** and aldehyde **49** using Jacobsen's HDA catalyst **35a** (Scheme 1.2.1.13).[24] The product was obtained in 89% yield with 90% *ee*. The 2,3-dihydro-*γ*-pyrone **50** was recognized as being a suitable building block for the synthesis of C(1–14) fragment of Phorboxazoles A and B.[24]



Scheme 1.2.1.13.

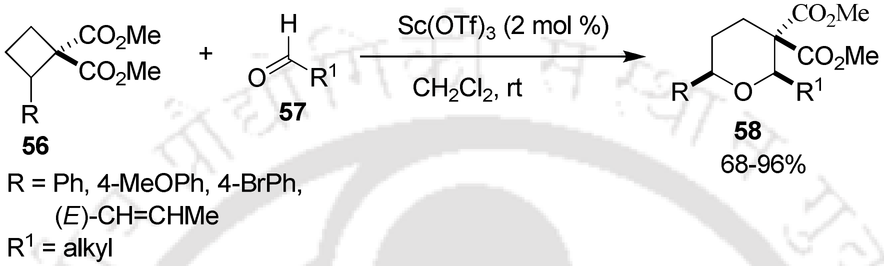
Wessjohann and co-workers have reported the synthesis of all *cis* 2,3,6-trisubstituted tetrahydro-*γ*-pyrones using a HDA reaction between enantiomerically pure chiral dienes and



Scheme 1.2.1.14.

α,β-unsaturated aldehydes (Scheme 1.2.1.14).[25]

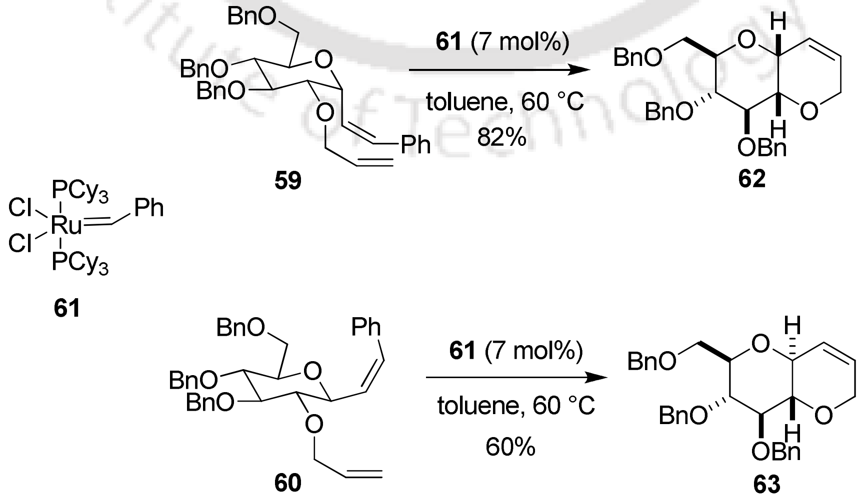
Recently Johnson and co-workers have reported the synthesis of *cis*-2,6-disubstituted tetrahydropyran derivatives via a HDA reaction between malonate derived cyclobutanes and aldehydes catalyzed by Lewis acid (Scheme 1.2.1.15).[26] The resulting THP products are of interest because of their prevalence in biologically relevant and structurally interesting molecules.[27]



Scheme 1.2.1.15.

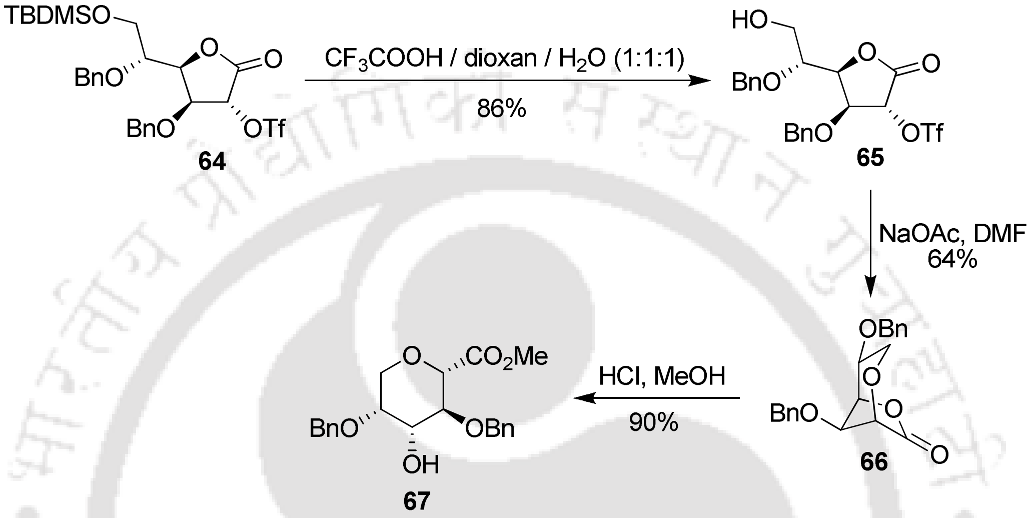
1.2.2 Manipulation of Carbohydrates

Carbohydrates are widely recognized as versatile building blocks in synthetic organic chemistry due to the wealth of functional, conformational and stereochemical information. The accessibility of carbohydrates in the acyclic (open chains) or cyclic form (five- or six membered rings) not only allows specific manipulations of the individual asymmetric centers, but also at either of the extremities (*i.e.* the reducing or non-reducing end). For example, van Boom and co-workers have reported the synthesis of *cis*- and *trans*-fused pyranopyrans **62** and **63** by performing RCM on the corresponding *cis*- and *trans*-1-vinyl-2-*O*-allyl systems **59** and **60** respectively (Scheme 1.2.2.1).[27]



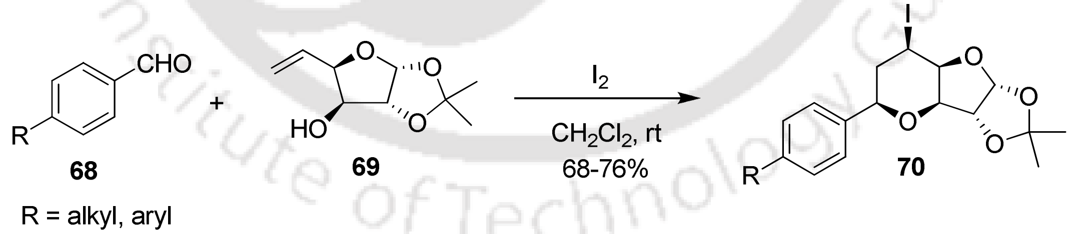
Scheme 1.2.2.1.

Estevez *et al.* have reported the synthesis of polysubstituted tetrahydropyran **67** starting from gluco triflate **64**. Treatment of gluco triflate **64** with CF_3COOH in dioxan produces gluco triflate **65,** with a free OH group at C-6. The triflate **65** on treatment with NaOAc in DMF gives bicyclic tetrahydropyran **66**. The bicyclic material **66** undergoes ring opening with 1% HCl in MeOH to give methyl ester **67** in 90% yield (Scheme 1.2.2.2).[28]



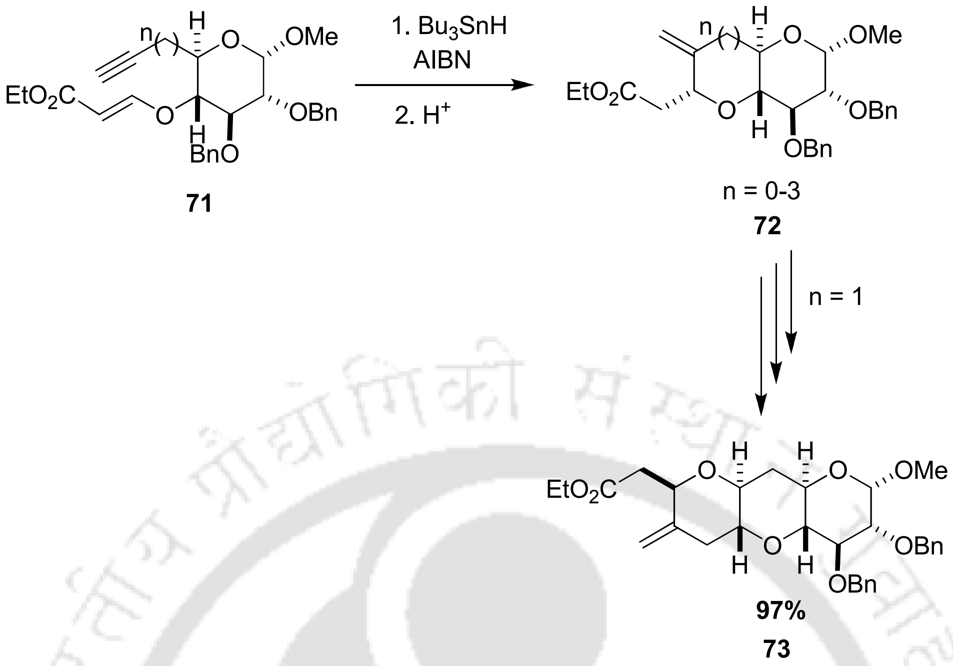
Scheme 1.2.2.2.

Yadav *et al.* have reported the synthesis of 7-iodofurano[3,2-*b*]pyrans **70** from the reaction of secondary homoallylic alcohol derived from D-glucose **69** with aldehydes **68** in the presence of molecular iodine (Scheme 1.2.2.3).[29]



Scheme 1.2.2.3.

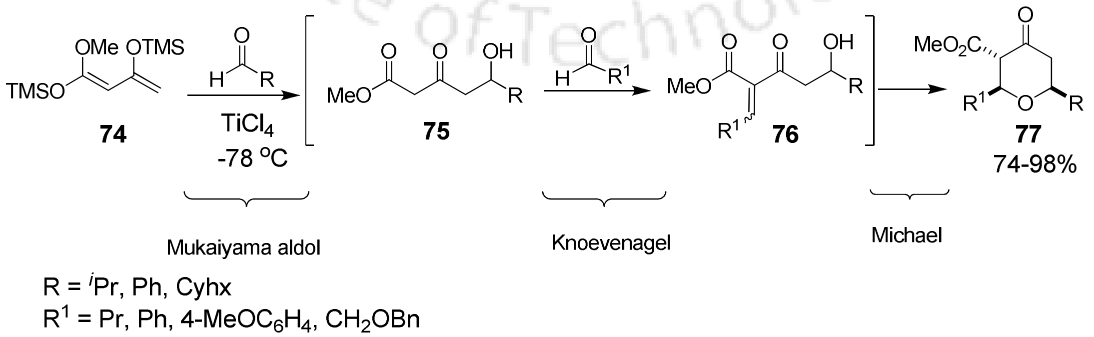
van Boom and co-workers have reported tributyltin radical mediated cyclization of carbohydrate-derived *β*-(alkynyloxy)acrylates **71** to highly functionalized *cis*- and *trans*-fused bicyclic ethers **73** of various ring sizes (Scheme 1.2.2.4).[30]



Scheme 1.2.2.4.

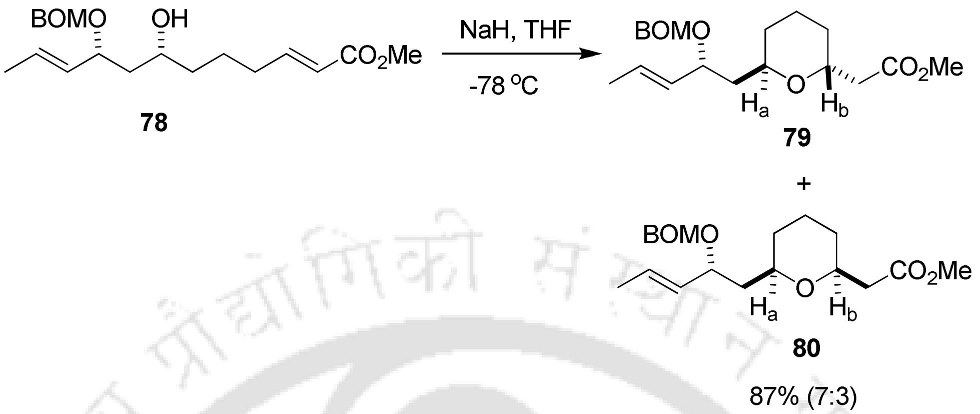
1.2.3 Intramolecular Michael Reaction

The intramolecular Michael addition is a facile method to construct a heterocyclic ring and has recently been used for the synthesis of tetrahydropyrans. For example, Clarke *et al.* have reported the synthesis of highly substituted tetrahydropyran-4-ones **77** starting from bis-trimethylsilyl enol ether **74** of methyl acetoacetate. Treatment of **74** with Lewis acid in the presence of an aldehyde generates aldol product **75**, which undergoes Lewis acid catalyzed Knoevenagel condensation with a second equivalent of a different aldehyde or ketone to furnish **76**. Finally Lewis acid catalyzed intramolecular oxy-Michael reaction produces tetrahydropyran-4-ones **77** (Scheme 1.2.3.1).[31]



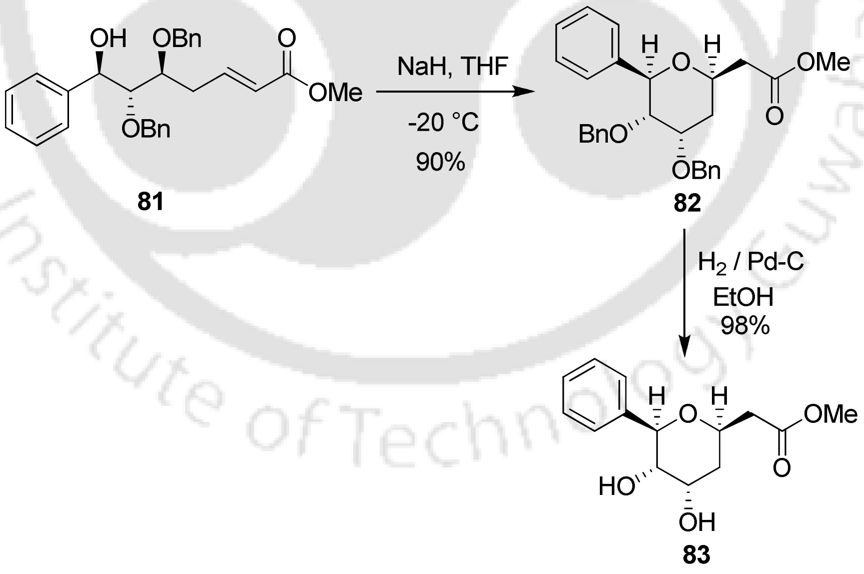
Scheme 1.2.3.1.

Bates *et al.* have reported the synthesis of tetrahydropyrans **79** and **80** in good yields starting from Michael precursor **78** (Scheme 1.2.3.2).[32]



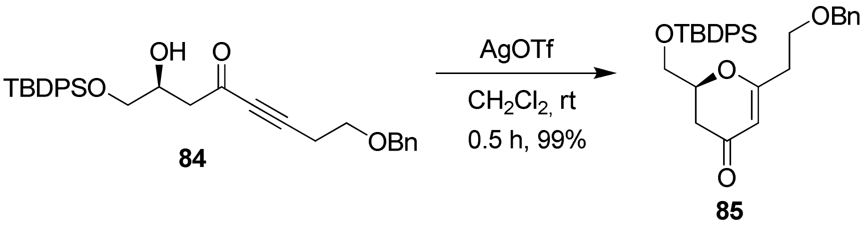
Scheme 1.2.3.2.

Fadnavis and co-workers have reported the synthesis of Goniothalesdiol A, **83** a natural product containing 2,3,4,6-tetrasubstituted tetrahydropyran ring from precursor **81** by using base-catalyzed intramolecular oxa-Michael addition reaction followed by debenzylation with Pd-C (Scheme 1.2.3.3).[33]



Scheme 1.2.3.3.

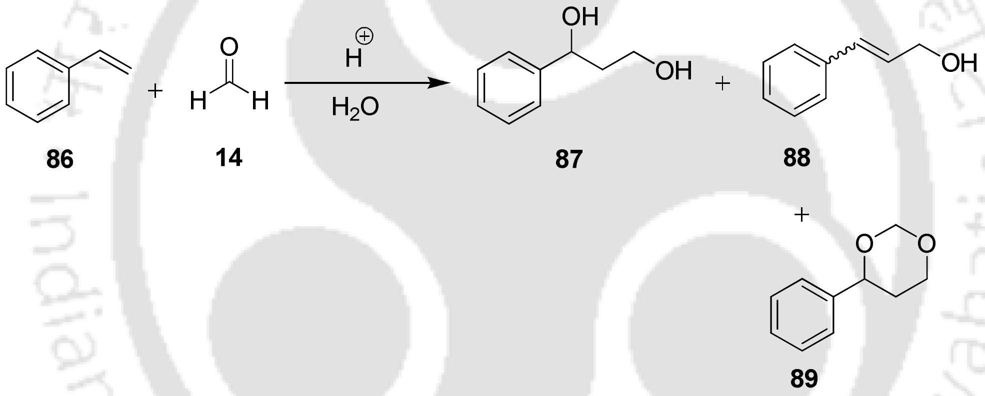
Reddy *et al.* have reported the synthesis of pyranone **85** via an intramolecular oxa-Michael addition of *β*-hydroxyynone **84** (Scheme 1.2.3.4). Here the pyranone **85** is an important intermediate for the synthesis of natural products (–)-Dactylolide and (–)-Zampanolide.[34]



Scheme 1.2.3.4.

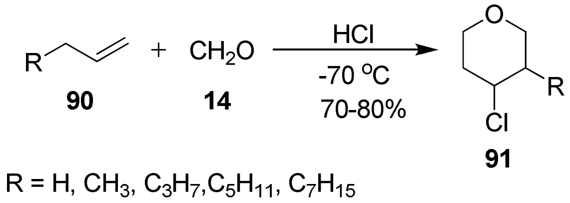
1.2.4 Prins Cyclization

Prins reaction was first reported by H. J. Prins in the year 1919.[35] In his initial study by using water as a solvent, he performed the reaction of styrene **86** with formaldehyde **14**. A mixture of 1,3-butanediol **87**, unsaturated alcohol **88** and 1,3-dioxane **89** were obtained as products (Scheme 1.2.4.1).



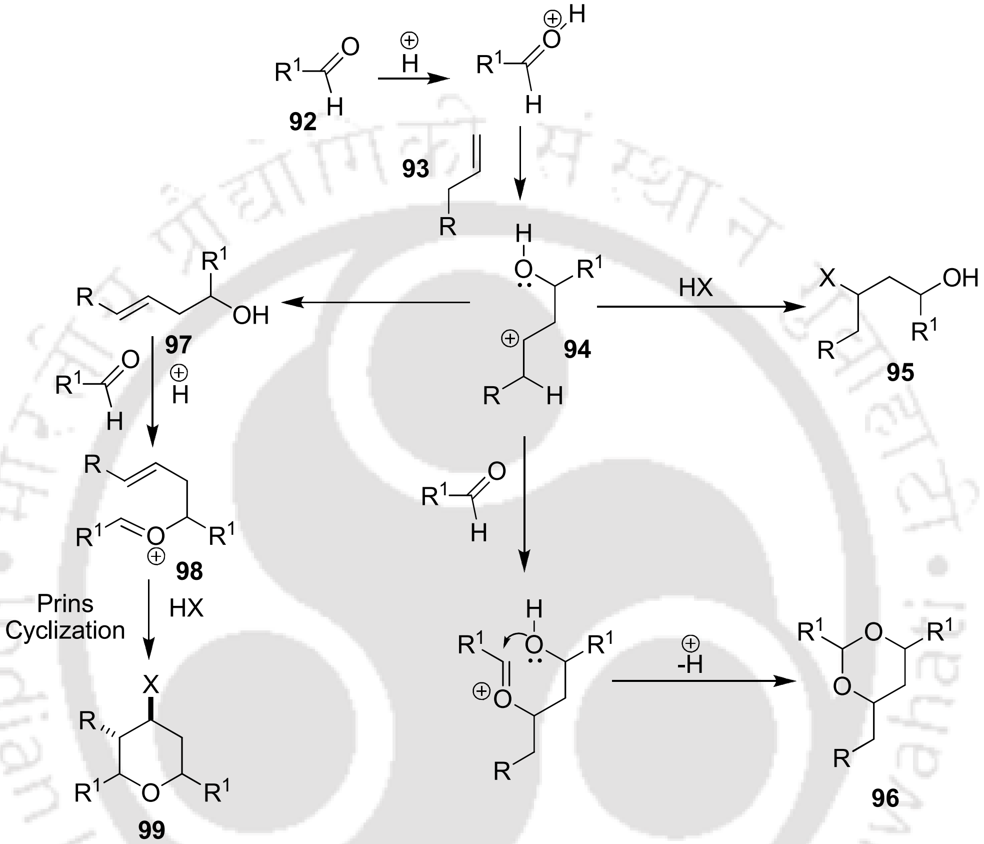
Scheme 1.2.4.1.

In the late 1960s the reaction was developed by Stapp to form tetrahydropyran derivatives.[36] This reaction proceeded in anhydrous media and involved the condensation of aliphatic terminal olefins **90** with paraformaldehyde **14** and hydrochloric acid to give 3-alkyl-4-chlorotetrahydropyrans **91** (Scheme 1.2.4.2). Furthermore, he demonstrated that homoallyl alcohols are the intermediates of this reaction, which induced the development of Prins cyclization that provides a powerful access to tetrahydropyran derivatives.



Scheme 1.2.4.2.

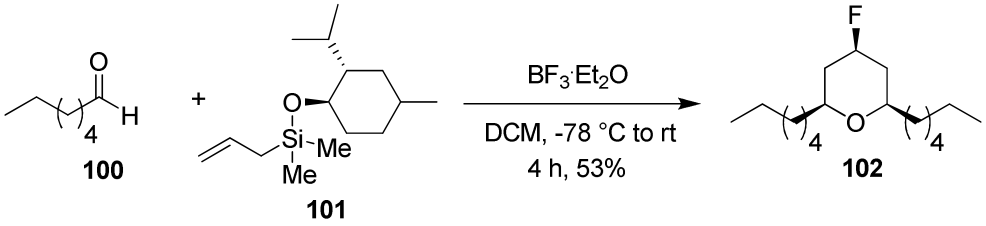
The general mechanism is shown in (Scheme 1.2.4.3). The alkene **93** reacts with carbonyl compouns **92** in the presence of Lewis or Bronsted acid and generates *β*-hydroxy carbocation **94** as a key intermediate, which either can react with a nucleophile such as chloride, water or acetate to give **95,** or adds to a second molecule of aldehyde to give **96**



Scheme 1.2.4.3.

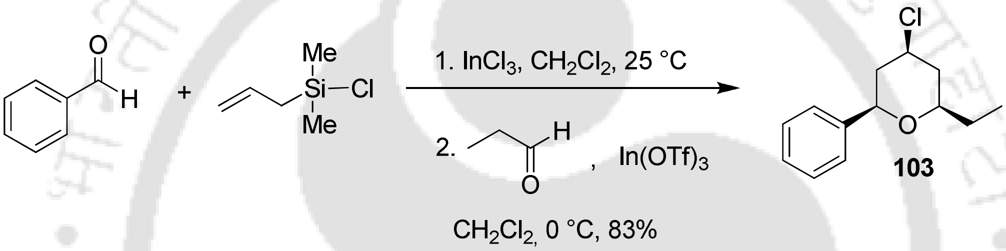
or loses a proton to give homoallylic alcohol **97**. Thus, the in situ generated homo allylalcohol **97** reacts with another molecule of aldehyde in the presence of acidic medium to afford oxocarbenium ion **98**, which after Prins cyclization and subsequent addition of neucleophile gives the 2,4,6-trisubstituted-tetrahydropyran **99**.[37]

Chan and co-workers have reported the synthesis of symmetrical *cis* 4-fluorotetrahydropyrans **102** from the reaction of two equivalents of aldehyde **100** and alkoxyallylsilane **101** (Scheme 1.2.4.4).[38]



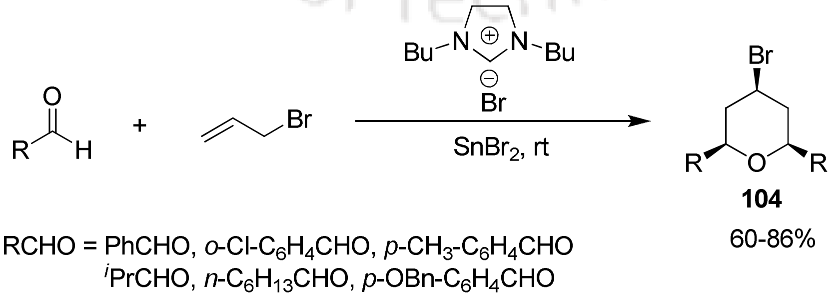
Scheme 1.2.4.4.

Loh and co-workers demonstrated the use of mild Lewis acid for the step-wise formation of homoallylic alcohol, which enable the coupling with another molecule of aldehyde in the presence of strong Lewis acid to form unsymmetrical 2,4,6-trisubstituted tetrahydropyran **103**, with high yields and selectivity (Scheme 1.2.4.5).[39]



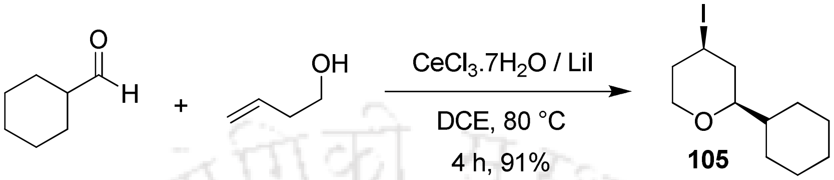
Scheme 1.2.4.5.

An interesting combination of Barbier reaction with Prins cyclization into a one-pot tandem reaction system for direct formation of tetrahydropyran was reported. Tetrahydropyran compounds can be directly synthesized from allyl bromide and carbonyl compounds by means of one-pot Barbier-Prins cyclization promoted by (N-benzyl pyridine halides) BPyX/SnX$_2$ or (Imidazole bromide salt) BBIMBr/SnBr$_2$ complex as ionic liquid under solvent-free conditions.[40] 2,6-Disubstituted-bromo-tetrahydropyrans **104** were prepared, with yields ranging from 60-86% (Scheme 1.2.4.6).



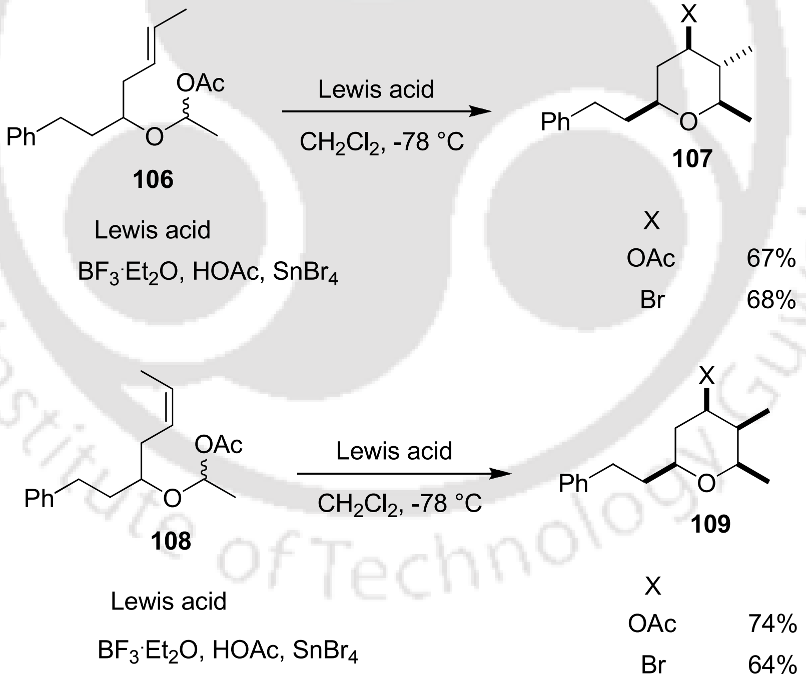
Scheme 1.2.4.6.

Homoallylic alcohols undergo smooth coupling with a variety of aldehydes in the presence of $CeCl_3.7H_2O$-LiI reagent system in refluxing dichloroethane under neutral conditions to produce the corresponding 4-iodotetrahydropyran derivatives **105** in high yields (Scheme 1.2.4.7).[41]



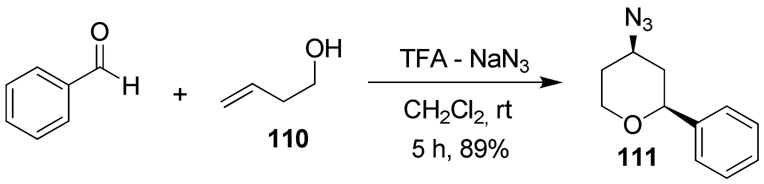
Scheme 1.2.4.7.

Rychnovsky and co-workers have reported the synthesis of highly substituted tetrahydropyrans by treatment of *α*-acetoxy ether, with Lewis acid. Here alkene geometries dictate the product configurations, with *E*-alkenes **106** leading to equatorial substituents **107** and *Z*-alkenes **108** leading to axial substituents **109** (Scheme 1.2.4.8).[42]



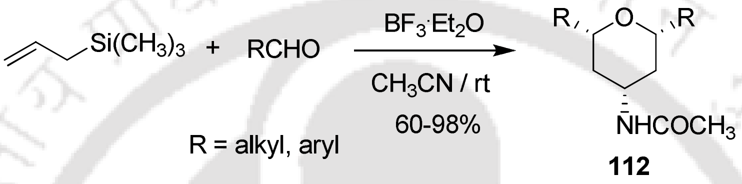
Scheme 1.2.4.8.

A three component coupling of aldehydes, homoallylic alcohols **110** and sodium azide in the presence of trifluoroacetic acid in dichloromethane had been developed to produce 4-azidotetrahydropyran **111** derivatives in high yields with all *cis*-selectivity (Scheme 1.2.4.9).[43]



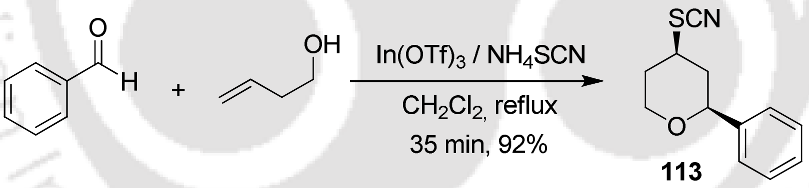
Scheme 1.2.4.9.

Saikia and co-workers have reported the synthesis of 4-amidotetrahydropyrans **112** from the reaction of aldehydes with allylsilane in acetonitrile mediated by boron trifluoride etherate in good yields and high stereoselectivity (Scheme 1.2.4.10).[44]



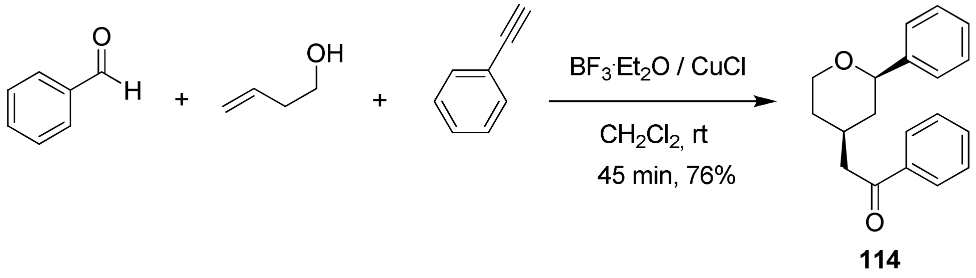
Scheme 1.2.4.10.

Jadav *et al.* have reported the synthesis of 4-thiocyanotetrahydropyrans **113** in good yields from the reaction of aldehydes, homoallylic alcohols and ammonium thiocyanate in the presence of 10 mol% In(OTf)$_3$ in refluxing dichloromethane (Scheme 1.2.4.11).[45]



Scheme 1.2.4.11.

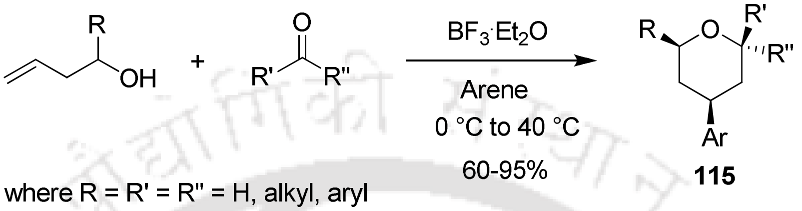
Aldehyde, homoallylic alcohol and alkyne undergo smooth Prins-type cyclization in the presence of BF$_3$·Et$_2$O / CuCl (10 mol% each) in dichloromethane under mild reaction conditions to afford 4-phenacyl tetrahydropyran derivatives **114** in good yields (Scheme



Scheme 1.2.4.12.

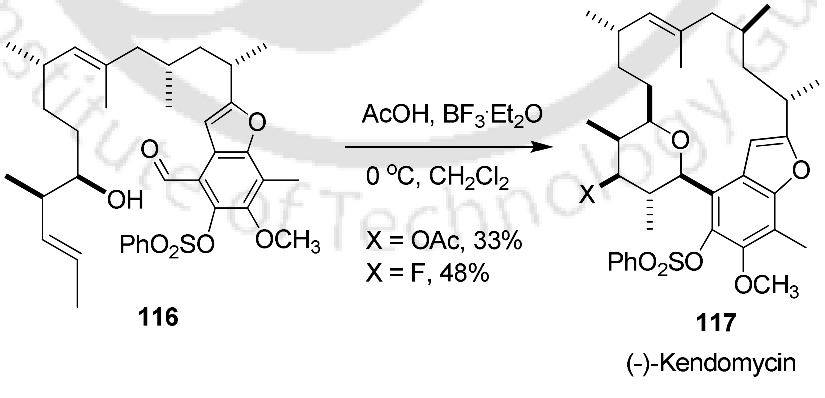
1.2.4.12).[46]

Saikia and co-workers have reported a diastereoselective one-pot, three-component Prins-Friedel-Crafts reaction for the synthesis of 4-aryltetrahydropyran derivatives **115** from the reaction of carbonyl compounds with homoallylic alcohol in the presence of arene promoted by boron trifluoride etherate (Scheme 1.2.4.13).[47]



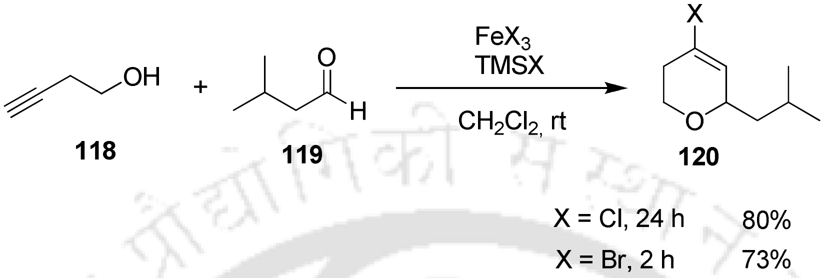
Scheme 1.2.4.13.

Kendomycin is an antitumor macrolide antibiotic isolated from the bacteria Streptomyces violaceoruber. It has potent activity as an endothelin receptor antagonist and anti-osteoporosis agent.[48] As shown in Scheme 1.2.4.14, intramolecular macro Prins cyclization using an electron-rich benzaldehyde and a homoallylic alcohol **116** efficiently delivered the fully substituted *C*-aryl tetrahydropyranoside Kendomycin **117**. The selective generation of three new stereocenters in the Prins cyclization facilitated the short and highly convergent assembly of the Kendomycin.[49] The reaction was mediated by $BF_3 \cdot Et_2O$ in a heterogeneous non-polar medium. For the electron rich benzaldehyde, the use of acetic acid as a trapping agent is necessary to suppress the side reactions.



Scheme 1.2.4.14.

More recently, Martin has also explored the synthetic potential of cyclization involving homopropargylic alcohols.[50] Reactions of homopropargylic alcohol **118** and aldehyde **119** mediated by anhydrous $FeCl_3$ or $FeBr_3$ led to 4-halo-2-alkyl-5,6-dihydro-2*H*-pyrans **120** in yields ranging from 30 to 98%. Optimization of the experimental conditions has established that the best source of halide anion was TMSX in the presence of 7 mol% of the iron catalyst FeX_3 (Scheme 1.2.4.15). The cyclization could also be mediated with $InCl_3$ and $InBr_3$, but the times of reaction were much longer and the yields were slightly lower.

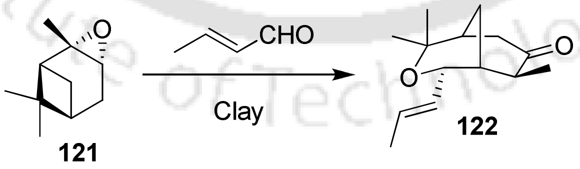


Scheme 1.2.4.15.

1.3 General Approaches for the Synthesis of Oxabicyclic Compounds

1.3.1 Method for the Synthesis of Oxabicyclo[3.3.1]nonanone

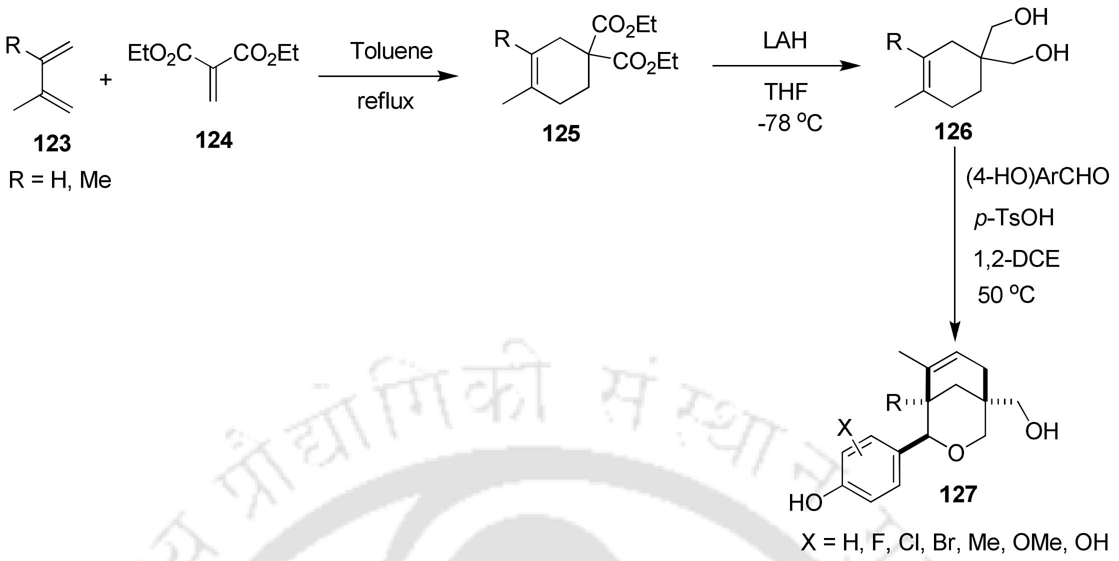
Oxygen-containing monoterpenes from the pinane series are commercially available compounds of high optical purity, and may serve as precursors of biologically active compounds[51] and intermediates in asymmetric synthesis.[52] In acidic media, they generally easily undergo numerous transformations, affording complex mixtures of products.[53] For example, Il'ina and co-workers have reported the synthesis of oxabicyclo[3.3.1]nonanone from *α*-pinene epoxide **121**.[54] The treatment of *α*-pinene epoxide **121** with crotonaldehyde in the presence of clay afforded oxabicyclo[3.3.1]nonanone **122**. But the yield of the product was less due to the formation of several side products (Scheme 1.3.1.1).



Scheme 1.3.1.1.

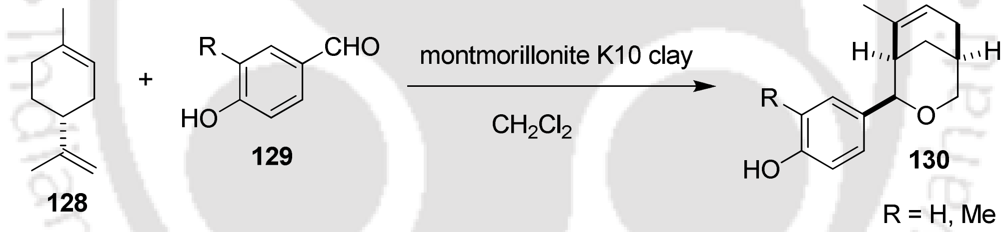
1.3.2 Method for the Synthesis of Oxabicyclo[3.3.1]nonene

Oxabicyclo[3.3.1]nonenes **127** are prepared by the reaction of aromatic aldehydes with olefin-containing compounds **126** in acidic media (Scheme 1.3.2.1).[55] The low yield and multistep reactions are the major drawback of these methods.



Scheme 1.3.2.1.

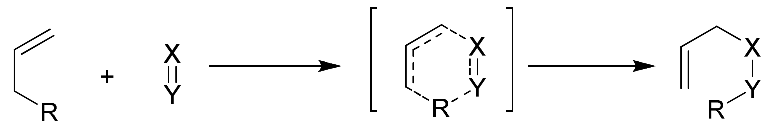
Again Hamann *et al.* have reported the synthesis of oxabicyclo[3.3.1]nonenes **130** from the reaction of Limonene **128** with aromatic aldehydes **129** in acidic medium (Scheme 1.3.2.2).[55]



Scheme 1.3.2.2.

1.4 Oxonium-Ene Reaction

The reaction of an alkene with an allylic hydrogen atom (the ene) with another alkene (enophile) to produce a new alkene is known as ene reaction (Scheme 1.4.1). 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



R = H or metal

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

Scheme 1.4.1. Ene reaction

or a nitroso group compared to simple alkene as enophile, in both of its intra- and intermolecular versions.[56] Ene cyclization that involves the oxonium ion as the enophile component, is called oxonium-ene cyclization reaction. Since, the ene and enophile can be connected in many ways, the ambiguity is inevitable. To make it unambiguous, Mikami classified the oxonium-ene reaction into three main categories namely (1,5), (2,5) and (3,5) depending upon the connectivity between enophile to the ene (Figure 1.4.1).[57] Although (1,5) and (2,5) oxonium-ene-type cyclizations have been well studied, the (3,5)-oxonium-ene cyclization has not been investigated extensively.

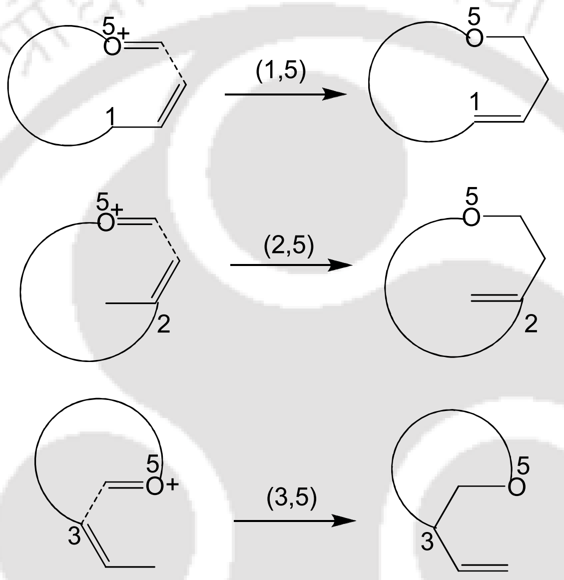
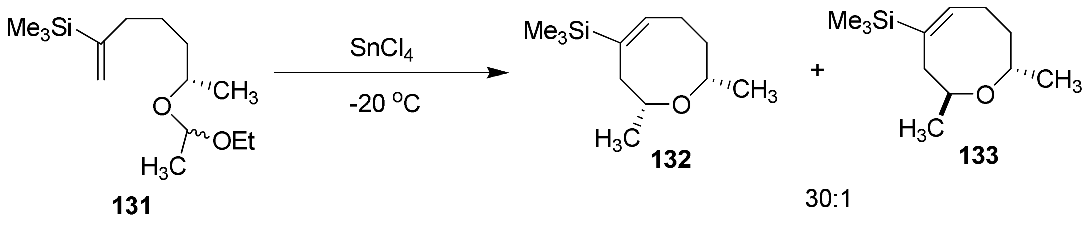


Figure 1.4.1. Classification of oxonium-ene cyclization reaction

1.4.1 (1,5)-Oxonium-Ene Reaction

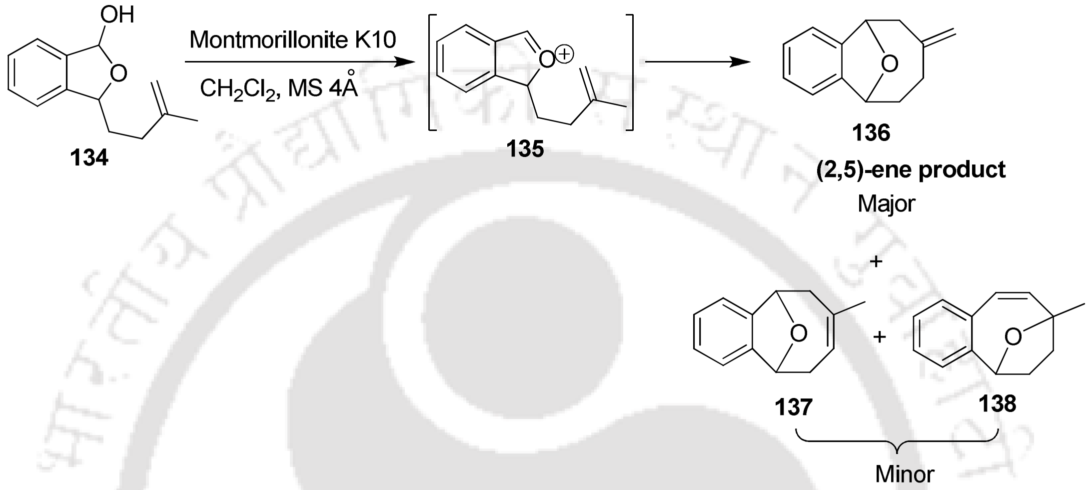
(1,5)-Oxonium-ene reaction have been well studied by Overman and co-workers. They have utilized this protocol for the synthesis of higher membered oxacycles. For example, treatment of unsaturated acetal **131** with $SnCl_4$ generates an oxocarbenium ion, which then undergoes cyclization via (1,5)-oxonium-ene reaction to afford mixture of 8-membered cyclic ethers **132** and **133** with excellent diastereoselectivity (Scheme 1.4.1.1).[58]



Scheme 1.4.1.1.

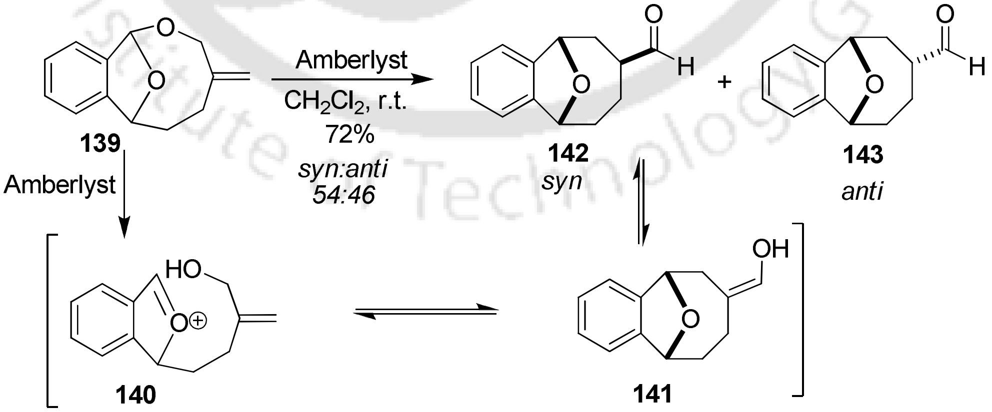
1.4.2 (2,5)-Oxonium-Ene Reaction

Mikami and co-workers have studied the (2,5)-oxonium-ene reaction. Lactol **134** on treatment with mesoporous solid acids such as montmorillonite K-10 produces tricyclic compound with exocyclic double bond **136** as a major product and its endo cyclic regioisomers **137** and **138** as minor products (Scheme 1.4.2.1).[59]



Scheme 1.4.2.1.

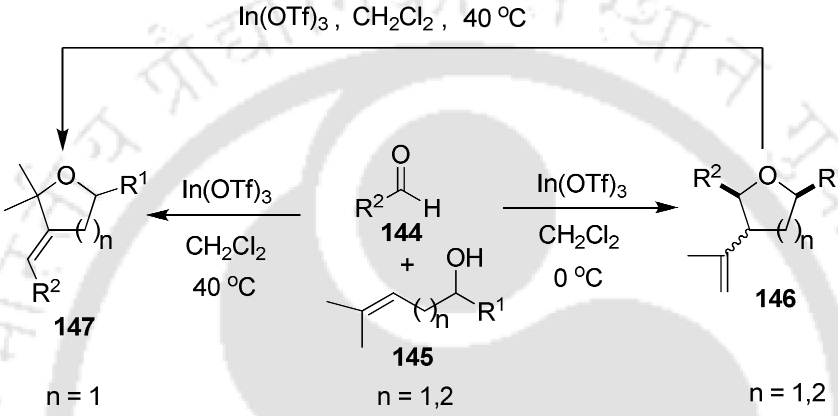
In addition to (2,5)-oxonium-ene reaction, Mikami investigated the mechanism of the reaction by trapping the (2,5) ene product in its enol form **141**, which immediately transformed to corresponding aldehydic forms **142** and **143** to restrict the regioisomerization to its endo cyclic isomers (Scheme 1.4.2.2).[59]



Scheme 1.4.2.2.

1.4.3 (3,5)-Oxonium-Ene Reaction

Loh *et al*. have developed a facile method for the synthesis of tetrahydro-furans and pyrans **146** from the reaction of aldehyde **144** and unsaturated alkenes having γ and δ hydroxyl groups **145** promoted by $In(OTf)_3$ via intramolecular (3,5)-oxonium-ene reaction at 0 °C (Scheme 1.4.3.1). By increasing the reaction temperature from 0 °C to 40 °C, they observed the formation of exocyclic isomer **147** as a major product. However, this rearrangement is limited to the tetrahydrofurans skeletons only, but not to the tetrahydropyran counterparts.[60]



n = 1, R^1 = c-C_6H_{11}, R^2 = alkyl, aryl

n = 2, R^1 = Me, R^2 = alkyl, aryl

Scheme 1.4.3.1.

1.5 References

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CHAPTER 2

A Novel Synthesis of Oxabicyclo[3.3.1]nonanone via (3,5)-Oxonium-Ene Reaction

2.1 Importance and Applications

Oxabicyclic compounds are important due to their potential biological properties. Oxabicyclo[3.3.1]nonene and its selected derivatives (Figure 2.1.1, **B**) are known to behave as estrogen receptor ligands.[1] The estrogen receptor (ER) is a member of the nuclear hormone receptor superfamily of ligand-dependent transcription factors, which mediate a broad range of physiological processes in response to binding of the endogenous ligand 17*β*-estradiol (Figure 2.1.1, **A**).[1b]

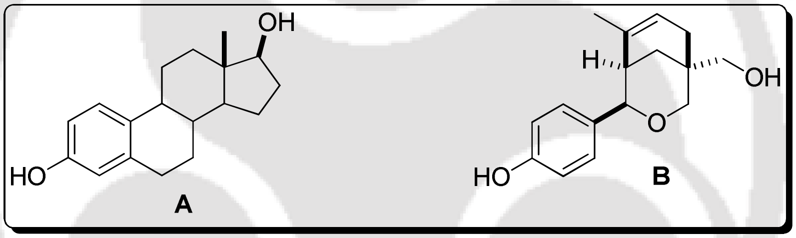
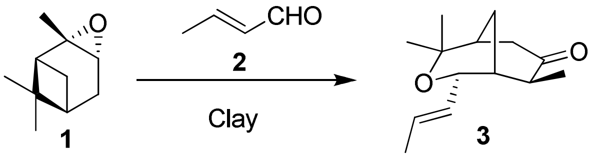


Figure 2.1.1. Estrogen receptor ligand

2.2 An Overview of Relevant Synthetic Methods

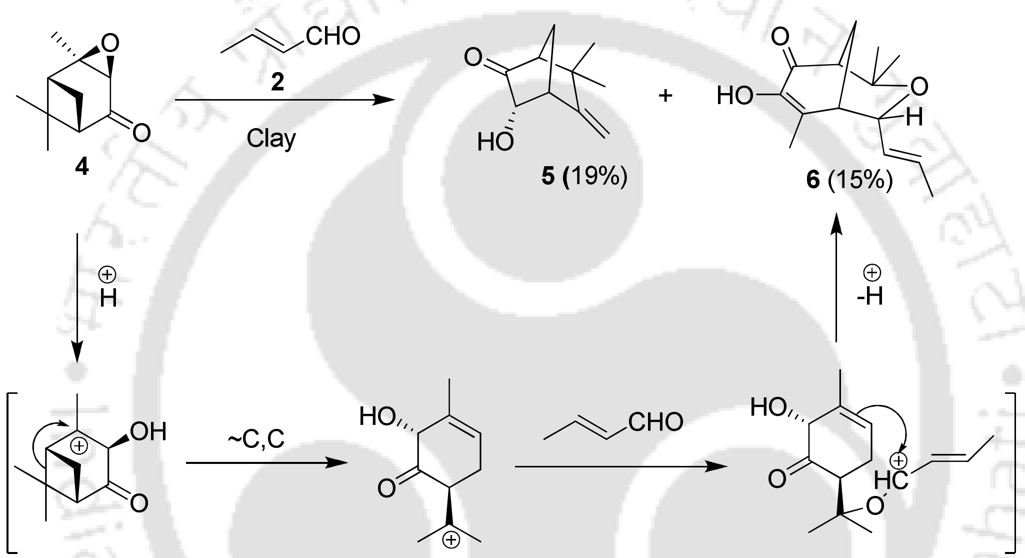
Review of literature reveals that there is only one strategy for the synthesis of oxabicyclo[3.3.1]nonanone and that has come from Il'ina's group. They have prepared oxabicyclo[3.3.1]nonanone from *α*-pinene epoxide and verbenone epoxide in acidic medium.[2]

Treatment of *α*-pinene epoxide **1** with aliphatic aldehydes such as crotonaldehyde **2** in the presence clay produces oxabicyclo[3.3.1]nonanone **3** in low yield due to the formation of several side products (Scheme 2.2.1).[2]



Scheme 2.2.1.

On the other hand verbenone epoxide **4** on treatment with aliphatic and aromatic aldehydes in the presence of askanite-bentonite clay undergoes intermolecular cyclization. Thus, reaction of **4** with crotonaldehyde in the presence of clay afforded, besides the isomerization product **5**, the heterocyclic 1,2-diketone **6** (Scheme 2.2.2).[2] This compound was isolated in its enol form, which turned to be stable even upon heating to 40 °C. The mechanism includes protonation and cleavage of the epoxide ring, skeletal rearrangement into a cation with a *para*-menthane framework and further reaction of the cation with crotonaldehyde (Scheme 2.2.2).

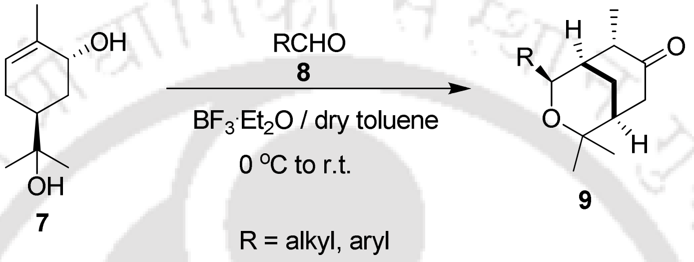


Scheme 2.2.2.

2.3 Present Work

An important objective of contemporary synthesis endeavors is the development of new transformations that rapidly evolve molecular complexity in a stereo controlled fashion. One approach towards this goal is to combine two or more distinct reactions into a single transformation, producing a process often referred to as sequential, tandem, cascade or domino reaction. Oxonium-ene reactions are powerful tool for construction of various cyclic ethers.[3,4] There are three different types of oxonium-ene cyclization reactions, namely, (1,5), (2,5) and (3,5).[3e,5] In this chapter, we discuss the Lewis acid catalyzed (3,5)-oxonium-ene reaction[3e,6] for the synthesis of oxabicyclo[3.3.1]nonanone.

We have developed an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonanone via (3,5)-oxonium-ene reaction from the reaction of aldehydes or epoxides with commercially available *trans-p*-menth-6-ene-2,8-diol, mediated by boron trifluoride etherate (Scheme 2.3.1). *trans*-*p*-Menth-6-ene-2,8-diol has long been used as starting material for many organic transformations.[7] We envisioned that treatment of *trans*-*p*-menth-6-ene-2,8-diol with boron trifluoride etherate would provide carbocation at the side chain, which after nucleophilic attack by aldehyde and subsequent (3,5)-oxonium-ene cyclization will give bicyclic product. Thus, the treatment of *trans*-*p*-menth-6-ene-2,8-diol with benzaldehyde and boron trifluoride etherate in dry toluene gave 2,2,6-trimethyl-4-phenyl-3-oxabicyclo[3.3.1]nonan-7-one in 80% yield.



Scheme 2.3.1. Synthesis of oxabicyclo[3.3.1]nonanone

The scope of the reaction was investigated by using different types of aliphatic and aromatic aldehydes (Table 2.3.1). It was observed that the aromatic aldehydes, except benzaldehyde, gave low yield, irrespective of electron withdrawing or donating groups on the ring, than the aliphatic aldehydes. The reason might be due to the formation of some highly non polar side products, which were unable to characterize by spectroscopic methods. The reaction was diastereoselective and in all the cases the substituents at 4 and 6 are in *trans* position. The structure and stereochemistry of the compound was determined by ^{1}H NMR, NOE experiment (Figure 2.3.1) and X-ray crystallographic analysis (Figure 2.3.2).[8] In the ^{1}H NMR spectrum of compound **9h** the coupling constant between H_{5e} (2.30 ppm) and H_{9e} (2.22 ppm) is 3.2 Hz which indicates that they are in equatorial position. Again the coupling constant between H_{8a} (2.48 ppm) and H_{1e} (1.70-1.90 ppm) is 4.8 Hz which indicates that

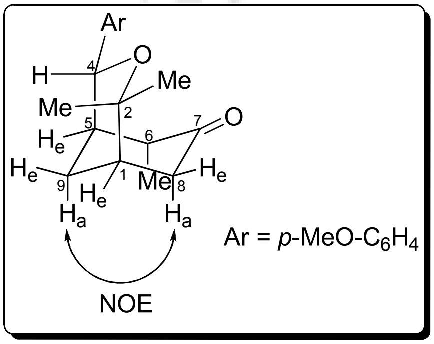
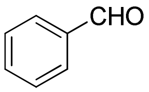
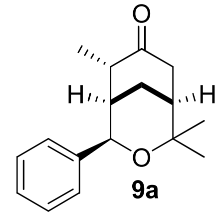
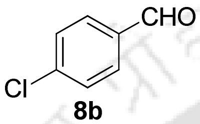
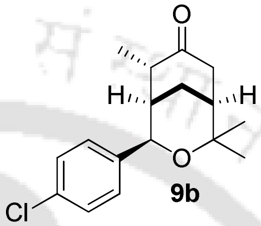
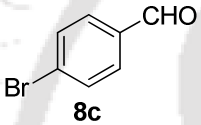
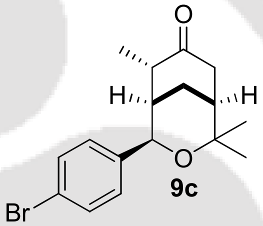
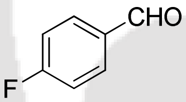
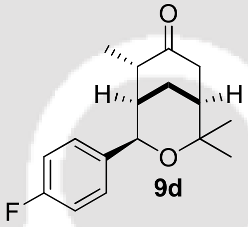
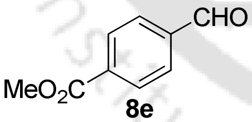
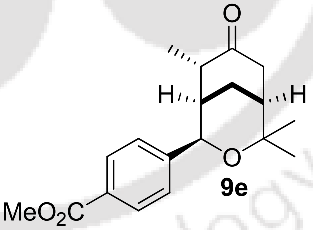
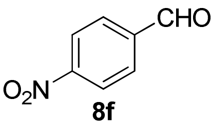
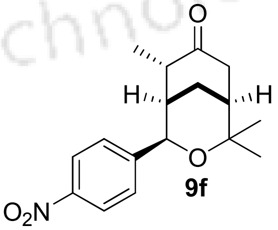
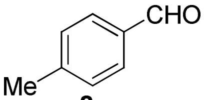
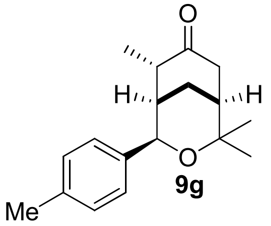
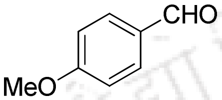
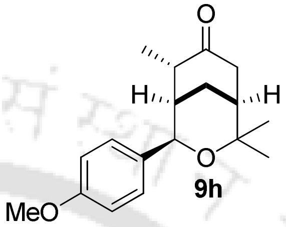
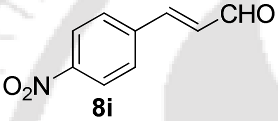
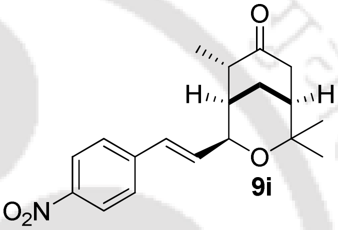
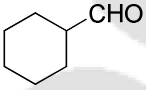
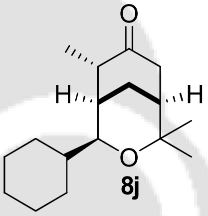
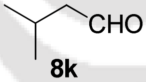
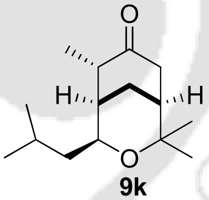
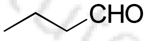
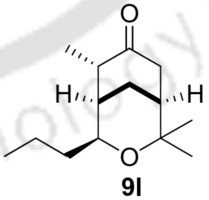
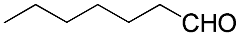
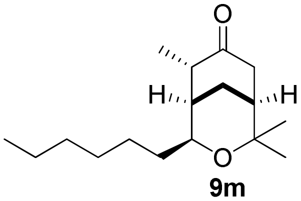


Figure 2.3.1. NOE diagram of compound **9h**

Table 2.3.1. Synthesis of oxabicyclo[3.3.1]nonanone

Entry	Aldehyde **8**	Time / h	Product **9**	Yield[a] (%)
1	 **8a**	8	 **9a**	80
2	 **8b**	10	 **9b**	50
3	 **8c**	10	 **9c**	51
4	 **8d**	10	 **9d**	62
5	 **8e**	12	 **9e**	52
6	 **8f**	12	 **9f**	50

continue….

Entry	Aldehyde **8**	Time / h	Product **9**	Yield[a] (%)
7	 **8g**	10	 **9g**	68
8	 **8h**	10	 **9h**	56
9	 **8i**	12	 **9i**	62
10	 **8j**	5	 **8j**	90
11	 **8k**	6	 **9k**	82
12	 **8l**	6	 **9l**	98
13	 **8m**	5	 **9m**	80

[a] Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR and Mass spectroscopy.

one proton is in an axial position and the other in an equatorial position. The presence of a strong NOE between H_{8a} and H_{9a} (1.93-1.95 ppm) confirms that they are in a 1,3-diaxial position. Therefore H_{1e} is in an equatorial position. Thus H_{1e} and H_{5e} are in equatorial positions and hence the fusion between two rings is *cis* fusion (Figure 2.3.1).

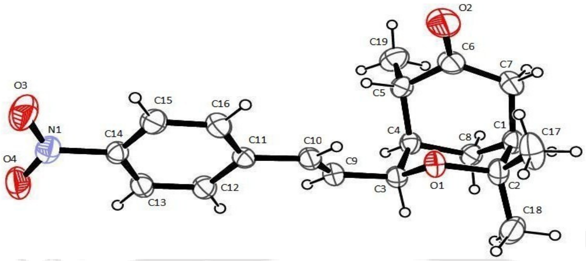
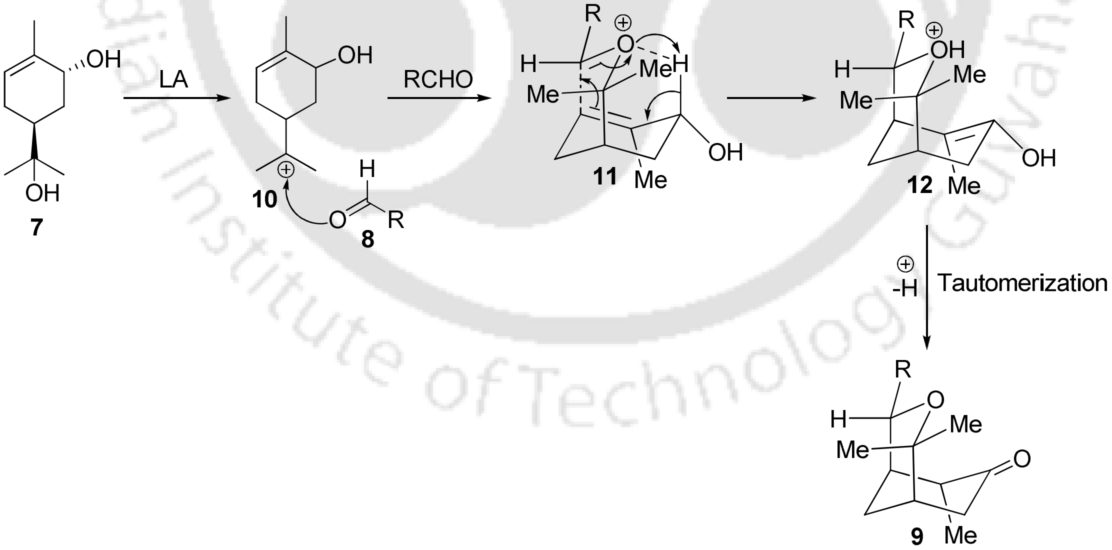


Figure 2.3.2. ORTEP diagram of 2,2,6-trimethyl-4-[2-(4-nitrophenyl-vinyl)]-3-oxabicyclo[3.3.1]nonan-7-one (**9i**)

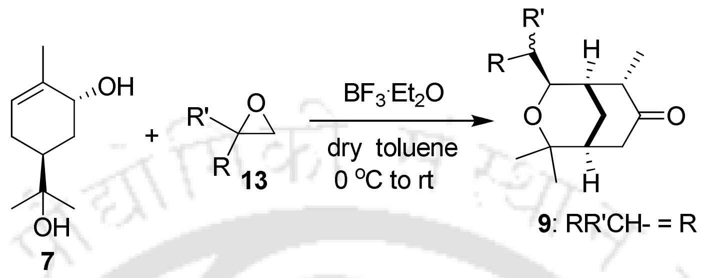
The mechanism of the reaction can be explained as follows. The reaction of compound **7** with Lewis acid generates carbocation **10**, which after nucleophilic attack by aldehyde provides oxocarbenium ion **11**, which forms a stable six membered transition state. The oxocarbenium ion **11** undergoes (3,5)-oxonium-ene cyclization reaction to give enol **12**, which after tautomerization gives **9** (Scheme 2.3.2).

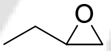
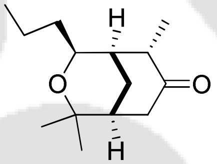
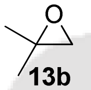
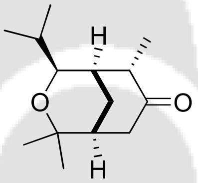
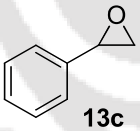
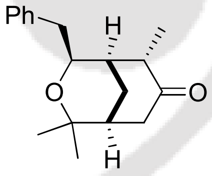
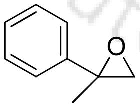
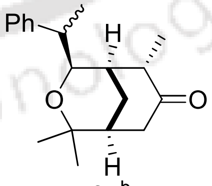
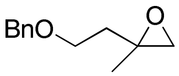
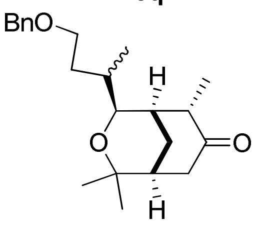


Scheme 2.3.2. Proposed mechanism of the reaction

The same oxabicyclic compounds can also be prepared by using epoxide as aldehyde equivalent as shown in Table 2.3.2. Here also the scope of the reaction was investigated by using various mono- and disubstituted epoxides. It was observed that monosubstituted terminal epoxides are non reactive whereas the 2,2-disubstituted and styrene oxides are reactive and gives good to moderate yields. This is attributed to the lower stability of the carbocation **14**, obtained from monosubstituted epoxides, compared to 2,2-disubstituted

Table 2.3.2. Synthesis of oxabicyclo[3.3.1]nonanone from epoxides

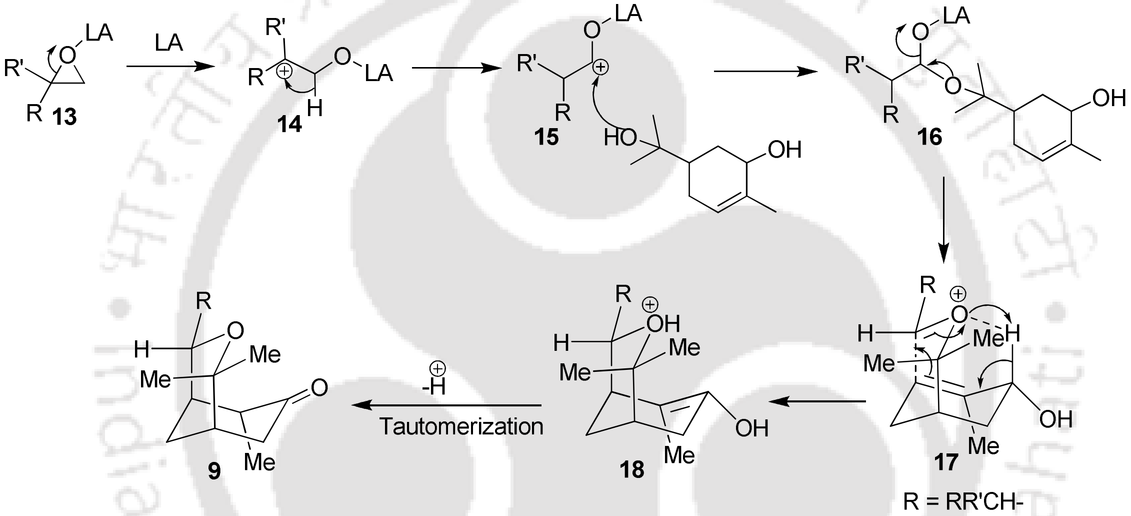


Entry	Epoxide **13**	Time / h	Product **9**	Yield[a] (%)
1	 **13a**	24	 **9n**	0
2	 **13b**	9	 **9o**	78
3	 **13c**	10	 **9p**	45
4	 **13d**	10	 **9q**[b]	44
5	 **13e**	9	 **9r**[b]	75

[a]Yields refer to isolated yield. The compounds are characterized by IR, NMR and Mass spectroscopy. [b]Mixture of two isomers with a ratio of 1:1.

epoxides and styrene oxides, where carbocation **14** is better stabilized due to tertiary and benzylic centers, respectively.[9a] However, the low yield obtained in case of styrene epoxides is also due to the formation of similar type of nonpolar side products**.** Epoxide **13d** gave two separable isomers whereas **13e** gave two inseparable isomers.

The mechanism of the reaction with epoxide can be explained by considering the already reported fact that epoxide after ring opening with Lewis acid rearranges to aldehyde.[9] Here the intermediate **15** is attacked by alcohol to give acetal **16**, which after (3,5)-oxonium-ene cyclization gives enol **18**. The enol **18** tautomerizes to give oxabicyclic compound **9** (Scheme 2.3.3).



Scheme 2.3.3. Mechanism of the reaction with epoxide

Conclusions:

In conclusion, we have demonstrated an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonanone in moderate to good yields. The bicyclic unit can further be transformed by manipulating carbonyl functionalities and therefore, can be used as a precursor for the synthesis of complex molecules.

2.4 Experimental Section

2.4.1 Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded with a Büchi B-540 melting point apparatus. Mass spectra were recorded using Waters LC-MS/MS system (Q-TOF–Premier). HRMS (ESCi-TOF) were calibrated with sodium formate solution and leucine enkephalin (SIGMA) was used as an external standard. Fourier transform-infra red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (400 MHz) or ^{13}C (100 MHz). Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic $Mock_\alpha$ radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

2.4.2 General Procedure for the Synthesis of Oxabicyclic Compounds from Aldehydes (9a-9m, Table 2.3.1): To a solution of *trans*-*p*-menth-6-ene-2,8-diol (0.59 mmol, 1 equiv.) and aldehyde (1 equiv.) in 4 mL dry toluene at 0 °C was added boron trifluoride etherate (0.71 mmol, 1.2 equiv.) drop by drop over 5 minutes. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of 2,2,6-Trimethyl-4-phenyl-3-oxabicyclo[3.3.1]nonan-7-one (9a, Table 2.3.1): To a solution of *trans*-*p*-menth-6-ene-2,8-diol (100 mg, 0.59 mmol) in dry toluene (2 mL) at 0 °C, was added boron trifluoride etherate (100 mg, 0.71 mmol). To this solution benzaldehyde (62 mg, 0.59 mmol) in dry toluene (2 mL) was added drop by drop over 5 min. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for 8 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (1:4) as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **9a** (121.0 mg, 80%) as a crystalline solid; M.P. 92-96 ^oC.

2.4.3 General Procedure for the Synthesis of Oxabicyclic Compounds from Epoxides (9n-9r, Table 2.3.2): To a solution of *trans-p*-menth-6-ene-2,8-diol (0.59 mmol, 1 equiv.) in dry toluene (2 mL) at 0 ^oC was added boron trifluoride etherate (0.7 mmol, 1.2 equiv.). To this solution epoxide (1.18 mmol, 2 equiv.) in dry toluene (2 mL) was added drop by drop over 5 minutes. The temperature was slowly brought to room temperature in 15 minutes. The reaction mixture was stirred at room temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The crude product was extracted with ethyl acetate, then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of 4-Isopropyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9o, Table 2.3.2): To a solution of *trans-p*-menth-6-ene-2,8-diol (100 mg, 0.59 mmol) in dry toluene (2 mL) at 0 ^oC was added boron trifluoride etherate (100 mg, 0.7 mmol). To this solution 1,2-epoxy-2-methyl propane (85 mg, 1.18 mmol) in dry toluene (2 mL) was added drop by drop over 5 minutes. The temperature was slowly brought to room temperature in 15 minutes. The reaction mixture was stirred at room temperature for 9 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (1:9) as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The crude product was extracted with ethyl acetate, and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **9o** (109 mg, 78%) as a liquid.

2.5 References and Notes

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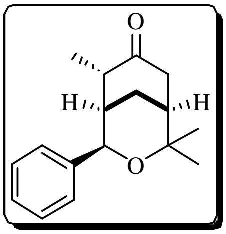
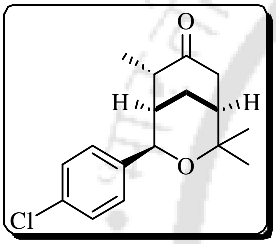
2.6 Spectral Data

2,2,6-Trimethyl-4-phenyl-3-oxabicyclo[3.3.1]nonan-7-one (9a):



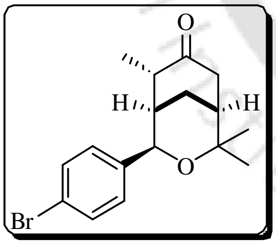
Solid (122 mg, 80%); **M.P.**: 92-96 °C; **^{1}H NMR** (CDCl$_3$, 400 MHz): *δ* 1.07 (d, *J* = 7.2 Hz, 3 H), 1.30 (s, 3 H), 1.41 (s, 3 H), 1.90-2.0 (m, 2 H), 2.25 (dt, *J* = 14.0 and 3.2 Hz, 1 H), 2.29-2.37 (m, 2 H), 2.48 (dd, *J* = 15.6 and 4.8 Hz, 1 H), 2.57-2.64 (m, 1 H), 4.92 (brs, 1 H), 7.20-7.26 (m, 3 H), 7.30-7.35 (m, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 18.0, 23.4, 25.0, 27.8, 39.4, 40.6, 42.7, 43.5, 75.4, 75.5, 125.9, 126.9, 128.2, 141.1, 213.8; **IR** (KBr) 2964, 1699, 1450, 1380, 1231, 1065, 1044, 739, 697 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O_2$ (M+H)$^+$ requires 259.1698; found 259.1691.

4-(4-Chlorophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9b):



Solid (86 mg, 50%); **M.P.**: 116-120 °C; **^{1}H NMR** (CDCl$_3$, 400 MHz): *δ* 1.08 (d, *J* = 7.6 Hz, 3 H), 1.30 (s, 3 H), 1.40 (s, 3 H), 1.88-2.0 (m, 2 H), 2.18-2.36 (m, 3 H), 2.48 (dd, *J* = 15.6 and 5.2 Hz, 1 H), 2.56-2.63 (m, 1 H), 4.89 (brs, 1 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 18.1, 23.6, 25.1, 27.9, 39.5, 40.7, 42.9, 43.6, 75.2, 75.7, 127.5, 128.5, 132.8, 139.8, 213.5; **IR** (KBr) 2983, 2940, 1702, 1491, 1382, 1234, 1083, 1070, 1048, 795 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}ClO_2$ (M+H)$^+$ requires 293.1308; found 293.1315 (^{35}Cl).

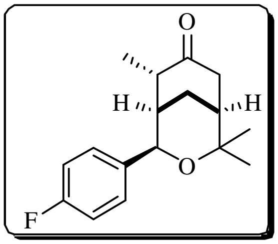
4-(4-Bromophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9c):



Solid (101 mg, 51%); **M.P.**: 128-130 °C; **^{1}H NMR** (CDCl$_3$, 400 MHz): *δ* 1.08 (d, *J* = 7.6 Hz, 3 H), 1.30 (s, 3 H), 1.41 (s, 3 H), 1.88-2.02 (m, 2 H), 2.17-2.36 (m, 3 H), 2.49 (dd, *J* = 15.6 and 4.4 Hz, 1 H), 2.56-2.64 (m, 1 H), 4.89 (brs, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 18.1, 23.6, 25.1, 27.9, 39.5, 40.7, 42.9, 43.5, 75.2, 75.8, 120.9, 127.8, 131.4, 140.3, 213.5; **IR** (KBr) 2972, 2918, 1706, 1484, 1460, 1369, 1232, 1069, 1050, 793 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}BrO_2$ (M+H)$^+$ requires 337.0803; found 337.0804 (^{79}Br).

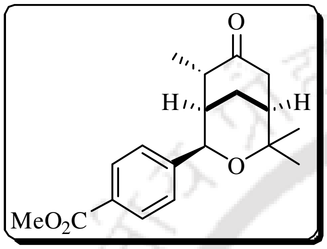
4-(4-Fluorophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9d):

Solid (101 mg, 62%); **M.P.**: 112-115 °C; **^{1}H NMR** (CDCl$_3$, 400 MHz): *δ* 1.08 (d, *J* = 7.6 Hz, 3 H), 1.30 (s, 3 H), 1.41(s, 3 H), 1.88-2.01 (m, 2 H), 2.20-2.36 (m, 3 H), 2.49 (dd, *J* = 15.6 and 4.8 Hz, 1 H), 2.56-2.64 (m, 1 H), 4.90 (brs, 1 H), 7.02 (t, *J* = 8.8 Hz, 2 H), 7.21 (t, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 18.1, 23.6, 25.1, 27.9, 39.5, 40.7, 42.8,



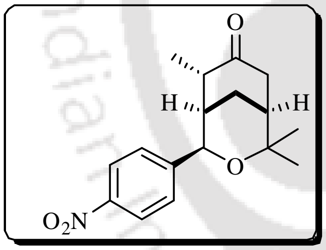
43.7, 75.2, 75.7, 115.1 (d, J = 20.6 Hz), 127.6 (d, J = 7.7 Hz), 136.9, 161.9 (d, J = 243.3 Hz), 213.6; **^{19}F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -220.72-(-219.73) (m, 1 F); **IR** (KBr) 2966, 2941, 1702, 1510, 1465, 1380, 1221, 1066, 1044, 808, 784 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}FO_2$ $(M+H)^+$ requires 277.1604; found 277.1610.

Methyl 4-(4,4,8-trimethyl-7-oxo-3-oxabicyclo[3.3.1]nonan-2-yl)benzoate (9e):



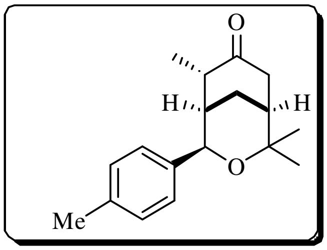
Solid (97 mg, 52%); **M.P.**: 115-120 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.06 (d, J = 7.6 Hz, 3 H), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.96-2.02 (m, 2 H), 2.15 (q, J = 7.2 Hz, 1 H), 2.26 (dt, J = 13.6 and 2.8 Hz, 1 H), 2.32-2.38 (m, 1 H), 2.49 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.58-2.65 (m, 1 H), 3.90 (s, 3 H), 4.97 (brs, 1 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.99 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.9, 23.4, 24.9, 27.8, 39.3, 40.5, 42.9, 43.3, 52.1, 75.2, 75.7, 125.9, 128.7, 129.5, 146.5, 167.1, 213.4; **IR** (KBr) 2984, 2952, 1717, 1703, 1435, 1384, 1276, 1111, 1098, 1070, 754, 706 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{24}O_4$ $(M+H)^+$ requires 317.1753; found 317.1753.

4-(4-Nitrophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9f):



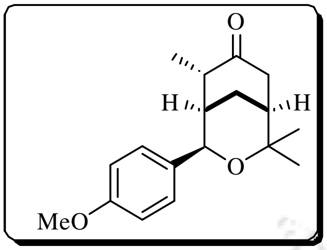
Semisolid (89 mg, 50%); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.00 (d, J = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.35 (s, 3 H), 1.90-2.02 (m, 3 H), 2.21 (dt, J = 14.4 and 2.4 Hz, 1 H), 2.26-2.33 (m, 1 H), 2.44 (dd, J = 15.2 and 4.4 Hz, 1 H), 2.48-2.57 (m, 1 H), 4.93 (brs, 1 H), 7.35 (d, J = 8.8 Hz, 2 H), 8.10 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.0, 23.5, 25.0, 27.8, 39.4, 40.6, 43.1, 43.4, 75.1, 76.1, 123.6, 126.9, 147.1, 148.8, 213.1; **IR** (KBr) 2967, 2923, 1703, 1517, 1344, 1229, 1094, 1067, 1048, 861, 740, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}NO_4$ $(M+H)^+$ requires 304.1549; found 304.1551.

2,2,6-Trimethyl-4-(*p*-tolyl)-3-oxabicyclo[3.3.1]nonan-7-one (9g):



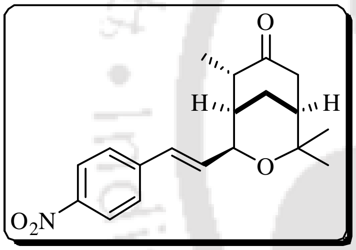
Solid (109 mg, 68%); **M.P.**: 100-104 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.07 (d, J = 7.2 Hz, 3 H), 1.30 (s, 3 H), 1.40 (s, 3 H), 1.85-1.98 (m, 2 H), 2.20-2.31 (m, 3 H), 2.32 (s, 3 H), 2.48 (dd, J = 15.6 and 4.4 Hz, 1 H), 2.55-2.62 (m, 1 H), 4.90 (brs, 1 H), 7.13 (brs, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.1, 21.2, 23.6, 25.1, 27.9, 39.5, 40.7, 42.7, 43.6, 75.4, 75.5, 125.9, 128.9, 136.5, 138.2, 213.9; **IR** (KBr) 2926, 2878, 1698, 1455, 1380, 1230, 1066, 1046, 799, 772 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_2$ $(M+H)^+$ requires 273.1855; found 273.1853.

4-(4-Methoxyphenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9h):



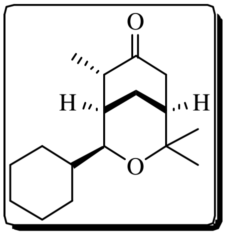
Solid (95 mg, 56%); **M.P.**: 97-101 °C; ^{1}**H NMR** (CDCl$_3$, 400 MHz): δ 1.07 (d, J = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.40 (s, 3 H), 1.70-1.90 (m, 1 H), 1.93-1.95 (m, 1 H), 2.22 (dt, J = 13.6 and 3.2 Hz, 1 H), 2.27-2.31 (m, 1 H), 2.32-2.36 (m, 1 H), 2.48 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.56-2.63 (m, 1 H), 3.78 (s, 3 H), 4.88 (brs, 1 H), 6.86 (d, J = 8.8 Hz, 2 H), 7.16 (d, J = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 18.1, 23.6, 25.1, 28.0, 39.6, 40.7, 42.7, 43.7, 55.4, 75.4, 75.5, 113.7, 127.2, 133.4, 158.6, 214.0; **IR** (KBr) 2929, 2846, 1699, 1513, 1461, 1376, 1249, 1042, 1035, 842, 803 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_3$ $(M+H)^+$ requires 289.1803; found 289.1808.

4-(4-Nitrostyryl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9i):



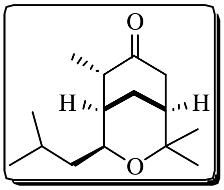
Solid (120 mg, 62%); **M.P.**: 135-138 °C; ^{1}**H NMR** (CDCl$_3$, 400 MHz): δ 1.22 (d, J = 7.2 Hz, 3 H), 1.28 (s, 3 H), 1.39 (s, 3 H), 1.64-1.68 (m, 1 H), 1.87-1.90 (m, 1 H), 1.93-1.98 (m, 1 H), 2.20-2.24 (m, 1 H), 2.48 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.56-2.65 (m, 2 H), 4.54 (brd, J = 4.4 Hz, 1 H), 6.32 (dd, J = 16.0 and 4.4 Hz, 1 H), 6.66 (d, J = 16.0 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 2 H), 8.16 (d, J = 8.8 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 18.0, 23.4, 24.6, 27.7, 39.3, 40.4, 41.9, 43.8, 73.8, 75.5, 123.9, 126.9, 128.4, 134.1, 143.5, 146.7, 213.5; **IR** (KBr) 2975, 2898, 1700, 1594, 1508, 1345, 1228, 1109, 1074, 974, 869 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{23}NO_4$ $(M+H)^+$ requires 330.1705; found 330.1714.

4-Cyclohexyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9j):



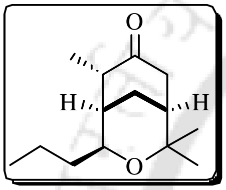
Solid (140 mg, 90%); **M.P.**: 73-77 °C; ^{1}**H NMR** (CDCl$_3$, 400 MHz): δ 0.69-0.84 (m, 3 H), 1.14 (s, 3 H), 1.20 (d, J = 7.6 Hz, 3 H), 1.25 (s, 3 H), 1.37-1.47 (m, 3 H), 1.60-1.73 (m, 3 H), 1.81-1.89 (m, 2 H), 1.98-2.16 (m, 4 H), 2.41 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.49-2.60 (m, 2 H), 3.24 (d, J = 9.2 Hz, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 18.0, 23.5, 25.1, 25.6, 25.9, 26.6, 27.8, 27.9, 30.6, 38.1, 38.2, 40.0, 40.5, 43.3, 74.3, 78.5, 214.2; **IR** (KBr) 2927, 2852, 1702, 1450, 1382, 1234, 1099, 1040, 907 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{28}O_2$ $(M+H)^+$ requires 265.2167; found 265.2171.

4-Isobutyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9k):



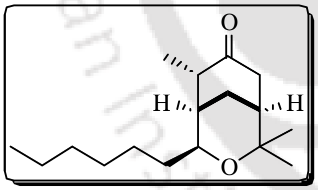
Liquid (115 mg, 82%); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.86 (d, J = 6.4 Hz, 3 H), 0.87 (d, J = 6.4 Hz, 3 H), 1.15 (s, 3 H), 1.22 (d, J = 7.6 Hz, 3 H), 1.30 (s, 3 H), 1.43-1.51 (m, 2 H), 1.58-1.70 (m, 2 H), 1.84-1.89 (m, 1 H), 2.00-2.18 (m, 2 H), 2.43 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.49-2.54 (m, 1 H), 2.63 (q, J = 7.2 Hz, 1 H), 3.75-3.79 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.1, 22.5, 23.0, 23.5, 24.6, 25.2, 27.8, 39.8, 40.5, 41.5, 41.8, 43.4, 71.7, 74.4, 213.9; **IR** (Neat) 2955, 2928, 1710, 1468, 1381, 1231, 1096, 1028, 912 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O_2$ $(M+H)^+$ requires 239.2011; found 239.2009.

4-Propyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9l):



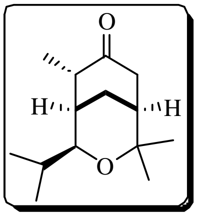
Liquid (130 mg, 98%); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.89 (t, J = 7.2 Hz, 3 H), 1.16 (s, 3 H), 1.22 (d, J = 7.6 Hz, 3 H), 1.25-1.35 (m, 2 H), 1.30 (s, 3 H), 1.42-1.56 (m, 2 H), 1.64-1.70 (m, 1 H), 1.83-1.89 (m, 1 H), 2.04-2.17 (m, 2 H), 2.43 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.49-2.54 (m, 1 H), 2.62 (q, J = 7.6 Hz, 1 H), 3.68 (t, J = 6.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 17.9, 19.0, 23.5, 25.0, 27.8, 34.8, 39.8, 40.4, 41.0, 43.1, 73.5, 74.4, 213.8; **IR** (Neat) 2960, 2873, 1710, 1458, 1381, 1229, 1096, 1041, 913 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O_2$ $(M+H)^+$ requires 225.1854; found 225.1844.

4-Hexyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9m):



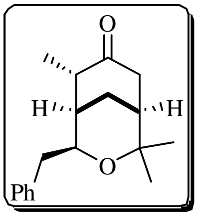
Liquid (126 mg, 80%); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.87 (t, J = 6.0 Hz, 3 H), 1.16 (s, 3 H), 1.23 (d, J = 7.6 Hz, 3 H), 1.25-1.28 (m, 6 H), 1.30 (s, 3 H), 1.32-1.36 (m, 2 H), 1.47-1.54 (m, 2 H), 1.65-1.70 (m, 1 H), 1.84-1.90 (m, 1 H), 2.04-2.16 (m, 2 H), 2.43 (dd, J = 15.2 and 4.4 Hz, 1 H), 2.49-2.56 (m, 1 H), 2.62 (q, J = 7.2 Hz, 1 H), 3.67 (t, J = 5.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 18.1, 22.6, 23.6, 25.1, 25.9, 27.9, 29.3, 31.8, 32.8, 39.9, 40.5, 41.0, 43.2, 73.9, 74.5, 214.0; **IR** (Neat) 2931, 2858, 1710, 1465, 1381, 1234, 1066, 1040, 910 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{30}O_2$ $(M+H)^+$ requires 267.2324; found 267.2328.

4-Isopropyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9o):



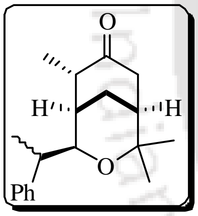
Liquid (103 mg, 78%); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.75 (dd, J = 6.4 and 1.2 Hz, 3 H), 0.92 (dd, J = 6.4 and 1.2 Hz, 3 H), 1.15 (s, 3 H), 1.22 (dd, J = 7.6 Hz and 1.2 Hz, 3 H), 1.27 (s, 3 H), 1.67 (octet, J = 6.4 Hz, 1 H), 1.86 (brs, 2 H), 1.98-2.18 (m, 2 H), 2.42 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.49 (brs, 1 H), 2.56 (q, J = 7.6 Hz, 1 H), 3.14 (d, J = 9.6 Hz, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 17.9, 18.1, 20.4, 23.6, 25.2, 27.8, 29.2, 38.7, 39.8, 40.6, 43.3, 74.5, 79.9, 214.1; **IR** (Neat) 2964, 2935, 1710, 1470, 1381, 1232, 1096, 1042 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O_2$ $(M+H)^+$ requires 225.1855; found 225.1852.

4-Benzyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9p):



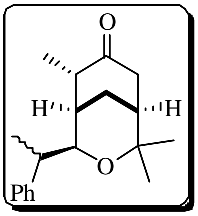
Liquid (72 mg, 45%); ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 1.19 (s, 3 H), 1.20 (d, J = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.57-1.59 (m, 1 H), 1.84-1.90 (m, 1 H), 1.97-2.0 (m, 1 H), 2.10 (dt, J = 13.6 and 2.8 Hz, 1 H), 2.44 (dd, J = 15.6 and 5.2 Hz, 1 H), 2.53-2.58 (m, 1 H), 2.66 (dd, J = 13.6 and 7.6 Hz, 1 H), 2.80-2.89 (m, 2 H), 3.94 (dt, J = 7.6 and 1.6 Hz, 1 H), 7.16-7.22 (m, 3 H), 7.25-7.30 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 18.0, 23.7, 25.2, 27.9, 39.1, 39.7, 39.8, 40.7, 43.3, 75.2, 75.3, 126.3, 128.5, 129.2, 138.8, 214.1; **IR** (Neat) 2970, 2930, 1708, 1454, 1381, 1235, 1089, 1041, 752, 700 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_2$ $(M+H)^+$ requires 273.1855; found 273.1860.

2,2,6-Trimethyl-4-(1-phenyl-ethyl)-3-oxabicyclo[3.3.1]nonan-7-one (Lower fraction, 9qL):



Solid (40 mg, 24%); M.P. 116-120 °C; ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 0.97 (s, 3 H), 1.03 (s, 3 H), 1.08 (d, J = 7.2 Hz, 3 H), 1.28 (d, J = 7.6 Hz, 3 H), 1.80-1.86 (m, 1 H), 1.97-2.14 (m, 2 H), 2.19 (dt, J = 14.0 and 2.8 Hz, 1 H), 2.43 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.48-2.56 (m, 1 H), 2.71 (q, J = 7.6 Hz, 1 H), 2.77-2.86 (m, 1 H), 3.69 (d, J = 10.0 Hz, 1 H), 7.13-7.19 (m, 3 H), 7.22-7.27 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 17.6, 18.3, 23.1, 25.5, 27.6, 38.9, 39.9, 40.7, 41.2, 43.3, 74.6, 78.3, 125.9, 127.9, 128.0, 145.7, 213.9; **IR** (KBr) 2965, 2928, 1697, 1454, 1382, 1233, 1070, 1045, 698 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_2$ $(M+H)^+$ requires 287.2011; found 287.2003.

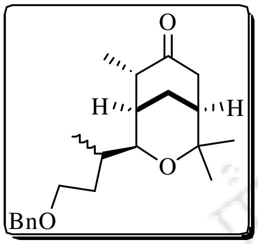
2,2,6-Trimethyl-4-(1-phenyl-ethyl)-3-oxabicyclo[3.3.1]nonan-7-one (Upper fraction, 9qU):



Solid (34 mg, 20%); M.P. 150-153 °C; ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 0.98 (d, J = 7.6 Hz, 3 H), 1.20 (s, 3 H), 1.27 (d, J = 6.8 Hz, 3 H), 1.35 (s, 3 H), 1.83-1.86 (m, 1 H), 1.91-2.04 (m, 3 H), 2.37 (dd, J = 15.6 and 4.8 Hz, 1 H), 2.53 (m, 1 H), 2.70 (q, J = 7.6 Hz, 1 H), 2.79-2.87 (m, 1 H), 3.65 (d, J = 10.0 Hz, 1 H), 7.13-7.21 (m, 3 H), 7.25-7.31 (m, 2 H); ^{13}**C NMR** (100 MHz,

$CDCl_3$): *δ* 17.9, 20.0, 23.9, 25.5, 27.9, 38.6, 39.8, 40.9, 41.8, 43.5, 75.2, 79.4, 126.6, 127.8, 128.8, 144.1, 214.5; **IR** (KBr) 2971, 2923, 1704, 1455, 1379, 1238, 1095, 1017, 711 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_2$ $(M+H)^+$ requires 287.2011; found 287.2022.

4-(3-Benzyloxy-1-methyl-propyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one: {(9r, mixture of two isomers (1:1)}:

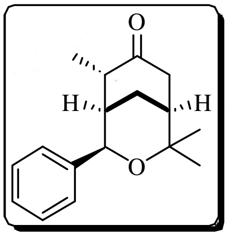


Liquid (152 mg, 75%); ^{1}**H NMR** ($CDCl_3$, 400 MHz): *δ* 0.76 (d, *J* = 6.8 Hz, 1.5 H), 0.90 (d, *J* = 6.4 Hz, 1.5 H), 1.12 (s, 1.5 H), 1.15 (s, 1.5 H), 1.21 (d, *J* = 6.8 Hz, 1.5 H), 1.22 (d, *J* = 6.8 Hz, 1.5 H), 1.23 (s, 1.5 H), 1.26 (s, 1.5 H), 1.56-1.75 (m, 2 H), 1.82-1.92 (m, 2 H), 1.95-2.08 (m, 2 H), 2.10-2.18 (m, 1 H), 2.38-2.58 (m, 2 H), 3.22-3.28 (m, 2 H), 3.42-3.56 (m, 3 H), 4.48 (s, 2 H), 7.25-7.40 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 15.3, 16.7, 18.2, 23.5, 23.7, 25.3 (2C), 27.9, 29.9, 31.6, 31.7, 31.9, 33.9, 38.7, 39.9, 40.0, 40.6, 40.7, 42.8, 43.2, 43.4, 43.6, 68.5, 69.3, 73.0, 73.3, 74.7, 74.8, 78.4, 78.8, 127.6, 127.7, 127.8, 128.0, 128.5, 128.7, 138.5, 138.7, 214.4 (2C); **IR** (Neat) 2927, 2855, 1709, 1454, 1234, 1096, 1042, 737, 698 cm^{-1}. **HRMS** (APCI) cald. for $C_{22}H_{32}O_3(M+H)^+$ requires 345.2430; found 345.2423.

2.7 Selected Spectra of Oxabicyclo[3.3.1]nonanone

2,2,6-Trimethyl-4-phenyl-3-oxabicyclo[3.3.1]nonan-7-one (9a):

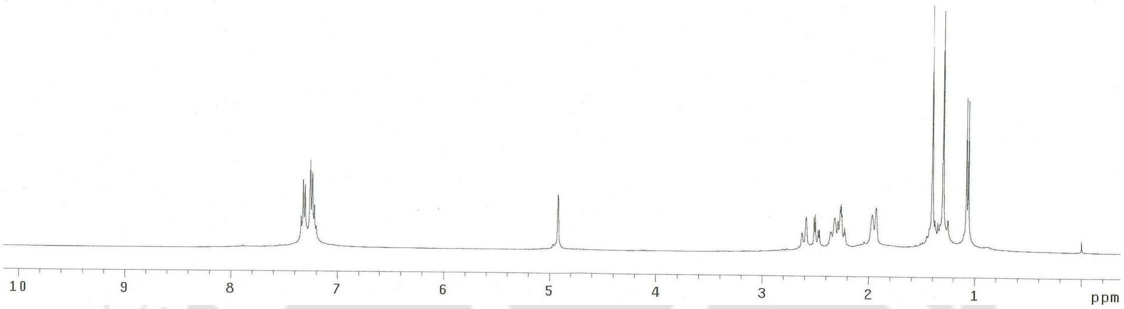
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_201_L

exp2  s2pul

      SAMPLE              SPECIAL
date    Dec  2 2009  temp       not used
solvent       CDC13  gain       not used
file            exp  spin       not used
   ACQUISITION       hst           0.008
sw           6389.8  pw90         19.700
at            1.998  alfa         20.000
np            25528         FLAGS
fb         not used  il                n
bs                4  in                n
d1            1.000  dp                y
nt               32  hs               nn
ct               32       PROCESSING
   TRANSMITTER       lb             0.10
tn               H1  fn            65536
sfrq        399.853        DISPLAY
tof           362.8  sp           -163.6
tpwr             57  wp           4273.6
pw            9.850  rfl           793.5
    DECOUPLER        rfp               0
dn              C13  rp            112.8
dof               0  lp            -94.5
dm              nnn          PLOT
dmm               c  wc              250
dpwr             50  sc                0
dmf           15900  vs               56
                     th               20
                     nm  cdc  ph
```

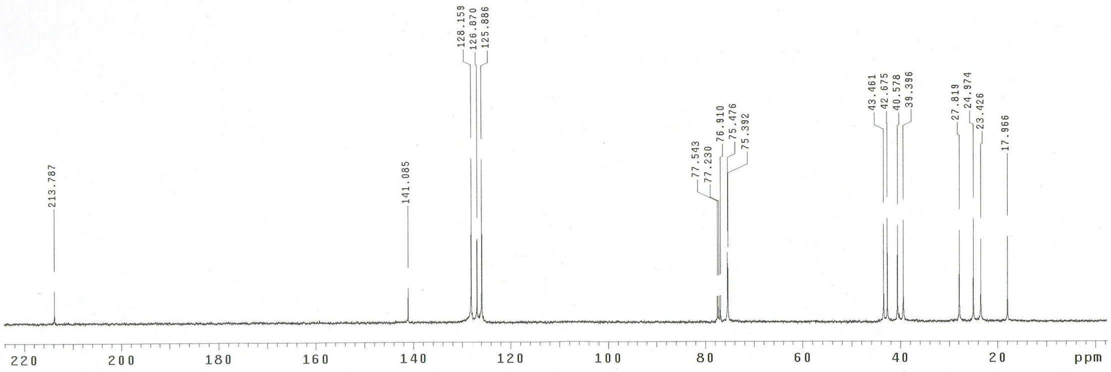


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_201_L

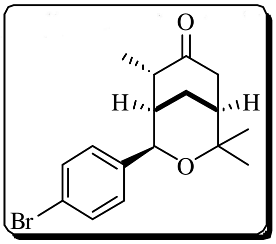
exp2  s2pul

      SAMPLE               SPECIAL
date    Dec  2 2009  temp        not used
solvent       CDC13  gain        not used
file /export/home/~  spin        not used
asaikia/PS_201L_C1~  hst            0.008
              3.fid  pw90          18.600
   ACQUISITION       alfa          20.000
sw          25125.6          FLAGS
at            1.199  il                 n
np            60270  in                 n
fb            13800  dp                 y
bs               16  hs                nn
d1            1.000       PROCESSING
nt             4000  lb              2.00
ct              592  fn             65536
   TRANSMITTER              DISPLAY
tn              C13  sp            -236.4
sfrq        100.554  wp           22780.1
tof          1536.3  rfl           9289.5
tpwr             61  rfp           7764.9
pw            9.300  rp             -48.6
    DECOUPLER        lp            -312.2
dn               H1          PLOT
dof               0  wc               250
dm              yyy  sc                 0
dmm               w  vs                40
dpwr             42  th                 3
dmf            8900  nm  no  ph
```



4-(4-Bromophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9c):

^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_177_L

exp1  s2pul

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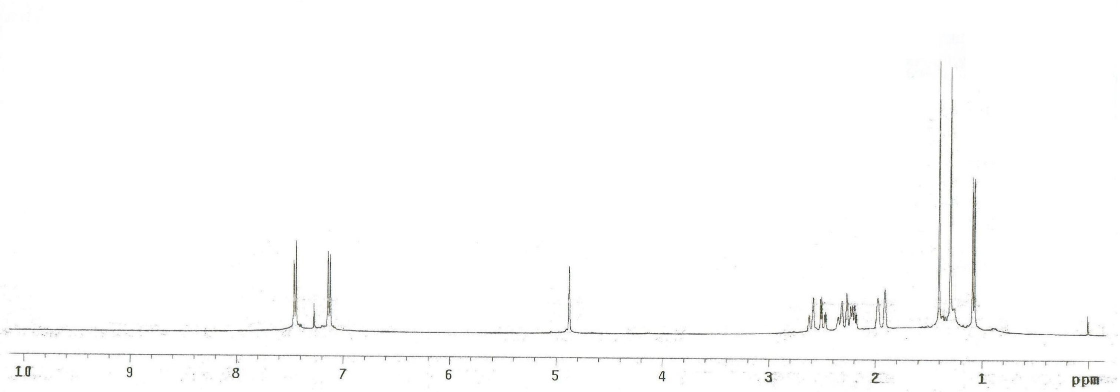
date   Nov  2 2009  temp       not used
solvent      CDC13  gain       not used
file /export/home/~ spin       not used
asaikia/PS_177_L.f~ hst           0.008
                id  pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8         FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               4  hs               nn
d1           1.000       PROCESSING
nt              32  lb             0.10
ct              12  fn            65536
   TRANSMITTER             DISPLAY
tn              H1  sp            -60.5
sfrq       399.853  wp           4114.1
tof          362.8  rfl           791.1
tpwr            57  rfp               0
pw           9.850  rp            128.8
    DECOUPLER       lp            -90.9
dn             C13          PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               61
dpwr            50  th               30
dmf          15900  nm  cdc  ph
```

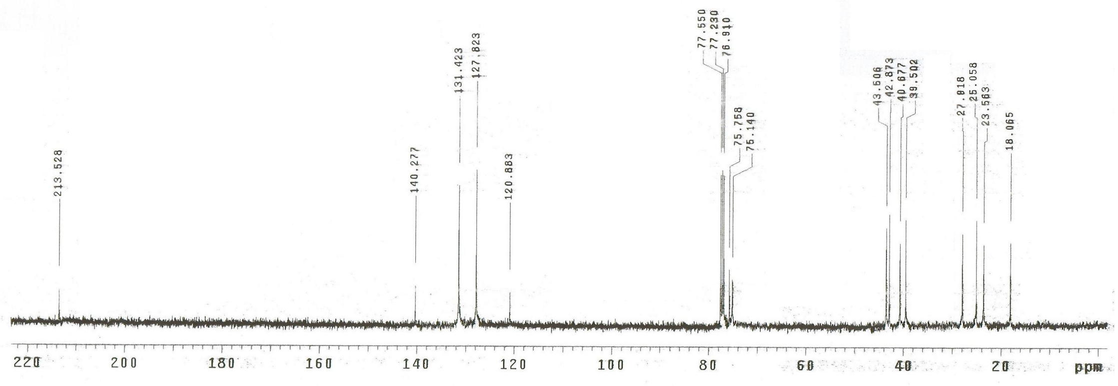


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_177_L

exp1  s2pul

     SAMPLE              SPECIAL
date   Nov  2 2009  temp       not used
solvent      CDC13  gain       not used
file /export/home/~ spin       not used
asaikia/PS_177L_C1~ hst           0.008
            3.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6         FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000       PROCESSING
nt            3000  lb             2.00
ct            1792  fn            65536
   TRANSMITTER             DISPLAY
tn             C13  sp           -186.5
sfrq       100.554  wp          22648.2
tof         1536.3  rfl          9272.6
tpwr            61  rfp          7764.9
pw           9.300  rp            -36.9
    DECOUPLER       lp           -362.0
dn              H1          PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               34
dpwr            42  th                5
dmf           8900  nm  no  ph
```



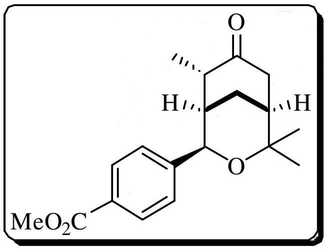
4-(4,4,8-Trimethyl-7-oxo-3-oxabicyclo[3.3.1]non-2-yl)-benzoic acid methyl ester (9e):

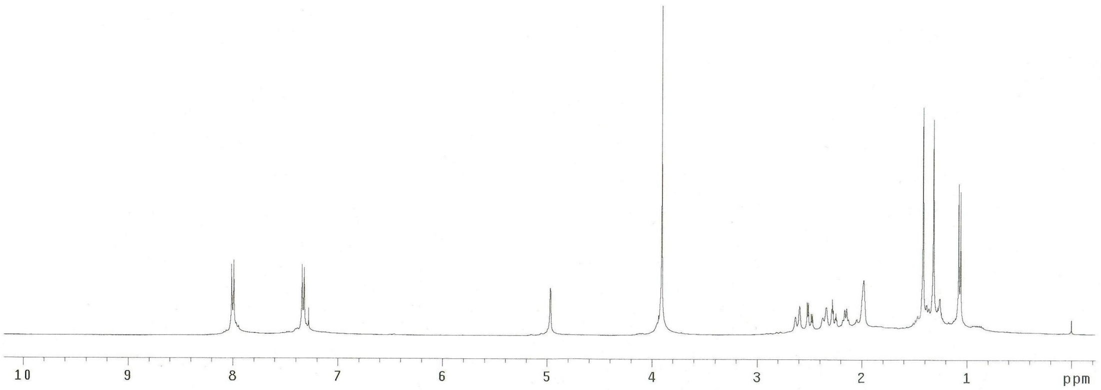
^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_203_L

exp3  s2pul

      SAMPLE                 SPECIAL
date   Dec  4 2009   temp       not used
solvent       CDC13  gain       not used
file            exp  spin       not used
   ACQUISITION       hst           0.008
sw           6389.8  pw90         19.700
at            1.998  alfa         20.000
np            25528          FLAGS
fb         not used  il                n
bs                4  in                n
d1            1.000  dp                y
nt               32  hs               nn
ct               32        PROCESSING
   TRANSMITTER       lb             0.10
tn               H1  fn            65536
sfrq        399.853          DISPLAY
tof           362.8  sp            -91.5
tpwr             57  wp           4164.4
pw            9.850  rfl           788.4
    DECOUPLER        rfp               0
dn              C13  rp            114.2
dof               0  lp           -110.7
dm              nnn            PLOT
dmm               c  wc              250
dpwr             50  sc                0
dmf           15900  vs               76
                     th               52
                     nm  cdc  ph
```



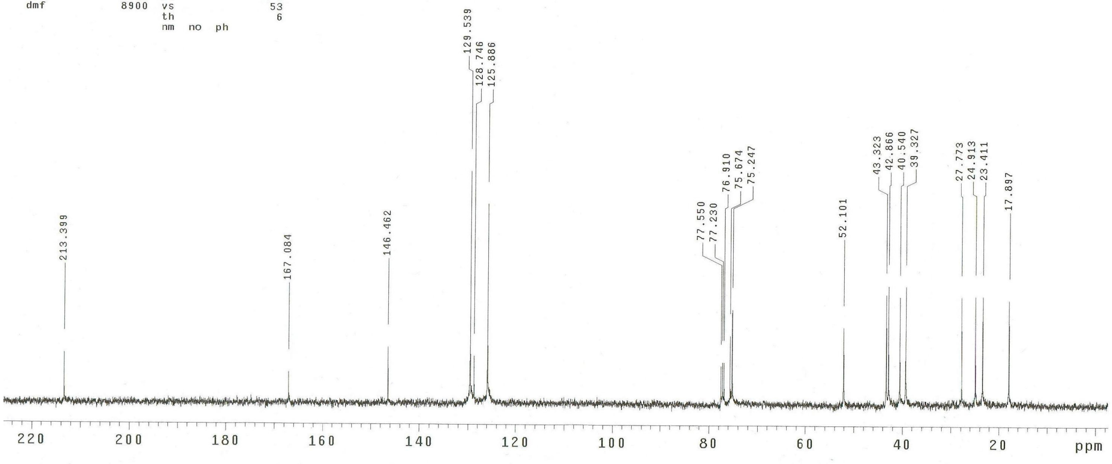


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_203_L

exp3  s2pul

      SAMPLE                 SPECIAL
date   Dec  4 2009   temp       not used
solvent       CDC13  gain       not used
file            exp  spin       not used
   ACQUISITION       hst           0.008
sw          25125.6  pw90         18.600
at            1.199  alfa         20.000
np            60270          FLAGS
fb            13800  il                n
bs               16  in                n
d1            1.000  dp                y
nt             2000  hs               nn
ct              320        PROCESSING
   TRANSMITTER       lb             2.00
tn              C13  fn            65536
sfrq        100.554          DISPLAY
tof          1536.3  sp           -263.2
tpwr             61  wp          23044.6
pw            9.300  rfl          9283.3
    DECOUPLER        rfp          7764.9
dn               H1  rp            -53.2
dof               0  lp           -332.3
dm              yyy            PLOT
dmm               w  wc              250
dpwr             42  sc                0
dmf            8900  vs               53
                     th                6
                     nm  no  ph
```



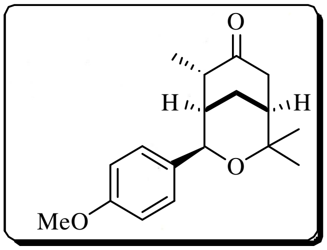
4-(4-Methoxyphenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9h):

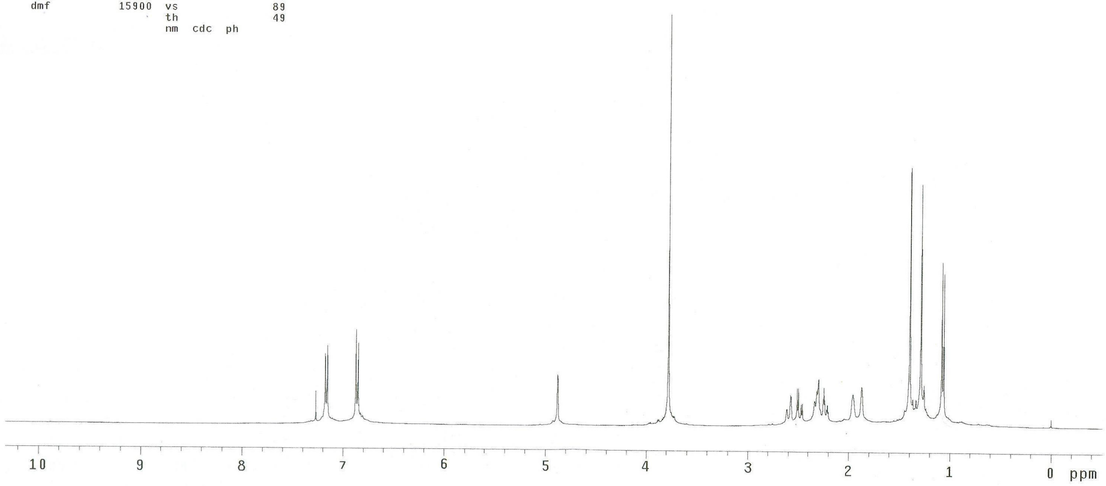
^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_202_L

exp3  s2pul

      SAMPLE               SPECIAL
date    Dec  3 2009   temp       not used
solvent        CDCl3   gain       not used
file             exp   spin       not used
   ACQUISITION         hst           0.008
sw            6389.8   pw90         19.700
at             1.998   alfa         20.000
np             25528           FLAGS
fb          not used   il               n
bs                 4   in               n
d1             1.000   dp               y
nt                32   hs              nn
ct                32        PROCESSING
   TRANSMITTER         lb            0.10
tn                H1   fn           65536
sfrq         399.853          DISPLAY
tof            362.8   sp           -203.4
tpwr              57   wp           4332.3
pw             9.850   rfl           791.3
    DECOUPLER          rfp               0
dn               C13   rp            115.1
dof                0   lp           -102.2
dm               nnn            PLOT
dmm                c   wc              250
dpwr              50   sc                0
dmf            15900   vs               89
                       th               49
                       nm   cdc   ph
```



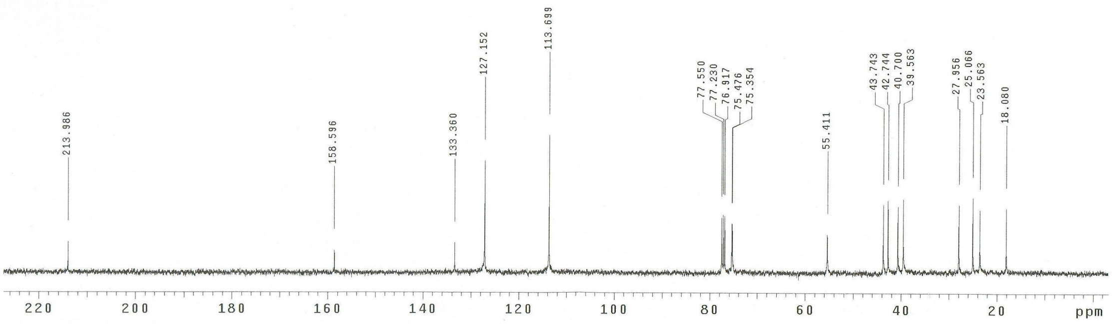


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_202_L

exp3  s2pul

      SAMPLE               SPECIAL
date    Dec  3 2009   temp       not used
solvent        CDCl3   gain       not used
file             exp   spin       not used
   ACQUISITION         hst           0.008
sw           25125.6   pw90         18.600
at             1.199   alfa         20.000
np             60270           FLAGS
fb             13800   il               n
bs                16   in               n
d1             1.000   dp               y
nt              2000   hs              nn
ct               992        PROCESSING
   TRANSMITTER         lb            2.00
tn               C13   fn           65536
sfrq         100.554          DISPLAY
tof           1536.3   sp           -323.0
tpwr              61   wp          23176.5
pw             9.300   rfl          9277.2
    DECOUPLER          rfp          7764.9
dn                H1   rp            -69.5
dof                0   lp           -287.9
dm               yyy            PLOT
dmm                w   wc              250
dpwr              42   sc                0
dmf             8900   vs               33
                       th                5
                       nm   no   ph
```



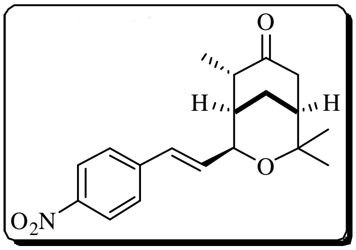
2,2,6-Trimethyl-4-[2-(4-nitrophenyl-vinyl)]-3-oxabicyclo[3.3.1]nonan-7-one (9i):

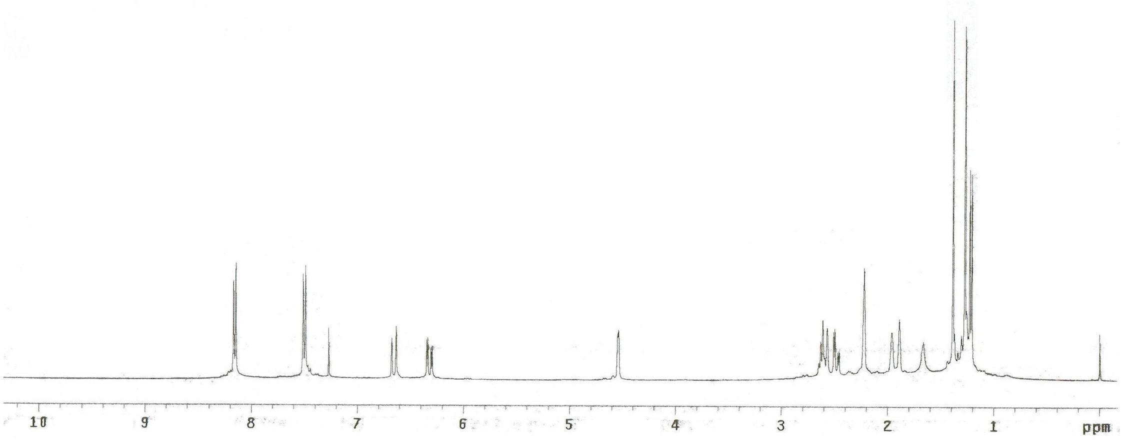
^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_192_L

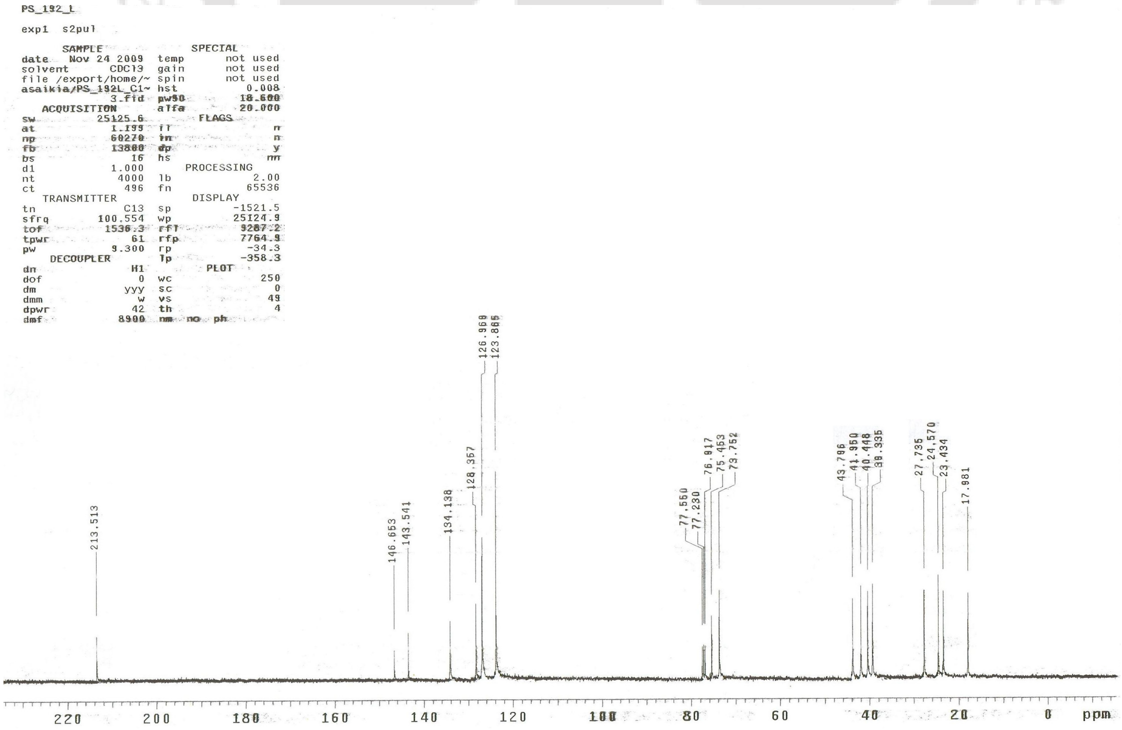
exp1  s2pul

      SAMPLE                SPECIAL
date   Nov 24 2009  temp        not used
solvent      CDC13  gain        not used
file /export/home/~ spin        not used
asaikia/PS_192_L.f~ hst            0.008
                id  pw90          19.700
   ACQUISITION      alfa          20.000
sw          6389.8          FLAGS
at           1.998  il                 n
np           25528  in                 n
fb        not used  dp                 y
bs               4  hs                nn
d1           1.000         PROCESSING
nt              32  lb              0.10
ct              32  fn             65536
   TRANSMITTER              DISPLAY
tn              H1  sp             -61.0
sfrq       399.853  wp            4198.0
tof          362.8  rfl            791.7
tpwr            57  rfp                0
pw           9.850  rp             116.0
    DECOUPLER       lp            -101.7
dn             C13            PLOT
dof              0  wc               250
dm             nnn  sc                 0
dmm              c  vs                79
dpwr            50  th                27
dmf          15900  nm  cdc  ph
```





^{13}C NMR (100 MHz, $CDCl_3$)



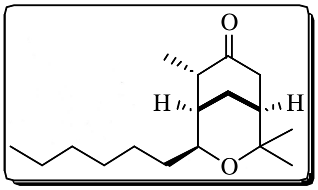
```
PS_192_L

exp1  s2pul

      SAMPLE                SPECIAL
date   Nov 24 2009  temp        not used
solvent      CDC13  gain        not used
file /export/home/~ spin        not used
asaikia/PS_192L_C1~ hst            0.008
             3.fid  pw90          18.600
   ACQUISITION      alfa          20.000
sw         25125.6          FLAGS
at           1.199  il                 n
np           60270  in                 n
fb           13800  dp                 y
bs              16  hs                nn
d1           1.000         PROCESSING
nt            4000  lb              2.00
ct             496  fn             65536
   TRANSMITTER              DISPLAY
tn             C13  sp           -1521.5
sfrq       100.554  wp           25124.9
tof         1536.3  rfl           9287.2
tpwr            61  rfp           7764.9
pw           9.300  rp             -34.3
    DECOUPLER       lp            -358.3
dn              H1            PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                49
dpwr            42  th                 4
dmf           8900  nm  no  ph
```

4-Hexyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]nonan-7-one (9m):

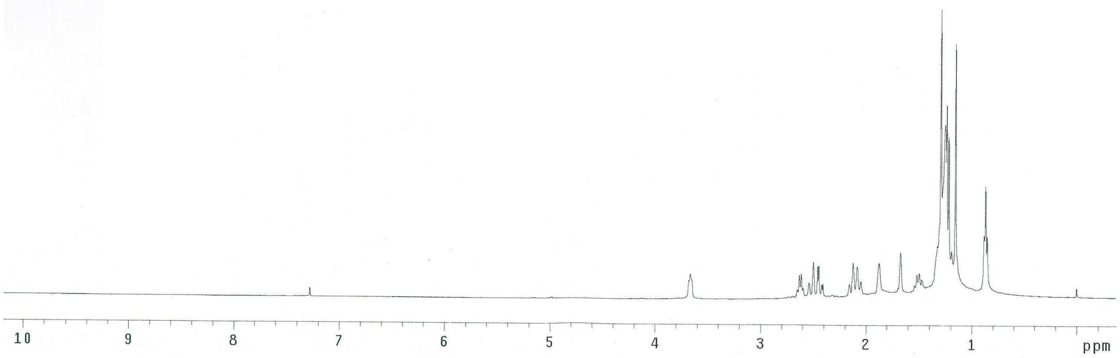
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_198_L

exp2  s2pul

      SAMPLE                SPECIAL
date   Nov 29 2009  temp       not used
solvent      CDC13  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32        PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853          DISPLAY
tof          362.8  sp           -149.4
tpwr            57  wp           4231.7
pw           9.850  rfl           787.6
    DECOUPLER       rfp               0
dn             C13  rp            107.9
dof              0  lp            -58.5
dm             nnn           PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               61
                    th               47
                    nm  cdc  ph
```

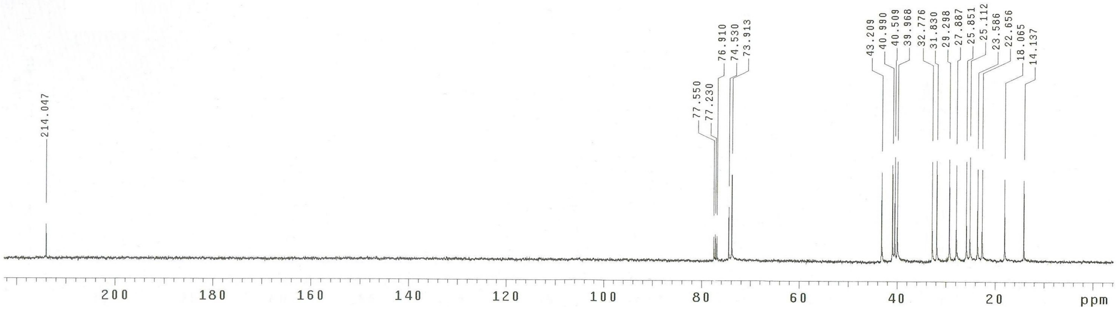


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_198_L

exp2  s2pul

      SAMPLE                SPECIAL
date   Nov 29 2009  temp       not used
solvent      CDC13  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270          FLAGS
fb           13800  il                n
bs              16  in                n
d1           1.000  dp                y
nt            8000  hs               nn
ct             336        PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554          DISPLAY
tof         1536.3  sp           -427.3
tpwr            61  wp          22813.0
pw           9.300  rfl          9281.8
    DECOUPLER       rfp          7764.9
dn              H1  rp            -51.0
dof              0  lp           -301.1
dm             yyy           PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               25
                    th                3
                    nm  no  ph
```



2.8 The Crystal Parameters of Compound 9i

Crystal Parameters	**9i-**CCDC 760090
Formula	$C_{19}H_{23}NO_4$
Formula weight	329.38
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)/c
a/Å	18.1890(4)
b/Å	10.0277(2)
c/Å	9.4674(2)
α/º	90.00
β/º	93.858 (2)
γ/º	90.00
V/Å^3	1722.88(6)
Z	4
Abs. Coeff./mm^{-1}	0.089
Abs. Correction	Multi-Scan
GOF on F^2	0.993
Final R indices	$R1 = 0.0507$
[$I > 2\sigma$(I)]	$wR2 = 0.1505$
R indices [all data]	$R1 = 0.0880$
	$wR2 = 0.1660$

CHAPTER 3

Synthesis of Oxabicyclo[3.3.1]nonenes and Substituted Tetrahydropyrans via (3,5)-Oxonium-Ene Reaction

3.1 Importance and Applications

Oxabicyclo[3.3.1]nonenes and selected derivatives (Figure 3.1.1, **A**-**B**) are known to behave as estrogen receptor ligands.[1] Estrogen receptors (ER) have quickly emerged as attractive targets for therapeutic invention in a wide variety of diseases, including osteoporosis[2] and cancer.[3] On the other hand, tetrahydropyrans are found in many biologically active natural products and pharmaceuticals.[4] Alkyl substituted tetrahydropyrans (Figure 3.1.1, **C**) are used as aroma and flavouring substances for pharmaceuticals, cosmetics and food stuff.[5]

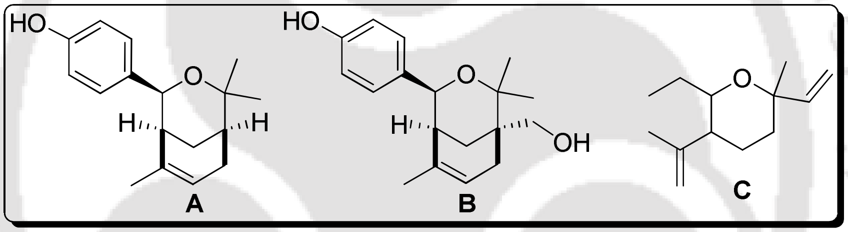
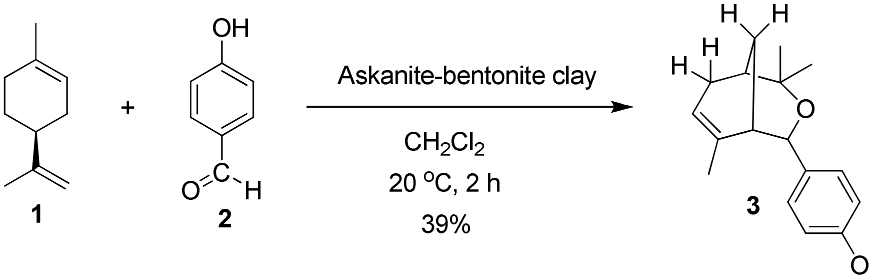


Figure 3.1.1. Biologically active cyclic ethers

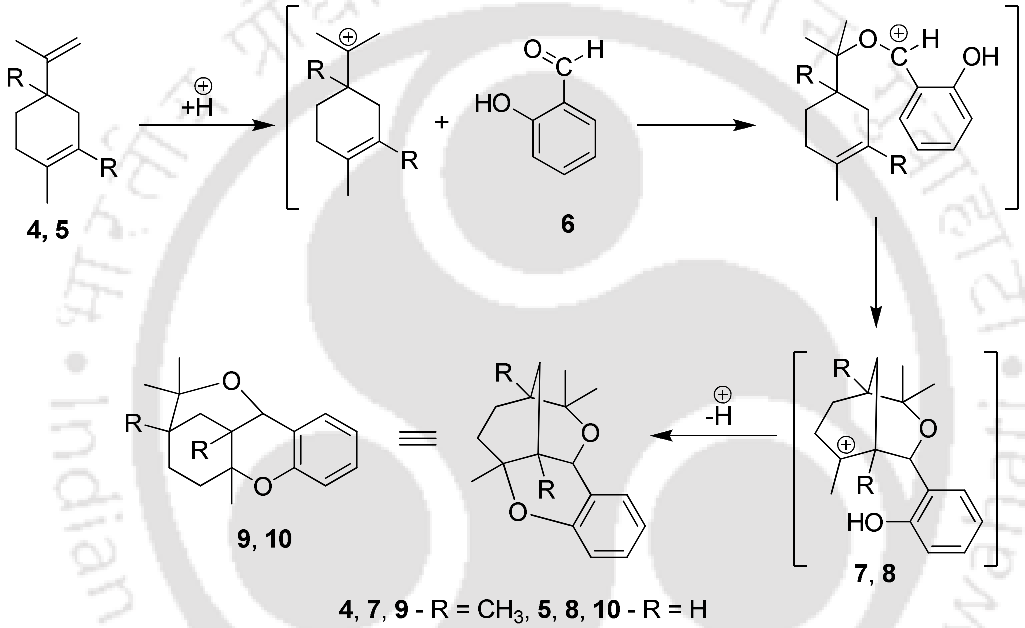
3.2 An Overview of Relevant Synthetic Methods

Review of literature reveals that oxabicyclo[3.3.1]nonenes are prepared by the reaction of aromatic aldehydes with naturally occurring terpenoids or olefin-containing compounds in acidic media.[1,6] The low yield and multistep reactions are the major draw back of those methods.[1,6] For example, Barkhash and co-workers reported the synthesis of 2,2,6-trimethyl-4-(4-hydroxyphenyl)-3-oxabicyclo[3.3.1]non-6-ene **3** from the reaction of *p*-hydroxybenzaldehyde **2** with R-(+)-limonene **1** in the presence of askanite-bentonite clay.



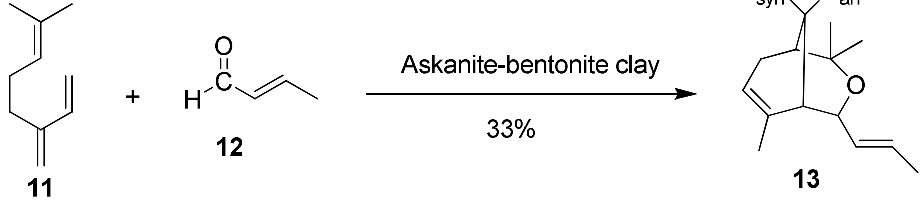
Scheme 3.2.1.

The oxabicyclic compound was obtained only in 39% yield (Scheme 3.2.1).[6a] A very careful observation from the same group also revealed that in the case of the interaction of dienes **4** or **5** with salicyldehyde **6** (in the presence of askanite-bentonite clay, 20 °C, CH_2Cl_2, 6-9 hr) the process does not stop as in the previous cases, at the stage of the formation of bicyclic ethers. The cationic center in the presumed intermediates **7** and **8** could be trapped by the phenolic hydroxy group to yield 1,2,2,8,12-pentamethyl-3,7-dioxa-5,6-benzotricyclo[6.2.2.$0^{4,12}$]dodecane **9** (yield 75%) and 2,2,8-trimethyl-3,7-dioxa-5,6-benzotricyclo[6.2.2.$0^{4,12}$]dodecane **10** (yield 29%) (Scheme 3.2.2).[6a]



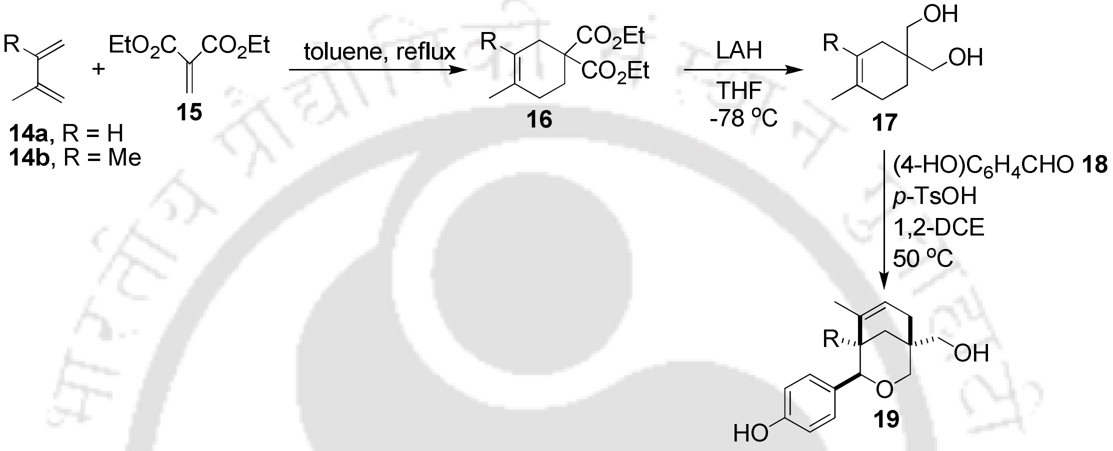
Scheme 3.2.2.

Salakhutdinov *et al.* reported the synthesis of 2,2,6-trimethyl-4-(prop-1-enyl)-3-oxabicyclo[3.3.1]non-6-ene **13** (Scheme 3.2.3) from the reaction of triene **11** with crotonaldehyde **12** in the presence of askanite-bentonite clay.[6b] According to them this was an example of homo-Diels-Alder reaction as in the course of formation of bicyclic ether **11**, three π-bonds transform into three σ-bonds, producing two new rings.



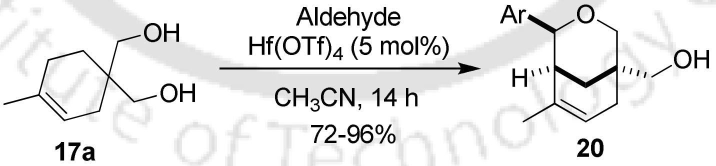
Scheme 3.2.3.

Hamann *et al.* reported the synthesis of oxabicyclo[3.3.1]nonene analogues **19** in good to excellent yields from the reaction of diols **17** with 4-hydroxybenzaldehyde **18** mediated by *p*-Toluenesulfonic acid (Scheme 3.2.4).[1b] The starting diols **17** were synthesized by using Diels-Alder cycloaddition of isoprene or 2,3-dimethyl-1,3-butadiene **14a**,**b** with diethylmethylene malonate **15** to produce dicarboethoxycyclohexenes **16**, which were then reduced to the corresponding diols **17** with lithium aluminium hydride (Scheme 3.2.4).



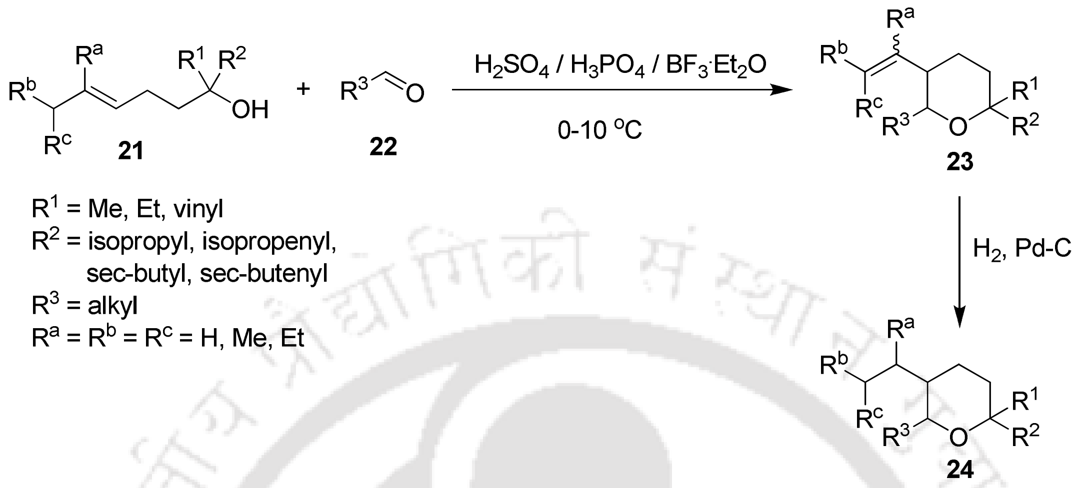
Scheme 3.2.4.

Nakamura *et al.* reported a versatile method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives **20** by using a Prins type cyclization reaction between diol **17a** and various aldehydes, including substituted benzaldehydes and heteroaromatic carbaldehydes catalyzed by hafnium triflate in good yields (Scheme 3.2.5).[1d]



Scheme 3.2.5.

On the other hand method for the synthesis of alkyl substituted tetrahydropyrans are limited. Only one report is available in the literature and that has come from Oertling group. They have prepared alkyl substituted tetrahydropyrans from the reaction of alcohol component **21** with aldehyde **22** in the presence of acid catalysts like sulfuric acid, phosphoric acid and boron trifluoride etherate to the corresponding cyclized tetrahydropyran compound **23** which on catalytic hydrogenation gives saturated tetrahydropyran compound **24** (Scheme 3.2.6).[5]



Scheme 3.2.6.

3.3 Present Work

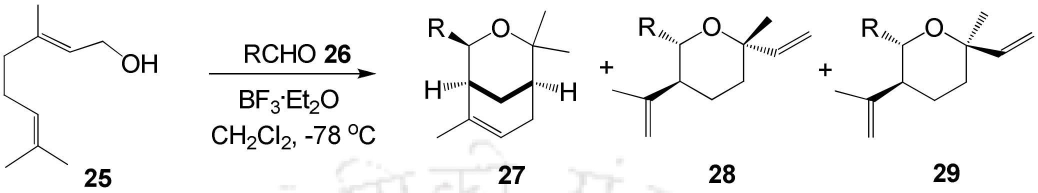
In the previous chapter we have described a novel methodology for the synthesis of oxabicyclo[3.3.1]nonanone by using (3,5)-oxonium-ene reaction. In this chapter an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans from the reaction of geraniol with aldehydes and epoxides promoted by boron trifluoride etherate is presented.

Taking clues from our previous work[7] and the literature,[6] and the fact that geraniol gives *α*-terpineol under acidic conditions; we envisioned that treatment of geraniol **25** with boron trifluoride etherate would provide carbocation **30**, which after cyclization and subsequent nucleophilic attack by aldehyde would give oxocarbenium ion **32**. The oxocarbenium ion **32** after (3,5)-oxonium-ene cyclization would give the oxabicyclic compound **27**. Accordingly, geraniol was reacted with benzaldehyde in dry dichloromethane using boron trifluoride etherate as Lewis acid and 2,2,6-trimethyl-4-phenyl-3-oxabicyclo[3.3.1]non-6-ene **27a** was obtained in 52% yield along with an inseparable mixture of two substituted tetrahydropyrans **28a** and **29a** with 25% overall yield. The reaction is generalized as shown in Table 3.3.1.

To prove its general applicability different types of aromatic and aliphatic aldehydes were subjected to react with geraniol and it was observed that aromatic aldehydes and cyclohexanecarboxaldehyde give oxabicyclo[3.3.1]nonene as the major product (Table 3.3.1), whereas simple aliphatic aldehydes give tetrahydropyrans as major product (Scheme

3.3.2). This might be due to the better nucleophilicity and smaller size of the aliphatic aldehydes compared to the aromatic aldehydes, which makes it an easy approach to the

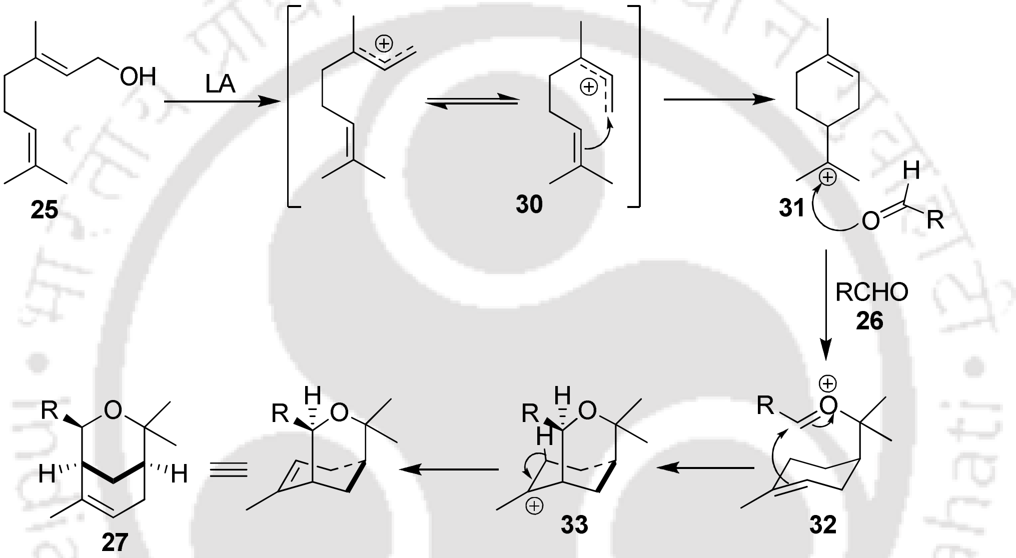
Table 3.3.1. Reaction of geraniol with aldehydes



Entry	Aldehyde R =	Time/h	Product ratio **27**:**28**:**29**^{a}	Product	
				27 Yield^b (%)	**28**+**29** Yield^c (%)
a	C_6H_5	2.5	4:2:1	52	25
b	*p*-Cl-C_6H_4	2.5	1:0:0	70	0
c	*p*-Br-C_6H_4	2.5	1:0:0	70	0
d	*p*-F-C_6H_4	2.5	1:0:0	68	0
e	*p*-NO_2-C_6H_4	3	2:1:0	50	15
f	*o*-NO_2-C_6H_4	3	1:0:0	54	0
g	$C_{10}H_7$ (2-Naphthyl)	2.5	1:0:0	55	0
h	C_6H_4-CH=CH	2	1:0:0	62	0
i	*p*-NO_2-C_6H_4-CH=CH	2	1:0:0	55	0
j	*p*-MeO_2C-C_6H_4	3	1:0:0	57	0
k	*p*-OH-C_6H_4	3	1:0:0	60	0
l	*p*-CH_3-C_6H_4	2.5	1:0:0	68	0
m	Cyclo-C_6H_{11}	2	1:0:0	62	0
n	C_2H_5	2	1:3:1	8	65
o	C_3H_7	2	1:3:1	8	65
p	$(CH_3)_2CHCH_2$	2	1:3:1	10	67
q	$CH_3(CH_2)_5$	2	1:3:1	15	60
r	$CH_3(CH_2)_{14}$	2	1:3:1	10	62

^{a}Ratios are determined by ^{1}HNMR of crude product. ^{b}Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C NMR and Mass spectroscopy. ^{c}Total isolated yield of **28** and **29**.

carbocation **30** rather than allowing it to transform into **31** (Scheme 3.3.1). Among the aromatic aldehydes, simple benzaldehyde and 4-nitro benzaldehyde gave a small amount of tetrahydropyrans. The formation of some tetrahydropyrans in the case of benzaldehyde and *p*-nitrobenzaldehyde might be due to the electron-withdrawing effect of phenyl and *p*-nitrophenyl ring, which destabilizes the oxocarbenium ion. On the other hand, the electron-donating groups on aromatic ring (entry c-d, k-l) stabilize the oxocarbenium ion.[8] However, the formation of only one tetrahydropyran in case of 4-nitrobenzaldehyde is quite uncommon The structure and stereochemistry of bicyclic compounds and substituted tetrahydropyrans were determined by ^{1}H NMR and NOE experiments (Figure 3.3.1). The coupling constant of H_{4e} (4.88 ppm) proton of **27a** is 2.0 Hz, which is typical for vicinal diequatorial coupling and therefore, H_{4e} and H_{5e} (2.19-2.21 ppm) are in equatorial position. This is in accordance with the Dreiding model where H_{5e} proton cannot be axial. Again the coupling constant between H_{1e} (1.56 ppm) and H_{8a} (2.32-2.43 ppm) is 3.2 Hz which indicates that one proton is in an axial position and the other in an equatorial position. The presence of a strong NOE between H_{8a} and H_{9syn} (1.73 ppm) confirms that they are in a 1,3-diaxial position. Therefore, H_{1e} is in an equatorial position. This is also in accordance with the Dreiding model. Thus H_{5e} and H_{1e} are in equatorial positions and hence the fusion between two rings is *cis* fusion (**27a**, Figure 3.3.1). Similarly, the stereochemistry of substituted tetrahydropyran **28e** was determined as follows. The coupling constant of H_{6a} (4.56 ppm) is 10.0 Hz and it indicates that H_{5a} (2.11-2.19 ppm) and H_{6a} are in axial



Scheme 3.3.1. Mechanism for the formation of oxabicyclic compounds

positions. The presence of NOE between H_{6a} and C-7 methyl protons (1.31 ppm) and between H_{5a} and H_{3a} (1.80-1.92) further confirms that the protons H_{5a} and H_{6a} are in axial position and are *trans* to each other, whereas H_{6a} and C-7 methyl protons are *cis* (**28e**, Figure 3.3.1).

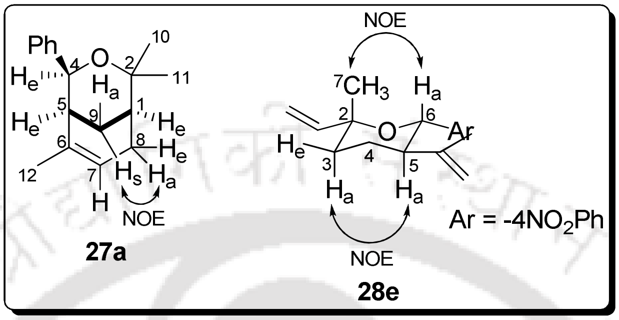
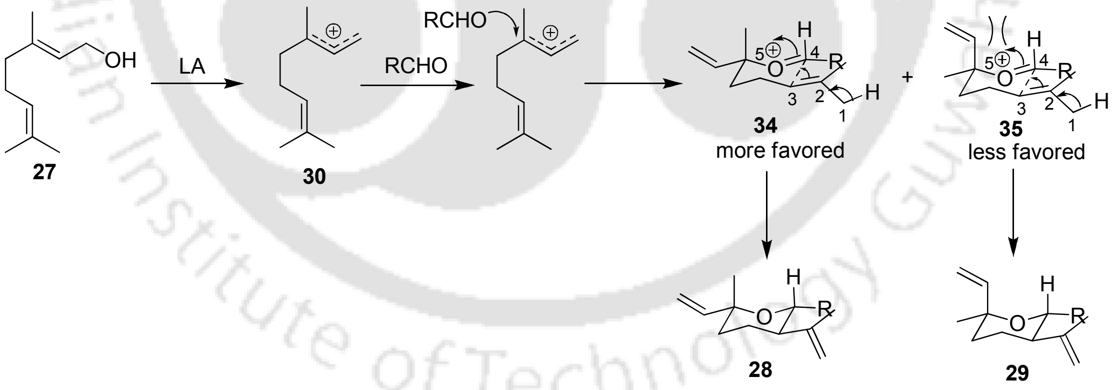


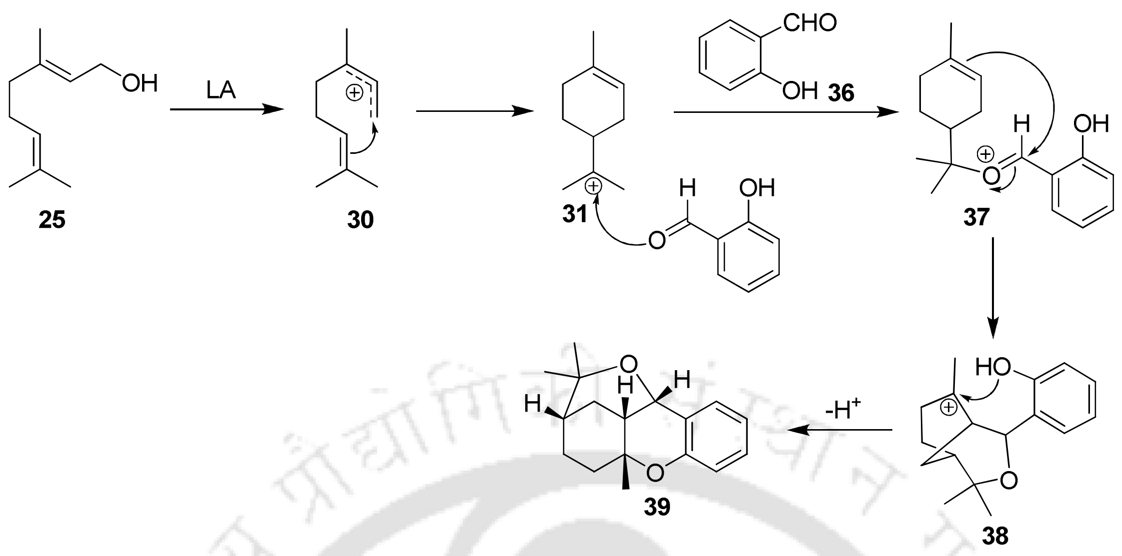
Figure 3.3.1. NOE of **27a** and **28e**

The mechanism of the formation of tetrahydropyrans can be represented as shown in Scheme 3.3.2. Here the smaller aliphatic aldehydes attack the carbocation **30** to form more favored transition state **34**, which after cyclization gives the more stable isomer **28** as a major product and a minor product **29** from the less favored transition state **35** (Scheme 3.3.2).[9]



Scheme 3.3.2.

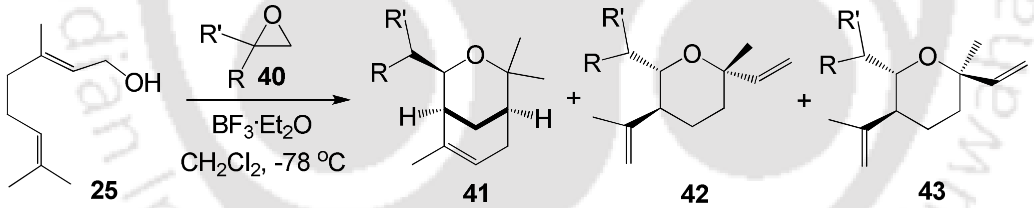
In the case of salicyldehyde **36** a tretracyclic compound **39** was obtained in 40% yield. The formation of **39** can be explained as shown in Scheme 3.3.3. Here carbocation **31** is attacked by phenolic group to give tetracyclic compound **39**. The structure and stereochemistry of the compound was determined from ^{1}H NMR, COSY and NOE experiments.

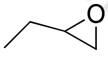
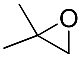
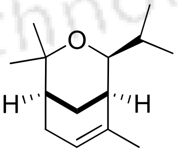
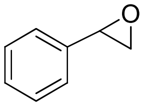
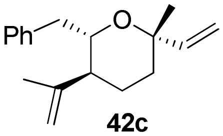
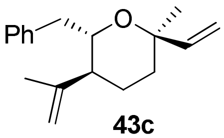


Scheme 3.3.3. Reaction with salicyldehyde

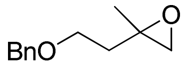
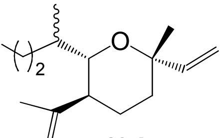
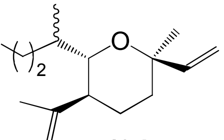
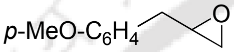
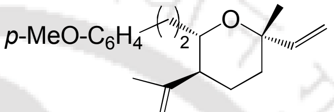
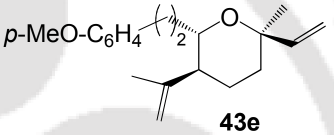
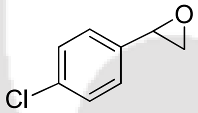
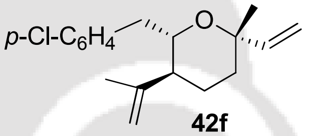
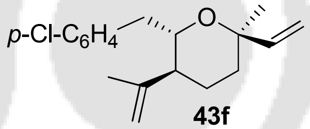
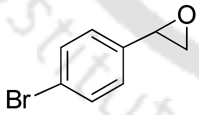
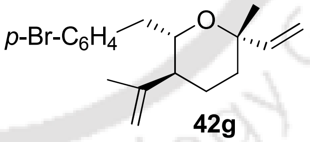
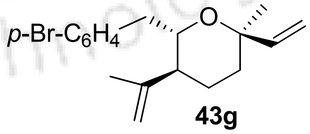
The reaction of geraniol with epoxides was also performed and the results are summarized in Table 3.3.2. It was observed that monosubstituted terminal epoxides are non-reactive, whereas the 2,2-disubstituted and styrene oxides are active and give good to moderate

Table 3.3.2. Reaction of geraniol with epoxides



Entry	Epoxide	Time/h	Products	Yield[a] (%)
1	 **40a**	12	No reaction	0
2	 **40b**	3	 **41b**	45
3	 **40c**	3	 **42c**  **43c** **42c**:**43c** = 3:2[b]	52

continue…

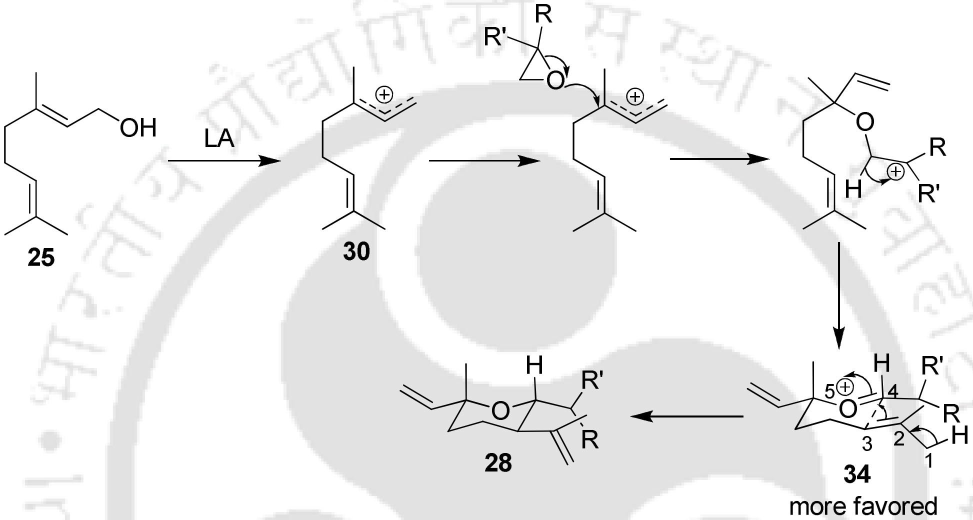
Entry	Epoxide	Time/h	Products	Yield[a] (%)
4	 **40d**	3	 **42d**  **43d** **42d:43d** = 2:1[b]	48
5	 **40e**	3	 **42e**  **43e** **42e:43e** = 2:1[b]	45
6	 **40f**	3	 **42f**  **43f** **42f:43f** = 3:2[b]	48
7	 **40g**	3	 **42g**  **43g** **42g:43g** = 3:2[b]	48

[a] Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C NMR and Mass spectroscopy.
[b] Ratios are determined by ^{1}H NMR of crude products.

yields.[7] Interestingly monosubstituted benzylic terminal epoxide (entry 5) was also found to give corresponding tetrahydropyrans. The formation of substituted tetrahydropyrans **42c-42g** and **43c-43g** from epoxides **40c–40g** are in accordance with the facts already discussed; but the formation of bicyclic compound **41b** in case of 2,2-dimethyl oxirane **40b** is not clear

(Table 3.3.2).

The mechanism of the formation of tetrahydropyrans can be explained as follows. The carbocation **30** is attacked by epoxide to give oxocarbenium intermediate **34**, which after oxonium-ene cyclization gives tetrahydropyran **28** (Scheme 3.3.4). In the case of 2,2-dimethyl oxirane the carbocation **30** rearranges to **31** and then attacked by epoxide to give the oxabicyclic compound **41b**.



Scheme 3.3.4. Mechanism of the reaction with epoxide

Conclusions:

In summary, an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans has been developed from readily available starting material in moderate to good yields. The bicyclic unit can further be transformed by manipulating olefinic functionality and therefore, can be used as a precursor for the synthesis of complex organic molecules.

3.4 Experimental Section

3.4.1 Instrumentation and Characterization

As described in Chapter 2, Section 2.4.1.

3.4.2 General Procedure for the Synthesis of Oxabicyclic and Substituted Tetrahydropyran from Aldehyde: To a solution of geraniol (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 mL) at -78 ^oC was added boron trifluoride etherate (1.2 mmol, 1.2 equiv.). To this solution aldehyde (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 mL) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for a specified time. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, the solvent was removed by rotary evaporator. The resultant residue was quenched with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds. All compounds were obtained as colourless oil or semisolid and therefore boiling points were not determined.

Synthesis of 2,2,6-Trimethyl-4-phenyl-3-oxabicyclo[3.3.1]non-6-ene (27a, Table 3.3.1): To a solution of geraniol (154 mg, 1 mmol) in dry CH_2Cl_2 (2 mL) at -78 ^oC, was added boron trifluoride etherate (170 mg, 1.2 mmol). To this solution benzaldehyde (106 mg, 1.0 mmol) in dry CH_2Cl_2 (2 mL) was added drop by drop over 5 minutes. The reaction mixture was stirred at that temperature for 2.5 h. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, the solvent was removed by rotary evaporator. The resultant residue was quenced with saturated $NaHCO_3$ solution. The product was extracted with ethyl acetate and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **27a** as a colourless oil (126 mg, 52%).

3.4.3 General Procedure for the Synthesis of Oxabicyclic and Substituted Tetrahydropyran from Epoxide: To a solution of geraniol (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 mL) at -78 ^oC, was added boron trifluoride etherate (1.2 mmol, 1.2 equiv.). To this solution epoxide (2 mmol, 2 equiv) in dry CH_2Cl_2 (2 mL) was added drop by drop over 5 minutes. Then the temperature of the reaction was brought to room temperature. The reaction mixture was stirred at that temperature for a specified time. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, the solvent was removed by rotary evaporator. The resultant residue was quenched with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of 4-Isopropyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (41b, Table 3.3.2): To a solution of geraniol (154 mg, 1 mmol) in dry CH_2Cl_2 (2 mL) at -78 ^{o}C, was added boron trifluoride etherate (170 mg, 1.2 mmol). To this solution 1,2-epoxy-2-methylpropane (144 mg, 2.0 mmol) in dry CH_2Cl_2 (2 mL) was added drop by drop over 5 min. The temperature was slowly brought to room temperature. The reaction mixture was stirred at that temperature for 3 h. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, the solvent was removed by rotary evaporator. The resultant residue was quenced with saturated $NaHCO_3$ solution. The product was extracted with ethyl acetate and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **41b** as a colourless oil (94 mg, 45%).

3.5 References

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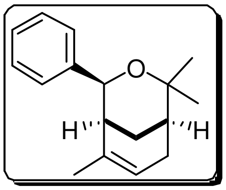
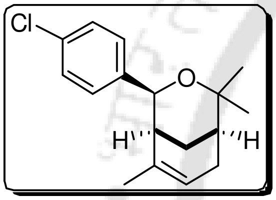
3.6 Spectral Data

2,2,6-Trimethyl-4-phenyl-3-oxabicyclo[3.3.1]non-6-ene (27a):



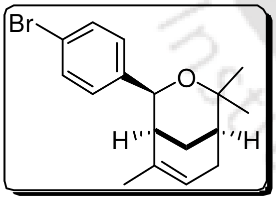
Colourless oil (126 mg, 52%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.86 (m, 3 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.56 (ddd, J = 6.4, 3.2 and 3.2 Hz, 1 H), 1.73 (ddd, J = 12.4, 3.2 and 3.2 Hz, 1 H), 2.08 (dddq, J = 18.8, 6.3, 3.2 and 2.4 Hz, 1 H), 2.19-2.21 (m, 1 H), 2.32-2.43 (m, 2 H), 4.88 (d, J = 2.0 Hz, 1 H), 5.40-5.44 (m, 1 H), 7.17-7.20 (m, 1 H), 7.25-7.28 (m, 2 H), 7.30-7.33 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.2, 24.3, 27.9, 28.5, 28.9, 34.2, 41.8, 74.4, 75.5, 123.5, 125.8, 126.7, 128.0, 133.4, 143.1; **IR** (Neat): 2935, 1450, 1379, 1207, 1084, 1057, 755, 700 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O$ (M^+) requires 242.1671; found 242.1663.

4-(4-Chlorophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]-non-6-ene (27b):



Colourless oil (194 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (m, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.56 (ddd, J = 6.0, 3.2 and 3.2 Hz, 1 H), 1.73 (ddd, J = 12.4, 3.2 and 3.2 Hz, 1 H), 2.08 (dddq, J = 19.2, 6.4, 3.2 and 2.4 Hz, 1 H), 2.15-2.18 (m, 1 H), 2.30-2.42 (m, 2 H), 4.84 (d, J = 2.0 Hz, 1 H), 5.44 (brs, 1 H), 7.22-727 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.2, 24.4, 27.9, 28.4, 28.8, 34.1, 41.6, 73.9, 75.7, 123.9, 127.4, 128.2, 132.4, 132.9, 141.7; **IR** (Neat): 2933, 1635, 1464, 1380, 1226, 1075, 1053, 801, 677 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}ClO$ (M^+) requires 276.1281; found 276.1269.

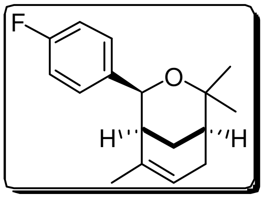
4-(4-Bromophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]-non-6-ene (27c):



Colourless oil (225 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (m, 3 H), 1.32 (s, 3 H), 1.37 (s, 3 H), 1.56 (ddd, J = 6.0, 3.2 and 2.8 Hz, 1 H), 1.73 (ddd, J = 12.4, 3.2 and 2.8 Hz, 1 H), 2.08 (dddq, J = 18.8, 6.0, 3.2 and 2.8 Hz, 1 H), 2.15-2.17 (m, 1 H), 2.30-2.42 (m, 2 H), 4.81 (d, J = 2.0 Hz, 1 H), 5.40-5.45 (m, 1 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.1, 24.5, 27.8, 28.4, 28.8, 34.0, 41.6, 73.9, 75.7, 120.5, 123.9, 127.7, 131.1, 132.9, 142.2; **IR** (Neat): 2932, 1461, 1369, 1204, 1072, 1056, 806, 801 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}BrO$ (M^+) requires 320.0776; found 320.0789.

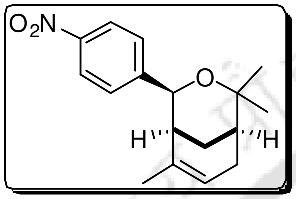
4-(4-Fluorophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27d):

Colourless oil (177 mg, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.54-1.62 (m, 1 H), 1.72 (ddd, J = 12.4, 3.2 and 3.2 Hz, 1 H), 2.05-2.16 (m, 2 H), 2.31-2.42 (m, 2 H), 4.85 (s, 1 H), 5.40-5.45 (m, 1 H), 6.96 (t, J = 8.4 Hz, 2 H), 7.28 (t,



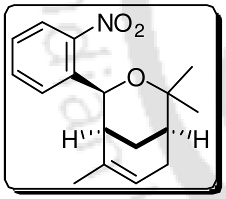
J = 7.6Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.2, 24.3, 27.9, 28.4, 28.9, 34.1, 41.7, 73.9, 75.7, 114.8 (d, J = 21.3 Hz), 123.8, 127.4 (d, J = 7.7 Hz), 133.0, 138.9, 162.0 (d, J = 242.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -220.69-(-220.77) (m, 1 F); **IR** (Neat): 2932, 1626, 1509, 1377, 1227, 1074, 1056, 824, 798 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}FO$ (M^+) requires 260.1576; found 260.1565.

4-(4-Nitrophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27e):



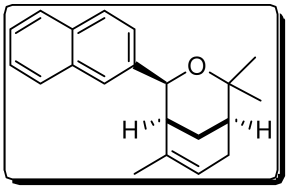
Colourless oil (144 mg, 50%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.82 (m, 3 H), 1.35 (s, 3 H), 1.40 (s, 3 H), 1.59 (ddd, J = 6.0, 3.2 and 2.8 Hz, 1 H), 1.77 (ddd, J = 12.8, 3.6 and 3.2 Hz, 1 H), 2.10 (dddq, J = 18.4, 6.4, 3.2 and 2.8 Hz, 1 H), 2.20-2.28 (m, 1 H), 2.35-2.43 (m, 2 H), 4.95 (s, 1 H), 5.47 (brs, 1 H), 7.50 (d, J = 8.4 Hz, 2 H), 8.14 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.1, 24.4, 27.8, 28.4, 28.7, 33.9, 41.6, 74.0, 76.0, 123.3, 124.6, 126.8, 132.1, 147.0, 150.9; **IR** (Neat): 2934, 1600, 1520, 1346, 1229, 1077, 1057, 851, 707 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}NO_3$ $(M+H)^+$ requires 288.1599; found 288.1609.

4-(2-Nitrophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27f):



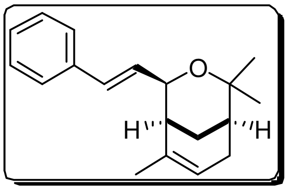
Colourless oil (155 mg, 54%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.85 (m, 3 H), 1.33 (s, 3 H), 1.40 (s, 3 H), 1.59 (ddd, J = 6.4, 3.2, and 3.2 Hz, 1 H), 1.72 (ddd, J = 12.4, 3.2 and 2.8 Hz, 1 H), 2.11 (dddq, J = 18.8, 6.0, 3.2 and 2.8 Hz, 1 H), 2.36-2.50 (m, 3 H), 5.45-5.47 (m, 1 H), 5.49-5.52 (m, 1 H), 7.36 (t, J = 8.4 Hz, 1 H), 7.55 (t, J = 8.0 Hz, 1 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.2, 24.3, 27.8, 28.2, 28.8, 33.9, 39.1, 70.1, 76.2, 124.2, 124.5, 127.6, 129.5, 132.4, 133.3, 138.3, 147.5; **IR** (Neat): 2933, 1525, 1345, 1228, 1067, 1055, 746, 709 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}NO_3$ (M^+) requires 287.1521; found 287.1528.

2,2,6-Trimethyl-4-naphthyl-3-oxabicyclo[3.3.1]non-6-ene (27g):



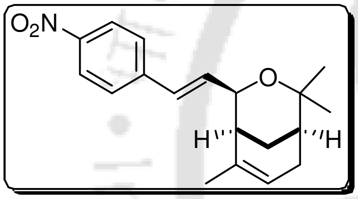
Colourless oil (161 mg, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.79 (m, 3 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 1.59 (ddd, J = 6.4, 3.6 and 2.8 Hz, 1 H), 1.76 (ddd, J = 12.0, 3.6 and 3.2 Hz, 1 H), 2.10 (dddq, J = 18.4, 6.4, 3.2 and 2.8 Hz, 1 H), 2.32-2.48 (m, 3 H), 5.03 (d, J = 1.2 Hz, 1 H), 5.46 (brs, 1 H), 7.38-7.45 (m, 3 H), 7.73-7.82 (m, 4 H); **^{13}C NMR** (100 MHz, CDCl3): δ 24.3, 24.4, 27.9, 28.7, 28.9, 34.2, 41.6, 74.6, 75.7, 123.6, 124.1, 124.7, 125.4, 125.8, 127.5, 127.7, 128.3, 132.8, 133.4, 133.5, 140.6; **IR** (Neat): 2931, 1461, 1368, 1284, 1126, 1097, 1078, 818, 776, 739 cm^{-1}. **HRMS** (APCI) cald. For $C_{21}H_{24}O$ (M^+) requires 292.1827; found 292.1818.

2,2,6-Trimethyl-4-styryl-3-oxabicyclo[3.3.1]non-6-ene (27h):



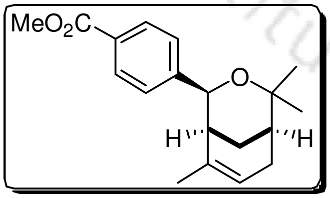
Colourless oil (166 mg, 62%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.29 (s, 3 H), 1.37 (s, 3 H), 164-1.68 (m, 1 H), 1.69 (s, 3 H), 1.70 (ddd, *J* = 12.0, 3.6 and 3.2 Hz, 1 H), 2.06-2.10 (m, 1 H), 2.11-2.16 (m, 1 H), 2.22-2.29 (m, 1 H), 2.35-2.44 (m, 1 H), 4.47 (d, *J* = 5.6 Hz, 1 H), 5.55-5.60 (m, 1 H), 6.16 (dd, *J* = 16.0 and 6.4 Hz, 1 H), 6.56 (d, *J* = 16.4 Hz, 1 H), 7.18-7.21 (m, 1 H), 7.27-7.32 (m, 2 H), 7.34-7.38 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 24.3, 25.3, 27.9, 28.2, 28.8, 34.2, 40.7, 74.7, 75.6, 124.0, 126.6, 127.4, 128.6, 129.0, 131.4, 133.5, 137.4; **IR** (Neat): 2930, 1646, 1456, 1374, 1226, 1083, 1061, 968, 746, 694 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{24}O$ (M^+) requires 268.1827; found 268.1838.

2,2,6-Trimethyl-4[2-(4-nitrophenyl)-vinyl]-3-oxabicyclo[3.3.1]-non-6-ene (27i):



Colourless oil (172 mg, 55%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.30 (s, 3 H), 1.37 (s, 3 H), 1.56 (ddd, *J* = 5.6, 2.8 and 2.8 Hz, 1 H), 1.64 (s, 3 H), 1.73 (ddd, *J* = 12.4, 3.2 and 2.8 Hz, 1 H), 2.08 2.17 (m, 2 H), 2.23-2.29 (m, 1 H), 2.34-2.42 (m, 1 H), 4.51(d, *J* = 5.2 Hz, 1 H), 5.56 (brs, 1 H), 6.37 (dd, *J* = 16.0 and 5.6 Hz, 1 H), 6.64 (d, *J* = 16.0 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 2 H), 8.15 (d, *J* = 8.8 Hz, 2 H), ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 24.1, 25.0, 27.8, 28.1, 28.6, 34.0, 40.2, 73.7, 75.7, 124.0, 124.3, 126.5, 126.8, 132.7, 136.5, 143.9, 146.7; **IR** (Neat): 2930, 1596, 1518, 1341, 1083, 1050, 973, 858, 746 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{23}NO_3$ (M^+) requires 313.1678; found 313.1686.

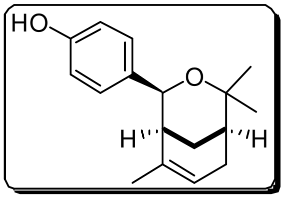
4-(4,4,8-Trimethyl-3-oxabicyclo[3.3.1]non-7-en-2-yl)-benzoic acid methyl ester (27j):



Colourless oil (171 mg, 57%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.82 (m, 3 H), 1.34 (s, 3 H), 1.40 (s, 3 H), 1.57 (ddd, *J* = 6.4, 3.6 and 2.8 Hz, 1 H), 1.74 (ddd, *J* = 12.8, 3.2 and 2.8 Hz, 1 H), 2.08 (dddq, *J* = 18.8, 6.0, 3.2 and 2.8 Hz, 1 H), 2.22-2.29 (m, 1 H), 2.32-2.43 (m, 2 H), 3.89 (s, 3 H), 4.92 (s, 1 H), 5.44 (brs, 1 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 24.1, 24.3, 27.8, 28.5, 28.8, 34.0, 41.6, 52.2, 74.3, 75.7, 124.0, 125.9, 128.6, 129.4, 132.8, 148.5, 167.4; **IR** (Neat): 2952, 1720, 1436, 1278, 1107, 1079, 1017, 768, 713 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{24}O_3$ $(M+H)^+$ requires 301.1803; found 301.1808.

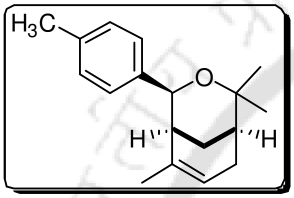
4-(4,4,8-Trimethyl-3-oxabicyclo[3.3.1]-non-7-en-2-yl)-phenol (27k):

Colourless oil (156 mg, 60%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.91 (m, 3 H), 1.32 (s, 3 H),



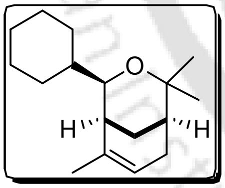
1.38 (s, 3 H), 1.54 (ddd, *J* = 6.0, 3.2 and 2.8 Hz, 1 H), 1.71 (ddd, *J* = 12.4, 3.2 and 2.8 Hz, 1 H), 2.08 (dddq, *J* = 18.8, 6.0, 3.2 and 2.8Hz, 1 H), 2.12-2.17 (m, 1 H), 2.30-2.42 (m, 2 H), 4.91 (brs, 1 H), 5.27 (brs, 1 H), 5.44 (brs, 1 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 24.1, 24.4, 27.8, 28.3, 28.8, 34.2, 41.7, 74.2, 75.7, 115.0, 123.4, 127.0, 133.4, 134.9, 154.6; **IR** (Neat): 3372, 2929, 1611, 1457, 1377, 1227, 1168, 1075, 1053, 828 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O_2$ $(M+H)^+$ requires 259.1698; found 259.1701.

2,2,6-Trimethyl-4-*p*-tolyl-3-oxabicyclo[3.3.1]non-6-ene (27l):



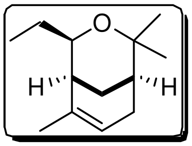
Colourless oil (174 mg, 68%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.88 (m, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.54 (ddd, *J* = 6.0, 3.2 and 2.8 Hz, 1 H), 1.71 (ddd, *J* = 12.4, 3.2 and 3.2 Hz, 1 H), 2.08 (dddq, *J* = 18.4, 6.4, 3.6 and 2.8 Hz, 1 H), 2.14-2.19 (m, 1 H), 2.30 (s, 3 H), 2.30-2.42 (m, 2 H), 4.84 (brs, 1 H), 5.43 (brs, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 21.2, 24.1, 24.4, 27.8, 28.4, 28.8, 34.0, 41.6, 74.2, 75.3, 123.2, 125.6, 128.5, 133.4, 135.9, 140.0; **IR** (Neat): 2967, 2930, 1610, 1445, 1375, 1285, 1109, 1075, 1020, 806, 754 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O$ (M^+) requires 256.1827; found 256.1827.

4-Cyclohexyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27m):



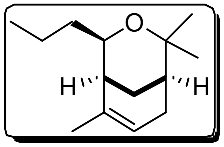
Colourless oil (154 mg, 62%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.70-1.00 (m, 4 H), 1.09-1.19 (m, 1 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 1.46 (ddd, *J* = 6.0, 3.2 and 2.8 Hz, 1 H), 1.58-1.70 (m, 4 H), 1.74 (s, 3 H), 1.84-1.92 (m, 2 H), 2.00-2.19 (m, 4 H), 2.30-2.40 (m, 1 H), 3.25 (d, *J* = 10.0 Hz, 1 H), 5.53 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDC13): *δ* 24.2, 25.3, 25.8, 26.0, 26.9, 28.1, 28.7, 29.0, 29.5, 30.6, 34.4, 35.0, 40.1, 75.0, 76.9, 124.4, 133.7; **IR** (Neat): 2923, 2851, 1641, 1449, 1378, 1228, 1063, 1045, 880, 801 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{28}O$ (M^+) requires 248.2140; found 248.2144.

2,2,6-Trimethyl-4-ethyl-3-oxabicyclo[3.3.1]non-6-ene (27n):



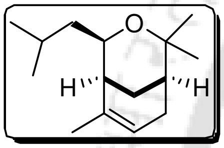
Colourless oil (16 mg, 8%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.93 (t, *J* = 7.6 Hz, 3 H), 1.21 (s, 3 H), 1.28, (s, 3 H), 1.40 (quin, *J* = 7.2 Hz, 2 H), 1.48 (ddd, *J* = 5.6, 3.2 and 2.8 Hz, 1 H), 1.63 (ddd, *J* = 12.4, 2.8 and 2.8 Hz, 1 H), 1.73 (s, 3 H), 1.92 1.96 (m, 1 H), 2.06 (dddq, *J* = 18.8, 6.4, 2.8 and 2.8 Hz, 1 H), 2.09-2.14 (m, 1 H), 2.28-2.38 (m, 1 H), 3.56 (t, *J* = 6.8 Hz, 1 H), 5.51 (brs, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 11.1, 24.2, 25.4, 27.8, 28.0, 28.6, 28.9, 34.5, 38.1, 75.0, 75.6, 123.9, 133.7; **IR** (Neat): 2959, 2931, 1648, 1458, 1377, 1108, 1068, 1042, 866, 743 cm^{-1}. **HRMS** (APCI) cald. for $C_{13}H_{22}O$ (M^+) requires 194.1671; found 194.1677.

4-Propyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27o):



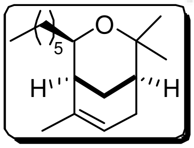
Colourless oil (17 mg, 8%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.8 Hz, 3 H), 1.20 (s, 3 H), 1.24-1.44 (m, 4 H), 1.29, (s, 3 H), 1.47 (ddd, *J* = 6.0, 3.6 and 2.8 Hz, 1 H), 1.62 (ddd, *J* = 12.4, 3.2 and 3.2 Hz, 1 H), 1.73 (s, 3 H), 1.88-1.92 (m, 1 H), 2.05 (dddq, *J* = 18.8, 6.0, 3.2 and 2.8 Hz, 1 H), 2.10-2.16 (m, 1 H), 2.30-2.38 (m, 1 H), 3.68 (ddd, *J* = 7.6, 4.8 and 1.6 Hz, 1 H), 5.52 (brs, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.1, 19.7, 24.2, 25.4, 28.0, 28.7, 28.9, 34.5, 37.1, 38.5, 73.5, 74.9, 123.9, 133.7; **IR** (Neat): 2957, 2931, 1645, 1458, 1378, 1111, 1077, 886, 806 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O$ (M^+) requires 208.1827; found 208.1824.

4-Isobutyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27p):



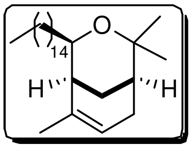
Colourless oil (22 mg, 10%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 1.08-1.16 (m, 1 H), 1.20 (s, 3 H), 1.30 (s, 3 H), 1.34-1.41 (m, 1 H), 1.48 (ddd, *J* = 6.4, 3.2 and 3.2 Hz, 1 H), 1.63 (ddd, *J* = 12.0, 3.6 and 3.2 Hz, 1 H), 1.74 (s, 3 H), 1.75-1.82 (m, 1 H), 1.83-1.88 (m, 1 H), 2.05 (dddq, *J* = 18.8, 6.4, 3.2 and 2.4 Hz, 1 H), 2.10-2.17 (m, 1 H), 2.29-2.37 (m, 1 H), 3.78 (ddd, *J* = 9.2, 4.4, and 2.8 Hz, 1 H), 5.51 (brs, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 22.0, 23.5, 24.1, 24.6, 25.5, 28.0, 28.8, 29.9, 34.4, 38.9, 43.9, 71.4, 74.9, 123.9, 133.8; **IR** (Neat): 2954, 2933, 1463, 1378, 1227, 1120, 1077, 1015, 892, 800 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O$ (M^+) requires 222.1984; found 222.1986.

4-Hexyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27q):



Colourless oil (38 mg, 15%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3 H), 1.20 (s, 3 H), 1.22-1.32 (m, 10 H), 1.28 (s, 3 H), 1.47 (ddd, *J* = 6.4, 3.2 and 3.2 Hz, 1 H), 1.62 (ddd, *J* = 12.4, 3.2 and 2.8 Hz, 1 H), 1.73 (s, 3 H), 1.85-1.92 (m, 1 H), 2.05 (dddq, *J* = 19.2, 6.0, 3.2 and 2.8 Hz, 1 H), 2.10-2.14 (m, 1 H), 2.28-2.40 (m, 1 H), 3.65 (t, *J* = 5.6 Hz, 1 H), 5.50 (brs, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.3, 22.8, 24.2, 25.4, 26.6, 28.1, 28.7, 28.9, 29.5, 32.1, 34.5, 35.1, 38.5, 73.9, 74.9, 123.9, 133.7; **IR** (Neat): 2929, 2868, 1647, 1458, 1377, 1077, 1017, 886, 724 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{30}O$ (M^+) requires 250.2297; found 250.2298.

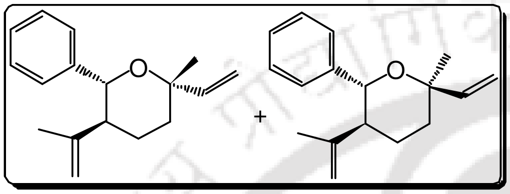
4-Pentadecyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27r):



Semisolid (38 mg, 10%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20 (s, 3 H), 1.21-1.28 (m, 20 H), 1.28 (s, 3 H), 1.30-1.49 (m, 5

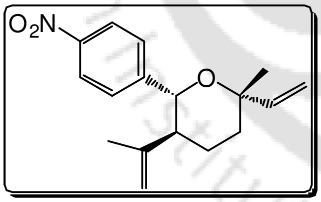
H), 1.62 (ddd, *J* = 12.4, 3.2 and 3.2 Hz, 1 H), 1.73 (s, 3 H), 1.90-1.93 (m, 2 H), 2.00-2.15 (m, 4 H), 2.26-2.37 (m, 2 H), 3.65 (t, *J* = 5.6Hz, 1 H), 5.51 (brs, 1 H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 14.3, 22.9, 24.2, 25.4, 26.6, 28.0, 28.7, 28.9, 29.85 (5C), 29.9 (5C), 32.1, 34.5, 35.0, 38.4, 73.9, 74.9, 123.8, 133.7; **IR** (KBr): 2924, 2854, 1644, 1459, 1378, 1226, 1076, 1067, 801, 721 cm^{-1}. **HRMS** (APCI) cald. for $C_{26}H_{48}O$ (M^+) requires 376.3705; found 376.3696.

5-Isopropenyl-2-methyl-6-phenyl-2-vinyltetrahydropyran (28a/29a) (2:1):



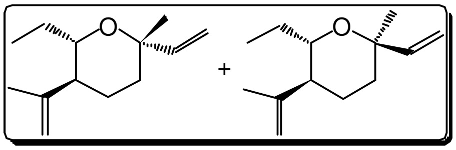
Colourless oil (61 mg, 25%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (s, 1 H), 1.29 (s, 2 H), 1.39 (s, 2 H), 1.42 (s, 1 H), 1.62-1.74 (m, 2 H), 1.79-1.90 (m, 1 H), 1.96-2.02 (m, 1 H), 2.20-2.28 (m, 1 H), 4.44 (d, *J* = 10.4 Hz, 1 H), 4.52 (brs, 0.33 H), 4.55 (brs, 0.67 H), 4.59 (brs, 0.67 H), 4.65 (brs, 0.33 H), 4.99 (d, *J* = 10.8 Hz, 0.33 H), 5.07 (d, *J* = 14.4 Hz, 0.33 H), 5.22 (dd, *J* = 18.0 and 1.2 Hz, 0.67 H), 5.29 (dd, *J* = 11.2 and 1.2 Hz, 0.67 H), 5.89 (dd, *J* = 18.0 and 12.0 Hz, 0.67 H), 5.99 (dd, *J* = 17.2 and 10.8 Hz, 0.33 H), 7.22-7.26 (m, 2 H), 7.28-7.31 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 27.1, 31.4, 34.6, 50.8, 75.8, 78.5, 112.1, 115.3, 127.7, 128.1, 128.2, 141.8, 143.1, 146.7 (major, **28a**); **IR** (Neat): 2967, 2930, 1643, 1450, 1370, 1116, 1050, 889, 759, 698 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O$ $(M+H)^+$ requires 243.1749; found 243.1760.

5-Isopropenyl-2-methyl-6-(4-nitrophenyl)-2-vinyl-tetrahydropyran (28e):



Colourless oil (43 mg, 15%); **^{1}H NMR** (400 MHz, CDC13): δ 1.31 (s, 3 H), 1.42 (s, 3 H), 1.54-1.78 (m, 2 H), 1.80-1.92 (m, 1 H), 2.00-2.05 (m, 1 H), 2.11-2.19 (m, 1 H), 4.53 (brs, 1 H), 4.56 (d, *J* = 10.0 Hz, 1 H), 4.63 (brs, 1 H), 5.22 (d, *J* = 17.6 Hz, 1 H), 5.32 (d, *J* = 11.2 Hz, 1 H), 5.86 (dd, *J* = 18.0 and 11.2 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.6, 26.8, 31.2, 34.4, 51.4, 76.1, 77.4, 113.1, 115.8, 123.4, 128.4, 142.4, 145.5, 147.6, 149.3; **IR** (Neat): 2928, 2857, 1606, 1520, 1346, 1262, 1108, 1055, 894, 751, 696 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}NO_3$ $(M+H)^+$ requires 288.1599; found 288.1605.

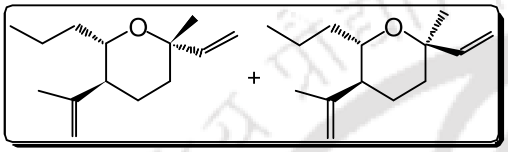
6-Ethyl-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (28n/29n) (3:1):



Colourless oil (126 mg, 65%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.2 Hz, 0.75 H), 0.94 (t, *J* = 7.2 Hz, 2.25 H), 1.23 (s, 3 H), 1.24-1.30 (m, 2 H), 1.47-1.57 (m, 2 H), 1.62 (s, 3 H), 1.61-1.65 (m, 1 H), 1.66-1.71 (m, 1 H), 1.85-1.94 (m, 1

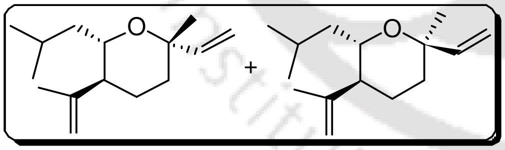
H), 3.36-3.42 (m, 0.75 H), 3.45-3.51 (m, 0.25 H), 4.70 (brs, 1.50 H), 4.75 (brs, 0.50 H), 4.99 (dd, *J* = 11.2 and 1.6 Hz, 0.25 H), 5.13 (dd, *J* = 18.0 and 1.6 Hz, 0.75 H), 5.19 (dd, *J* = 10.8 and 1.2 Hz, 0.75 H), 5.22 (dd, *J* = 17.6 and 1.6 Hz, 0.25 H), 5.76 (dd, *J* = 17.6 and 10.8 Hz, 0.75 H), 5.93 (dd, *J* = 17.6 and 11.2 Hz, 0.25 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.2, 20.3, 26.6, 27.0, 31.4, 34.6, 49.7, 74.8, 75.0, 111.7, 114.8, 143.5, 147.6 (major, **28n**); **IR** (Neat): 2928, 2873, 1641, 1458, 1377, 1116, 995, 888, 740 cm^{-1}. **HRMS** (APCI) cald. for $C_{13}H_{22}O$ $(M+H)^+$ requires 195.1749; found 195.1747.

6-Propyl-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (28o/29o) (3:1):



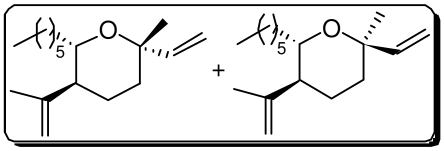
Colourless oil (135 mg, 65%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.6 Hz, 0.75 H), 0.88 (t, *J* = 7.2 Hz, 2.25 H), 1.20 (s, 0.75 H), 1.21 (s, 2.25 H), 1.23-1.35 (m, 4 H), 1.36-1.43 (m, 1 H), 1.45-1.60 (m, 2 H), 1.62 (s, 2.25 H), 1.64 (s, 0.75 H), 1.67-1.71 (m, 1 H), 1.85-1.92 (m, 1 H), 3.46 (dt, *J* = 9.2 and 2.0 Hz, 0.75 H), 3.56 (dt, *J* = 10.0 and 2.4 Hz, 0.25 H), 4.70 (brs, 1.50 H), 4.75 (brs, 0.50 H), 4.98 (dd, *J* = 10.8 and 1.6 Hz, 0.25 H), 5.12 (dd, *J* = 17.6 and 1.6 Hz, 0.75 H), 5.19 (dd, *J* = 11.2 and 1.2 Hz, 0.75 H), 5.20 (dd, *J* = 16.4 and 1.6 Hz, 0.25 H), 5.76 (dd, *J* = 18.0 and 12.2 Hz, 0.75 H), 5.92 (dd, *J* = 17.2 and 10.4 Hz, 0.25 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 18.8, 20.3, 27.0, 31.4, 34.5, 35.9, 50.1, 73.4, 74.8, 111.7, 114.7, 143.5, 147.6 (major, **28o**); **IR** (Neat): 2957, 2931, 1643, 1452, 1377, 1114, 1067, 1026, 916, 889, 746 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O$ $(M+H)^+$ requires 209.1905; found 209.1914.

6-Isobutyl-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (28p/29p) (3:1):



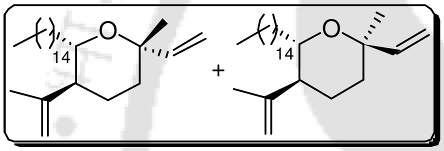
Colourless oil (149 mg, 67%); **^{1}HNMR** (400 MHz, $CDCl_3$): δ 0.83 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 1.11-1.18 (m, 2 H), 1.21 (s, 3 H), 1.23-1.31 (m, 2 H), 1.48-1.58 (m, 1 H), 1.61 (s, 3 H), 1.65-1.71 (m, 1 H), 1.83-1.92 (m, 2 H), 3.50 (dt, *J* = 10.4 and 2.0 Hz, 0.75 H), 3.62 (dt, *J* = 10.0 and 2.0 Hz, 0.25 H), 4.69 (brs, 1.50 H), 4.73 (brs, 0.50 H), 4.98 (dd, *J* = 10.8 and 2.0 Hz, 0.25 H), 5.12 (dd, *J* = 17.6 and 1.2 Hz, 0.75 H), 5.18 (dd, *J* = 8.0 and 1.6 Hz, 0.25 H), 5.21 (dd, *J* = 11.2 and 1.2 Hz, 0.75 H), 5.79 (dd, *J* = 18.0 and 11.2 Hz, 0.75 H), 5.92 (dd, *J* = 17.2 and 10.8 Hz, 0.25 H); **^{13}C NMR** (100 MHz, CDCl3): δ 20.1, 21.5, 23.9, 24.2, 27.0, 31.4, 34.2, 43.1, 50.6, 71.7, 74.7, 111.8, 114.8, 143.6, 147.6 (major, **28p**); **IR** (Neat): 2950, 2932, 1643, 1450, 1380, 1264, 1118, 1068, 997, 918, 890, 735 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O$ $(M+H)^+$ requires 223.2062.; found 223.2063.

6-Hexyl-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (28q/29q) (3:1):



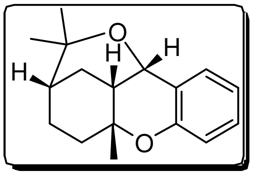
Colourless oil (150 mg, 60%); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.86 (t, J = 6.8 Hz, 3 H), 1.22 (s, 3 H), 1.23-1.34 (m, 10 H), 1.40-1.57 (m, 2 H), 1.62 (s, 3 H), 1.64-1.71 (m, 1 H), 1.85-1.91 (m, 2 H), 3.45 (t, J = 9.6 Hz, 0.75 H), 3.54 (t, J = 8.0 Hz, 0.25 H), 4.70 (brs, 1.50 H), 4.73 (brs, 0.50 H), 4.98 (dd, J = 10.8 and 1.2 Hz, 0.25 H), 5.12 (dd, J = 17.6 and 1.2 Hz, 0.75 H), 5.19 (dd, J = 11.2 and 1.6 Hz, 0.75 H), 5.20 (dd, J = 14.0 and 1.2 Hz, 0.25 H), 5.76 (dd, J = 18.0 and 11.2 Hz, 0.75 H), 5.93 (dd, J = 17.6 and 10.8 Hz, 0.25 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.3, 20.3, 22.9, 25.8, 27.1, 29.6, 31.4, 32.2, 33.9, 34.6, 50.1, 73.7, 74.8, 111.7, 114.7, 143.6, 147.7 (major, **28q**); **IR** (Neat): 2929, 2858, 1643, 1454, 1378, 1117, 1074, 916, 889 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{30}O$ $(M+H)^+$ requires 251.2375; found 251.2380.

5-Isopropenyl-2-methyl-6-pentadecyl-2-vinyltetrahydropyran (28r/29r) (3:1):



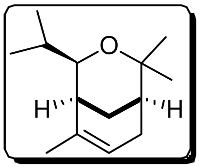
Colourless oil (233 mg, 62%); **^{1}H NMR** (400 MHz, CDCl3): δ 0.88 (t, J = 7.2 Hz, 3 H), 1.21 (s, 3 H), 1.22-1.30 (m, 24 H), 1.40-1.57 (m, 5 H), 1.62 (s, 2.25 H), 1.64 (s, 0.75 H), 1.66-1.71 (m, 2 H), 1.84-1.92 (m, 2 H), 3.42-3.47 (m, 0.75 H), 3.50-3.54 (m, 0.25 H), 4.70 (brs, 1.50 H), 4.74 (brs, 0.50 H), 4.98 (dd, J = 10.4 and 1.6 Hz, 0.25 H), 5.12 (dd, J = 18.0 and 1.2 Hz, 0.75 H), 5.19 (dd, J = 11.2 and 1.2 Hz, 0.75 H), 5.21 (dd, J = 16.0 and 1.6 Hz, 0.25 H), 5.76 (dd, J = 18.0 and 11.2 Hz, 0.75 H), 5.93 (dd, J = 17.6 and 10.8 Hz, 0.25 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.3, 20.3, 22.9, 25.8, 27.1, 29.6, 29.9 (9C), 31.4, 32.2, 33.9, 34.6, 50.2, 73.7, 74.8, 111.7, 114.7, 143.6, 147.7 (major, **28r**); **IR** (Neat): 2923, 2855, 1643, 1455, 1377, 1118, 1077, 889, 721, 683 cm^{-1}. **HRMS** (APCI) cald. for $C_{26}H_{48}O$ (M^+) requires 376.3705; found 376.3705.

Tetracyclic compound (39):



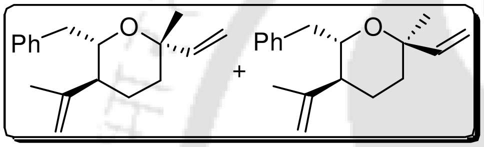
Colourless oil (103 mg, 40%); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.22 (s, 3 H), 1.39 (dddd, J = 4.4, 3.6, 3.6 and 3.6 Hz, 1 H), 1.42 (s, 3 H), 1.52 (d, J = 1.2 Hz, 3 H), 1.53-1.59 (m, 2 H), 1.80-1.84 (m, 1 H), 1.87 (ddd, J = 13.6, 3.2 and 2.8 Hz, 1 H), 2.06 (ddddd, J = 13.0, 5.2, 3.6, 3.2 and 2.8 Hz, 1 H), 2.33 (dddd, J = 13.6, 3.2, 3.2 and 2.8 Hz, 1 H), 2.63 (brddd, J = 14.8, 7.6, 5.6 and 3.6 Hz, 1 H), 4.62 (d, J = 2.4 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.85 (td, J = 7.2 and 1.2 Hz, 1 H), 7.15-7.21 (m, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 24.4, 26.2, 26.7, 26.9, 28.5, 32.4, 34.8, 36.7, 66.7, 74.9, 77.7, 117.0, 119.9, 122.2, 129.8, 130.6, 153.4; **IR** (Neat): 2961, 2934, 1611, 1484, 1366, 1247, 1107, 1094, 1049, 933, 753 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O_2$ (M^+) requires 258.1620; found 258.1621.

4-Isopropyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (41b):



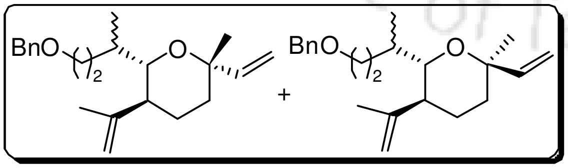
Colourless oil (94 mg, 45%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.92 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 1.21 (s, 3 H), 1.26 (s, 3 H), 1.46 (ddd, J = 6.4, 3.2 and 3.2 Hz, 1 H), 1.49-1.60 (m, 1 H), 1.65 (ddd, J = 12.4, 3.2 and 3.2 Hz, 1 H), 1.75 (s, 3 H), 2.00-2.12 (m, 2 H), 2.14-2.20 (m, 1 H), 2.28-2.38(m, 1 H), 3.14 (d, J = 10.0 Hz, 1 H), 5.52 (brs, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 19.5, 20.7, 24.2, 25.4, 28.2, 28.7, 29.1, 30.8, 34.3, 35.6, 75.1, 80.2, 124.4, 133.7; **IR** (Neat) 2956, 2931, 1642, 1458, 1377, 1226, 1067, 1050, 886, 801 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O$ (M^+) requires 208.1827; found 208.1832.

6-Benzyl-5-isopropyl-2-methyl-2-vinyltetrahydropyran (42c/43c) (3:2):



Colourless oil (133 mg, 52%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.01 (s, 1.8 H), 1.18 (s, 1.2 H), 1.27 (s, 1.8 H), 1.32 (s, 1.2 H), 1.37-1.47 (m, 2 H), 1.59-1.78 (m, 2 H), 1.90-2.00 (m, 1 H), 2.76-2.84 (m, 1 H), 3.02 (dd, J = 16 and 5.6 Hz, 1 H), 3.87-3.99 (m, 1 H), 4.98-5.26 (m, 4 H), 5.83 (dd, J = 18.0 and 10.8 Hz, 0.6 H), 5.97 (dd, J = 17.6 and 10.8 Hz, 0.4 H), 7.03-7.11 (m, 3 H), 7.13-7.19 (m, 1 H), 7.30-7.34 (m, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 20.5, 20.6, 27.7, 27.8, 28.5, 31.3, 35.4, 37.9, 38.2, 38.4, 47.2, 47.4, 66.9, 67.9, 73.0, 74.5, 111.4, 114.9, 125.8, 125.9, 126.3, 126.7, 128.4, 128.9, 129.2, 129.3, 133.6, 133.7, 143.0, 145.8, 145.9, 146.4; **IR** (Neat): 2967, 2934, 1643, 1448, 1382, 1117, 1076, 1037, 921, 759, 729 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O$ $(M+H)^+$ requires 257.1905; found 257.1914.

6-(3-Benzyloxy-1-methylpropyl)-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (42d/43d) (2:1):

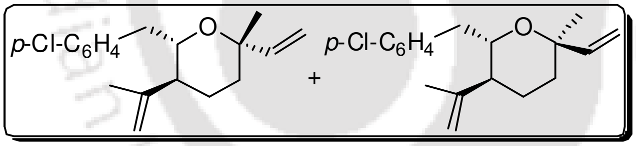


Colourless oil (157 mg, 48%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.85 (d, J = 6.4 Hz, 2 H), 0.97 (d, J = 6.4 Hz, 1 H), 1.15 (s, 2 H), 1.20 (s, 1 H), 1.23 (s, 1 H), 1.26 (s, 2 H), 1.33-1.53 (m, 2 H), 1.62-1.76 (m, 2 H), 1.80-1.88 (m, 1 H), 2.00-2.16 (m, 1 H), 3.38-3.57 (m, 3 H), 4.48 (s, 0.66 H), 4.56 (s, 1.34 H), 4.70-4.75 (m, 2 H), 4.91-5.20 (m, 4 H), 5.67-5.76 (m, 0.67 H), 5.87 (dd, J = 17.6 and 10.8 Hz, 0.33 H), 7.32-7.37 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 12.6, 19.8, 27.1, 29.9, 31.1, 31.2, 34.4, 46.8, 69.1, 72.3, 73.1, 75.2, 111.8, 114.7, 127.8, 128.0, 128.5, 128.6, 138.5, 143.8 (major, **42d**); **IR** (Neat): 2928, 2862, 1639, 1448, 1264, 1080, 1050, 1027, 795, 738 cm^{-1}. **HRMS** (APCI) cald. for $C_{22}H_{32}O_2$ $(M+H)^+$ requires 329.2480; found 329.2491.

5-Isopropenyl-6-[2-(4-methoxyphenyl)-ethyl]-2-methyl-2-vinyltetrahydropyran (42e/43e) (2:1):

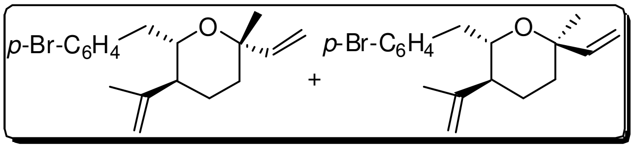
Colourless oil (135 mg, 45%); ^{1}**H NMR** (400 MHz, CDCl3): δ 1.24 (s, 2 H), 1.25 (s, 1 H), 1.55 (brs, 3 H), 1.48-1.80 (m, 5 H), 1.86-1.96 (m, 2 H), 2.47-2.60 (m, 1 H), 2.73-2.87 (m, 1 H), 3.41-3.52 (m, 1 H), 3.78 (brs, 3 H), 4.56-4.71 (m, 2 H), 5.00 (dd, J = 10.8 and 1.6 Hz, 0.33 H), 5.11 (dd, J = 18.0 and 1.2 Hz, 0.67 H), 5.17 (dd, J = 11.2 and 1.2 Hz, 0.67 H), 5.24 (dd, J = 17.6 and 1.6 Hz, 0.33 H), 5.76 (dd, J = 18.0 and 11.2 Hz, 0.67 H), 5.96 (dd, J = 17.6 and 10.8 Hz, 0.33 H), 6.80 (d, J = 8.8 Hz, 2 H), 7.10 (d, J = 8.8 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 20.2, 20.9, 22.5, 22.9, 26.3, 26.9, 29.6, 29.9, 30.8, 31.0, 31.3, 34.5, 34.9, 35.8, 40.0, 50.1, 55.5, 71.1, 73.0, 75.0, 110.4, 111.0, 111.9, 113.8, 114.0, 114.8, 124.6, 126.7, 128.4, 129.6, 129.7, 133.6, 135.1, 143.5, 146.7, 147.5; **IR** (Neat): 2929, 2857, 1633, 1454, 1246, 1078, 1039, 888, 827 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{28}O_2$ $(M+H)^+$ requires 301.2167; found 301.2168.

6-(4-Chlorobenzyl)-5-isopropenyl-2-methyl-2-vinyl-tetrahydropyran (42f/43f) (3:2):



Colourless oil (139 mg, 48%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.07 (s, 1.80 H), 1.17 (s, 1.20 H), 1.27 (s, 1.80 H), 1.33 (s, 1.20 H), 1.35-1.43 (m 1 H), 1.54-1.77 (m, 3 H), 1.96-2.04 (m, 1 H), 2.61-2.80 (m, 1 H), 2.98 (dd, J = 16.0 and 5.6 Hz, 1 H), 3.83-3.96 (m, 1 H), 4.91-5.10 (m, 1 H), 5.14-5.26 (m, 3 H), 5.83 (dd, J = 17.6 and 11.2 Hz, 0.60 H), 5.96 (dd, J = 17.6 and 10.8 Hz, 0.40 H), 6.96-7.0 (m, 1 H), 7.04-7.08 (m, 1 H), 7.23-7.32 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 20.5, 20.6, 27.7, 28.4, 31.2, 35.3, 35.4, 37.3, 37.6, 38.7, 46.9, 47.1, 66.7, 67.8, 73.2, 74.6, 74.8, 111.6, 115.0, 124.5, 126.1, 126.2, 126.8, 128.3, 130.6, 130.7, 132.0, 132.2 143.0, 146.3, 147.9; **IR** (Neat): 2968, 2929, 2872, 1633, 1467, 1369, 1227, 1116, 1077, 922, 881, 814, 802 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}ClO$ $(M+H)^+$ requires 291.1515; found 291.1519.

6-(4-Bromobenzyl)-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (42g/43g) (3:2):

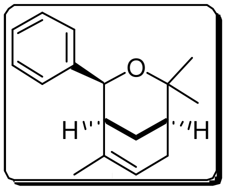


Colourless oil (160 mg, 48%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.07 (s, 1.80 H), 1.17 (s, 1.20 H), 1.27 (s, 1.80 H), 1.33 (s, 1.20 H), 1.35-1.42 (m, 1 H), 1.56-1.76 (m, 3 H), 1.94-2.0 (m, 1 H), 2.60-2.78 (m, 1 H), 2.98 (dd, *J* = 16.0 and 5.6 Hz, 1 H), 3.80-3.98 (m, 1 H), 5.04 (dd, *J* = 10.8 and 1.2 Hz, 1H), 5.14-5.28 (m, 3 H), 5.83 (dd, *J* = 17.6 and 11.2 Hz, 0.60 H), 5.96 (dd, *J* = 17.6 and 10.8 Hz, 0.40 H), 6.90-6.95 (m, 1 H), 7.18-7.23 (m, 1 H), 7.43 (dd, *J* = 8.4 and 2.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.4, 20.5, 27.7, 28.4, 31.2, 35.3, 35.4, 37.3, 37.6, 38.7, 46.8, 47.0, 66.6, 67.7, 73.1, 74.6, 111.6, 115.0, 120.0, 129.0, 129.8, 130.9, 131.0, 132.7, 143.0, 146.2, 148.3; **IR** (Neat): 2969, 2932, 2872, 1632, 1465, 1367, 1225, 1120, 1083, 923, 881, 814, 800 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}BrO$ $(M+H)^+$ requires 335.1010; found 335.1012.

3.7 Selected Spectra of Oxabicyclo[3.3.1]nonenes and Substituted Tetrahydropyrans

2,2,6-Trimethyl-4-phenyl-3-oxabicyclo[3.3.1]non-6-ene (27a):

^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_286_M

exp1  s2pul

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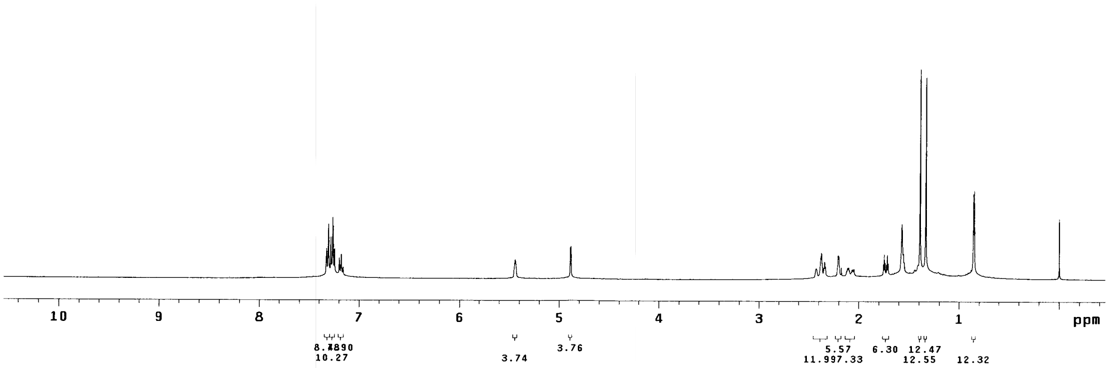
date   Mar  4 2011   temp        not used
solvent       CDCl3  gain        not used
file            exp  spin        not used
   ACQUISITION       hst            0.008
sw           6389.8  pw90          19.700
at            1.998  alfa          20.000
np            25528          FLAGS
fb         not used  il                 n
bs                8  in                 n
d1            1.000  dp                 y
nt              200  hs                nn
ct              176        PROCESSING
   TRANSMITTER       lb              0.10
tn               H1  fn             65536
sfrq        399.853          DISPLAY
tof           362.8  sp            -183.3
tpwr             57  wp            4399.7
pw            9.850  rfl            796.2
    DECOUPLER        rfp                0
dn              C13  rp             113.0
dof               0  lp             -96.4
dm              nnn            PLOT
dmm               c  wc               250
dpwr             50  sc                 0
dmf           15900  vs                49
                     th                14
                     nm  cdc  ph
```

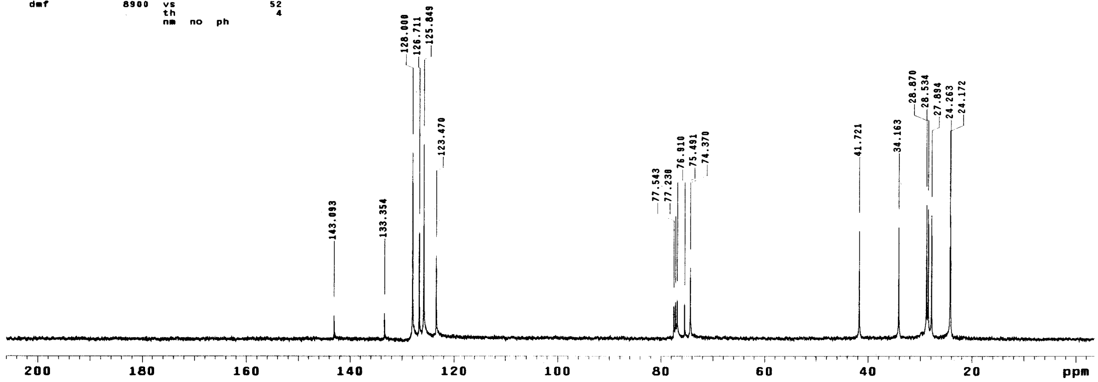


^{13}C NMR (100 MHz, $CDCl_3$)

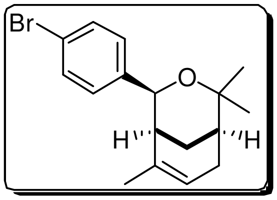
```
PS_286_M

exp1  s2pul

      SAMPLE                  SPECIAL
date   Sep 18 2010   temp        not used
solvent       CDCl3  gain        not used
file            exp  spin        not used
   ACQUISITION       hst            0.008
sw          25125.6  pw90          18.600
at            1.199  alfa          20.000
np            60270          FLAGS
fb            13800  il                 n
bs               16  in                 n
d1            1.000  dp                 y
nt             5000  hs                nn
ct             1520        PROCESSING
   TRANSMITTER       lb              2.00
tn              C13  fn             65536
sfrq        100.554          DISPLAY
tof          1536.3  sp            -353.9
tpwr             61  wp           21063.9
pw            9.300  rfl           9274.4
    DECOUPLER        rfp           7764.9
dn               H1  rp             -26.3
dof               0  lp            -388.2
dm              yyy            PLOT
dmm               w  wc               250
dpwr             42  sc                 0
dmf            8900  vs                52
                     th                 4
                     nm  no  ph
```



4-(4-Bromophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]-non-6-ene (27c):



^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_167_M

exp1  s2pul

       SAMPLE               SPECIAL
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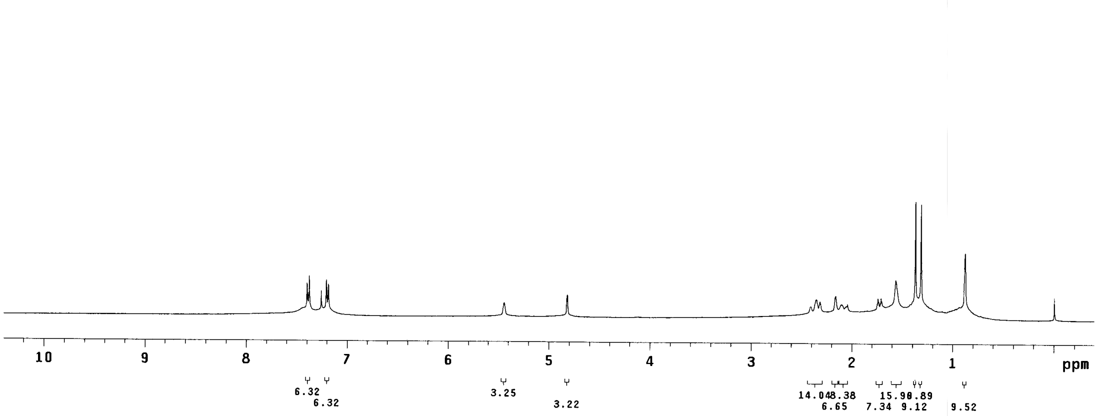
solvent       CDCl3   gain       not used
file            exp   spin       not used
   ACQUISITION        hst           0.008
sw           6389.8   pw90         19.700
at            1.998   alfa         20.000
np            25528          FLAGS
fb         not used   il                n
bs                8   in                n
d1            1.000   dp                y
nt              200   hs               nn
ct              120        PROCESSING
   TRANSMITTER        lb             0.10
tn               H1   fn            65536
sfrq        399.853          DISPLAY
tof           362.8   sp           -157.7
tpwr             57   wp           4315.7
pw            9.850   rfl           795.8
    DECOUPLER         rfp               0
dn              C13   rp            129.7
dof               0   lp            -89.9
dm              nnn           PLOT
dmm               c   wc              250
dpwr             50   sc                0
dmf           15900   vs               26
                      th               20
                      nm  cdc  ph
```



^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_167_M

exp1  s2pul

       SAMPLE               SPECIAL
date    Mar  4 2011   temp       not used
solvent       CDCl3   gain       not used
file            exp   spin       not used
   ACQUISITION        hst           0.008
sw          25125.6   pw90         18.600
at            1.199   alfa         20.000
np            60270          FLAGS
fb            13800   il                n
bs               16   in                n
d1            1.000   dp                y
nt             8000   hs               nn
ct             4272        PROCESSING
   TRANSMITTER        lb             2.00
tn              C13   fn            65536
sfrq        100.554          DISPLAY
tof          1536.3   sp           -453.6
tpwr             61   wp          21229.5
pw            9.300   rfl          9274.4
    DECOUPLER         rfp          7764.9
dn               H1   rp            -34.3
dof               0   lp           -372.2
dm              yyy           PLOT
dmm               w   wc              250
dpwr             42   sc                0
dmf            8900   vs               21
                      th                3
                      nm  no  ph
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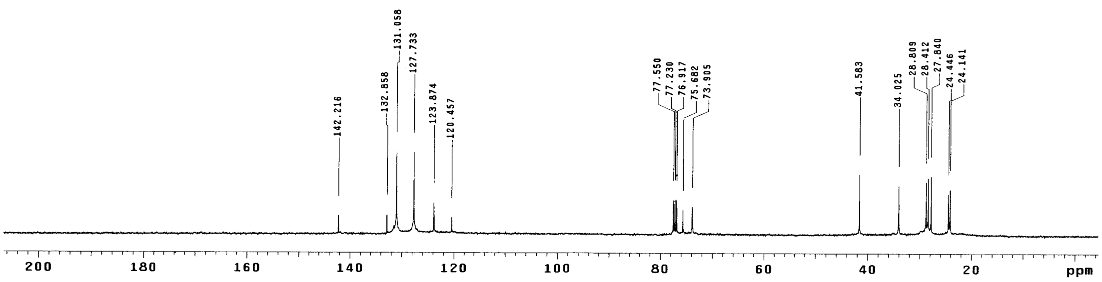

4-(2-Nitrophenyl)-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27f):

^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_175_M

exp3  s2pul

       SAMPLE                SPECIAL
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solvent       CDC13  gain       not used
file /export/home/~  spin       not used
asaikia/PS_175_M.f~  hst           0.008
                 id  pw90         19.700
   ACQUISITION       alfa         20.000
sw           6389.8         FLAGS
at            1.998  il                n
np            25528  in                n
fb         not used  dp                y
bs                4  hs               nn
d1            1.000        PROCESSING
nt               32  lb             0.10
ct               32  fn            65536
   TRANSMITTER              DISPLAY
tn               H1  sp           -122.3
sfrq        399.853  wp           4206.4
tof           362.8  rfl           794.0
tpwr             57  rfp               0
pw            9.850  rp            120.7
    DECOUPLER        lp            -93.7
dn              C13          PLOT
dof               0  wc              250
dm              nnn  sc                0
dmm               c  vs               60
dpwr             50  th               58
dmf           15900  nm   cdc   ph
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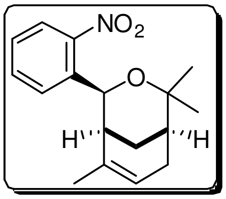

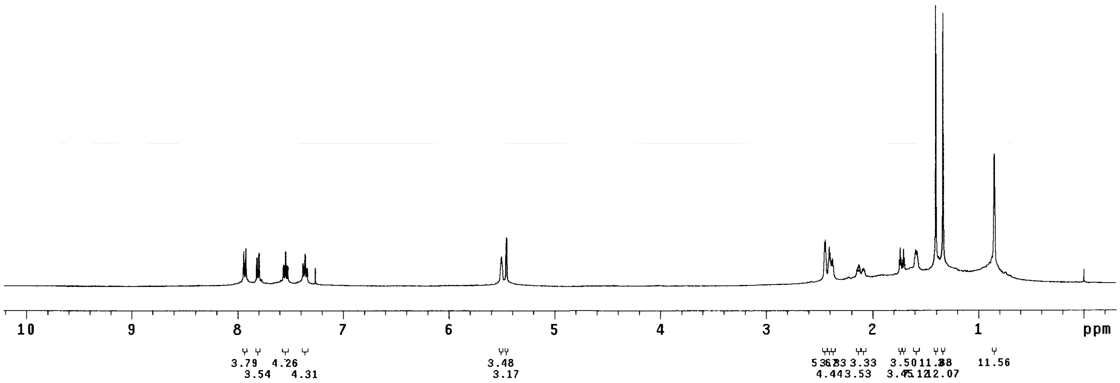

^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_175_M

exp3  s2pul

       SAMPLE                SPECIAL
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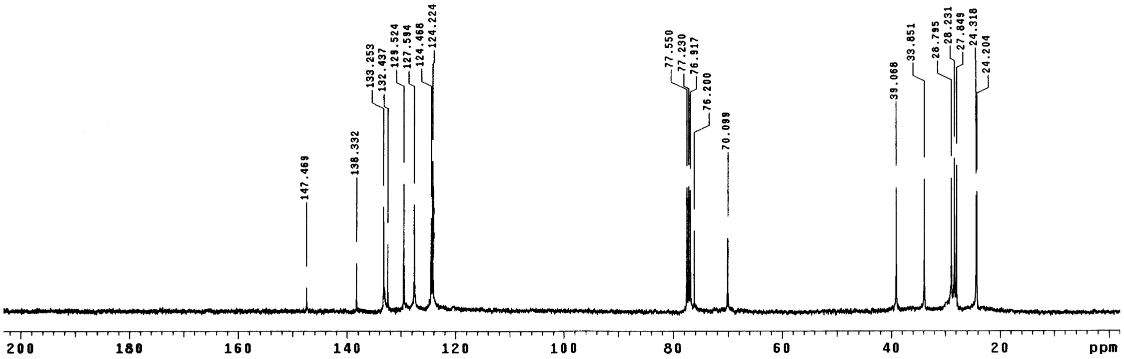
solvent       CDC13  gain       not used
file /export/home/~  spin       not used
asaikia/PS_175M_C1~  hst           0.008
              3.fid  pw90         18.600
   ACQUISITION       alfa         20.000
sw          25125.6         FLAGS
at            1.199  il                n
np            60270  in                n
fb            13800  dp                y
bs               16  hs               nn
d1            1.000        PROCESSING
nt             3000  lb             2.00
ct             3000  fn            65536
   TRANSMITTER              DISPLAY
tn              C13  sp           -256.3
sfrq        100.554  wp          20733.6
tof          1536.3  rfl          9276.4
tpwr             61  rfp          7764.9
pw            9.300  rp            -27.7
    DECOUPLER        lp           -395.5
dn               H1          PLOT
dof               0  wc              250
dm              yyy  sc                0
dmm               w  vs               35
dpwr             42  th                5
dmf            8900  nm   no   ph
```



4-Propyl-2,2,6-trimethyl-3-oxabicyclo[3.3.1]non-6-ene (27o):

^{1}H NMR (400 MHz, CDCl$_3$)

```
PS_212_M

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at           1.998  alfa         20.000
np           25528        FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32      PROCESSING
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dof              0  lp            -61.5
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dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               86
                    th               20
                    nm  cdc  ph
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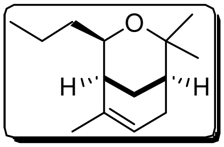

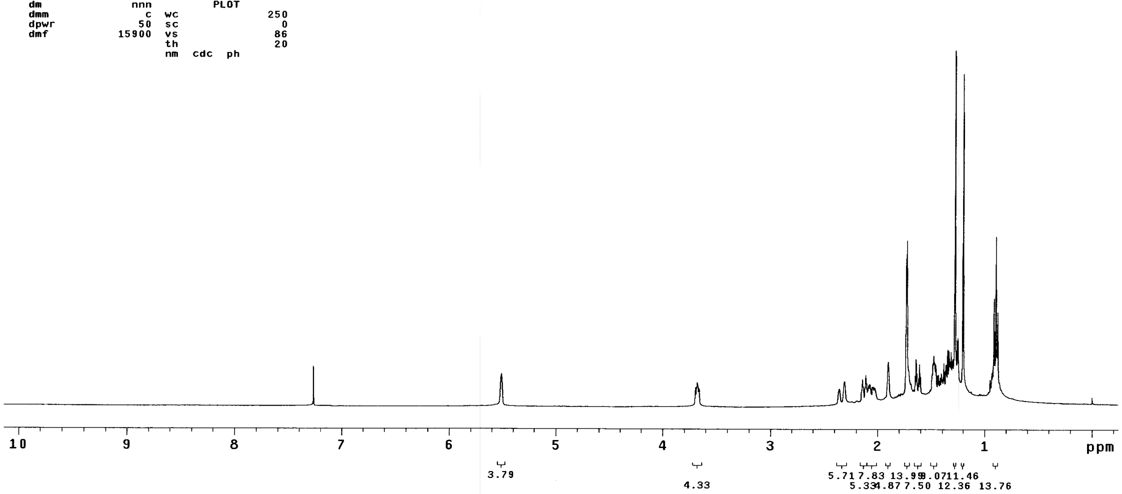

^{13}C NMR (100 MHz, CDCl$_3$)

```
PS_212_M

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tpwr            61  wp          20898.4
pw           9.300  rfl          9271.1
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dn              H1  rp            -35.7
dof              0  lp           -354.5
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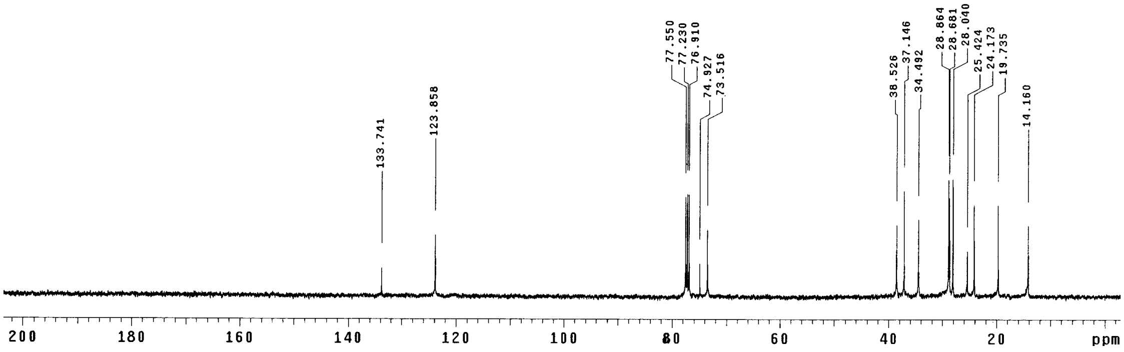
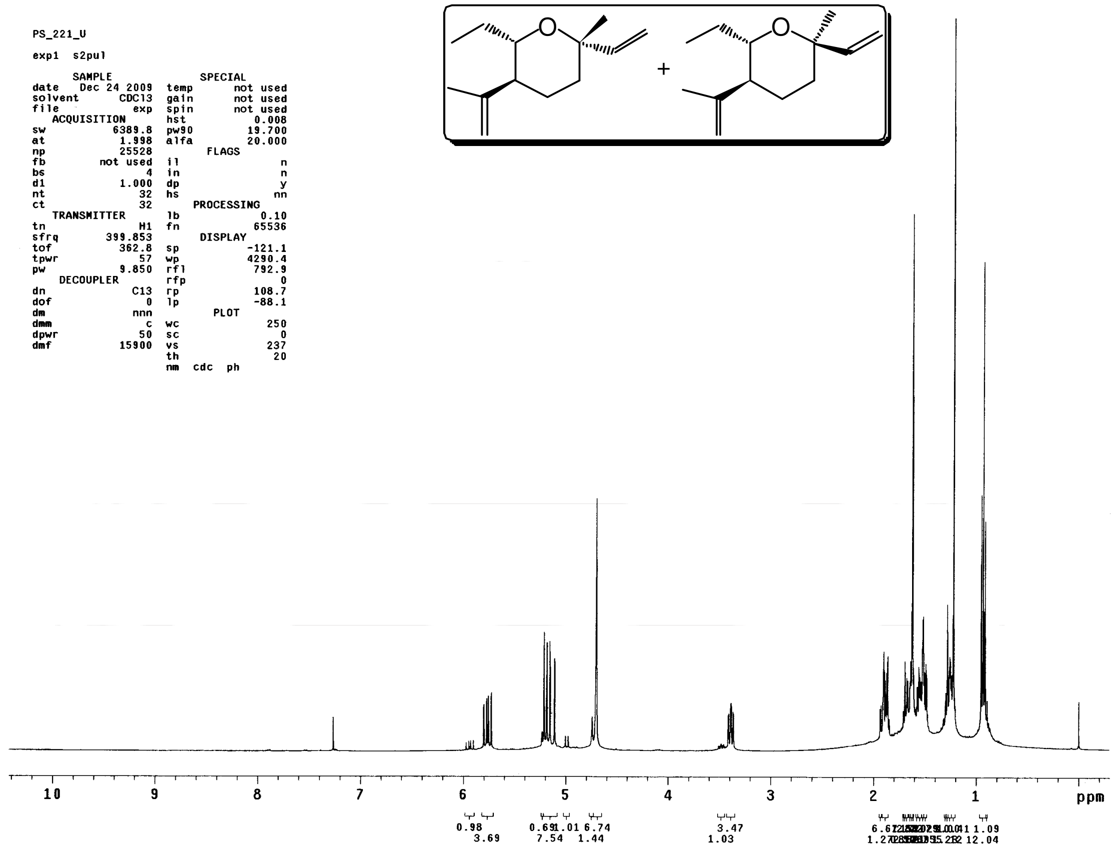
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               24
                    th                5
                    nm  no  ph
```



6-Ethyl-5-isopropenyl-2-methyl-2-vinyltetrahydropyran (28n/29n) (3:1):

^{1}H NMR (400 MHz, CDCl$_3$)



```
PS_221_U

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np            25528          FLAGS
fb         not used   il                n
bs                4   in                n
d1            1.000   dp                y
nt               32   hs               nn
ct               32       PROCESSING
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tn               H1   fn            65536
sfrq        399.853         DISPLAY
tof           362.8   sp           -121.1
tpwr             57   wp           4290.4
pw            9.850   rfl           792.9
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dn              C13   rp            108.7
dof               0   lp            -88.1
dm              nnn          PLOT
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dpwr             50   sc                0
dmf           15900   vs              237
                      th               20
                      nm   cdc   ph
```

^{13}C NMR (100 MHz, CDCl$_3$)

```
PS_221_U

exp1  s2pul

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asaikia/PS_221U_C1~  hst           0.008
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np            60270   in                n
fb            13800   dp                y
bs               16   hs               nn
d1            1.000       PROCESSING
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dpwr             42   th                4
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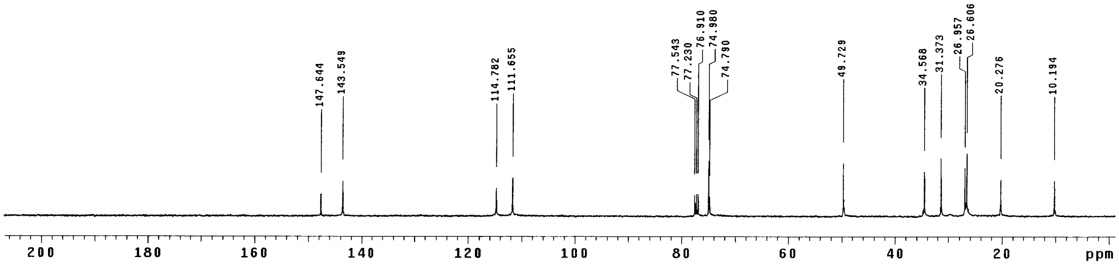
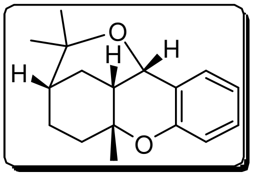


Tetracyclic compound (39):

^{1}H NMR (400 MHz, CDCl$_3$)



```
PS_168_L

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np            25528        FLAGS
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d1            1.000  dp                y
nt              200  hs               nn
ct              200      PROCESSING
   TRANSMITTER       lb             0.10
tn               H1  fn            65536
sfrq        399.853        DISPLAY
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tpwr             57  wp           4374.6
pw            9.850  rfl           797.6
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dof               0  lp            -68.8
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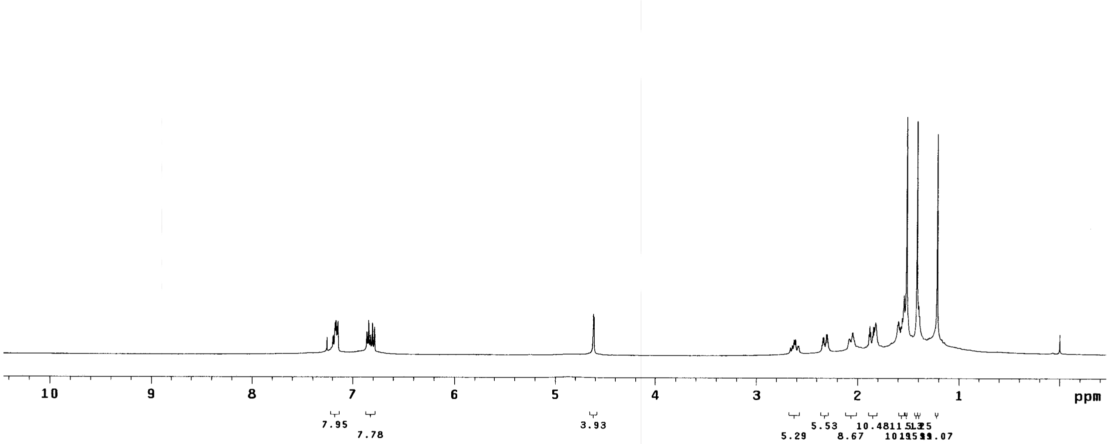
dmm               c  wc              250
dpwr             50  sc                0
dmf           15900  vs               56
                     th               20
                     nm  cdc  ph
```



^{13}C NMR (100 MHz, CDCl$_3$)

```
/S_168_L

exp1  s2pul

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asaikia/PS_168L_C1~  hst           0.008
              3.fid  pw90         18.600
   ACQUISITION       alfa         20.000
sw          25125.6        FLAGS
at            1.199  il                n
np            60270  in                n
fb            13800  dp                y
bs               16  hs               nn
d1            1.000      PROCESSING
nt             3000  lb             2.00
ct             1840  fn            65536
   TRANSMITTER             DISPLAY
tn              C13  sp           -223.3
sfrq        100.554  wp          20898.4
tof          1536.3  rfl          9276.4
tpwr             61  rfp          7764.9
pw            9.300  rp            -62.0
    DECOUPLER        lp           -293.6
dn               H1          PLOT
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dmm               w  vs               26
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dmf            8900  nm  no  ph
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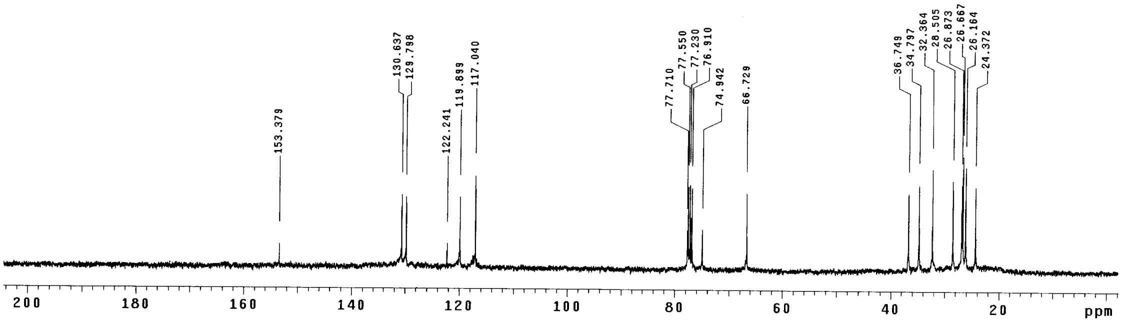


CHAPTER 4

Stereoselective Synthesis of 6-Oxabicyclo[3.2.1]octene via (3,5)-Oxonium-Ene Reaction

4.1 Importance and Applications

Oxabicyclo[3.2.1]octanes/octenes are important intermediates in organic synthesis for numerous organic transformations.[1] Two different types of oxabicyclo[3.2.1]octane/octene are well known, one is 6-oxabicyclo[3.2.1]octane/octene (Figure 4.1.1, **A**) and another one is 8-oxabicyclo[3.2.1]octane/octene (Figure 4.1.1, **B**). The 6-oxabicyclo[3.2.1]octane moiety is presenet in natural products like jiadifenin, jiadifenolide (Figure 4.1.2, **C**-**D**) which are potent promoter of neurite outgrowth.[2] On the other hand 8-oxabicyclo[3.2.1]octane moiety is present in aryloxatropanes (Figure 4.1.2, **E**-**F**) which are particularly potent inhibitors of the dopamine transporter[3]. Recently several 8-oxabicyclo[3.2.1]octanes have been found to possess moderate anti-HIV activity.[4]

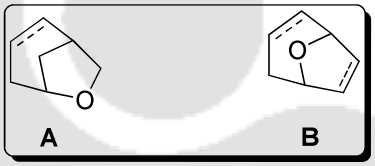


Figure 4.1.1. Different types of oxabicyclo[3.2.1]octane/octene

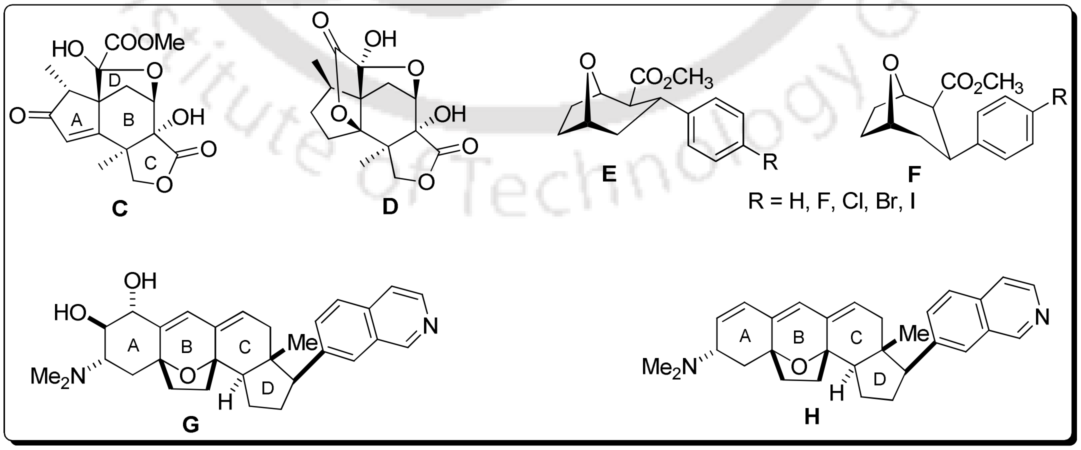


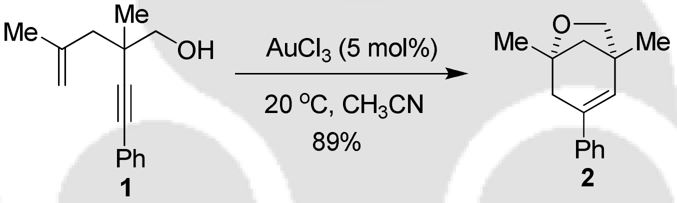
Figure 4.1.2. Some biologically important molecules containing oxabicyclo[3.2.1]octane/octene as core unit

8-Oxabicyclo[3.2.1]octene system is present in steroidal alkaloids cortistatin A and J (Figure 4.1.2, **G**-**H**) which are the most potent congener, exhibited strong inhibition against the proliferation of human umbilical vein endothelial cells (HUVECs: IC_{50} = 1.8 nM) with extreme selectivity among cell lines.[5]

4.2 An Overview of Relevant Synthetic Methods

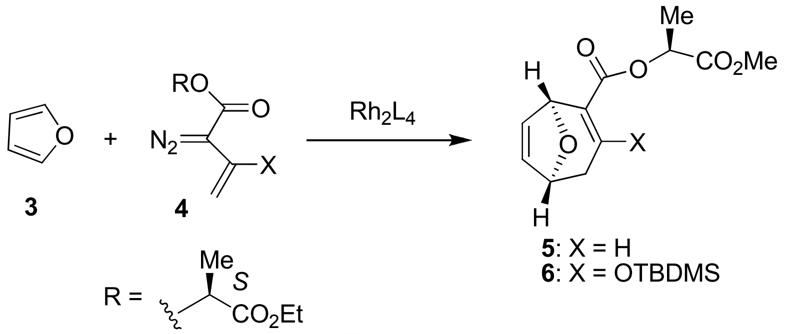
Review of literature reveals that several strategies are developed for the synthesis of 8-oxabicyclo[3.2.1]octane/octene. However only one methodology for the synthesis of 6-oxabicyclo[3.2.1]octene has been reported in the literature.

Kozmin and co-workers have reported a gold-catalyzed cycloisomerization of 1,5-enynes **1** for the synthesis of 6-oxabicyclo[3.2.1]octene.[6] Treatment of enyne **1** with either a Au(I) or Au(III) catalytic promoter afforded 6-oxabicyclo[3.2.1]octene **2** (Scheme 4.2.1). The optimized protocol entailed a brief exposure of alcohol **1** to a catalytic amount of $AuCl_3$ in CH_3CN, which furnished alkene **2** in 89% yield.



Scheme 4.2.1.

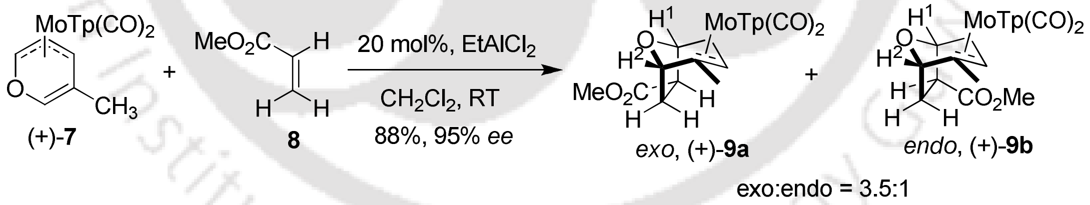
Davies *et al.* have reported a practical asymmetric synthesis of 8-oxabicyclo[3.2.1]octadienes by using the chemistry of rhodium-stabilized vinylcarbenoids. Treatment of vinylcarbenoids **4** having α-hydroxy ester auxiliaries with furan **3** in the presence of rhodium catalysts resulted in the formation of 8-oxabicyclo[3.2.1]octadienes **5** and **6** (Scheme 4.2.2).[1c]



Rh$_2$L$_4$	**5**, de, %	**6**, de, %
Rh$_2$(OOct)$_4$	57	79
Rh$_2$(*S*-TBSP)$_4$	68	80
Rh$_2$(*R*-TBSP)$_4$	0	53

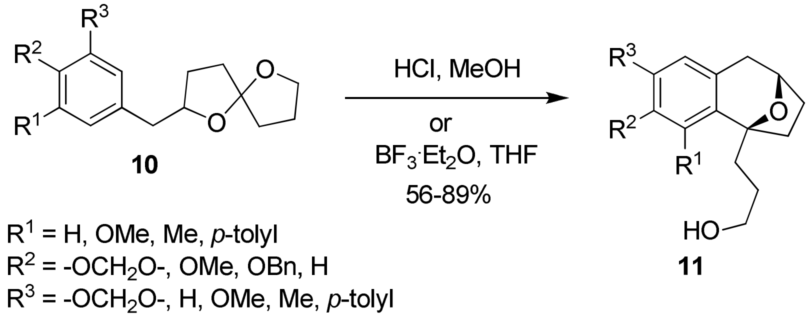
Scheme 4.2.2.

Liebeskind and co-workers have reported an enantiocontrolled [5+2] cycloaddition reaction for the synthesis of 8-oxabicyclo[3.2.1]octene with high enantiopurity. The reaction of η^3-3-methylpyranylmolybdenum complex (+)-**7** with electron deficient alkene **8** in the presence of catalytic amount of EtAlCl$_2$ in CH$_2$Cl$_2$ produce 8-oxabicyclo[3.2.1]octenes **9** in good yields with high enantioselectivity (Scheme 4.2.3).[7]



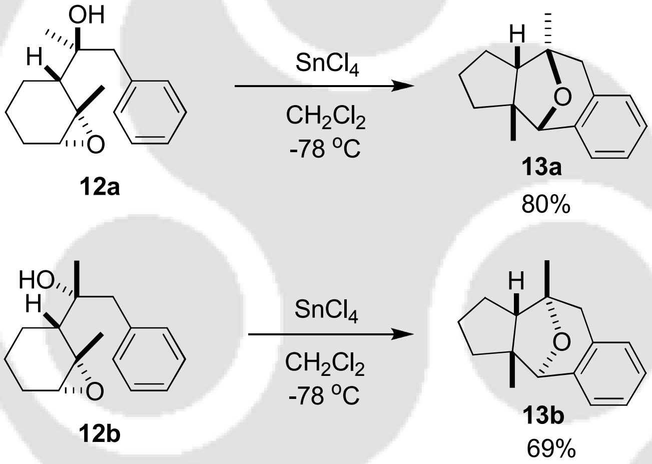
Scheme 4.2.3.

Fan *et al.* have reported an acid catalyzed intramolecular Friedel-Crafts alkylation (cyclization) using a spiroketal as electrophile leading to benzene-fused 8-oxabicyclo[3.2.1]octane ring system. Treatment of spiroketal **10** with either HCl in MeOH or BF$_3$·Et$_2$O in THF produces benzene-fused 8-oxabicyclo[3.2.1]octane **11** in good yields (Scheme 4.2.4).[8]



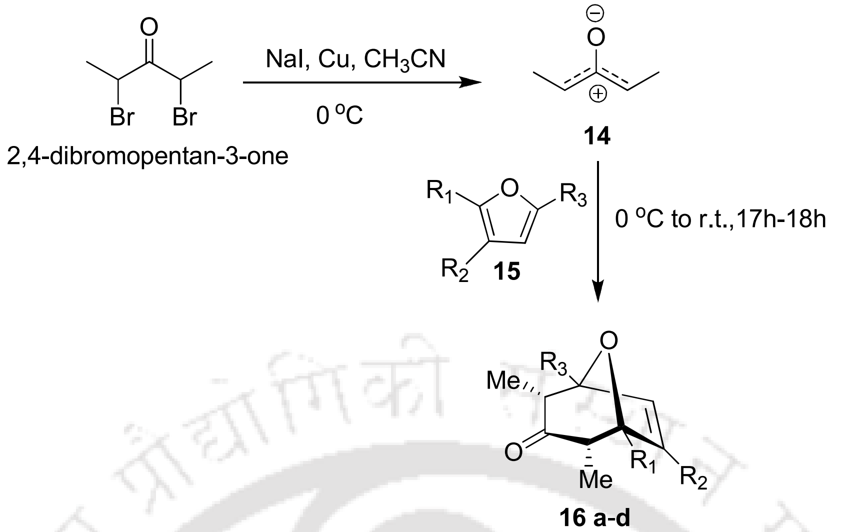
Scheme 4.2.4.

Marson *et al.* have reported a [3+4] cycloaddition reaction for the synthesis of fused 8-oxabicyclo[3.2.1]octane systems **13a** and **13b** starting from 3,4-epoxy alcohols **12a** and **12b** (Scheme 4.2.5).[9] This reaction sequence has led to the development of lactol cyclizations and hence a general route to bridged bicyclo ethers.



Scheme 4.2.5.

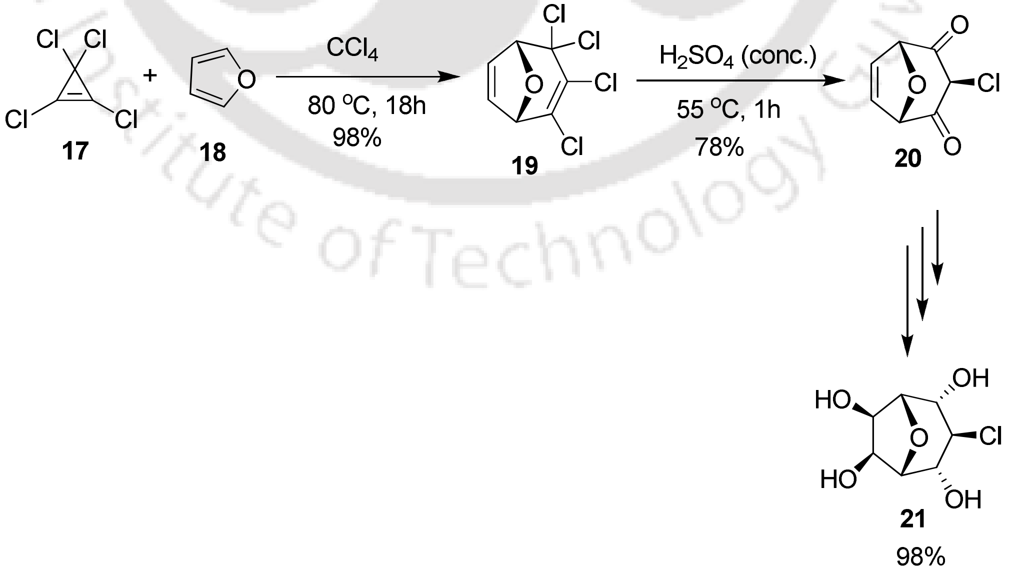
Barbosa *et al.* have reported a [4+3] cycloaddition reaction between oxyallyl carbocation **14** generated from 2,4-dibromopentan-3-one, and dienes **15** for the synthesis of 8-oxabicyclo[3.2.1]octene derivatives **16a-d** (Scheme 4.2.6).[10] The important thing is that most of the oxabicyclic compounds are biologically active.[11]



16a, R_1 = Me, R_2 = $COOCH_3$, R_3 = H (51%)
16b, R_1 = Me, R_2 = CH_2OH, R_3 = H (64%)
16c, R_1 = R_2 = R_3 = H (45%)
16d, R_1 = Me, R_2 = H, R_3 = Me (46%)

Scheme 4.2.6.

Recently Khlevin *et al.* have reported a methodology for the synthesis of polyhydroxylated 8-oxabicyclo[3.2.1]octane **21** with good yield and high stereoselectivity. They have prepared this bicyclic compound from a 1,3-dione **20** and several steps are involved in this conversion. However the initial 1,3-dione **20** have been prepared by using a [4+3] cyclocondensation between tetrachlorocyclopropene **17** and furan **18** to produce **19**. Direct



Scheme 4.2.7.

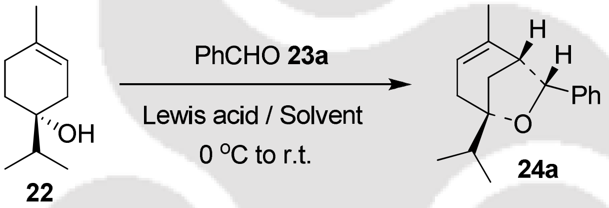
hydrolysis of **19** under strongly acidic conditions and elevated temperatures delivers the 1,3-dione **20** (Scheme 4.2.7).[4]

4.3 Present Work

In the previous chapter we have described an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans. In this chapter we report a stereoselective method for the synthesis of 6-oxabicyclo[3.2.1]octene via (3,5)-oxonium-ene reaction from the reaction of (-)-terpinen-4-ol with aldehyde or epoxide catalyzed by indium triflate, $In(OTf)_3$.

Initially (-)-terpinen-4-ol (1 equiv.), **22** was reacted with benzaldehyde (1 equiv), **23a** in dry toluene under boron trifluoride etherate (1 equiv.) at 0 °C and the desired cyclization product **24a** was obtained in 32% yield along with some decomposed products. Further

Table 4.3.1. Reaction with different Lewis acids and solvents



Entry	Lewis acid (equiv.)	Time/h	Solvent	Yield[a] (%)
1	$BF_3 \cdot OEt_2$ (1)	0.5	CH_2Cl_2	32
2	$Sc(OTf)_3$ (0.1)	24	CH_2Cl_2	0
3	$In(OTf)_3$ (0.1)	24	Toluene	45
4	$In(OTf)_3$ (0.1)	6	CH_2Cl_2	75
5	$In(OTf)_3$ (0.1)	24	CH_3CN	0
6	$In(OTf)_3$ (0.05)	24	CH_2Cl_2	40
7	$Bi(OTf)_3$ (0.1)	24	CH_2Cl_2	52
8	$Bi(OTf)_3$ (0.1)	24	Toluene	38
9	$InCl_3$ (0.1)	24	CH_2Cl_2	0
10	$InCl_3$ (0.2)	24	CH_2Cl_2	0

[a]Yields refer to isolated yield. The compound is characterized by IR, ^1H , ^{13}C NMR and Mass spectroscopy.

lowering the temperature to -30 °C resulted in the same yield. The reaction was also performed in the presence of other Lewis acids and the results are summarised in Table 4.3.1. These results showed that indium triflate ($In(OTf)_3$) was the efficient Lewis acid, which acted as a catalyst for this transformation. No reaction was observed when scandium triflate or indium trichloride was used. The reaction was also studied in different solvents. Among the solvents studied, dichloromethane was found to be the best solvent, whereas acetonitrile was found to be ineffective. Therefore, $In(OTf)_3$ in dry CH_2Cl_2 was considered as the best combination for this reaction and the scope of the reaction was investigated using various aldehydes (Table 4.3.2). In all of the cases studied, 6-oxabicyclo[3.2.1]octenes **24a-n** could be obtained in high purity without any side products as determined from ^{1}H to ^{13}C NMR spectrum of the crude product. Both aliphatic and aromatic aldehydes gave the corresponding products in good yields. The substituents on the aromatic ring have a promising effect on this reaction. The aromatic aldehydes having electron-donating groups on the aromatic ring gave higher yields compared to the electron-withdrawing groups on the ring. On the other hand, aliphatic aldehydes are better substrates than the aromatic aldehydes. This might be due to the better stability imparted to the oxocarbenium ion **26** (Scheme 4.3.1) by the aliphatic, and aromatic aldehydes having electron-donating groups on the aromatic ring, which in turn is attacked by the double bond efficiently. On the other hand, aromatic aldehydes having electron-withdrawing groups on the ring destabilize the oxocarbenium ion **26**. The reaction is stereoselective, and in all the cases the fusion between two rings is *cis*-fusion. The structure and stereochemistry of the compound was determined by NOE experiment and X-ray crystallographic analysis (Figure 4.3.1).[12] There is a strong NOE between H_1 (δ 2.29 ppm) and H_7 (δ 3.97 ppm) protons of **24j**, which confirms that they are *cis* to each other (**24j**, Figure 4.3.2). This structure is further confirmed by the fact that the olefinic methyl protons at C-2 position are resonating

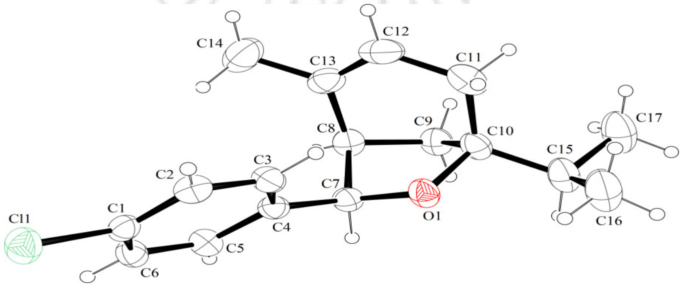
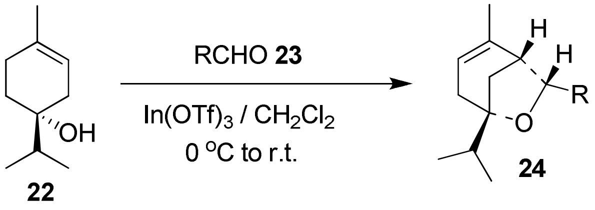
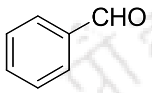
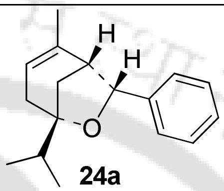
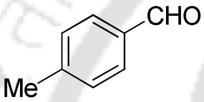
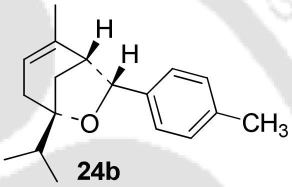
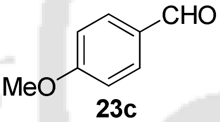
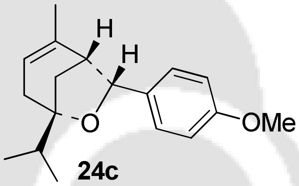
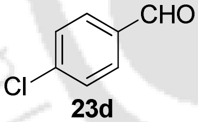
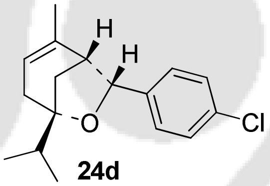
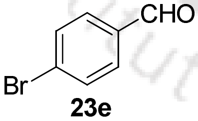
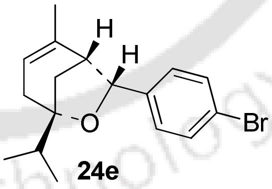
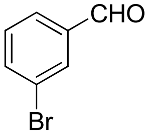
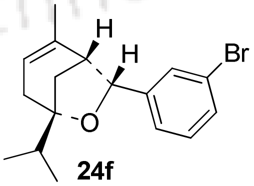


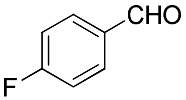
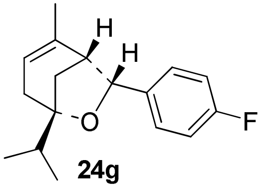
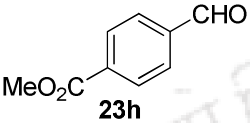
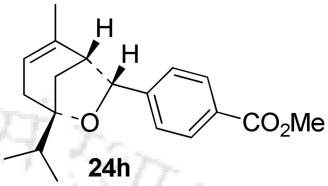
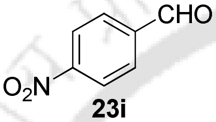
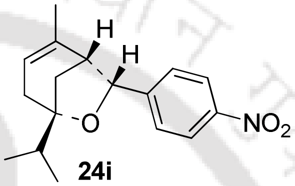
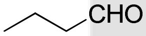
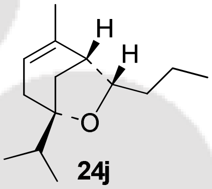
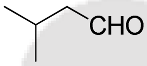
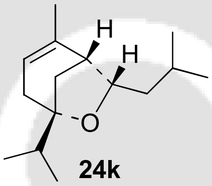
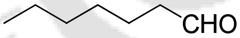
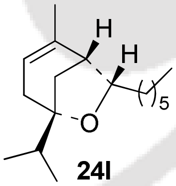
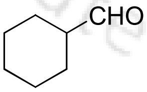
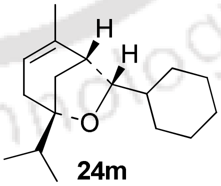
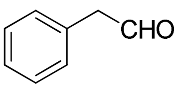
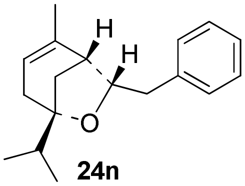
Figure 4.3.1. ORTEP diagram of (1*R*,5*R*,7*R*)-7-(4-chlorophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (**24d**).

Table 4.3.2. Synthesis of 6-oxabicyclo[3.2.1]octene



Entry	RCHO **23**	Time (h)	Product **24**	Yield[a] (%)
1	 **23a**	6	 **24a**	75
2	 **23b**	5	 **24b**	82
3	 **23c**	6	 **24c**	80
4	 **23d**	7	 **24d**	68
5	 **23e**	**7**	 **24e**	65
6	 **23f**	8	 **24f**	64

continue…

Entry	RCHO **23**	Time (h)	Product **24**	Yield[a] (%)
7	 **23g**	6	 **24g**	66
8	 **23h**	7	 **24h**	60
9	 **23i**	7	 **24i**	62
10	 **23j**	5	 **24j**	92
11	 **23k**	4	 **24k**	88
12	 **23l**	5	 **24l**	85
13	 **23m**	7	 **24m**	84
14	 **23n**	7	 **24n**	82

[a] Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR and Mass spectroscopy.

at higher field in the case of *endo* aromatic substituents at C-7 position than the corresponding aliphatic substituents. This indicates that the methyl protons are in the shielding region of the aromatic ring.

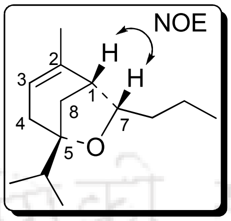
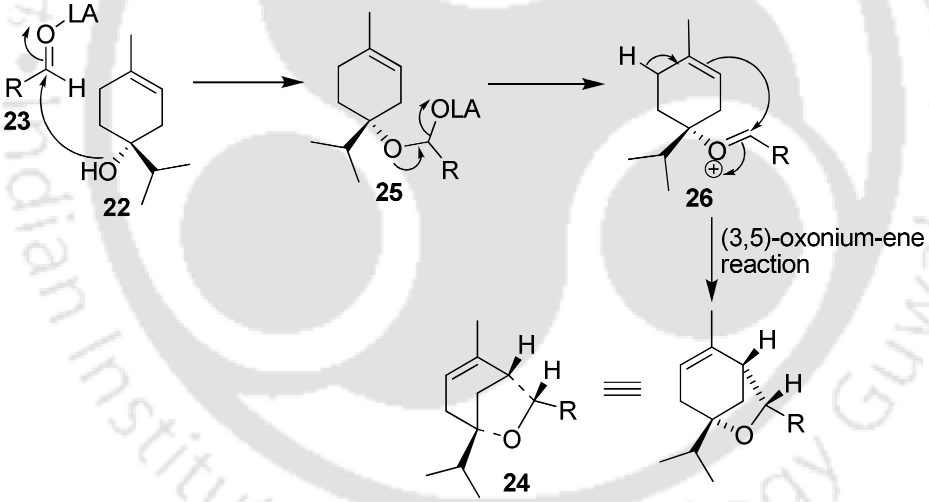


Figure 4.3.2. NOE diagram of compound **24j**

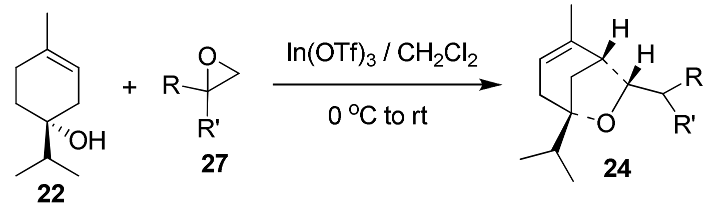
The mechanism of the reaction can be explained as follows. Lewis acid activates the aldehyde **23** for the nucleophilic attack by alcohol **22** to give acetal **25**, which after decomposition forms oxocarbenium ion **26**. The oxocarbenium ion **26** undergoes (3,5)-oxonium-ene cyclization reaction to give final product **24** (Scheme 4.3.1).

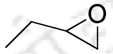
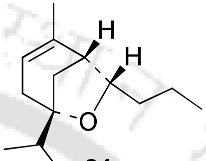
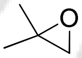
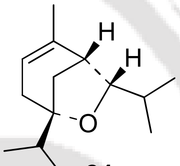
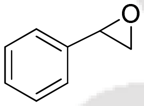
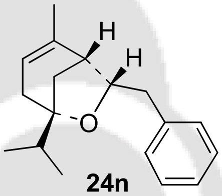
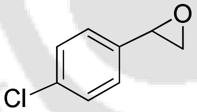
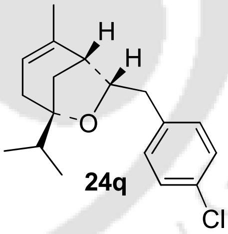
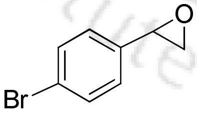
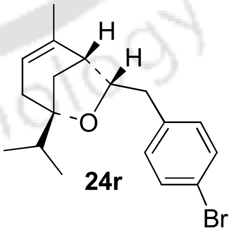
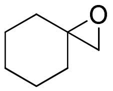
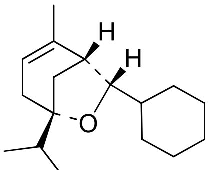


Scheme 4.3.1. Mechanism of the reaction

The reaction can also be extended to epoxides (Table 4.3.3). The epoxides under Lewis acid conditions rearrange to aldehyde equivalent.[13] The results in Table 4.3.3 showed that monosubstituted terminal epoxides (entry 1) are unreactive, whereas the 2,2-disubstituted and styrene oxides give the corresponding products in good to moderate yields. This is attributed to the lower stability of the carbocation **28**, formed from monosubstituted epoxides, compared to 2,2-disubstituted epoxides and styrene oxides, where carbocation **28** is better stabilized due to the tertiary and benzylic centres, respectively.

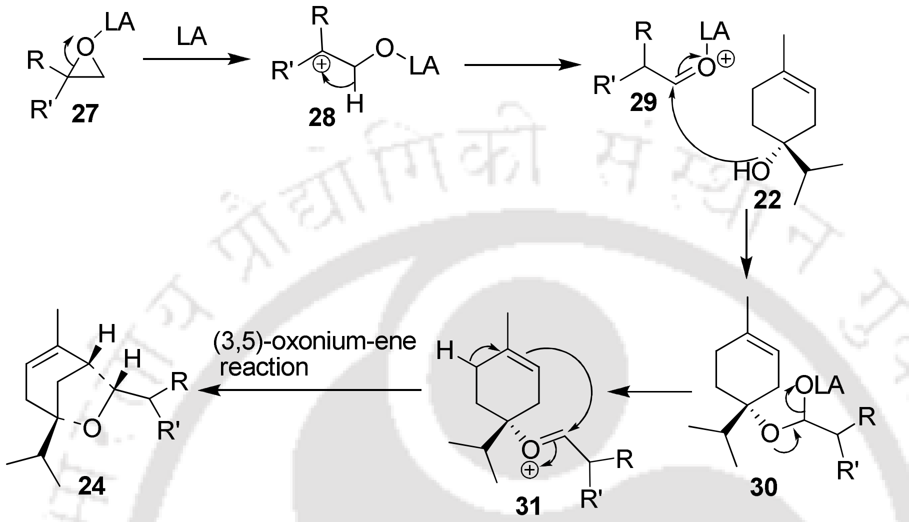
Table 4.3.3. Synthesis of 6-oxabicyclo[3.2.1]octene from epoxide



Entry	Epoxide **27**	Time/h	Product **24**	Yield[a] (%)
1		24	 **24o**	0
2		6	 **24p**	68
3		7	 **24n**	62
4		8	 **24q**	55
5		8	 **24r**	58
6		7	 **24m**	60

[a]Yields refer to isolated yield. The compounds are characterized by IR, 1H, ^{13}C NMR and Mass spectroscopy.

The mechanism of the reaction with epoxides is shown in Scheme 4.3.2. The epoxide **27** in the presence of Lewis acid rearranges to aldehyde equivalent **29**, which after nucleophilic attack by alcohol **22** gives acetal **30**. The acetal **30** decomposes to give oxocarbenium ion **31**, which after (3,5)-oxonium-ene cyclization reaction gives final product **24**.



Scheme 4.3.2. Mechanism of the reaction with epoxide

Conclusions:

In summary, we have developed an efficient methodology for the synthesis of 6-oxabicyclo[3.2.1]octene catalyzed by indium triflate in good to high yields. To the best of our knowledge, this is the first report for the synthesis of 6-oxabicyclo[3.2.1]octene starting from a readily available naturally occurring terpenoid.

4.4 Experimental Section

4.4.1 Instrumentation and Characterization

As described in Chapter 2, Section 2.4.1.

4.4.2 General Procedure for the Synthesis of Oxabicyclic Compounds from Aldehydes: To a suspension of In(OTf)$_3$ (0.1 mmol, 0.1 equiv.) in dry CH$_2$Cl$_2$ (2 ml) at 0 °C was added aldehyde (1 mmol, 1 equiv.). To this solution (-)-terpinen-4-ol (1 mmol, 1 equiv.) in dry CH$_2$Cl$_2$ (2 ml) was added drop by drop over 5 min. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of (1*R*,5*R*,7*R*)-5-Isopropyl-2-methyl-7-phenyl-6-oxabicyclo[3.2.1]oct-2-ene (24a, Table 4.3.2): To a suspension of $In(OTf)_3$ (56 mg, 0.1 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C was added benzaldehyde (106 mg, 1 mmol). To this solution (-)-terpinen-4-ol (154 mg, 1 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise over 5 min. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and then washed with brine and water. 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 (100% Hexane) to give **24a** (182 mg, 75%) as a colourless oil.

4.4.3 General Procedure for the Synthesis of Oxabicyclic Compounds from Epoxides: To a suspension of $In(OTf)_3$ (0.1 mmol, 0.1 equiv.) in dry CH_2Cl_2 (2 ml) at 0 °C was added epoxide (1.5 mmol, 1.5 equiv.). To this solution (-)-terpinen-4-ol (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 ml) was added drop by drop over 5 min. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for a specified time. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and then washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of (1*R*,5*R*,7*S*)-5,7-Diisopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24p, Table 4.3.3): To a suspension of $In(OTf)_3$ (56 mg, 0.1 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C was added 1,2-epoxy-2-methyl propane (108 mg, 1.5 mmol). To this solution (-)-terpinen-4-ol (154 mg, 1 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise over 5 min. The temperature was slowly brought to room temperature. The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC with hexane as eluent. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 and then washed with brine and water. 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 (100% Hexane) to give **24p** (142 mg, 68%) as a colourless oil.

4.5 References and Notes

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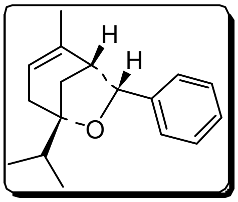
12. The crystallographic data for compound **24d** has been deposited with the Cambridge Crystallographic Data Centre and it has CCDC number 840604.
13. (a) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212-8216; (b) Li, J.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 793-796.

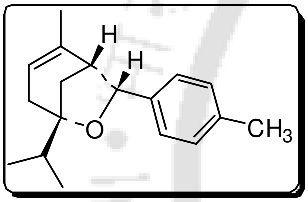
4.6 Spectral Data

(1*R*,5*R*,7*R*)-5-Isopropyl-2-methyl-7-phenyl-6-oxabicyclo[3.2.1]oct-2-ene (24a):



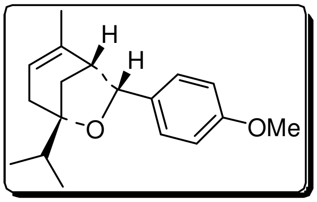
Colourless oil (182 mg, 75%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.00 (d, *J* = 6.8 Hz, 3 H), 1.01 (s, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 1.83-1.88 (m, 1 H), 1.95 (septet, *J* = 6.8 Hz, 1 H), 2.07 (dd, *J* = 10.4 and 4.0 Hz, 1 H), 2.13-2.21 (m, 1 H), 2.32-2.40 (m, 1 H), 2.55 (t, *J* = 3.6 Hz, 1 H), 5.22 (d, *J* = 3.2 Hz, 1 H), 5.27 (brs, 1 H), 7.17-7.21 (m, 1 H), 7.23-7.28 (m, 3 H), 7.29-7.33 (m, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 17.8, 18.0, 23.1, 36.0, 36.7, 38.5, 48.4, 85.8, 87.4, 120.0, 126.1, 126.9, 127.7, 136.6, 140.5; **IR** (Neat) 2962, 2934, 1602, 1449, 1380, 1286, 1053, 1017, 751, 702 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O$ $(M+H)^+$ requires 243.1749; found 243.1747. Specific rotation $[\alpha]^{25}_{D}$ +130 (*c* 1.07, $CHCl_3$).

(1*R*,5*R*,7*R*)-5-Isopropyl-2-methyl-7-*p*-tolyl-6-oxabicyclo[3.2.1]oct-2-ene (24b):



Colourless solid; M.P.: 58-60 °C (210 mg, 82%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.99 (d, *J* = 7.2 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.02 (s, 3 H), 1.81-1.86 (m, 1 H), 1.94 (septet, *J* = 7.2 Hz, 1 H), 2.05 (dd, *J* = 10.4 and 3.6 Hz, 1 H), 2.12-2.18 (m, 1 H), 2.30 (s, 3 H), 2.32-2.41 (m, 1 H), 2.51 (t, *J* = 3.6 Hz, 1 H), 5.17 (d, *J* = 3.2 Hz, 1 H), 5.25 (brs, 1 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 7.17 (d, *J* = 7.6 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 17.8, 18.0, 21.3, 23.3, 36.0, 36.8, 38.4, 48.4, 85.7, 87.4, 119.9, 126.1, 128.4, 136.3, 136.7, 137.5; **IR** (KBr) 2960, 2928, 1639, 1447, 1380, 1055, 1020, 800, 779 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O$ (M^+) requires 256.1827; found 256.1822. Specific rotation $[\alpha]^{25}_{D}$ +133 (*c* 0.24, $CHCl_3$).

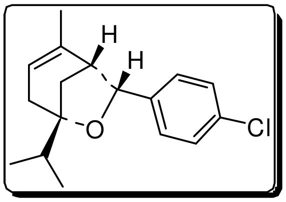
(1*R*,5*R*,7*R*)-5-Isopropyl-7-(4-methoxyphenyl)-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24c):



Colourless oil (218 mg, 80%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.99 (d, *J* = 7.2 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.04 (t, *J* = 1.2 Hz, 3 H), 1.81-1.86 (m, 1 H), 1.93 (septet, *J* = 6.8 Hz, 1 H), 2.04 (dd, *J* = 10.4 and 3.6 Hz, 1 H), 2.12-2.19 (m, 1 H), 2.32-2.39 (m, 1 H), 2.48 (t, *J* = 4.0 Hz, 1 H), 3.78 (s, 3 H), 5.16 (d, *J* = 3.2 Hz, 1 H), 5.27 (brs, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 17.8, 18.0, 23.2, 36.0, 36.8, 38.4, 48.4, 55.4, 85.7, 87.1, 113.2, 119.9, 127.2, 132.6, 136.8, 158.7; **IR** (Neat) 2960, 2928, 1613, 1511, 1463, 1363, 1246, 1055, 1037, 845, 803 cm^{-1}.

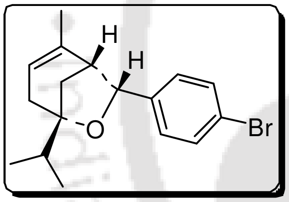
HRMS (APCI) cald. for $C_{18}H_{24}O_2$ $(M+H)^+$ requires 273.1854; found 273.1841. Specific rotation $[\alpha]^{25}_{D}$ +100 (*c* 0.32, $CHCl_3$).

(1*R*,5*R*,7*R*)-7-(4-Chlorophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24d):



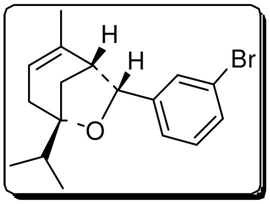
Colourless solid; M.P.: 78-80 °C (188 mg, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 7.2 Hz, 3 H), 1.03 (s, 3 H), 1.84-1.89 (m, 1 H), 1.93 (septet, *J* = 6.8 Hz, 1 H), 2.06 (dd, *J* = 10.4 and 3.6 Hz, 1 H), 2.11-2.18 (m, 1 H), 2.31-2.39 (m, 1 H), 2.52 (t, *J* = 3.6 Hz, 1 H), 5.17 (d, *J* = 3.6 Hz, 1 H), 5.27 (brs, 1 H), 7.18-7.28 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.8, 17.9, 23.2, 36.0, 36.7, 38.5, 48.4, 86.1, 86.7, 120.2, 127.6, 127.9, 132.5, 136.3, 139.2; **IR** (KBr) 2965, 2928, 1594, 1465, 1369, 1289, 1102, 1091, 849, 760 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}ClO$ $(M+H)^+$ requires 277.1359; found 277.1348 (^{35}Cl). Specific rotation $[\alpha]^{25}_{D}$ +109 (*c* 0.55, $CHCl_3$).

(1*R*,5*R*,7*R*)-7-(4-Bromophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24e):



Colourless solid; M.P.: 68-70 °C (209 mg, 65%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.03 (t, *J* = 2.0 Hz, 3 H), 1.83-1.88 (m, 1 H), 1.93 (septet, *J* = 6.8 Hz, 1 H), 2.05 (dd, *J* = 10.8 and 4.0 Hz, 1 H), 2.12-2.18 (m, 1 H), 2.31-2.39 (m, 1 H), 2.53 (t, *J* = 3.6 Hz, 1 H), 5.15 (d, *J* = 3.2 Hz, 1 H), 5.26 (brs, 1 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.7, 17.9, 23.2, 35.9, 36.6, 38.5, 48.2, 86.0, 86.6, 120.1, 120.6, 127.9, 130.7, 136.2, 139.7; **IR** (KBr) 2959, 2929, 1595, 1465, 1375, 1281, 1055, 1010, 847, 802 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}BrO$ $(M+H)^+$ requires 321.0854; found 321.0852 (^{79}Br). Specific rotation $[\alpha]^{25}_{D}$ +103 (*c* 1.84, $CHCl_3$).

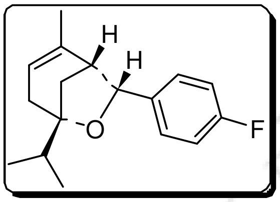
(1*R*,5*R*,7*R*)-7-(3-Bromophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24f):



Colourless oil (206 mg, 64%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.04 (dd, *J* = 2.0 and 1.6 Hz, 3 H), 1.84-1.88 (m, 1 H), 1.93 (septet, *J* = 6.8 Hz, 1 H), 2.05 (dd, *J* = 10.8 and 4.0 Hz, 1 H), 2.12-2.20 (m, 1 H), 2.31-2.40 (m, 1 H), 2.55 (t, *J* = 3.6 Hz, 1 H), 5.15 (d, *J* = 3.2 Hz, 1 H), 5.29 (brs, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.18-7.22 (m, 1 H), 7.31-7.34 (m, 1 H), 7.43 (s, 1 H); **^{13}C NMR** (100 MHz,

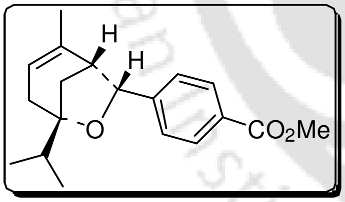
$CDCl_3$): δ 17.8, 17.9, 23.2, 35.9, 36.7, 38.5, 48.3, 86.2, 86.6, 120.2, 122.1, 124.9, 129.2, 129.3, 130.0, 136.1, 143.2; **IR** (Neat) 2965, 2934, 1593, 1467, 1421, 1369, 1294, 1260, 1050, 781, 747 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}BrO$ $(M+H)^+$ requires 321.0854; found 321.0848 (^{79}Br). Specific rotation $[\alpha]^{25}_D$ +105 (*c* 0.63, $CHCl_3$).

(1*R*,5*R*,7*R*)-7-(4-Fluorophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24g):



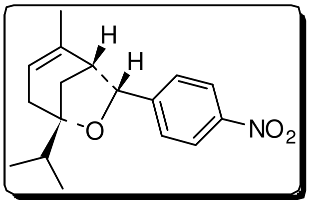
Colourless oil (172 mg, 66%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.02 (s, 3 H), 1.82-1.88 (m, 1 H), 1.94 (septet, *J* = 6.8 Hz, 1 H), 2.05 (dd, *J* = 10.8 and 4.0 Hz, 1 H), 2.12-2.19 (m, 1 H), 2.32-2.40 (m, 1 H), 2.51 (t, *J* = 3.6 Hz, 1 H), 5.18 (d, *J* = 3.6 Hz, 1 H), 5.27 (brs, 1 H), 6.95 (t, *J* = 8.8 Hz, 2 H), 7.22-7.28 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.8, 18.0, 23.2, 36.0, 36.8, 38.5, 48.5, 86.0, 86.8, 114.6 (d, *J* = 21.3 Hz), 120.1 (d, *J* = 6.9 Hz), 127.7 (d, *J* = 7.6 Hz), 136.2, 136.4, 162.1 (d, *J* = 243.3 Hz); **^{19}F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -220.51-(-220.43) (m, 1 F); **IR** (Neat) 2961, 2933, 1606, 1508, 1465, 1380, 1221, 1056, 1020, 825, 803 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}FO$ (M^+) requires 260.1576; found 260.1568. Specific rotation $[\alpha]^{25}_D$ +131 (*c* 0.26, $CHCl_3$).

Methyl 4-((1*R*,5*R*,7*R*)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-en-7-yl)benzoate (24h):



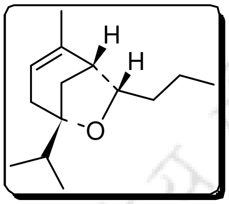
Colourless oil (180 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 1.6 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H) 1.86-1.90 (m, 1 H), 1.95 (septet, *J* = 6.8 Hz, 1 H), 2.08 (dd, *J* = 10.4 and 3.6 Hz, 1 H), 2.15-2.22 (m, 1 H), 2.33-2.43 (m, 1 H), 2.59 (t, *J* = 3.2 Hz, 1 H), 3.90 (s, 3 H), 5.24-5.27 (m, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.7, 17.9, 23.1, 35.9, 36.6, 38.5, 48.4, 52.0, 86.2, 87.0, 120.2, 126.1, 128.7, 129.1, 136.1, 146.2, 167.3; **IR** (Neat) 2961, 1722, 1611, 1435, 1277, 1111, 1056, 1017, 764, 713 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{24}O_3$ $(M+H)^+$ requires 301.1803; found 301.1795. Specific rotation $[\alpha]^{25}_D$ +116 (*c* 1.77, $CHCl_3$).

(1*R*,5*R*,7*R*)-5-Isopropyl-2-methyl-7-(4-nitrophenyl)-6-oxabicyclo[3.2.1]oct-2-ene (24i): Colourless oil (178 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (s, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 1.87-1.92 (m, 1 H), 1.96 (septet, *J* = 6.8 Hz, 1 H), 2.10 (dd, *J* = 10.8 and 4.0 Hz, 1 H), 2.16-2.23 (m, 1 H), 2.33-2.43 (m, 1 H), 2.64 (t, *J* = 3.6 Hz, 1



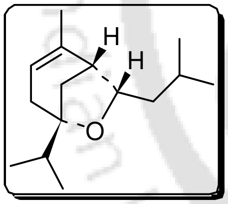
H), 5.27-5.30 (m, 2 H), 7.46 (d, J = 8.4 Hz, 2 H), 8.14 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.7, 17.8, 23.1, 35.9, 36.5, 38.7, 48.4, 86.5, 86.7, 120.6, 123.0, 127.0, 135.7, 147.1, 148.7; **IR** (Neat) 2966, 2928, 1606, 1525, 1348, 1288, 1104, 1051, 1011, 853, 720 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}NO_3$ $(M+H)^+$ requires 288.1599; found 288.1587. Specific rotation $[\alpha]^{25}_{D}$ +113 (*c* 0.30, $CHCl_3$).

(1*R*,5*R*,7*S*)-5-Isopropyl-2-methyl-7-propyl-6-oxabicyclo[3.2.1]oct-2-ene (24j):



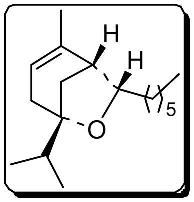
Colourless oil (192 mg, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.92 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 7.6 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.30-1.35 (m, 1 H), 1.36-1.46 (m, 2 H), 1.51-1.58 (m, 1 H), 1.65-1.69 (m, 1 H), 1.70-1.73 (m, 3 H), 1.77-1.85 (m, 2 H), 1.86-1.94 (m, 1 H), 2.17-2.25 (m, 1 H), 2.29 (t, J = 3.2 Hz, 1 H), 3.97 (ddd, J = 9.2, 6.0 and 3.2 Hz, 1 H), 5.31 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 17.8, 17.9, 20.2, 24.0, 34.4, 36.0, 36.8, 37.9, 44.5, 84.3, 86.6, 120.2, 136.7; **IR** (Neat) 2959, 2933, 2875, 1638, 1465, 1383, 1072, 1054, 968 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O$ $(M+H)^+$ requires 209.1905; found 209.1896. Specific rotation $[\alpha]^{25}_{D}$ +45 (*c* 0.56, $CHCl_3$).

(1*R*,5*R*,7*S*)-7-Isobutyl-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24k):



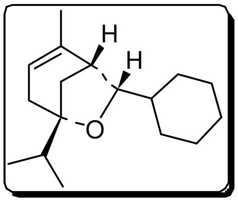
Colourless oil (196 mg, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.90 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 7.2 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 7.2 Hz, 3 H), 1.29 (septet, J = 7.2 Hz, 1 H), 1.42 (septet, J = 6.8 Hz, 1 H), 1.61-1.69 (m, 2 H), 1.70-1.73 (m, 3 H), 1.77-1.85 (m, 2 H), 1.86-1.93 (m, 1 H), 2.17-2.24 (m, 1 H), 2.26 (t, J = 4.0 Hz, 1 H), 4.07 (ddd, J = 10.0, 6.4 and 3.2 Hz, 1 H), 5.30 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.7, 18.0, 23.2, 23.3, 24.1, 25.9, 36.0, 37.0, 37.9, 41.1, 44.8, 84.3, 84.8, 120.2, 136.7; **IR** (Neat) 2957, 2931, 2873, 1638, 1466, 1382, 1077, 1048, 979 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O$ $(M+H)^+$ requires 223.1972; found 223.1968. Specific rotation $[\alpha]^{25}_{D}$ +41 (*c* 0.61, $CHCl_3$).

(1*R*,5*R*,7*S*)-7-Hexyl-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24l):



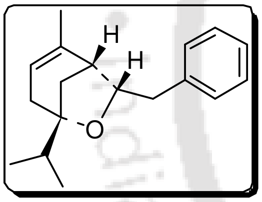
Colourless oil (213 mg, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 7.2 Hz, 3 H), 1.20-1.35 (m, 8 H), 1.38-1.45 (m, 1 H), 1.53-1.61 (m, 1 H), 1.65-1.70 (m, 1 H), 1.71-1.73 (m, 3 H), 1.77-1.85 (m, 2 H), 1.86-1.94 (m, 1 H), 2.17-2.25 (m, 1 H), 2.30 (t, J = 3.6 Hz, 1 H), 3.96 (ddd, J = 10.0, 6.8 and 3.2 Hz, 1 H), 5.31 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 17.8, 18.0, 22.8, 24.0, 27.0, 29.8, 32.0, 32.2, 36.0, 36.8, 38.0, 44.5, 84.4, 87.0, 120.2, 136.7; **IR** (Neat) 2958, 2930, 2873, 1639, 1466, 1383, 1075, 1054, 875 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{30}O$ $(M+H)^+$ requires 251.2375; found 251.2368. Specific rotation $[\alpha]^{25}_{D}$ +46 (*c* 0.48, $CHCl_3$).

(1*R*,5*R*,7*S*)-7-Cyclohexyl-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24m):



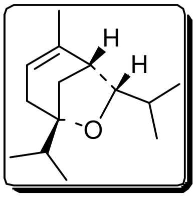
Colourless oil (209 mg, 84%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.80-0.91 (m, 4 H), 0.94 (d, *J* = 7.2 Hz, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H), 1.07-1.11 (m, 1 H), 1.12-1.17 (m, 2 H), 1.18-1.24 (m, 2 H), 1.25-1.29 (m, 1 H), 1.54-1.58 (m, 1 H), 1.60-1.66 (m, 1 H), 1.69 (dd, *J* = 2.0 and 1.6 Hz, 3 H), 1.71-1.76 (m, 1 H), 1.81 (septet, *J* = 6.8 Hz, 1 H), 1.97-2.05 (m, 1 H), 2.20 (t, *J* = 2.6 Hz, 1 H), 2.25-2.29 (m, 1 H), 3.51 (d, *J* = 9.6 Hz, 1 H), 5.18 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 18.1, 18.2, 22.1, 26.1(2C), 26.7, 29.7, 30.0, 34.4, 35.8, 36.2, 43.0, 43.1, 84.8, 92.7, 118.4, 140.9; **IR** (Neat) 2950, 2924, 2851, 1641, 1448, 1380, 1083, 1055, 861 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{28}O$ $(M+H)^+$ requires 249.2218; found 249.2212. Specific rotation $[\alpha]^{25}_{D}$ +42 (*c* 0.57, $CHCl_3$).

(1*R*,5*R*,7*S*)-7-Benzyl-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24n):



Colourless oil (210 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.92 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.68-1.76 (m, 4 H), 1.79-1.87 (m, 2 H), 1.97-2.04 (m, 1 H), 2.21-2.28 (m, 1 H), 2.34 (t, *J* = 3.6 Hz, 1 H), 2.72 (dd, *J* = 14.4 and 6.4 Hz, 1 H), 2.95 (dd, *J* = 14.4 and 7.2 Hz, 1 H), 4.33 (ddd, *J* = 10.0, 6.4 and 3.2 Hz, 1 H), 5.39 (brs, 1 H), 7.16-7.30 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 17.9(2C), 24.1, 36.1, 36.8, 38.2, 38.4, 44.8, 84.8, 86.6, 120.7, 126.0, 128.3, 129.2, 136.6, 140.1; **IR** (Neat) 2960, 2928, 1638, 1453, 1382, 1064, 1055, 751, 700 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O$ $(M+H)^+$ requires 257.1905; found 257.1894. Specific rotation $[\alpha]^{25}_{D}$ +20 (*c* 0.30, $CHCl_3$).

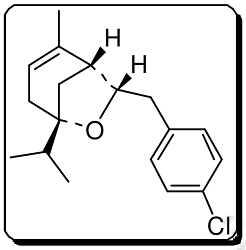
(1*R*,5*R*,7*S*)-5,7-diisopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24p):



Colourless oil (142 mg, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.86 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 1.56-1.64 (m, 1 H), 1.65-1.69 (m, 1 H), 1.74-1.78 (m, 3 H), 1.79-1.84 (m, 2 H), 1.85-1.93 (m, 1 H), 2.15-2.22 (m, 1 H), 2.40 (t, *J* = 2.8 Hz, 1 H), 3.50 (dd, *J* = 10.0 and 2.8 Hz, 1 H), 5.30 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 17.8, 17.9, 20.1, 20.7, 24.2, 30.2, 36.2, 36.7, 38.5, 43.7, 84.1, 93.2, 120.6, 136.9; **IR** (Neat) 2958, 2928, 1640, 1467, 1386, 1278, 1056, 1020, 858 cm^{-1}. **HRMS**

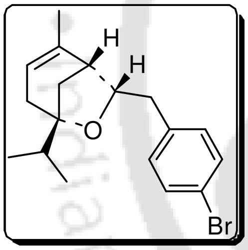
(APCI) cald. for $C_{14}H_{24}O$ $(M+H)^+$ requires 209.1905; found 209.1898. Specific rotation $[\alpha]^{25}_{D}$ +30 (*c* 0.20, $CHCl_3$).

(1*R*,5*R*,7*S*)-7-(4-Chlorobenzyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24q):



Colourless oil (160 mg, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.69-1.76 (m, 4 H), 1.77-1.85 (m, 2 H), 1.94-2.03 (m, 1 H), 2.20-2.28 (m, 1 H), 2.32 (t, *J* = 3.6 Hz, 1 H), 2.68 (dd, *J* = 14.4 and 5.2 Hz, 1 H), 2.87 (dd, *J* = 14.4 and 8.0 Hz, 1 H), 4.25 (ddd, *J* = 10.4, 6.0 and 3.2 Hz, 1 H), 5.39 (brs, 1 H), 7.17-7.26 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.9(2C), 24.0, 36.1, 36.7, 38.0, 38.2, 45.0, 85.0, 86.2, 120.8, 128.4, 130.6, 131.8, 136.5, 138.8; **IR** (Neat) 2961, 2928, 1637, 1467, 1380, 1078, 1055, 877, 831, 805 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}ClO$ $(M+H)^+$ requires 291.1515; found 291.1504 (^{35}Cl). Specific rotation $[\alpha]^{25}_{D}$ +20 (*c* 0.44, $CHCl_3$).

(1*R*,5*R*,7*S*)-7-(4-Bromobenzyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24r):

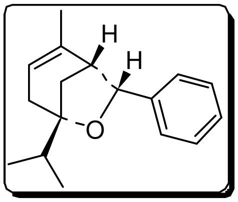


Colourless oil (194 mg, 58%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.90 (d, *J* = 7.2 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.69-1.76 (m, 4 H), 1.78-1.85 (m, 2 H), 1.94-2.02 (m, 1 H), 2.19-2.27 (m, 1 H), 2.32 (t, *J* = 3.6 Hz, 1 H), 2.66 (dd, *J* = 14.4 and 5.2 Hz, 1 H), 2.84 (dd, *J* = 14.8 and 8.0 Hz, 1 H), 4.24 (ddd, *J* = 10.4, 6.4 and 3.6 Hz, 1 H), 5.39 (brs, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.9(2C), 24.1, 36.1, 36.7, 38.0, 38.2, 45.0, 85.0, 86.2, 119.8, 120.8, 131.0, 131.3, 136.5, 139.3; **IR** (Neat) 2960, 2928, 1641, 1467, 1382, 1071, 1053, 878, 834, 802 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}BrO$ $(M+H)^+$ requires 335.1010; found 335.1019 (^{79}Br). Specific rotation $[\alpha]^{25}_{D}$ +32 (*c* 0.40, $CHCl_3$).

4.7 Selected Spectra of 6-Oxabicyclo[3.2.1]octenes

(1*R*,5*R*,7*R*)-5-Isopropyl-2-methyl-7-phenyl-6-oxabicyclo[3.2.1]oct-2-ene (24a):

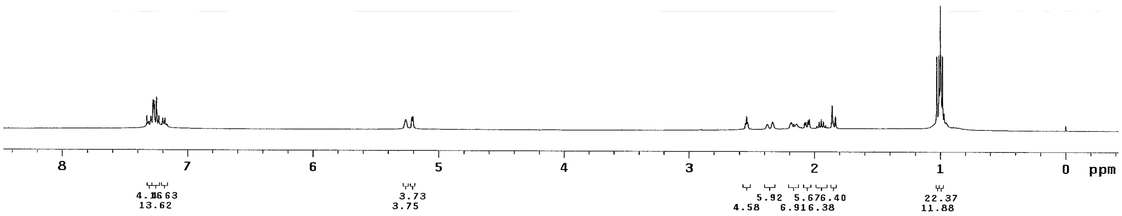
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_498_U

exp1  s2pul

       SAMPLE                SPECIAL
date   Jul 11 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_498~ hst            0.008
         U_Pdt.fid  pw90          19.700
   ACQUISITION      alfa          20.000
sw          6389.8            FLAGS
at           1.998  il                 n
np           25528  in                 n
fb        not used  dp                 y
bs               8  hs                nn
d1           1.000         PROCESSING
nt             200  lb              0.10
ct             200  fn             65536
   TRANSMITTER               DISPLAY
tn              H1  sp            -177.1
sfrq       399.853  wp            3568.4
tof          362.8  rfl            798.4
tpwr            57  rfp                0
pw           9.850  rp             118.7
    DECOUPLER       lp             -99.7
dn             C13             PLOT
dof              0  wc               250
dm             nnn  sc                 0
dmm              c  vs                30
dpwr            50  th                 2
dmf          15900  nm  cdc  ph
```

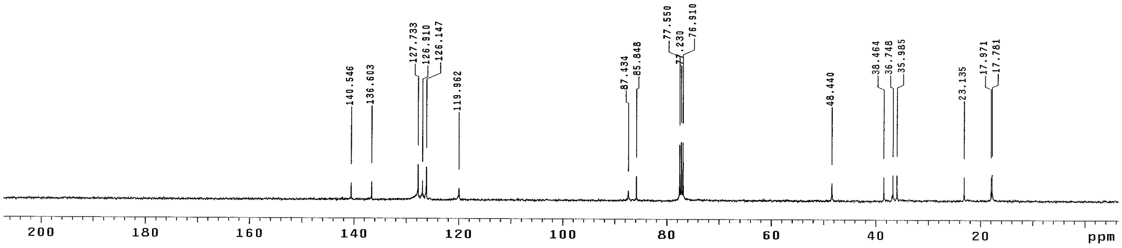


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_498_U

exp1  s2pul

       SAMPLE                SPECIAL
date   Jul 11 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_498~ hst            0.008
        U1_C13.fid  pw90          18.600
   ACQUISITION      alfa          20.000
sw         25125.6            FLAGS
at           1.199  il                 n
np           60270  in                 n
fb           13800  dp                 y
bs              16  hs                nn
d1           1.000         PROCESSING
nt            4000  lb              2.00
ct            2176  fn             65536
   TRANSMITTER               DISPLAY
tn             C13  sp            -684.4
sfrq       100.554  wp           21559.3
tof         1536.3  rfl           9274.4
tpwr            61  rfp           7764.9
pw           9.300  rp             -75.3
    DECOUPLER       lp            -271.4
dn              H1             PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                15
dpwr            42  th                 2
dmf           8900  nm  no  ph
```



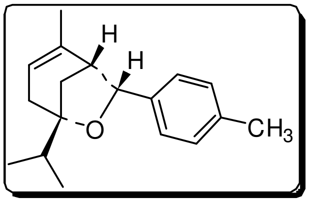
(1*R*,5*R*,7*R*)-5-Isopropyl-2-methyl-7-*p*-tolyl-6-oxabicyclo[3.2.1]oct-2-ene (24b):

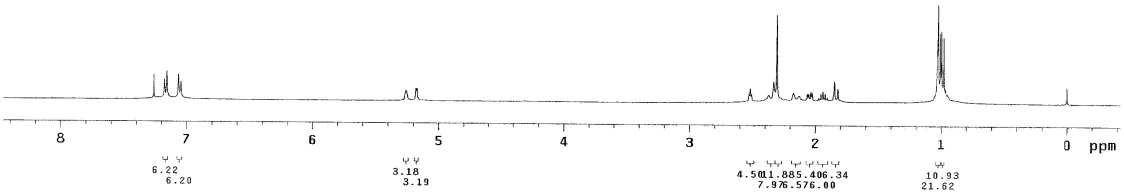
^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_554_U

exp1  s2pul

      SAMPLE              SPECIAL
date   Oct 21 2011  temp       not used
solvent      CDC13  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528         FLAGS
fb        not used  il                n
bs               8  in                n
d1           1.000  dp                y
nt             200  hs               nn
ct             200       PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853        DISPLAY
tof          362.8  sp           -173.9
tpwr            57  wp           3560.0
pw           9.850  rfl           795.2
    DECOUPLER       rfp               0
dn             C13  rp            114.2
dof              0  lp            -98.6
dm             nnn         PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               23
                    th                2
                    nm   cdc   ph
```



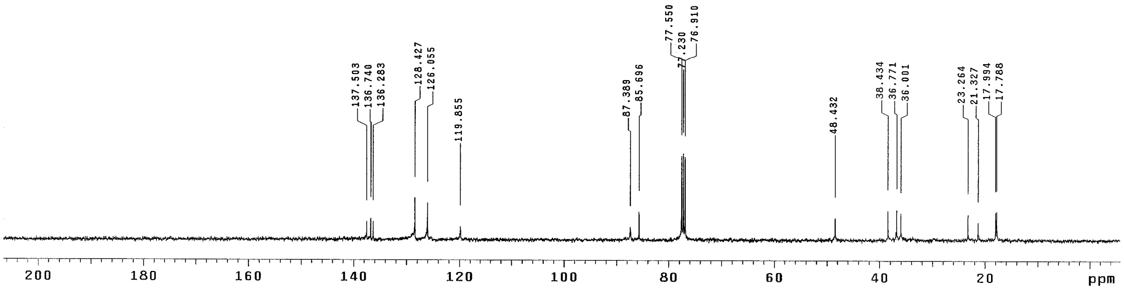


^{13}C NMR (100 MHz, $CDCl_3$)

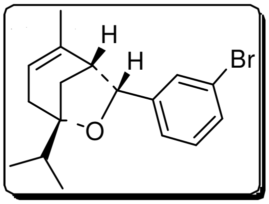
```
PS_497_U

exp1  s2pul

      SAMPLE              SPECIAL
date   Jun 15 2011  temp       not used
solvent      CDC13  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_497~ hst           0.008
       U1_C13.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6         FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000       PROCESSING
nt            5000  lb             2.00
ct            2128  fn            65536
   TRANSMITTER            DISPLAY
tn             C13  sp           -584.0
sfrq       100.554  wp          21361.4
tof         1536.3  rfl          9272.9
tpwr            61  rfp          7764.9
pw           9.300  rp            -71.8
    DECOUPLER       lp           -271.4
dn              H1         PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               21
dpwr            42  th                3
dmf           8900  nm   no   ph
```



(1*R*,5*R*,7*R*)-7-(3-Bromophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24f):

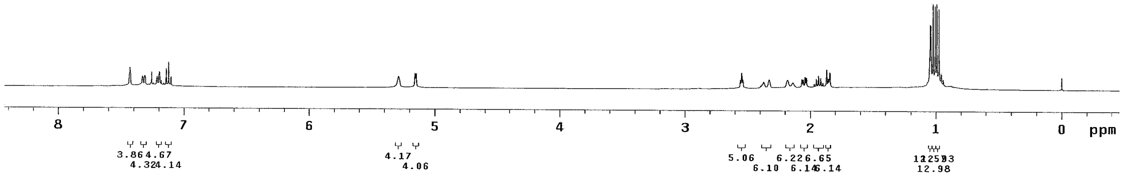


^{1}H NMR (400 MHz, CDCl$_3$)

```
PS_502_U

exp1  s2pul

      SAMPLE                   SPECIAL
date   Jun 22 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_502~ hst            0.008
           _U.fid   pw90          19.700
   ACQUISITION      alfa          20.000
sw          6389.8          FLAGS
at           1.998  il                 n
np           25528  in                 n
fb        not used  dp                 y
bs               8  hs                nn
d1           1.000         PROCESSING
nt             200  lb              0.10
ct               0  fn             65536
   TRANSMITTER              DISPLAY
tn              H1  sp            -191.5
sfrq       399.853  wp            3568.4
tof          362.8  rfl            796.0
tpwr            57  rfp                0
pw           9.850  rp             115.8
    DECOUPLER       lp             -92.3
dn             C13           PLOT
dof              0  wc               250
dm             nnn  sc                 0
dmm              c  vs                21
dpwr            50  th                 6
dmf          15900  nm   cdc  ph
```

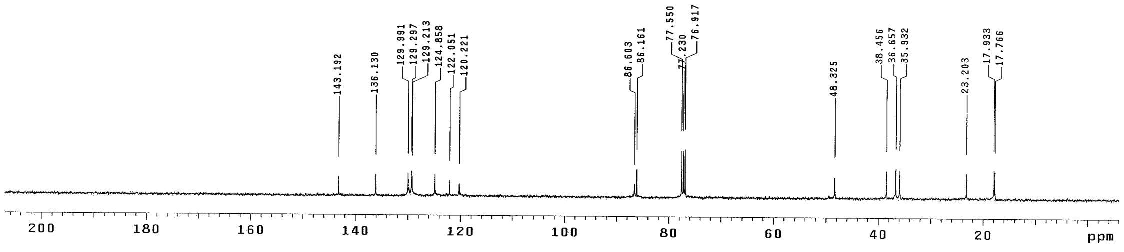


^{13}C NMR (100 MHz, CDCl$_3$)

```
PS_502_U

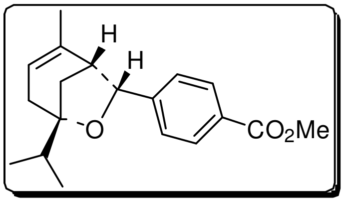
exp1  s2pul

      SAMPLE                   SPECIAL
date   Jun 23 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_502~ hst            0.008
       U_C13.fid    pw90          18.600
   ACQUISITION      alfa          20.000
sw         25125.6          FLAGS
at           1.199  il                 n
np           60270  in                 n
fb           13800  dp                 y
bs              16  hs                nn
d1           1.000         PROCESSING
nt            4000  lb              2.00
ct            1200  fn             65536
   TRANSMITTER              DISPLAY
tn             C13  sp            -619.3
sfrq       100.554  wp           21427.4
tof         1536.3  rfl           9275.2
tpwr            61  rfp           7764.9
pw           9.300  rp             -34.8
    DECOUPLER       lp            -367.6
dn              H1           PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                12
dpwr            42  th                 2
dmf           8900  nm   no   ph
```



Methyl 4-((1*R*,5*R*,7*R*)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-en-7-yl)benzoate (24h):

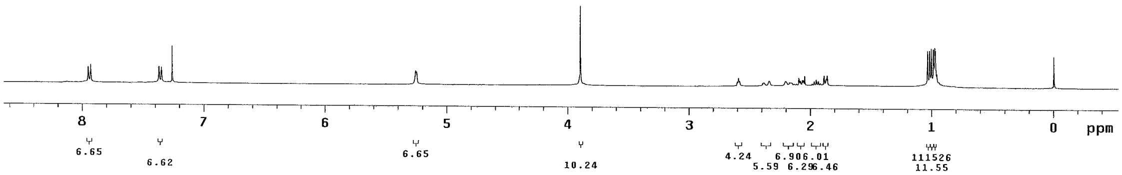
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_542_M

exp1  s2pul

      SAMPLE                  SPECIAL
date   Sep 21 2011  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               8  in                n
d1           1.000  dp                y
nt             200  hs               nn
ct             200       PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853          DISPLAY
tof          362.8  sp           -215.3
tpwr            57  wp           3677.6
pw           9.850  rfl           794.5
    DECOUPLER       rfp               0
dn             C13  rp            118.0
dof              0  lp            -96.3
dm             nnn           PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               18
                    th                2
                    nm   cdc   ph
```

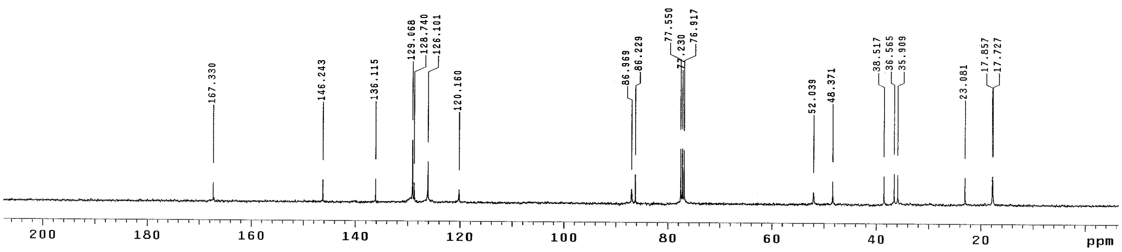


^{13}C NMR (100 MHz, $CDCl_3$)

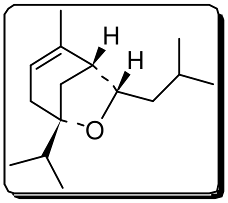
```
PS_542_M

exp1  s2pul

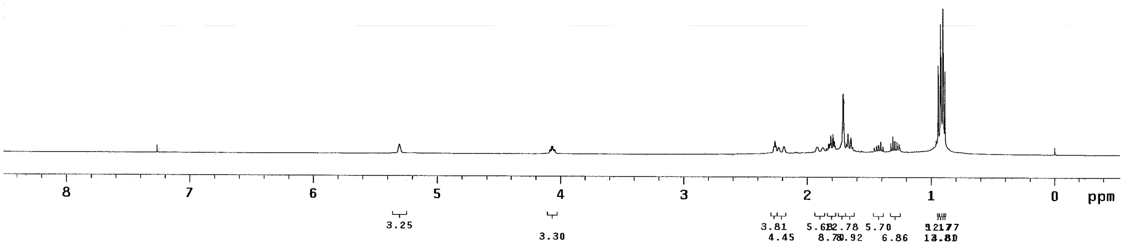
      SAMPLE                  SPECIAL
date   Sep 21 2011  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270          FLAGS
fb           13800  il                n
bs              16  in                n
d1           1.000  dp                y
nt            4000  hs               nn
ct            1552       PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554          DISPLAY
tof         1536.3  sp           -653.8
tpwr            61  wp          21526.3
pw           9.300  rfl          9276.7
    DECOUPLER       rfp          7764.9
dn              H1  rp            -55.1
dof              0  lp           -309.2
dm             yyy           PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               16
                    th                3
                    nm   no   ph
```



(1*R*,5*R*,7*S*)-7-Isobutyl-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24k):



^{1}H NMR (400 MHz, $CDCl_3$)

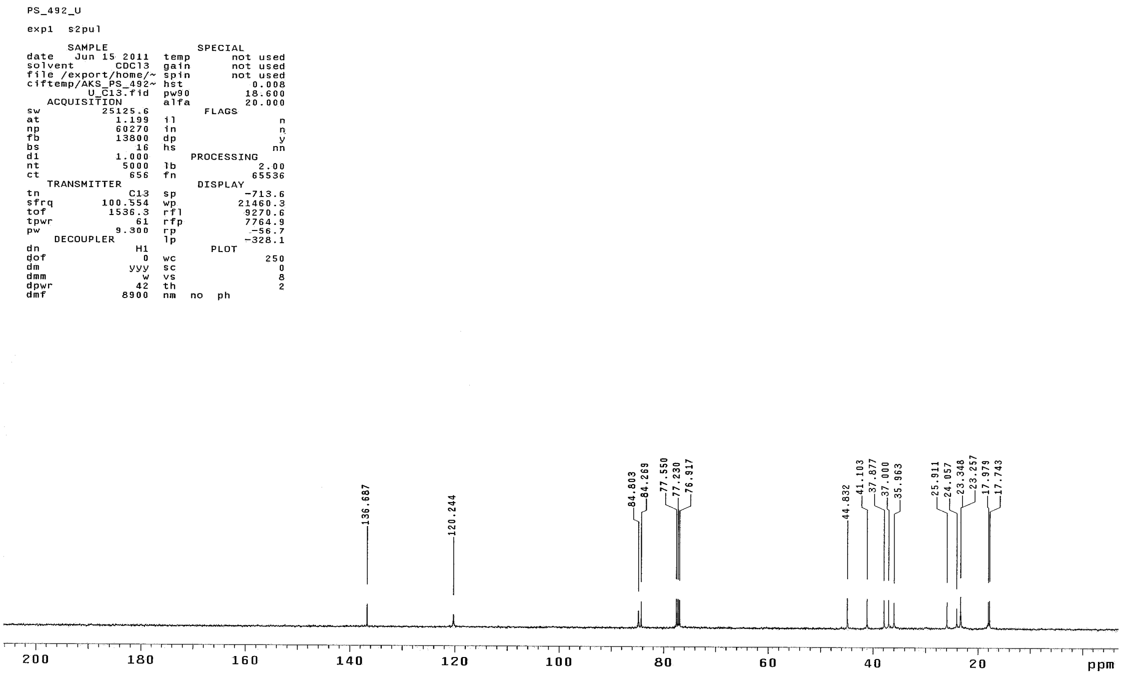


```
PS_492_U

exp1  s2pul

       SAMPLE                 SPECIAL
date   Jun 14 2011   temp        not used
solvent      CDCl3   gain        not used
file /export/home/~  spin        not used
ciftemp/AKS_PS_492~  hst            0.008
           _U.fid    pw90          19.700
   ACQUISITION       alfa          20.000
sw          6389.8           FLAGS
at           1.998   il                 n
np           25528   in                 n
fb        not used   dp                 y
bs               8   hs                nn
d1           1.000         PROCESSING
nt             100   lb              0.10
ct             100   fn             65536
   TRANSMITTER               DISPLAY
tn              H1   sp            -213.7
sfrq       399.853   wp            3618.7
tof          362.8   rfl            792.9
tpwr            57   rfp                0
pw           9.850   rp             122.8
    DECOUPLER        lp            -108.5
dn             C13             PLOT
dof              0   wc               250
dm             nnn   sc                 0
dmm              c   vs                33
dpwr            50   th                20
dmf          15900   nm  cdc  ph
```

^{13}C NMR (100 MHz, $CDCl_3$)



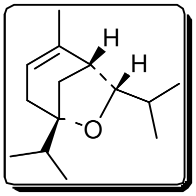
```
PS_492_U

exp1  s2pul

       SAMPLE                 SPECIAL
date   Jun 15 2011   temp        not used
solvent      CDCl3   gain        not used
file /export/home/~  spin        not used
ciftemp/AKS_PS_492~  hst            0.008
       U_C13.fid     pw90          18.600
   ACQUISITION       alfa          20.000
sw         25125.6           FLAGS
at           1.199   il                 n
np           60270   in                 n
fb           13800   dp                 y
bs              16   hs                nn
d1           1.000         PROCESSING
nt            5000   lb              2.00
ct             656   fn             65536
   TRANSMITTER               DISPLAY
tn             C13   sp            -713.6
sfrq       100.554   wp           21460.3
tof         1536.3   rfl           9270.6
tpwr            61   rfp           7764.9
pw           9.300   rp             -56.7
    DECOUPLER        lp            -328.1
dn              H1             PLOT
dof              0   wc               250
dm             yyy   sc                 0
dmm              w   vs                 8
dpwr            42   th                 2
dmf           8900   nm  no  ph
```

(1*R*,5*R*,7*S*)-5,7-diisopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (24p):

^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_510_U

exp1  s2pul

      SAMPLE                 SPECIAL
date    Jul  7 2011  temp        not used
solvent       CDCl3  gain        not used
file /export/home/~  spin        not used
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              _U.fid  pw90          19.700
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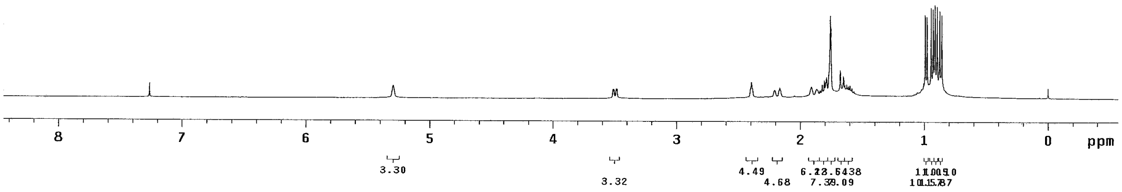

^{13}C NMR (100 MHz, $CDCl_3$)

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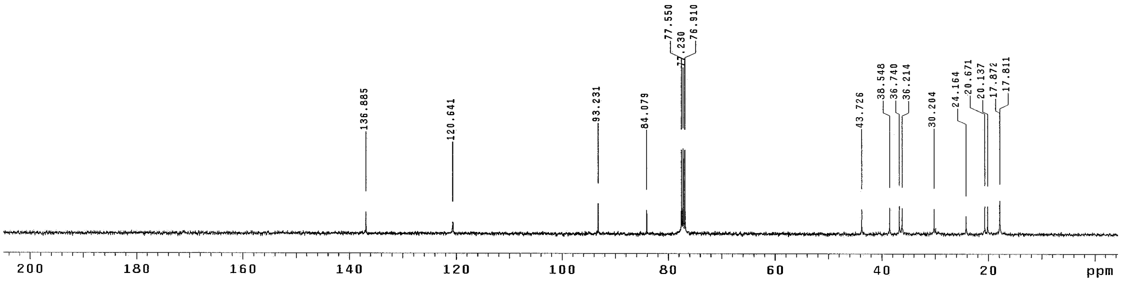


4.8 The Crystal Parameters of Compound 24d

Crystal Parameters	**24d-**CCDC 840604
Formula	$C_{17}H_{21}ClO$
Formula weight	276.62
T/K	293(2)
Crystal system	Monoclinic
Space group	P 21
a/Å	7.251(2)
b/Å	7.497(2)
c/Å	13.967(4)
α/°	90.00(17)
β/°	92.81(2)
γ/°	90.00(18)
V/Å^3	758.3(4)
Z	2
Abs. Coeff./mm^{-1}	0.242
Abs. Correction	None
GOF on F^2	0.993
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0384
	wR2 = 0.0932
R indices [all data]	*R1* = 0.0484
	wR2 = 0.1014

CHAPTER 5

Synthesis of 2,3,5,6-Tetrasubstituted Tetrahydropyrans via (3,5)-Oxonium-Ene Reaction

5.1 Importance and Applications

The tetrahydropyrans 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 2,3,5,6-tetrasubstituted tetrahydropyran units are found in antibiotics such as FR-901464 and X-206 (Figure 5.1.1, **A-B**).[3] The presence of ester group in the tetrahydropyran ring is important because a diverse functionalization could be achieved in the tetrahydropyran molecule.

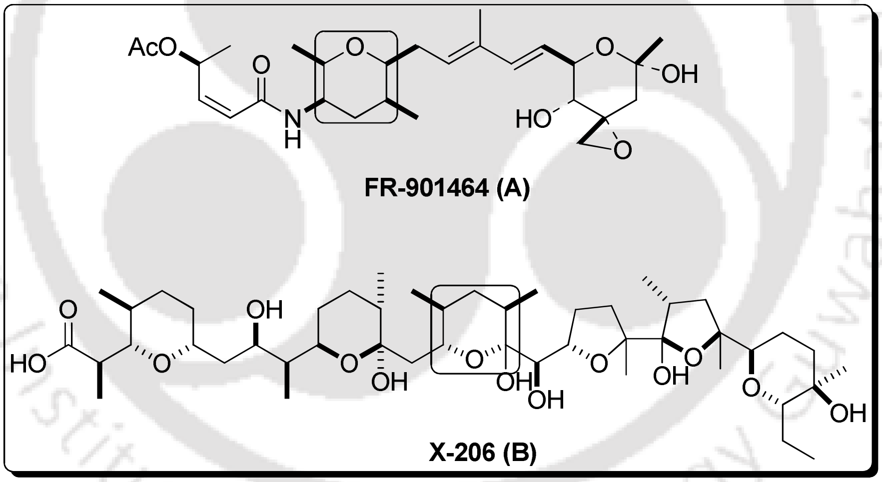
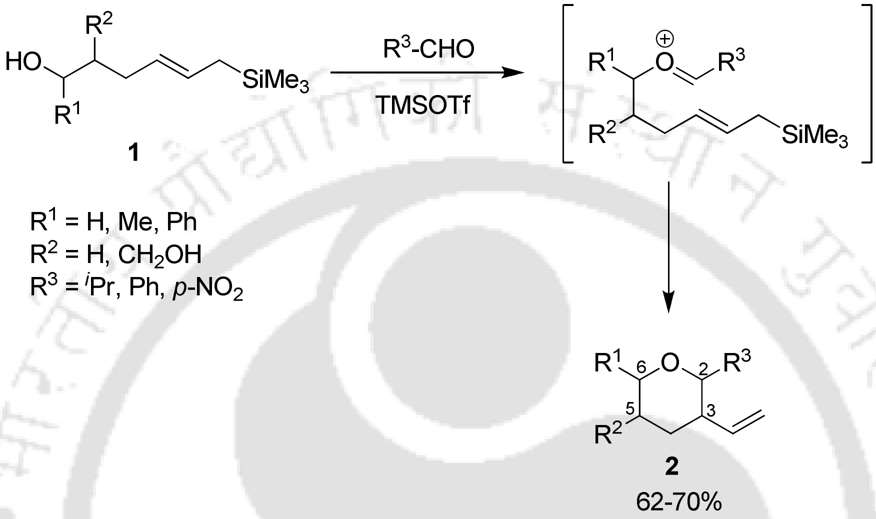


Figure 5.1.1. Some biologically important molecules containing tetrahydropyran as core unit

5.2 An Overview of Relevant Synthetic Methods

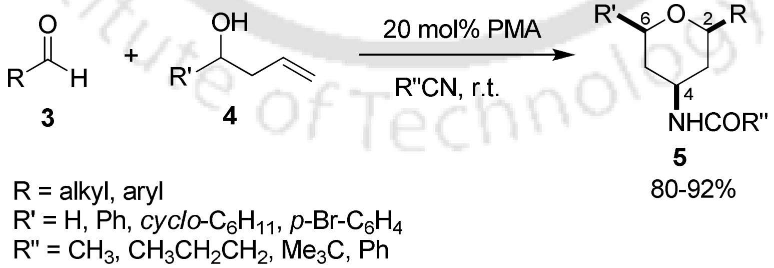
Review of literature reveals that several strategies are developed for the synthesis of 2,4-, 2,6-, 2,3,6-, 2,4,5-, 2,4,6-, 2,3,4,6- and 2,4,5,6-substituted tetrahydropyrans. However synthetic procedure for the synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans are limited.[4] Tetrahydropyrans are generally prepared by hetero Diels-Alder reactions, manipulation of carbohydrates, intramolecular Michael reactions and Prins cyclization. These are already discussed in the introductory part (Chapter 1).

Szabó and co-workers have reported a methodology for the synthesis of 2,3,5,6-substituted tetrahydropyrans from the reaction of functionalized allylsilanes **1** and aldehydes **2** mediated by Lewis acid with excellent stereoselectivity (Scheme 5.2.1).[4] According to DFT calculations the high stereoselectivity arises from electronically induced steric effects occurring in the key-intermediate of the cyclization.



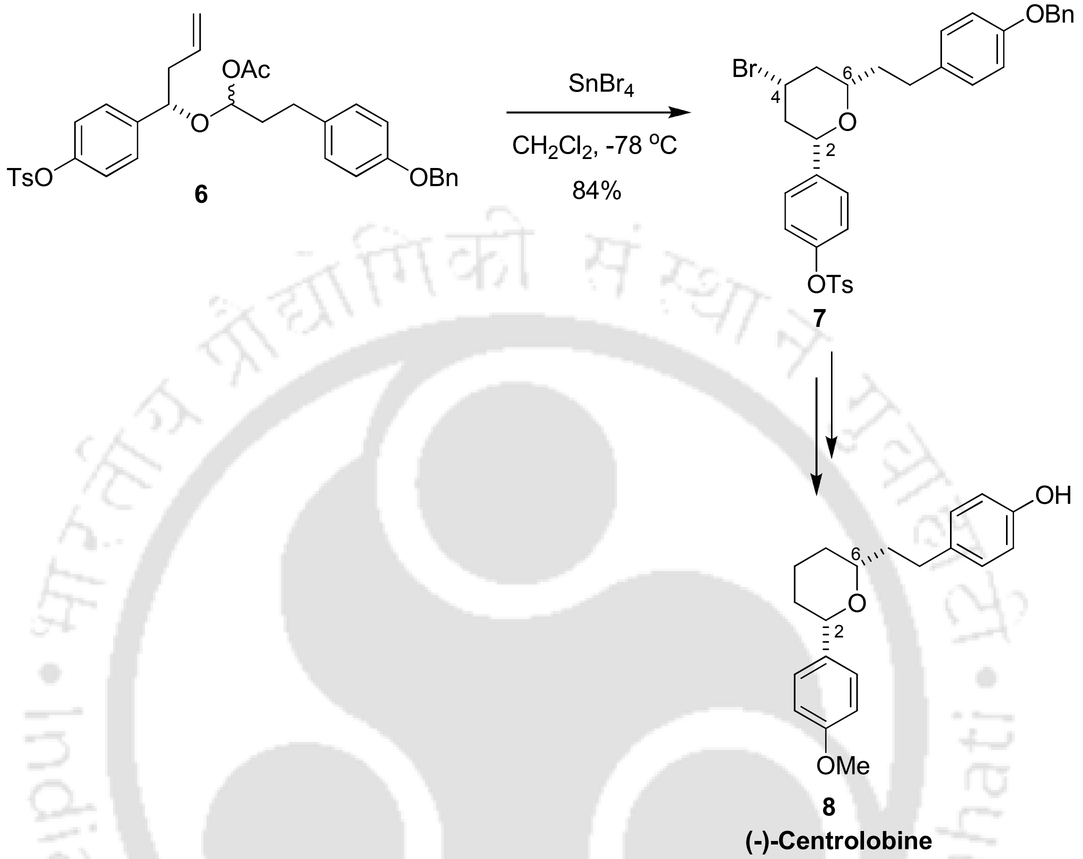
Scheme 5.2.1.

Yadav *et al.* have reported an efficient Prins-Ritter reaction to produce 2,4- and 2,4,6-substituted 4-amidotetrahydropyrans via a three component coupling of carbonyl compounds **3**, homoallylic alcohols **4** and nitriles in the presence of 20 mol % of phosphomolybdic acid (Scheme 5.2.2).[5] The reaction is diastereoselective and the tetrahydropyrans are obtained in high yields with all *cis* selectivity.



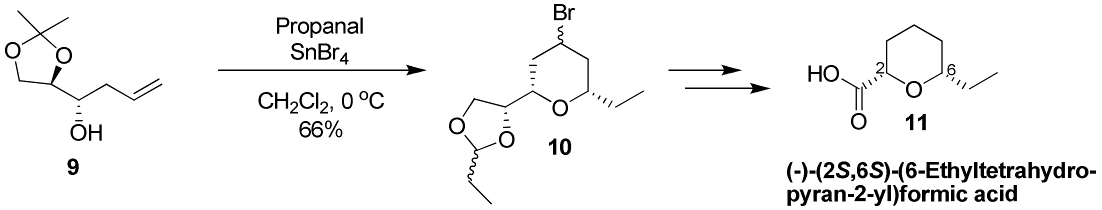
Scheme 5.2.2.

Rychnovsky and co-workers have reported the synthesis of (-)-centrolobine **8**, an antibiotic isolated from the heartwood of *Centrolobium robustum*, via the Prins cyclization of enantiopure α-acetoxy ether **6** in the presence of $SnBr_4$. The initially formed 4-bromotetrahydropyran **7** has been converted to (-)-centrolobine **8** via consecutive steps (Scheme 5.2.3).[6]



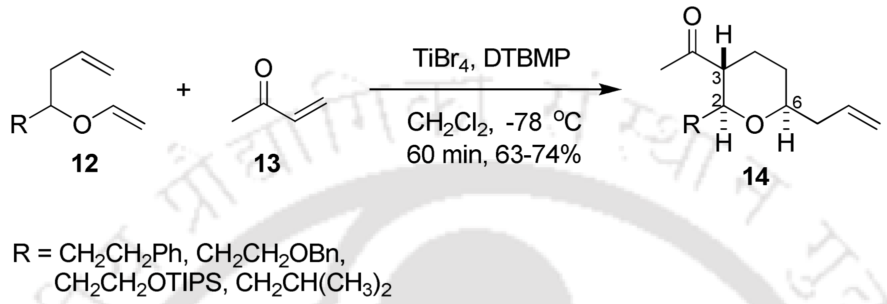
Scheme 5.2.3.

(±)-*cis*-(6-Ethyltetrahydropyran-2-yl)formic acid **11**, 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 **11** in five steps (30% overall yield, 87% *ee*), from the commercial chiral template (*R*)-2,3-isopropylideneglyceraldehyde. An efficient Prins cyclization reaction between **9** with propanal mediated by SnBr$_4$ resulted in a mixture of four diastereomers **10** (Scheme 5.2.4).[7] Reduction of the latter, followed by oxidative cleavage of diol, led to the levo enantiomer of **11** in 87% *ee*.



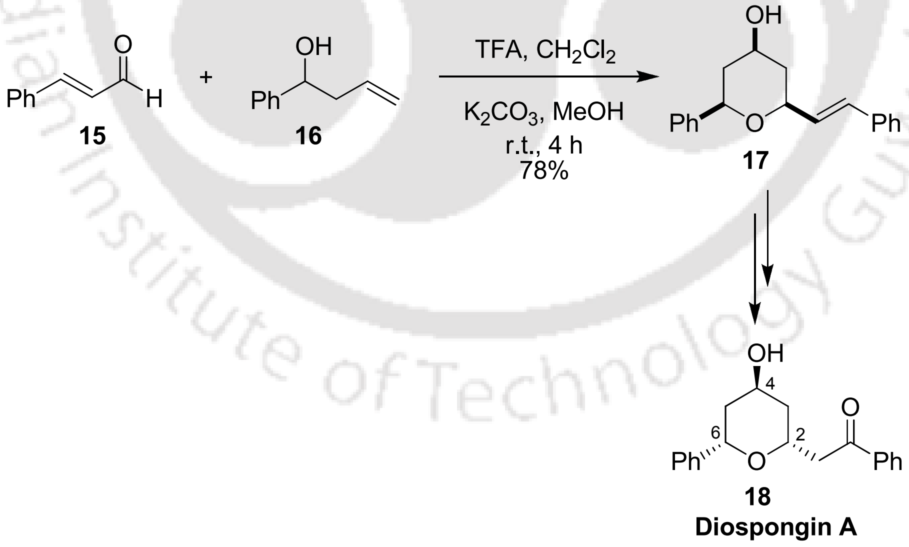
Scheme 5.2.4.

Rychnovsky and co-workers have reported the synthesis of 2,3,6-substituted tetrahydropyrans **14** from a Mukaiyama-Michael cascade reaction of homoallylic enol ethers **12** and 3-butene-2-one **13** promoted by $TiBr_4$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (Scheme 5.2.5).[8] The resulting tetrahydropyrans **14** are obtained in high yields and as a single diastereomer.



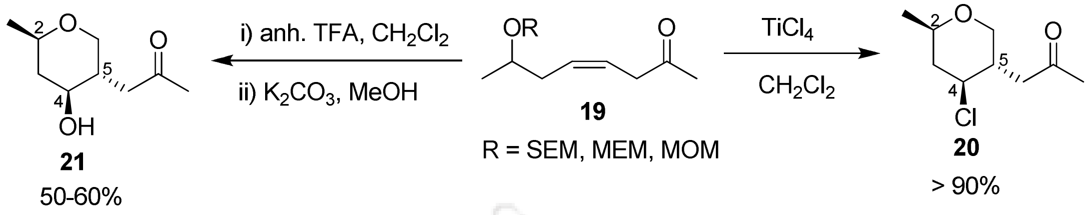
Scheme 5.2.5.

Yadav *et al.* developed a concise and efficient total synthesis of diospongin A using Prins cyclization and enzymatic kinetic resolution as key steps. Diospongin A is active against osteoporosis and 2,4,6-*cis*-trisubstituted tetrahydropyran ring was achieved via a Prins reaction of cinnamaldehyde and homoallylic alcohol (Scheme 5.2.6).[9]



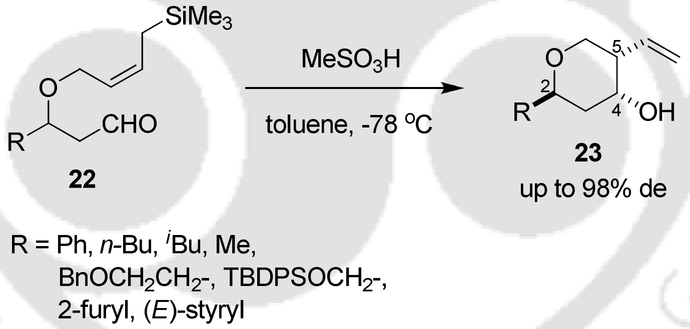
Scheme 5.2.6.

Willis and co-workers have reported a Prins type cyclization of homoallylic acetals for the synthesis of 2,4,5-trisubstituted tetrahydropyrans (Scheme 5.2.7).[10] The reaction is versatile and by varying the acid and nucleophile a halide (bromide, chloride or fluoride), oxygenated group (hydroxyl, ether or ester) or a nitrogen containing substituent may be introduced at C-4 of the tetrahydropyran.



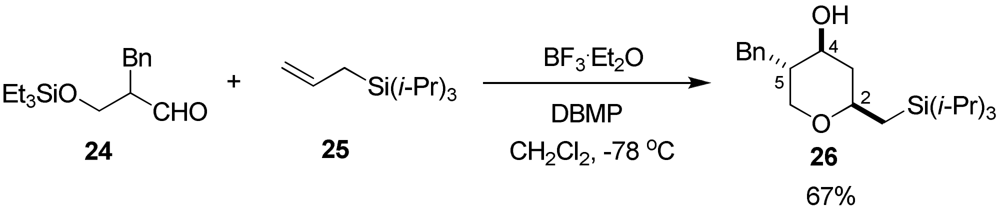
Scheme 5.2.7.

Cox and co-workers have reported a highly stereoselective route for the synthesis of 2,4,5-trisubstituted tetrahydropyrans **23** (Scheme 5.2.8).[11] The key step employs an intramolecular allylation of a (*Z*)-allylsilane onto an aldehyde under Brønsted acid activation. Complete 1,4-stereoinduction accounts for the formation of only two out of the possible four THP products. The level of 1,3-stereoinduction is optimal when the reaction is carried out in an apolar solvent, which is in accord with electrostatics being key to controlling this aspect of the stereoselectivity.



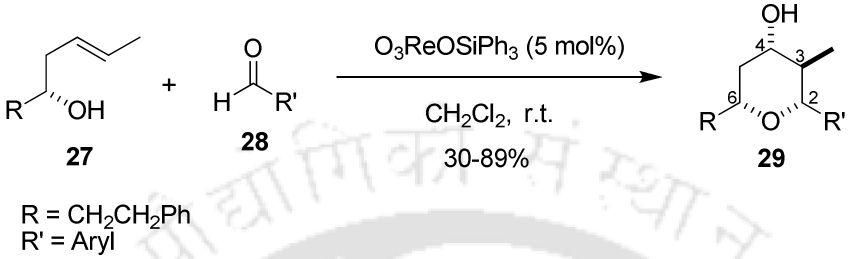
Scheme 5.2.8.

Angle *et al.* have reported stereoselective synthesis of 2,4,5-trisubstituted tetrahydropyrans via a formal [4+2]-cycloaddition of allylsilane.[12] The reaction of triethylsilyl-protected *β*-hydroxy aldehyde **24** with allyltriisopropylsilane **25** in the presence of $BF_3 \cdot Et_2O$ produces 2,4,5-trisubstituted tetrahydropyran **26** in good yields (Scheme 5.2.9).



Scheme 5.2.9.

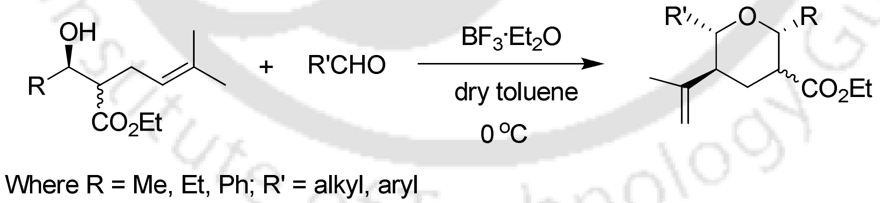
Rychnovsky and co-workers have reported the synthesis of 2,3,4,6-substituted tetrahydropyrans via Rhenium(VII) complex ($O_3ReOSiPh_3$) catalyzed Prins cyclization reaction between aromatic and *α,β*-unsaturated aldehydes with an enantiomerically pure homoallylalcohol (Scheme 5.2.10).[13]



Scheme 5.2.10.

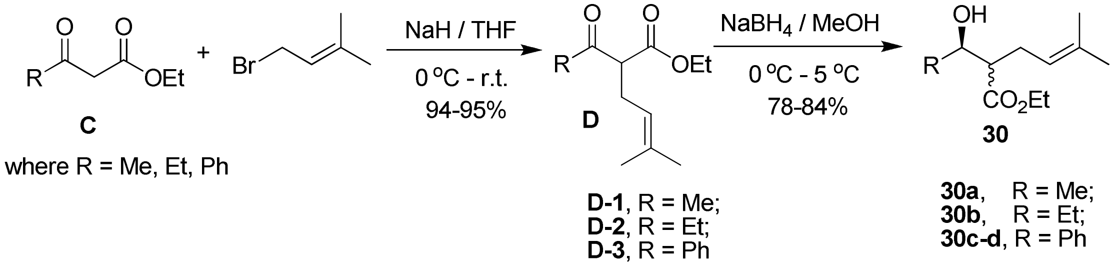
5.3 Present Work

In the previous chapters we have described efficient methodologies for the synthesis of oxabicyclo[3.3.1]nonanones, oxabicyclo[3.3.1]nonenes and substituted tetrahydropyrans, 6-oxabicyclo[3.2.1]octenes by using (3,5)-oxonium-ene reaction. In this chapter we are going to present an efficient methodology for the synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans from the reaction of aldehydes and ethyl 2(1-hydroxyalkyl/hydroxy(phenyl)methyl)-5-methylhex-4-enoate using (3,5)-oxonium-ene reaction promoted by boron trifluoride etherate in good yields under mild conditions. The reaction can be generalized as shown in Scheme 5.3.1.



Scheme 5.3.1.

The ethyl 2-(1-hydroxyalkyl/hydroxy(phenyl)methyl)-5-methylhex-4-enoate **30** was synthesized starting from *β*-keto ester **C** and 1-bromo-3-methylbut-2-ene as shown in Scheme 5.3.2.[14] Thus the reaction of *β*-keto ester **C** with 1-bromo-3-methylbut-2-ene in presence of sodium hydride in THF afforded *α*-substituted *β*-keto ester **D**, which after reduction with sodium borohydride in methanol gives alcohol **30** in 78-84% yields.

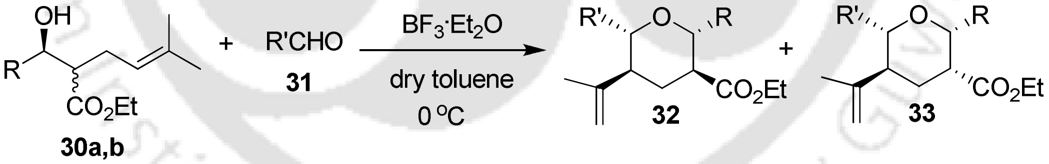


Scheme 5.3.2. Synthesis of ethyl 2-(1-hydroxyalkyl/hydroxy(phenyl)methyl)-5-methylhex-4-enoate

The methyl and ethyl substituted *β*-keto esters **D-1** and **D-2** afforded two inseparable diastereomers[15] **30a,b** whereas phenyl substituted *β*-ketoester **D-3** gave two separable *anti*- and *syn*-diastereomers **30c** and **30d**, respectively. The structures of all compounds are determined from IR, ^{1}H, ^{13}C NMR and mass spectroscopy. The stereochemistry of compounds **30c** and **30d** are determined from coupling constants values.[15b,16]

The reaction of alcohols ethyl 2-(1-hydroxyethyl)-5-methylhex-4-enoate **30a** (1:1 diastereomeric mixture) and ethyl 2-(1-hydroxypropyl)-5-methylhex-4-enoate **30b** (1:1 diastereomeric mixture) with different aldehydes in dry toluene in the presence of boron trifluoride etherate afforded a mixture of diastereomeric products **32** and **33** with an epimeric center on C-3 bearing an ester group (Table 5.3.1). In all the cases the

Table 5.3.1. Synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans



Entry	Alcohol **30a**, R = Me; **30b**, R = Et	Aldehyde R' =	Time (min)	**32**+**33** Yield[a,b] (%)
a	Me	C_6H_5	60	78
b	Me	*p*-Me-C_6H_4	60	72
c	Me	*p*-Br-C_6H_4	60	66
d	Me	*p*-Cl-C_6H_4	60	62
e	Me	*p*-F-C_6H_4	60	64
f	Me	*p*-NO_2-C_6H_4	60	62
g	Me	*p*-MeO_2C-C_6H_4	60	68

continue…

Entry	Alcohol **30a**, R = Me; **30b**, R= Et	Aldehyde R' =	Time (min)	**32**+**33** Yield[a,b] (%)
h	Me	C_3H_7	30	86
i	Me	C_6H_{13}	30	82
j	Me	$(CH_3)_2CHCH_2$	30	84
k	Et	C_6H_5	90	74
l	Et	*p*-Me-C_6H_4	90	70
m	Et	*p*-MeO_2C-C_6H_4	90	68
n	Et	C_3H_7	50	88
o	Et	C_6H_{13}	50	80
p	Et	$(CH_3)_2CHCH_2$	50	84

[a] The ratio of formation of **32** and **33** is (1:1) and is determined by ^{1}H NMR of crude products. [b] Total isolated yield of **32** and **33**. The compounds are characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR and mass spectroscopy.

diastereomeric ratio was 1:1. The diastereomers **32** and **33** could be separated by column chromatography. The stereochemistry of **32** and **33** was determined by X-ray crystallographic analysis (Figure 5.3.1).[18] In the ^{1}H NMR spectrum the axial proton at position C-4 (H_{4a}) of **32a** shows a ddd with coupling constants 12.8, 12.4 and 12.4 Hz at δ 1.99 ppm, which indicates that the proton is coupled with two neighbouring axial protons H_{3a} and H_{5a}. On the other hand same proton (H_{4a}) of **33a** shows a ddd with coupling constants 13.6, 12.8 and 5.2 Hz at δ 1.90 ppm, which is indicative of coupling with one axial H_{5a} and one equatorial proton H_{3e}. This clearly indicates that **32a** and **33a** are epimeric at C-3. A comparison of other ^{1}H NMR signals of **32a** and **33a** is shown in Table 5.3.2.

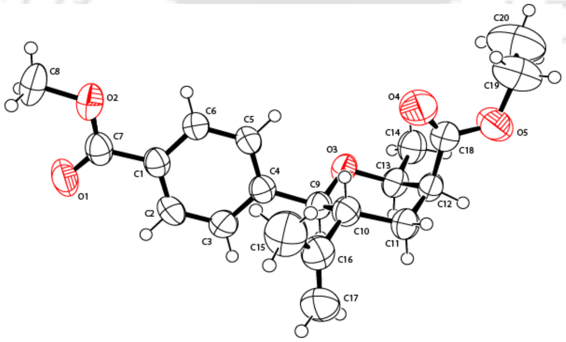
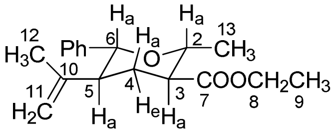
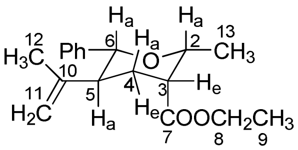


Figure 5.3.1. ORTEP diagram of (2*R**,3*R**,5*S**,6*R**)-ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (**33g**).

Table 5.3.2. Comparision of ^{1}H NMR data of **32a** and **33a**



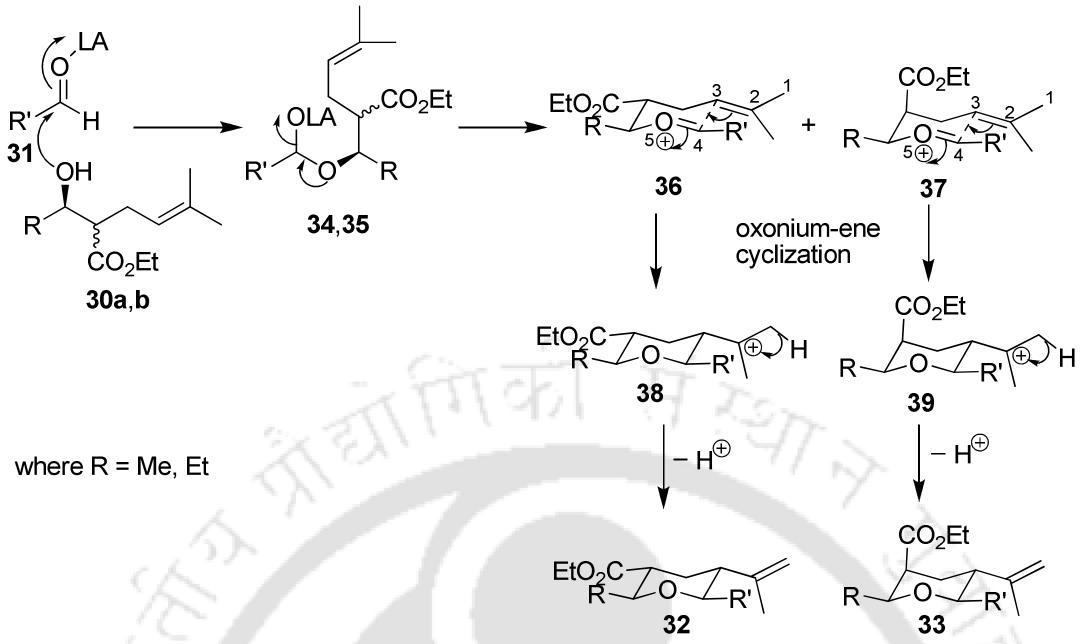
32a



33a

Assignment	δ (ppm)	Multiplicity	Coupling constants (Hz)
13-CH$_3$	1.27 (**32a**)	d	7.2
	1.32 (**33a**)	d	6.4
9-CH$_3$	1.28 (**32a**)	t	7.2
	1.33 (**33a**)	t	7.2
12-CH$_3$	1.43 (**32a**)	s	-
	1.42 (**33a**)	s	-
H$_{4a}$	1.99 (**32a**)	ddd	12.8, 12.4, 12.4
	1.90 (**33a**)	ddd	13.6, 12.8, 5.2
H$_{4e}$	2.09 (**32a**)	ddd	12.8, 4.0, 4.0
	2.14 (**33a**)	ddd	13.6, 4.0, 4.0
H$_{3a}$	2.33 (**32a**)	ddd	12.4, 10.4, 4.0
H$_{3e}$	2.60-2.67 (**33a**)	m	-
H$_{5a}$	2.46 (**32a**)	ddd	12.4, 10.0, 4.0
	3.01 (**33a**)	ddd	12.8, 12.4, 3.6
H$_{2a}$	3.76-3.85 (**32a**)	m	-
	3.82-3.89 (**33a**)	m	-
8-CH$_2$-	4.17 (**32a**)	q	7.2
	4.14-4.28 (**33a**)	m (overlapping)	-
H$_{6a}$	4.29 (**32a**)	d	10.0
	4.14-4.28 (**33a**)	m (overlapping)	-
11H	4.62 (**32a**)	brs	-
	4.63 (**33a**)	brs	-
11H	4.66 (**32a**)	brs	-
	4.67 (**33a**)	brs	-
Ar-H	7.22-7.32 (**32a**)	m	-
	7.22-7.25,7.26-7.31 7.32-7.36 (**33a**)	m	-

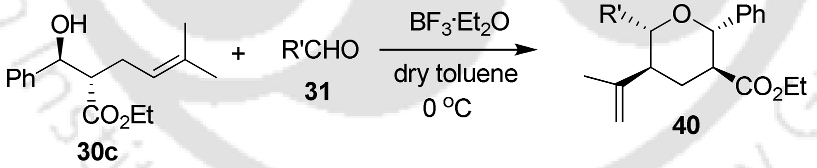
The mechanism for the formation of two diastereomers **32** and **33** from alcohols **30a** and **30b** can be explained as follows (Scheme 5.3.3). Here, Lewis acid activates the aldehyde **31** for the nucleophilic attack by alcohols **30a** and **30b** to give acetals **34** and **35**, which after decomposition generate oxocarbenium ions **36** and **37**. The species **36** and 37 after (3,5)-oxonium-ene reaction form carbocations 3**8** and **39**, which after deprotonation give **32** and **33** in equal amounts.



Scheme 5.3.3. Mechanism for the formation of tetrahydropyrans

The reaction was also performed with *anti*- and *syn*-alcohols **30c** and **30d**. The reaction of aldehyde **31** with *anti*-ethyl 2-(hydroxy(phenyl)methyl)-5-methylhex-4-enoate **30c** gave single diastereomer **40** in good yields (Table 5.3.3). The stereochemistry of the compounds was determined by X-ray crystallographic analysis (Figure 5.3.2).[18]

Table 5.3.3. Synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans from *anti*-alcohol **30c**



Entry	Aldehyde R' =	Time (min)	Product	Yield^a (%)
1	C_6H_5 (a)	60	**40a**	80
2	*p*-Me-C_6H_4 (b)	60	**40b**	70
3	*p*-MeO-C_6H_4 (c)	60	**40c**	74
4	*p*-F-C_6H_4 (d)	60	**40d**	60
5	*p*-NO_2-C_6H_4 (e)	60	**40e**	60
6	*p*-MeO_2C-C_6H_4 (f)	60	**40f**	65
7	C_2H_5 (g)	30	**40g**	92
8	$(CH_3)_2CHCH_2$ (h)	30	**40h**	87

^{a}Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR and mass spectroscopy.

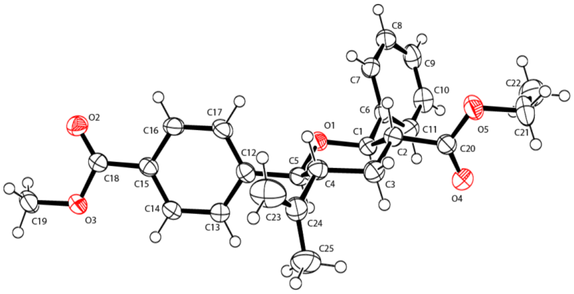
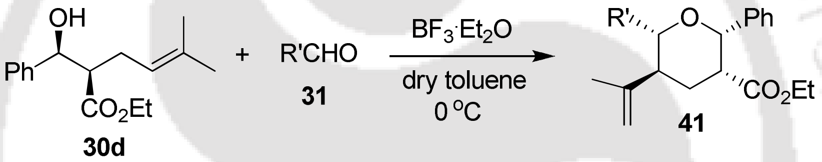


Figure 5.3.2. ORTEP diagram of (2*S**,3*S**,5*S**,6*R**)-ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (**40f**).

Similarly, the reaction of *syn*-ethyl 2-(hydroxy(phenyl)methyl)-5-methylhex-4-enoate **30d** gave single diastereomer **41** in good yields (Table 5.3.4). The stereochemistry of the compounds was determined by NOE experiment (Figure 5.3.3). In the ^{1}H NMR spectrum of **41e** the coupling constant between H_{2a} (4.69 ppm) and H_{3e} (2.94-2.98 ppm) is 3.2 Hz which indicates that one proton is in an axial position and other in an equatorial position. The

Table 5.3.4. Synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans from *syn*-alcohol **30d**



Entry	Aldehyde R' =	Time (min)	Product	Yield[a] (%)
1	*p*-Me-C_6H_4 (a)	60	**41a**	72
2	*p*-Br-C_6H_4 (b)	60	**41b**	58
3	*p*-Cl-C_6H_4 (c)	60	**41c**	55
4	*p*-MeO_2C-C_6H_4 (d)	60	**41d**	62
5	C_3H_7 (e)	30	**41e**	90
6	*cyclo*-C_6H_{11} (f)	30	**41f**	80

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

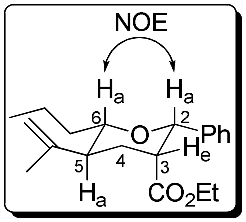


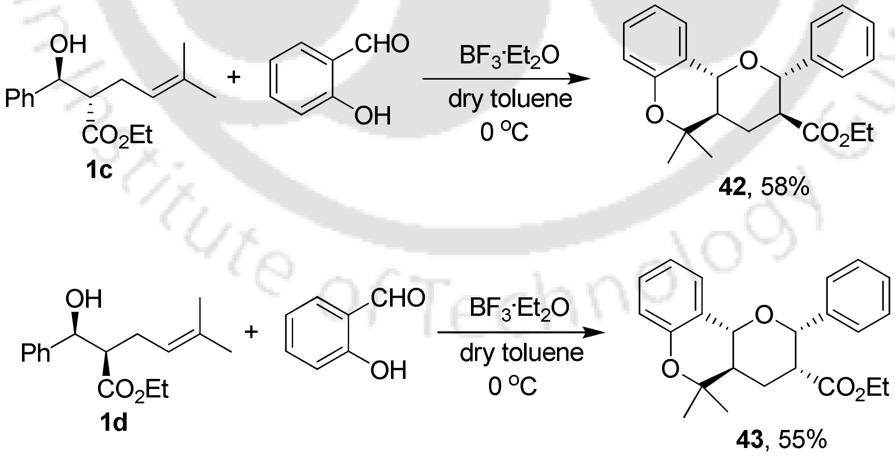
Figure 5.3.3. NOE diagram of compound **41e**

presence of a strong NOE between H_{2a} and H_{6a} (3.47 ppm) confirms that they are in a 1,3-diaxial position. Therefore H_{3e} proton is in an equatorial position. Again the coupling constant between H_{5a} (2.79 ppm) and H_{6a} proton is 10.4 Hz which indicates that they are in diaxial positions.

It was observed from Tables 5.3.1, 5.3.3 and 5.3.4 that aliphatic aldehydes gave better yields compared to the aromatic aldehydes. The aromatic aldehydes having electron-withdrawing groups gave lower yield than the aromatic aldehydes having electron-donating groups. This might be due to the better stability imparted to the oxocarbenium ions **36** and **37** (Scheme 5.3.3) by the aliphatic and aromatic aldehydes having electron donating groups on the aromatic ring, which in turn is attacked by the double bond efficiently. On the other hand aromatic aldehydes having electron withdrawing groups on the ring destabilize the oxocarbenium ions **36** and **37**.

The mechanisms for the formation of 2,3,5,6-substituted tetrahydropyrans **40** and **41** is similar to one shown in Scheme 5.3.3.

The reaction of salicyldehyde with *anti*/*syn*-ethyl 2-(hydroxy(phenyl)methyl)-5-methylhex-4-enoate, **30c** and **30d** gave tricyclic chromene compounds **42** and **43** with 58% and 55% yields, respectively (Scheme 5.3.4). Here in both the cases 30% unreacted starting materials were recovered. The structure and stereochemistry of the compounds was determined by X-ray crystallographic analysis.[18]



Scheme 5.3.4. Reaction with salicyldehyde

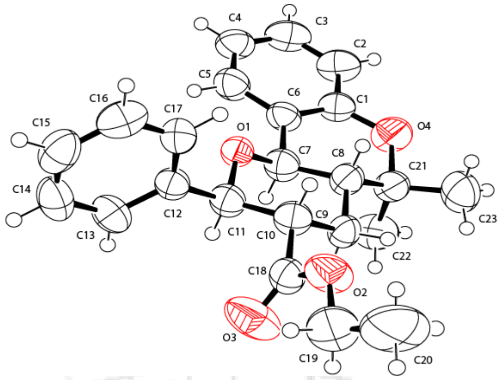


Figure 5.3.4. ORTEP diagram of (2*S**,3*S**,4a*R**,10b*R**)-ethyl 2,3,4,4a,5,10b-hexahydro-5,5-dimethyl-2-phenylpyrano[3,2-*c*]chromene-3-carboxylate (**42**)

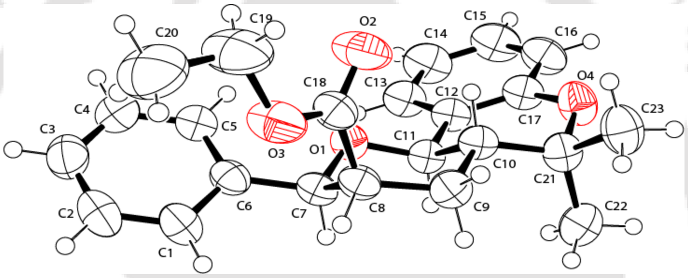
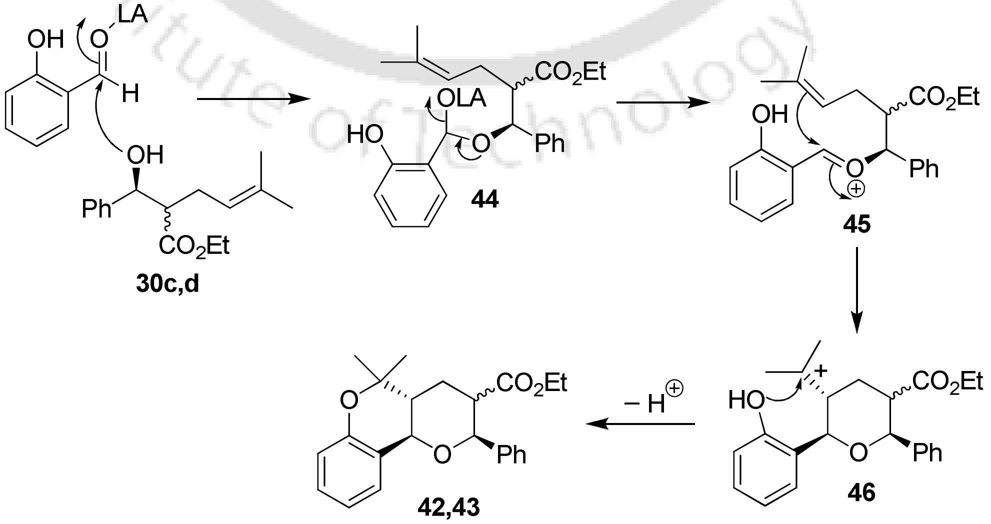


Figure 5.3.5. ORTEP diagram of (2*S**,3*R**,4a*R**,10b*R**)-ethyl 2,3,4,4a,5,10b-hexahydro-5,5-dimethyl-2-phenylpyrano[3,2-*c*]chromene-3-carboxylate (**43**)

The mechanism for the formation of chromenes is shown in Schemes 5.3.5. Here the carbocation **46** formed after oxonium-ene cyclization of **45** is attacked by nucleophilic phenolic group to form the tricyclic chromene compounds **42** and **43**. The mechanism is in accordance with the mechanism reported in the literature.[17a,b]



Scheme 5.3.5. Mechanism for the formation of chromenes

Conclusions:

In conclusion we have developed an efficient methodology for the synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans from aldehydes and *δ*-unsaturated alcohols using (3,5)-oxonium-ene reaction mediated by boron trifluoride etherate in good yields under mild conditions. Synthesis of highly substituted tetrahydropyrans is of great importance in organic synthesis as they are the key structural features in many biologically active natural products and pharmaceuticals. Therefore, the present method would be beneficial to synthetic chemistry community.

5.4 Experimental Section

5.4.1 Instrumentation and Characterization

As described in Chapter 2, Section 2.4.1.

5.4.2 General Procedure for the Synthesis of *α*-Alkyl-*β*-keto esters (D-1-3):

To a suspension of sodium hydride (15.69 mmol, 1 equiv.) in THF (15 mL) at 0 ^{o}C was added *β*-keto ester (15.69 mmol, 1 equiv.) dropwise via syringe. After 20 min, a solution of 3,3-dimethylallyl bromide (17.26 mmol, 1.1 equiv.) in THF (5 mL) was added and the mixture was left at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (10 mL) and washed with brine (25 ml). The organic layer was dried and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel to afford the title compounds as colourless oil.

Synthesis of Ethyl 2-acetyl-5-methylhex-4-enoate (D-1): To a suspension of sodium hydride (0.378 g, 15.69 mmol) in THF (15 mL) at 0 ^{o}C was added ethyl acetoacetate (2 mL, 15.69 mmol) dropwise via syringe. After 20 min, a solution of 3,3-dimethylallyl bromide (2 mL, 17.26 mmol) in THF (5 mL) was added and the mixture was left at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (10 mL) and washed with brine (25 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (10% EtOAc/hexane) to afford ethyl 2-acetyl-5-methylhex-4-enoate **D-1** (2.97 g, 95%) as a colourless oil.

5.4.3 General Procedure for the Synthesis of Ethyl 2-(1-hydroxyalkyl/hydroxy(phenyl)methyl)-5-methylhex-4-enoate (30a-d): To a solution of *α*-alkyl-*β*-keto esters (14.98 mmol, 1 equiv.) in dry MeOH (15 mL) at 0 °C, was added sodium borohydride (39.25 mmol, 2.62 equiv.) in small portions. The reaction mixture was stirred in between 0 °C to 5 °C for 1.5 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the product was extracted with ethyl acetate (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by column chromatography over silica gel to give the title compounds.

Synthesis of Ethyl 2-(1-hydroxyethyl)-5-methylhex-4-enoate (30a): To a solution of ethyl 2-acetyl-5-methylhex-4-enoate (2.97 g, 14.98 mmol) in dry MeOH (15mL) at 0 °C, was added sodium borohydride (1.485 g, 39.25 mmol) in small portions. The reaction mixture was stirred in between 0 °C to 5 °C for 1.5 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (3:22) as eluents. After completion of the reaction, the product was extracted with ethyl acetate (30 mL) and then washed with water (15 mL) and brine (15 mL). 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 an inseparable mixture of two diastereomers **30a** (2.40 g, 80% overall yield) as a colourless oil.

5.4.4 General Procedure for the Synthesis of 2,3,5,6-Tetrasubstituted Tetrahydropyrans and Chromenes: To a solution of aldehyde (1 mmol, 1 equiv.) in dry toluene (2 mL) at 0 °C was added boron trifluoride etherate (1.1 mmol, 1.1 equiv.). To this solution ethyl 2-(1-hydroxyalkyl/hydroxy(phenyl)methyl)-5-methylhex-4-enoate (1 mmol, 1 equiv.) in dry toluene (2 mL) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of (2*R,3*S**,5*S**,6*R**)/(2*R**,3*R**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32a & 33a):** To a solution of benzaldehyde (106 mg, 1.00 mmol) in dry toluene (2 mL) at 0 °C was added boron trifluoride etherate (156 mg, 1.10 mmol). To this solution ethyl 2-(1-

hydroxyethyl)-5-methylhex-4-enoate (200 mg, 1 mmol) in dry toluene (2 mL) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for another 55 min. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (1:24) as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude products, which were separated by column chromatography over silica gel to give **32a** (115 mg, 40%) and **33a** (110 mg, 38%) as colourless oil.

5.5 References and Notes

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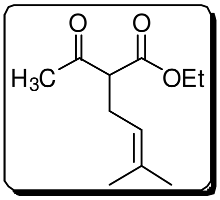
18. The crystallographic data for compounds **33g, 40f, 42** and **43** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication numbers CCDC 819363, 819365, 819364 and 819366.

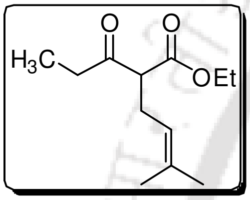
5.6 Spectral Data

Ethyl 2-acetyl-5-methylhex-4-enoate (D-1):



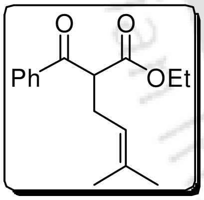
Colourless oil (2.97 g, 95%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.27 (t, *J* = 7.2 Hz, 3 H), 1.63 (s, 3 H), 1.68 (s, 3 H), 2.22 (s, 3 H), 2.54 (t, *J* = 7.2 Hz, 2 H), 3.43 (t, *J* = 7.6 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 5.03 (dt, *J* = 7.6 and 1.6 Hz, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 14.1, 17.8, 25.8, 27.0, 29.1, 59.8, 61.3, 119.9, 134.7, 169.7, 203.2; **IR** (Neat): 2981, 2930, 1739, 1718, 1205, 1150 cm^{-1}. **HRMS** (APCI) cald. for $C_{11}H_{18}O_3$ $(M+H)^+$ requires 199.1334; found 199.1337.

Ethyl 5-methyl-2-propionylhex-4-enoate (D-2):



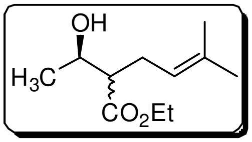
Colourless oil (3.13 g, 94%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.06 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2, 3 H), 1.62 (s, 3 H), 1.67 (s, 3 H), 2.47-2.60 (m, 4 H), 3.45 (t, *J* = 7.2 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.02 (dt, *J* =7.6 and 1.6 Hz, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 7.8, 14.2, 17.9, 25.9, 27.2, 35.6, 58.9, 61.4, 120.1, 134.8, 169.9, 206.0; **IR** (Neat): 2980, 2937, 1741, 1716, 1198, 1156 cm^{-1}. **HRMS** (APCI) cald. for $C_{12}H_{20}O_3$ (M^+) requires 212.1412; found 212.1408.

Ethyl 2-benzoyl-5-methylhex-4-enoate (D-3):



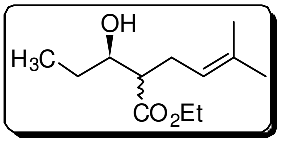
Colourless oil (3.88 g, 95%); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.67 (t, *J* = 7.2 Hz, 3 H), 1.62 (s, 3 H), 1.65 (s, 3 H), 2.61-2.78 (m, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.30 (t, *J* = 7.2 Hz, 1 H), 5.11 (dt, *J* = 7.2 and 1.6 Hz, 1 H), 7.44-7.50 (m, 2 H), 7.55-7.61 (m, 1 H), 7.97-8.00 (m, 2 H) ; ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 14.1, 17.9, 25.8, 27.8, 54.6, 61.4, 120.3, 128.7, 128.8, 133.5, 134.7, 136.4, 169.9, 195.2; **IR** (Neat): 2979, 2929, 1737, 1688, 1448, 1379, 1241, 1153 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{20}O_3$ $(M+H)^+$ requires 261.1490; found 261.1494.

Ethyl 2-(1-hydroxyethyl)-5-methylhex-4-enoate (30a):



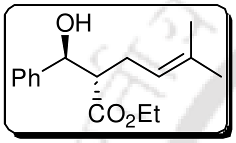
Colourless oil (2.40 g, 80% overall yield); ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.19-1.29 (m, 6 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 2.29-2.47 (m, 3 H), 2.51 (brs 0.5 H), 2.69 (brs, 0.5 H), 3.86-3.96 (m, 0.5 H), 3.98-4.06 (m, 0.5 H), 4.08-4.24 (m, 2 H), 5.04-5.14 (m, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): *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 $C_{11}H_{20}O_3$ $(M+H)^+$ requires 201.1490; found 201.1498.

Ethyl 2-(1-hydroxypropyl)-5-methylhex-4-enoate (30b):



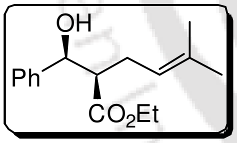
Colourless oil (2.50 g, 78%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (t, J = 7.6 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 1.5 H), 1.26 (t, J = 7.2 Hz, 1.5 H), 1.45-1.54 (m, 2 H), 1.61 (s, 1.5 H), 1.62 (s, 1.5 H), 1.69 (s, 3 H), 2.28-2.50 (m, 3 H), 2.67 (brs, 1 H), 3.56-3.64 (m, 0.5 H), 3.70-3.78 (m, 0.5 H), 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 $C_{12}H_{22}O_3$ $(M+H)^+$ requires 215.1647; found 215.1653.

***anti*-Ethyl 2-(hydroxy(phenyl)methyl)-5-methylhex-4-enoate (30c):**



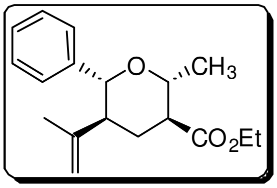
Colourless oil (1.73 g, 44%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3 H), 1.50 (s, 3 H), 1.65 (s, 3 H), 2.05 (ddd, J = 13.2, 7.6 and 5.6 Hz, 1 H), 2.25 (ddd, J = 14.8, 8.0 and 6.8 Hz, 1 H), 2.75 (ddd, J = 12.8, 8.8, 5.2 Hz, 1 H), 3.16 (d, J = 5.2 Hz, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 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) cald. for $C_{16}H_{22}O_3$ (M^+) requires 262.1569; found 262.1573.

***syn*-Ethyl 2-(hydroxy(phenyl)methyl)-5-methylhex-4-enoate (30d):**



Colourless oil (1.58 g, 40%); **^{1}H 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 $C_{16}H_{22}O_3$ $(M+H)^+$ requires 263.1647; found 263.1652.

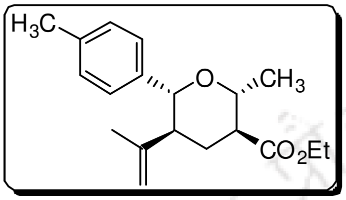
(2*R,3*S**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32a):**



Colourless oil (115 mg, 40%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (d, J = 6.4 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.99 (ddd, J = 12.8, 12.4 and 12.4 Hz, 1 H), 2.09 (ddd, J = 12.8, 4.0 and 4.0 Hz, 1 H), 2.33 (ddd, J = 12.4, 10.4 and 4.0 Hz, 1 H), 2.46 (ddd, J = 12.4, 10.0 and 4.0 Hz, 1 H), 3.76-3.85 (m, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.29 (d, J =

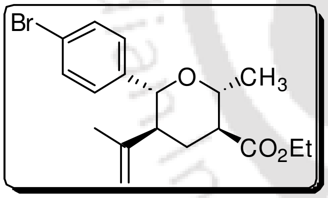
10.0 Hz, 1 H), 4.62 (brs, 1 H), 4.66 (brs, 1 H), 7.22-7.32(m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.4, 20.3, 21.5, 34.0, 49.5, 49.8, 60.6, 75.1, 84.1, 113.0, 127.5, 128.0, 128.3, 140.7, 145.1, 173.9; **IR** (Neat): 2978, 2933, 1730, 1644, 1452, 1375, 1175, 1102, 1064, 755, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_3$ $(M+H)^+$ requires 289.1803; found 289.1803.

(2*R**,3*S**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-5-(prop-1-en-2-yl)-6-*p*-tolyl-2*H*-pyran-3-carboxylate (32b):



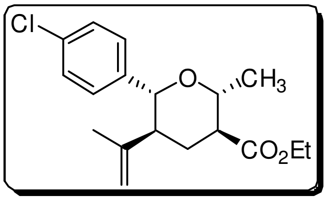
Colourless oil (115 mg, 38%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.24 (d, *J* = 6.4 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 3 H), 1.97 (ddd, *J* = 12.8, 12.6 and 12.4 Hz, 1 H), 2.10 (ddd, *J* = 12.8, 4.0 and 3.6 Hz, 1 H), 2.30 (s, 3 H), 2.34 (ddd, *J* = 12.6, 12.4 and 3.6 Hz, 1 H), 2.44 (ddd, *J* = 12.4, 10.4 and 4.0 Hz, 1 H), 3.75-3.84 (m, 1 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.26 (d, *J* = 10.4 Hz, 1 H), 4.63 (brs, 1 H), 4.65 (brs, 1 H), 7.09 (d, *J* = 7.6 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.4, 20.3, 21.3, 21.5, 34.1, 49.3, 49.8, 60.6, 75.1, 83.8, 112.9, 127.5, 129.0, 137.6, 137.7, 145.3, 174.0; **IR** (Neat): 2977, 2929, 2857, 1731, 1375, 1101, 1065, 812 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ $(M+H)^+$ requires 303.1960; found 303.1952.

(2*R**,3*S**,5*S**,6*R**)-Ethyl 6-(4-bromophenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32c):



Colourless oil (132 mg, 36%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.24 (d, *J* = 6.0 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 3 H), 1.98 (ddd, *J* = 12.8, 12.4 and 12.4 Hz, 1 H), 2.09 (ddd, *J* = 12.8, 4.0 and 3.6 Hz, 1 H), 2.25 (ddd, *J* = 12.8, 11.6 and 3.6 Hz, 1 H), 2.44 (ddd, *J* = 12.4, 10.0 and 4.0 Hz, 1 H), 3.75-3.83 (m, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.26 (d, *J* = 10.0 Hz, 1 H), 4.62 (brs, 1 H), 4.68 (brs, 1 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.4, 20.3, 21.6, 33.9, 49.7 (2C), 60.7, 75.2, 83.3, 113.4, 121.8, 129.2, 131.4, 139.9, 144.8, 173.9; **IR** (Neat): 2977, 2931, 2866, 1729, 1644, 1375, 1175, 1102, 1069, 894, 810 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}BrO_3$ $(M+H)^+$ requires 367.0909; found 367.0905 (^{79}Br).

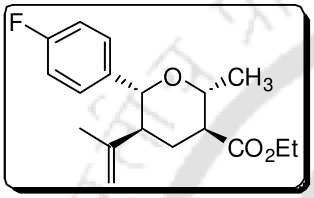
(2*R**,3*S**,5*S**,6*R**)-Ethyl 6-(4-chlorophenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32d):



Colourless oil (106 mg, 33%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.25 (d, *J* = 6.0 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 3 H), 1.97 (ddd, *J* = 12.8, 12.8 and 12.4 Hz, 1 H), 2.09 (ddd, *J* =

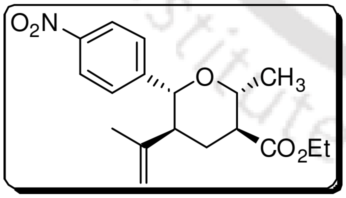
12.8, 4.0 and 3.6 Hz, 1 H), 2.25 (ddd, *J* = 12.8, 12.8 and 3.6 Hz, 1 H), 2.44 (ddd, *J* = 12.4, 10.0 and 4.0 Hz, 1 H), 3.76-3.84 (m, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.27 (d, *J* = 10.0 Hz, 1 H), 4.62 (brs, 1 H), 4.68 (brs, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 20.3, 21.6, 33.9, 49.7 (2C), 60.7, 75.2, 83.2, 113.4, 128.5, 128.8, 133.6, 139.3, 144.7, 173.8; **IR** (Neat): 2978, 2932, 2866, 1729, 1645, 1449, 1376, 1175, 1099, 1067, 894, 824 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}ClO_3$ $(M+H)^+$ requires 323.1414; found 323.1407 (^{35}Cl).

(2*R,3*S**,5*S**,6*R**)-Ethyl 6-(4-fluorophenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32e):**



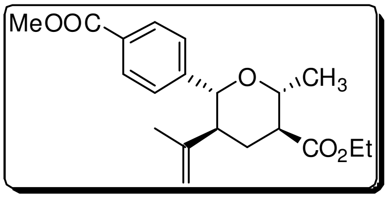
Colourless oil (89 mg, 29%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.0 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.44 (s, 3 H), 1.97 (ddd, *J* = 14.0, 12.8 and 12.0 Hz, 1 H), 2.09 (ddd, *J* = 14.0, 4.0 and 4.0 Hz, 1 H), 2.27 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 2.44 (ddd, *J* = 12.0, 10.0 and 4.0 Hz, 1 H), 3.76-3.84 (m, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.28 (d, *J* = 10.0 Hz, 1 H), 4.62 (brs, 1 H), 4.67 (brs, 1 H), 6.98 (t, *J* = 8.4 Hz, 2 H), 7.24-7.28 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 20.3, 21.5, 33.9, 49.7, 49.8, 60.7, 75.2, 83.2, 113.2, 115.0 (d, *J* = 21.3 Hz), 129.1 (d, *J* = 8.4 Hz), 136.7, 144.9, 162.5 (d, *J* = 244.1 Hz), 173.8; **^{19}F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -218.70-(-218.62) (m, 1F); **IR** (Neat): 2979, 2934, 2867, 1729, 1644, 1450, 1376, 1176, 1102, 1065, 832, 788 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}FO_3$ $(M+H)^+$ requires 307.1709; found 307.1715.

(2*R,3*S**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-(4-nitrophenyl)-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32f):**



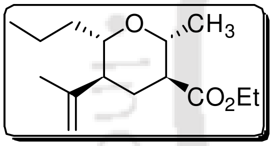
Colourless oil (117 mg, 35%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.0 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.47 (s, 3 H), 1.99 (ddd, *J* = 13.2, 12.5 and 12.4 Hz, 1 H), 2.12 (ddd, *J* = 13.2, 3.6 and 3.6 Hz, 1 H), 2.24 (ddd, *J* = 12.8, 12.5 and 3.6 Hz, 1 H), 2.47 (ddd, *J* = 12.4, 10.0 and 3.6 Hz, 1 H), 3.78-3.87 (m, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.41 (d, *J* = 10.0 Hz, 1 H), 4.61 (brs, 1 H), 4.70 (brs, 1 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 8.16 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 20.2, 21.6, 33.7, 49.5, 50.2, 60.9, 75.3, 82.8, 114.0, 123.5, 128.3, 144.1, 147.7, 148.2, 173.6; **IR** (Neat): 2975, 2935, 2871, 1726, 1643, 1519, 1372, 1344, 1170, 1101, 1060, 849 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}NO_5$ $(M+H)^+$ requires 334.1654; found 334.1652.

(2*R,3*S**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32g):**



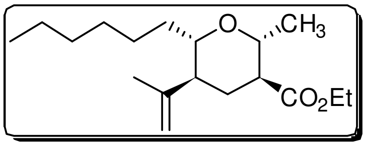
Colourless oil (125 mg, 36%); ^{1}**H NMR** (400 MHz, CDCl$_3$): *δ* 1.27 (d, *J* = 6.0 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.99 (ddd, *J* = 12.8, 12.8 and 12.4 Hz, 1 H), 2.10 (ddd, *J* = 12.8, 4.0 and 3.6 Hz, 1 H), 2.28 (ddd, *J* = 12.8, 12.0 and 4.0 Hz, 1 H), 2.47 (ddd, *J* = 12.4, 10.0 and 3.6 Hz, 1 H), 3.78-3.86 (m, 1 H), 3.90 (s, 3 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.35 (d, *J* = 10.0 Hz, 1 H), 4.60 (brs, 1 H), 4.66 (brs, 1 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.97 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): *δ* 14.3, 20.1, 21.5, 33.7, 49.5, 49.8, 52.1, 60.6, 75.0, 83.4, 113.3, 127.4, 129.5, 130.2, 144.4, 145.8, 167.0, 173.6; **IR** (Neat): 2979, 2936, 2867, 1725, 1645, 1437, 1376, 1279, 1102, 1066, 896, 772, 706 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{26}O_5$ $(M+H)^+$ requires 347.1858; found 347.1865.

(2*R,3*S**,5*S**,6*S**)-Ethyl tetrahydro-2-methyl-5-(prop-1-en-2-yl)-6-propyl-2*H*-pyran-3-carboxylate (32h):**



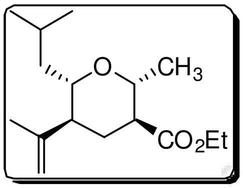
Colourless oil (115 mg, 45%); ^{1}**H NMR** (400 MHz, CDCl$_3$): *δ* 0.88 (t, *J* = 7.2 Hz, 3 H), 1.19 (d, *J* = 6.4 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.27-1.35 (m, 2 H), 1.42-1.56 (m, 2 H), 1.67 (s, 3 H), 1.80 (ddd, *J* = 12.8, 12.4 and 12.0 Hz, 1 H), 1.91 (ddd, *J* = 12.8, 4.0 and 3.6 Hz, 1 H), 1.99 (ddd, *J* = 12.4, 10.0 and 3.6 Hz, 1 H), 2.27 (ddd, *J* = 12.0, 10.0 and 4.0 Hz, 1 H), 3.31 (dt, *J* = 9.2 and 7.2 Hz, 1 H), 3.54-3.63 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.76 (brs, 1 H), 4.77 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): *δ* 14.1, 14.3, 18.8, 20.2(2C), 33.8, 35.5, 48.8, 49.8, 60.5, 74.5, 79.5, 112.7, 146.1, 174.1; **IR** (Neat): 2960, 2937, 2872, 1732, 1644, 1452, 1376, 1150, 1113, 1037, 893, 750 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O_3$ $(M+H)^+$ requires 255.1960; found 255.1964.

(2*R,3*S**,5*S**,6*S**)-Ethyl 6-hexyl-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32i):**



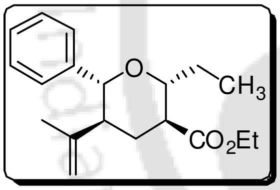
Colourless oil (127 mg, 43%); ^{1}**H NMR** (400 MHz, CDCl$_3$): *δ* 0.87 (t, *J* = 6.8 Hz, 3 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 1.24-1.34 (m, 8 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.47-1.52 (m, 2 H), 1.67 (s, 3 H), 1.80 (ddd, *J* = 12.8, 12.4 and 12.0 Hz, 1 H), 1.91 (ddd, *J* = 12.8, 4.0 and 3.6 Hz, 1 H), 1.97 (ddd, *J* = 12.4, 10.4 and 3.6 Hz, 1 H), 2.28 (ddd, *J* = 12.0, 10.4 and 4.0 Hz, 1 H), 3.29 (dt, *J* = 8.8 and 8.4 Hz, 1 H), 3.55-3.64 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.75 (brs, 1 H), 4.77 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): *δ* 14.3, 14.4, 20.2(2C), 22.9, 25.7, 29.5, 32.1, 33.5, 33.9, 48.8, 49.8, 60.6, 74.6, 79.9, 112.8, 146.1, 174.2; **IR** (Neat): 2929, 2858, 1732, 1643, 1455, 1376, 1174, 1115, 1035, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{32}O_3$ $(M+H)^+$ requires 297.2429; found 297.2424.

(2*R,3*S**,5*S**,6*S**)-Ethyl tetrahydro-6-isobutyl-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32j):**



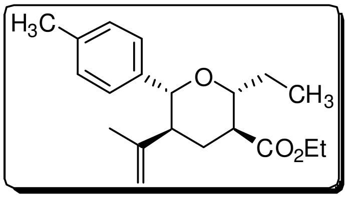
Colourless oil (110 mg, 41%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.85 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 1.19 (d, *J* = 6.0 Hz, 3 H), 1.24-1.30 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.66 (s, 3 H), 1.76-1.99 (m, 4 H), 2.28 (ddd, *J* = 10.0, 10.0 and 4.0 Hz, 1 H), 3.37 (dt, *J* = 10.0 and 7.6 Hz, 1 H), 3.54-3.62 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.75 (brs, 1 H), 4.77 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 14.4, 20.1, 20.2, 21.6, 24.0, 24.2, 33.9, 42.4, 49.3, 49.8, 60.5, 74.6, 77.9, 112.8, 146.1, 174.1; **IR** (Neat): 2955, 2928, 2870, 1732, 1644, 1451, 1374, 1176, 1115, 1068, 1035, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{28}O_3$ $(M+H)^+$ requires 269.2116; found 269.2122.

(2*R,3*S**,5*S**,6*R**)-Ethyl 2-ethyl-tetrahydro-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32k):**



Colourless oil (118 mg, 39%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.96 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.46-1.57 (m, 1 H), 1.58-1.68 (m, 1 H), 2.01 (ddd, *J* = 12.8, 12.4 and 12.0 Hz, 1 H), 2.08 (ddd, *J* = 12.8, 4.4 and 4.0 Hz, 1 H), 2.28 (ddd, *J* = 12.4, 10.0 and 4.0 Hz, 1 H), 2.56 (ddd, *J* = 12.0, 10.0 and 4.4 Hz, 1 H), 3.64 (ddd, *J* = 10.0, 7.2, 3.2 Hz, 1 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.28 (d, *J* = 10.0 Hz, 1 H), 4.62 (brs, 1 H), 4.66 (brs, 1 H), 7.24-7.30 (m, 5 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 9.7, 14.4, 21.6, 27.2, 34.2, 47.5, 49.8, 60.6, 79.7, 83.9, 113.0, 127.5, 127.8, 128.2, 141.1, 145.3, 174.2; **IR** (Neat): 2963, 2929, 2855, 1724, 1644, 1447, 1379, 1177, 1102, 1061, 1027, 747, 697 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ $(M+H)^+$ requires 303.1960; found 303.1962.

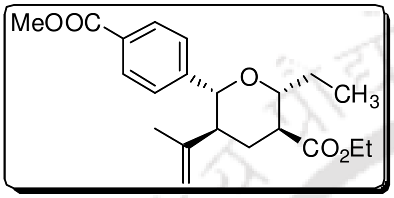
(2*R,3*S**,5*S**,6*R**)-Ethyl 2-ethyl-tetrahydro-5-(prop-1-en-2-yl)-6-*p*-tolyl-2*H*-pyran-3-carboxylate (32l):**



Colourless oil (108 mg, 34%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 3 H), 1.47-1.55 (m, 1 H), 1.56-1.65 (m, 1 H), 2.00 (ddd, *J* = 12.8, 12.0 and 12.0 Hz, 1 H), 2.07 (ddd, *J* = 12.8, 4.0 and 4.0 Hz, 1 H), 2.31 (s, 3 H), 2.32 (ddd, *J* = 12.0, 10.4 and 4.0 Hz, 1 H), 2.54 (ddd, *J* = 12.0, 10.0 and 4.0 Hz, 1 H), 3.62 (ddd, *J* = 10.4, 7.2 and 3.2 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.25

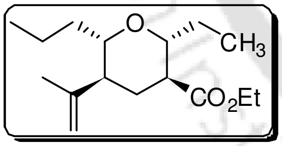
(d, *J* = 10.0 Hz, 1 H), 4.63 (brs, 1 H), 4.66 (brs, 1 H), 7.09 (d, *J* = 7.6 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 9.7, 14.4, 21.4, 21.5, 27.1, 34.3, 47.5, 49.5, 60.6, 79.7, 83.6, 112.8, 127.4, 128.9, 137.4, 138.1, 145.5, 174.2; **IR** (Neat): 2965, 2935, 2862, 1730, 1645, 1451, 1375, 1173, 1108, 1067, 967, 891, 815, 768 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{28}O_3$ $(M+H)^+$ requires 317.2116; found 317.2128.

(2*R,3*S**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-2-ethyl-tetrahydro-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32m):**



Colourless oil (133 mg, 37%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.96 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.48-1.58 (m, 1 H), 1.60-1.69 (m, 1 H), 2.02 (ddd, *J* = 13.2, 12.8 and 12.0 Hz, 1 H), 2.09 (ddd, *J* = 13.2, 4.0 and 4.0 Hz, 1 H), 2.24 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 2.57 (ddd, *J* = 12.0, 10.0 and 4.0 Hz, 1 H), 3.65 (ddd, *J* = 10.4, 7.2 and 2.8 Hz, 1 H), 3.90 (s, 3 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.33 (d, *J* = 10.0 Hz, 1 H), 4.60 (brs, 1 H), 4.67 (brs, 1 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.97(d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 9.6, 14.4, 21.7, 27.1, 34.0, 47.4, 50.0, 52.2, 60.7, 76.7, 83.3, 113.4, 127.4, 129.5(2C), 144.7, 146.2, 167.2, 174.0; **IR** (Neat): 2935, 2857, 1726, 1645, 1437, 1375, 1278, 1176, 1108, 1069, 895, 760 cm^{-1}. **HRMS** (APCI) cald. for $C_{21}H_{28}O_5$ $(M+H)^+$ requires 361.2015; found 361.2023.

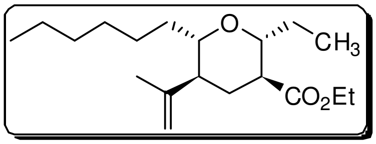
(2*R,3*S**,5*S**,6*S**)-Ethyl 2-ethyl-tetrahydro-5-(prop-1-en-2-yl)-6-propyl-2*H*-pyran-3-carboxylate (32n):**



Colourless oil (113 mg, 42%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.89 (t, *J* = 6.8 Hz, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.28-1.58 (m, 6 H), 1.67 (s, 3 H), 1.82 (ddd, *J* = 12.8, 12.4 and 12.0 Hz, 1 H), 1.92 (ddd, *J* = 12.8, 4.0 and 3.6 Hz, 1 H), 1.98 (ddd, *J* = 12.4, 10.0 and 3.6 Hz, 1 H), 2.34 (ddd, *J* = 12.0, 10.0 and 4.0 Hz, 1 H), 3.28 (dt, *J* = 10.0 and 7.2 Hz, 1 H), 3.36 (dt, *J* = 10.0 and 6.8 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.75 (brs, 1 H), 4.77 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 10.2, 14.1, 14.4, 19.0, 20.2, 27.5, 34.0, 35.6, 48.3, 49.1, 60.5, 79.4, 79.6, 112.7, 146.1, 174.3; **IR** (Neat): 2960, 2937, 2873, 1732, 1644, 1454, 1375, 1175, 1116, 1038, 1011, 893, 859 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{28}O_3$ $(M+H)^+$ requires 269.2116; found 269.2108.

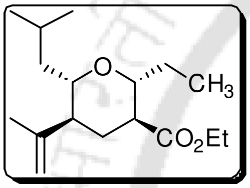
(2*R,3*S**,5*S**,6*S**)-Ethyl 2-ethyl-6-hexyl-tetrahydro-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32o):**

Colourless oil (127 mg, 41%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.87 (t, *J* = 6.4 Hz, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.25-1.35 (m, 9 H), 1.37-1.46 (m, 1 H),



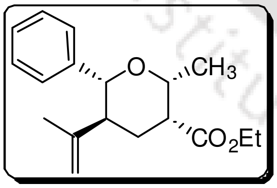
1.47-1.57 (m, 2 H), 1.66 (s, 3 H), 1.82 (ddd, J = 12.4, 12.4 and 12.4 Hz, 1 H), 1.92 (ddd, J = 12.4, 4.0 and 3.6 Hz, 1 H), 1.98 (ddd, J = 12.4, 10.0 and 3.6 Hz, 1 H), 2.33 (ddd, J = 12.4, 10.0 and 4.0 Hz, 1 H), 3.27 (dt, J = 10.0 and 8.8 Hz, 1 H), 3.35 (dt, J = 10.0 and 6.8 Hz, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.75 (brs, 1 H), 4.77 (brs, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 10.2, 14.3, 14.4, 20.2, 22.8, 25.7, 27.4, 29.3, 32.1, 33.5, 34.0, 48.3, 49.1, 60.5, 79.6, 79.7, 112.7, 146.1, 174.3; **IR** (Neat): 2930, 2857, 1732, 1640, 1454, 1375, 1173, 1117, 1038, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{34}O_3$ $(M+H)^+$ requires 311.2586; found 311.2587.

(2*R,3*S**,5*S**,6*S**)-Ethyl 2-ethyl-tetrahydro-6-isobutyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32p):**



Colourless oil (124 mg, 44%); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.86 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H), 1.17-1.58 (m, 4 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.66 (s, 3 H), 1.78-2.00 (m, 4 H), 2.33 (ddd, J = 12.0, 10.0 and 4.0 Hz, 1 H), 3.32-3.38 (m, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.75 (brs, 1 H), 4.76 (brs, 1 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 10.4, 14.4, 20.1, 21.4, 24.1, 24.3, 27.4, 34.1, 42.5, 48.4, 49.4, 60.5, 77.8, 79.8, 112.8, 146.1, 174.3; **IR** (Neat): 2956, 2928, 2870, 1732, 1644, 1462, 1374, 1175, 1153, 1117, 1070, 1016, 892, 856 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{30}O_3$ $(M+H)^+$ requires 283.2273; found 283.2275.

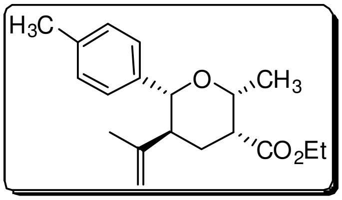
(2*R,3*R**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33a):**



Colourless oil (110 mg, 38%); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.32 (d, J = 6.4 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 1.42 (s, 3 H), 1.90 (ddd, J = 13.6, 12.8 and 5.2 Hz, 1 H), 2.14 (ddd, J = 13.6, 4.0 and 4.0 Hz, 1 H), 2.60-2.67 (m, 1 H), 3.01 (ddd, J = 12.8, 12.4 and 4.0 Hz, 1 H), 3.82-3.89 (m, 1 H), 4.14-4.28 (m, 3 H), 4.63 (brs, 1 H), 4.67 (brs, 1 H), 7.22-7.25 (m, 1 H), 7.26-7.31(m, 2 H), 7.32-7.36 (m, 2 H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.6, 20.0, 21.8, 32.7, 44.4, 45.2, 60.3, 74.3, 85.0, 112.6, 127.7, 127.8, 128.2, 141.3, 145.8, 173.0; **IR** (Neat): 2979, 2934, 1732, 1644, 1449, 1383, 1174, 1160, 1073, 758, 700 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_3$ $(M+H)^+$ requires 289.1803; found 289.1799.

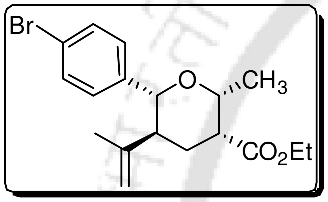
(2*R,3*R**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-5-(prop-1-en-2-yl)-6-*p*-tolyl-2*H*-pyran-3-carboxylate (33b):**

Colourless oil (103 mg, 34%); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.32 (d, J = 6.8 Hz, 3 H),



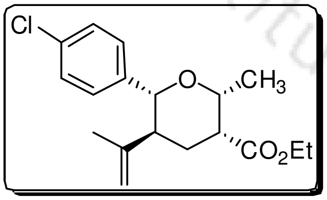
1.33 (t, J = 7.2 Hz, 3 H), 1.44 (s, 3 H), 1.90 (ddd, J = 13.6, 13.2 and 4.8 Hz, 1 H), 2.14 (ddd, J = 13.6, 4.0 and 4.0 Hz, 1 H), 2.30 (s, 3 H), 2.59-2.66 (m, 1 H), 3.02 (ddd, J = 13.2, 10.4 and 4.0 Hz, 1 H), 3.80-3.89 (m, 1 H), 4.15-4.28 (m, 3 H), 4.64 (brs, 1 H), 4.67 (brs, 1 H), 7.09 (d, J = 7.6 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 20.1, 21.4, 21.7, 32.8, 44.5, 45.0, 60.3, 74.3, 84.8, 112.5, 127.6, 129.0, 137.4, 138.4, 146.1, 173.1; **IR** (Neat): 2978, 2927, 2855, 1733, 1644, 1380, 1174, 1157, 1075, 810 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ $(M+H)^+$ requires 303.1960; found 303.1958.

(2*R,3*R**,5*S**,6*R**)-Ethyl 6-(4-bromophenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33c):**



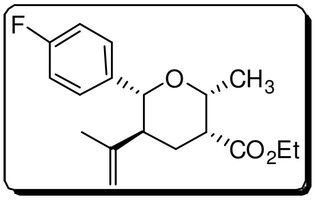
Colourless oil (110 mg, 30%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31 (d, J = 5.6 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 1.44 (s, 3 H), 1.90 (ddd, J = 13.6, 12.8 and 5.2 Hz, 1 H), 2.13 (ddd, J = 13.6, 4.0 and 3.6 Hz, 1 H), 2.60-2.67 (m, 1 H), 2.95 (ddd, J = 12.8, 12.8 and 4.0 Hz, 1 H), 3.81-3.88 (m, 1 H), 4.12-4.28 (m, 3 H), 4.62 (brs, 1 H), 4.68 (brs, 1 H), 7.22 (d, J = 8.4 Hz, 2 H), 7.41 (d, J = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 20.0, 21.8, 32.6, 44.2, 45.2, 60.3, 74.3, 84.1, 113.0, 121.7, 129.4, 131.4, 140.5, 145.4, 172.9; **IR** (Neat): 2979, 2934, 2855, 1732, 1644, 1446, 1383, 1174, 1157, 1074, 921, 813 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}BrO_3$ $(M+H)^+$ requires 367.0909; found 367.0911 (^{79}Br).

(2*R,3*R**,5*S**,6*R**)-Ethyl 6-(4-chlorophenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33d):**



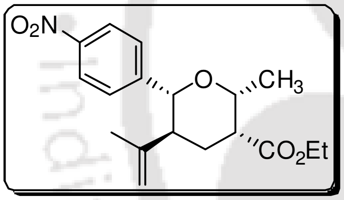
Colourless oil (94 mg, 29%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (d, J = 6.0 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.89 (ddd, J = 13.2, 12.8 and 4.8 Hz, 1 H), 2.14 (ddd, J = 13.2, 4.0 and 3.6 Hz, 1 H), 2.60-2.68 (m, 1 H), 2.95 (ddd, J = 12.8, 12.8 and 3.6 Hz, 1 H), 3.80-3.89 (m, 1 H), 4.16-4.29 (m, 3 H), 4.62 (brs, 1 H), 4.69 (brs, 1 H), 7.26 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 20.0, 21.8, 32.6, 44.2, 45.3, 60.3, 74.3, 84.1, 113.0, 128.4, 129.0, 133.4, 140.0, 145.5, 172.9; **IR** (Neat): 2978, 2933, 2857, 1731, 1644, 1447, 1382, 1174, 1157, 1076, 894, 815 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}ClO_3$ $(M+H)^+$ requires 323.1414; found 323.1405 (^{35}Cl).

(2*R**,3*R**,5*S**,6*R**)-Ethyl 6-(4-fluorophenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33e):



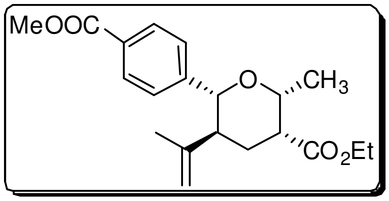
Colourless oil (107 mg, 35%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.32 (d, J = 6.4 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.89 (ddd, J = 13.6, 12.8 and 4.6 Hz, 1 H), 2.14 (ddd J = 13.6, 4.0 and 3.6 Hz, 1 H), 2.60-2.67 (m, 1 H), 2.97 (ddd, J = 12.8, 10.4 and 4.0 Hz, 1 H), 3.82-3.89 (m, 1 H), 4.18-4.28 (m, 3 H), 4.63 (brs, 1 H), 4.69 (brs, 1 H), 6.98 (t, J = 8.8 Hz, 2 H), 7.30-7.34 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.6, 20.0, 21.8, 32.6, 44.3, 45.4, 60.3, 74.3, 84.1, 112.8, 115.1 (d, J = 20.6 Hz), 129.3 (d, J = 9.7 Hz), 137.3, 145.7, 162.5 (d, J = 244.1 Hz), 173.0; ^{19}**F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -219.09-(-219.01) (m, 1F); **IR** (Neat): 2979, 2934, 2858, 1732, 1644, 1448, 1382, 1176, 1157, 1075, 832 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}FO_3$ $(M+H)^+$ requires 307.1709; found 307.1702.

(2*R**,3*R**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-(4-nitrophenyl)-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33f):



Colourless oil (90 mg, 27%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.33 (d, J = 5.6 Hz, 3 H), 1.34 (t, J = 7.2 Hz, 3 H), 1.46 (s, 3 H), 1.89 (ddd, J = 14.0, 12.8 and 5.2 Hz, 1 H), 2.16 (ddd, J = 14.0, 4.0 and 2.0 Hz, 1 H), 2.63-2.70 (m, 1 H), 2.95 (ddd, J = 12.8, 12.4 and 4.0 Hz, 1 H), 3.84-3.92 (m, 1 H), 4.17-4.28 (m, 2 H), 4.37 (d, J = 10.4 Hz, 1 H), 4.62 (brs, 1 H), 4.72 (brs, 1 H), 7.51 (d, J = 8.8 Hz, 2 H), 8.16 (d, J = 8.8 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.6, 19.9, 21.7, 32.4, 44.0, 45.6, 60.5, 74.3, 83.6, 113.6, 123.5, 128.5, 144.7, 147.6, 148.8, 172.8; **IR** (Neat): 2979, 2935, 2858, 1728, 1643, 1520, 1447, 1345, 1174, 1077, 851, 752 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}NO_5$ $(M+H)^+$ requires 334.1654; found 334.1666.

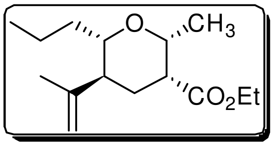
(2*R**,3*R**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33g):



Colourless solid; M.P.: 100-102 °C (111 mg, 32%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3 H), 1.34 (d, J = 6.8 Hz, 3 H), 1.41 (s, 3 H), 1.92 (ddd, J = 14.0, 12.8 and 5.2 Hz, 1 H), 2.15 (ddd, J = 14.0, 4.0 and 2.0 Hz, 1 H), 2.63-2.70 (m, 1 H), 2.97 (ddd, J = 12.8, 10.0 and 4.0 Hz, 1 H), 3.81-3.88 (m, 1 H), 3.89 (s, 3 H), 4.16-4.28 (m, 2 H), 4.30 (d, J = 10.0 Hz, 1 H), 4.62 (brs, 1 H), 4.68 (brs, 1 H), 7.42 (d, J = 8.4 Hz, 2 H), 7.97 (d, J = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ

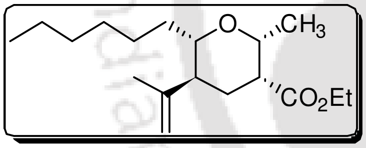
14.6, 19.9, 21.8, 32.5, 44.2, 45.4, 52.2, 60.4, 74.3, 84.4, 113.1, 127.6, 129.6 (2C), 145.2, 146.5, 167.2, 172.9; **IR** (KBr): 2955, 2928, 2873, 1726, 1643, 1449, 1277, 1173, 1158, 1076, 772, 705 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{26}O_5$ $(M+H)^+$ requires 347.1858; found 347.1868.

(2*R,3*R**,5*S**,6*S**)-Ethyl tetrahydro-2-methyl-5-(prop-1-en-2-yl)-6-propyl-2*H*-pyran-3-carboxylate (33h):**



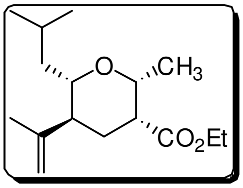
Colourless oil (104 mg, 41%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.6 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.28 (d, *J* = 6.0 Hz, 3 H), 1.30-1.42 (m, 2 H), 1.43-1.58 (m, 2 H), 1.67 (s, 3 H), 1.72 (ddd, *J* = 13.6, 12.8 and 5.2 Hz, 1 H), 1.98 (ddd, *J* = 13.6, 4.0 and 2.4 Hz, 1 H), 2.49-2.55 (m, 1 H), 2.63 (ddd, *J* = 12.8, 10.0 and 4.0 Hz, 1 H), 3.26 (dt, *J* = 10.0 and 6.0 Hz, 1 H), 3.62-3.70 (m, 1 H), 4.11-4.21 (m, 2 H), 4.77 (brs, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.4, 18.8, 19.8, 20.2, 32.6, 35.6, 44.2, 44.3, 60.1, 73.9, 80.7, 112.4, 146.7, 173.0; **IR** (Neat): 2960, 2936, 2872, 1735, 1648, 1382, 1173, 1115, 1084, 992, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O_3$ $(M+H)^+$ requires 255.1960; found 255.1965.

(2*R,3*R**,5*S**,6*S**)-Ethyl 6-hexyl-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33i):**



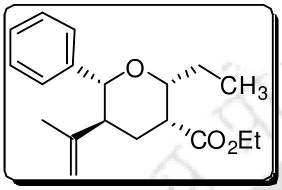
Colourless oil (116 mg, 39%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 3 H), 1.20-1.40 (m, 8 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.28 (d, *J* = 6.0 Hz, 3 H), 1.45-1.53 (m, 2 H), 1.67 (s, 3 H), 1.72 (ddd, *J* = 12.8, 12.8 and 5.2 Hz, 1 H), 1.97 (ddd, *J* = 12.8, 4.0 and 2.0 Hz, 1 H), 2.50-2.56 (m, 1 H), 2.63 (ddd, *J* = 12.8, 10.0 and 4.0 Hz, 1 H), 3.25 (dt, *J* = 10.0 and 8.4 Hz, 1 H), 3.62-3.69 (m, 1 H), 4.11-4.21 (m, 2 H), 4.77 (brs, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.3. 14.5, 19.9, 20.4, 22.9, 25.8, 29.5, 32.1, 32.6, 33.6, 44.3, 44.4, 60.2, 74.0, 81.1, 112.5, 146.8, 173.1; **IR** (Neat): 2927, 2856, 1735, 1640, 1445, 1380, 1173, 1113, 1083, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{32}O_3$ $(M+H)^+$ requires 297.2429; found 297.2424.

(2*R,3*R**,5*S**,6*S**)-Ethyl tetrahydro-6-isobutyl-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33j):**



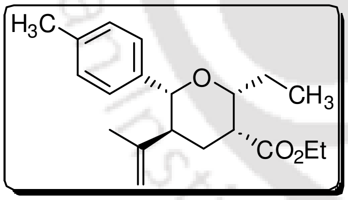
Colourless oil (115 mg, 43%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.84 (d, *J* = 6.4 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 1.19 (ddd, *J* = 10.4, 8.0 and 6.0 Hz, 1 H), 1.27 (t, *J* = 6.8 Hz, 3 H), 1.28 (d, *J* = 6.4 Hz, 3 H), 1.39 (ddd, *J* = 10.4, 6.4 and 4.0 Hz, 1 H), 1.67 (s, 3 H), 1.73 (ddd, *J* = 13.6, 13.2 and 5.2 Hz, 1 H), 1.83-1.91 (m, 1 H), 1.98 (ddd, *J* = 13.6, 4.0 and 2.0 Hz, 1 H), 2.49-2.55 (m, 1 H), 2.60 (ddd, *J* = 13.2, 10.8 and 4.0 Hz, 1 H), 3.32 (dt, *J* = 10.8 and 8.4 Hz, 1 H), 3.62-3.69 (m, 1 H), 4.11-4.21 (m, 2 H), 4.77 (brs, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 19.9, 20.2, 21.6, 24.0, 24.1, 32.7, 42.5, 44.3, 44.8, 60.2, 74.0, 79.0, 112.5, 146.8, 173.1; **IR** (Neat): 2954, 2928, 2868, 1736, 1644, 1448, 1383, 1173, 1116, 1082, 1026, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{28}O_3$ $(M+H)^+$ requires 269.2116; found 269.2112.

(2*R,3*R**,5*S**,6*R**)-Ethyl 2-ethyl-tetrahydro-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33k):**



Colourless oil (106 mg, 35%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.6 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.43 (s, 3 H), 1.57-1.74 (m, 2 H), 1.88 (ddd, *J* = 13.6, 13.2 and 5.6 Hz, 1 H), 2.16 (ddd, *J* = 13.6, 4.0 and 2.0 Hz, 1 H), 2.70-2.76 (m, 1 H), 3.03 (ddd, *J* = 13.2, 10.4 and 4.0 Hz, 1 H), 3.55 (dt, *J* = 6.8 and 2.8 Hz, 1 H), 4.16-4.26 (m, 3 H), 4.63 (brs, 1 H), 4.67 (brs, 1 H), 7.20-7.31 (m, 3 H), 7.33-7.35 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.8, 14.6, 21.8, 27.1, 32.8, 42.5, 45.5, 60.3, 80.4, 85.1, 112.6, 127.7, 128.0, 128.2, 141.5, 146.0, 173.0; **IR** (Neat): 2965, 2935, 2856, 1733, 1644, 1453, 1376, 1173, 1071, 892, 756, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ $(M+H)^+$ requires 303.1960; found 303.1969.

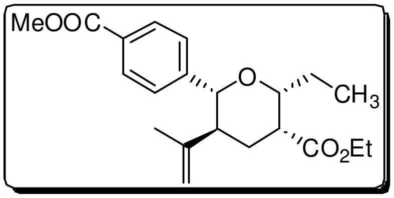
(2*R,3*R**,5*S**,6*R**)-Ethyl 2-ethyl-tetrahydro-5-(prop-1-en-2-yl)-6-*p*-tolyl-2*H*-pyran-3-carboxylate (33l):**



Colourless oil (114 mg, 36%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.6 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 3 H), 1.57-1.72 (m, 2 H), 1.86 (ddd, *J* = 13.6, 13.2 and 5.2 Hz, 1 H), 2.15 (ddd, *J* = 13.6, 4.0 and 2.0 Hz, 1 H), 2.30 (s, 3 H), 2.68-2.74 (m, 1 H), 3.03 (ddd, *J* = 13.2, 10.8 and 4.0 Hz, 1 H), 3.54 (dt, *J* = 7.2 and 4.4 Hz, 1 H), 4.14-4.26 (m, 3 H), 4.64 (brs, 1 H), 4.67 (brs, 1 H), 7.09 (d, *J* = 7.6 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.8, 14.6, 21.4, 21.7, 27.1, 32.9, 42.6, 45.3, 60.2, 80.4, 84.8, 112.5, 127.6, 128.9, 137.3, 138.5, 146.2, 173.1; **IR** (Neat): 2961, 2935, 2956, 1733, 1644, 1449, 1376, 1174, 1160, 1074, 890, 813 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{28}O_3$ $(M+H)^+$ requires 317.2116; found 317.2122.

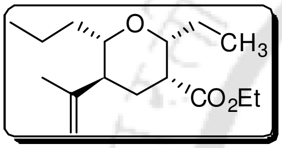
(2*R,3*R**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-2-ethyl-tetrahydro-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33m):**

Colourless oil (112 mg, 31%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.6 Hz, 3 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 1.42 (s, 3 H), 1.57-1.74 (m, 2 H), 1.89 (ddd, *J* = 12.8, 12.8 and 5.2



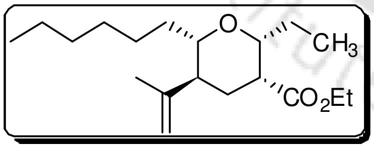
Hz, 1 H), 2.16 (ddd, *J* = 12.8, 4.0 and 2.0 Hz, 1 H), 2.71-2.77 (m, 1 H), 2.98 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 3.56 (dt, *J* = 9.6 and 3.2 Hz, 1 H), 3.89 (s, 3 H), 4.17-4.30 (m, 2 H), 4.28 (d, *J* = 10.4 Hz, 1 H), 4.62 (brs, 1 H), 4.68 (brs, 1 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.97 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.7, 14.6, 21.8, 27.1, 32.7, 42.4, 45.7, 52.2, 60.3, 80.3, 84.5, 113.0, 127.7, 129.3, 129.5, 145.4, 146.7, 167.3, 172.9; **IR** (Neat): 2935, 2851, 1726, 1644, 1436, 1376, 1278, 1176, 1112, 1078, 859, 767 cm^{-1}. **HRMS** (APCI) cald. for $C_{21}H_{28}O_5$ $(M+H)^+$ requires 361.2015; found 361.2012.

(2*R,3*R**,5*S**,6*S**)-Ethyl 2-ethyl-tetrahydro-5-(prop-1-en-2-yl)-6-propyl-2*H*-pyran-3-carboxylate (33n):**



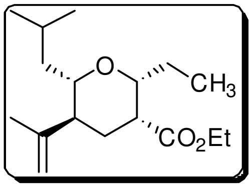
Colourless oil (123 mg, 46%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.29-1.51 (m, 4 H), 1.52-1.64 (m, 2 H), 1.67 (s, 3 H), 1.71 (ddd, *J* = 14.0, 12.4 and 5.2 Hz, 1 H), 1.98 (ddd, *J* = 14.0, 4.0 and 2.0 Hz, 1 H), 2.56-2.62 (m, 1 H), 2.64 (ddd, *J* = 12.4, 10.0 and 4.0 Hz, 1 H), 3.23 (dt, *J* = 10.0 and 6.8 Hz, 1 H), 3.35 (ddd, *J* = 8.4, 5.6 and 3.2 Hz, 1 H), 4.08-4.20 (m, 2 H), 4.77 (brs, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.0, 14.1, 14.5, 19.0, 20.4, 27.2, 32.7, 35.7, 43.0, 44.9, 60.1, 80.1, 80.9, 112.4, 146.9, 173.1; **IR** (Neat): 2960, 2936, 2874, 1736, 1644, 1456, 1379, 1174, 1115, 1084, 1033, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{16}H_{28}O_3$ $(M+H)^+$ requires 269.2116; found 269.2125.

(2*R,3*R**,5*S**,6*S**)-Ethyl 2-ethyl-6-hexyl-tetrahydro-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33o):**



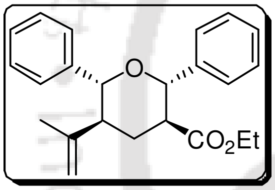
Colourless oil (121 mg, 39%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3 H), 0.99 (t, *J* = 7.6 Hz, 3 H), 1.24-1.40 (m, 10 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.47-1.54 (m, 1 H), 1.55-1.64 (m, 1 H), 1.67 (s, 3 H), 1.71 (ddd, *J* = 13.2, 12.8 and 5.2 Hz, 1 H), 1.98 (ddd, *J* = 13.2, 4.0 and 1.6 Hz, 1 H), 2.55-2.61 (m, 1 H), 2.64 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 3.22 (dt, *J* = 10.4 and 8.4 Hz, 1 H), 3.34 (ddd, *J* = 8.4, 5.6 and 3.2 Hz, 1 H), 4.09-4.20 (m, 2 H), 4.77 (brs, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.9, 14.2, 14.4, 20.3, 22.8, 25.8, 27.1, 29.4, 32.1, 32.7, 33.6, 42.9, 44.8, 60.0, 80.1, 81.1, 112.3, 146.8, 173.0; **IR** (Neat): 2930, 2857, 1736, 1644, 1457, 1378, 1173, 1157, 1085, 1032, 892 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{34}O_3$ $(M+H)^+$ requires 311.2586; found 311.2588.

(2*R,3*R**,5*S**,6*S**)-Ethyl 2-ethyl-tetrahydro-6-isobutyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33p):**



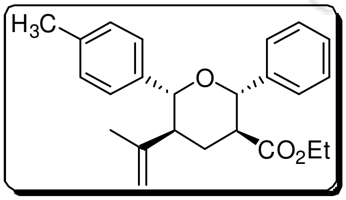
Colourless oil (113 mg, 40%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.85 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.99 (t, J = 7.2 Hz, 3 H), 1.19 (ddd, J = 10.8, 8.8 and 8.4 Hz, 1 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.42 (ddd, J = 10.4, 6.4 and 4.0 Hz, 1 H), 1.50-1.64 (m, 2 H), 1.66 (s, 3 H), 1.73 (ddd, J = 12.8, 12.8 and 4.0 Hz, 1 H), 1.85-1.94 (m, 1 H), 1.98 (ddd, J = 12.8, 4.0 and 2.0 Hz, 1 H), 2.55-2.61 (m, 1 H), 2.62 (ddd, J = 12.8, 10.0 and 4.0 Hz, 1 H), 3.27-3.37 (m, 2 H), 4.08-4.20 (m, 2 H), 4.77 (brs, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.1, 14.5, 20.2, 21.4, 24.0, 24.1, 27.1, 32.7, 42.5, 43.0, 45.2, 60.1, 79.1, 80.2, 112.5, 146.7, 173.1; **IR** (Neat): 2956, 2934, 2870, 1735, 1643, 1465, 1382, 1173, 1116, 1084, 1015, 891, 853 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{30}O_3$ $(M+H)^+$ requires 283.2273; found 283.2280.

(2*S,3*S**,5*S**,6*R**)-Ethyl tetrahydro-2,6-diphenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40a):**



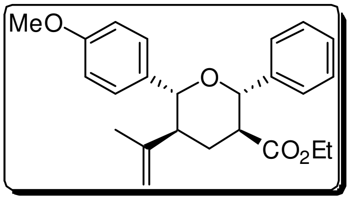
Colourless oil (280 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (t, J = 6.8 Hz, 3 H), 1.48 (s, 3 H), 2.17-2.23 (m, 2 H), 2.48 (ddd, J = 10.4, 10.0 and 3.2 Hz, 1 H), 2.87 (ddd, J = 10.0, 9.6 and 2.4 Hz, 1 H), 3.94 (q, J = 6.8 Hz, 2 H), 4.49 (d, J = 10.0 Hz, 1 H), 4.69-4.73 (m, 3 H), 7.23-7.32 (m, 4 H), 7.33-7.40 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 21.7, 34.2, 49.7, 50.5, 60.4, 81.8, 84.6, 113.2, 127.2, 127.4, 127.9, 128.2(2C), 128.4, 140.2, 140.6, 144.9, 173.1; **IR** (Neat): 2978, 2934, 2865, 1728, 1644, 1452, 1373, 1174, 1089, 1064, 755, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{26}O_3$ $(M+H)^+$ requires 351.1960; found 351.1962.

(2*S,3*S**,5*S**,6*R**)-Ethyl tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-6-*p*-tolyl-2*H*-pyran-3-carboxylate (40b):**



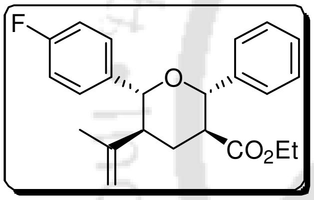
Colourless oil (255 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.2 Hz, 3 H), 1.50 (s, 3 H), 2.16-2.21 (m, 2 H), 2.29 (s, 3 H), 2.48 (ddd, J = 9.6, 9.6 and 2.4 Hz, 1 H), 2.84 (ddd, J = 9.6, 9.6 and 2.8 Hz, 1 H), 3.93 (q, J = 7.2 Hz, 2 H), 4.45 (d, J = 9.6 Hz, 1 H), 4.69-4.72 (m, 3 H), 7.08 (d, J = 7.6 Hz, 2 H), 7.22-7.30 (m, 5 H), 7.38 (d, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 21.3, 21.6, 34.2, 49.5, 50.5, 60.4, 81.8, 84.3, 113.1, 127.2, 127.4, 128.1, 128.3, 128.9, 137.5, 137.6, 140.3, 145.1, 173.2; **IR** (Neat): 2978, 2930, 2865, 1728, 1644, 1452, 1373, 1173, 1062, 892, 768 cm^{-1}. **HRMS** (APCI) cald. for $C_{24}H_{28}O_3$ $(M+H)^+$ requires 365.2116; found 365.2112.

(2*S,3*S**,5*S**,6*R**)-Ethyl tetrahydro-6-(4-methoxyphenyl)-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40c):**



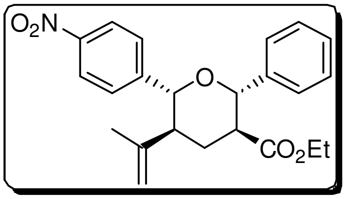
Colourless solid; M.P. 114-116 °C (281 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.2 Hz, 3 H), 1.49 (s, 3 H), 2.16-2.21 (m, 2 H), 2.47 (ddd, J = 10.0, 9.6 and 2.8 Hz, 1 H), 2.84 (ddd, J = 10.0, 9.6 and 3.2 Hz, 1 H), 3.75 (s, 3 H), 3.93 (q, J = 7.2 Hz, 2 H), 4.44 (d, J = 10.0 Hz, 1 H), 4.68-4.73 (m, 3 H), 6.82 (d, J = 7.8 Hz, 2 H), 7.20-7.31 (m, 5 H), 7.38 (d, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 21.7, 34.3, 49.7, 50.6, 55.3, 60.5, 81.9, 84.1, 113.1, 113.6, 127.3, 128.2, 128.4, 128.7, 133.0, 140.3, 145.2, 159.3, 173.2; **IR** (Neat): 2936, 2868, 1727, 1643, 1454, 1372, 1174, 1059, 1039, 910, 768 cm^{-1}. **HRMS** (APCI) cald. for $C_{24}H_{28}O_4$ $(M+H)^+$ requires 381.2066; found 381.2062.

(2*S,3*S**,5*S**,6*R**)-Ethyl 6-(4-fluorophenyl)-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40d):**



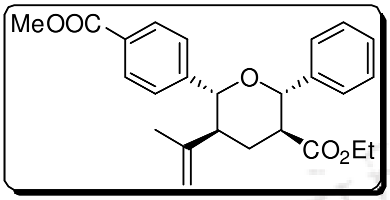
Colourless oil (221 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.2 Hz, 3 H), 1.49 (s, 3 H), 2.17-2.21 (m, 2 H), 2.42 (ddd, J = 10.4, 10.0 and 2.4 Hz, 1 H), 2.85 (ddd, J = 10.0, 9.6 and 2.8 Hz, 1 H), 3.93 (q, J = 7.2 Hz, 2 H), 4.47 (d, J = 10.4 Hz, 1 H), 4.68-4.72 (m, 3 H), 6.98 (t, J = 8.4 Hz, 2 H), 7.23-7.34 (m, 5 H), 7.38 (d, J = 7.6 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 21.7, 34.1, 50.0, 50.5, 60.5, 82.0, 83.8, 113.4, 115.0 (d, J = 21.4 Hz), 127.2, 128.4 (d, J = 10.7 Hz), 129.0, 129.1, 136.6, 140.1, 144.8, 162.5 (d, J = 243.2 Hz), 173.1; **^{19}F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -219.01-(-218.94) (m, 1F); **IR** (Neat): 2929, 2857, 1728, 1640, 1453, 1374, 1174, 1157, 1086, 1064, 836, 769 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{25}FO_3$ $(M+H)^+$ requires 369.1866; found 369.1873.

(2*S,3*S**,5*S**,6*R**)-Ethyl tetrahydro-6-(4-nitrophenyl)-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40e):**



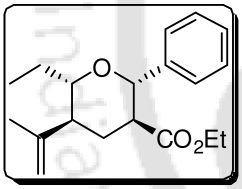
Colourless oil (237 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (t, J = 6.8 Hz, 3 H), 1.52 (s, 3 H), 2.18-2.30 (m, 2 H), 2.40 (ddd, J = 10.0, 10.0 and 2.4 Hz, 1 H), 2.89 (ddd, J = 10.4, 10.0 and 2.4 Hz, 1 H), 3.95 (q, J = 6.8 Hz, 2 H), 4.61 (d, J = 10.0 Hz, 1 H), 4.68 (brs, 1 H), 4.74 (d, J = 10.0 Hz, 1 H), 4.76 (brs, 1 H), 7.26-7.41 (m, 5 H), 7.52 (d, J = 8.8 Hz, 2 H), 8.16 (J = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 21.6, 33.9, 50.1, 50.2, 60.7, 81.9, 83.3, 114.2, 123.5, 127.2, 128.2, 128.6 (2C), 139.6, 143.9, 147.6, 147.9, 172.9; **IR** (Neat): 2978, 2927, 2855, 1729, 1606, 1522, 1347, 1176, 1070, 751, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{25}NO_5$ $(M+H)^+$ requires 396.1811; found 396.1815.

(2*S,3*S**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40f):**



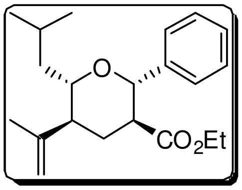
Colourless solid; M.P. 118-120 °C (266 mg, 65%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2 Hz, 3 H), 1.48 (s, 3 H), 2.17-2.23 (m, 2 H), 2.44 (ddd, *J* = 10.0, 9.6 and 2.8 Hz, 1 H), 2.89 (ddd, *J* = 10.0, 9.6 and 3.2 Hz, 1 H), 3.89 (s, 3 H), 3.94 (q, *J* = 7.2 Hz, 2 H), 4.54 (d, *J* = 10.0 Hz, 1 H), 4.67 (brs, 1 H), 4.72 (brs, 1 H), 4.73 (d, *J* = 9.6 Hz, 1 H), 7.27-7.33 (m, 3 H), 7.39-7.43 (m, 4 H), 7.97 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.0, 21.6, 33.9, 49.9, 50.3, 52.0, 60.4, 81.7, 83.9, 113.5, 127.1, 127.3, 128.2, 128.3, 129.4, 129.6, 139.9, 144.2, 145.6, 166.9, 172.8; **IR** (KBr): 2978, 2950, 2862, 1725, 1643, 1374, 1278, 1176, 1111, 1065, 897, 763 cm^{-1}. **HRMS** (APCI) cald. for $C_{25}H_{28}O_5$ $(M+H)^+$ requires 409.2015; found 409.2025.

(2*S,3*S**,5*S**,6*S**)-Ethyl 6-ethyl-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40g):**



Colourless oil (278 mg, 92%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 1.38-1.47 (m, 1 H), 1.61-1.71 (m, 1 H), 1.72 (s, 3 H), 1.99-2.05 (m, 2 H), 2.20 (ddd, *J* = 10.4, 10.0 and 5.6 Hz, 1 H), 2.67 (ddd, *J* = 10.0, 10.0 and 5.6 Hz, 1 H), 3.47 (ddd, *J* = 10.4, 10.0 and 7.6 Hz, 1 H), 3.91 (q, *J* = 7.2 Hz, 2 H), 4.51 (d, *J* = 10.0 Hz, 1 H), 4.82 (brs, 2 H), 7.24-7.36 (m, 5 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 9.8, 14.1, 20.2, 26.2, 34.0, 47.8, 50.4, 60.4, 81.2, 81.4, 112.9, 127.2, 128.1, 128.4, 140.8, 146.0, 173.5; **IR** (Neat): 2961, 2931, 2875, 1730, 1644, 1374, 1344, 1174, 1067, 894, 754, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ $(M+H)^+$ requires 303.1960; found 303.1954.

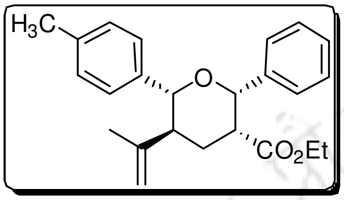
(2*S,3*S**,5*S**,6*S**)-Ethyl tetrahydro-6-isobutyl-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40h):**



Colourless oil (288 mg, 87%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.84 (d, *J* = 6.4 Hz, 3 H), 0.85 (d, *J* = 7.2 Hz, 3 H), 1.00 (t, *J* = 7.2 Hz, 3 H), 1.26 (ddd, *J* = 14.0, 10.0 and 2.0 Hz, 1 H), 1.40 (ddd, *J* = 14.0, 10.0 and 4.0 Hz, 1 H), 1.71 (s, 3 H), 1.77-1.87 (m, 1 H), 1.99-2.05 (m, 2 H), 2.11 (ddd, *J* = 9.6, 9.6 and 5.2 Hz, 1 H), 2.68 (ddd, *J* = 10.0, 10.0 and 5.6 Hz, 1 H), 3.57 (dt, *J* = 10.0 and 7.6 Hz, 1 H), 3.92 (q, *J* = 7.2 Hz, 2 H), 4.51 (d, *J* = 10.0 Hz, 1 H), 4.81 (brs, 2 H), 7.25-7.29 (m, 2 H), 7.29-7.35 (m, 3 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ

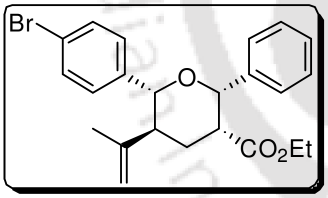
14.1, 20.1, 21.6, 24.0 (2C), 34.2, 42.5, 49.1, 50.1, 60.3, 78.5, 81.2, 113.0, 127.1, 128.0, 128.3, 140.8, 145.9, 173.5; **IR** (Neat): 2954, 2928, 2869, 1730, 1644, 1371, 1173, 1093, 1066, 849, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{21}H_{30}O_3$ $(M+H)^+$ requires 331.2273; found 331.2262.

(2*S,3*R**,5*S**,6*R**)-Ethyl tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-6-*p*-tolyl-2*H*-pyran-3-carboxylate (41a):**



Colourless oil (262 mg, 72%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.2 Hz, 3 H), 1.47 (s, 3 H), 2.12 (ddd, *J* = 14.0, 12.8 and 5.2 Hz, 1 H), 2.23 (ddd, *J* = 14.0, 4.4 and 4.0 Hz, 1 H), 2.32 (s, 3 H), 3.01-3.03 (m, 1 H), 3.15 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 3.83 (q, *J* = 7.2 Hz, 2 H), 4.38 (d, *J* = 10.4 Hz, 1 H), 4.70 (brs, 1 H), 4.72 (brs, 1 H), 4.86 (d, *J* = 3.2 Hz, 1 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.18-7.21 (m, 1 H), 7.24-7.29 (m, 2 H), 7.32-7.37 (m, 4 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.0, 21.4, 21.9, 32.8, 45.1, 45.7, 60.0, 79.4, 84.9, 112.7, 125.7, 127.3, 127.6, 128.0, 128.9, 137.4, 138.4, 140.7, 145.9, 172.4; **IR** (Neat): 2926, 2854, 1731, 1644, 1451, 1373, 1174, 1067, 1028, 814, 748 cm^{-1}. **HRMS** (APCI) cald. for $C_{24}H_{28}O_3$ $(M+H)^+$ requires 365.2116; found 365.2108.

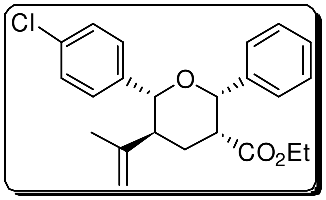
(2*S,3*R**,5*S**,6*R**)-Ethyl 6-(4-bromophenyl)-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (41b):**



Colourless oil (249 mg, 58%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.48 (s, 3 H), 2.11 (ddd, *J* = 13.6, 12.8 and 4.8 Hz, 1 H), 2.23 (ddd, *J* = 13.6, 4.0 and 2.0 Hz, 1 H), 2.98-3.02 (m, 1 H), 3.10 (ddd, *J* = 12.8, 10.0 and 4.0 Hz, 1 H), 3.84 (q, *J* = 7.2 Hz, 2 H), 4.38 (d, *J* = 10.0 Hz, 1 H), 4.69 (brs, 1 H), 4.75 (brs, 1 H), 4.86 (d, *J* = 3.2 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.20-7.36 (m, 5 H), 7.45 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.0, 21.9, 32.6, 45.2, 45.5, 60.0, 79.3, 84.2, 113.2, 126.1, 127.4, 128.1, 129.4, 130.7, 131.3, 140.3, 140.5, 145.2, 172.3; **IR** (Neat): 2978, 2934, 2859, 1730, 1644, 1484, 1374, 1174, 1070, 1031, 817, 748 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{25}BrO_3$ $(M+H)^+$ requires 429.1065; found 429.1060 (^{79}Br).

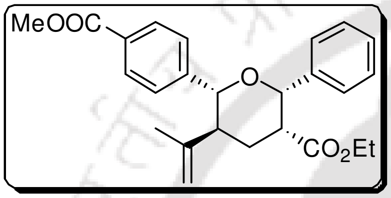
(2*S,3*R**,5*S**,6*R**)-Ethyl 6-(4-chlorophenyl)-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (41c):**

Colourless oil (212 mg, 55%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.48 (s, 3 H), 2.12 (ddd, *J* = 14.0, 12.8 and 4.8 Hz, 1 H), 2.23 (ddd, *J* = 14.0, 4.0 and 2.0 Hz, 1 H), 2.99-3.03 (m, 1 H), 3.10 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 3.84 (q, *J* = 7.2 Hz,



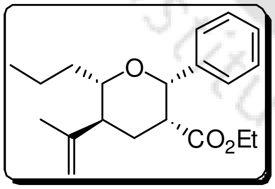
2 H), 4.40 (d, *J* = 10.4 Hz, 1 H), 4.69 (brs, 1 H), 4.75 (brs, 1 H), 4.86 (d, *J* = 3.2 Hz, 1 H), 7.20-7.31 (m, 5 H), 7.35(d, *J* = 8.8 Hz, 2 H), 7.39 (*J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 13.9, 21.9, 32.5, 45.2, 45.5, 60.0, 79.3, 84.2, 113.1, 125.6, 127.4, 128.1, 128.3, 129.0, 130.3, 140.0, 140.3, 145.2, 172.2; **IR** (Neat): 2978, 2933, 2857, 1730, 1644, 1452, 1374, 1174, 1088, 1069, 895, 748 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{25}ClO_3$ $(M+H)^+$ requires 385.1570; found 385.1565 (^{35}Cl).

(2*S,3*R**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (41d):**



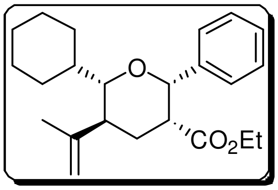
Colourless oil (253 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.90 (t, *J* = 7.2 Hz, 3 H), 1.46 (s, 3 H), 2.13 (ddd, *J* = 14.0, 12.8 and 4.8 Hz, 1 H), 2.25 (ddd, *J* = 14.0, 4.0 and 2.4 Hz, 1 H), 3.02-3.06 (m, 1 H), 3.12 (ddd, *J* = 12.8, 10.4 and 4.0 Hz, 1 H), 3.86 (q, *J* = 7.2 Hz, 2 H), 3.91 (s, 3 H), 4.48 (d, *J* = 10.4 Hz, 1 H), 4.69 (brs, 1 H), 4.74 (brs, 1 H), 4.88 (d, *J* = 3.2 Hz, 1 H), 7.20-7.24 (m, 1 H), 7.26-7.32 (m, 2 H), 7.34-7.38 (m, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 13.9, 21.9, 32.5, 45.3, 45.5, 52.1, 59.9, 79.3, 84.5, 113.3, 125.6, 127.4, 127.6, 128.1, 128.4, 129.5, 140.2, 145.0, 146.5, 167.2, 172.2; **IR** (Neat): 2983, 2951, 2857, 1725, 1644, 1372, 1276, 1177, 1100, 1070, 898, 758 cm^{-1}. **HRMS** (APCI) cald. for $C_{25}H_{28}O_5$ $(M+H)^+$ requires 409.2015; found 409.2021.

(2*S,3*R**,5*S**,6*S**)-Ethyl tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-6-propyl-2*H*-pyran-3-carboxylate (41e):**



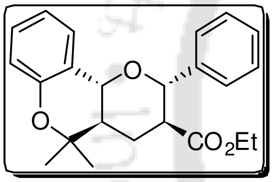
Colourless oil (285 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.83 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 6.8 Hz, 3 H), 1.39-1.46 (m, 1 H), 1.49-1.68 (m, 3 H), 1.72 (s, 3 H), 1.94 (ddd, *J* = 13.6, 13.2 and 5.6 Hz, 1 H), 2.10 (ddd, *J* = 13.6, 3.6 and 2.0 Hz, 1 H), 2.79 (ddd, *J* = 13.2, 10.4 and 3.6 Hz, 1 H), 2.94-2.98 (m, 1 H), 3.47 (ddd, *J* = 10.4, 7.2 and 7.2 Hz, 1 H), 3.77 (q, *J* = 7.2 Hz, 2 H), 4.69 (d, *J* = 3.2 Hz, 1 H), 4.83 (brs, 1 H), 4.84 (brs, 1 H), 7.20-7.26 (m, 2 H), 7.28-7.36 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 13.8, 14.3, 18.7, 20.3, 32.6, 35.6, 43.9, 45.3, 59.7, 78.9, 80.8, 112.6, 125.5, 127.0, 128.0, 141.2, 146,5, 172.3; **IR** (Neat): 2958, 2934, 2871, 1732, 1643, 1378, 1175, 1098, 1047, 894, 746 cm^{-1}. **HRMS** (APCI) cald. for $C_{20}H_{28}O_3$ $(M+H)^+$ requires 317.2116; found 317.2110.

(2*S,3*R**,5*S**,6*S**)-Ethyl 6-cyclohexyl-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (41f):**



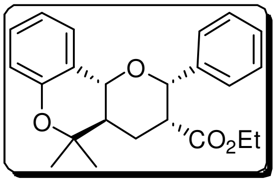
Colourless oil (285 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.2 Hz, 3 H), 1.15-1.28 (m, 4 H), 1.43-1.66 (m, 5 H), 1.72 (s, 3 H), 1.75-1.87 (m, 2 H), 1.94 (ddd, J = 13.6, 12.4 and 5.2 Hz, 1 H), 2.08 (ddd, J = 13.6, 4.4 and 2.0 Hz, 1 H), 2.90-2.93 (m, 1 H), 3.04 (ddd, J = 12.4, 10.0 and 4.0 Hz, 1 H), 3.32 (d, J = 10.0 Hz, 1 H), 3.77 (q, J = 7.2 Hz, 2 H), 4.64 (d, J = 3.2 Hz, 1 H), 4.83 (brs, 1 H), 4.84 (brs, 1 H), 7.20-7.40 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 20.2, 25.7, 26.8, 26.9, 27.0, 31.3, 32.8, 39.7, 40.1, 45.6, 59.8, 78.9, 84.8, 112.8, 125.6, 127.0, 128.0, 141.5, 146.6, 172.3; **IR** (Neat): 2933, 2854, 1737, 1643, 1373, 1168, 1157, 1099, 1058, 890, 751 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{32}O_3$ $(M+H)^+$ requires 357.2429; found 357.2435.

(2*S,3*S**,4a*R**,10b*R**)-Ethyl 2,3,4,4a,5,10b-hexahydro-5,5-dimethyl-2-phenylpyrano[3,2-*c*]chromene-3-carboxylate (42):**



Colourless solid; M.P.: 166-169 °C (213 mg, 58%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (t, J = 7.2 Hz, 3 H), 1.27 (s, 3 H), 1.45 (s, 3 H), 1.82 (ddd, J = 12.4, 12.0 and 12.0 Hz, 1 H), 1.91 (ddd, J = 12.4, 4.0 and 3.2 Hz, 1 H), 2.21 (ddd, J = 12.0, 10.0 and 3.2 Hz, 1 H), 2.77 (ddd, J = 12.0, 10.0 and 4.0 Hz, 1 H), 3.94 (q, J = 7.2 Hz, 2 H), 4.53 (d, J = 10.0 Hz, 1 H), 4.77 (d, J = 10.0 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.84-6.88 (m, 1 H), 7.14-7.19 (m, 1 H), 7.28-7.43 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 20.7, 27.9, 29.6, 43.9, 50.4, 60.7, 73.8, 78.3, 81.5, 116.9, 120.1, 122.0, 126.6, 127.4, 128.4(2C), 129.2, 140.1, 152.8, 173.2; **IR** (KBr): 2978, 2934, 2855, 1731, 1612, 1458, 1371, 1167, 1122, 1065, 759, 704 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{26}O_4$ $(M+H)^+$ requires 367.1909; found 367.1905.

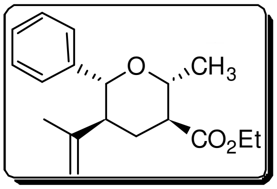
(2*S,3*R**,4a*R**,10b*R**)-Ethyl 2,3,4,4a,5,10b-hexahydro-5,5-dimethyl-2-phenylpyrano[3,2-*c*]chromene-3-carboxylate (43):**



Colourless solid; M.P.: 150-152 °C (202 mg, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.77 (t, J = 7.2 Hz, 3 H), 1.23 (s, 3 H), 1.44 (s, 3 H), 1.74 (ddd, J = 13.2, 12.8 and 5.2 Hz, 1 H), 2.27 (ddd, J = 13.2, 3.8 and 2.0 Hz, 1 H), 2.57(ddd, J = 12.8, 10.8 and 3.8 Hz, 1 H), 3.06-3.11 (m, 1 H), 3.67-3.79 (m, 2 H), 4.45 (d, J = 10.8 Hz, 1 H), 4.96 (d, J = 3.2 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.88-6.92 (m, 1 H), 7.15-7.19 (m, 1 H), 7.23-7.42 (m, 5 H), 7.52 (d, J = 7.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.8, 20.4, 27.8, 28.1, 39.6, 45.2, 60.0, 74.5, 78.4, 79.2, 116.8, 120.0, 122.3, 125.7, 126.5, 127.3, 128.1, 129.0, 140.6, 153.0, 171.8; **IR** (KBr): 2979, 2942, 2862, 1731, 1607, 1459, 1371, 1172, 1100, 1076, 760, 748 cm^{-1}. **HRMS** (APCI) cald. for $C_{23}H_{26}O_4$ $(M+H)^+$ requires 367.1909; found 367.1914.

5.7 Selected Spectra of 2,3,5,6-Tetrasubstituted Tetrahydropyrans

(2*R,3*S**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32a):**



^{1}H NMR (400 MHz, $CDCl_3$)

```
PS_392_U

exp1  s2pul

      SAMPLE                 SPECIAL
date   Nov 26 2010  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_392~ hst           0.008
           _U.fid   pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8          FLAGS
at           1.998  il               n
np           25528  in               n
fb        not used  dp               y
bs               4  hs              nn
d1           1.000       PROCESSING
nt              32  lb             0.10
ct              32  fn            65536
   TRANSMITTER            DISPLAY
tn              H1  sp           -208.5
sfrq       399.853  wp           3602.0
tof          362.8  rfl           796.2
tpwr            57  rfp               0
pw           9.850  rp            106.1
    DECOUPLER       lp            -85.7
dn             C13          PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               48
dpwr            50  th               39
dmf          15900  nm  cdc  ph
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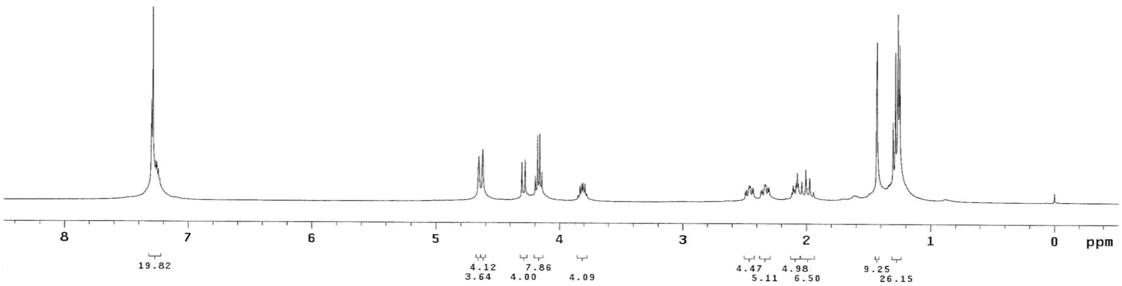

^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_392_U

exp1  s2pul

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solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_392~ hst           0.008
       U_C13.fid    pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6          FLAGS
at           1.199  il               n
np           60270  in               n
fb           13800  dp               y
bs              16  hs              nn
d1           1.000       PROCESSING
nt            3000  lb             2.00
ct             528  fn            65536
   TRANSMITTER            DISPLAY
tn             C13  sp           -620.8
sfrq       100.554  wp          21262.5
tof         1536.3  rfl          9276.7
tpwr            61  rfp          7764.9
pw           9.300  rp            -52.1
    DECOUPLER       lp           -305.8
dn              H1          PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               36
dpwr            42  th                3
dmf           8900  nm  no  ph
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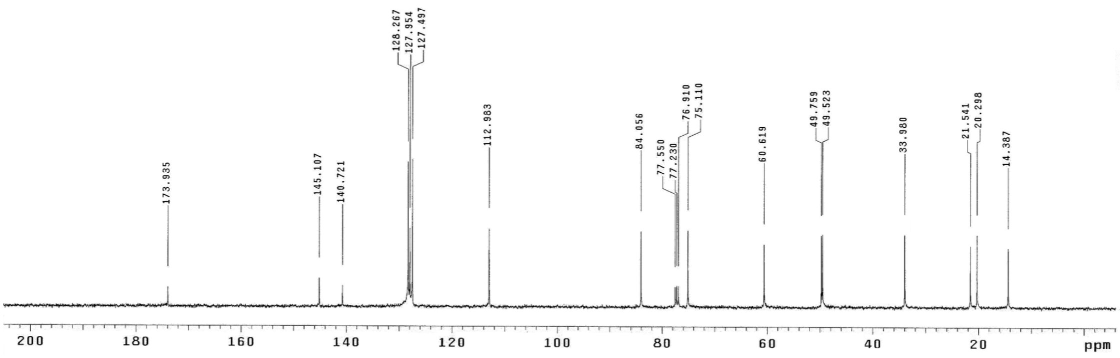
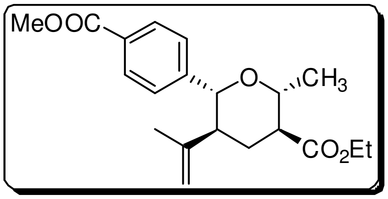


(2*R,3*S**,5*S**,6*R**)-Ethyl 6-(4-(methoxycarbonyl)phenyl)-tetrahydro-2-methyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (32g):**

^{1}H NMR (400 MHz, $CDCl_3$)



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PS_338_U

exp1  s2pul

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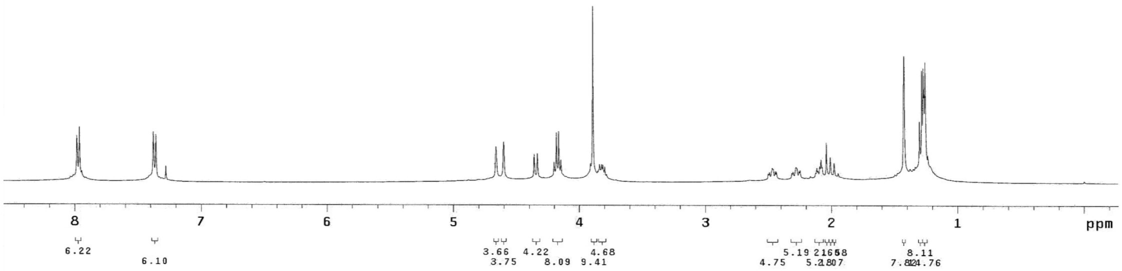
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
guest123/AKS_PS_33~ hst           0.008
         8_U.fid    pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8           FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               4  hs               nn
d1           1.000         PROCESSING
nt              32  lb             0.10
ct              32  fn            65536
   TRANSMITTER              DISPLAY
tn              H1  sp           -108.0
sfrq       399.853  wp           3531.4
tof          362.8  rfl           786.9
tpwr            57  rfp               0
pw           9.850  rp            125.8
    DECOUPLER       lp            -81.9
dn             C13            PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               42
dpwr            50  th               50
dmf          15900  nm  cdc  ph
```

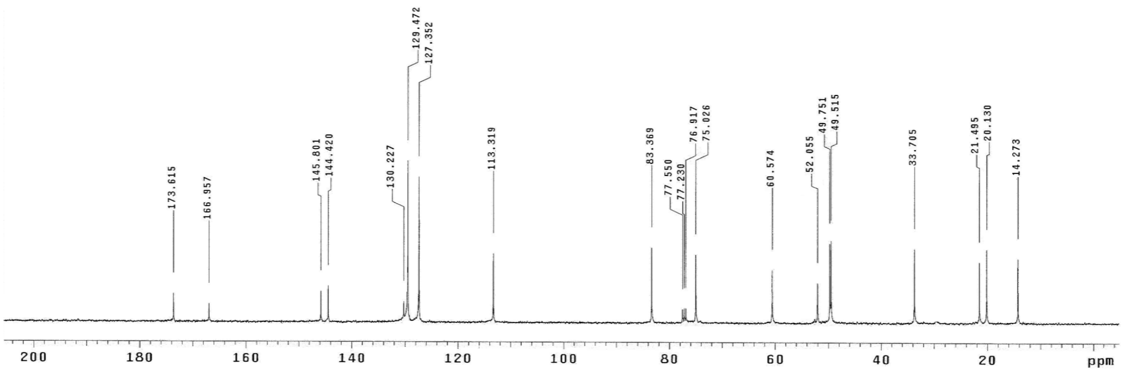


^{13}C NMR (100 MHz, $CDCl_3$)

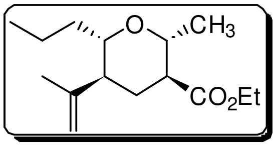
```
PS_338_U

exp1  s2pul

      SAMPLE                SPECIAL
date   Aug  6 2010  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
guest123/AKS_PS_33~ hst           0.008
       8U_C13.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6           FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000         PROCESSING
nt            3000  lb             2.00
ct             992  fn            65536
   TRANSMITTER              DISPLAY
tn             C13  sp           -492.7
sfrq       100.554  wp          21163.6
tof         1536.3  rfl          9280.5
tpwr            61  rfp          7764.9
pw           9.300  rp            -45.6
    DECOUPLER       lp           -314.3
dn              H1            PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               39
dpwr            42  th                3
dmf           8900  nm  no  ph
```



(2*R,3*S**,5*S**,6*S**)-Ethyl tetrahydro-2-methyl-5-(prop-1-en-2-yl)-6-propyl-2*H*-pyran-3-carboxylate (32h):**

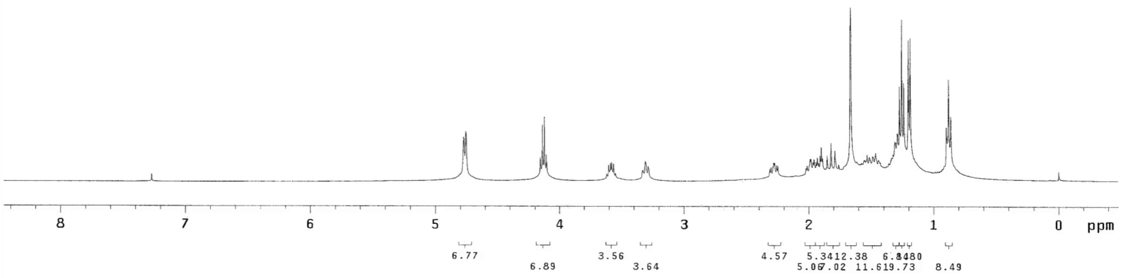


^{1}H NMR (400 MHz, CDCl$_3$)

```
PS_468_U

exp1  s2pul

      SAMPLE              SPECIAL
date   Mar 23 2011  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528        FLAGS
fb        not used  il                n
bs               8  in                n
d1           1.000  dp                y
nt             100  hs               nn
ct             100      PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853        DISPLAY
tof          362.8  sp           -194.2
tpwr            57  wp           3576.8
pw           9.850  rfl           790.4
    DECOUPLER       rfp               0
dn             C13  rp            105.1
dof              0  lp            -55.9
dm             nnn         PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               40
                    th               20
                    nm  cdc  ph
```

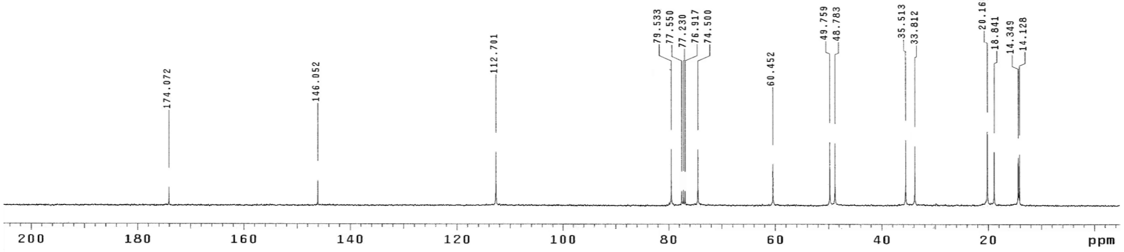


^{13}C NMR (100 MHz, CDCl$_3$)

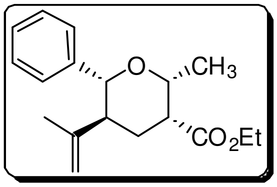
```
PS_468 U

exp1  s2pul

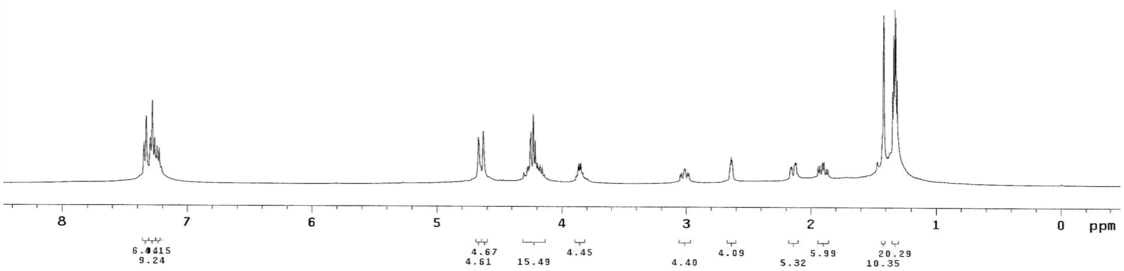
      SAMPLE              SPECIAL
date   Mar 24 2011  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270        FLAGS
fb           13800  il                n
bs              16  in                n
d1           1.000  dp                y
nt            2000  hs               nn
ct            1008      PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554        DISPLAY
tof         1536.3  sp           -482.8
tpwr            61  wp          21130.6
pw           9.300  rfl          9270.6
    DECOUPLER       rfp          7764.9
dn              H1  rp            -47.6
dof              0  lp           -338.3
dm             yyy         PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               19
                    th                2
                    nm  no  ph
```



(2*R,3*R**,5*S**,6*R**)-Ethyl tetrahydro-2-methyl-6-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (33a):**



^{1}H NMR (400 MHz, CDCl$_3$)

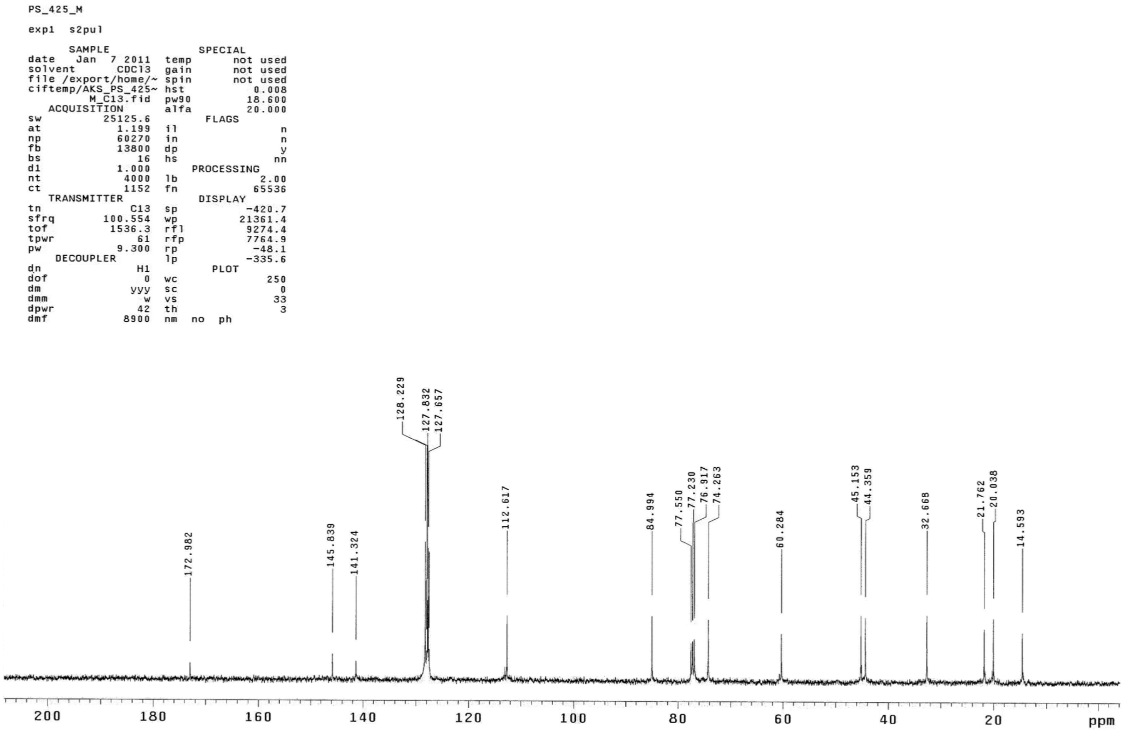


```
PS_425_M

exp1  s2pul

      SAMPLE              SPECIAL
date   Jan  7 2011  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_425~ hst           0.008
            _M.fid  pw90         19.700
   ACQUISITION      alfa         20.000
sw           6389.8           FLAGS
at            1.998  il                n
np            25528  in                n
fb         not used  dp                y
bs                8  hs               nn
d1            1.000         PROCESSING
nt              100  lb             0.10
ct              100  fn            65536
   TRANSMITTER             DISPLAY
tn               H1  sp           -193.8
sfrq        399.853  wp           3585.2
tof           362.8  rfl           798.4
tpwr             57  rfp               0
pw            9.850  rp            118.5
    DECOUPLER        lp            -98.5
dn              C13            PLOT
dof               0  wc              250
dm              nnn  sc                0
dmm               c  vs               43
dpwr             50  th               31
dmf           15900  nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$)



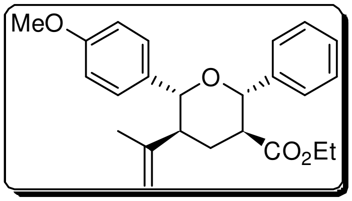
```
PS_425_M

exp1  s2pul

      SAMPLE              SPECIAL
date   Jan  7 2011  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_425~ hst           0.008
        M_C13.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw          25125.6           FLAGS
at            1.199  il                n
np            60270  in                n
fb            13800  dp                y
bs               16  hs               nn
d1            1.000         PROCESSING
nt             4000  lb             2.00
ct             1152  fn            65536
   TRANSMITTER             DISPLAY
tn              C13  sp           -420.7
sfrq        100.554  wp          21361.4
tof          1536.3  rfl          9274.4
tpwr             61  rfp          7764.9
pw            9.300  rp            -48.1
    DECOUPLER        lp           -335.6
dn               H1            PLOT
dof               0  wc              250
dm              yyy  sc                0
dmm               w  vs               33
dpwr             42  th                3
dmf            8900  nm  no  ph
```

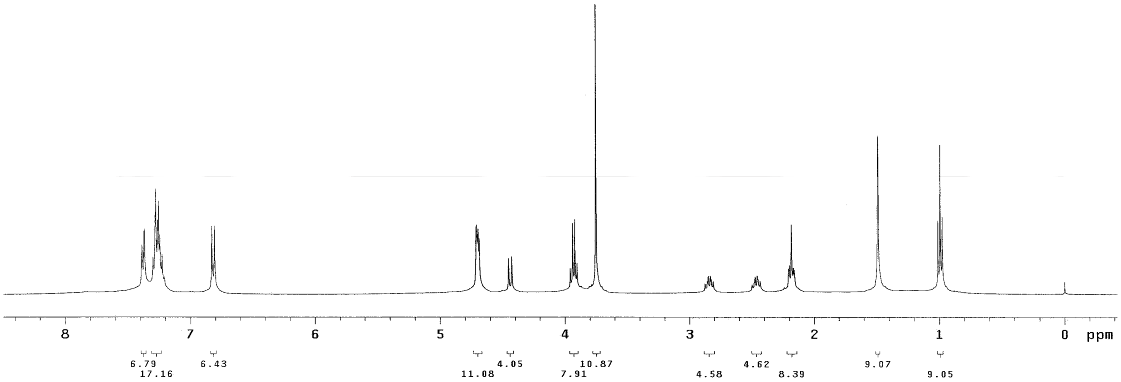
(2*S,3*S**,5*S**,6*R**)-Ethyl tetrahydro-6-(4-methoxyphenyl)-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (40c):**

^{1}H NMR (400 MHz, $CDCl_3$)



```
exp1  s2pul

      SAMPLE                SPECIAL
date   Jun  9 2011  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_494~ hst           0.008
        M_Pdt.fid   pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8         FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               4  hs               nn
d1           1.000       PROCESSING
nt              32  lb             0.10
ct              32  fn            65536
   TRANSMITTER             DISPLAY
tn              H1  sp           -171.8
sfrq       399.853  wp           3568.4
tof          362.8  rfl           801.5
tpwr            57  rfp               0
pw           9.850  rp            119.8
    DECOUPLER       lp            -91.4
dn             C13           PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               69
dpwr            50  th               42
dmf          15900  nm  cdc  ph
```

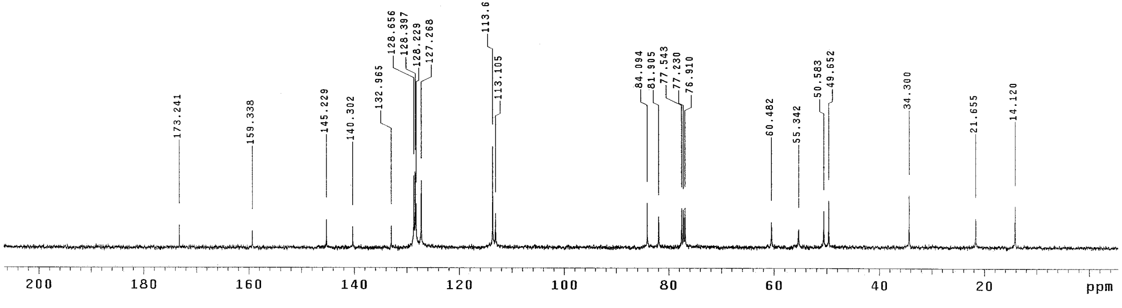


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_494_M

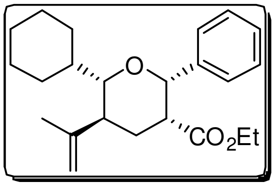
exp1  s2pul

      SAMPLE                SPECIAL
date   Jun  9 2011  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270         FLAGS
fb           13800  il                n
bs              16  in                n
d1           1.000  dp                y
nt            4000  hs               nn
ct            1552       PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554         DISPLAY
tof         1536.3  sp           -551.8
tpwr            61  wp          21328.5
pw           9.300  rfl          9273.6
    DECOUPLER       rfp          7764.9
dn              H1  rp            -47.4
dof              0  lp           -349.1
dm             yyy           PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               24
                    th                3
                    nm  no  ph
```



(2*S,3*R**,5*S**,6*S**)-Ethyl 6-cyclohexyl-tetrahydro-2-phenyl-5-(prop-1-en-2-yl)-2*H*-pyran-3-carboxylate (41f):**

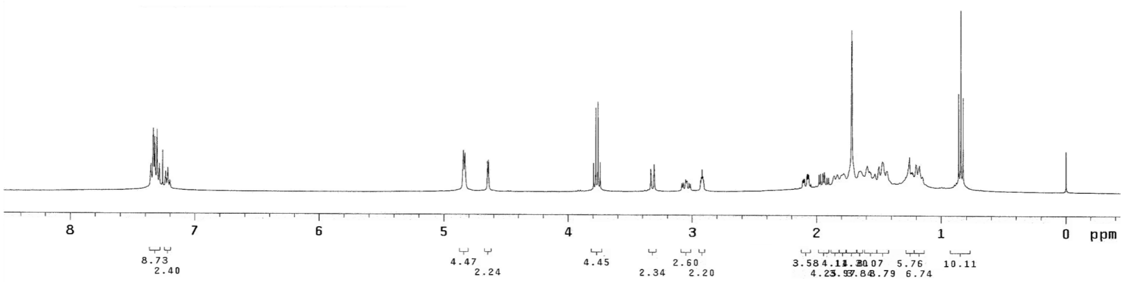
^{1}H NMR (400 MHz, CDCl$_3$)



```
PS_452_M

exp1  s2pul

      SAMPLE                 SPECIAL
date   Feb 23 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_452~ hst            0.008
           _M.fid   pw90          19.700
   ACQUISITION      alfa          20.000
sw          6389.8          FLAGS
at           1.998  il                 n
np           25528  in                 n
fb        not used  dp                 y
bs               8  hs                nn
d1           1.000        PROCESSING
nt             100  lb              0.10
ct             100  fn             65536
   TRANSMITTER               DISPLAY
tn              H1  sp            -181.4
sfrq       399.853  wp            3593.6
tof          362.8  rfl            794.3
tpwr            57  rfp                0
pw           9.850  rp             114.1
    DECOUPLER       lp             -91.7
dn             C13           PLOT
dof              0  wc               250
dm             nnn  sc                 0
dmm              c  vs                43
dpwr            50  th                20
dmf          15900  nm  cdc  ph
```

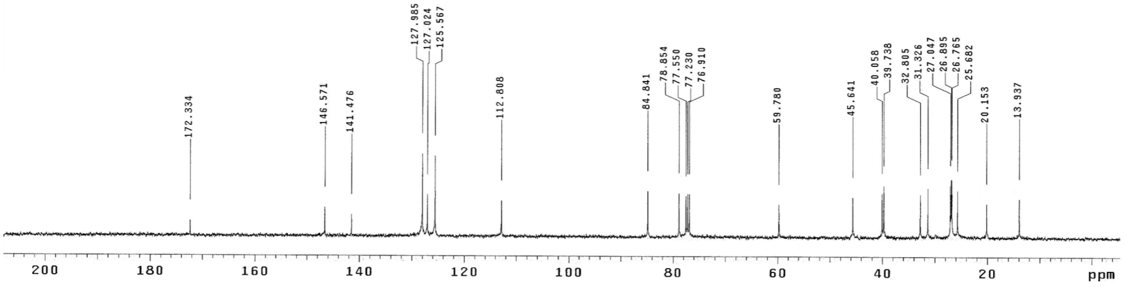


^{13}C NMR (100 MHz, CDCl$_3$)

```
PS_452_M

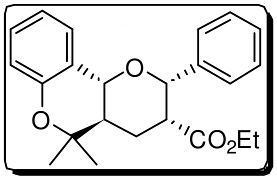
exp1  s2pul

      SAMPLE                 SPECIAL
date   Feb 23 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_452~ hst            0.008
       M_C13.fid    pw90          18.600
   ACQUISITION      alfa          20.000
sw         25125.6          FLAGS
at           1.199  il                 n
np           60270  in                 n
fb           13800  dp                 y
bs              16  hs                nn
d1           1.000        PROCESSING
nt            5000  lb              2.00
ct            2080  fn             65536
   TRANSMITTER               DISPLAY
tn             C13  sp            -549.5
sfrq       100.554  wp           21460.3
tof         1536.3  rfl           9271.3
tpwr            61  rfp           7764.9
pw           9.300  rp             -61.1
    DECOUPLER       lp            -302.7
dn              H1           PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                21
dpwr            42  th                 3
dmf           8900  nm  no  ph
```



(2*S,3*R**,4a*R**,10b*R**)-Ethyl 2,3,4,4a,5,10b-hexahydro-5,5-dimethyl-2-phenylpyrano[3,2-*c*]chromene-3-carboxylate (43):**

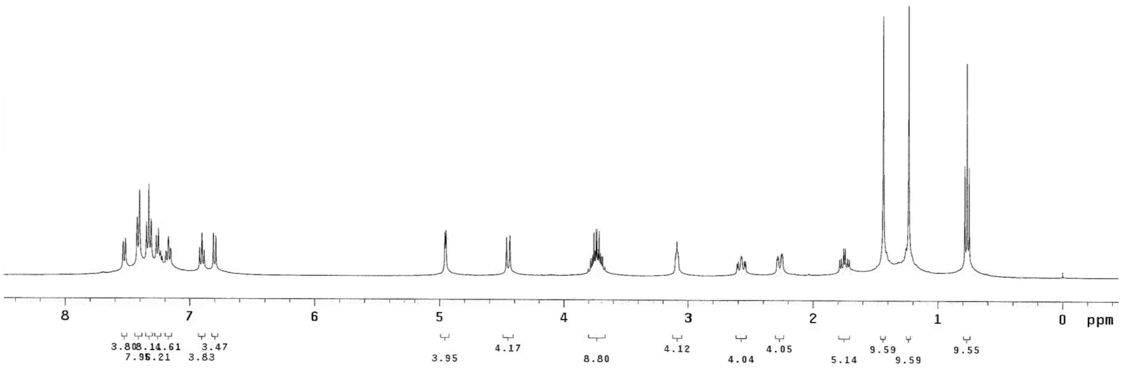
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_433_L

exp1  s2pul

      SAMPLE              SPECIAL
date   Feb 14 2011  temp      not used
solvent      CDCl3  gain      not used
file /export/home/~ spin      not used
ciftemp/AKS_PS_433~ hst          0.008
          _L1.fid   pw90        19.700
   ACQUISITION      alfa        20.000
sw          6389.8          FLAGS
at           1.998  il               n
np           25528  in               n
fb        not used  dp               y
bs               4  hs              nn
d1           1.000       PROCESSING
nt              32  lb            0.10
ct              32  fn           65536
   TRANSMITTER            DISPLAY
tn              H1  sp          -180.8
sfrq       399.853  wp          3576.8
tof          362.8  rfl          810.4
tpwr            57  rfp              0
pw           9.850  rp           129.6
    DECOUPLER       lp           -97.3
dn             C13           PLOT
dof              0  wc             250
dm             nnn  sc               0
dmm              c  vs              62
dpwr            50  th              20
dmf          15900  nm  cdc  ph
```

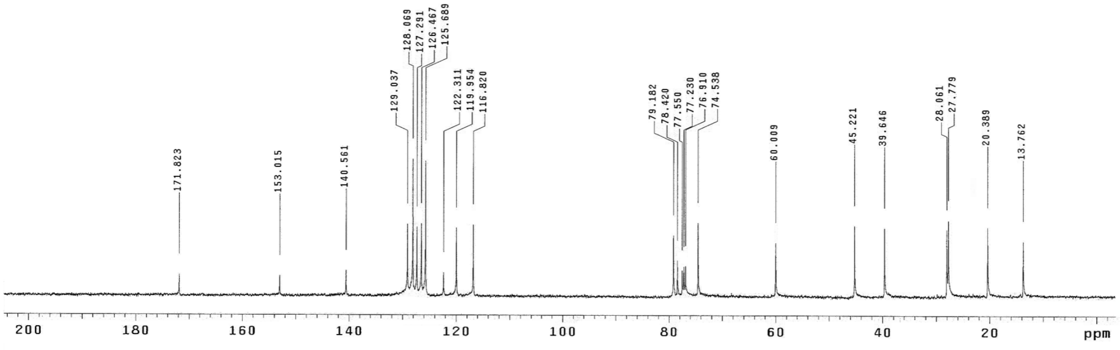


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_433_L1

exp1  s2pul

      SAMPLE              SPECIAL
date   Feb 21 2011  temp      not used
solvent      CDCl3  gain      not used
file /export/home/~ spin      not used
ciftemp/AKS_PS_433~ hst          0.008
      L1_C13.fid    pw90        18.600
   ACQUISITION      alfa        20.000
sw         25125.6          FLAGS
at           1.199  il               n
np           60270  in               n
fb           13800  dp               y
bs              16  hs              nn
d1           1.000       PROCESSING
nt            3000  lb            2.00
ct            3000  fn           65536
   TRANSMITTER            DISPLAY
tn             C13  sp          -358.5
sfrq       100.554  wp         20932.0
tof         1536.3  rfl         9279.0
tpwr            61  rfp         7764.9
pw           9.300  rp           -77.9
    DECOUPLER       lp          -269.1
dn              H1           PLOT
dof              0  wc             250
dm             yyy  sc               0
dmm              w  vs              34
dpwr            42  th               4
dmf           8900  nm  no  ph
```



5.8 Crystal Parameters

The crystal parameters of compound **33g**

Parameters	**33g**-CCDC 819363
Formula	$C_{20}H_{26}O_5$
Formula weight	346.41
T/K	296(2)
Crystal system	Orthorhombic
Space group	P n a 21
a/Å	19.8370(10)
b/Å	15.2026(8)
c/Å	6.3744(4)
α/°	90.00
β/°	90.00
γ/°	90.00
V/Å^3	1922.35(18)
Z	4
Abs. Coeff./mm^{-1}	0.085
Abs. Correction	multi-scan
GOF on F^2	0.943
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0677$ $wR2 = 0.1644$
R indices [all data]	$R1 = 0.0856$ $wR2 = 0.1735$

The crystal parameters of compound **40f**

Parameters	**40f**-CCDC 819365
Formula	$C_{25} H_{28} O_5$
Formula weight	408.47
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	12.0752(3)
b/Å	15.3970(4)
c/Å	12.4647(3)
α/°	90.00
β/°	104.3910(10)
γ/°	90.00
V/Å^3	2244.74(10)
Z	4
Abs. Coeff./mm^{-1}	0.083
Abs. Correction	multi-scan
GOF on F^2	1.070
Final *R* indices [$I > 2\sigma(I)$]	*R1* =0.0615 *wR2* = 0.1806
R indices [all data]	*R1* = 0.0759 *wR2* = 0.2203

The crystal parameters of compound **42**

Parameters	**42**-CCDC 819364
Formula	$C_{23}H_{26}O_4$
Formula weight	366.44
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/n
a/Å	8.9913(7)
b/Å	19.6654(14)
c/Å	11.4452(9)
α/°	90.00
β/°	103.239(4)
γ/°	90.00
V/Å^3	1969.9(3)
Z	4
Abs. Coeff./mm^{-1}	0.084
Abs. Correction	Multi-scan
GOF on F^2	1.064
Final R indices [$I > 2\sigma$(I)]	$R1 = 0.0667$ $wR2 = 0.1815$
R indices [all data]	$R1 = 0.0923$ $wR2 = 0.1973$

The crystal parameters of compound **43**

Parameters	**43**-CCDC 819366
Formula	$C_{23}H_{26}O_4$
Formula weight	366.44
T/K	296(2)
Crystal system	Monoclinic
Space group	P 21/c
a/Å	12.5282(8)
b/Å	8.7884(6)
c/Å	18.2013(12)
α/°	90.00
β/°	94.582(2)
γ/°	90.00
V/Å^3	1997.6(2)
Z	4
Abs. Coeff./mm^{-1}	0.082
Abs. Correction	Multi-scan
GOF on F^2	1.373
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0613$
	$wR2 = 0.1695$
R indices [all data]	$R1 = 0.0967$
	$wR2 = 0.2108$

CHAPTER 6

Diastereoselective Synthesis of Substituted Dihydropyrans via Oxonium-Ene Cyclization Reaction

6.1 Importance and Applications

Dihydropyrans are important intermediates for the synthesis of biologically active natural products such as ambruticin, phorboxazoles, leucascandrolide, kendomycin, neopeltolide, clavisolides and diospongins.[1] The 4-methyl substituted dihydropyran unit is present in macrolide natural products laulimalide and okadaic acid (Figure 6.1.1).[2] The olefin functionality of dihydropyrans can be manipulated for the synthesis of polysubstittuted tetrahydropyrans.[3] Substituted dihydropyrans are also used as a flavoring or aroma material for food and other products.[4]

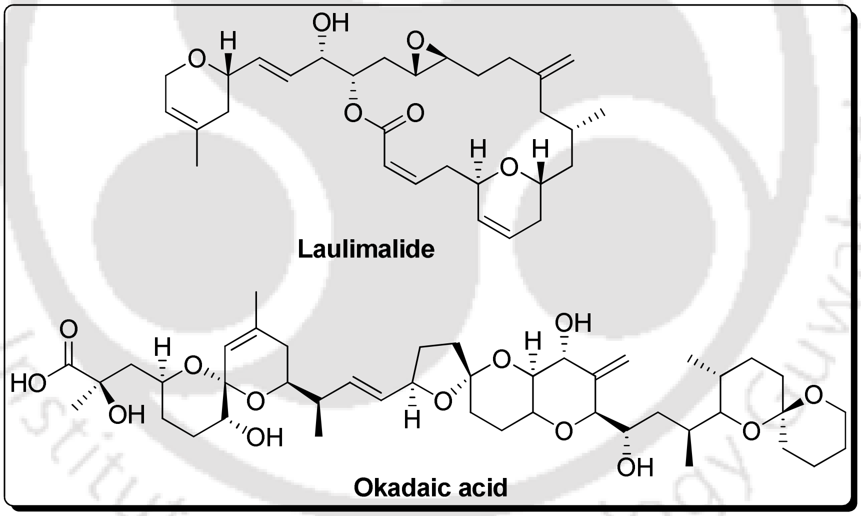


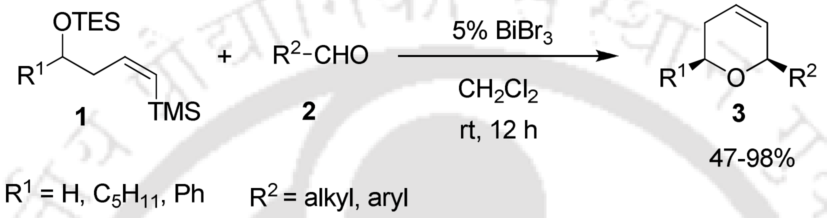
Figure 6.1.1. Biologically active natural products containing 4-methyl dihydropyran as core unit

6.2 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 because it provides the desired product in a single step. Usally Lewis acid is used for this reaction and in most of the cases, the product is a 4-halosubstituted dihydropyran, but the synthetic access to 4-alkyldihydropyrans is limited in the literature.

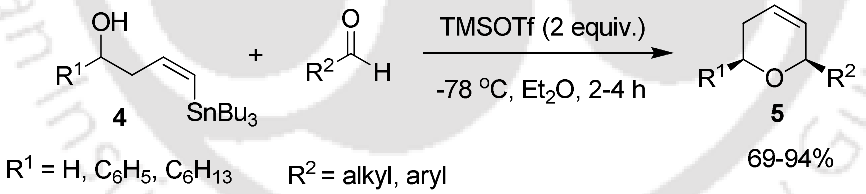
6.2.1 Prins Cyclization

Hinkle and co-workers have reported a tandem silyl-Prins reaction between δ-triethylsilyloxyvinyltrimethylsilanes and a variety of aldehydes to afford *cis*-2,6-disubstituted dihydropyrans (DHPs) using 5 mol % of $BiBr_3$ in CH_2Cl_2 (Scheme 6.2.1.1).[5] The diastereoselectivities in the crude products were significantly affected by aldehyde substitution with electron-rich aldehydes, providing 2-3:1 (*cis:trans*) and neutral (or electron-poor) aldehydes affording dr ≥ 19:1 (*cis:trans*).

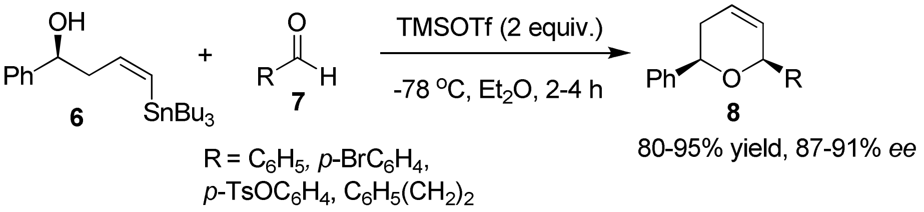


Scheme 6.2.1.1.

Furman and co-workers have reported a stereoselective synthesis of *cis*-2,6-disubstituted dihydropyrans (DHPs) via stannyl-Prins cyclization. The reaction of vinylstannanes **4** with aldehydes in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded *cis*-2,6-disubstituted dihydropyrans **5** in good yields with excellent stereoselectivity (Scheme 6.2.1.2).[6] Although the dihydropyrans are obtained in the racemic form but the use of optically pure vinylstannane afforded optically pure 2,6-disubstituted dihydropyrans (Scheme 6.2.1.3). Finally they applied this methodology for the synthesis of natural product (-)-centrolobine.[6]

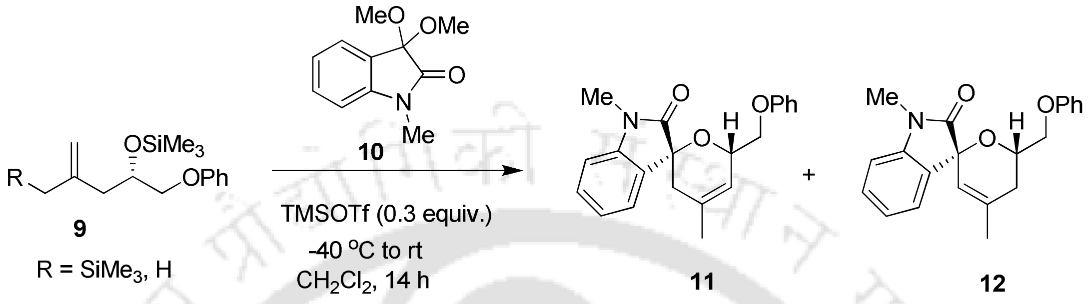


Scheme 6.2.1.2.



Scheme 6.2.1.3.

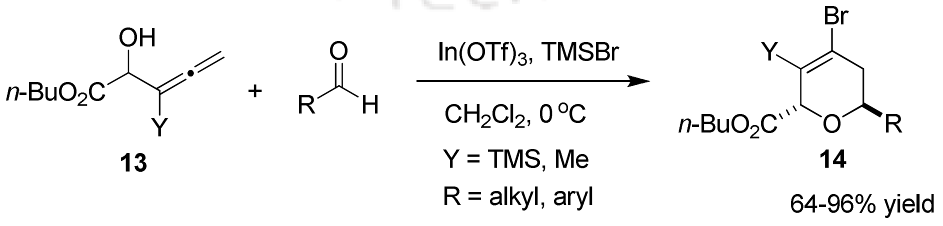
Porco, Jr. and co-workers have reported the synthesis of spirocyclic oxindole pyrans having 4-methyl substituted dihydropyran unit. These spirocyclic compounds are prepared from the reaction of homoallyl alcohols **9** with isatin ketals **10** in the presence of trimethylsilyl trifluoromethanesulfonate (Scheme 6.2.1.4).[7]



Entry	R	Additive	Yield
1	$SiMe_3$	DBMP (0.1 equiv.)	**11** = 38%, **12** = 19%
2	H	DBMP (0.1 equiv.)	**11** = 46%, **12** = 20%
3	H	None	**11** = 58%, **12** = 24%

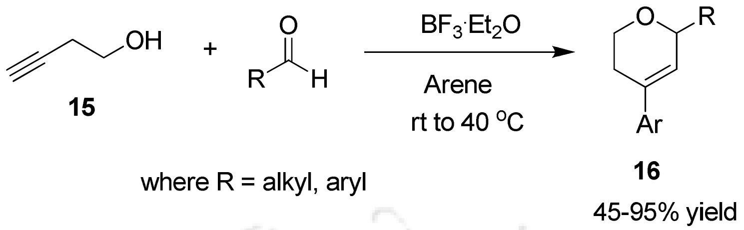
Scheme 6.2.1.4.

Loh and co-workers have reported the synthesis of 2,6-*trans* dihydropyrans from the reaction of allenic alcohols and aldehydes in the presence of indium salt catalyst in good yields.[8] However a good diastereoselectivity was obtained by using bulky-silicon substituted allenic alcohols under the same condition (Scheme 6.2.1.5). 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.[8]



Scheme 6.2.1.5.

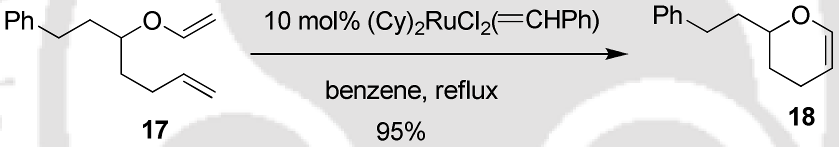
Saikia and co-workers have reported the synthesis of 4-aryl-5,6-dihydro-2*H*-pyrans from the reaction of carbonyl compounds or epoxides with homopropargyl alcohol and arenes mediated by boron trifluoride etherate by using alkyne-Prins-Friedel-Crafts reaction (Scheme 6.2.1.6).[9]



Scheme 6.2.1.6.

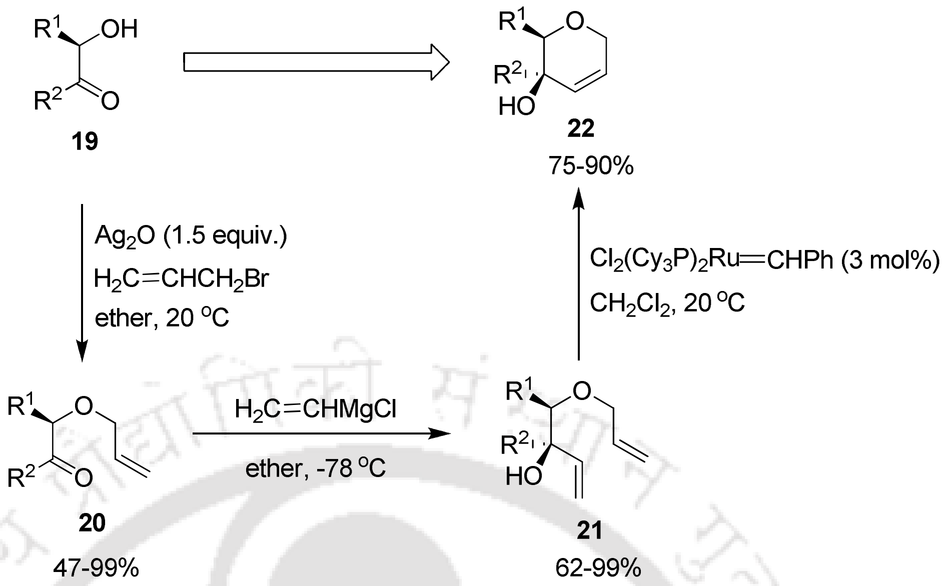
6.2.2 Olefin Metathesis

Sturino *et al.* have reported the synthesis of dihydropyrans (DHPs) by ring closing metathesis (RCM) of acyclic vinyl ethers with Grubb's catalyst (Scheme 6.2.2.1).[10] They found that vinyl ethers are excellent substrates for the ring closing metathesis (RCM) with ruthenium based catalysts.



Scheme 6.2.2.1.

Schmidt and co-workers have reported a highly diastereoselective route to enantiomerically pure dihydropyrans.[11] The synthetic concept is based on the use of *R*-hydroxy ketones which are conveniently obtained in enantiomerically pure form, a highly diastereoselective vinylation relying on efficient chelate control and a ringclosing olefin metathesis step (Scheme 6.2.2.2).

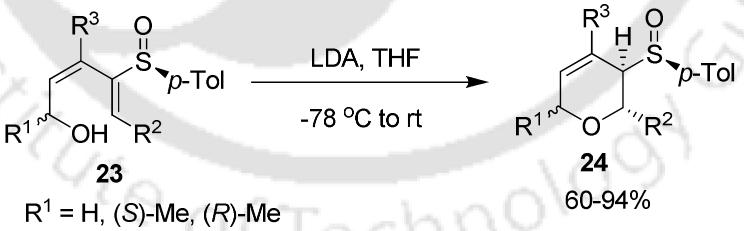


R^1 = Ph, Me, 3-OMe-Ph, 2-Cl-Ph, 4-Br-Ph
R^2 = Ph, 3-OMe-Ph, 2-Cl-Ph, 4-Br-Ph

Scheme 6.2.2.2.

6.2.3 Base-promoted Cyclization of Sulfinyl Dienols

de la Pradilla *et al.* have reported a base-promoted intramolecular cyclization of 2-sulfinyl dienols to afford sulfinyl dihydropyrans.[12] This strategy allows for creation of two asymmetric centers within a synthetically useful dihydropyran framework in an expedient manner (Scheme 6.2.3.1).



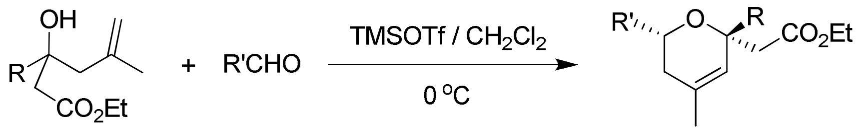
R^1 = H, (*S*)-Me, (*R*)-Me
R^2 = *n*-Bu, Ph
R^3 = H, Me

Scheme 6.2.3.1.

6.3 Present Work

In the previous chapter we have described an efficient methodology for the synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans via (3,5)-oxonium-ene reaction. In this chapter we are going to present a diastereo- and regioselective synthesis of substituted dihydropyrans from the reaction of aldehydes or epoxides and ethyl 3-alkyl-3-hydroxy-5-methylhex-5-

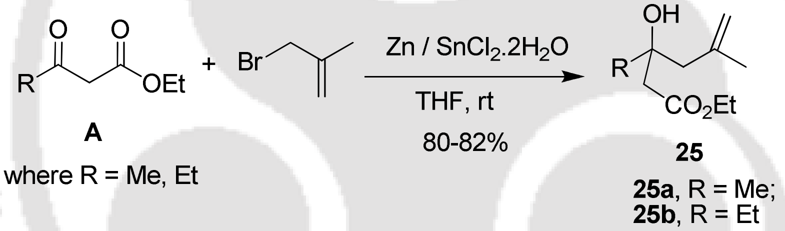
enoate using oxonium-ene reaction catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) under mild conditions. The reaction can be generalized as shown in Scheme 6.3.1.



R = Me, Et; R' = alkyl, aryl

Scheme 6.3.1.

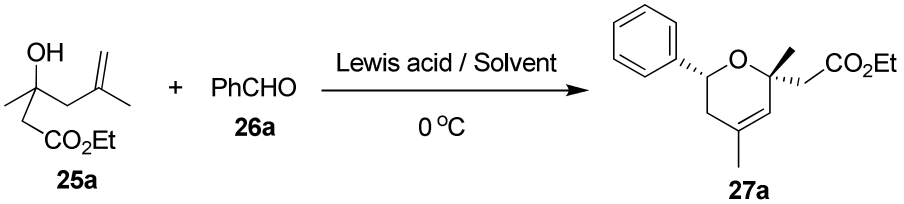
The ethyl 3-alkyl-3-hydroxy-5-methylhex-5-enoate **25** was synthesized starting from *β*-keto ester **A** and 3-bromo-2-methylpropene as shown below.[13] The reaction of *β*-keto ester **A** with 3-bromo-2-methylpropene in presence of metallic Zn and $SnCl_2.2H_2O$ in THF gives alcohol **25** in 80-82% yields (Scheme 6.3.2).



Scheme 6.3.2. Synthesis of ethyl 3-alkyl-3-hydroxy-5-methylhex-5-enoate

To determine the optimum reaction conditions, the reaction of benzaldehyde **26a** and ethyl 3-hydroxy-3,5-dimethylhex-5-enoate **25a** with a varied amount of different Lewis acids with variation of solvents have been studied. The results are summarized in Table 6.3.1. It was found that the reaction proceeds smoothly with one equivalent of boron trifluoride etherate in dry CH_2Cl_2 yielding 68% of desired product, whereas only 10 mol% of trimethylsilyl trifluoromethanesulfonate produces 78% of same product in the same solvent. A low yield was obtained with bismuth triflate (0.1 equiv.) in dry CH_2Cl_2 and no reaction was observed with indium triflate ($In(OTf)_3$) (0.1 equiv.) in both CH_2Cl_2 and toluene. Therefore, TMSOTf in dry CH_2Cl_2 was considered as the best combination for this reaction and the scope of the reaction was investigated by using different types of aliphatic and aromatic aldehydes (Table 6.3.2). Both aliphatic and aromatic aldehydes gave the corresponding products in good yields. The reaction is diastereoselective as well as

Table 6.3.1. Optimization of reaction conditions

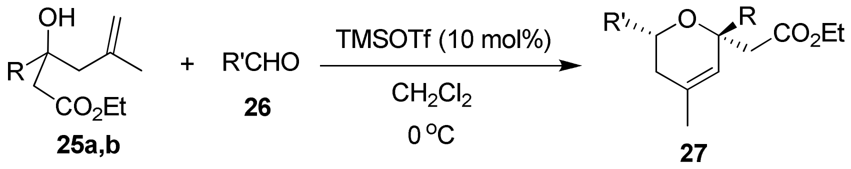


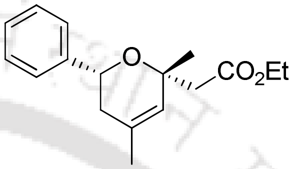
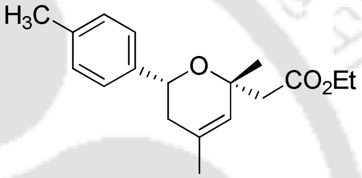
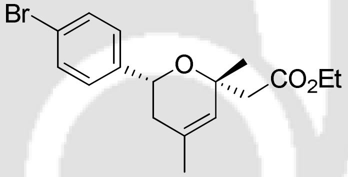
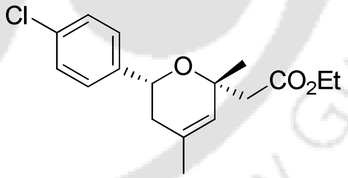
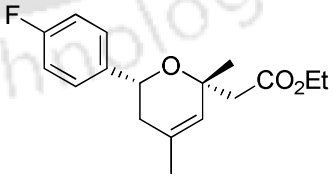
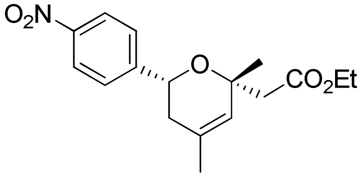
Entry	Lewis acid (equiv.)	Time / h	Solvent	Yield[a] (%)
1	$BF_3{\cdot}Et_2O$ (1)	1	CH_2Cl_2	68
2	$BF_3{\cdot}Et_2O$ (1)	1	Toluene	64
3	$BF_3{\cdot}Et_2O$ (1)	24	CH_3CN	45
4	TMSOTf (0.1)	1	CH_2Cl_2	78
5	TMSOTf (0.1)	1	Toluene	70
6	$Bi(OTf)_3$ (0.1)	24	CH_2Cl_2	40
7	$Bi(OTf)_3$ (0.1)	24	Toluene	35
8	$In(OTf)_3$ (0.1)	24	Toluene	0
9	$In(OTf)_3$ (0.1)	24	CH_2Cl_2	0

[a] Yields refer to isolated yield. The compound is characterized by IR, ^{1}H, ^{13}C NMR and Mass spectroscopy.

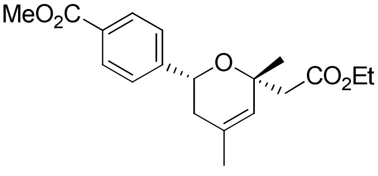
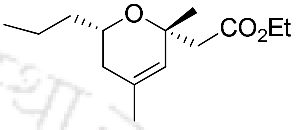
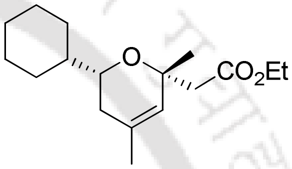
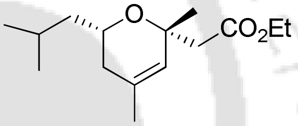
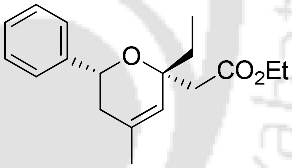
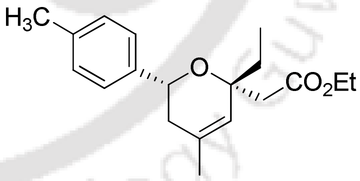
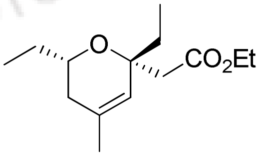
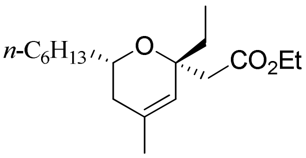
regioselective and in all the cases studied, substituted dihydropyrans **27a-27n** could be obtained in high purity without any other diastereo- and regioisomeric products as determined from ^{1}H and ^{13}C NMR spectrum of the crude product. The substituents on the aromatic ring have a promising effect on this reaction. The aromatic aldehydes having electron-donating groups on the aromatic ring gave higher yields compared to the electron-withdrawing groups on the ring. On the other hand, aliphatic aldehydes are better substrates than the aromatic aldehydes. This might be due to the better stability imparted to the oxocarbenium ion **29** (Scheme 6.3.3) by the aliphatic, and aromatic aldehydes having electron-donating groups on the aromatic ring, which in turn is attacked by the double bond efficiently. On the other hand, aromatic aldehydes having electron-withdrawing groups on the ring destabilize the oxocarbenium ion **29**. The structure and stereochemistry of the compound was determined by ^{1}H NMR and NOE experiment. In the ^{1}H NMR spectrum the proton at position C-6 of **27a** shows a dd with coupling constants 10.4 and 3.2 Hz at δ 4.71 ppm, which indicates that the proton is coupled with two neighbouring diastereotropic

Table 6.3.2. Synthesis of substituted dihydropyrans



Entry	Alcohol **25a**, R = Me **25b**, R = Et	Aldehyde R' =	Time / h	Product **27**	Yield[a] (%)
a	Me	C_6H_5-	1	 **27a**	78
b	Me	*p*-Me-C_6H_4-	1	 **27b**	82
c	Me	*p*-Br-C_6H_4-	1	 **27c**	65
d	Me	*p*-Cl-C_6H_4-	1	 **27d**	64
e	Me	*p*-F-C_6H_4-	1	 **27e**	62
f	Me	*p*-NO_2-C_6H_4-	1	 **27f**	62

continue…

Entry	Alcohol **25a**, R = Me **25b**, R = Et	Aldehyde R' =	Time / h	Product **27**	Yield[a] (%)
g	Me	*p*-MeO_2C-C_6H_4-	1	 **27g**	68
h	Me	C_3H_7-	0.5	 **27h**	90
i	Me	*Cyclo*-C_6H_{11}-	0.5	 **27i**	84
j	Me	$(CH_3)_2CHCH_2$-	0.5	 **27j**	86
k	Et	C_6H_5-	1	 **27k**	74
l	Et	*p*-Me-C_6H_4-	1.5	 **27l**	80
m	Et	C_2H_5-	0.8	 **27m**	88
n	Et	*n*-C_6H_{13}-	0.8	 **27n**	82

[a]Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR and Mass spectroscopy.

methylene protons H_{5a} and H_{5b}. On the other hand proton H_{5a} shows a dd with coupling constants 16.8 and 3.2 Hz at δ 2.01 ppm. Similarly proton H_{5b} also shows a dd with coupling constants 16.8 and 10.4 Hz at δ 2.13 ppm. This indicates that these two protons are coupling each other and neighbouring H_6 proton. Thus the position of the double bond between C-3 and C-4 carbons has been confirmed. The presence of a strong NOE between H_6 and C-2 methyl protons of **27a** clearly indicates that they are *cis* to each other (Figure 6.3.1).

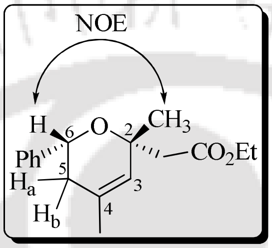
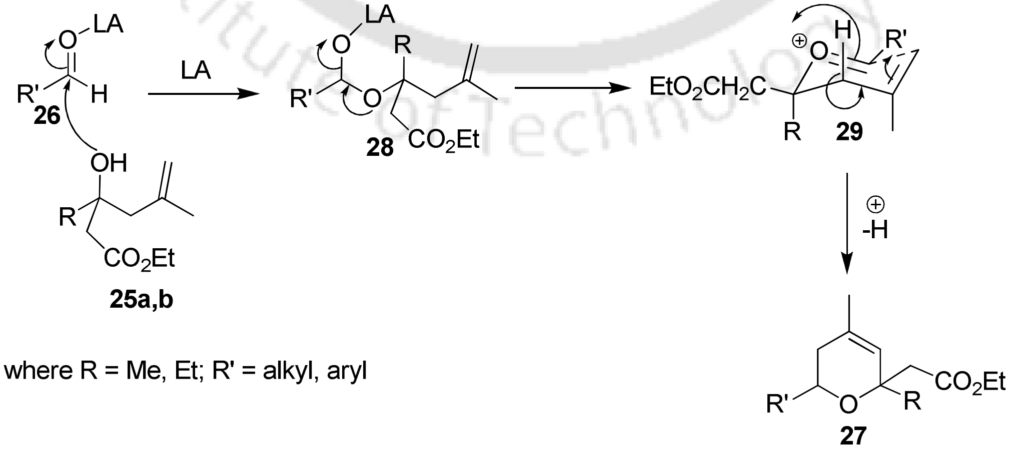


Figure 6.3.1. NOE diagram of compound **27a**

The mechanism of the reaction can be explained as follows. Lewis acid activates the aldehyde **26** for the nucleophilic attack by alcohol **25** to give acetal **28**, which after decomposition forms oxocarbenium ion **29**. The oxocarbenium ion **29** undergoes oxonium-ene cyclization reaction to give final product **27** (Scheme 6.3.3). The formation of single regioisomer supports the concerted mechanism. On the other hand formation of single diastereomer may be explained as follows. After decomposition of acetal **28**, it forms six membered chair like transition state **29**, in which the more bulkier methylene ester group occupies the equatorial position to minimize the 1,3-diaxial interaction.

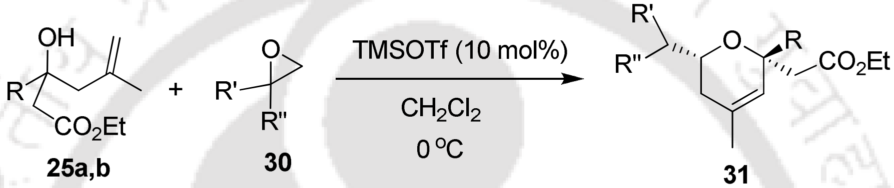


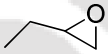
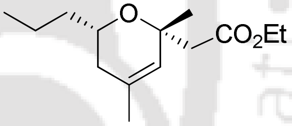
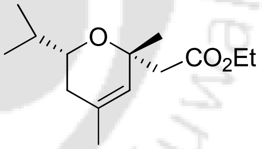
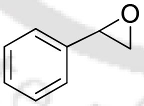
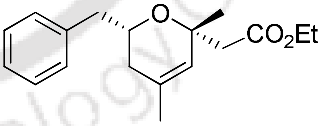
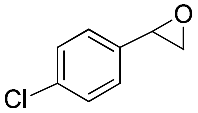
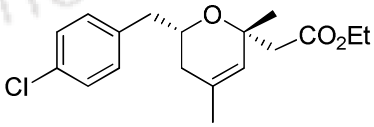
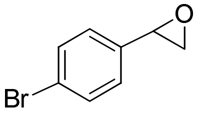
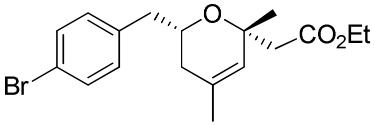
where R = Me, Et; R' = alkyl, aryl

Scheme 6.3.3. Mechanism of the reaction

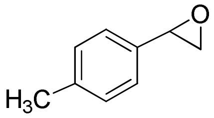
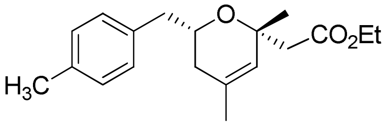
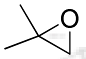
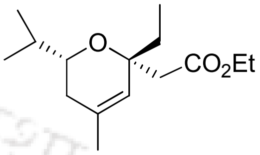
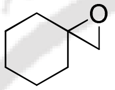
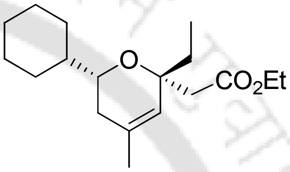
The same substituted dihydropyrans can also be prepared by using epoxides (Table 6.3.3). This is due to the fact that epoxides under Lewis acid conditions rearrange to aldehyde equivalent.[14] Here monosubstituted terminal epoxides (entry a) fail to give substituted dihydropyran, whereas the 2,2-disubstituted and styrene oxides give the corresponding products in good to moderate yields. This is attributed to the lower stability of the carbocation **32**, obtained from monosubstituted epoxides, compared to 2,2-disubstituted epoxides and styrene oxides, where carbocation **32** is better stabilized due to tertiary and benzylic centers, respectively.[14a]

Table 6.3.3. Synthesis of substituted dihydropyran from epoxide



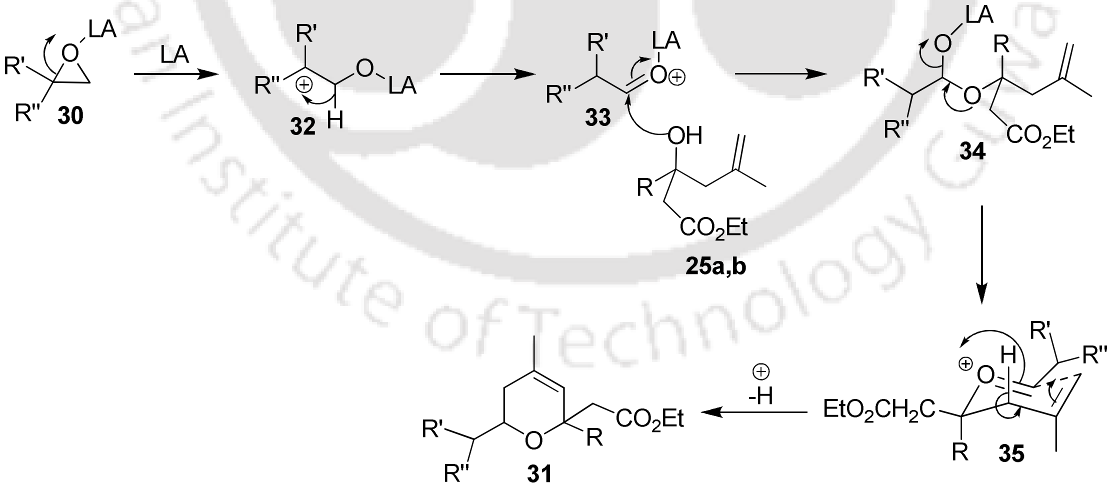
Entry	Alcohol **25a**, R = Me **25b**, R = Et	Epoxide	Time / h	Product **31**	Yield[a] (%)
a	Me		24	 **31a**	0
b	Me		1.5	 **31b**	68
c	Me		1.5	 **31c**	64
d	Me		1.5	 **31d**	60
e	Me		1.5	 **31e**	62

continue…

Entry	Alcohol **25a**, R = Me **25b**, R = Et	Epoxide	Time / h	Product **31**	Yield[a] (%)
f	Me		1.5	 **31f**	64
g	Et		2	 **31g**	65
h	Et		2	 **31h**	62

[a]Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C NMR and Mass spectroscopy.

The mechanism of the reaction with epoxides is shown in Scheme 6.3.4. The epoxide **30** in the presence of Lewis acid rearranges to aldehyde equivalent **33**, which after nucleophilic attack by alcohol **25** gives acetal **34**. The acetal **34** decomposes to give oxocarbenium ion **35**, which after oxonium-ene cyclization reaction gives final product **31**.



Scheme 6.3.4. Mechanism of the reaction with epoxides

Conclusions:

In summary, we have developed a simple and efficient methodology for the synthesis of substituted dihydropyrans in good yields. The reaction is diastereoselective as well as regioselective. The presence of methylene ester functionality in the C-2 position of the dihydropyran ring will increase its synthetic applicability as the ester group could further be converted to other groups.

6.4 Experimental Section

6.4.1 Instrumentation and Characterization

As described in Chapter 2, Section 2.4.1.

6.4.2 General Procedure for the Synthesis of Ethyl 3-alkyl-3-hydroxy-5-methylhex-5-enoate (25a-b):

A 250 mL round-bottom flask was charged with metallic Zn (20 mmol, 2 equiv.), $SnCl_2.2H_2O$ (10 mmol, 1 equiv.) and 20 mL of THF. To this solution β-keto ester (10 mmol, 1 equiv.) and 3-bromo-2-methylpropene (15 mmol, 1.5 equiv.) were added sequentially and the mixture was stirred at room temperature for 24 h. The reaction mixture was then filtered and the filtrate was washed with ethyl acetate (2 X 20 mL). The combined filtrate was concentrated and purified by column chromatography over silica gel to afford the title compounds as colourless oil.

Synthesis of Ethyl 3-hydroxy-3,5-dimethylhex-5-enoate (25a): A 250 mL round-bottom flask was charged with metallic Zn (1.31 g, 20 mmol), $SnCl_2.2H_2O$ (2.25 g, 10 mmol) and 20 mL of THF. To this solution ethyl acetoacetate (1.30 g, 10 mmol) and 3-bromo-2-methylpropene (2.02 g, 15 mmol) were added sequentially and the mixture was stirred at room temperature for 24 h. The reaction mixture was then filtered and the filtrate was washed with ethyl acetate (2 X 20 mL). The combined filtrate was concentrated and purified by column chromatography over silica gel (10% EtOAc/hexane) to afford ethyl 3-hydroxy-3,5-dimethylhex-5-enoate **25a** (1.53 g, 82%) as a colourless oil.

6.4.3 General Procedure for the Synthesis of Substituted Dihydropyrans from Aldehydes: To a solution of aldehyde (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 mL) at 0 ^oC was added trimethylsilyl trifluoromethanesulfonate (0.1 mmol, 0.1 equiv.). To this solution ethyl 3-alkyl-3-hydroxy-5-methylhex-5-enoate (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 ml) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of Ethyl 2-((2*R,6*R**)-5,6-dihydro-2,4-dimethyl-6-phenyl-2*H*-pyran-2-yl)acetate (27a):** To a solution of benzaldehyde (106 mg, 1.00 mmol) in dry CH_2Cl_2 (2 mL) at 0 ^oC was added trimethylsilyl trifluoromethanesulfonate (22 mg, 0.1 mmol). To this solution ethyl 3-hydroxy-3,5-dimethylhex-5-enoate (186 mg, 1 mmol) in dry CH_2Cl_2 (2 mL) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for 1 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (1:24) as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **27a** (214 mg, 78 %) as a colourless oil.

6.4.4 General Procedure for the Synthesis of Substituted Dihydropyrans from Epoxides: To a solution of epoxide (1.5 mmol, 1.5 equiv.) in dry CH_2Cl_2 (2 mL) at 0 ^oC was added trimethylsilyl trifluoromethanesulfonate (0.1 mmol, 0.1 equiv.). To this solution ethyl 3-alkyl-3-hydroxy-5-methylhex-5-enoate (1 mmol, 1 equiv.) in dry CH_2Cl_2 (2 ml) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

Synthesis of Ethyl 2-((2*R,6*R**)-5,6-dihydro-6-isopropyl-2,4-dimethyl-2*H*-pyran-2-yl)acetate (31b):** To a solution of 1,2-epoxy-2-methyl propane (108 mg, 1.5 mmol) in dry CH_2Cl_2 (2 mL) at 0 ^oC was added trimethylsilyl trifluoromethanesulfonate (22 mg, 0.1 mmol). To this solution ethyl 3-hydroxy-3,5-dimethylhex-5-enoate (186 mg, 1 mmol) in dry CH_2Cl_2 (2 mL) was added drop by drop over 5 min. The reaction mixture was stirred at that temperature for 1.5 h. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (1:49) as eluents. After completion of the reaction, it was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (30 mL) and then washed with water (15 mL) and brine (15 mL). The organic layer was dried

(Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give **31b** (163 mg, 68%) as a colourless oil.

6.5 References

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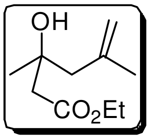
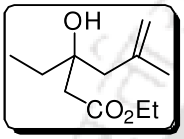
6.6 Spectral Data

Ethyl 3-hydroxy-3,5-dimethylhex-5-enoate (25a):



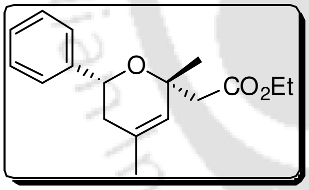
Colourless oil (1.53 g, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (s, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.85 (t, J = 1.2 Hz, 3 H), 2.27 (brs, 2 H), 2.43 (d, J = 15.6 Hz, 1 H), 2.56 (d, J = 15.6 Hz, 1 H), 3.68 (brs, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.70-4.74 (m, 1 H), 4.89-4.92 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 24.5, 27.3, 44.8, 49.6, 60.5, 71.1, 115.0, 142.4, 173.1; **IR** (Neat) 3482, 2980, 2935, 1716, 1642, 1374, 1190, 1095, 1031 cm^{-1}. **HRMS** (APCI) cald. for $C_{10}H_{18}O_3$ $(M+H)^+$ requires 187.1334; found 187.1328.

Ethyl 3-ethyl-3-hydroxy-5-methylhex-5-enoate (25b):



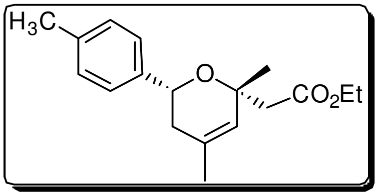
Colourless oil (1.6 g, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.55-1.63 (m, 2 H), 1.85 (s, 3 H), 2.22 (d, J = 13.6 Hz, 1 H), 2.28 (d, J = 13.6 Hz, 1 H), 2.44 (d, J = 15.6 Hz, 1 H), 2.52 (d, J = 15.6 Hz, 1 H), 3.64 (brs, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.72 (brs, 1 H), 4.90 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 8.4, 14.3, 24.7, 32.8, 42.3, 46.8, 60.8, 73.6, 115.2, 142.7, 173.7; **IR** (Neat) 3504, 2977, 2940, 1715, 1642, 1372, 1186, 1095, 1029 cm^{-1}. **HRMS** (APCI) cald. for $C_{11}H_{20}O_3$ $(M+H)^+$ requires 201.1490; found 201.1486.

Ethyl 2-((2*R,6*R**)-5,6-dihydro-2,4-dimethyl-6-phenyl-2*H*-pyran-2-yl)acetate (27a):**



Colourless oil (214 mg, 78 %); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.74 (s, 3 H), 2.01 (dd, J = 16.8 and 3.2 Hz, 1 H), 2.13 (dd, J = 16.8 and 10.4 Hz, 1 H), 2.59 (d, J = 13.6 Hz, 1 H), 2.65 (d, J = 13.6 Hz, 1 H), 4.10-4.18 (m, 2 H), 4.71 (dd, J = 10.4 and 3.2 Hz, 1 H), 5.55 (brs, 1 H), 7.26-7.29 (m, 1 H), 7.32-7.36 (m, 2 H), 7.38-7.42 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.1, 25.2, 37.9, 47.6, 60.2, 70.8, 74.5, 126.0, 126.2, 127.4, 128.4, 131.7, 143.1, 170.7; **IR** (Neat) 2971, 2927, 1734, 1674, 1450, 1367, 1211, 1094, 1076, 752, 699 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{22}O_3$ $(M+H)^+$ requires 275.1647; found 275.1642.

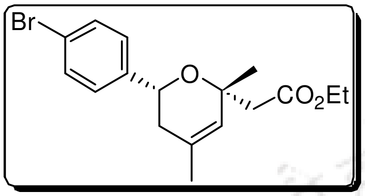
Ethyl 2-((2*R,6*R**)-5,6-dihydro-2,4-dimethyl-6-*p*-tolyl-2*H*-pyran-2-yl)acetate (27b):**



Colourless oil (236 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3 H), 1.40 (s, 3 H), 1.73 (s, 3 H), 1.97 (dd, J = 16.8 and 3.2 Hz, 1 H), 2.12 (dd, J = 16.8 and 10.8 Hz, 1 H), 2.33 (s, 3 H), 2.58 (d, J = 13.6 Hz, 1 H), 2.63 (d, J = 13.6 Hz, 1 H), 4.10-4.18 (m, 2 H), 4.67 (dd, J = 10.8 and 3.2 Hz, 1 H), 5.54 (brs, 1 H), 7.15 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz,

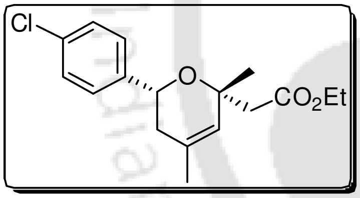
$CDCl_3$): δ 14.4, 21.2, 23.1, 25.1, 37.9, 47.6, 60.1, 70.7, 74.5, 126.0, 126.2, 129.0, 131.7, 136.9, 140.1, 170.7; **IR** (Neat) 2973, 2926, 1734, 1687, 1446, 1367, 1215, 1089, 1033, 808, 716 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_3$ $(M+H)^+$ requires 289.1803; found 289.1790.

Ethyl 2-((2*R,6*R**)-6-(4-bromophenyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27c):**



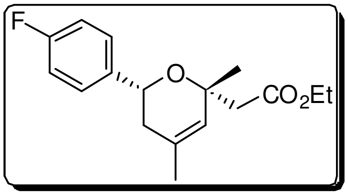
Colourless oil (230 mg, 65%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3 H), 1.39 (s, 3 H), 1.74 (s, 3 H), 1.98 (dd, J = 16.4 and 3.6 Hz, 1 H), 2.06 (dd, J = 16.4 and 10.4 Hz, 1 H), 2.56 (d, J = 13.6 Hz, 1 H), 2.63 (d, J = 13.6 Hz, 1 H), 4.09-4.18 (m, 2 H), 4.66 (dd, J = 10.8 and 3.2 Hz, 1 H), 5.54 (brs, 1 H), 7.27 (d, J = 8.4 Hz, 2 H), 7.46 (d, J = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.1, 25.2, 37.8, 47.6, 60.3, 70.2, 74.6, 121.1, 126.3, 127.8, 131.5 (2C), 142.2, 170.6; **IR** (Neat) 2974, 2927, 1734, 1679, 1445, 1367, 1217, 1088, 1033, 815, 710 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}BrO_3$ $(M+H)^+$ requires 353.0754; found 353.0742 (^{79}Br).

Ethyl 2-((2*R,6*R**)-6-(4-chlorophenyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27d):**



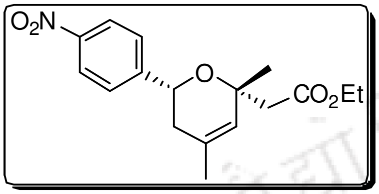
Colourless oil (198 mg, 64%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3 H), 1.39 (s, 3 H), 1.74 (s, 3 H), 1.97 (dd, J = 16.8 and 3.6 Hz, 1 H), 2.05 (dd, J = 16.4 and 10.4 Hz, 1 H), 2.58 (d, J = 13.6 Hz, 1 H), 2.63 (d, J = 13.6 Hz, 1 H), 4.08-4.18 (m, 2 H), 4.67 (dd, J = 10.4 and 3.6 Hz, 1 H), 5.54 (brs, 1 H), 7.28-7.34 (m, 4 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.1, 25.2, 37.8, 47.6, 60.3, 70.2, 74.7, 126.3, 127.4, 128.5, 131.5, 133.0, 141.7, 170.7; **IR** (Neat) 2963, 2926, 1735, 1685, 1445, 1368, 1217, 1087, 1033, 817, 692 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}ClO_3$ $(M+H)^+$ requires 309.1257; found 309.1247 (^{35}Cl).

Ethyl 2-((2*R,6*R**)-6-(4-fluorophenyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27e):**



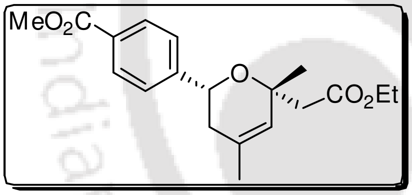
Colourless oil (181 mg, 62%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3 H), 1.40 (s, 3 H), 1.74 (s, 3 H), 1.98 (dd, J = 16.8 and 3.2 Hz, 1 H), 2.06-2.13 (dd, J = 16.8 and 10.8 Hz, 1 H), 2.58 (d, J = 13.6 Hz, 1 H), 2.64 (d, J = 13.6 Hz, 1 H), 4.09-4.18 (m, 2 H), 4.69 (dd, J = 10.8 and 3.6 Hz, 1 H), 5.54 (brs, 1 H), 7.02 (t, J = 8.8 Hz, 2 H), 7.33-7.37 (m, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.5, 23.1, 25.3, 38.0, 47.7, 60.3, 70.4, 74.7, 115.2 (d, J = 21.3 Hz), 126.3, 127.7 (d, J = 8.4 Hz), 131.6, 139.1, 162.2 (d, *J* = 243.3 Hz), 170.7; ^{19}**F NMR** (376 MHz, $CDCl_3/C_6F_6$): δ -219.7-(-219.6) (m, 1 F); **IR** (Neat) 2977, 2930, 1734, 1685, 1511, 1444, 1368, 1223, 1086, 1033, 826, 774 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}FO_3$ $(M+H)^+$ requires 293.1553; found 293.1545.

Ethyl 2-((2*R,6*R**)-5,6-dihydro-2,4-dimethyl-6-(4-nitrophenyl)-2*H*-pyran-2-yl)acetate (27f):**



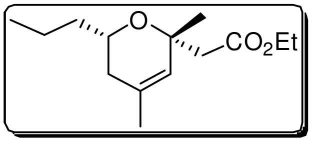
Colourless oil (198 mg, 62%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.76 (s, 3 H), 2.02-2.09 (m, 2 H), 2.60 (d, *J* = 13.6 Hz, 1 H), 2.66 (d, *J* = 13.6 Hz, 1 H), 4.10-4.19 (m, 2 H), 4.82 (t, *J* = 7.2 Hz, 1 H), 5.57 (brs, 1 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 8.20 (d, *J* = 8.8 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.0, 25.1, 37.6, 47.4, 60.3, 70.0, 74.8, 123.6, 126.4, 126.6, 131.1, 147.2, 150.6, 170.5; **IR** (Neat) 2975, 2928, 1733, 1605, 1521, 1446, 1374, 1212, 1091, 1032, 855, 749 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{21}NO_5$ $(M+H)^+$ requires 320.1498; found 320.1485.

Methyl 4-((2*R,6*R**)-6-((ethoxycarbonyl)methyl-3,6-dihydro-4,6-dimethyl-2*H*-pyran-2-yl)benzoate (27g):**



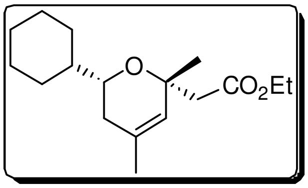
Colourless oil (226 mg, 68%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.75 (s, 3 H), 1.99-2.10 (m, 2 H), 2.60 (d, *J* = 13.6 Hz, 1 H), 2.66 (d, *J* = 13.6 Hz, 1 H), 3.91 (s, 3 H), 4.10-4.19 (m, 2 H), 4.77 (dd, *J* = 10.0 and 4.0 Hz, 1 H), 5.55 (brs, 1 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.4 Hz, 2 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.1, 25.1, 37.7, 47.5, 52.1, 60.3, 70.4, 74.6, 125.9, 126.3, 129.1, 129.8, 131.4, 148.4, 167.1, 170.6; **IR** (Neat) 2953, 2927, 1725, 1613, 1436, 1368, 1278, 1090, 1033, 768, 704 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{24}O_5$ $(M+H)^+$ requires 333.1702; found 333.1692.

Ethyl 2-((2*R,6*S**)-5,6-dihydro-2,4-dimethyl-6-propyl-2*H*-pyran-2-yl)acetate (27h):**



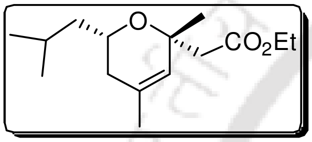
Colourless oil (216 mg, 90%); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.30 (s, 3 H), 1.35-1.43 (m, 2 H), 1.45-1.54 (m, 2 H), 1.62-1.72 (m, 4 H), 1.82 (dd, *J* = 16.0 and 10.8 Hz, 1 H), 2.49 (brs, 2 H), 3.61-3.66 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.45 (brs, 1 H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.2, 14.4, 18.7, 23.2, 24.6, 35.6, 38.0, 47.7, 60.1, 68.2, 73.6, 126.4, 131.7, 170.8; **IR** (Neat) 2961, 2930, 2873, 1736, 1678, 1456, 1370, 1216, 1081, 1034, 825 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O_3$ $(M+H)^+$ requires 241.1803; found 241.1794.

Ethyl 2-((2*R,6*R**)-6-cyclohexyl-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27i):**



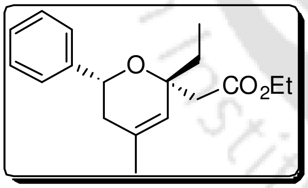
Colourless oil (236 mg, 84%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.93-1.04 (m, 2 H), 1.11-1.21 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.28 (s, 3 H), 1.34-1.42 (m, 2 H), 1.65-1.76 (m, 7 H), 1.83-1.96 (m, 3 H), 2.47 (brs, 2 H), 3.33-3.38 (m, 1 H), 4.06-4.15 (m, 2 H), 5.43 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 14.4, 23.4, 24.4, 26.2, 26.3, 26.8, 28.5, 29.1, 32.6, 42.5, 47.7, 60.1, 72.6, 73.5, 126.5, 131.8, 170.9; **IR** (Neat) 2967, 2925, 2852, 1736, 1679, 1449, 1367, 1216, 1097, 1034, 833 cm^{-1}. **HRMS** (APCI) cald. for $C_{17}H_{28}O_3$ $(M+H)^+$ requires 281.2116; found 281.2112.

Ethyl 2-((2*R,6*S**)-5,6-dihydro-6-isobutyl-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27j):**



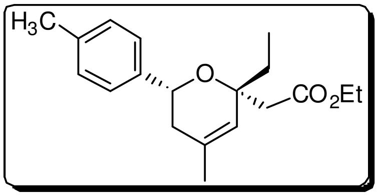
Colourless oil (219 mg, 86%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.89 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.31 (s, 3 H), 1.44-1.52 (m, 2 H), 1.65-1.72 (m, 4 H), 1.78-1.86 (m, 2 H), 2.48 (brs, 2 H), 3.67-3.74 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 5.45 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 14.4, 22.4, 23.3, 23.4, 24.5 (2C), 36.2, 45.1, 47.7, 60.2, 66.6, 73.6, 126.5, 131.8, 171.0; **IR** (Neat) 2957, 2927, 2867, 1736, 1654, 1458, 1369, 1215, 1086, 1034, 971 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O_3$ $(M+H)^+$ requires 255.1960; found 255.1954.

Ethyl 2-((2*R,6*R**)-2-ethyl-5,6-dihydro-4-methyl-6-phenyl-2*H*-pyran-2-yl)acetate (27k):**



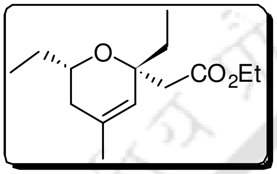
Colourless oil (213 mg, 74%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.93 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.64-1.72 (m, 1 H), 1.76 (s, 3 H), 1.77-1.86 (m, 1 H), 2.01 (dd, *J* = 16.8 and 3.2 Hz, 1 H), 2.09-2.18 (dd, *J* = 16.8 and 10.8 Hz, 1 H), 2.56 (d, *J* = 13.6 Hz, 1 H), 2.63 (d, *J* = 13.6 Hz, 1 H), 4.06-4.17 (m, 2 H), 4.68 (dd, *J* = 10.4 and 3.2 Hz 1 H), 5.59 (brs, 1 H), 7.24-7.28 (m, 1 H), 7.32-7.36 (m, 2 H), 7.38-7.42 (m, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 8.3, 14.5, 23.3, 30.7, 37.7, 44.2, 60.2, 70.8, 76.8, 125.7, 126.1, 127.4, 128.4, 132.2, 143.3, 171.1; **IR** (Neat) 2970, 2927, 2854, 1734, 1676, 1450, 1369, 1207, 1095, 1031, 752, 698 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_3$ $(M+H)^+$ requires 289.1803; found 289.1794.

Ethyl 2-((2*R,6*R**)-2-ethyl-5,6-dihydro-4-methyl-6-*p*-tolyl-2*H*-pyran-2-yl)acetate (27l):** Colourless oil (242 mg, 80%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.92 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.63-1.72 (m, 1 H), 1.75 (s, 3 H), 1.77-1.84 (m, 1 H), 1.98 (dd, *J* = 16.8 and 3.2 Hz, 1 H), 2.09-2.17 (dd, *J* = 16.8 and 10.4 Hz, 1 H), 2.34 (s, 3 H), 2.55 (d, *J* =



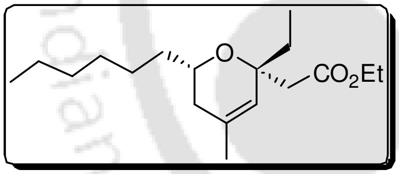
13.6 Hz, 1 H), 2.61 (d, J = 13.6 Hz, 1 H), 4.07-4.17 (m, 2 H), 4.64 (dd, J = 10.4 and 3.2 Hz, 1 H), 5.58 (brs, 1 H), 7.15 (d, J = 7.6 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 8.3, 14.5, 21.3, 23.3, 30.7, 37.7, 44.2, 60.2, 70.7, 76.7, 125.7, 126.1, 129.1, 132.2, 137.0, 140.3, 171.1; **IR** (Neat) 2969, 2926, 2856, 1734, 1679, 1445, 1368, 1206, 1088, 1033, 809, 668 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ (M+H)$^+$ requires 303.1960; found 303.1948.

Ethyl 2-((2_R_*,6_S_*)-2,6-diethyl-5,6-dihydro-4-methyl-2_H_-pyran-2-yl)acetate (27m):



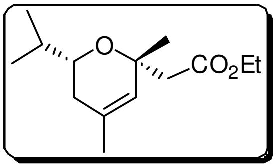
Colourless oil (212 mg, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.6 Hz, 3 H), 0.95 (t, J = 7.6 Hz, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.41-1.65 (m, 3 H), 1.69 (s, 3 H), 1.70-1.85 (m, 3 H), 2.48 (brs, 2 H), 3.48-3.54 (m, 1 H), 4.07-4.15 (m, 2 H), 5.50 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 8.0, 10.2, 14.5, 23.4, 29.0, 29.8, 35.4, 43.9, 60.2, 69.8, 75.7, 126.0, 131.9, 171.2; **IR** (Neat) 2965, 2929, 2878, 1735, 1676, 1463, 1378, 1208, 1074, 1037, 941 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O_3$ (M+H)$^+$ requires 241.1803; found 241.1798.

Ethyl 2-((2_R_*,6_S_*)-2-ethyl-6-hexyl-5,6-dihydro-4-methyl-2_H_-pyran-2-yl)acetate (27n):



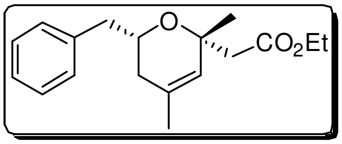
Colourless oil (243 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3 H), 0.90 (t, J = 7.6 Hz, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.25-1.35 (m, 8 H), 1.37-1.47 (m, 2 H), 1.51-1.62 (m, 2 H), 1.69 (s, 3 H), 1.71-1.75 (m, 1 H), 1.78-1.85 (m, 1 H), 2.48 (brs, 2 H), 3.52-3.60 (m, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.50 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 7.97, 14.3, 14.4, 22.8, 23.4, 25.7, 29.5, 29.7, 32.1, 35.8, 36.2, 43.8, 60.2, 68.4, 75.8, 126.0, 132.0, 171.2; **IR** (Neat) 2959, 2928, 2856, 1736, 1676, 1461, 1368, 1205, 1091, 1033, 869 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{32}O_3$ (M+H)$^+$ requires 297.2429; found 297.2418.

Ethyl 2-((2_R_*,6_R_*)-5,6-dihydro-6-isopropyl-2,4-dimethyl-2_H_-pyran-2-yl)acetate (31b):



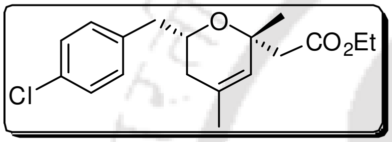
Colourless oil (163 mg, 68%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.64-1.72 (m, 5 H), 1.82-1.89 (m, 1 H), 2.48 (brs, 2 H), 3.30-3.36 (m, 1 H), 4.06-4.17 (m, 2 H), 5.44 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 18.2, 18.7, 23.4, 24.5, 32.4, 32.8, 47.7, 60.1, 73.4, 73.6, 126.5, 131.7, 171.0; **IR** (Neat) 2965, 2929, 1736, 1676, 1448, 1368, 1211, 1081, 1035, 841 cm^{-1}. **HRMS** (APCI) cald. for $C_{14}H_{24}O_3$ (M+H)$^+$ requires 241.1803; found 241.1794.

Ethyl 2-((2*R,6*R**)-6-benzyl-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (31c):**



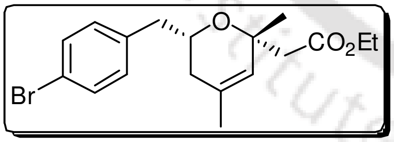
Colourless oil (185 mg, 64%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.60-1.67 (m, 4 H), 1.84-1.91 (m, 1 H), 2.51 (brs, 2 H), 2.69 (dd, *J* = 13.6 and 6.8 Hz, 1 H), 2.95 (dd, *J* = 13.6 and 6.8 Hz, 1 H), 3.81-3.87 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.42 (brs, 1 H), 7.20-7.30 (m, 5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.2, 24.7, 35.0, 42.5, 47.6, 60.2, 69.6, 74.0, 126.2, 126.4, 128.2, 129.6, 131.4, 138.8, 170.8; **IR** (Neat) 2974, 2927, 1734, 1674, 1453, 1369, 1214, 1086, 1032, 751, 700 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{24}O_3$ $(M+H)^+$ requires 289.1803; found 289.1797.

Ethyl 2-((2*R,6*R**)-6-(4-chlorobenzyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (31d):**



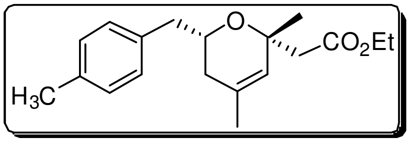
Colourless oil (194 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.61-1.68 (m, 4 H), 1.83-1.90 (m, 1 H), 2.51 (brs, 2 H), 2.68 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 2.86 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 3.81-3.88 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.43 (brs, 1 H), 7.17 (d, *J* = 8.4, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.2, 24.6, 35.0, 41.7, 47.6, 60.3, 69.3, 74.0, 126.5, 128.3, 131.0, 131.3, 132.0, 137.4, 170.8; **IR** (Neat) 2972, 2927, 1734, 1676, 1492, 1369, 1214, 1091, 1033, 822, 798 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}ClO_3$ $(M+H)^+$ requires 323.1414; found 323.1404 (^{35}Cl).

Ethyl 2-((2*R,6*R**)-6-(4-bromobenzyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (31e):**



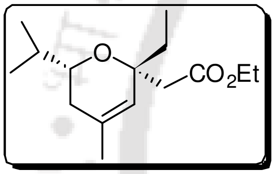
Colourless oil (228 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.60-1.68 (m, 4 H), 1.83-1.90 (m, 1 H), 2.49 (brs, 2 H), 2.67 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 2.85 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 3.80-3.88 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 5.43 (brs, 1 H), 7.12 (d, *J* = 8.4, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.2, 24.6, 35.0, 41.7, 47.6, 60.2, 69.2, 74.0, 120.0, 126.5, 128.1, 131.2, 131.4, 137.9, 170.7; **IR** (Neat) 2973, 2927, 1734, 1674, 1488, 1369, 1213, 1073, 1033, 863, 820 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{23}BrO_3$ $(M+H)^+$ requires 367.0909; found 367.0892 (^{79}Br).

Ethyl 2-((2*R,6*R**)-6-(4-methylbenzyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (31f):**



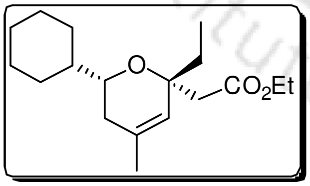
Colourless oil (194 mg, 64%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.24 (t, J = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.60-1.67 (m, 4 H), 1.82-1.89 (m, 1 H), 2.32 (s, 3 H), 2.51 (brs, 2 H), 2.65 (dd, J = 13.6 and 6.8 Hz, 1 H), 2.92 (dd, J = 13.6 and 6.8 Hz, 1 H), 3.82-3.89 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.43 (brs, 1 H), 7.08 (d, J = 8.0, 2 H), 7.13 (d, J = 8.0 Hz, 2 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 14.4, 21.2, 23.2, 24.7, 35.0, 42.1, 47.7, 60.2, 69.7, 74.0, 126.4, 129.0, 129.5, 131.5, 135.6, 135.7, 170.9; **IR** (Neat) 2975, 2926, 1734, 1676, 1445, 1369, 1213, 1078, 1033, 807, 749 cm^{-1}. **HRMS** (APCI) cald. for $C_{19}H_{26}O_3$ $(M+H)^+$ requires 303.1960; found 303.1948.

Ethyl 2-((2*R,6*R**)-2-ethyl-5,6-dihydro-6-isopropyl-4-methyl-2*H*-pyran-2-yl)acetate (31g):**



Colourless oil (165 mg, 65%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.89 (t, J = 7.6 Hz, 3 H), 0.90 (d, J = 7.2 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 1.23 (t, J = 7.6 Hz, 3 H), 1.50-1.61 (m, 2 H), 1.63-1.74 (m, 5 H), 1.80-1.87 (m, 1 H), 2.47 (brs, 2 H), 3.26-3.31 (m, 1 H), 4.05-4.13 (m, 2 H), 5.50 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 8.0, 14.4, 18.4, 18.9, 23.5, 29.7, 32.7, 33.1, 43.8, 60.1, 73.2, 75.7, 126.0, 131.9, 171.2; **IR** (Neat) 2963, 2928, 1735, 1685, 1449, 1368, 1207, 1073, 1033, 867 cm^{-1}. **HRMS** (APCI) cald. for $C_{15}H_{26}O_3$ $(M+H)^+$ requires 255.1960; found 255.1952.

Ethyl 2-((2*R,6*R**)-6-cyclohexyl-2-ethyl-5,6-dihydro-4-methyl-2*H*-pyran-2-yl)acetate (31h):**

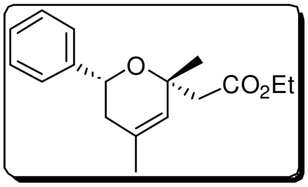


Colourless oil (183 mg, 62%); ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.89 (t, J = 7.6 Hz, 3 H), 0.94-1.03 (m, 2 H), 1.12-1.19 (m, 2 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.31-1.40 (m, 2 H), 1.48-1.57 (m, 2 H), 1.62-1.76 (m, 7 H), 1.81-1.88 (m, 2 H), 1.98-2.02 (m, 1 H), 2.47 (brs, 2 H), 3.28-3.34 (m, 1 H), 4.05-4.12 (m, 2 H), 5.49 (brs, 1 H); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 8.0, 14.5, 23.6, 26.3, 26.5, 26.9, 28.8, 29.4, 29.6, 32.9, 42.9, 43.8, 60.2, 72.5, 75.7, 126.1, 132.0, 171.3; **IR** (Neat) 2965, 2925, 1735, 1675, 1449, 1377, 1207, 1096, 1033, 844 cm^{-1}. **HRMS** (APCI) cald. for $C_{18}H_{30}O_3$ $(M+H)^+$ requires 295.2273; found 295.2265.

6.7 Selected Spectra of Substituted Dihydropyrans

Ethyl 2-((2*R**,6*R**)-5,6-dihydro-2,4-dimethyl-6-phenyl-2*H*-pyran-2-yl)acetate (27a):

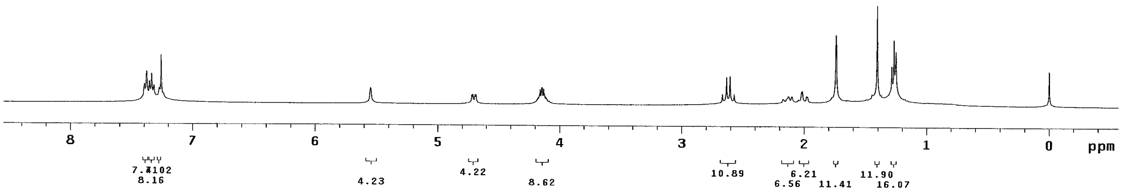
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_573_M

exp1  s2pul

      SAMPLE               SPECIAL
date   Feb  5 2012  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_573~ hst           0.008
        M_Pdt.fid   pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8          FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               8  hs               nn
d1           1.000        PROCESSING
nt             200  lb             0.10
ct             160  fn            65536
   TRANSMITTER             DISPLAY
tn              H1  sp           -232.6
sfrq       399.853  wp           3652.5
tof          362.8  rfl           795.0
tpwr            57  rfp               0
pw           9.850  rp            110.4
    DECOUPLER       lp            -98.1
dn             C13           PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               24
dpwr            50  th               13
dmf          15900  nm  cdc  ph
```

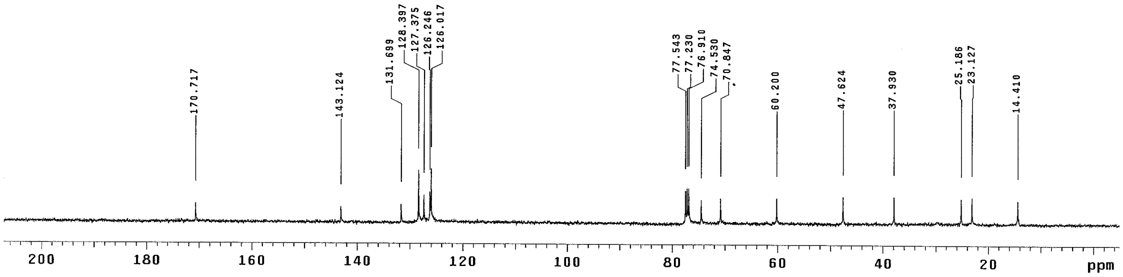


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_573_M

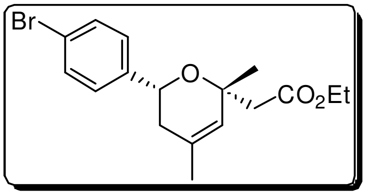
exp1  s2pul

      SAMPLE               SPECIAL
date   Jan  8 2012  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_573~ hst           0.008
        M_C13.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6          FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000        PROCESSING
nt            4000  lb             2.00
ct            1808  fn            65536
   TRANSMITTER             DISPLAY
tn             C13  sp           -498.1
sfrq       100.554  wp          21328.5
tof         1536.3  rfl          9285.9
tpwr            61  rfp          7764.9
pw           9.300  rp            -56.9
    DECOUPLER       lp           -369.4
dn              H1           PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               12
dpwr            42  th                3
dmf           8900  nm  no  ph
```



Ethyl 2-((2*R**,6*R**)-6-(4-bromophenyl)-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27c):

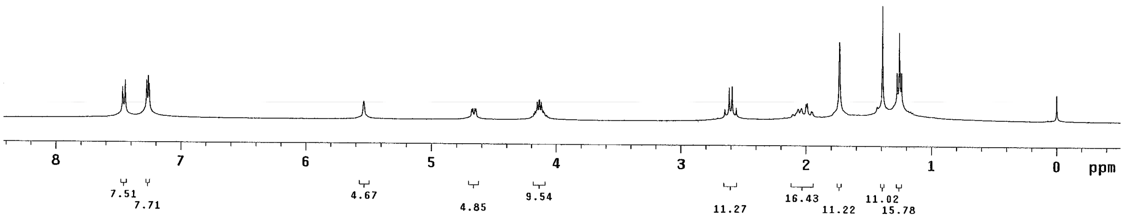
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_580_M

exp1  s2pul

       SAMPLE               SPECIAL
date   Jan 28 2012  temp       not used
solvent      CDC13  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_580~ hst           0.008
         M_Pdt.fid  pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8           FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               8  hs               nn
d1           1.000        PROCESSING
nt             200  lb             0.10
ct              64  fn            65536
   TRANSMITTER              DISPLAY
tn              H1  sp           -206.9
sfrq       399.853  wp           3576.8
tof          362.8  rfl           794.7
tpwr            57  rfp               0
pw           9.850  rp            100.7
    DECOUPLER       lp            -87.0
dn             C13             PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               25
dpwr            50  th               20
dmf          15900  nm  cdc  ph
```

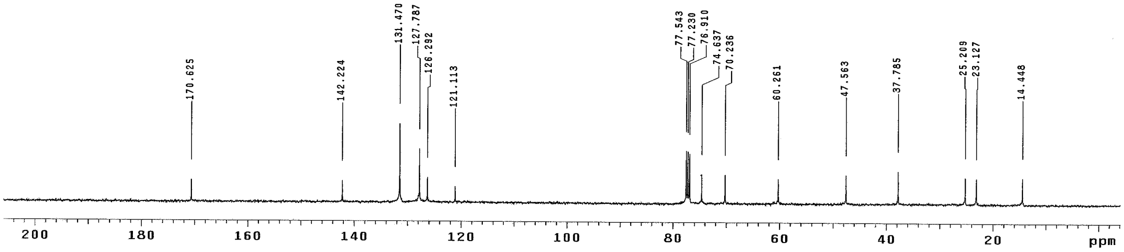


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_580_M

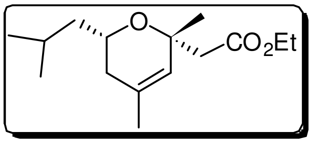
exp1  s2pul

       SAMPLE               SPECIAL
date   Jan 28 2012  temp       not used
solvent      CDC13  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_580~ hst           0.008
         M_C13.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6           FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000        PROCESSING
nt            5000  lb             2.00
ct            2832  fn            65536
   TRANSMITTER              DISPLAY
tn             C13  sp           -426.0
sfrq       100.554  wp          21130.6
tof         1536.3  rfl          9279.8
tpwr            61  rfp          7764.9
pw           9.300  rp            -49.3
    DECOUPLER       lp           -360.6
dn              H1             PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               20
dpwr            42  th                3
dmf           8900  nm  no  ph
```



Ethyl 2-((2*R,6*S**)-5,6-dihydro-6-isobutyl-2,4-dimethyl-2*H*-pyran-2-yl)acetate (27j):**

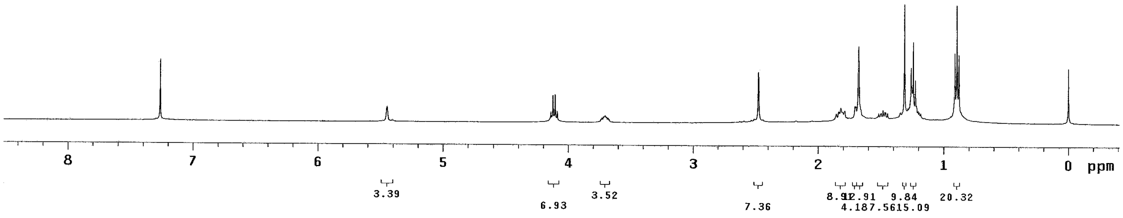
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_587_M

exp1  s2pul

      SAMPLE                 SPECIAL
date   Feb  8 2012  temp        not used
solvent       CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_587~ hst            0.008
           _M.fid  pw90          19.700
   ACQUISITION      alfa          20.000
sw          6389.8          FLAGS
at           1.998  il                 n
np           25528  in                 n
fb        not used  dp                 y
bs               8  hs                nn
d1           1.000         PROCESSING
nt             200  lb              0.10
ct             200  fn             65536
   TRANSMITTER              DISPLAY
tn              H1  sp            -164.0
sfrq       399.853  wp            3568.4
tof          362.8  rfl            793.7
tpwr            57  rfp                0
pw           9.850  rp             110.6
    DECOUPLER       lp             -90.4
dn             C13           PLOT
dof              0  wc               250
dm             nnn  sc                 0
dmm              c  vs                27
dpwr            50  th                 9
dmf          15900  nm   cdc   ph
```

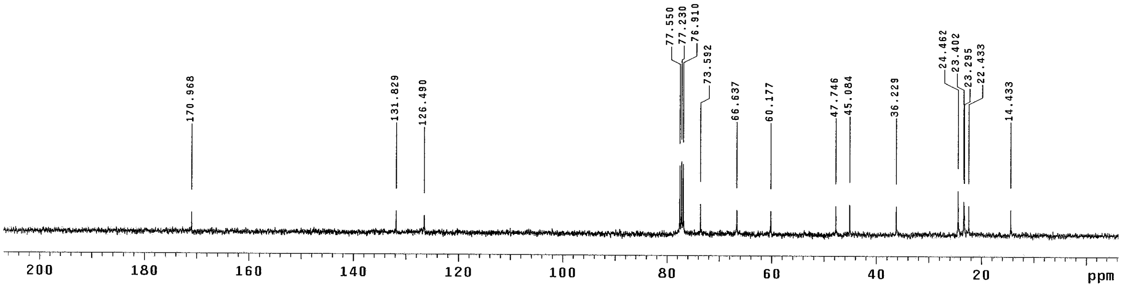


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_587_M

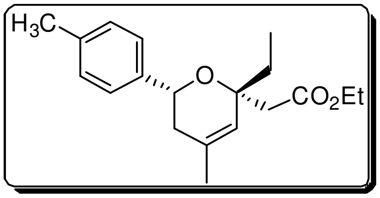
exp1  s2pul

      SAMPLE                 SPECIAL
date   Feb  8 2012  temp        not used
solvent       CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/AKS_PS_587~ hst            0.008
        M_C13.fid  pw90          18.600
   ACQUISITION      alfa          20.000
sw         25125.6          FLAGS
at           1.199  il                 n
np           60270  in                 n
fb           13800  dp                 y
bs              16  hs                nn
d1           1.000         PROCESSING
nt            4000  lb              2.00
ct             992  fn             65536
   TRANSMITTER              DISPLAY
tn             C13  sp            -649.2
sfrq       100.554  wp           21493.3
tof         1536.3  rfl           9272.1
tpwr            61  rfp           7764.9
pw           9.300  rp             -88.6
    DECOUPLER       lp            -271.4
dn              H1           PLOT
dof              0  wc               250
dm             yyy  sc                 0
dmm              w  vs                16
dpwr            42  th                 4
dmf           8900  nm   no   ph
```



Ethyl 2-((2*R**,6*R**)-2-ethyl-5,6-dihydro-4-methyl-6-*p*-tolyl-2*H*-pyran-2-yl)acetate (27l):

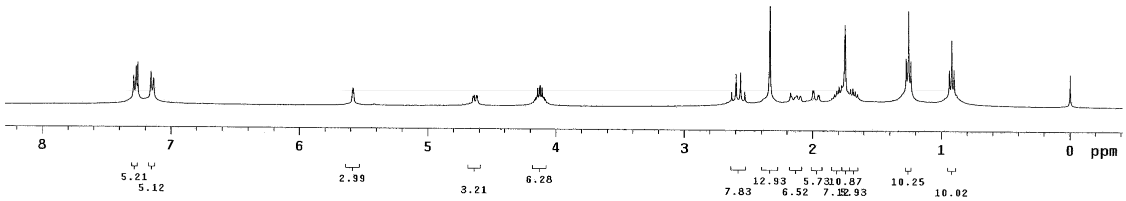
^{1}H NMR (400 MHz, $CDCl_3$)



```
PS_592_M

exp1  s2pul

      SAMPLE              SPECIAL
date   Feb 19 2012  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_592~ hst           0.008
            _M.fid  pw90         19.700
   ACQUISITION      alfa         20.000
sw           6389.8         FLAGS
at            1.998  il               n
np            25528  in               n
fb         not used  dp               y
bs                8  hs              nn
d1            1.000       PROCESSING
nt              200  lb            0.10
ct              200  fn           65536
   TRANSMITTER             DISPLAY
tn               H1  sp          -166.0
sfrq        399.853  wp          3484.6
tof           362.8  rfl          795.6
tpwr             57  rfp              0
pw            9.850  rp           109.2
    DECOUPLER        lp           -97.8
dn              C13          PLOT
dof               0  wc             250
dm              nnn  sc               0
dmm               c  vs              23
dpwr             50  th               6
dmf           15900  nm  cdc  ph
```

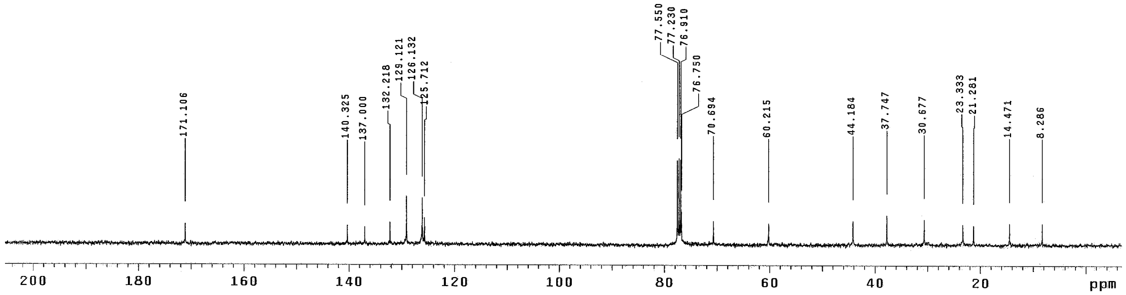


^{13}C NMR (100 MHz, $CDCl_3$)

```
PS_592_M

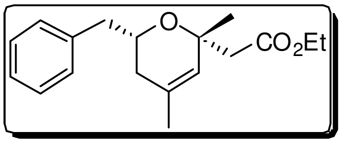
exp1  s2pul

      SAMPLE              SPECIAL
date   Feb 19 2012  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_592~ hst           0.008
         M_C13.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw          25125.6         FLAGS
at            1.199  il               n
np            60270  in               n
fb            13800  dp               y
bs               16  hs              nn
d1            1.000       PROCESSING
nt             8000  lb            2.00
ct             3200  fn           65536
   TRANSMITTER             DISPLAY
tn              C13  sp          -685.2
sfrq        100.554  wp         21361.4
tof          1536.3  rfl         9275.2
tpwr             61  rfp         7764.9
pw            9.300  rp           -60.3
    DECOUPLER        lp          -349.0
dn               H1          PLOT
dof               0  wc             250
dm              yyy  sc               0
dmm               w  vs              20
dpwr             42  th               3
dmf            8900  nm  no  ph
```



Ethyl 2-((2*R**,6*R**)-6-benzyl-5,6-dihydro-2,4-dimethyl-2*H*-pyran-2-yl)acetate (31c):

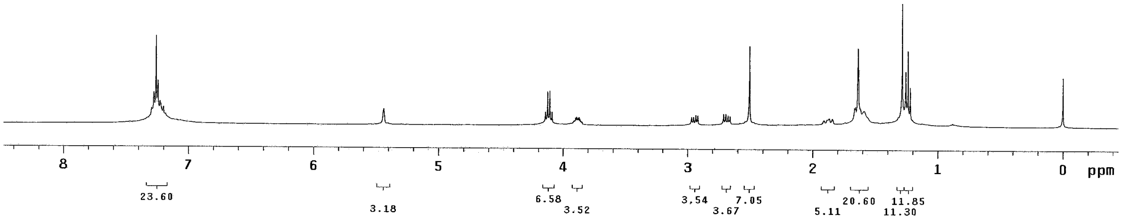
^{1}H NMR (400 MHz, CDCl$_3$)



```
PS_595_M

exp1  s2pul

      SAMPLE                SPECIAL
date   Feb 25 2012  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_595~ hst           0.008
            _M.fid  pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8          FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               8  hs               nn
d1           1.000        PROCESSING
nt             300  lb             0.10
ct             264  fn            65536
   TRANSMITTER              DISPLAY
tn              H1  sp           -181.9
sfrq       399.853  wp           3576.8
tof          362.8  rfl           794.8
tpwr            57  rfp               0
pw           9.850  rp            108.6
    DECOUPLER       lp            -88.8
dn             C13           PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               27
dpwr            50  th                4
dmf          15900  nm   cdc   ph
```

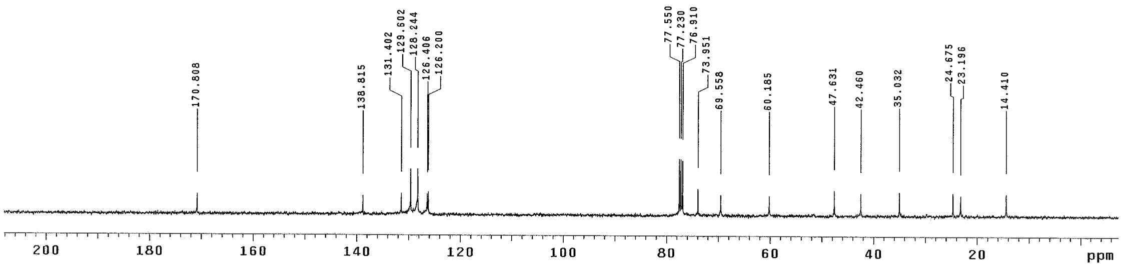


^{13}C NMR (100 MHz, CDCl$_3$)

```
PS_595_M

exp1  s2pul

      SAMPLE                SPECIAL
date   Feb 25 2012  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
ciftemp/AKS_PS_595~ hst           0.008
        M_C13.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6          FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000        PROCESSING
nt            5000  lb             2.00
ct            2240  fn            65536
   TRANSMITTER              DISPLAY
tn             C13  sp           -756.5
sfrq       100.554  wp          21691.1
tof         1536.3  rfl          9280.5
tpwr            61  rfp          7764.9
pw           9.300  rp            -76.1
    DECOUPLER       lp           -301.3
dn              H1           PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               13
dpwr            42  th                2
dmf           8900  nm   no   ph
```



List of Publications

1. A Novel Synthesis of Oxabicyclo[3.3.1]nonanone via (3,5)-Oxonium-Ene Reaction.
   Saha, P.; Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Org. Lett.* **2010**, *12*, 1824-1826.
2. Synthesis of Oxabicyclo[3.3.1]nonenes and Substituted Tetrahydropyrans via (3,5)-Oxonium-Ene Reaction.
   Saha, P.; Gogoi, P.; Saikia, A. K. *Org. Biomol. Chem*. **2011**, *9*, 4626-4634.
3. Stereoselective Synthesis of 6-Oxabicyclo[3.2.1]octene via (3,5)-Oxonium-Ene Reaction.
   Saha, P.; Saikia, A. K. *Tetrahedron*. **2012**, *68*, 2261-2266.
4. Synthesis of 2,3,5,6-Tetrasubstituted Tetrahydropyrans via (3,5)-Oxonium-Ene Reaction.
   Saha, P.; Bhunia, A.; Saikia, A. K. *Org. Biomol. Chem.* **2012**, *10*, 2470-2481.
5. Diastereoselective Synthesis of Substituted Dihydropyrans via Oxonium-Ene Cyclization Reaction.
   Saha, P.; Ghosh, P.; Sultana, S.; Saikia, A. K. *Org. Biomol. Chem.* **2012**, *10*, 8730-8738.
6. An Efficient Synthesis of 10-Amino Artemisinin Derivative.
   Saha, P.; Saikia, A. K. *J. Heterocycl. Chem.* **2012** (Article in press).
7. An Efficient Synthesis of Dihydro- and Tetrahydropyrans via Oxonium-Ene Cyclization Reaction.
   Bondalapati, S.; Reddy, U. C.; **Saha, P.**; Saikia, A. K. *Org. Biomol. Chem*. **2011**, *9*, 3428-3438.
8. Application of a Novel 1,3-Diol with a Benzyl Backbone as Chiral Ligand for Asymmetric Oxidation of Sulfides to Sulfoxides.
   Gogoi, P.; Kotipalli, T.; Indukuri, K.; Bondalapati, S.; **Saha, P.**; Saikia, A. K. *Tetrahedron Lett*. **2012**, *53*, 2726-2729.